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The neural correlates of reading impairment in adults with developmental dyslexia

evidence from fMRI between group analyses and an fMRI multiple-case study

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THE NEURAL CORRELATES OF READING IMPAIRMENT IN ADULTS WITH DEVELOPMENTAL DYSLEXIA:
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The goal of this project was to investigate the neural correlates of reading impairment in dyslexia as hypothesised by the main theories – the phonological deficit, visual magnocellular deficit and cerebellar deficit theories, with emphasis on individual differences. This research took a novel approach by: 1) contrasting the predictions in one sample of participants with dyslexia (DPs); 2) using a multiple-case study (and between-group comparisons) to investigate differences in BOLD between each DP and the controls (CPs); 3) demonstrating a possible relationship between reading impairment and its hypothesised neural correlates by using fMRI and a reading task. The multiple-case study revealed that the neural correlates of reading in dyslexia in all cases are not in agreement with the predictions of a single theory. The results show striking individual differences - even, where the neural correlates of reading in two DPs are consistent with the same theory, the areas can differ. A DP can exhibit under-engagement in an area in word, but not in pseudoword reading and vice versa, demonstrating that underactivation in that area cannot be interpreted as a 'developmental lesion'. Additional analyses revealed complex results. Within-group analyses between behavioural measures and BOLD showed correlations in the predicted regions, areas outside ROI, and lack of correlations in some predicted areas. Comparisons of subgroups which differed on Orthography Composite supported the MDT, but only for Words. The results suggest that phonological scores are not a sufficient predictor of the under-engagement of phonological areas during reading. DPs and CPs exhibited correlations between Purdue Pegboard Composite and BOLD in cerebellar areas only for Pseudowords. Future research into reading in dyslexia should use a more holistic approach, involving genetic and environmental factors, gene by environment interaction, and comorbidity with other disorders. It is argued that multidisciplinary research, within the multiple-deficit model holds significant promise here.

Key words: dyslexia, fMRI, multiple-case study, reading, comorbidity

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1 Introduction

Developmental dyslexia (henceforth dyslexia) is a prevalent specific childhood disorder the symptoms of which persist throughout the entire life-span of an individual. According to the definition approved by the British Dyslexia Association in October 2007, "dyslexia is a specific learning difficulty that mainly affects the development of literacy and language related skills. It is likely to be present at birth and to be life-long in its effects. It is characterised by difficulties with phonological processing, rapid naming, working memory, processing speed, and the automatic development of skills that may not be consistent with an individual's other cognitive abilities. It tends to be resistant to conventional teaching methods, but its effect can be mitigated by appropriate, specific intervention, including the application of information technology and supportive counseling" (British Dyslexia Association, 2007).

Before proceeding further some terms used in the definition of dyslexia are defined below. *Phonological processing* refers to detecting and discriminating differences in phonemes (speech sounds) defined as minimal units in the sound system of a given language that distinguish words, which are otherwise identical, such as *pet* and *bet* (c.f. Crystal, 1991). *Rapid naming* refers to participants' ability to retrieve phonological information from long-term memory. It is usually measured using a Rapid Automatized Naming (RAN) task. This task measures how quickly participants are able to name aloud: colours, pictures of objects, digits and letters. *Working memory* is defined as 'a brain system that provides temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning' (Baddeley, 1992).

1.1 Diagnosis of dyslexia

Dyslexia in children is currently diagnosed in UK by a discrepancy method, according to which a child must exhibit a significant difference ($\leq$ 1.5 SDs) between their reading ability and the level of ability predicted by their score on full scale IQ (FSIQ). Some critics (Siegel, 1992) have emphasised that this method introduces a bias against diagnosing dyslexia in less able children because the child has to have a relatively high IQ score for a discrepancy to be found. There is an ongoing debate regarding the validity of this diagnostic method. Some researchers (e.g., Siegel, 1988; 1989; 1992) argue that diagnosis of dyslexia should not involve

IQ measurement because poor readers at all IQ levels exhibit qualitatively similar reading and spelling difficulties. Conversely, other researchers (e.g., Fawcett, Nicolson, & Maclagan, 2001; Nicolson, 1996) argue that diagnosis should involve IQ measurement because the literacy differences between poor IQ non-discrepant and IQ-discrepant readers may be characterised by different underlying causes, such as mild general learning difficulty and specific learning difficulty, respectively. From the research point of view, the way dyslexia is diagnosed has important implications, because if non-discrepant readers (with mild general learning difficulty) are labelled as persons with dyslexia, along with the ones who are discrepant readers (with specific learning difficulty) this could result in confounding the samples in studies on the underlying causes of dyslexia.

Dyslexia diagnosis in adults can be more challenging than in children because an adult's literacy difficulties may be at least partially compensated – their literacy performance, at least on word reading, could therefore be within the average range. Hence, given that their FSIQ performance is also at least within the average range, there may be no significant discrepancy between their reading and FSIQ measures. Current approaches to diagnosis of adults in UK advocate that diagnosis of dyslexia needs to be based on careful assessment of cognitive, literacy and phonological processing, with particular attention paid to any discrepancies between FSIQ and certain specific areas, such as: literacy, working memory and phonological processing (McLoughlin, Fitzgibbon, & Young, 1994; National Working Party on Dyslexia in Higher Education, 1999; Turner, 1997). One problem with this approach is that DPs with high IQ are likely to be over-diagnosed.

The prevalence rates for dyslexia range from 5 to 17.5% (Shaywitz, 1998). Some researchers have indicated that dyslexia occurs more often in males than in females, nevertheless, such an outcome could also result from referral bias (Habib, 2000; Shaywitz et al., 2003). A more recent publication (Rutter et al., 2004), however, demonstrated that in four independent epidemiological studies the rates of reading disability were significantly higher in boys than in girls. The authors concluded that reading disabilities are clearly less frequent in girls than in boys.

1.2 Dyslexia as a broader phenotype

Broadly speaking, the difficulties experienced by participants with dyslexia (DPs) are not usually limited to difficulties in the development of literacy and language related skills and the aforementioned cognitive abilities. Difficulties with distinguishing between right and left (Miles, 1993), temporal sequencing (learning to tell the time, remembering days of the week, months, etc.) (Miles, 1993),

planning and organization (Brunswick, 2011) and poor spatial sequencing (Stein & Walsh, 1997), may also occur, to mention a few. The key issue here is the extent to which non-literacy deficits found in dyslexia are part of the broader dyslexia syndrome and to what extent they are related to other developmental disorders which co-occur with dyslexia.

1.3 Findings from behavioural and molecular genetics

Dyslexia is characterized by a strong heritable component (Poelmans, Buitelaar, Pauls, & Franke, 2011). The findings from behavioural and molecular genetics are extremely important because they shape the understanding of this disorder (and its co-occurrence with other developmental disorders) (please see also Chapter 8). Hallgren (1950) and Thomas (1905) noted that dyslexia runs in families, implicating a genetic basis, however, this is not sufficient, because co-occurrence of literacy problems can result from a shared environment. Hence, scientists started to study MZ twins (Monozygotic), who have almost identical genetic material, and DZ (Dizygotic) twins who share approximately half their genes. Both types of twins are assumed to share the same environment (there is also non-shared environment within and outside a family; the non-shared environment component of variance refers to variance not accounted for by shared environment or by heredity, it also includes error measurement (Plomin, DeFries, McClearn, & McGuffin, 2008)). If MZ twins' reading ability (on the populational level) is more similar than DZ twins' reading ability (on the populational level), it suggests that genetic factors play a role in reading ability. Such a pattern of results was found in the Colorado Learning Disabilities Research Centre's study. A concordance rate (identity of traits within twins) for dyslexia of 38% in DZ twins, as compared to 68% in MZ twins was reported (DeFries, Fulker, & LaBuda, 1987). This finding suggests that genetic influence is of moderate importance (DeFries & Alarcon, 1996).

One problem with a method which relies on concordance rates is that it is best for studying traits which are categorical. Because DPs are characterized by reading problems which vary in degree, DeFries and Fulker (1985) developed a method which deals with continuous traits in twins. Using this method with DPs, the authors reported an estimated group heritability of approximately 50%; this means that 50% of the difference in reading scores between the general population and the probands can be accounted for by genetic differences. It should be mentioned,

however, that heritability seems to be higher in children with higher IQs (Olson, Datta, & DeFries, 1999) and in children who have more serious reading problems (Bishop, 2001). These findings, therefore suggest that genetic influence may be stronger in some sub-groups of DPs than in other subgroups.

Molecular genetics started a new chapter on the identification of genes implicated in dyslexia and so far seventeen such genes have been suggested by cytogenetic findings, linkage and association studies. These include: *DYX1C1* on the longer arm of chromosome 15 (15q21) (Taipale et al., 2003); *KIAA0319* (Cope et al., 2005; Francks et al., 2004), *DCDC2* (Meng et al., 2005), *THEM2* (Deffenbacher et al., 2004) and *VMP* (Londin, Meng, & Gruen, 2003) on the shorter arm of chromosome 6 (6p22); *ROBO1* on the shorter arm of chromosome 3 (3p12) (Hannula-Jouppi et al., 2005); *C2ORF3* and *MROL19* on the shorter arm of chromosome 2 (2p12-p16) (Anthoni et al., 2007); *KIAA0319L* on the short arm of chromosome 1 (1p35) (Couto et al., 2008); *S100B* and *DIP2A,* on the longer arm of chromosome 21 (21q22.3) (Poelmans et al., 2009); *FMR1* on the longer arm of chromosome X (Xq27) (de Kovel et al., 2004) and on the longer arm of chromosome 7 - *GTF2I* (7q11.23) (Antonell et al., 2010; Meyer-Lindenberg, Mervis, & Berman, 2006) and *DOCK4* (7q31.1) (Pagnamenta et al., 2010).

Ten out of the fourteen candidate genes (*KIAA0319, KIAA0319L, DYX1C1, S100B, DOCK4, ROBO1, FMR1, DCDC2 DIP2A* and *GTF2I*) are compatible with a theoretical molecular network involved in neurite outgrowth and neuronal migration. More recently, three novel dyslexia candidate genes (from known linkage regions) were proposed (Poelmans et al., 2011). These included: *SLIT2* on the shorter arm of chromosome 4 (4p15.32) (Bates et al., 2007); *HMGB1* on the longer arm of chromosome 13 (13q12.3) (Igo et al., 2006) and *VAPA* on the shorter arm of chromosome 18 (18p11.2) (Bates et al., 2007; Fisher, Francks, Marlow et al., 2002).

Linkage studies suggest that more ‘dyslexia genes’ will be identified. There are at least two reasons for this. First, although, a single gene mutation may be associated with dyslexia, as with *ROBO1*, such cases should be rare because it is a heterogeneous disorder and therefore it is likely that most cases will be associated with several susceptibility alleles, each contributing a portion to an individual’s risk of developing this disorder (Fisher, 2006). It is possible that there are a large number of such genes and their dyslexia susceptibility may be frequent in the general population and there may be large numbers of possible combinations of

alleles conferring a high susceptibility to dyslexia. Second, behavioural findings point to the fact that dyslexia is a heterogeneous developmental disorder and even within a given cognitive subtype of dyslexia, several genotypes may be compatible with it. For instance, many genes are involved in neural migration, and therefore neuronal migration can be potentially affected in a similar way by many different genes.

1.4 Dyslexia and comorbidity with other developmental disorders

There is now considerable evidence that dyslexia co-occurs more frequently than would be expected by chance with other developmental disorders such as ADHD (Attention Deficit Hyperactivity Disorder) and Developmental Coordination Disorder (DCD). Heritability estimates for ADHD range from 60-80% (Smalley, 1997). Approximately 25-40% of children with ADHD or dyslexia also have another developmental disorder (August & GarWnkel, 1990; Carroll, Maughan, Goodman, & Meltzer, 2005; Dykman & Ackerman, 1991; Semrud-Clikeman et al., 1992; Willcutt & Pennington, 2000). Kaplan, Wilson, Dewey and Crawford (1998) revealed that 42% of their reading disabled children also met the criteria for ADHD.

DCD (also known as dyspraxia) is a marked impairment in the development of motor coordination. It has been estimated that approximately 6% of 5-11 year old children have this disorder (American Psychiatric Association, 1994). There is growing evidence that some reading impaired individuals exhibit motor difficulties (Denckla, 1985; Fawcett & Nicholson, 1995; Haslum, 1989; Iversen, Berg, Ellertsen, & Tonnessen, 2005; McPhillips & Sheehy, 2004; Miles, 1993; Wolff, Cohen, & Drake, 1984). The prevalence of dyslexia and DCD comorbidity was assessed to be 63% in Kaplan et al.'s (1998) sample. However, it should be emphasised that comorbidity depends on the characteristics of the reference sample. DCD in dyslexia is not the same as dyslexia in DCD.

1.5 Current main theories of the underlying cause of dyslexia

Although the current thinking about dyslexia is changing, especially in the light of the findings from behavioural and molecular the genetics (Pennington, 2006; 2011), there have been and still currently are three main causal theories of dyslexia: the Phonological Deficit Theory (PDT) (Bradley & Bryant, 1983; Paulesu et al., 1996; Ramus, Rosen et al., 2003; Shaywitz et al., 1998; Snowling, 2000; Vellutino, 1979), the visual Magnocellular Deficit Theory (MDT) (Hansen, Stein, Orde,

Winter, & Talcott, 2001; Lovegrove et al., 1982; Stein, 2001; 2003; Stein & Talcott, 1999; Stein, Talcott, & Witton, 2001; Stein & Walsh, 1997) and the Cerebellar Deficit Theory (CDT) (Fawcett & Nicolson, 1999; Nicolson & Fawcett, 1990; Nicolson & Fawcett, 2008; Nicolson et al., 1999; Nicolson, Fawcett, & Dean, 2001). Each theory postulates a different underlying cause of literacy difficulties in dyslexia. Each theory also predicts a different set of associated difficulties; these difficulties may be linked to a reading deficit, but not necessarily (please see below).

Morton and Frith (1995) proposed that it is helpful to make a distinction between different levels of explanation within a given theory. The authors proposed: 1) the biological level and the environmental level (where search for cause/s and cure/s take place), 2) the behavioural level (where assessments and observations are recorded) and 3) the cognitive level (where disorder is presented as a recognizable and distinct entity, in spite of variable symptoms).

1.5.1 The Phonological Deficit Theory

The PDT was formulated first on the cognitive level. According to the PDT (Frith, 1999; Lundberg & Hoien, 2001; Rack, Snowling, & Olson, 1992; Ramus, Rosen et al., 2003; Snowling, 2000; Snowling & Caravolas, 2007; Vellutino, Fletcher, Snowling, & Scanlon, 2004) *phonological deficit* is the underlying cause of dyslexia on the cognitive level (see Figure 1.1). This means that DPs have a specific impairment in the representation and processing of speech sounds (phonemes) (Snowling, 2000; Snowling & Caravolas, 2007). According to this theory, the phonological deficit leads to poor grapheme-phoneme conversion (defined as a process which is required when pseudowords are presented visually and have to be recognised in the auditory modality (Snowling, 1980)) and this in turn leads to poor reading (as measured by reading tests on the behavioural level).

It is claimed that the phonological deficit also manifests itself on the behavioural level by difficulties in: phonological awareness (Bradley & Bryant, 1983; Olson, Wise, Conners, Rack, & Fulker, 1989; Ramus, Rosen et al., 2003), phonological fluency (naming tasks) (Denckla & Rudel, 1976; Paulesu et al., 2001; Ramus, Rosen et al., 2003; Reid, Szczerbinski, Iskierka-Kasperek, & Hansen, 2007) and verbal short-term memory (Brady, Shankweiler, & Mann, 1983; Paulesu et al., 2000; Ramus, Rosen et al., 2003). According to Frith (1997) the underlying cause of dyslexia on the biological level is abnormality within the perisylvian brain

region. This issue will be discussed in more detail in the section on neuroimaging studies presented below.

For clarity the terms which describe the manifestation of the phonological deficit on the behavioural level are defined below. *Phonological awareness* refers to an individual's awareness and ability to manipulate the sound structure of spoken words; it usually involves the detection and manipulation of sounds at three levels (Stahl & Murray, 1994): phoneme (defined above), onset (the part of the syllable which contains the consonant, or consonants, that precedes the vovel, e.g., *'sl-'* in *sleuthhound*), rime (a part of the syllable which contains the vowel and the coda, e.g., *'-at'* in *mat*, and syllable (a unit of organization for a sequence of phonemes, comprising a vowel sound (nucleus) and usually consonant sound/s preceding the vowel (onset) and/or following it (coda), e.g., the word *water* consists of two syllables *'wa-'* and *'-ter'*). *Phonological fluency* is usually measured by rapid automatised naming (RAN) tasks (see below). These tasks require efficient retrieval of phonological information from long-term memory. The fluency with which readers are able to retrieve phonological codes for phonemes, word segments and words influences the degree to which phonological information is useful in decoding written words (Wagner, Torgesen, & Rashotte, 1999). *Verbal short-term memory* is the capacity for holding a small amount of verbal information in one's mind in a readily available state for a short time.

Figure 1.1 Graphical representation of the PDT (Frith, 1997).

More recently the PDT has been updated (Hulme & Snowling, 2009) (see Figure 1.2). The updated version of the PDT is essentially the same as the older version of the PDT (Frith, 1997), with a few exceptions. First, a genetic level was added to the biological level. The authors focused on genes on chromosomes 6, 15 and 18, arguing that they affect the development of the L hemisphere brain networks and especially the development of temporo-parietal cortex. Second, also

on the biological level, the term 'perisylvian region' was replaced with 'L temporo-parietal' and 'L frontal' regions. Third, as in the older model (Frith, 1997) brain abnormalities are hypothesised to lead to a reading deficit through the phonological deficit; however in the updated model it is hypothesised that reading deficit could be also caused by "language delay" which leads to phonological deficit. According to the updated version of the PDT a more severe phonological deficit leads to more severe reading difficulties and feedback to reduce brain activity in areas subserving phonological processing and reading.

Figure 1.2 A graphical representation of the updated version of the PDT (Hulme & Snowling, 2009). Bold arrows denote causal links for which, according to the authors, there is evidence; dotted lines denote testable hypotheses.

1.5.2 The Magnocellular Deficit Theory

The visual MDT (Hansen et al., 2001; Stein, 2003; Stein & Kapoula, 2012; Stein & Walsh, 1997) claims that the underlying cause of literacy problems in dyslexia is not language specific, but a more general impairment of the visual magnocellular system (which is specialized for processing fast temporal visual information) with spared parvocellular system. Magnocellular cells are characterized by thick myelination and rapidly conducting axons. They have greater dendritic area which allows them to get information from an area of the retina ten times larger than that

for parvocells. They respond best to lower spatial frequencies but they have a contrast sensitivity, luminance and temporal sensitivity ten times higher than parvocells. The MDT was the first to propose a route from the biological level to the cognitive level.

The magnocellular pathway from the retina projects through the LGN (lateral geniculate nucleus) to V1 (the primary visual cortex). A subset of cells in V1 projects directly to V5/MT and to V2 (the secondary visual cortex) (Wurtz & Kandel, 2000). V5/MT is hypothesised to be receiving the input predominantly from the magnocellular stream (Tootell & Taylor, 1995; Watson et al., 1993) and hence is usually the main target of investigations into the magnocellular system (e.g., Eden et al., 1996) (for more details see: 1) the section 'Neuroimaging studies investigating visual magnocellular processing' and 2) Figure 1.6).

The results in support of the MDT include: unsteady binocular fixation (binocular fixation being defined as the steadiness with which one can have both eyes directed at the same object at the same time) (e.g., Stein, 2001), reduced contrast sensitivity (contrast sensitivity being defined as a measure of one's ability to see details at low contrast levels) (e.g., Lovegrove et al., 1982) and a significantly higher threshold for perception of coherent movement in random dot kinematograms in DPs than CPs (e.g., Hansen et al., 2001). For further details on the visual MDT see the review by Stein and Walsh (1997) and for a critical review of the MDT see Skottun (2000).

It should be noted here that the MDT differs from the temporal processing deficit theory (TPDT) (De Martino, Espesser, Rey, & Habib, 2001; Farmer & Klein, 1995; Tallal, 1980). According to the TPDT the underlying cause of developmental dyslexia is a deficit in the perception of short or rapidly changing sounds (Tallal, 1980). Support for this theory comes from evidence that DPs exhibit poor performance on auditory tasks, such as temporal order judgement (Tallal, 1980) and frequency discrimination (Ahissar, Protopapas, Reid, & Merzenich, 2000; McAnally & Stein, 1996). There is also evidence that DPs show poorer categorical perception (Adlard & Hazan, 1998; Mody, Studdert-Kennedy, & Brady, 1997). Furthermore, a number of authors (Kujala et al., 2000; McAnally & Stein, 1996; Temple et al., 2000) reported abnormal neurophysiological responses in DPs to different auditory stimuli. The original version of the TPDT was not defined at the biological level.

The difference between the MDT and TPDT lies in the fact that not all large cells are magnocellular cells. Magnocellular cells come from a specific

embryological cell line and are primarily concerned with visual perception. Although the auditory system is not characterised by an anatomically distinct magnocellular pathway, large neurons, responsible for analysing acoustic transients were identified in this system. It has been reported (Galaburda, Menard, & Rosen, 1994) that these auditory neurons in the medial geniculate nucleus are abnormal in the brains of DPs. The TPDT can potentially explain the deficits in multiple systems, in fast temporal processing in auditory, motor and vestibular systems.

From a developmental point of view, the MDT claims that the visual magnocellular system is impaired from birth and has a genetic origin. The clearest genetic result is for linkage to the region on the short arm of chromosome 6 which helps to control the production of antibodies (Stein, 2001). Broadly speaking the magnocellular system is hypothesised to play an important role in reading and orthographic and phonological representations (Stein, 2001). First, it subserves the process of image stabilization and/or letter localization in words during reading (see a study by Liederman et al. (2003) presented in the section 'Neuroimaging studies investigating visual magnocellular processing'); this engagement of the magnocellular system in reading is tested in this thesis. Second, visual magnocellular impairment affects (through reading skill) orthographic knowledge (information (stored in memory) that tells one how to represent spoken language in written form (Apel, 2011)) (this is addressed in Chapter 7 in a post-hoc analysis). Third, the magnocellular system affects phonological representations through orthographic representations (Stein, 2001) (the methodology used in this thesis does not allow one to address this issue).

Because it is difficult to disentangle the orthographic from the phonological influences in reading, a number of experiments involving magnocellular function in reading and orthography have been performed on exception words (e.g., pint and yacht) and on Olson's pseudophomophone test (Olson et al., 1989). The processing of exception words, which cannot be read by assembling the constituent phonemes, biases towards orthographic processing. For instance, Talcott et al. (2000) reported that visual motion sensitivity explained independent variance in orthographic skill in unselected 10-year-old primary school children, after controlling for overall reading ability and IQ. Furthermore, in a study, which involved three hundred and fifty randomly selected primary school children (Talcott et al., 2002), visual motion sensitivity was a significant predictor of children's literacy skills and their orthographic and phonological skills.

1.5.3 The Cerebellar Deficit Theory

The CDT was originally formulated on the behavioural level as an automatization deficit theory (Nicolson & Fawcett, 1990). It is supported by the findings from a dual task paradigm, which involved balancing, defined as maintaining one's body in a state of equilibrium, while performing a secondary task. The results revealed that although under optimal conditions DPs could balance as well as CPs, in a dual task, DPs balanced significantly worse than the CPs (Nicolson & Fawcett, 1990). The authors suggested that one explanation of the results is that, unlike the CPs, DPs need to invest significant conscious effort for monitoring balance, and therefore their performance is significantly influenced by any secondary task which distracts attention from the primary task. This suggests that DPs' motor balance is poorly automatized. The authors concluded that it could be that DPs' reading problems are symptoms of the failure to fully automatize skills, which may be a more general learning deficit.

More recently the automatization deficit theory was re-formulated as the CDT. According to the CDT the underlying cause of dyslexia is a cerebellar impairment. Cerebellar disfunction has been linked to a range of behavioural deficits, such as problems in: 1) motor skills (Holmes, 1939), 2) automatisation of motor skills (Ito, 1990), 3) classical conditioning of the eyeblink response (Daum et al., 1993) and 4) perception and production of timing tasks (Ivry & Keele, 1989).

Research on dyslexia by Nicolson and Fawcet reported that DPs indeed have deficits over a range of functions which rely on cerebellar processing, such as: motor skills, including balancing – a gross motor skill, (Fawcett & Nicolson, 1999), eye-blink conditioning (Nicolson, Daum, Schugens, Fawcett, & Schulz, 2002) and time estimation (Nicolson et al., 1995). Note, however, that a recent meta-analysis (Rochelle & Talcott, 2006) showed that balance deficit in dyslexia can be accounted for by comorbid developmental disorders, such as ADHD and DCD (see also Wimmer, Mayringer, & Raberger, 1999). For further details on the CDT see reviews (Fawcett & Nicolson, 2004; Nicolson & Fawcett, 2008; Nicolson et al., 2001).

On the basis of findings implicating cerebellar impairment in dyslexia, Nicolson et al. (2001) proposed a hypothetical ontogenetic causal chain linking cerebellar impairment with phonological and reading deficits, (as well as with spelling and hand writing deficits) (see Figure 1.3). According to this model there are two routes by which cerebellar impairment could lead to reading difficulties in dyslexia. According to the first - a major route (marked in Figure 1.3 by a smaller rectangle

and bold arrows), cerebellar impairment (probably dating back to gestation) leads to mild articulatory problems, which lead to an impoverished representation of the phonological characteristics of speech. This in turn leads to difficulties in phonological awareness at approximately five years of age (it is not clear why at approximately this age, because presumably the poor awareness of speech would be present since birth) and subsequently results in difficulties with learning to read. Additionally, reduced articulation speed leads to reduced working memory.

According to the second route (outside the smaller rectangle in Figure 1.3) difficulties in reading acquisition stem from cerebellar impairment which causes problems with automatizing skills and knowledge, leading to difficulties with: 1) automatic grapheme-phoneme conversion, 2) automatic word recognition, 3) automatic verbal working memory and 4) automatic awareness of the orthographic regularities of a given language.

According to this hypothetical ontogenetic causal chain, cerebellar impairment is also the underlying cause of impairment of motor skills which leads to writing impairment (dys-graphia). Furthermore, cerebellar deficit leads to balance deficits. However, the motor difficulties (with the exception of the articulatory motor difficulties) and problems with balance do not lead to reading difficulties (Nicolson et al., 2001).

Figure 1.3 **A hypothetical ontogenetic causal chain (Nicolson et al., 2001).**

Note: Time (experience) and the way difficulties with reading, spelling and writing are caused by difficulties with skill acquisition, are represented on the x-axis. The main route is highlighted in a smaller rectangle within the bigger rectangle and bold arrows. The other route shows problems outside the phonological domain, such as difficulties with: 1) automatising skills and knowledge, 2) balance and 3) motor skills (including writing).

1.6 Neuroimaging studies (mainly involving tasks specifically developed to probe phonological, visual magnocellular and cerebellar function) which have a bearing on the main theories of dyslexia

There have been a number of neuroimaging studies - some with CPs and some comparing DPs and CPs, with the latter motivated by each of the three current main theories of dyslexia, but conducted with the focus usually on one theoretical framework. The results from these studies have a bearing on the PDT, visual MDT and CDT.

Before reviewing the neuroimaging studies three issues need to be introduced: 1) labelling conventions of brain areas; 2) brain activation and 3) the related terms of *overactivation* and *underactivation*. Regarding the first issue, there are a number of different ways to label a given brain area. One of the oldest systems, which is still widely used is a system invented by Korbinian Brodmann (a German neurologist) who reported the cytoarchitectural organization of neurons in the cerebral cortex using the Nissl stain. Each area was given a unique number from 1 to 52 and labeled for instance BA44, where 'BA' stands for Brodmann area and 44 is the unique number of the brain area; these were designed to be neutral names, as Brodmann did not argue for the concept of an extreme localisation of functions. Nowadays Brodmann's areas are in common use for descriptive purposes (Crossman & Neary, 2005). However, it should be noted here that although Brodmann's map and cytoarchitectonic analysis constitute a considerable scientific achievement, recent data obtained using imaging techniques underscore several shortcomings of these early architectonic maps. These include: 1) their presentation in two-dimensional schematic drawings; 2) the definition of the criteria which describe a given cortical area and its borders are observer dependent; and 3) the fact of inter-subject differences in brain architecture and macroscopy were neglected. These criticisms have been addressed in the seminal work of Karl Zilles and his colleagues (Zilles, Schleicher, Palomero-Gallagher, & Amunts, 2002) and incorporated, as much as possible (not all brain areas have yet been labeled using the new methods), in this thesis (see the section 'Labelling of the activations' in Chapter 5). All areas investigated in this thesis, for which there are probabilistic cytoarchitectonic labels, were labeled as such, using the Anatomy Toolbox (AT) (Eickhoff et al., 2005). Areas, for which there are no probabilistic cytoarchitectonic labels, were labeled using the Automated Anatomical Labelling (AAL) software (Tzourio-Mazoyer et al., 2002). Areas reported from studies by other authors are

always reported using the same labels as in the original source, unless (on rare occasions) stated otherwise.

Moving on to the second issue of brain activation - it is measured in fMRI experiments by the BOLD (Blood Oxygenation Level Dependent) contrast (see Chapter 2 for details). It should be emphasised that the terms 'activates', 'activated', 'activation' refer to localised changes in BOLD which: 1) do not provide a direct measure of neuronal activity and 2) are related to the neural activity evoked by a given experimental task, such as, deciding whether a given pair of consonants rhyme. 'Activation' is usually relative to a control condition, such as deciding whether a Korean letter looked similar to a Korean target letter (Paulesu et al., 1996).

The third issue has to do with two terms related to the term 'activation' which need to be introduced here: *'underactivation'* (synonymous term - *hypoactivation*) – activation which is significantly less than a given activation. For instance, there may be significantly less activation in a given brain area in an impaired group in comparison to the activation (in the same area, in the same task) in a control group. '*Overactivation* (synonymous term – *'hyperactivation'*) can be defined as activation which is significantly larger than a given activation. An impaired group could exhibit a significant overactivation of a given area in comparison to the control group. It is common to observe underactivation and overactivation in the neuroimaging studies of patients as compared to the control group (Hoeft, Meyler et al., 2007), of DPs in comparison with the CPs (Hoeft, Meyler et al., 2007) and in neuroimaging studies of normal aging in older participants, as compared to younger participants (Cabeza, Anderson, Locantore, & McIntosh, 2002).

The deficit postulated by the PDT has been also specified on the biological level as the L Perisylvian region abnormality (Frith, 1997) or more recently as the L temporo-parietal abnormality and L frontal abnormality (Hulme & Snowling, 2009). As these descriptive terms seem not to be detailed enough to thoroughly test the PDT on the neural level, the approach taken in this thesis is as follows. First the neuroimaging studies, which have tested the involvement of brain areas used in phonological processing, are reviewed below. The studies, to be included, had to investigate phonological processing using classical tests which tap into phonological processing, namely: *phonological awareness*, *naming* and *short term memory* tasks. The other criterion here was that the studies had to focus either on just CPs, or on DPs (as compared with the CPs). Second, the areas which consistently come up in these studies as involved in phonological processing were

used in this study to test the PDT. The role of these areas was also validated with the broader literature review in a section 'Brain regions and associated phonological processing' which follows the review of the neuroimaging studies on phonological awareness, naming and short term memory.

Neuroimaging studies on CPs have shown that *phonological awareness* tasks which involve segmented phonology (e.g. silently making a decision whether a given consonant rhymes with another consonant – "Does *'p'* rhyme with *'t'* ?") activate the perisylvian structures in the L (left) hemisphere, including: the L inferior frontal gyrus - BA44/45 (Broca's area), the L posterior superior temporal gyrus - BA22/21 (including Wernicke's area), the anterior and posterior parts of the L insula, as well as the L SMA (supplementary motor area) (BA6) and L PMC premotor cortex (BA6) (Paulesu et al., 1996) (some other areas were also activated (see Appendix A, Table 10.1 and Figure 1.4 below)).

Phonological awareness studies which involved word rhyming in CPs (e.g., Booth, Wood, Lu, Houk, & Bitan, 2007; Xu et al., 2001) also revealed activation in Broca's and Wernicke's areas, however, additionally the L fusiform gyrus (BA19/37) and L inferior temporal occipital junction (BA37) were activated. Nonword rhyming, similarly to word rhyming, activated the L inferior temporal occipital junction (BA37) in CPs, but additionally the L supramarginal gyrus (BA40) was activated (Xu et al., 2001) (for details, including other activated areas, see Appendix A, Table 10.1).

Neuroimaging studies of *covert object naming* (a task where a participant is asked to fixate on the visually presented object and to think silently of its name) (single item per trial) elicited activation in Broca's and Wernicke's areas, the L posterior fusiform gyrus (BA37), L middle temporal gyrus (BA21) and L premotor cortex (Lurito et al., 2000; Moore & Price, 1999). Other areas were also involved (see Appendix A, Table 10.1).

Moving on to investigations of *verbal short term memory* in CPs, Paulesu et al. (1996) conducted a study where participants were instructed to remember sequences of six consonants and two seconds later to make a judgement whether a target consonant appeared in the previously presented sequence. CPs exhibited a similar pattern of activations to those evoked in the consonant rhyming task reported above (Paulesu et al., 1996). The following areas were activated: the L inferior frontal gyrus (BA6/44), SMA (BA6), PMC (BA6), the L insula, L superior temporal gyrus (BA22) and the L supramarginal gyrus (BA40). Other areas were also activated (see Appendix A, Table 10.1). Moreover, a study by Paulesu, Frith,

and Frackowiak (1993) confirmed the crucial role of the supramarginal gyrus (BA 40) in verbal short term memory.

1.6.1 Neuroimaging studies testing the phonological skills of DPs (as compared to CPs)

Investigations of phonological processing in DPs, similar to the studies on CPs, have included *phonological awareness, naming and short-term memory* tasks. The aforementioned study by Paulesu et al. (1996) also investigated the performance of DPs in a covert consonant rhyming task. The results revealed that DPs exhibited significantly less activation than CPs in the L superior temporal gyrus (BA21/22), L insula and the L premotor cortex (PMC) (BA6). Some other areas were also involved (see Appendix A, Table 10.1).

Figure 1.4 A schematic drawing of the human brain with Brodmann's areas, including the areas predicted by the PDT to be underactivated in DPs (Demonet, Thierry, & Cardebat, 2005).

A further study by Shaywitz et al. (1998) with a sample of teenage and adult DPs, used (among others) the *covert single letter rhyming* task. This is a task where the subject viewed two simultaneously presented stimuli, e.g., [t] and [v], one above the other, and was asked to indicate (by pressing an appropriate response button) whether these letters rhymed. The authors found that DPs exhibited significantly less activation in L posterior areas: the angular gyrus (BA39) and the

posterior superior temporal gyrus (BA22). The other areas significantly less activated by DPs involved the striate cortex (BA17) and the R hemisphere homologues. In contrast, when performing the same task DPs showed significantly more activation than CPs in the L inferior frontal gyrus, including pars opercularis (BA44) and pars triangularis (BA45) and their R hemisphere homologues (R BA44 and R BA45). Shaywitz et al. (1998) concluded that the results support the PDT.

Regarding *naming* in DPs and CPs, McCrory, Mechelli, Frith and Price (2005) used a PET study to look for a common neurological impairment for reading and naming deficit in DPs. The results revealed that despite their unimpaired behavioural performance, DPs showed significantly less activation during picture naming and reading words in the L occipito-temporal area. Interestingly, the reduced activation for these tasks in DPs corresponds to 'the visual word form area' (VWFA) – claimed by some researchers (Cohen et al., 2000; Cohen et al., 2002; Cohen et al., 2003) to be specific to orthographic processing. McCrory et al. (2005), on the basis of their results demonstrating activation in both reading and picture naming (which does not involve orthographic processing), concluded that the L occipito-temporal area cannot be specific to orthographic processing, as claimed earlier (Cohen et al., 2000; Cohen et al., 2002; Cohen et al., 2003), but must be involved in a more general deficit in binding visual with phonological information (for further discussion see Cohen & Dehaene, 2004; Price & Devlin, 2003).

Finally, Paulesu et al.'s (1996) study, described above, also investigated *verbal short term memory* which taps into phonological processing in DPs and CPs. CPs exhibited a similar pattern of activations found in other neuroimaging studies of short term memory (e.g., Paulesu et al., 1993). The largest differences between DPs and CPs were noted in Broca's area (BA44) and in the L insula. In contrast, no significant differences between the groups in this task were found in Wernicke's area. The other areas where DPs exhibited significantly less activation included: the L SMA (BA6) and L superior middle gyrus (BA40) (for further details and other areas involved, see Appendix A, Table 10.1). On the basis of the neuroimaging results from this experiment and the consonant rhyming experiment reported above, the authors put forward a hypothesis that dyslexia may be caused by a disconnection between the anterior and posterior language areas. The authors proposed that this could be due to an impaired L insula which may act as an anatomical bridge between Broca's area and the superior temporal cortex, and inferior parietal cortex. This interpretation, taken together with other findings, suggests that there may be different types of phonological deficit, some to do with

disconnection between the involved areas and some with deficit within the involved areas.

It is important to point out here that the update of the PDT (Hulme & Snowling, 2009) postulates that abnormality in the L anterior areas (together with abnormality in the L temporo-parietal areas) are the underlying cause of reading impairment in dyslexia. The earlier version of the PDT (Frith, 1997) did not include the anterior areas. As the L frontal anterior areas are involved in phonological processing (see details below), it is only natural (from the perspective of the PDT) to assume that they could be the underlying cause of reading impairment. However, the literature reviewed above shows that the anterior areas are overactivated in some studies and this overactivation has been interpreted as a manifestation of a compensatory mechanism. However, a more recent meta-analysis (using the activation likelihood estimate (ALE) method) (Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008) revealed no support for overactivation in the L anterior areas in DPs, suggesting that these findings, are likely to be more variable in spatial location and in their reproducibility.

As a range of areas were activated in the phonological tasks, it is not clear whether they are all necessary for phonological processing. The role of these areas, which have been validated as involved in phonological processing by other studies also, is discussed below in more detail because they are used in this study for testing the PDT.

1.6.2 Brain regions and associated phonological processing

In 1861, Paul Broca (a French surgeon) reported a postmortem study of a patient who suffered from language articulation impairment. The results revealed that the patient had damage in the LH third frontal convolution. By deduction, Paul Broca associated this area with the motor images of speech. The involvement of Broca's area (BA44/45) in phonological processing has been consistently underscored (e.g., Gainotti, Miceli, Silveri, & Villa, 1982). Current neuroimaging evidence suggests that Broca's area seems to play a major role in the phonological rehearsal system (Paulesu et al., 1996). It also plays a role in segmented phonology which involves representations of the separated sub-syllabic components, such as onsets and 'rimes', e.g., *'b'* and *'ee'*, in case of the item *'bee'* (Paulesu et al., 1996). BA44 has been hypothesised to be involved in: sub-vocal rehearsal (Paulesu et al., 1996), short term memory (Romero, Walsh, & Papagno, 2006), support of grapheme-to-phoneme conversion (Heim et al., 2005) and performance of sensory-motor integration during sublexical processing (on the level of sublexical units, such as

phonemes) (Hickok & Poeppel, 2004). BA45 has been associated with explicit lexical search (Heim et al., 2005). Please see Figure 1.4 for the Brodmann areas of the areas discussed in this section.

In 1874 Carl Wernicke (a German neuroanatomist and psychiatrist) reported a postmortem study of a patient who had problems with speech comprehension. The results showed that the patient had damage in the L H posterior superior temporal cortex (known nowadays as Wernicke's area). Carl Wernicke associated this area with the auditory images of speech. Since then the role of Wernicke's area (BA22) has been consistently implicated in phonological processing (e.g., Seines, Knopman, Niccum, & Rubens, 1985). This area is hypothesised to be involved in the processing of unsegmented phonology (e.g., phoneme *'[b]'*). As Wernicke's area is also activated by language tasks which do not involve auditory language input (Price, Wise, & Frackowiak, 1996) some authors (Paulesu et al., 1996) have proposed that Wernicke's area may be involved in phonological modality-independent representations (phonological representations which are activated regardless of the modality in which they were presented).

The L middle temporal gyrus (BA21) is argued to be the substrate for lexical representation (Poeppel, Idsardi, & Wassenhove, 2009). It is activated in neuroimaging studies which tap into phonological and semantic processing - processing of the meaning of words, phrases, sentences, etc. (Lurito et al., 2000; McDermott, Petersen, Watson, & Ojemann, 2003; Moore & Price, 1999; Tivarus, Hillier, Schmalbrock, & Beversdorf, 2008). It is also involved in speech comprehension at the sentence level (Price, 2010).

Although the insula (see Figure 1.5 for the location of this structure in the human brain) has long been implicated in phonological processing (e.g., Damasio & Damasio, 1980), its role was not clear. Paulesu et al. (1996) hypothesised that the role of the L insula is to convert unsegmented and segmented phonological codes between Broca's area, the superior temporal cortex and the inferior parietal cortex.

Figure 1.5 Coronal section of the human brain showing Insula (23).

Note: Other brain areas are also labelled for completeness; 1=Medulla spinalis; 2=Decussatio pyramidum; 3=Hilum nuclei olivaris inferioris; 4=Nucleus olivaris inferior; 5=Pons; 6=Arteria cerebri posterior (?); 7=Tractus cerebellorubralis); 8=Nucleus rubber; 9=Ventriculus tertius; 10=Thalamus; 11=Capsula interna; 12=Putamen; 13=Capsula externa / Claustrum / Capsula extrema; 14=Nucleus caudatus (Corpus); 15= Nucleus caudatus (Corpus); 6=Lamina affixa / Ventriculus lateralis, Pars centralis; 17=Taenia choroidea / Plexus choroideus ventriculi lateralis; 18=Fornix, Crus; 19=Corpus callosum, Truncus; 20=Gyrus cinguli; 21=Fissura longitudinalis cerebri; 22=Gyrus frontalis superior (?); 23=Insula; 24=Sulcus lateralis; 25=Ventriculus lateralis, Cornu temporale; 26=Hippocampus; 27=Gyrus parahippocampalis; 28=Crus cerebri and 29=Substantia nigra. Picture and descriptions sorced from the internet under the following address: http://en.wikipedia.org/wiki/File:Human_brain_frontal_(coronal)_section_description_2.JPG.

Damage to the L supramarginal gyrus (part of the L inferior parietal lobule; part of BA40) (together with damage to BA39, see below) was described as early as 1891 by Dejerine (1891, 1892; cited in Shaywitz et al., 2001). Dejerine suggested that the L supramarginal gyrus (with angular gyrus) is critical for reading. The role of the L supramarginal gyrus in phonological processing was implicated in studies on patient populations (e.g., Benson et al., 1973; Kertesz, Harlock, & Coates, 1979; Warrington, Logue, & Pratt, 1971). Results of neuroimaging studies suggested that the L supramarginal gyrus may act as a 'phonological storehouse' that becomes activated for word retrieval (Paulesu et al., 1993; Paulesu et al., 1996; Price, Moore, Humphreys, & Wise, 1997). More recently, it has been suggested (Zatorre & Gandour, 2009) that this area supports phonological encoding-recoding processes in a variety of different tasks. It is also engaged in phonological short-term memory (Paulesu et al., 1993; Romero et al., 2006). Furthermore, it also supports both

phonological and semantic processing in reading (Stoeckel, Gough, Watkins, & Devlin, 2009).

Damage to L angular gyrus (BA39; situated in the L inferior parietal lobule) was described by Dejerine (1891, 1892; cited in Price, 2000) in patients who had alexia (acquired deficits in reading) with agraphia (acquired writing deficit). Hence, the L angular gyrus has been historically linked to memories of visual word forms. More recently the L angular gyrus started to be considered as a part of an association cortex which is involved in cross-modal mapping of graphemes to phonemes (Geschwind, 1965; Shaywitz et al., 1998). (There is also evidence that the L angular gyrus plays a role in semantic processing (Price, 2000)).

The anterior aspect of the L precentral gyrus PMC (Premotor cortex) (BA6), also known as SMA (the supplementary motor area) is involved in both vocalisation of speech and sub-vocalisation of speech (internal speech). It is activated both for reading aloud and silently (Dietz, Jones, Gareau, Zeffiro, & Eden, 2005) and is associated with the initiation of speech. It was reported (Mesulam, 1990) that lesions of this area result in transcortical motor aphasia (impaired spontaneous speech production with preserved repetition).

The L fusiform gyrus (BA 19/37) is engaged in word rhyming tasks (relative to visual baseline) (Booth et al., 2007) and covert object naming (Lurito et al., 2000; Moore & Price, 1999). It was reported (Brockway, 2011) that electrical stimulation of the fusiform gyrus, with grid electrodes, during computerized speech and object naming tasks, resulted in language deficits including speech arrest, dysnomia (a severe problem with recalling words or names) and jargon aphasia (fluent and effortless speech with intact grammar and syntax, but difficulties with the selection of words).

Finally, the L posterior fusiform gyrus (also known as VWFA) mediates between visual form information and phonological and semantic information. Its function is most likely not limited to reading, but it is also engaged when processing any meaningful visual stimulus (Devlin, Jamison, Gonnerman, & Matthews, 2006) (for further discussion see Cohen & Dehaene, 2004; Price & Devlin, 2003).

Summarising, although it is not currently clear which areas are absolutely crucial for phonological processing, the areas described above seem to be good candidates and are used to test the PDT in this thesis.

1.6.3 Neuroimaging studies investigating visual magnocellular processing

Focusing on the visual MDT (according to which the underlying cause of literacy problems in dyslexia is impairment of the visual magnocellular system), motion perception is widely used to tap into magnocellular processing (Cornelissen, Richardson, Mason, Fowler, & Stein, 1995; Newsome & Pare, 1988; Samar & Parasnis, 2005; Stein, 2001). Magnocellular neurons are defined at the level of the retinal ganglion cell (conveying the output from the retina) which have specific projections to LGN. Magnocellular cells have large receptive fields and respond relatively transiently to sustained illumination; they are able to follow rapid changes in stimulus. They are therefore concerned with the movement of a stimulus and its gross features (Tessier-Lavigne, 2000).

The magnocellular pathway is characterised by a hierarchical nature of anatomical connections (Albright, 1993). From the LGN, magnocellular neurons project to the primary visual (striate) cortex (V1) - first to layer 4Cα and then to layer 4B. Cells in layer 4B (which themselves are not magnocells) project directly to the V5/MT as well as to V2 (secondary – extrastriate visual cortex) from which cells also project to the V5/MT (Wurtz & Kandel, 2000). This is known as the magnocellular-dorsal pathway (Wurtz & Kandel, 2000). Motion sensitivity arises first in V1 and V2. However, in V1 and presumably in V2, only a small proportion of cells show motion sensitivity, and each cell is sensitive to motion in a small portion of the entire visual space (due to small receptive fields) (Wurtz & Kandel, 2000). Motion detection across space relies on convergent output from V1 (and V2) to higher order regions, such as the V5/MT.

Motion perception has been the target of research for many years. Human homologues of motion sensitive areas which were originally identified in the monkey's brain have been reported, e.g., V5/MT (Zeki et al., 1991), V3a (Tootell et al., 1997) and V6/V6a (Dechent & Frahm, 2003) (see Figure 1.6). Interestingly, V1 (striate cortex) and V2 (extrastriate cortex) areas were active not only for colour, but also for motion stimulation (Zeki et al., 1991), confirming that V1 and V2 are characterised by magnocellular input, as well as parvocellular input.

Moving on to the neuroimaging studies which have a bearing on the visual MDT in the context of reading, a study by Liederman et al. (2003) is of importance. The study investigated: 1) a task which biased towards phonological processing (participants had to indicate whether pronounceable non-word letter strings sounded like real English words) and 2) non-word reading. The processing, during these tasks in unimpaired adults in V5/MT+, was disrupted using rTMS (repeated

Transcranial Magnetic Stimulation - a neurophysiological technique which can be used to induce an electric current in the brain using a magnetic field which crosses the scull, disrupting sensory and cognitive processing by creating temporary 'virtual lesions' (Pascual-Leone & Walsh, 2002)). The results revealed that there was no effect of rTMS on a task which biased towards phonological processing. This suggests that the grapheme to phoneme transformation process was intact after rTMS was applied to V5/MT+. On the basis of this result the authors concluded that the process by which V5/MT+ is correlated with rate of reading is not likely to be due to a direct role of V5/MT+ in phonological processing. In contrast, the results revealed significantly decreased performance on non-word reading, compared to the condition where no rTMS stimulation was applied. Error analysis showed that most errors involved vowels and consonants and consisted of substitutions, omissions, position changes and additions. Phonological errors, defined as: changes in voicing, in place of articulation, in manner of articulation, cases of labialization, gliding, depalatelization or stopping almost never occurred.

For clarity, these potential phonological errors are explained below. Voicing is a parameter referring to the auditory result of the vibration of the vocal cords; phonemes produced with vibrating vocal cords are voiced and those produced with no vibration are voiceless. An example of an error made during reading non-words which involves a change in voicing would be reading *'denreb'* instead of *'tenrep'* (Liederman et al., 2003). Place of articulation is a parameter which refers to where in the vocal apparatus a sound is produced, e.g., labial, dental, alveolar, etc. An example of place of articulation error in non-word reading would be reading *'tazmar'* instead of *'cazmar'* (Liederman et al., 2003). Manner of articulation is a parameter that refers to the type of articulatory processes used in a sound's production. An example of manner of articulation error in reading non-words would be reading *'tandac'* instead of *'sandac'* (Liederman et al., 2003). Labialization is a parameter that refers to active use of two lips (as in bilabial consonants, e.g., [b]) or one lip (as in labio-dental sounds, e.g., [f]). An example of labialization error in non-word reading would be reading *'fanpill' instead of 'tanpill'*. Gliding is a parameter which refers to a transitional sound as the vocal organs move towards or away from an articulation. An example of gliding error in non-word reading would be reading *'britwak'* instead of *'britlak'* (Liederman et al., 2003). Depalatelization can be defined as the loss of palatalization (where palatelization refers to a sound made when the front of the tongue is in contact with or approaches the hard palate). An example of depalatelization error in non-word reading would be reading *'lasip'*

instead of *'laship'* (Liederman et al., 2003). Finally, stopping is a parameter that refers to any sound which is made by total closure in the vocal tract. An example of stopping error in non-word reading would be reading *'litfar'* instead of *'lisfar'* (Liederman et al., 2003).

The significance of Liederman et al.'s (2003) findings is that they demonstrated that V5/MT+ (traditionally labelled as a 'visual motion area') is also implicated in the reading process, not by being involved in phonological processing, but most likely by image stabilization and/or letter localization. This role of V5/MT+ was inferred on the basis of the visual errors which occurred in non-word reading during virtual lesions of V5/MT+. This finding suggests that the processing in V5/MT+ has an independent contribution to the reading process from that of the areas responsible for phonological processing. Importantly, this aspect of magnocellular involvement in the reading process should be relevant throughout most of the life-span of a given individual – usually from reading acquisition age to death.

Regarding findings on DPs, four studies need to be mentioned here (Demb, Boynton, & Heeger, 1997; 1998; Eden et al., 1996; Vanni, Uusitalo, Kiesila, & Hari, 1997). Eden et al. (1996) showed, in an fMRI study, that the presentation of moving stimuli in a motion coherence task failed to detect activation in V5/MT in DPs, as compared to CPs (see Appendix A, Table 10.2). Conversely, presentation of visual stationary patterns, in the control condition, elicited equivalent activations in V1/V2 and the extrastriate cortex in DPs and CPs. These results were obtained in both the single participant analysis and the between-group analysis.

Figure 1.6 A schematic drawing of the human brain with marked visual cortices, including V5/MT, V1, V2 and V3a predicted by the MDT to be deficient in DPs. Note that V6/V6a is not depicted here. (Picture courtesy of Colorado edu.).

In two other fMRI studies which investigated magnocellular processing (Demb et al., 1997; 1998), the authors found that DPs showed significantly lower responses than CPs in V5/MT+ (and other extrastriate areas, including: V2, V3, V3a, V4v) as well as in V1 when responding to moving visual grating stimuli presented at a low mean luminance. Such stimuli, likely stimulate magnocellular inputs to cortex (Purpura, Kaplan, & Shapley, 1988). On the other hand, DPs were not impaired when responding in the control condition to contrast-reversing grating stimuli presented at a higher mean luminance. There were significant correlations (assessed jointly for DPs and CPs) between brain activity under low mean luminance moving grating conditions and reading rate in all investigated areas. There was a range of contrasts for which the correlations were significant, including: MT+ (3 to 100%), V1 (31 to 100%), V2 (54 to 100%), V3 (52 to 100%), V3A (14 to 92%) and V4v (70 to 100%). The responses which corresponded to contrasts that produced the strongest correlations were as follows: V5/MT+, ct=30%, r=0.8; V1, ct=85%, r=0.68; V2, ct=100%, r=0.8; V3, ct=100%, r=0.77; V3A, ct=53%, r=0.60; V4v, ct=100%, r=0.80. The authors interpreted their findings as being consistent with a specific magnocellular pathway deficit in dyslexia.

Although Demb et al. (1997; 1998) demonstrated significant differences between DPs and CPs, the authors, in contrast to Eden et al.'s (1996) study, found activation of V5/MT+ in DPs in response to moving versus stationary dot patterns. Furthermore, the results involving V1 (Demb et al., 1997; 1998) are not consistent with Eden et al.'s (1996) study. Different results for V5/MT+ and V1 in these two studies could be due to the different samples of DPs or to different magnocellular tasks. However, Demb et al. (1997; 1998) advocate that their results provide support for a magnocellular pathway deficit in dyslexia. The main finding comes from the significant differences between DPs and CPs in V5/MT+ activity for stimuli which elicit activity from magnocellular inputs to the brain as early as V1.

Vanni, Uusitalo, Kiesila, and Hari (1997), on the other hand, reported a study that used magnetoencephalography (MEG) (a non-invasive neuroimaging technique which directly records weak magnetic fields generated by electrical currents in the brain (Hämäläinen & Hari, 2002)). Both high and low contrast motion stimuli elicited similar activation in DPs and CPs in V5/MT. This result is not consistent

with the M-pathway deficit which would predict impairment at low contrast motion stimuli, but not at high contrast motion stimuli. The finding that the authors were able to localise V5/MT in DPs is in line with Demb et al.'s (1997; 1998), but not with Eden et al.'s (1996) findings. The result of not finding significant differences in activation patterns between the CPs and DPs in V5/MT contrasts with Demb et al.'s (1997; 1998) and Eden et al.'s (1996) results. It is not clear what underlies this difference, it may be because of different samples of DPs, different experimental stimuli, or different techniques used, with MEG, in contrast to fMRI, being able to pick up small and transient changes in neuronal oscillatory power. The different samples of DPs is a very likely source of discrepant results, because there is high heterogeneiety among DPs some of whom have a magnocellular deficit and some of whom do not (Ramus, Rosen et al., 2003; Reid et al., 2007).

1.6.4 Neuroimaging studies investigating the cerebellum

It should be emphasised that the role of the cerebellum has traditionally been associated with balance, posture, muscle tone, walking, coordination of movement in precise motor tasks (such as performing surgery), visual guidance of movement and the motoric aspects of articulation (Brodal, 1981; Fiez & Raichle, 1997; Holmes, 1939; Kiernan, 2009; Snell, 2001; Stein & Glickstein, 1992). However, since approximately 15 to 20 years ago (with improved technology to image the whole brain) there is now growing evidence that the cerebellum is involved in cognitive tasks, including language (for reviews see Fiez & Raichle, 1997; Marien, Engelborghs, Fabbro, & De Deyn, 2001; Schmahmann, 1997; Stoodley, 2012; Stoodley & Schmahmann, 2009; Stoodley, Valera, & Schmahmann, 2012). However, involvement of the cerebellum in cognitive tasks has met with considerable controversy (for a comprehensive summary of older and modern approaches to studying and understanding the role of the cerebellum, see Schmahmann, 1997).

Leiner, Leiner and Dow (1993) reported that the human cerebellum, especially the cerebellar ventro-lateral dentate nucleus and lateral cerebellar hemispheres evolved in humans to become connected not only with the frontal lobe motor areas, but also with Broca's area, incorporating the cerebellum into the language network (see Figure 1.7).

Figure 1.7 The Cerebellum and its connections to the frontal lobes in the human brain (adopted from Nicolson & Fawcett (2008)).

Regarding neuroimaging studies with CPs, which have a bearing on the CDT, an fMRI study (Fulbright et al., 1999) which investigated cerebellar activation during reading with adult CPs, needs to be mentioned here (for more details on studies involving the cerebellum see Appendix A, Table 10.3). It investigated, among other conditions, two tasks: a rhyming judgement for pseudoword pairs (e.g., Does *leat* rhyme with *jete*?) and a semantic category judgement for real words (Do *man* and *boy* belong to the same semantic category?), both relative to a control task requiring judgements of line orientation. The results revealed differential patterns of activation in the cerebellum between these two tasks. In the first task, which heavily relied on phonological processing, cerebellar activation was noted in the middle and posterior aspects of the posterior superior fissure and adjacent (bilateral) hemispheric (H) simple lobule (R & L H lobule VI) and semilunar lobule bilaterally. Activation was also found in posterior aspects of the simple lobule, superior semilunar lobule (R & L H Crus I), and inferior semilunar lobule (R & L H Crus II & R & L H lobule VIIB). See Figure 1.8 for a flattened anatomical representation of the cerebellum and Table 1.1 for the lobes and lobules of the human cerebellum. In contrast, the second task, which largely relies on semantic processing, elicited activation in the deep nuclear region on the right and in the inferior vermis, in addition to the posterior areas activated in the phonological task reported above. The significance of this study lies in the fact that it clearly shows that the cerebellum, among other areas, plays a role in phonological and semantic processing during reading. Furthermore, a recent meta-analysis (Stoodley & Schmahmann, 2009) of fMRI studies confirmed that the cerebellum subserves language processing; this conclusion is based on the broad range of language

processing studies in this meta-analysis, including: word generation, phonological, semantic and morphological processing. The areas with significant activation likelihood estimate included: R H lobule VI, R H Crus I, R H Crus I/II, R Vermal lobule VIIAt and L H lobule VI.

Figure 1.8 The gross anatomy of the cerebellum. The nomenclature for the human cerebellum is shown in (H); The comparative nomenclature for the mammalian cerebellum is shown in (G); N.B. some of the nomenclature used for the mammalian cerebellum is also used for the human cerebellum. Homologous lobules are indicated with the same colours. Taken from Voogd and Glickstein (1998).

Table 1.1 Lobes and lobules in the human cerebellum

Note. V = Vermal; H = Hemispheric. Schmahmann et al. (1999) devised an atlas of the human cerebellum and the labels presented in this atlas have been most widely used in the recent neuroimaging studies. There are many alternative labels for cerebellar areas; Jansen and Brodal's (1958) labels are given here as an example; for a review of labels see Schmahmann et al. (1999).

As stated earlier, according to the CDT (Nicolson et al., 2001) the underlying cause of dyslexia is a cerebellar impairment. The exact nature of the cerebellar deficit is not specified, hence studies have probed the whole range of cerebellar function in DPs, as compared to CPs. The support for this theory came first from behavioural studies which tested cerebellar function, such as eye-blink conditioning (Nicolson, Daum, Schugens, Fawcett, & Schulz, 2002). However, more recently a significant number of neuroimaging studies (using various neuroimaging techniques) have reported evidence that there are significant differences between DPs and CPs in the cerebellum. These neuroimaging studies are reviewed below.

Brain activation was shown to be significantly lower in adult DPs compared to CPs in the R cerebellar cortex when learning a new sequence of finger presses and in the R cerebellar cortex (and the L cingulate gyrus) when performing a pre-learned sequence of finger presses (Nicolson et al., 1999).

A more recent fMRI study with child DPs (Baillieux et al., 2009) used a noun-verb association paradigm where high frequency nouns were presented via headphones and participants had to silently generate a semantically related verb. The results showed that CPs, in comparison to DPs, exhibited activation in the anterior and posterior areas of the cerebellar hemispheres (R lobule V, R and L lobule VI and L lobule VIIIA). In contrast, DPs showed activation only in the posterior areas of the cerebellar hemispheres (L lobule VI, L Curs I and R Crus II). However, DPs also showed activation in the anterior and posterior parts of the vermis (R lobule I & II, R lobule III, L lobule V and R lobule VIIAt and VIIAf). These results suggest that the pattern of activation in the cerebellum in DPs (as compared with CPs) is atypical during language processing. These results, however, have to be treated with caution because they are based on only the 1st level neuroimaging analysis (See Chapter 5) which does not allow generalisation onto the population of DPs.

Converging evidence for anatomical cerebellar abnormalities in dyslexia has come from studies based on neuroimaging methods other than fMRI, including magnetic resonance spectroscopy and histological studies. Rae et al. (1998), used magnetic resonance spectroscopy (MRS) (a technique which uses Magnetic Resonance imaging to detect concentrations of low-molecular-weight metabolites *in vivo* (Maudsley, 2002)), found significant differences in concentrations of some neurometabolites in the cerebellum of adult DPs as compared to CPs. The study revealed that the Cho/Naa ratio (choline-containing compounds/N-acetylaspartate) was significantly lower in DPs than in CPs in particular brain areas, most likely due to a decrease of Cho and increase of Naa in DPs. As 'Cho' is believed to be a surrogate marker of overall cellular density and 'Na' is a surrogate marker of neuronal density, the authors interpreted these differences as resulting from a decrease in total cell membranes, without a corresponding decrease in the total neuronal volume. A more recent study (Laycock et al., 2008), also using spectroscopy, found that DPs exhibited a higher ratio of Cho/Cr (creatine) in the L cerebellar hemisphere accompanied by a lower ratio of Na/Cho in the R cerebellar hemisphere. Furthermore, cerebellar white and grey matter volumes of the same DPs and CPs were investigated using volumetric MRI. The results revealed that DPs had a larger volume of white matter in L and R cerebellar hemispheres. The authors stated that both results could be accounted for by abnormal myelination or excessive connectivity in the cerebellum of DPs.

Further evidence on cerebellar abnormalities in DPs comes from studies using structural MRI. Structural MRI is often analysed using voxel-based morphometry (VBM), a technique, which in its simplest form, investigates a voxel-wise comparison of the local concentration of grey matter between two groups of participants (Ashburner & Friston, 2000). In contrast to traditional morphometry, which involves measuring the volume of the whole brain or its subparts, risking that smaller differences in volume may be overlooked, in VBM the image volume is compared across brains at every voxel. Significantly smaller grey matter volume in DPs than CPs has been reported in the following areas: the bilateral anterior cerebellum (Kronbichler et al., 2008), the L semilunar lobule (Brown et al., 2001; Eckert et al., 2003) and R semilunar lobule (Brown et al., 2001). It has also been reported (Rae et al., 2002) that DPs, exhibited grey matter symmetry of the L and R cerebellum. This contrasted with the findings for CPs who showed significantly more grey matter in the R cerebellum than in the L cerebellum. DPs' degree of cerebellar symmetry was correlated with the severity of their phonological decoding deficit. Moreover, Pernet, Poline, Demonet, and Rousselet (2009), used CPs' brains to build a 'typical' brain using bootstrapped confidence intervals (confidence intervals obtained in bootstrapping – a statistical procedure in which confidence intervals are calculated over a large number of replications, with samples drawn with replacement from a data set (Tabachnick & Fidell, 2001)). Pernet et al. (2009) repeated the sampling 4999 times (a total of 5000 samples). The authors obtained a distribution of bootstrapped estimates of the mean, averaged across subjects. The 95% percent confidence intervals were calculated based on the histograms (alpha = 0.05)). Each DP's grey matter was classified at each voxel as being outside or within the normal range, as determined by CPs. The results revealed that the grey matter volume of the R cerebellar declive (R Vermal lobule VI) (and the R lentiform nucleus which consists of: the R putamen, R globus palidus and R basal ganglia) differentiated DPs and CPs in such a way that 100% of DPs fell outside the 95% confidence interval boundaries of CPs.

Finally, evidence on cerebellar abnormalities comes from a post-mortem histological study of the cerebellum by Finch, Nicolson, and Fawcett (2002). The authors investigated the size and density of cerebellar Purkinje cells (some of the largest (GABAergic) neurons in the human brain, found only in the cerebellum), with samples systematically taken from the anterior, posterior and flocculonodular lobes. It should be noted that Finch et al. (2002) used the same specimens from the Orton Society brain bank, as Galaburda and colleagues used, to determine

abnormalities in the magnocellular layers of the LGN in DPs' brains (e.g., Galaburda & Kemper, 1979; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). The cell size analysis revealed that Purkinje cells were significantly larger in DPs than in CPs in the posterior cerebellar cortex. No significant differences between the groups were found in the anterior and flocculonodular lobes. Distributional analyses showed significant differences in posterior and anterior lobes due to DPs having more large Purkinje cells and fewer small Purkinje cells. Currently it is not clear what effect these differences in cell sizes may have; one possible difference on the neuropsychological level would perhaps be increased oxygen utilasation in DPs with more large Purkinje cells. The biggest difference between the groups was noted in the medial Crus II and paramedian lobule (VIIB). Both these areas receive somatotopic information. For instance, the paramedian lobule (VIIB) exhibited a rise to action potentials during stimulation (natural or electrical) from skin or cutaneous nerves. The paramedian lobule (VIIB) has a representation of the whole body (Brodal, 1981), while the medial Crus II receives input from the peri-oral and intra-oral structures. This result suggests differences in DPs, as compared to CPs, in the representation of head or upper body. The authors interpreted the finding as being consistent with Fawcett, Nicolson, and Dean's (1996) hypothesis according to which cerebellar deficit may cause early speech problems because fluent speech requires coordination of articulators in the neck and head. Furthermore, there were no significant differences between DPs and CPs in the dentate nucleus. In contrast, the groups differed in the distribution of Purkinje cell sizes in the inferior olive, due to fewer small Purkinje cells and more large Purkinje cells in DPs than in CPs.

It has been postulated that cerebellar cortex contains relatively independent microzones which consist of Purkinje cells and their associated outputs and inputs (Ito, 2000). In combination with associated pathways from and to deep cerebellar nuclei, a given microzone may be conceptualised as a microcomplex which can undertake different tasks. The Purkinje cells receive input from: 1) up to 175.,000 parallel fibres formed from the granule cells axon and 2) one climbing fibre (from the inferior olivary nucleus). The cortico-olivary fibres arise from neurons in the temporal, parietal, frontal and occipital lobes, go through the corona radiata and internal capsule and terminate in the L and R inferior olivary nuclei. Fibres from the inferior olivary nuclei cross the middle and enter the contralateral cerebellar hemisphere. These fibres terminate as the climbing fibres in the cerebellum. This pathway is known as the cerebro-olivocerebellar pathway (Snell, 2001) which is

afferent and therefore concerned with input. The dentate nucleus is one of the deep cerebellar nuclei. Axons of neurons in this nucleus go through the superior cerebellar penduncle and cross the middle to the contralateral side. The fibres end by synapsing with cells in the ventrolateral nucleus of the contralateral thalamus. The axons of thalamic neurons go through the internal capsule and corona radiata and terminate in the cerebral cortex. This is known as the dento-thalamic pathway (Snell, 2001) and it is efferent in nature, hence concerned with the output. Many different models of cerebellar function have been hypothesised, however the Marr/Albus composite model is still currently valid for skill execution and acquisition (Ito, 2000). The Marr/Albus model hypothesises that the climbing fibres act as an error signal to the cerebellar microzone, constituting an inner loop.

According to Finch et al. (2002), the abnormality patterns, found in the histological study described above, are in line with the hypothesis that the problems in dyslexia are to do with the input side (especially the error feedback loop which is mediated in the inferior olive by the climbing fibres) and not with a hypothesis that the deficits are to do with the output side to the dentate nucleus (Nicolson & Fawcett, 2008).

Summarising, a considerable number of neuroimaging studies (using various neuroimaging techniques) reported that there are significant differences between DPs and CPs in the cerebellum. These findings provide some support for the CDT. Therefore it seems that the cerebellum is a good candidate to consider when trying to establish the neural correlates of reading impairment in dyslexia.

1.6.5 Summary of the neuroimaging studies motivated by the main theories of dyslexia, criticisms and approach taken in this thesis

In summary, neuroimaging studies based on samples from the non-reading impaired population provide potentially important insights into the neural correlates of phonological, visual magnocellular and cerebellar processing. Guided by these frameworks, studies comparing DPs with CPs have revealed some support the existence of phonological, visual magnocellular and cerebellar deficits in dyslexia. With few exceptions (e.g., Eden et al., 1996), these neuroimaging studies, have involved only group comparisons. Given that recent research on dyslexia emphasises the heterogeneity of the deficits in this developmental disorder (Heim et al., 2008; Menghini et al., 2010; Ramus, Rosen et al., 2003; Reid et al., 2007; Snowling, 2008), it is unclear what proportion of DPs exhibit a specific functional and/or structural brain abnormality consistent with one of these causal theories.

Currently it is not clear why there are so many heterogeneous deficits in dyslexia. As described at the beginning of this chapter, definitions of dyslexia state that this disorder mainly affects literacy (i.e. reading impairment) (American Psychiatric Association, 1994; British Dyslexia Association, 2007; International Dyslexia Association, 2009; World Federation of Neurology, 1968). Therefore to uncover the core neural correlates of impairment in developmental dyslexia, one needs to uncover the neural correlates of a reading disorder (which occurs in dyslexia, despite normal IQ, cognitive skills, appropriate motivation and education, and lack of any known cognitive and psychiatric disorders). However, the majority of neuroimaging studies, motivated by the main theories of dyslexia have focused on hypothesised deficits in DPs without demonstrating a relationship with reading disorder. Demonstration of a between group (DPs and CPs) difference on a given variable does not necessarily demonstrate a relationship with reading, even if there are significant differences between the groups on the behavioural tests of reading. In other words, just because there is significant difference between DPs and CPs on a given variable, this does not mean that this variable causes a reading deficit in DPs. This is because a given variable may be a correlate of dyslexia which has no relationship to reading. For instance, Eden et al. (1996) showed, using fMRI, that DPs exhibited a visual magnocellular deficit, in contrast to CPs, but no correlation between the neuroimaging data and reading was presented in this study. Hence it is difficult to link a visual magnocellular deficit in DPs and the reading deficit in DPs reported by Eden et al. (1996). Eden et al.'s (1996) result was criticised on the grounds that the visual magnocellular deficit found in the sample of DPs in their study could be explained as a correlate, or biological marker of dyslexia, which is independent from reading (Frith & Frith, 1996). Frith and Frith (1996) also argued that such a marker could potentially be useful in the early detection of dyslexia because, according to these authors, V5/MT+ is fully myelinated before birth hence it is unlikely that its connections would change. A criticism on the grounds of 'a correlate of dyslexia' can also be put forward regarding Nicolson, Fawcett et al.'s (1999) study which revealed a significantly lower BOLD signal in adult DPs compared to CPs in the R cerebellar cortex when learning a new sequence of finger presses and when performing a pre-learned sequence of finger presses. Finally, this criticism can be made for all studies which have demonstrated structural brain differences between DPs and CPs, without any attempt at demonstrating a relationship with reading.

Showing that a given deficit (defined by the main theories of dyslexia) is found in DPs without demonstrating its relationship with a reading deficit becomes even more alarming once evidence for the presence of a given deficit in a sample with a different developmental disorder is reported. For instance, a magnocellular deficit, measured on the behavioural level was demonstrated in individuals with autism and spared reading (White et al., 2008) and children with Williams syndrome (Braddick, Atkinson, & Wattam-Bell, 2003) who develop reading skills commensurate with their verbal mental age (Laing, Hulme, Grant, & Karmiloff-Smith, 2001). Furthermore, cerebellar abnormalities were reported in ADHD (e.g., Berquin et al., 1998), schizophrenia (e.g., Nopoulos, Ceilley, Gailis, & Andreasen, 1999) and autism (e.g., Allen & Courchesne, 2003).

In the search for the underlying cause of dyslexia therefore, studies should not only demonstrate that there is a given deficit, but also should relate the results of this deficit to DPs' reading performance. It needs be born in mind, however, that the best way to investigate such a relationship is in a longitudinal study, and not in a cross-sectional study involving adults, because it is possible that a given deficit was present earlier in development and influenced reading acquisition, but is not detectable, or it is very difficult to detect in adulthood.

The approach taken in this thesis is different to the previous neuroimaging studies run within theoretical frameworks of the main theories of dyslexia. First, in contrast to these studies, this study does not investigate tasks designed to selectively tap into phonological, magnocellular or cerebellar functioning, but focuses on reading. A reading task is particularly suited here, because it taps into an impairment which, according to the definitions of dyslexia is a defining impairment of this developmental disorder (American Psychiatric Association, 1994; British Dyslexia Association, 2007; International Dyslexia Association, 2009; World Federation of Neurology, 1968). Secondly, because of the unique characteristics of fMRI technique this thesis contrasts the predictions of the main theories of dyslexia regarding the neural correlates of reading impairment in DPs (as compared to the CPs). One potential caveat here is that although each theory makes unique predictions about which brain areas should be significantly underactivated in DPs (in comparison to the CPs), the MDT and CDT also predict underactivation in phonological areas for the reasons specified in the section 'Hypotheses'; this stands in contrast to the predictions of the PDT according to which the underlying cause of reading deficit in dyslexia is the impairment of phonological areas and not impairment of the magnocellular system and/or cerebellum. The other potential

caveat here is the fact that it is possible that a given area was impaired and involved in reading acquisition but is not involved in adult reading. Thirdly, the predictions of the main theories of dyslexia, in contrast to the previous research, are tested on one sample of DPs.

Before the goals of this thesis are fully specified, however, to put them in context, an overview of the development of the reading network is introduced. After this a brief review of some relevant issues arising from the results on neuroimaging studies of DPs' single Word and Pseudoword reading is presented.

1.7 Development of the reading network

A review of the behavioural findings on reading development is beyond the scope of this thesis (for a literature review see (Ehri, 2005)). According to an influential behavioural model of reading acquisition (Frith, 1985), during this process a child moves through three stages: 1) logographic (or pictorial), 2) alphabetic/phonological and 3) orthographic. In the first stage, child's visual system attempts to recognise words as they were objects; they rely on all available visual features (colour, shape, letter orientation, etc.). In order to move from the pictorial stage, the child must grasp the fact that words are built up of the individual letters and they can be linked to phonemes. The child learns to attend to individual letters and letter groups; during this stage, the child can sound out unfamiliar words by concatenating the sounds of individual letters in a given word. This ability indicates that the child has mastered the first reading pathway (the phonological route).When a child acquires a certain level of expertise, they reach the third stage. In the third stage, the child has a considerable number of words in its orthographic (visual) lexicon. They also have rich information about the frequency of these items and their neighbours. Word length and grapheme complexity no longer determine reading time. In contrast, reading time is determined by the frequency with which a word is encountered. All of these signs point to the fact that the second reading pathway (lexical route) has been gradually established.

The non-lexical (the phonological) route and the lexical route are postulated, by the Dual Route Cascaded (DRC) model, to be the two routes for mapping orthography to phonology, which supplement each other. The DRC is a computational model of reading aloud and visual word recognition. The model can perform the two tasks most commonly used to study reading: reading aloud and lexical decision. (For more details on the DRC model, see also the section 'Within-group correlational analyses involving literacy measures' in Chapter 7). Support for the existence of these two routes comes from patients with brain damage (Coltheart

& Colheart, 1997; McCarthy & Warrington, 1990; Shallice, 1988). Some patients with brain damage are no longer able to compute efficiently the pronunciation of written words, indicating that they have damage to their phonological route and present characteristics of a syndrome called acquired phonological dyslexia. They are no longer able to read aloud low frequency words with even regular spelling. However, they may still be able to read aloud irregular high frequency words. Patients with the opposite difficulty in reading suffer from a syndrome called surface dyslexia. These patients have damage to their lexical route hence they do not have direct access to word meaning. Therefore, they have to concatenate the word sound from the orthographic representation (using the phonological route) before accessing a meaning of a given word. Patients with surface dyslexia can read words with regular spellings, but are no longer able to read words with irregular spelling.

It is currently unclear whether the three stages in a child's reading acquisition (described above) have clear neural correlates. One of the major problems is that it is very difficult to collect noiseless data (on a millimetre scale) from the brains of young children in an fMRI experiment.

One of the first studies to investigate the neural correlates of a child's reading is a study by Gaillard, Balsamo, Ibrahim, Sachs and Xu (2003). The authors reported that at the age of seven, a child's reading network is activated when the child reads words. In a group analysis, Gaillard et al. (2003) found activation in the L fusiform gyrus (BA 37), L inferior temporal occipital junction, middle temporal gyrus (BA21 and BA22), middle frontal gyrus (BA44 and BA45), and the supplementary motor area. BOLD in Wernicke's area and the middle frontal gyrus was strongly left lateralized. These results suggest that the reading network of a seven year old child is similar to the adult reading network. The unimpaired average adult reading system consists of two posterior subsystems in the LH: a dorsal (temporo-parietal) system, a ventral (occipito-temporal) system and an anterior system localized in L IFG (Pugh, Mencl, Jenner et al., 2000; Sandak, Mencl, Frost, & Pugh, 2004). Also, there is emerging evidence (Fulbright et al., 1999; Turkeltaub, Eden, Jones, & Zeffiro, 2002) that the cerebellum is part of the average adult's reading system.

One problem with such a study as the one reported by Gaillard et al. (2003), is that it provides only a snapshot in time and does not track the complete development of reading acquisition. In order to provide a complete picture, longitudinal studies are needed. Currently, however, the only robust data on reading acquisition come from cross-sectional studies. However, the outcomes from such

studies need to be interpreted with caution because their results are potentially confounded by the individual differences of participants from different age groups.

Shaywitz et al. (2002) reported findings from a cross-sectional study which suggests that normally developing children, younger than ten and a half years of age, without reading difficulties, exhibit considerable engagement of the anterior and dorsal areas of the reading network during reading, with limited engagement of the ventral areas of the reading system. On the other hand, children older than ten and a half years of age exhibit increased engagement of the ventral areas of the reading system and this is associated with increasingly skilled reading. These results suggest that as reading expertise increases, the L ventral areas become more active in reading and more central to the rapid recognition of written words. Similar findings from a cross-sectional study were also reported by Turkeltaub, Gareau, Flowers, Zeffiro and Eden (2003).

Finally, in a detailed fMRI study (Schlaggar et al., 2002) the authors addressed the issue of functional neuroanatomical differences involving the frontal regions (and L extrastriate regions) between children and adults in visual word recognition. The authors contrasted reading in three groups: 1) adults, 2) children, performance-matched (on a task performed in the fMRI scanner) to adults and 3) children, performance-non-matched (to adults) in an fMRI study. The comparisons revealed that: 1) activation in some of the frontal regions (BA9 and BA44) was independent of age and performance; 2) activation in one L frontal area (BA45/47) (and in the extrastriate region (BA18)) was related to performance level (with both areas exhibiting significantly greater activation in the 3rd group). Finally, activation in one L frontal region (BA44/6) (and one L extrastriate region (BA18)) was age-related. There was significantly greater activation in adults than in children in the frontal region (in contrast BA18 revealed significantly more activation in children than in adults). The significance of this study lies in the fact that it clearly demonstrated that during development, the reading network undergoes some important changes in the frontal areas which is consistent with the findings reported by Shaywitz et al. (2002). The findings regarding phonological areas have implications for the PDT. The results of this study also demonstrated that there are some significant developmental changes in reading acquisition in the extrastriate regions – a finding which has implications for the understanding of visual processing during reading in DPs. Furthermore, it clearly showed that differences in activation in areas within the reading network can be accounted for by: age, performance (reading ability) and factors independent of age and performance.

1.8 Neuroimaging studies of reading in adult DPs, as compared to CPs

Neuroimaging studies on Words and Pseudowords with group comparisons involving DPs and CPs show clear functional differences between these two groups. In DPs these differences manifest as relative (in comparison with the CPs) underactivation of both the L hemisphere ventral and dorsal reading networks (e.g., Brunswick, McCrory, Price, Frith, & Frith, 1999; Paulesu et al., 2001; Pugh, Mencl, Jenner et al., 2000; Salmelin, Service, Kiesila, Uutela, & Salonen, 1996). In contrast, these also show that DPs exhibit significantly more activation than CPs in the L anterior cortex (e.g., Brunswick et al., 1999; Shaywitz et al., 1998), a finding that is usually interpreted in terms of a compensatory mechanism. More specifically, Brunswick et al. (1999) interpreted underactivation in BA37 as a specific impairment in lexical retrieval and overactivation in terms of an 'enforced use of an effortful compensatory strategy involving sublexical assembly of articulatory routines'. Shaywitz et al. (1998) stated that the overactivation in DPs in the anterior areas 'may represent the neural consequences of the increased effort required of dyslexic readers in carrying out phonologic analysis, an increase in effort measured behaviorally as an increased error rate on tasks that make demands on such analysis'. Underactivation of the dorsal and ventral cortex is consistent with the predictions of the PDT, the overactivation for the anterior area in adult DPs is not in agreement with the PDT because as anterior areas are involved in phonological processing (see discussion on this issue above), deficient anterior areas would be predicted by the PDT to be one of the potential sources of impaired reading in dyslexia (Hulme & Snowling, 2009). However, as pointed out earlier, a more recent meta-analysis (Maisog et al., 2008) revealed no support for overactivation in L frontal cortex in DPs, suggesting that these findings, are likely to be variable in spatial location and in reproducibility.

For more details on the differences between DPs and CPs' reading of single words and pseudowords see reviews (Demonet, Taylor, & Chaix, 2004; Frost et al., 2008; Habib, 2000; Perfetti & Bolger, 2004; Price & Mechelli, 2005; Pugh, Mencl, Jenner et al., 2000; Salmelin & Helenius, 2004; Sandak et al., 2004; Temple, 2002).

1.8.1 Functional connectivity studies (adult DPs vs CPs)

Interestingly, there have been a few studies on word and pseudoword reading within the framework of functional connectivity. Functional connectivity can be defined as temporal correlations between spatially remote neurophysiological

events (Friston, Frith, Liddle, & Frackowiak, 1993). It considers relationships between different brain areas that function in a cooperative manner to process information during a given cognitive task (Horwitz, Rumsey, & Donohue, 1998). For instance, Horwitz et al. (1998) reported a PET study of men with dyslexia and matched CPs. It was found that the cerebral blood flow in the L angular gyrus (BA39) in DPs showed only weak within-task and across-subject correlations (functional connectivity) with cerebral blood flow in the extrastriate occipital and temporal lobe regions during reading aloud of single words, indicating a lack of functional connectivity between these structures. In contrast, the CPs exhibited strong and significant correlations within these areas, indicative of functional connectivity. The authors concluded that dyslexia is due to a functional disconnection in the cortical reading network.

A subsequent study (Pugh, Mencl, Shaywitz et al., 2000) also investigated the functional connectivity of the angular gyrus (to BA22, medial and lateral BA18/19 and BA17). The results for a nonword rhyming task revealed that functional connectivity was disrupted in DPs between the L angular gyrus and the following areas within the L hemisphere: Wernicke's area, the lingual gyrus, the lateral extrastriate cortex and the primary visual cortex. No such disruption was observed in DPs for the single letter rhyming task (with low demand on phonological assembly). However, functional connectivity was not disrupted in the R hemisphere. The authors concluded that a phonological processing deficit underlies dyslexia and that posterior regions in the R hemisphere play a compensatory role in phonological processing in DPs. The differences in functional connectivity between DPs and CPs, on a task with high demand on phonological assembly, suggest potential differences on the behavioural measures of reading between DPs and CPs. Indeed there was a significant difference between these groups on non-word reading (the mean standard score on the Woodcock Johnson-Revised word attack test was 81 (SD=1.9) for DPs and 114 (SD=1.5) for CPs, with no overlap between the groups.

The significance of the results from the connectivity studies on adult DPs lies in the suggestion that although the ventral and dorsal systems are poorly developed in DPs, DPs' systems do not seem to be characterised by 'developmental lesions' and presumably can be altered with appropriate reading intervention (Eden et al., 2004; Shaywitz et al., 2004; see reading intervention studies by: Simos et al., 2002; Temple et al., 2003).

1.8.2 Studies on functional connectivity in normally developing adults and children and in children with reading difficulties

In his review on the maturation of structural and functional connectivity in the human brain, Paus (2007) concluded that fMRI functional connectivity studies are in their infancy. More recently, several studies on functional connectivity in normally developing adults and children, as well as in children with reading difficulties have been published. Two studies investigating functional connectivity within the reading network in unimpaired participants should be mentioned first. A study by Hampson et al. (2006) investigated functional connectivity in reading unimpaired adults. The authors reported significant correlations between the strength of participants' functional connection between Broca's area and L BA39 during reading and their reading ability measured behaviourally. The authors concluded that their results suggest that the disconnection of BA39 reported previously (Horwitz et al., 1998; Pugh, Mencl, Shaywitz et al., 2000) for DPs is part of a larger continuum in which poorer (but non-impaired readers) also show reduced connectivity to that region.

A more recent study (Koyama et al., 2011) investigated the reading network using resting-state functional connectivity (RSFC) with fMRI data from 25 adults (21-46 years) and 25 children (8-14 years). The results revealed that for both adults and for children, RSFC correlated positively with reading standard scores in the L precentral gyrus and other motor regions (including the L supplementary motor area/posterior cingulate cortex, and the R postcentral/precentral gyrus), and between Wernicke's and Broca's areas. These results suggest that stronger coupling between language areas, as well as among motor regions, subserves more skilful, reading, in children and in adults. There were also results which differed between adults and children. Better reading performance was associated with stronger positive correlations between Broca's area and the L inferior parietal lobule and L fusiform gyrus in adults, but not in children. Furthermore, better reading performance in adults (but not in children) was associated with stronger negative relationships between the L fusiform gyrus and regions of the "task-negative" default network. (Task-negative is one of two elements of the default network (a network consisting of brain regions active when a person's brain is awake and resting and they are not focused on the outside world). The main role of the task-negative element is to refocus attention towards important stimuli. It is hypothesised to be mostly, but not exclusively, involved in involuntary actions (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006)).

The authors concluded that their results suggest that both positive RSFC (functional coupling) between reading areas and negative RSFC (functional segregation), between a reading area and default network areas, are important for skilled reading, characteristic of adult readers.

Also the results from two functional connectivity studies on children with and without reading impairment should be mentioned. A study by Vourkas et al. (2011) investigated patterns of sensor-level functional connectivity (real-time functional connectivity of the brain network primarily at the sensor level (surface level)), obtained from single-trial, whole-head MEG data during a letter-sound naming task and a pseudoword reading. Participants consisted of children with reading impairment (RI) (mean age - 10.6 years) and children with no reading impairment (NI) (mean age - 9.8 years). In the analysis of their data, the authors used graph theory. (In mathematics, graph theory is the study of graphs. They are defined as abstract representations of networks consisting of sets of nodes and connections. The method derived from this theory, can be applied to investigate long and short distance functional connectivity in complex networks. Graph theory can provide a unique insight into the dynamics of distributed and local interactions occurring in the brain. It can also allow one to define what should be considered an optimal network (Micheloyannis et al., 2006)). Vourkas et al. (2011) estimated two parameters derived from graph theory: 1) local efficiency - a measure of local effective connectedness and 2) global efficiency - a measure of overall effective integration. The results revealed that RI children exhibited significantly lower global efficiency than NI children in alpha and gamma bands for the whole MEG recording epoch. RI children also showed reduced local network efficiency in the alpha band. The authors interpreted their results as being in line with the hypothesis that RD children exhibit aberrant short-range and long-range functional connectivity which is task-dependent.

Finally, the focus here is on a study by van der Mark et al. (2011). This study investigated functional connections of the L occipitotemporal VWF-network with other major language areas in 18 children with dyslexia and 24 age-matched controls (age range 9.7–12.5 years) during a continuous reading task (which involved phonological and orthographic processing). The results showed that children with dyslexia exhibited a significant disruption of functional connectivity between the VWFA and the L inferior frontal and L inferior parietal language areas. The authors interpreted these findings as demonstration that functional disconnection of the L occipitotemporal system is limited to the small VWFA

region crucial for automatic visual word processing, and emerges early during reading acquisition in children with dyslexia.

The results of these studies undoubtedly contribute to knowledge on the functional connectivity of DPs and CPs. However, because none of these studies is longitudinal the question of how functional connectivity changes in normal development and in dyslexia awaits future investigation.

1.8.3 Criticisms of neuroimaging studies on reading and approach taken here

Three criticisms concerning the neuroimaging studies on single word/pseudoword reading with DPs should be raised in connection with the goals of this thesis. First, the majority of the neuroimaging studies on dyslexia have been carried out within one theoretical framework, mostly the PDT, and have focused only on selected brain regions and not on the entire reading network. Such an approach, although important because it allows for exploring specific brain regions, cannot provide a complete picture of the underlying neural underpinnings of reading deficits in dyslexia. Unimpaired reading involves a whole network of brain areas (Price, 2000; Turkeltaub et al., 2002), all of which are potentially important and can impair reading when deficient. Therefore the study in this thesis explores the entire reading network. The study presented in this thesis used a voxel-by-voxel whole brain SPM analysis, but in the discussion focussed only on the areas hypothesised by the main theories of dyslexia. Although such an approach has limitations (only the areas hypothesised by the three main theories of dyslexia are taken into consideration), it goes much beyond the narrower approach taken within each theoretical framework, where only the areas hypothesised by one theory were usually considered. Some analyses presented in Chapter 7 used a different approach (see Chapter 7 for details).

Second, the findings of previous studies were usually designed and interpreted within the PDT. It is interesting to mention here that such studies have also revealed significant between group differences in some other areas crucially associated with the remaining main theories, such as the cerebellum (Paulesu et al., 1996) and the primary visual cortex (Shaywitz et al., 1998). This criticism is addressed here by taking into consideration the predictions of all three main theories of dyslexia tested on the same sample of DPs.

Third, bearing in mind the large heterogeneity of DPs (Heim et al., 2008; Menghini et al., 2010; Ramus, Rosen et al., 2003; Reid et al., 2007; Snowling, 2008), a comparison of individual DPs to the control group provides the

opportunity to detect deficits on the neural level which otherwise could be obscured in the between group analysis due to considerable individual variability within the DP group. Despite the importance of such an approach in the dyslexia research, none of the neuroimaging studies on reading, involving fMRI, has compared individual DPs with the control group. Therefore this thesis, although it will present an fMRI group analysis in Chapter 5, for comparison with other studies, will mainly focus on a multiple case analysis with fMRI as the main technique, with particular emphasis on individual differences among DPs.

Moreover, Chapter 7 presents further analyses investigating the relationship between the considerable number of psychometric measurements, collected for the main study, and neuroimaging measures. More specifically, within-group correlation analyses between behavioural phonological measures (*Phonological Awareness and Phonological Fluency Composites* as well as *Digit Span*) and the orthographic measure (*Orthography Composite*) and the BOLD for Words and Pseudowords are examined. Also, the correlation analyses between the literacy measures (*TOWRE*, *Pseudoword Composite*, *WRAT Spelling* and *Irregular Word Composite*) and the BOLD for Words and Pseudowords are explored in DPs and in CPs. The second part of Chapter 7 investigates the relationship between orthographic skills, reading and magnocellular processing. Also in this part, the relationship between *PA* and *PF Composites* and under-engagement of the phonological areas during reading in sub-groups of DPs and individual DPs is presented. Finally, the third part of Chapter 7 asks the question whether there is an association between a score on *Purdue Pegboard Composite* and the BOLD signal for Words and Pseudowords in the cerebellar areas involved in reading and language.

1.9 The aims, stimuli and hypotheses

The main goal of this thesis is to shed more light on the neural correlates of reading impairment in developmental dyslexia as hypothesised by the main theories of this disorder. The study presented in this thesis takes a broader ROI approach than has been used previously and places particular emphasis on a case study approach to investigate individual differences among DPs.

1.9.1 Words and pseudowords

The predictions of the three main current theories of dyslexia are tested using two types of stimuli: words and pseudowords. Words are ecologically valid stimuli, however some DPs may have reading skills that are highly compensated when

measured at the behavioural level. It may be that the compensation also involves the neural level and that their BOLD response for words will not be significantly different from that of the CPs. For this reason, pseudoword stimuli were also included, because even compensated DPs may have difficulties with reading pseudowords as they tap into the underlying mechanisms of phonological assembly because they do not exist in the participants' mental lexicon.

None of the main theories on dyslexia makes explicit differential predictions regarding word and pseudoword reading. If the neural correlates of the reading deficit are within the phonological processing network (as specified by the PDT) and/or the magnocellular processing network (as defined by the MDT) and/or the cerebellar processing network (as specified by the CDT) it should affect both word and pseudoword reading.

Single words and pseudowords, rather than sentences or connected text, were chosen in the current study to enable comparison with previous studies (see the section 'Neuroimaging studies of reading in DPs, as compared to CPs') and with the existing models of reading, most of which have been developed for single word/pseudoword reading. Furthermore, stimuli of these types do not introduce many complexities, such as the processing of grammar, pragmatics or the reading of text which involves eye movements, and comprehension processes, all of which could potentially confound the BOLD signal, especially where comparisons between DPs and CPs are involved.

1.9.2 Underactivation and overactivation

As described earlier, 'underactivation' can be defined as activation which is significantly less than a given activation. In contrast, 'overactivation' is defined as activation which is significantly greater than a given activation. Underactivation is usually interpreted as a correlate of a deficit. Overactivation, on the other hand, is usually interpreted as a correlate of a compensatory process (Brunswick et al., 1999; Shaywitz et al., 1998). As the main theories of dyslexia are concerned with a deficit in this developmental disorder (and not compensatory mechanisms), underactivation is interpreted as evidence in support of a given theory, whereas overactivation is not interpreted as evidence in support of a given theory. See the section on underactivation and overactivation in Chapter 5 for more details.

1.9.3 Hypotheses

First, if as predicted by the PDT, the neural correlates of reading deficit in DPs lie within the phonological processing network, then DPs should exhibit abnormal

activation in comparison with CPs in all or some areas within this network. As can be seen from the literature review, presented above, phonological processing involves many brain areas and it is still unclear what exact role a given area plays in phonological processing. A summary of areas involved in phonological processing, together with their hypothesised functions was presented earlier. Broadly speaking, the phonological processing network includes the following areas: the L inferior frontal gyrus (BA 44/45) - Broca's area, L BA22 (Wernicke's area), the L middle temporal gyrus (BA21), the L insula, L inferior parietal lobule (including the L angular gyrus (BA39) and the L supramarginal gyrus (BA40)), the L precentral gyrus PMC (Premotor cortex) (BA6) (also known as SMA), the L fusiform gyrus (BA19/37) and the L posterior fusiform gyrus. The role of the L posterior fusiform gyrus is controversial, as discussed above, with some researchers claiming that it is involved exclusively in orthographic processing (Cohen et al., 2000; Cohen et al., 2002; Cohen et al., 2003) and others (McCrory et al., 2005; Price & Devlin, 2003) that it is involved in mapping orthography on to phonology. These areas are used to test the PDT.

To detect abnormality in the neural correlates of reading impairment of a given DP (or a group of DPs), not all the areas involved in phonological processing need to exhibit abnormal activation, because there may be differences between individuals in the neural implementation of the phonological network. The PDT further predicts that DPs should not show abnormal activations in magnocellular system areas - such as the V5/MT and the cerebellum, as predicted by the visual MDT and CDT, respectively.

Second, if, as predicted by the visual MDT, reading impairment in dyslexia is due to magnocellular dysfunction, then DPs should exhibit significantly lower activation (during reading single words and peudowords) in comparison to CPs in the V5/MT, because this area is thought to be receiving the input predominantly from the magnocellular stream (Tootell & Taylor, 1995; Watson et al., 1993). As described above, this prediction is supported by the finding that a virtual lesion of V5/MT, created by rTMS during nonword reading, resulted in visual errors, but not in difficulties with phonological processing. Furthermore, there should also be differences between DPs and CPs in other areas with magnocellular input, as reviewed above. In this thesis, three areas in both hemispheres are targeted: the L & R V5/MT, L & R V1 and L & R V2. This is because of reported correlations between these areas and reading performance (Demb et al., 1998), and because they can be more reliably localised than the remaining motion sensitive areas, using

currently existing cytoarchitectonic maps (Amunts, Malikovic, Mohlberg, Schormann, & Zilles, 2000; Malikovic et al., 2007). Underactivation in V1 and/or in V2 was interpreted in support of the MDT only if found jointly with underactivation in the V5/MT. The V5/MT receives input predominantly from the magnocellular stream, but V1 and V2 consist of partially separated magno and parvo cell inputs. Hence, the underactivation of V1 and V2 may reflect underactivation of either magno cells or parvo cells, or a combination of these. Underactivation in V1 and/or V2, with no underactivation in the V5/MT was interpreted as a visual, but not a magnocellular deficit. A hypothetical Visual Deficit Theory (VDT) was postulated and it was argued that in such cases, underactivation in DPs was in agreement with the VDT and not with the MDT.

Third, as described above, the CDT makes clear predictions regarding the involvement of the cerebellum in reading acquisition. According to this theory the impaired cerebellum in DPs who are acquiring reading will lead to difficulties with learning to read. However, the theory is less explicit regarding the involvement of the cerebellum in reading in adults. According to Roderick Nicolson (email communication, 1st of March 2013) the CDT would predict less cerebellar involvement in unimpaired adult reading, nevertheless it would predict some involvement of this brain structure in adult reading. This prediction is supported by the results from the neuroimaging studies in skilled adult readers, including the results from a meta-analysis of neuroimaging studies (Fulbright et al., 1999; Milne, Syngeniotis, Jackson, & Corballis, 2002; Turkeltaub et al., 2002) and a study which investigated cerebellar activation (other than sensori-motor activation related to finger movements) during Braille reading in blind participants (Gizewski, Timmann, & Forsting, 2004). Given that according to the CDT, the underlying cause of dyslexia is cerebellar impairment, one would predict on the basis of this theory that it is very likely that the neural correlates of reading problems in DPs are within the cerebellum and therefore DPs, in comparison to CPs, should show abnormal activation during reading in some regions in this brain structure. However, the CDT does not specify which cerebellar area/s should be affected. As the cerebellum consists of approximately 50% of all the brain neurons (Brodal, 1981) and is a heterogeneous structure, additional predictions must be made about which areas should exhibit significantly lower activation in DPs, as compared to CPs, during silent reading. As this thesis focuses on a task which involves language processing, the focus here is mainly on the cerebellar language areas.

Probably the most robust results regarding the language areas in the cerebellum come from the meta-analysis by Stoodley and Schmahmann (2009), reported above. These areas include: the R H lobule VI (Hem), R & L H Crus I (Hem), R H Crus II (Hem), R Vermal lobule VIIAt (R Vermal lobule VI) and L H lobule VI (Hem). These areas were selected to test the CDT in DPs' reading. As Stoodley and Schmahmann's (2009) findings overlap with some other important cerebellar findings reported above, selecting them as ROIs would allow relation of the findings from this thesis to these earlier important findings. First, the R Vermal lobule VI was also reported by Pernet et al. (2009) as a structure which (together with the R lentiform nucleus) differentiated between DPs and CPs. Second, the R & L H Crus I, R & L H Crus II, R & L H lobule VI and R & L H lobule VIIB significantly differed between CPs and DPs in silent reading in a study by Fulbright et al. (1999). Finally, four cerebellar areas of interest here are: the medial R & L H Crus II and the paramedian R & L H lobule (VIIB). It should be noted here that the L H Crus II and R & L H lobule (VIIB) were not reported in Stoodley and Schmahmann's (2009) findings. As reported above, DPs exhibited the biggest difference in the R & L H Crus II and the paramedian R & L H lobule (VIIB) in comparison with CPs, in a histological study which may indicate an abnormal representation of the head and neck, together with an abnormal representation of the articulators in DPs (Finch et al., 2002). This in turn could cause early speech problems and presumably could affect inner speech which is important for silent reading (Rayner & Pollatsek, 1989).

Before proceeding further two important issues need to be emphasised. The first issue relates to the predictions of the theories and the interpretation of the results within these theories. The second point has to do with the fact that the study presented in this thesis involves adult participants tested at one point in time. Regarding the first issue, each theory makes unique predictions about the brain areas which underline reading impairment in DPs. Additionally, the CDT (Nicolson, et al., 2001) predicts that a phonological deficit (in phonological awareness and in reading) can be caused by a cerebellar impairment. Therefore it is possible that underactivation in phonological areas in DPs during reading, in the study presented here, may also be consistent with the CDT. However, the methods used in this study do not allow for teasing apart whether the underactivation in phonological areas is 'purely phonological' or has been influenced by cerebellar malfunctioning. The underactivation in DPs in phonological areas in the presence

(but not in the absence) of the underactivation of cerebellar areas is also interpreted as being consistent with the CDT (and with the PDT, as specified above).

Furthermore, the MDT postulates that the magnocellular system is important in the acquisition of 'accurate visual representations of the written, orthographic, form of words' and that this is essential in order to grasp their structure at the phonemic level. Therefore, it has been hypothesised (Stein, 2003) that a deficient magnocellular system could be the underlying cause of deficient phonological representations and therefore of a phonological deficit. Hence it is possible that underactivation in phonological areas in DPs during reading in this study is also consistent with the MDT. Again, 'pure phonological' effects in phonological areas and magnocellular effects on the underactivation in phonological areas cannot be teased apart in this study. The underactivation in DPs in phonological areas in the presence (but not in the absence) of the underactivation of magnocellular areas is also interpreted as being consistent with the MDT (and with the PDT, as specified above).

It is important to keep in mind that interpreting underactivation within the phonological areas as being also consistent with the CDT and the MDT, holds only if one takes the view of the CDT or the MDT, respectively. In contrast, from the theoretical perspective of the PDT such interpretations do not hold. This is because according to the PDT, the underlying cause of reading deficit in dyslexia on the biological level is within the L Perisylvian region or L temporo-parietal and L frontal region (Frith, 1997; Hulme & Snowling, 2009) and not within the magnocellular and/or cerebellar areas.

Focusing on the second issue, cross-sectional studies are valuable, as they provide an insight into a neural and/or cognitive system at a given time, however, one needs to bear in mind that if adults with developmental disorders are studied, there is a possibility that their neural system may have been significantly altered or partially altered due to compensatory mechanisms. Also it could be the case that a given deficit is present during reading acquisition and influences this process, but is not detectable or is very difficult to detect in adulthood. Therefore, longitudinal studies starting with infants with familial risk of dyslexia and control infants are indispensable in investigation of the developmental disorders (Goswami, 2003; Karmiloff-Smith, 1998; Ramus, 2004). Such studies, however, require a long time commitment of both researcher and the participants and are significantly more expensive than cross-sectional studies.

It should be noted that the phonological areas listed above are for individuals who have the L hemisphere as the language dominant one. The participants recruited for this study were screened for L-handedness (see the Method section in Chapter 3), as it has been demonstrated that in the vast majority of R handed persons language is L lateralised (Knecht et al., 2000). Only the L hemisphere areas are reported in the context of testing the PDT, however, the R hemisphere areas are also reported, as they may be involved in a compensatory mechanism (Rumsey et al., 1999; Sarkari et al., 2002; Shaywitz et al., 1998). Regarding the areas associated with the visual MDT, the V5/MT, V1 and V2 in both hemispheres were important for testing the visual MDT. This is because visual processing from the binocular zone is processed by homologous areas in both L and R hemispheres (Wurtz & Kandel, 2000) and neuroimaging studies which have investigated activation in the magnocellular system have usually tested both L and R hemisphere areas (Demb et al., 1998; Eden et al., 1996).

Finally, the areas described above were used to test the CDT. They mostly involve homologous areas in both hemispheres, except for the R Lobule VI (vermis). It should be noted that the areas chosen here as ROIs in the cerebellum are most likely best suited to assess involvement of the cerebellum in reading, as presented in the main route of the hypothetical causal ontogenetic chain (Nicolson et al., 2001). Although the experiment presented in this thesis was not set-up to investigate the involvement of the cerebellum in automatic skills, it is possible that some aspect of automaticity in reading/language processing (as specified in the non-main route of the hypothetical ontogenetic causal chain) (Nicolson et al., 2001) can also be assessed by testing the activation in the R Lobule VI (vermis), which is included in the ROI. This is because it was suggested (Pernet et al., 2009) that this area, in connection with other areas outside the cerebellum, such as the R lentiform nucleus, is engaged in the process of automatisation of skills.

2 MRI, fMRI, BOLD signal and experimental issues in neuroimaging

2.1 A brief history of MRI and fMRI

NMR (Nuclear Magnetic Resonance) goes back to the 1940s, when Felix Bloch at Stanford University and Edward Purcell at Harvard University simultaneously discovered a resonance phenomenon (Bloch, Hansen, & Packard, 1946; Purcell, Torrey, & Pound, 1946, cited in Jezzard & Clare, 2001). In 1973 magnetic imaging was performed for the first time on a small test tube sample. The first human scan – a cross sectional image of a finger – was done in Nottingham by Sir Peter Mansfield's team in 1976. A year later Sir Peter Mansfield developed the echo-planar imaging technique (Mansfield 1977, cited in Jones, Brookes, & Moonen, 2001). Also in 1977 Raymond Damadian demonstrated MRI on a whole body. The imaging time (needed to acquire a single image) was reduced to approximately 5 seconds in 1986. NMR involves measuring the resonance of atomic nuclei, but it does not produce any radioactivity. To avoid patients' concerns, the word 'nuclear' has typically been dropped from the name and the term 'MRI' is now widely used instead.

Although it was known that a regional increase in cerebral blood flow accompanies neuronal activity (Roy & Sherrington, 1890, cited in Raichle, 2006), there was no way of measuring the blood flow in cortical areas non-invasively until the 1990s. In 1990 functional Magnetic Resonance Imaging (fMRI) was developed. Seiji Ogawa and colleagues (Ogawa, Lee, Kay, & Tank, 1990; Ogawa et al., 1993) discovered that oxygenated blood acts as a natural contrast agent in MR images and is related to neural activity in the brain. Now called the BOLD (Blood Oxygenation Level Dependent) contrast, it is measured by fMRI. Due to its lack of radiation, low invasiveness, lack of recognized risks in repeated applications, relatively low cost per examination and wide availability, fMRI has become one of the most popular neuroimaging techniques (Matthews, 2001).

2.2 The basic physics of MRI

When placed in a uniform magnetic field (e.g. an MRI scanner, see Figure 2.1), the magnetic moments of the majority of the human body's hydrogen atomic nuclei (protons and neutrons) change from random orientation, and gradually align in parallel with the magnetic field, resulting in longitudinal magnetisation.

Figure 2.1 A diagram of an MRI scanner. Signals that are amplified before being sent to the RF coil or the gradient coils are produced by the scanner electronics. The scanner computer digitises the detected signal for processing. Taken from Jezzard and Clare (2001).

2.2.1 Signal and contrast generated in MRI

The scanner electronics produce signals that are amplified and sent to gradient coils (see Figure 2.1) to produce three-dimensional variations in the main magnetic field, and to an RF coil to excite hydrogen nuclei in the human body to generate the measured MRI "echo". The detected signal is digitised for processing by computer.

The decay of the perturbation caused by the RF pulse has three components: 1) *longitudinal relaxation* (or spin-lattice-relaxation) occurring in time T1, 2) *transversal relaxation* (spin-spin relaxation), during which the phases of hydrogen nuclei randomize, occurs in time T2 or the *transversal relaxation time*, and 3) the *relaxation due to larger scale variations* in the static magnetic field which can occur because of inhomogenieties of the magnet over the sample (usually minimal effect) and/or different magnetic susceptibilities between different areas of the sample (a more serious effect), such as at the boundary between tissue and air, or blood vessels, in the presence of deoxyhaemoglobin. This process happens at a rate called T2* which is faster than T2 decay.

Different tissues in the head have different relaxation rates, giving different image contrasts based on T1, T2 and T2*. Images obtained in such a way are called: T1, T2 and T2*-weighted, respectively. By manipulating TR (the repetition time between subsequent RF excitation pulses) and TE (the time to echo following the excitation pulse), during acquisition, relaxation time contrasts can be obtained. A short TR and a short TE will give a T1-weighted contrast. A long TR and a long TE will give a T2-weighted image. Finally, a T2*-weighted image results from

using a long TE. It is the T2*-weighted contrast, which provides the basis of BOLD imaging (see section 'the BOLD signal' for further details). fMRI images are T2*-weighted and very sensitive to inhomogenieties of the magnetic field, hence to obtain a good signal to noise ratio a stable external magnetic field is needed.

2.2.2 Spatial specificity

When given an excitation pulse, particles within the field gradients of an MRI scanner resonate at frequencies dependent upon their position according to the *Larmor equation* (Jezzard & Clare, 2001) (for clarity this equation is explained in the next paragraph). The resultant frequencies encode the location of each resonance in the x, y and z dimensions; the y-axis has to be decoded by phase rather than frequency due to that axis being used for the transient RF excitation that causes the resonance. This is possible because after the frequencies return to normal state, the phase remains proportional to distance along the axis (Logothesis 2002).

In the lowest energy state the nuclear moment (of the hydrogen nucleus) is aligned parallel to the external magnetic field. When it is aligned anti-parallel to the external magnetic field it is in its higher energy state. The thermal energy of physiological processes is significant with respect to the energy difference between anti-parallel and parallel spins, causing higher energy states such that there is only a small imbalance between the types of spin. The imbalance is detectable however as a net magnetic moment (or magnetization). The difference between the anti-parallel and parallel states is captured in the *Larmor equation* which relates the magnetic field strength to the resonant frequency of the spins. When an additional radiofrequency magnetic field excites the sample, energy transmissions can be induced between the two energy states leading to perturbation of the net magnetisation and the signal can be registered. The *Larmor equation* (Jezzard & Clare, 2001), has the following form:

$$\nu = \gamma \, x \, B0$$

Where ν is the frequency in MK+Hz, γ is the gyromagnetic ratio (ratio of the magnetic dipole moment of a system to its angular momentum) in MHz/Tesla for the spin under consideration and $B0$ is the magnetic field strength in Tesla. MRI relies upon it being possible to spatially resolve the MR signal when the magnetic field is spatially varied. This important fact is captured in the Larmor equation by adding the spatial variation as z. The Larmor equation takes the following form:

$$\nu(z) = \gamma \, x \, B0(z),$$

where the Larmor frequency of the spins depends on their position on the z axis.

2.2.3 Ultrafast fMRI

fMRI acquisition can be speeded up by: 1) echo planar imaging (EPI), or 2) spiral imaging methods (Donaldson & Buckner, 2001). The work reported here used the EPI sequence, which acquires whole brain volume images in 5 seconds or less to maximise statistical significance (Jezzard & Clare, 2001). Fast fMRI acquisition is crucial when using event-related designs, as in this thesis. This is because the data space following the radiofrequency excitation pulse needs to be sampled and acquired over the time course of the individual event (Donaldson & Buckner, 2001).

2.2.4 The BOLD signal

In fMRI, the BOLD signal provides an indirect measure of neuronal activation elicited during performance on a given cognitive task. In neuroimaging, brain activation levels need to always be considered relative to another condition. The strength of a signal in a given brain area depends on many factors, such as inherent location with respect to the coil, metabolic rate, etc. therefore the absolute level of a signal is rarely informative on its own. Consequently, neuroimaging experiments (including the one reported in this thesis) need to rely on results for differential activation between reading and a control task (Culham, 2006).

As stated in the Introduction both *underactivation* (significantly lower activation in affected group, e.g. patients in comparison to the activation of the control group) and *overactivation* (significantly higher activation in affected group, e.g. patients in comparison to the activation of the control group) (Illes & Shahakian, 2011) are used here to explore the neural correlates of the reading impairment in dyslexia.

Detection of the fMRI BOLD signal by the MRI scanner depends on: 1) the type of imaging technique, 2) the strength of the magnetic field and 3) the echo time. The fMRI BOLD signal is also susceptible to various artefacts, such as field-in-homogeneities, ghosting and head motion.

Because the processes involved in understanding BOLD are complex, the following sections provide more details on the crucial issues. First, the nature of the processes which underlie the BOLD contrast are presented. Second, data on the relationship between the BOLD and electrical signal are presented. Third, the issues on temporal and spatial resolution of BOLD are discussed. Fourth, new findings on the regulation of CBF are introduced. Finally, the issues on modeling of the BOLD signal are discussed.

2.2.4.1 BOLD – the processes underlying the contrast

The resting state (basal state) of the brain is characterised by normal blood flow and a 'resting' level of deoxyhaemoglobin (haemoglobin without bound oxygen) and Cerebral Blood Volume (CBV) (see Figure 2.2). In this state, blood delivered by arteries mostly contains oxyhaemoglobin (oxygen-loaded haemoglobin), which is diamagnetic (weakens the magnetic field of the scanner). The local concentration of deoxyhaemoglobin, which is paramagnetic (strengthens the magnetic field of the scanner), increases and usually prevails, when oxyhaemoglobin passes through the capillary bed. Hence, a T2* gradient occurs across the vascular tree (the system of blood vessels from arteries to veins) from oxyhaemoglobin-rich surroundings (with a longer relative T2*) to the deoxyhaemoglobin surroundings (with a shorter T2*). The ratio of deoxyhaemoglobin to oxyhaemoglobin in the blood within a voxel determines the local T2*, which is crucial in the fMRI contrast in the basal state.

As neurons do not have oxygen reserves, increases in their metabolic rate in the activated state cause demand for oxygen (see Figure 2.2). This results in: 1) an increase in blood flow to areas of increased neuronal firing, 2) decreased deoxyhaemoglobin (lower field gradients around vessels) and 3) increased CBV. A rise in oxygenated arterially delivered blood, due to local activation, therefore results in more oxyhaemoglobin in the venous vascular beds and capillaries, creating a longer regional T2*. This increases the MRI signal from the lower field gradients, which in turn increases image intensity. A decrease in deoxyhaemoglobin gives a longer effective T2*. The MRI signal obtained, as described above, is called the BOLD signal.

Figure 2.2 The BOLD signal; HbO2 - oxygenated haemoglobin (non-magnetic); Hbr - deoxygenated haemoglobin (magnetic); CBV – Cerebral Blood Volume; courtesy of Peter Jezzard, FMRIB (http://www.fmrib.ox.ac.uk/education/fmri/brief-introduction-to-fmri-physiology).

2.2.4.2 The BOLD and the electrical signal

Several publications have reported a linear relationship between the BOLD signal and neuronal activity on the basis of both non-simultaneous, but spatially registered measurements (Rees, Friston, & Koch, 2000) and simultaneous measurements (Brinker et al., 1999; Ogawa et al., 2000). According to Bandettini and Ungerleider (2001) a recent paper by Logothetis, Pauls, Augath, Trinath, and Oeltermann (2001) should be regarded as a landmark, because of the most definitive, detailed and comprehensive comparisons made. To determine the origin of the BOLD signal, Logothetis et al. (2001) investigated the degree of correlation of the BOLD signal, local field potential (LFP) and single and multi-unit activity (MUA) in the primary visual cortex of monkeys. Both MUA and LFP originate from the dynamic interaction of cellular and synaptic mechanisms. MUA mostly results from the output of a neuronal population (within a couple of hundred microns of the electrode tip) (Freeman, 1975). LFP originates mostly from a weighted average of synchronised dendro-somatic constituents of the input signals of the neural population (within a few millimetres of the electrode tip) (Mitzdorf, 1987). Logothetis et al. (2001) found that both MUA and the spike-density function, which represents a neuron's instantaneous firing rate, returned to the baseline at about 2.5s after stimulus onset. LFPs, on the other hand, continued to be high for the duration of the visual stimulus. Both MUA and LFP correlated with the haemodynamic response, but LFP was the better predictor. These findings support the hypothesis that BOLD activation may reflect more the neural activity associated with the input and the local processing in a given area, rather than the spiking activity that is commonly considered as the output of the area. More recently, the MEG signal has also been directly related to LFPs (Zhu et al., 2009).

2.2.4.3 The temporal and spatial resolution of BOLD signal

The temporal resolution of fMRI is limited (see Figure 2.3). One of the obvious factors which limits temporal resolution of fMRI is the rate of much slower haemodynamic change which co-occurs with neuronal depolarisation (Matthews, 2001) (see section ‘Modelling the BOLD signal’ for more details). Other factors

include: haemodynamic variability between tasks and cortical areas (Rajapakse, Kruggel, Maisog, & von Cramon, 1998) and inter-participant variability of haemodynamic response (Aguirre, Zarahn, & D'Esposito, 1998).

Aguirre et al. (1998) found that there was significant variability in the shape of the haemodynamic responses collected across participants in an event-related, simple reaction time task. The distribution of time-to-peak values in the responses obtained across participants ranged from 2.7 to 6.2 s. However, it has to be emphasised that these data were obtained from one brain area – the central sulcus – and it has been shown that the shape of the haemodynamic response varies from one cortical region to another (Rajapakse et al., 1998). One solution to this problem, suggested by Aguirre et al. (1998), was to obtain an estimate of the haemodynamic response from each individual participant and each cortical area under study during a pilot test. However, such a solution is potentially time consuming and computationally expensive. Therefore in this thesis the canonical Haemodynamic Response Function (HRF) was used together with the time and dispersion derivatives which account for variations in subject-to-subject and voxel-to-voxel and responses.

fMRI, in comparison with other neuroimaging techniques, has a relatively high spatial resolution of approximately 1-10 mm (Matthews, 2001) (see Figure 2.3). Spatial resolution is affected mainly by three factors: First, haemodynamic effects (spatial extent and locality of flow/oxygenation increases); Second, resolution of MRI technique (limited by MRI hardware, diffusion limit of water in tissue, and participants' ability to avoid movement in the scanner); Third, spatial sensitivity of the contrast mechanism.

The best spatial resolution of BOLD provides resolution of the order of one cortical column which contains approximately 10^5 neurons (Kim, Duong, & Kim, 2000). The majority of fMRI experimental paradigms achieve lower spatial resolutions (approximately 8-50 mm^3), which contain at least 10^6 neurons. Hence, fMRI BOLD measures the haemodynamic result of a population of neurons, even on the level of the individual voxel.

Figure 2.3 The relative spatial and temporal sensitivities of fMRI as compared to other neuroimaging techniques. Taken from Gazzaniga, Ivry and Mangun (1998).

A recent study by Kim et al. (2004) extended the results from the single electrode recordings reported by Logothesis et al. (2001) through multiple-unit recordings over the entire cat area 18, providing a detailed account of the spatial relationship between BOLD and neuronal activity. The authors asked the question: to what extent does the spatial relationship between neuronal activity and BOLD continue to be linear? The data suggested that when all BOLD–single unit pairs were averaged, there were robust correlations between neuronal activity and BOLD (at the scale of several millimetres), which agrees with Logothestis et al.'s (2001) findings from the single electrode recordings. However, correlations between individual single unit responses and BOLD varied markedly; the correlation coefficients between single-unit responses at the individual recording sites and BOLD signal varied over a considerable range ($0.0 < R^2 < 0.86$, $n = 58$, mean = 0.18). Kim et al. (2004) also demonstrated that the correlation between single-unit responses and the BOLD response may differ with the position of a voxel across the cortex. Using a Monte Carlo permutation, the authors determined that the maximum amount of variance (70%) in neuronal modulation which can be explained by T2*-based positive BOLD is with a voxel size of 3-5 mm. Voxels

smaller than 2.6 x 2.6 x 2.6 mm reduce the amount of variance explained to 50%. Therefore voxels of 3 x 3 x 3 mm were used in this thesis.

Spatial resolution can also be influenced by a number of other factors, such as: 1) the static field strength of the scanner which determines its maximum signal to noise ratio, 2) physiological noise (e.g., respiratory and cardiac cycles) and 3) large vessel effects. Furthermore, inter-participant variability limits spatial resolution on a group level, and this in turn limits the effective spatial resolution (Brett et al., 2002).

2.2.4.4 The regulation of CBF

It has usually been assumed that the CBF increases associated with neural activity is a direct consequence of the metabolic demands of the cells or its oxygen consumption. Attwell and Iadecola (2002) reviewed evidence which suggests that this may not be the case. Firstly, energy usage does not directly increase blood flow. The reported data (Malonek & Grinvald, 1996) suggest that despite the oxygen usage linked to neuronal activity, the blood flow due to neuronal activity occurs in a larger area, implying that other factors than energy usage control blood flow. Secondly, local blood flow is controlled by fast neurotransmitters, such as glutamate, and perhaps GABA (gamma amino-butyric acid) in the cerebellum (Akgören, Fabricius, & Lauritzen, 1994; Li & Iadecola, 1994), hippocampus and neocortex. Thirdly, BOLD and local blood flow, do not correlate with neuron spike rate. The data indicate that parallel fibre stimulation inhibits Purkinje cell spiking in the cerebellar cortex, but increases blood flow. In the cerebellum of mice with cyclin D2 knocked out, which results in a decrease of the number of inhibitory stellate cells, there is a reduction in the blood flow response to neural activity. This suggests that stellate cells (which contain NOS (nitric oxide synthase)) are important for cerebellar blood flow and that BOLD, rather than reflecting the firing output of Purkinje cells or the input mossy fibres, may reflect information processing in the cerebellum (Attwell & Iadecola, 2002). Fourthly, additional to the spatially restricted blood control due to fast transmitters (e.g., glutamate and GABA), there may be more widespread regulation by dopaminergenic, noradrenergic and cholinergic fibres (Krimer, Muly, Williams, & Goldman-Rakic, 1998; Raichle, Hartman, Eichling, & Sharpe, 1975). Also, a general increase in CBF, without a change in metabolism can be due to the activation of certain neural pathways, such as those passing through the cerebellar fastigial nucleus.

Summarising, evidence suggests that BOLD should be understood in the context of neuronal signalling and not as the locus of increased usage of energy. BOLD could be associated with processing within a given brain area, rather than with input or output from that area. A change of spiking output, with no change to the signalling circuits controlling blood flow, could result in no BOLD signal. Also, a change of processing without a change of energy utilisation could result in a BOLD signal. Furthermore, caution is needed when comparing the BOLD signal obtained for different brain areas because of differences in processing systems, neuromodulatory control and vasculature. Finally, because of differences in vasculature, neuromodulatory control and circuitry between areas, obtaining a larger BOLD signal for a given area than in another area does not mean that the neural activity in the former is larger that in the latter.

2.2.4.5 Modelling the BOLD signal and experimental SOAs (Stimulus Onset Asynchrony)

Response to the stimulus (after a brief stimulus onset) at time zero is a function of: 1) blood oxygenation, 2) blood flow, and 3) blood volume (Buxton, Wong, & Frank, 1998). It peaks (maximal oxygenation) 4-6 seconds post-stimulus (see Figure 2.4), is quite sustained and sluggish and it does not return to baseline until 20-30 seconds post stimulus. An initial undershoot, due to a transient increase in local deoxyhaemoglobin, can be observed (Malonek & Grinvald, 1996). However, the initial undershoot is not always observed, possibly because of the low signal to noise ratio. Often a post-stimulus undershoot is observable, which can be attributed to volume changes (Buxton et al., 1998; Frahm, Kruger, Merboldt, & Kleinschmidt, 1996; Kruger, Kleinschmidt, & Frahm, 1996; Logothetis, Guggenberger, Peled, & Pauls, 1999).

Figure 2.4 BOLD response after brief stimulus onset at t=0; PST denotes peri-stimulus time which is defined as the times at which neurons fire in relation to an external stimulus or event; taken from Henson (2005).

Early event-related studies used long SOAs. They allowed 20 seconds between stimuli, so that the activation would return to baseline between events. Although at shorter SOAs, the responses to successive trials will overlap, this can be modeled via the Canonical Haemodynamic Response Function (HRF) and its partial derivatives (see Figure 2.5). These responses can be modeled using SPM (Statistical Parametric Mapping), software which was developed to test hypotheses about functional imaging data (Friston, 2002). In SPM, the Canonical HRF is defined as the typical BOLD response, distinguished by two gamma functions, one modeling the under-shoot and the other the peak. To model variations of the canonical form, two partial derivatives can be used: the temporal derivative (which captures the differences in the latency of the peak response) and the dispersion derivative (which captures differences due to the duration of the peak response) (Friston et al., 1998).

Figure 2.5 Canonical HRF (red) together with its dispersion (green) and temporal (blue) derivatives. PST denotes peri-stimulus time. Taken from Henson (2004).

It is argued (Henson, 2004) that shorter SOAs in fMRI tasks are statistically more efficient and comparable to those used in most behavioural experiments. Furthermore, an experiment with shorter SOAs is also more easily tolerated by participants, as they need to spend a shorter time in the MRI scanner. Therefore the experimental design used in this thesis employed relatively short SOAs (see Method section in Chapter 5 for further details).

2.3 Experimental design and timing issues

In fMRI (EPI) imaging, there is a trade off between spatial and temporal resolution. If a high spatial resolution and full brain coverage (including the cerebellum) is needed, it will require approximately 48 slices and will take about 3-4 seconds per volume. Therefore TR needs to be relatively long. This means that stimuli are probed (sampled) every scan onset or every 2 scans. The response is sampled every 3 or 4 seconds. This may mean that significant variability in the response is missed. There are two ways of achieving a more effective sampling rate. The first method adds random jitter (Dale, 1999). For instance, one could have basic SOA of 2 TRs, but add ± 0.5 TR. The second method ensures that SOA is not a simple multiple of

TR (Price, Veltman, Ashburner, Josephs, & Friston, 1999), therefore over trials one samples at different times. For instance, with an SOA of 6 seconds and TR of 4 seconds, one samples the response every 2 seconds over trials. Both methods can achieve the same effect of increasing the sampling rate. Depending on the parameters, the methods differ from the participant's point of view in that events occur more irregularly in the first method and are more regular in the second one. There are two reasons why the second method was used in the experimental design used in this thesis. Firstly, it is more straight-forward to implement. Secondly and more importantly, the reading of DPs was being tested and they tend to get tired quicker (during reading tasks) than CPs. Therefore it was ensured that the task had a steady pace, so that DPs would know how long they had for the reading and how long for rest and preparation for the next stimulus.

2.3.1 Experimental paradigms

There are two main experimental designs for fMRI: the block design and the event-related design. Block designs have been used in PET studies and were the first approaches used in fMRI designs (Ogawa et al., 1992; Price et al., 1999). In such a design, a series of trials from a condition are presented during a discrete epoch of time. Epochs are periods of sustained stimulation (e.g., box-car functions) (see Figure 2.6). Blocks usually range from 16 to 60 seconds (see Price et al., 1999, for the critical relationship between the timing of stimulus presentation and data acquisition in block designs). Activation acquired from condition A (e.g., reading words) is compared to the activation acquired in condition B (e.g. the control condition – fixating on a cross). An advantage of the block design is that it allows for considerable statistical power when comparing the activation between conditions (Donaldson & Buckner, 2001). One potential problem with block designs is that it may be difficult to interpret the results because of potential bias due to participants' strategies (see further discussion of this issue in the paragraph on the event-related design below), adaptation effects or other effects associated with non-randomised designs.

Figure 2.6 An example of block design and boxcar epoch model. Simulated data (black), neural model (blue) and fitted response (red) for two event-types (A and B). Taken from Henson (2004).

In the event-related design, responses to individual trials are measured in a similar way to event-related potentials (ERPs). A delta function, which is an 'event' at the trial onset is used to model the neural activity associated with every trial (Henson, 2004). In such a design two types of stimuli, e.g. words (A) and items from the control condition (B) are randomly intermixed (see Figure 2.7). In the analysis, the contributions of the two types of trial type are directly compared. The advantages of this kind of design (Henson, 2004) are that it allows for: 1) post hoc classification of trials, 2) implementing trials which cannot be blocked e.g. "oddball" designs (Strange, Henson, Friston, & Dolan, 2000), 3) *post hoc* rejection of trials which contain artefacts (errors, outlier responses and large movements in the scanner). Furthermore, more accurate models of the data obtained from blocked trials can be modeled as event-related trials, accounting for additional variability. This is particularly important for ISIs (Inter Stimulus Interval) larger than a few seconds (Price et al., 1999)).

Most importantly for the experimental design employed in this thesis, trials from different conditions can be intermixed (as shown in Figure 2.7), rather than blocked (as shown in Figure 2.6). Intermixing different trial types, which traditionally has been employed in behavioural or electrophysiological studies, enables one to eliminate the bias due to the specific context or history of preceding trial-type from the average response to a trial type. This is crucial because blocking

of trial types may introduce differences in the data from different types of block (Henson, 2004) or differences in strategies used by participants (i.e., once participants identify that they are 'in a word block', they may rely on a more holistic reading strategy, than if they were 'in a pseudoword block', which requires a more phonologically based reading strategy. If this is the case, any difference in the mean activity between blocks may be due to differences in strategies rather than effects due to a particular type of trial. For instance, once participants establish that they are reading words, they could rely on more holistic reading strategies. In contrast, when participants establish that they have to read pseudowords, they may be more alert to use phonological assembly. Furthermore, these strategies could differ between DPs and CPs.

Figure 2.7 Randomised design and event-related model. Simulated data (black), neural model (blue) and fitted response (red) for two event-types (A and B). Taken from Henson (2004).

2.4 Neuroimaging experiments involving comparisons of DPs and CPs on linguistic stimuli

There are a number of considerations in designing a neuroimaging experiment which aims to compare reading across CPs and DPs (see Table 2.1 for a summary of decisions involved in designing the fMRI experiment reported in this thesis). One of the most important considerations is to ensure that the potential differences in reading between the groups in BOLD are likely to be due to qualitative differences (due to different subsets of neuronal systems involved in each group), rather than quantitative differences (due to differences in the number of words read)

(Brunswick et al., 1999). Two steps were taken here to minimise such risks. First, only relatively short words, with regular spellings, (as confirmed by referring to Venezky (1970)), with high familiarity, imageability and concreteness were selected (see Method section in Chapter 5 for further details). The words and pseudowords were pre-tested in a behavioural pilot experiment with five DPs and four CPs (the groups did not take part in the fMRI experiment). The task was the same as in the fMRI study (see Chapter 5), except it involved reading aloud, so that reading errors could be recorded. The items which produced errors were excluded from the stimuli set. Second, it was ensured (from the behavioural pilot experiment), that the stimulus display time and the ISI allowed for comfortable reading speed by both DPs and CPs. These steps ensured high reading accuracy in both groups in the fMRI experiment. Some authors (Rumsey et al., 1997) used a self-paced reading paradigm with DPs and CPs. Although this paradigm seems appealing for use with DPs because participants themselves decide how long they need for reading a given item, it may introduce a potential confound. It is likely that in a self-paced reading experiment CPs will read faster than DPs and this could be reflected in differences in BOLD signal between the groups (Brunswick et al., 1999; Rumsey et al., 1997). Therefore, this paradigm was not used in this thesis.

Even though an experimental paradigm based on reading aloud allows one to straightforwardly test participants' reading accuracy in the scanner, there were three reasons why the silent reading paradigm was favoured. Firstly, and most importantly, there is evidence that the cerebellum is involved in reading aloud (e.g., Price, 2000; Turkeltaub et al., 2002) which, to some extent, could be accounted for by the articulatory movements of pronouncing words. As one of the main aims here was to test potential involvement of the cerebellum in reading other than articulation effects, a paradigm based on reading aloud was avoided. Secondly, it was desirable to avoid participants processing their own voice which causes activation within the temporal areas (Price, Wise, & Frackowiak, 1996). Finally, fMRI is much more susceptible than PET to head movement artefacts which can be induced due to articulatory movements during reading aloud (Matthews, 2001).

More generally, the importance of incorporating into the experiment one or more control conditions, so that stimulus effects could be evaluated, was underscored (Mechelli, Gorno-Tempini, & Price, 2003). Because fMRI methods are limited to providing information about the relative change in signal, it is important to include a control condition (Culham, 2006; Donaldson & Buckner, 2001). The study reported in this thesis used a fixation cross as a control condition for words

and pseudowords. Comparison of an experimental condition with such a control condition is called ‘loose’ task comparison (Donaldson & Buckner, 2001). This is because the comparison is between tasks that are not closely matched and employ a broader comparison across task variables (Donaldson & Buckner, 2001). There were four reasons for using a fixation cross as a control condition. First, it is a commonly used control condition therefore it should facilitate comparisons between the study reported here and other studies. Second, as the main interest here was to identify the entire network activated during reading by CPs and DPs, using a ‘loose’ control condition was well suited. Third, a single cross, rather than a string of crosses (of word length) or a string of letter-like forms was used to ensure that the potential magnocellular processes responsible for encoding the grapheme order in a word were not elicited in the control condition, because they were of interest in the experimental condition and if present in the control condition they would have been subtracted from the activation in the experimental condition. Finally, a number of studies used ‘rest’ as the control condition, however, the fixation cross was considered as a more suitable control condition, because the ‘rest’ control condition provides an opportunity for the participants to ‘daydream’ or ‘ruminate’ which results in stimulus-independent thoughts (Binder et al., 1999) and because thoughts quite often have language content it could be a potential confound in the observed brain activation in an experiment which investigates a task based on language.

Table 2.1 A summary of decisions involved in designing the fMRI experiment

Design question	Decision & more important reasons
Long or shorter SOAs?	Shorter, they are: **1)** statistically more efficient; **2)** easier to implement; **3)** DPs & CPs spend shorter time in MRI scanner.
How to achieve a more effective sampling rate?	By SOA that is not a simple multiple of TR. It is: **1)** easier to implement; **2)** task has a steady pace, **3)** well suited for DPs.
Experimental design: block or event related?	Event related, it allows for: **1)** intermixing different trials; **2)** eliminating the bias due to the specific context or history of preceding trial-type from the average response to a trial type.
How to ensure that differences in BOLD between the groups are due to qualitative rather than quantitative differences?	By selecting items which are easy to read by both groups: **1)** Short words, with regular spelling, high familiarity, imageability & concreteness; **2)** Items which produced errors in the pre-test were excluded; **3)** Stimulus display time & ISI allowed for comfortable reading speed by both DPs & CPs; **4)** Pseudowords were based on words; created by consonantal change.
A self-paced reading paradigm or not?	Not, because in a self-paced reading experiment CPs may read faster than DPs & this could be reflected in differences in BOLD signal between the groups.
Reading aloud or silently?	Reading silently, because: **1)** evidence that the cerebellum is involved in reading aloud; **2)** desirable to avoid participants processing their own voice; **3)** fMRI more susceptible than PET to head movement artefacts.
Include control condition & if 'Yes' which one?	Yes, because fMRI methods limited to providing information about the relative change in signal; Fixation cross used because: **1)** it is a commonly used control condition (easily comparable with other studies); **2)** main interest to identify the entire network using a 'loose' control condition.

3 Psychometric measurements and group analysis

3.1 Motivation for the measures used in the current study

A broad battery of behavioural measures is needed to capture a range of effects associated with dyslexia. Tests used here can be classified in the following categories: general psychometrics, literacy measures, phonological processing (awareness and fluency) and orthographic processing.

Measures of intellectual ability, and some demographic measures, such as, gender, age, ADHD and DCD, etc. have four main roles. First, they can be used to ensure that DPs and CPs are matched on variables such as years of education, gender, age, handedness, Performance IQ and Full IQ, so that any between-group differences on literacy, phonological and orthographic measures are unlikely to be due to differences on these potential confounding variables. Second, they allow for screening for cases 'at risk' of clinical forms of comorbid developmental disorders, such as ADHD and DCD. Third, they provide additional information on the individual profiles of DPs (in comparison to CPs) on measures, such as short term memory (which can be linked to phonological processing (Ramus & Szenkovits, 2008), or analysed as a memory measure) and other behavioural symptoms which usually show significant differences between the groups. Finally, they allow screening of participants for handedness; only right-handed participants were recruited, because the neural correlates of language processing for a right handed person are usually localised in the L hemisphere and this hemisphere is dominant for language function.

Because it is possible that the reading and spelling skills of DPs become compensated in adulthood, a set of widely used literacy measures was employed to investigate how DPs' performance compared to CPs' performance around the time of the fMRI reading study. Additionally, two pseudoword reading tests (TOWRE and Castles and Coltheart's test (1993)) and a test of English irregular word reading (Castles & Coltheart, 1993) were used to see whether the groups differed on phonological decoding and decoding of irregular words, and to test whether there were any subgroups in DPs (see Chapter 5 and Chapter 7).

Finally, widely used measures of phonological processing (the Spoonerism task, Phonological Pseudoword Forced-Choice test (Olson, Forsberg, Wise, & Rack, 1994) and RAN tasks) and orthographic processing (Orthographic Word-Pseudohomophone Choice test (Olson et al., 1994)) were used. These measures

usually differentiate well between DPs and CPs: the Spoonerism task (significant difference between the groups on either speed or accuracy, or both were reported (Brunswick et al., 1999; Ramus, Rosen et al., 2003; Reid et al., 2007; Snowling, Nation, Moxham, Gallagher, & Frith, 1997; Vukovic, Wilson, & Nash, 2004); significant differences between DPs and CPs were reported on RAN tasks (Misra, Katzir, Wolf, & Poldrack, 2004; Reid et al., 2007; Vukovic et al., 2004); Finally significant differences between the DPs and CPs on the Phonological Pseudoword Forced-Choice test and the Orthographic Word-Pseudohomophone Choice test were reported (Wadsworth, DeFries, Olson, & Willcutt, 2007).

All published tests were administered according to the instructions in the manuals. Additionally, for the WRAT reading test, the time needed by a participant to read the items, was recorded, but the other instructions were not changed.

3.2 Materials

3.2.1 General psychometrics, ADHD and DCD

3.2.1.1 The Edinburgh Handedness Inventory

This instrument (Oldfield, 1971) consists of a list of 10 questions which investigate the direction and strength of hand preference in 10 everyday activities (such as: *writing*, *drawing* and *throwing*). The participants were asked to put one check in a given column (R for R-hand or L for L-hand). They were advised to put two checks in a given column in a situation where their hand preference was so strong that they would never use the other hand; they were asked to put a check in both columns (L and R) if they were indifferent about which had to use for a given activity. Each check was given a score of '1', the scores for R and L hands were added separately. The dependent variable was handedness index, calculated according to the following equation:

$$H = \frac{(R - L)}{(R + L)} * 100\%$$

Where H denotes handedness, R is the number of checks assigned by a participant to the actions performed with the right hand and L is the number checks assigned by a participant to the actions performed with the left hand. As can be seen from the above equation, a positive H index denotes R-hand preference, whereas a negative H index denotes L-hand preference. The larger the H index, the stronger the hand preference. The score range for L-hand preference is from -10 to -100; whereas for R-hand preference is from 10 to 100.

3.2.1.2 Intelligence tests

All DPs in our study had recent dyslexia assessment reports (completed within the last three years from the date of testing in this study). To avoid practice effects due to repetition of IQ testing, an IQ test was not administered to DPs and the scores were taken from their psychological assessment reports. This is considered as common practice because IQ measures are relatively stable across lifespan, with scores collected in earlier life used to predict educational outcome and employment prospects in later years (McCall, 1977) (see, however, a recent report by Ramsden et al. (2011)). All IQ scores were from the Wechsler Adult Intelligence Scale - III (WAIS-III) (Wechsler, 1997).

IQ scores for CPs were obtained using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), which consists of two verbal subtests (vocabulary and similarities) and two performance subtests (block design and matrix reasoning). Variables here were: Full Scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ). No participants with the FSIQ lower than the average score (90) were included in the study.

It should be noted here that some caution needs to be exercised when making comparisons between the scores obtained using WAIS-III (Wechsler, 1997) and WASI (Wechsler, 1999). Historically the WASI was developed at the same time as WAIS-III and started to be perceived as a standardized method of gaining an estimate of WAIS-III summary scores. The correlations which compared WASI to WAIS-III summary scores were high and ranged from .84 to .92 in the standardization sample. However, Axelrod (2002) reported lower correlations (0.71 to 0.82) for a heterogeneous clinical sample (which did not include DPs). He also found that in his clinical sample the WASI PIQ and FSIQ (based on 4 sub-tests) overestimated the comparable WAIS-III scores, whereas the WASI VIQ summary score underestimated WAIS-III VIQ. On the basis of these results, Axelrod (2002) stated that if the goal is to obtain an accurate estimation of general intelligence, one should not use WASI with individual patients. It should be noted that WASI was only used in the current study with the CPs and it is likely that their IQ profile will not be as spiky as the profile of the heterogeneous clinical sample in Axelrod's (2002) study, hence one would predict that the correlations here with WAIS-III would be higher.

3.2.1.3 Digit Span

A subtest of the WAIS-III (Wechsler, 1997) – Digit Span (Digits Forward (maximum raw score = 16) and Digits Backward (maximum raw score = 14) was administered to all participants. The combined score was calculated and converted to age adjusted scores.

3.2.1.4 ADHD measure

ADHD shows higher rates of comorbidity with dyslexia than expected by chance (Gilger, Pennington, & DeFries, 1992) and it was found to mediate various deficits in developmental dyslexia, including, for instance between-group differences in postural sway and reading (Fergusson & Horwood, 1992; Reid & Hansen, 2013; Rochelle, Witton, & Talcott, 2009). Therefore, Conners' Adult ADHD Rating Scale (CAARS-Self-Report, Screening Version: 30 questions) (Conners, Erhardt, & Sparrow, 1999) was used to screen the participants identified as being 'at risk' of the clinical form of this disorder. Four indexes were obtained: ADHD Index (D) (designed in order to identify the adults in a population that are likely to be diagnosed with clinical ADHD), Inattention (A), Hyperactivity/Impulsivity (B) and Combined ADHD Score (A+B) (an index which combines both scores of Inattention (A) and Hyperactivity/Impulsivity (B). The exclusion criterion was a T-score above 70 on the ADHD Index (D). The reason for this cut-off point is that a T-score above 70 indicates that an individual is likely to have significant levels of symptoms that may meet DSM-IV diagnostic criteria for clinical ADHD (Conners et al., 1999).

3.2.1.5 DCD (also known as Developmental Dyspraxia)

The questionnaire used was based on the DSM-IV (APA, 1994) and on the questions in the Adult DCD Checklist provided by Dyspraxia Foundation and Developmental Adult Neuro-Diversity Association (DANDA) and on questions devised by A. Reid. The questions devised by A. Reid were designed to provide more detailed information on gross motor coordination (e.g., *Did you have difficulties with learning to ride a bike and/or any other sports which need good balance, e.g. walking on a beam, snow-boarding, rollerblading, windsurfing?*; *Do you have problems with motor coordination while dancing?*) and fine motor coordination (e.g., *Do you have difficulties with your motor coordination while playing a musical instrument?*; *Do you have problems with your motor coordination while opening/locking a door with a key?*). It consisted of 5 parts: 1) motor-coordination problems throughout early development (5 questions), 2) gross motor

coordination difficulties (9 questions), 3) fine motor coordination difficulties (16 questions), 4) the DSM-IV (APA, 1994) questions on whether motor coordination deficit significantly interferes with academic achievement or activities of daily living (4 questions) and 5) the DSM-IV (APA, 1994) question on any other medical conditions which could cause or increase motor coordination difficulties. Including this questionnaire into the test battery had two aims. First, as DCD was found to co-occur with dyslexia (Portwood, 2000), any participant who was identified as being 'at risk' of the clinical level of this disorder according the DSM-IV (APA, 1994) was excluded from the between-group analyses. Second, as adult DPs sometimes report difficulties with gross and fine motor coordination, more detailed questions about these problems were administered to collect richer profiles of the participants. One point was given for every question answered positively, denoting the presence of a difficulty. Dependent variables were: the total number of motor coordination problems throughout early development (max.=5), the number of gross motor coordination difficulties (max.=9), the number of fine motor coordination difficulties (max.=16) and a total score on motor coordination disorder (collapsing across the three categories detailed above) (max.=30). There are no clinical cut-offs available here.

3.2.1.6 Manual dexterity test

Purdue Pegboard Test (Tiffin, 1987) was used. Five measures were collected: right hand (R), left hand (L), both hands (B=R+L), the sum of the three measures (R+L+B), and an assembly measure. The assembly measure involved building an 'assembly' with both hands simultaneously. The 'assembly' consisted of pins positioned in holes in a wooden board and collars and washers. During the process of building of each assembly both hands needed to operate all the time. It started with the R-hand picking a pin from the R-hand cup and while the R hand was placing it in the top hole, the participant was picking up the washer with the L-hand and so forth till an assembly was built. There was one trial per measure. Note that there was overlap between some measures. One point was given for every pin the participant placed in a given condition. The first four tasks measured gross movements of hands, fingers and arms. The assembly task measured "fingertip" dexterity. Purdue Pegboard Test was planned to be used (together with the DCD questionnaire) as a measure to screen for DCD.

3.2.1.7 Revised Adult Dyslexia Check List (ADCL)

A shortened version of the revised version of the ADCL was administered. It was derived from the 20-item version (Vinegrad, 1994); it consists of 12 questions which are the best at predicting dyslexia (Vinegrad, 1994). Vinegrad (1994) revised the British Dyslexia Association Adult Check List which consists of twenty yes/no questions. Vinegrad (1994) then examined which of the 20 questions were best at discriminating between adults with and without dyslexia in a sample of 647 CPs and 32 DPs. First, he found that (on the 20-item list) the mean number of 'yes' responses for DPs equaled 12.7; whereas the mean number of 'yes' responses for CPs was 4.4. Second, Vinegrad (1994) found that twelve items on the list were particularly good indicators of dyslexia. He further concluded that a high score on the 12-question list might have greater significance than a high result on the whole 20-item list.

In the research reported in this thesis the list of twelve questions, which were found to be the best predictors of dyslexia (Vinegrad, 1994), was administered. According to the procedure, one point was given for every question answered positively, denoting the presence of a difficulty. The dependent variable was the number of positive responses which indicated difficulties. It should be noted here that there is considerable variability between DPs on this test. Some DPs indicate one or more areas of difficulty, whereas others indicate much more widely spread difficulties (Reid & Hansen, 2013). It should also be underscored that many items on this list may not be specific to dyslexia. For instance, question number one: 'Do you find difficulty telling left from right?' could possibly be answered positively by participants with DCD; this is because participants with DCD may have an inadequate sense of direction and difficulty distinguishing right from left (Dyspraxia Foundation, 2012). Furthermore, item number eight 'Do you mix up dates and times and miss appointments?' could be perhaps answered positively by participants with ADHD, as they often report (on CAARS-Self-Report) that they have problems organizing tasks and activities, and are forgetful in daily activities. In this study the ADCL was used as an indicator whether a given DP has just a few difficulties or quite a number of difficulties.

3.2.2 Literacy tests

To obtain richer profiles of participants' single word reading skills, two tests were used: TOWRE (The Test of Word Reading Efficiency) (Torgesen, Wagner, & Rashotte, 1999), which measures reading fluency (it assesses the speed) and accuracy using relatively high frequency single words and the Wide Range

Achievement Test 3 (WRAT3) (Wilkinson, 1993) which measures reading accuracy.

3.2.2.1 Single Word Reading TOWRE (Torgesen et al., 1999)

As this test only has norms up to 24.11 years and the age range of the participants in the study reported here was from 18 to 42 years (see 'Participants' section below), normalised scores were not used as a performance measure. Hence, the dependent variable was based on raw score for the number of words read aloud correctly from the Sight Word Efficiency Form A in 45 seconds. List 'A' presented one hundred and four words. Each correctly read word was given a score of '1', hence the maximum raw score was 104. It is a graded reading test and consists of one syllable words (e.g., *'is'*, *'men'*), followed by two syllable words (e.g., *'paper'*, *'people'*) and three syllable words (e.g., *'confident'*, *'detective'*).

3.2.2.2 Wide Range Achievement Test 3 (WRAT3) (Wilkinson, 1993) (Blue sheet)

The dependent variable was a raw score of percent correct. Additionally time (in sec), which a participant needed to read the items, was recorded. Forty two words were presented, some of the words were high frequency items, such as *'in'*, *'cat'* and some were low frequency items, such as '*usurp'*, '*disingenuous'*. Each correctly read word was given one point, so the maximum raw score was forty two. A raw score of percent correct was used, rather than the raw score, as for TOWRE, because in this test all participants read the same number of words (42), whereas in TOWRE each participant read a different number of words as the test was terminated after 45 seconds.

3.2.2.3 Single Pseudoword Reading (TOWRE) (Torgesen et al., 1999)

The dependent variable was based on raw score (for the same reason as for Single Word Reading) for the number of pseudowords read aloud correctly from the Phonemic Decoding Efficiency Form A in 45 seconds. The form started with simple Pseudowords, such as *'ip'* and *'dess'*, continued to more difficult items, such as *'meest'* and *'linaf'*, and became most difficult towards the end of the test, e.g., *'pelnador'* and *'crenidmoke'*. The accuracy of pronunciation was judged according to the key provided in the test; Participants' performance was also recorded and the pronunciation was double checked by an English native speaker.

3.2.2.4 English pseudowords (Castles & Coltheart, 1993)

The test consisted of thirty English Pseudowords (created in line with the rules of English phonology and orthography), such as *'gop'*, *'toud'* and *'lishon'*. One point was given for each correctly read Pseudoword (the maximum score was 30). Participants' performance was recorded and the correctness of their pronunciation was double checked by an English native speaker. The dependent variables were: percent correct and time taken to read all the items.

3.2.2.5 English irregular words (Castles & Coltheart, 1993)

The test consisted of thirty English irregular (exception) words, characterised by an irregular grapheme-to-phoneme correspondence, such as *'yacht'*, *'quay'* and *'bouquet'*. These words cannot be read using the sub-lexical route which utilises grapheme-to-phoneme conversion rules because incorrect responses are produced; irregular words need to be read via the lexical route which involves semantics. The dependent variables were: percent correct and time taken to read all the items.

3.2.2.6 WRAT3 Spelling (Wilkinson, 1993) (Blue sheet)

Forty words (e.g., *'and'*, '*reasonable'*, *'cacophony'* and *'vicissitude'*) were presented. First, a word was pronounced by the experimenter without a context, then a sentence was read with the word in it, and finally the word was said again. The participants were asked to write the word on an answer sheet in an allocated space. Participants were told that if they were not sure how to spell a word, it was o.k. to take a guess. One point was given for each correctly spelled word; the maximum score was 40. The dependent variable was percent correct.

3.2.3 Phonological awareness tests

3.2.3.1 Spoonerism test (Brunswick et al., 1999)

As, no standardised Spoonerism test for adults in English was known, the test reported by Brunswick et al. (1999) was used. It consisted of 12 word pairs, e.g. *basket* and *lemon*. The participants were told that they were going to play around with some words and do Spoonerisms. It was explained to the participants that a Spoonerism is where one has a pair of words and they swap over the initial sounds of each word to make a new, non-existing pair of words (pseudowords). For instance, the Spoonerised pair of words presented above would become a pair of pseudowords, such as ***l****asket* and ***b****emon.* The participants were given practice items (before the real test) to ensure that they understood the principle of making

Spoonerisms. One point was given for each correctly Spoonerised pair of words. The maximum raw score was 12. The dependent variables were: percent correct and time needed to create Spoonerisms between all the word pairs.

3.2.3.2 Phonological Pseudoword Forced-Choice test (Olson et al., 1994)

This is a computerized test of phonological skill adapted from Olson, et al. (1994), which is based on silent phonological decoding. The test contained 64 (including four practice) trials. Each trial consisted of a triplet of pseudowords, e.g. *pake, kake, dake* and participants needed to determine which of the items *sounds* like a real word (in the example given above *kake* sounds like a real English word *cake*). This task minimized the input of orthographic processing to the determination of the correct answer since all the items needed to be decoded and compared with the phonological representation of the items in the lexicon. The participant had to indicate, by pressing one of the three response keys, which item sounded like a real English word. The dependent variables were: percent correct and mean RT in milliseconds (calculated for all trials, except for the four practice trials). Participants were encouraged to respond as fast as possible, while being as accurate as possible.

3.2.3.3 Phonological fluency tests

Random Automatised Naming (RAN) tests for colours, pictures, digits and letters (Forms A & B with nine items in four rows per form) from the Comprehensive Test of Phonological Processing (CTOPP) (Wagner et al., 1999) were used. The participants were given practice items and each item was named aloud by the experimenter, so there was no doubt regarding the name of any item involved. Next, the participants were informed that they would need to name items in rows, as fast as they could, starting with item number one in the first row and finishing on the last item in the right hand corner in the forth row. The dependent variable was the sum of time (in seconds) necessary to name all the items in a given category on forms A and B. Both forms (A and B) were administered (using standard administration and scoring) because according to the manual each RAN test consists of 72-items (36 items per form) (Wagner et al., 1999).

3.2.4 Orthographic processing

The Orthographic Word-Pseudohomophone Choice test (Olson et al., 1994) was used. Similar orthographic choice tasks were used by other researchers (Barker, Torgesen, & Wagner, 1992; Stanovich & West, 1989). Olson et al.'s (1994) test

was inspired by Baron & Strawson (1976). The test contained 88 (including eight practice) trials. Each trial consisted of a pseudohomophone pair, e.g. *rain* and *rane*. In contrast to the phonological choice task, the participant had to indicate, by pressing an appropriate response key which item was a real English word (i.e., *rain*). The rationale behind this task is that, although there may occur some automatic phonological processing (which would yield the same output for both items), the task biases towards orthographic processing because in order to make a decision, the participant had to base it on their memory of the target word's specific orthographic form. The dependent variables were: percent correct and mean RT in milliseconds (calculated for all trials, except for the eight practice trials).

3.3 Participants

Thirty eight students from three UK universities participated in the study. The participants were recruited via adverts posted on the student information boards in three universities. In case of one university the study was also advertised via website. They were all right handed, with native English, with normal, or corrected to normal, vision, without clinical ADHD (defined as a score < 70 on ADHD D index on Conners' scales), without clinical DCD, as defined in DSM-IV, or any other known neurological or psychiatric disorder. None of the participants reported current use of any psychoactive medication. Three control participants (CPs) were excluded from the analysis because of high motion parameters due to movement in the MRI scanner (see Chapter 5). One DP was excluded from the study because she did not provide her dyslexia diagnosis and two participants with dyslexia (DPs) (DP8 and DP15) were excluded from the group analysis (but not from the multiple case study analysis) because there was an indication that they may be 'at risk' of clinical DCD. They were excluded from the group analysis because they could potentially confound the results involving the group with dyslexia, the members of which were screened for being at risk of clinical ADHD and DCD. The between group comparison was concerned with differences due to dyslexia and not other comorbid disorders. However, they were not excluded from the multiple case study, (Chapter 6) because in this analysis, each participant is treated individually and it is acknowledged that some effects observed could be due to the fact that a participant was at risk of clinical DCD and not dyslexia, or an interaction between DCD and dyslexia.

Thirty two participants were entered into the between group analysis (Chapter 5). All DPs (eleven females and five males; Mean age 21.2 years (SD=3.4)) had a formal diagnosis of developmental dyslexia by an educational psychologist. Twelve

DPs (66.7%) reported literacy difficulties occurring in one or more first-degree relatives. The remaining six DPs were not aware of a family history of literacy difficulties. CPs (eleven females and five males; Mean age 21.4 years (SD=6.0)) had no reading and spelling difficulties or any other known psychiatric or developmental disorders. DPs and CPs were matched for: years of education (all participants were studying at a UK university; all studied sciences, except for three DPs who studied arts), gender, age, handedness, Performance IQ and Full IQ measures (see Results for details).

3.4 Procedure

The study obtained local ethics committee approval. Prior to taking part in the study, participants were informed about the procedures to be used and that the collected data were confidential and anonymous. Written informed consent to participate in the study was given by all the participants. The research presented in this thesis was carried out in accordance with the ethical standards of the British Psychological Society and approved by the Human Sciences Ethics Committee at Aston University, UK.

Every participant was tested individually in a quiet room. Each session lasted approximately 2 hours. The effects of the order of tests was not controlled for, however, the order of tests was reversed for half of each group of participants. Olson's Orthographic Word-Pseudohomophone Choice test (Olson et al., 1994) and the Phonological Pseudoword Forced-Choice test (Olson et al., 1994) were run using SuperLab V.2 on Dell Pentium 4 PC with RB-410/RB-610 response box (Cedrus Corporation).

3.5 Results

The assumption that the data come from the normal distribution was tested using Shapiro-Wilks' test. The reason for choosing this test was that it is characterised by good power in comparison with other tests of normality (Conover, 1980). The data (within each group) that did not violate assumptions of normality were analysed using a parametric ANCOVA (*'F'* value reported) and an independent samples t-test (*'t'* value reported), whereas the data which had a distribution significantly different from normal were analysed using a nonparametric ANCOVA (Quade, 1967) (*'F'* value reported) and a Mann-Whitney test (*'Z'* value reported). In order to minimize the chance of a Type I error when using multiple statistical tests, alpha was set to $p \leq .01$.

As DVs relied on different measurement units (e.g., percent correct (% cor.) and seconds, etc.) to facilitate comparisons between their effects, a standardized measure of effect - *Cohen's d* (Cohen, 1988) was calculated for every measure. Cohen's (1988) criteria for effect size are as follows: 0.2 (or less) - small, 0.5 - medium, and 0.8 (or above) - large. It needs to be emphasised here that the terms 'small', 'medium' and 'large' are relative, not only to each other but also to the research method used in an investigation. Therefore there is a certain risk in using these operational definitions in power analysis in various branches of behavioural science and they have to be used with caution (Cohen, 1988).

Despite screening participants for being 'at risk' of clinical ADHD and DCD, the groups significantly differed on most measures involving these disorders (see below). Therefore to control for the potential confounds in the analyses, an ANCOVA with ADHD (A+B) measure and DCD total score as covariates was run on all the measures taken in this study, except age, handedness and the remaining measures of ADHD and DCD (see Appendix B, Table 11.1 and Table 11.2 for results involving covariates).

3.5.1 General psychometric, ADHD and DCD

There were no significant differences between the groups on age [$Z=1.3$, $p=.201$] and handedness [$Z=1.05$, $p=.295$]. DPs and CPs did not differ on Verbal, Performance and Full scale IQ [$F(1, 28)=3.35$, $p=.078$; $F(1, 28)=0.127$, $p=.724$; $F(1, 28)=1.09$, $p=.31$, respectively] (see Table 3.1 & Table 3.2 below and Appendix B, Table 11.1 & Table 11.2 for the results for covariates – ADHD and DCD). There were no significant differences between the groups on the Digit Span measure [$F(1, 28)=1.11$, $p=.302$]. DPs and CPs significantly differed on the Adult Dyslexia Check List (ADCL) [$F(1, 28)=24.43$, $p<.001$] (see Table 3.1 & Table 3.3).

The groups significantly differed on: ADHD Index (D) and ADHD (A+B) measure [$Z=2.6$, $p<.01$; $t(30)=2.55$, $p<.01$, respectively]. They did not differ on Inattention measure (A) and the Hyperactivity/Impulsivity measure (B) [$Z=2.02$, $p<.05$; $t(30)=2.28$, $p<.05$, respectively]. Furthermore, the groups significantly differed on Fine motor coordination [$Z=3.0$, $p<.01$], Gross motor coordination [$Z=2.6$, $p\leq0.01$], DCD early development score [$Z=2.6$, $p<.01$] and DCD total score [$Z=3.1$, $p<.01$]. The groups did not significantly differ on any manual dexterity measures from the Purdue Pegboard test (Tiffin, 1987): Right hand [$F(1, 28)=0.001$, $p=.978$], Left hand [$F(1, 28)=0.62$, $p=.438$], Both hands [$F(1, 28)=1.57$, $p=.22$], Right + Left + Both [$F(1, 28)= 0.469$, $p=.499$] and Assembly [$F(1, 28)=0.208$, $p=.652$], (see Table 3.2 & Table 3.3).

Table 3.1 Performance on Psychometric tests

Measure	DPs (11 Females, 5 Males)		CPs (11 Females, 5 Males)		Effect size (d)[f]
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
Age (years)	21.2 (3.4)	18-31	21.4 (6.0)	18-42	0.0
Handedness[a]	80.6 (18.7)	30-100	84.8 (21.4)	30-100	-0.2
FSIQ[b]	107.8 (8.8)	91-121	112.4 (9.0)	99-127	-0.5
VIQ[b]	106.4 (11.9)	79-121	111.5 (6.6)	99-123	-0.5^
PIQ[b]	108.0 (8.8)	94-127	110.4 (12.7)	93-137	-0.2
Digit Span[c]	8.8 (1.8)	6-14	10.9 (3.0)	8-18	-0.8
ADHD Index (D)[d]	54.9 (7.0)	34-63	50.6 (5.3)	42-62	0.7*
Inattention (A)[d]	64.7 (11.6)	45-85	56.8 (9.8)	43-85	0.7^^
Hyperactivity/ Impulsivity (B)[d]	56.1 (8.6)	30-70	49.6 (7.3)	38-66	0.8^^
ADHD (A+B)[d]	61.9 (9.6)	44-77	54.4 (6.8)	41-68	0.9*
ADCL[e]	6.3 (2.6)	1-11	0.9 (1.3)	0-4	2.6**

Note. ^p≤0.1 (considered not significant), ^^p≤0.05 (considered here as not significant, see text), *p≤0.01, **p≤0.001; [a]Laterality quotients (Oldfield, 1971), range from: -100 (left-handed) to 100 (right-handed); [b]Full scale, Verbal & Performance IQ measured with English WAIS-III and Wide Range Intelligence Test (WRIT) (DPs), and WASI (CPs); [c]Measured using WAIS-III subtest (Age adjusted scores); [d]Conners' Adult ADHD Rating Scales (CAARS-Self-Report: Screening Version: 30 questions); [e]Adult Dyslexia Check List (list of 12 questions); [f]Effect size = Cohen's d, the negative sign = DPs scored lower than CPs.

Table 3.2 Performance on Motor tests

Measure	DPs (11 Females, 5 Males)		CPs (11 Females, 5 Males)		Effect Size (d)[g]
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	
DCD (early development)[e] (max.= 5)	0.8 (0.9)	0-2	0.1 (0.5)	0-2	1.0*
Gross Motor Coordination[e] (max.= 9)	1.6 (1.5)	0-6	0.4 (0.8)	0-2	1.0*
Fine Motor Coordination[e] (max. = 16)	3.1 (2.2)	0-9	0.9 (1.3)	0-4	1.2*
DCD Total (max=30)	5.5 (3.8)	0-13	1.5 (2.0)	0-6	1.3**
Purdue Pegboard (R)[f]	14.1 (1.9)	11-18	14.6 (1.4)	13-17	-0.3
Purdue Pegboard (L)[f]	13.3 (1.8)	10-17	13.3 (1.9)	11-17	0.0
Purdue Pegboard Both (B)[f]	11.6 (1.6)	8-14	11.5 (1.4)	9-14	0.1
Purdue Pegboard (R+L+B)[f]	38.8 (4.7)	31-47	39.4 (4.2)	34-48	-0.1
Purdue Pegboard (Assembly)[f]	39.1 (5.7)	31-52	43.0 (4.5)	35-53	-0.8

Note. *$p \leq 0.01$, **$p \leq 0.001$; [e]A score on a questionnaire based on DSM-IV and on the Adult DCD Checklist; [f]Purdue Pegboard Test (Tiffin, 1987), R = score for the right hand, L = score for the left hand, B = score for both hands working together, Assembly = score for both hands working together when building assembly; [g] Effect size = Cohen's d, the negative sign = DPs scored lower than CPs.

Table 3.3 Summary of statistical results for general psychometric, ADHD & DCD measures

measures	statistics	p
Age	Z=1.3	p=.201
Handedness	Z=1.05	p=.295
PIQ	F(1, 28)=0.127	p=.724
FSIQ	F(1, 28)=1.09	p=.31
VIQ	F(1, 28)=3.35	p=.078
Digit Span	F(1, 28)=1.11	p=.302
ADCL	F(1, 28)=24.43	p<.001
ADHD Index (D)	Z=2.6	p<.01
Inattention (A)	Z=2.02	p<.05
Hyperactivity/Impulsivity (B)	t(30)=2.28	p<.05
ADHD (A+B)	t(30)=2.55	p<.01
DCD (early development)	Z=2.6	p<.01
Gross Motor Coordination	Z=2.6	p≤0.01
Fine Motor Coordination	Z=3.0	p<.01
DCD Total	Z=3.1	p<.01
Purdue Pegboard (R)	F(1, 28)=0.001	p=.978
Purdue Pegboard (L)	F(1, 28)=0.62	p=.438
Purdue Pegboard Both (B)	F(1, 28)=1.57	p=.22
Purdue Pegboard Both (R+L+B)	F(1, 28)= 0.469	p=.499
Purdue Pegboard (Assembly)	F(1, 28)=0.208	p=.652

Note. The order of tests is as in the text; Abbreviations as in Table 3.1 & Table 3.2.

3.5.2 Literacy tests

DPs scored significantly lower than CPs on almost all word reading measures, including: TOWRE (number of items) [F(1, 28)=11.07, p<.01], WRAT (% correct) [F(1, 28)=19.107, p<.001], and WRAT (time) [F(1, 28)=14.04, p=.001] (see Table 3.4 & 3.5). DPs were not significantly different from CPs on Irregular word reading (% correct, [F(1, 28)=4.73, p<.05], but they clearly scored significantly lower than CPs on Irregular word reading (time) [F(1, 28)=9.62, p<.01].

Similarly, DPs scored significantly lower than CPs on the TOWRE pseudoword test [F(1, 28)=29.28, p<.001]. Although, the groups did not differ on Pseudoword reading (CC) (% correct) [F(1, 28)=4.35, p<.05], DPs scored significantly lower than CPs on Pseudoword reading (CC) (time) F(1, 28)=14.35, p=.001 (see Table 3.4 & Table 3.5). Finally, regarding spelling, DPs scored significantly lower than CPs on WRAT (% correct) F(1, 28)=22.72, p<.001 (see Table 3.4 & Table 3.5).

Table 3.4 Performance on Literacy tests

Measure	DPs		CPs		
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	Effect size[a]
Word reading (TOWRE) (number of items read correctly in 45s)	76.6 (13.3)	55-99	95.3 (5.0)	87-104	-1.9*
Word reading (WRAT 3) (% cor.)	73.2 (11.0)	54.8-95.2	84.5 (6.9)	66.7-95.2	-1.2**
Word reading (WRAT 3) (time – in seconds)	84.6 (37.1)	35-171	44.8 (7.6)	31-58	1.5**
Pseudoword reading (TOWRE) (number of items read correctly in 45 s)	37.8 (11.6)	18-58	57.1 (5.0)	46-63	-2.2**
Pseudoword reading (CC) (% cor.)	76.7 (20.5)	26.7-100.0	90.0 (10.2)	60-100	-0.8^^
Pseudoword reading (CC) (time in seconds)	46.1 (22.1)	21-99	23.1 (4.4)	15-32	1.4**
Irregular word reading (CC) (% cor.)	84.6 (9.3)	63-100	88.5 (6.3)	80-100	-0.5^^
Irregular word reading (CC) (time in seconds)	29.7 (10.4)	19-59	18.9 (2.9)	15-24	1.4*
Spelling (WRAT 3) (% cor.)	62.5 (10.8)	32.5-77.5	80.0 (4.0)	72.5-87.5	-2.1**

Note. ^^$p \leq 0.05$ (considered here as not significant, see text), *$p \leq 0.01$, **$p \leq 0.001$; [a]Effect size = Cohen's d, the negative sign = DPs scored lower than CPs. CC denotes Castles and Coltheart's (1993) test;

Table 3.5 Summary of statistical results for literacy tests

measure	statistics	p
Word reading (TOWRE)	F(1, 28)=11.07	p<.01
Word reading (WRAT 3) (% cor.)	F(1, 28)=19.107	p<.001
Irregular word reading (% cor.)	F(1, 28)=4.73	p<.05
Word reading (WRAT 3) (time)	F(1, 28)=14.04	p=.001
Irregular word reading (time)	F(1, 28)=9.62	p<.01
Pseudoword reading (TOWRE)	F(1, 28)=29.28	p<.001
Pseudoword reading (CC) (% cor.)	F(1, 28)=4.35	p<.05
Pseudoword reading (CC) (time)	F(1, 28)=14.35	p=.001
Spelling (WRAT3) (% cor.)	F(1, 28)=22.72	p<.001

Note. The order of tests is as in the text; Abbreviations the same as in Table 3.4.

3.5.3 Phonological Awareness, Phonological Fluency and Orthographic processing

Focusing on Phonological Awareness measures, DPs scored significantly lower than CPs on the Phonological Force Choice test (% correct) [F(1, 28)=7.95, p<.01] and Spoonerisms (time) [F(1, 28)=10.21, p<.01]. DPs did not differ from CPs on Spoonerisms (% correct) [F(1, 28)=6.1, p<.05] and the RT measure for the Phonological Forced-Choice test [F(1, 28)=1.32, p<.27] (see Table 3.6 & Table 3.7).

On the phonological fluency measures, DPs scored significantly lower on RAN letters [F(1, 28)=9.26, p<.01], but not on RAN colours [F(1, 28)=2.82, p=.104], RAN pictures [F(1, 28)=2.73, p=.11] or RAN digits [F(1, 28)=5.3, p<.05] (see Table 3.6 & Table 3.7).

Finally, DPs did not score significantly lower on the mean RT measure for the Olson's Word-Pseudohomophone Choice test and % correct [F(1, 28)=4.68, p<.05; F(1, 28)=3.8, p=.062, respectively] (see Table 3.6 & Table 3.7).

It should be noted here that at the first glance it may appear that DPs were not significantly impaired on most of the phonological processing tasks. However, for the tests where percent correct and time were measured, the impairment may be manifested in only one component – percent correct or time. This is because accuracy and time are not independent in these tests and participants may trade speed for accuracy. Indeed, this is true for the Spoonerism test and the Phonological Force Choice test. Furthermore, this study applied a more conservative value for the

significance level ($p<.01$) than most studies, where this threshold is usually set up to $p<0.05$. If this threshold was lowered to $p<.05$, the mean RT measure for the Olson's Phonological Pseudoword Forced-Choice test, Spoonerisms (% correct), and RAN digits would be treated as significant. Finally it is possible that the DPs who took part in this study exhibited some practice effects due to previous testing, which was not encountered by the CPs.

Table 3.6 Performance on the Phonological Awareness, Phonological Fluency and Orthographic processing tests

Measure	DPs		CPs		
	Mean (SD)	Min-Max	Mean (SD)	Min-Max	Effect size [d]
Spoonerism test[a] (% correct)	70.3 (20.2)	41.7-100	93.2 (7.0)	83.3-100	-1.5^^
Spoonerisms[a] (time in seconds)	153 (71.0)	56-346	81.3 (22.1)	52-129	1.4*
Phonological Choice test[b] (% correct)	76.1 (15.3)	36.7-96.7	86.8 (9.1)	66.7-100	-0.9*
Phonological Choice test[b] (mean RT in milliseconds)	3672 (1186.39)	1623.2-6368.0	2973.2 (492.7)	2239.4-3807.2	0.8
RAN Colours[c] (time in seconds)	40.1 (5.8)	30-49	34.4 (6.4)	25-49	0.9
RAN Pictures[c] (time in seconds)	46.2 (7.9)	34 -59	39.4 (6.7)	30-53	0.9
RAN Digits[c] (time in seconds)	26.4 (4.0)	19-35	22.6 (2.4)	19-27	1.2^^
RAN Letters[c] (time in seconds)	30.4 (6.2)	24-50	23.8 (3.0)	19-29	1.4*
Olson's pseudohomophone test[b] (% correct)	93.0 (5.1)	82.5-98.8	95.0 (2.8)	90-98.8	-0.5^
Olson's pseudohomophone test[b] (mean RT in msec)	1136.85 (322.3)	773.6-1950.4	850.5 (163.7)	548.4-1263.9	1.1^^

Note. ^$p \leq 0.1$ (not significant), ^^$p \leq 0.05$ (considered here as not significant, see text), *$p \leq 0.01$, [a]Brunswick et al. (1999); [b]Olson, Forsberg, Wise, & Rack, (1994); [c]CTOPP (Wagner et al., 1999); [d] Effect size = Cohen's d, the negative sign denotes that DPs scored lower than CPs.

Table 3.7 Summary of statistical results for the Phonological Awareness, Phonological Fluency & Orthographic measures

measures	statistics	p
Spoonerisms (% cor.)	F(1, 28)=6.1	p<.05
Spoonerisms (time)	F(1, 28)=10.21	p<.01
Phonological Force Choice (% cor.)	F(1, 28)=7.95	p<.01
Phonological Force Choice (mean RT)	F(1, 28)=1.32	p<.27
RAN digits (time)	F(1, 28)=5.3	p<.05
RAN letters (time)	F(1, 28)=9.26	p<.01
RAN colours (time)	F(1, 28)=2.82	p=.104
RAN pictures (time)	F(1, 28)=2.73	p=.11
Olson's pseudohomophone test (mean RT)	F(1, 28)=4.68	p<.05
Olson's pseudohomophone test (% cor.)	F(1, 28)=3.8	p=.062

3.6 Summary and discussion

Regarding the general psychometric measures, the groups were well-matched on: gender, age, handedness, years of education, FSIQ and PIQ. The descriptive statistics showed (Table 3.1) that the groups were less well-matched on VIQ, but this difference was not statistically significant. Therefore any differences in literacy, phonological or orthographic processing is unlikely to result from differences in these variables. There was a trend for DPs to score lower on Digit Span, but this difference was not significant. The groups differed on ADHD Index D and ADHD (A+B). The groups also differed on all DCD measures. Therefore the ADHD (A+B) and DCD Total score were used as covariates in the analyses. Hence, the differences on literacy, phonological and orthographic processing cannot be accounted for by differences in the scores on ADHD and DCD. Given that there were significant differences between DPs and CPs on all DCD measures, it was surprising that there were no significant differences between groups on any measure on the Purdue Pegboard Test (Tiffin, 1987), especially the measure which tapped into 'fingertip' dexterity. As both groups had the same amount of time for completing each task on the Purdue Pegboard Test, it is possible that those DPs, who had these types of difficulty, were able to compensate, by making greater effort, for their weaker motor and dexterity skills. Using a parallel task with the

Purdue Pegboard Test, in future research, may be a way of preventing DPs from being able to compensate for their potential weaknesses in this test.

Moving on to literacy skills, DPs, as a group, exhibited clear deficits compared to CPs across most measures: Word reading (TOWRE), word reading (WRAT), Pseudoword reading (TOWRE), pseudoword reading (Castles & Coltheart, 1993) time, irregular word reading (Castles & Coltheart, 1993) (time) and Spelling (WRAT). The largest effect size (d=-2.2) was observed for the number of pseudowords read (TOWRE) and % correct on the spelling test (d=-2.1). These results presented above confirm that literacy difficulties in dyslexia persist to adulthood (Bruck, 1990; Paulesu et al., 1996; Ramus, 2003; Reid et al., 2007; Snowling et al., 1997).

Focusing on phonological awareness tests, DPs did not differ from CPs on two measures: the Phonological Choice test mean RT and Spoonerisms % correct. However, the groups clearly differed on Phonological Choice test (% correct) and on Spoonerisms (time). The largest effect size (d=-1.5) was observed for the Spoonerisms (% correct), however this result, as discussed above, was not significant. The second largest effect was noted for Spoonerisms (time) (d=-1.4). Usually the Spoonerisms measures (time and/or % correct) differentiate quite well between the adult DPs and CPs (Brunswick et al., 1999; Hatcher, Snowling, & Griffiths, 2002; Paulesu et al., 2001; Ramus, Rosen et al., 2003; Snowling et al., 1997; Vukovic et al., 2004). Also, DPs showed a deficit on % correct on the Phonological Pseudoword Forced-Choice test (Olson, Forsberg, Wise, & Rack, 1994).

Moving on to the phonological fluency tests, although there was a trend for DPs as a group, to require longer than CPs to name all the items on the colour, pictures and digits tests than CPs (note also that Cohen's d=-0.9, -0.9, -1.2, respectively, which indicates large effects), these differences were not significant. This finding stands in contrast to previous reports (Ramus, Rosen et al., 2003; Reid et al., 2007; Vukovic et al., 2004). This could be due to larger variability within DPs in this sample and/or to DPs having managed to automatise the access to these items. However, there was significant difference between the groups on letter items. The RAN results for letters are in line with previous reports (e.g., Paulesu et al., 2001; Ramus, 2003; Reid et al., 2007; Vukovic et al., 2004).

Finally, focusing on orthographic processing, there was not a significant difference between the groups in the mean RT and % correct on the Orthographic Word-Pseudohomophone Choice test. It may be the case that using a test where a

target and foil are displayed on a computer screen, one by one, rather than one next to the other, would differentiate the groups on percentage correct better. This is because if only the foil word is displayed, DPs' accuracy criterion seems to be lower than when both items are displayed next to each other (Olson et al., 1994). However, this experimental manipulation introduces additional demands on the short term memory and can potentially introduce a confounding variable to the results.

Taken together, the groups were well matched on potential confounding variables, such as gender, age, years of education, handedness Performance IQ and Full IQ. Therefore any between-group differences on literacy, phonological and orthographic measures are unlikely to be confounded by these variables. Furthermore, DPs, as a group, scored significantly lower than CPs on literacy and phonological measures while the effects of ADHD and DCD were statistically accounted for. Hence, the observed between-group differences cannot be due to DPs having higher scores for ADHD and DCD measures.

4 DPs' individual performance on the psychometric measurements

4.1 Introduction

The deficits in information processing associated with dyslexia are usually characterised by considerable heterogeneity. Group analyses can therefore obscure the importance of individual deficits at the group level. A multiple case study approach was therefore adopted in this chapter. A multiple case study is a more detailed study of individual cases, compared to a control group (Ramus, Rosen et al., 2003; Reid et al., 2007; White et al., 2006).

For a detailed description of the tests and measurements used, please consult Chapter 3. Within the individual case study approach, measures for a given DP, were converted to z-scores (see Table 4.1, Table 4.2 and Table 4.3), with reference to the mean and the SD of the control group. The equation used to calculate z-scores is shown below.

$$z = \frac{y_{\mathrm{dp}} - x_{\mathrm{cg}}}{SD_{\mathrm{cg}}}$$

Where z = z-score; y_{dp} = raw score of an individual participant with dyslexia; x_{cg} = mean of the control group; SD_{cg} = standard deviation of the control group.

The z-scores are reported in the tables for each participant. For some tests, individual z-scores were averaged across relevant measures to yield composite scores. It should be underscored here that these composite variables are independent - the measures used for a given composite variable are not used in any other composite variable. As averaging several imperfectly correlated z-scores resulted in composites which, for the control group, had a mean of zero but reduced standard deviations (<1), the composite scores were re-standardized by dividing them by the standard deviation of the control group (Ramus, Rosen et al., 2003). These re-standardised z-scores are reported as composite scores. Composite scores (marked in yellow in Table 4.1, Table 4.2 and Table 4.3) were calculated for the following measures: PURDUE PEGBOARD (see Table 4.1); WRAT WORD READING, PSEUDOWORD READING and IRREGULAR WORD READING (see Table 4.2); PHONOLOGICAL AWARENESS, PHONOLOGICAL FLUENCY and ORTHOGRAPHY (see Table 4.3). Abnormal performance was defined as $z \leq -1.65$, which corresponds to performance at or below the 5th

percentile. The 5th percentile was used in previous multiple-case studies to define deviant performance (e.g., Ramus, Rosen et al., 2003; Reid et al., 2007; White et al., 2006). Negative z-scores denote performance that is worse than that of the control group.

PURDUE PEGBOARD consisted of the following measures: Right hand (R), Left hand (L), Both hands (B) and Assembly. Note that the R+L+B measure was not included here because it overlapped with the first three measures.

WRAT WORD READING consisted of WRAT word reading percent correct and WRAT word reading time. This composite did not include the TOWRE word reading score (Torgesen et al., 1999), because these two tests included words with different characteristics. WRAT included not only high frequency words, but also low frequency words such as, *'terpsichorean'* and *'oligarchy'* which were not known to the participants. TOWRE performance relies mostly on higher frequency words that are well known to the participants. Therefore TOWRE z-scores were chosen as summary variables for word reading in Table 4.4 and Figure 4.2. PSEUDOWORD READING consisted of the following measures: number of pseudowords read correctly (TOWRE), and percent correct and reading time for the Pseudoword reading test (Castles & Coltheart, 1993). IRREGULAR WORD READING (Castles & Coltheart, 1993) consisted of Irregular word reading percent correct and reading time.

PHONOLOGICAL AWARENESS consisted of the following measures: Spoonerisms time, Spoonerisms percent correct, Phonological Pseudoword Forced-Choice test (Olson et al., 1994) RT and percent correct. These measures were combined because they involve the appreciation that phonological representations of words/pseudowords consist of smaller units – phonemes. PHONOLOGICAL FLUENCY consisted of time for RAN Colour, Picture, Digit and Letter (CTOPP) (Wagner et al., 1999). Finally, ORTHOGRAPHY consisted of Orthographic Word-Pseudohomophone Choice test (Olson et al., 1994) percent correct and RT.

Composite variables were not calculated for ADHD and DCD because some measures overlapped (e.g. ADHD D overlapped with ADHD A+B, ADHD A+B overlapped with ADHD A, and DCD Total overlapped with every other measure of DCD), and therefore would violate the assumption that a composite variable is computed from independent measures of the same construct. Most ADHD measures (see Table 4.1) are given as T-scores. DCD scores are raw scores; they were not based on a standardised test. Every DP was compared on ADHD A+B and DCD Total to CPs using the z-score calculated according to the equation given

above. It was demonstrated (Willcutt & Pennington, 2000) that reading difficulties are most strongly associated with the inattentive sub-type of ADHD, but also, albeit less strongly with the hyperactive sub-type. Therefore, the ADHD A+B measure, which includes both ADHD types, was chosen. A PURDUE PEGBOARD composite was calculated. However, this measure turned out to be less sensitive than the DCD Total measure - only three DPs were impaired on PURDUE PEGBOARD, but 11 DPs were impaired on DCD Total measure. Furthermore all DPs who had a deficit on PURDUE PEGBOARD also had a deficit on DCD Total. Hence, the DCD Total measure was used in the analysis and not the PURDUE PEGBOARD composite.

The structure of this chapter is as follows. First measures for each individual DP are shown (Tables 4.1 - 4.3). Second, Table 4.4 presents the deviance analysis for DPs across the summary variables. Third, three Venn diagrams are presented: Figure 4.1 shows the distribution of deviant z-scores on ADHD (A+B) and the DCD Total; Figure 4.2 presents the distribution of pseudoword and irregular word reading composite scores and z-scores for real word reading and spelling; Figure 4.3 displays the distribution of the composite scores on the phonological and orthographic measures. Finally, the chapter is concluded with a summary and discussion of the results.

4.2 Results

Table 4.1 Individual performance of DPs on general psychometric tests

Measures/Participant number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Age	27	20	21	19	31	22	18	25	19	20	23	20	19	20	19	20	20	20
VIQ SS	121	119	97	114	116	108	112	107	106	117	96	111	97	88	101	114	79	108
PIQ SS	107	102	105	109	124	102	120	106	94	104	105	106	127	98	90	110	108	107
FIQ SS	116	112	100	114	121	106	118	107	101	112	100	109	110	91	97	114	92	108
Digit Span^	9	8	9	6	14	9	8	7	7	8	9	9	10	9	8	10	7	8
Verbal Comprehension^^	124	124	94	-	118	110	-	103	112	136	98	107	105	91	107	109	-	120
Perceptual Organisation^^	107	111	109	-	128	109	-	116	95	114	105	109	128	103	91	-	-	111
Working Memory^^	108	104	97	-	115	94	-	80	97	88	92	97	90	92	94	-	-	80
Processing Speed^^	114	86	106	-	117	91	-	96	68	73	108	111	120	86	71	-	-	91
ADHDD@	57	63	58	53	59	55	57	57	57	57	58	58	48	53	55	34	48	63
ADHDA@	74	78	77	56	56	64	85	56	79	63	60	65	56	54	66	51	45	72
ADHDB@	70	61	66	55	64	54	51	50	59	48	55	48	45	57	59	39	57	68
ADHD (A+B)@	64	73	77	57	62	61	72	54	74	57	59	58	51	57	66	44	51	73
ADHD (A+B)*	-1.4	**-2.7**	**-3.3**	-0.4	-1.1	-1.0	**-2.6**	0.1	**-2.9**	-0.4	-0.7	-0.5	0.5	-0.4	**-1.7**	1.5	0.5	**-2.7**
ADCL*	**-4.7**	**-6.2**	**-3.9**	**-5.5**	-0.1	**-2.4**	**-3.9**	**-2.4**	**-7.8**	**-7.0**	**-3.2**	**-4.7**	**-2.4**	**-5.5**	**-4.7**	-1.6	**-4.7**	**-3.2**
DCD (Early dev.)*	**-3.8**	**-3.8**	**-1.8**	0.2	0.2	0.2	**-3.8**	0.2	**-3.8**	**-3.8**	**-1.8**	**-1.8**	0.2	0.2	0.2	0.2	0.2	0.2
Gross Motor Coordination*	**-2**	**-7**	-0.8	0.5	-0.8	-0.8	**-3.3**	-0.8	-0.8	**-2**	**-3.3**	**-2**	0.5	0.5	**-4.5**	0.5	-0.8	**-2**
Fine Motor Coordination*	**-5.5**	**-2.4**	-1.6	-0.1	0.7	-0.8	**-3.2**	-1.6	**-3.9**	-1.6	-1.6	-0.8	-0.1	**-3.9**	**-3.9**	0.7	-1.6	-1.6
DCD Total*	**-5.3**	**-5.3**	**-1.8**	0.3	0.3	-0.8	**-4.3**	-1.3	**-3.8**	**-2.8**	**-2.8**	**-1.8**	0.3	**-2.3**	**-4.3**	0.8	-1.3	**-1.8**
Purdue Pegboard (R)*	-0.4	-0.4	**-1.9**	-1.1	1.0	-0.4	-1.1	**1.7**	**-2.6**	**-2.6**	**2.4**	1.0	0.3	1.0	**-2.6**	-1.1	0.3	-0.4
Purdue Pegboard (L)*	0.4	-0.2	**-1.7**	-0.7	0.9	0.4	-0.7	2.5	-0.2	-1.2	1.9	-0.7	0.9	0.4	0.4	-0.7	0.9	-0.2
Purdue Pegboard Both (B)*	1.1	0.4	**-1.8**	-0.4	1.1	1.1	**-2.5**	1.8	-1.1	0.4	0.4	-0.4	0.4	1.1	0.4	-0.4	1.8	-0.4
Purdue Pegboard (R+L+B)*	0.4	-0.1	**-2.0**	-0.8	1.1	0.4	-1.5	2.3	-1.5	-1.3	1.8	-0.1	0.6	0.9	-0.6	-0.8	1.1	-0.3
Purdue Pegboard (Assembly)*	-0.4	-1.6	**-1.8**	-0.7	2.0	-0.9	**-2.7**	0.2	**-2.2**	**-2.4**	0.9	-0.7	0.2	-1.6	-1.1	-1.3	0.4	-1.3
Purdue Pegboard Composite	0.2	-0.6	**-2.2**	-0.9	1.6	0.0	**-2.2**	1.9	**-1.9**	**-1.8**	1.8	-0.2	0.5	0.3	-0.9	-1.1	1.1	-0.7

Note (for Table 4.1). SS Standard Score; ^Age adjusted score; ^^ Index Scores; Qualitative descriptions of IQ SS and Index Scores, percentage included in bell-shaped distribution are given in parenthesis : ≥ 130 (2.2%)=Very Superior, 120-129 (6.7%)=Superior, 110-119 (16.1%)=High Average, 90-109 (50%)=Average, 80-89 (16.1%)=Low Average, 70-79 (6.7%)=Borderline , ≤ 69 (2.2%)=Extremely Low; @ T-scores with Mean=50; SD=10, scores from 66 to 70 – much above average, scores >70 – very much above average, D=ADHD Index, A=Inattention, B=Hyperactivity/Impulsivity;* z-score (relative to the control group used in this study); Deviant scores (≤ -1.65) are marked in bold; Composite scores are shown in yellow; z-scores used as classificatory variables in Figure 4.1 marked in green. It was not possible to calculate IQ Index Scores for DP4, DP7, DP16 and DP17 because the relevant scores were not provided in their reports (see Table 4.1). However, as the IQ Index Scores were of secondary interest here and were not used to address the main questions investigated in this thesis, DP4, DP7, DP16 and DP17 were included in the main study reported in this thesis. No participants with an FSIQ lower than the average score (90) were included in the study. As a result of this cut-off procedure, there were two DPs (DP14 and DP17) who had a VIQ lower than 90. Because the core deficits in dyslexia are in the language domain, scores on VIQ may be significantly lower in adult DPs than in the control group (Ramus, Rosen et al., 2003). Although the CPs (as a group) exhibited higher mean scores on VIQ (mean=111.5, sd=6.6) than the DPs (mean=106.4, sd=11.9), the groups did not significantly differ on this measure [$F(1,28)=3.35$, $p=.078$].

Table 4.2 Performance of individual DPs on literacy tests, pseudoword and irregular words reading tests

Measures/Participant number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
TOWRE Word Correct*	-1.3	**-6.5**	**-5.1**	**-3.1**	0.7	0.7	**-7.5**	**-2.3**	**-8.1**	**-4.7**	-0.9	**-4.9**	**-4.7**	**-4.5**	**-10.3**	**-4.3**	**-4.7**	-1.5
WRATR Word % correct*	1.6	0.9	**-3.3**	**-3.3**	0.2	-1.5	-0.9	**-3.6**	-1.5	-1.5	**-2.9**	**-2.6**	**-2.6**	-1.5	**-5.0**	-0.5	**-4.3**	**-2.2**
WRATR Word Time (sec)*	0.2	**-2.4**	**-2.9**	-1.6	1.3	-0.3	**-4.4**	**-3.8**	**-10.9**	**-16.6**	**-4.5**	**-10.7**	**-10.0**	**-5.0**	**-12.0**	**-8.2**	**-5.6**	**-2.1**
WRAT Word Reading Composite	1.3	-1.1	**-4.4**	**-3.5**	1.0	-1.3	**-3.7**	**-5.3**	**-8.9**	**-13.0**	**-5.3**	**-9.5**	**-9.0**	**-4.7**	**-12.1**	**-6.2**	**-7.0**	**-3.1**
WRAT Spelling (% correct)*	-0.6	**-5.6**	**-4.4**	**-3.1**	-0.6	**-3.8**	**-2.5**	**-6.3**	**-5.0**	**-11.9**	**-3.8**	**-6.3**	**-1.9**	**-6.9**	**-12.5**	**-5.0**	**-5.0**	**-3.8**
TOWRE Pseudoword Correct*	0.2	**-3.8**	**-5.6**	**-4.4**	0.0	-1.0	**-3.0**	**-5.6**	**-5.2**	**-7.8**	**-3.2**	**-6.0**	**-5.2**	**-2.0**	**-8.2**	**-3.6**	**-7.0**	**-3.8**
Pseudoword (Coltheart) % correct*	1.0	-0.3	-0.7	-1.6	0.7	-0.3	-0.3	-0.3	-1.6	**-5.2**	0.0	**-2.6**	-1.6	0.3	**-1.9**	0.0	**-6.2**	**-2.3**
Pseudoword (Coltheart) Time (s)*	0.5	**-3.4**	**-8.2**	-1.1	0.3	-0.7	**-1.8**	**-3.1**	**-6.6**	**-17.3**	**-4.3**	**-8.2**	**-10.2**	**-2.3**	**-22.8**	**-4.5**	**-12.9**	**-2.9**
Pseudoword Reading Composite	0.8	**-3.6**	**-6.9**	**-3.4**	0.4	-1.0	**-2.4**	**-4.3**	**-6.4**	**-14.4**	**-3.6**	**-8.0**	**-8.1**	**-1.9**	**-15.7**	**-3.9**	**-12.5**	**-4.3**
Irregular word reading (% correct)*	1.3	-0.3	-0.8	-1.3	1.8	-0.3	0.8	**-4.2**	1.3	-1.3	-0.3	-0.3	-1.3	**-4.0**	-1.0	-1.3	**-2.4**	-1.3
Irregular word reading[a] (time in sec.)*	-0.4	**-5.6**	**-13.8**	**-2.1**	-0.7	-0.7	-0.7	**-6.6**	**-8.0**	-1.4	0.0	**-4.5**	**-5.2**	**-4.2**	**-13.6**	**-5.6**	**-4.9**	**-1.8**
Irregular Word Reading Composite	0.5	**-3.2**	**-8.1**	**-1.9**	0.6	-0.6	0	**-6**	**-3.7**	-1.5	-0.2	**-2.7**	**-3.6**	**-4.5**	**-8.1**	**-3.8**	**-4**	**-1.7**

Note. * z-score (relative to the control group used in this study); Deviant scores (≤ -1.65) are marked in bold; Composite scores are marked in yellow; z-scores used as summary variables in Table 4.2 and Figure 4.2 are marked in green.

Table 4.3 Performance of individual DPs on phonological awareness, phonological fluency and orthography measures

Measures/Participant number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Spoonerisms (time in secs)*	-0.3	**-3.8**	-0.1	-0.7	1.1	**-5.1**	-0.1	**-3.9**	**-5.4**	**-12.0**	**-5.9**	**-5.6**	**-1.9**	**-2.7**	**-3.4**	**-3.1**	**-4.0**	**-2.6**
Spoonerisms (% correct)*	-0.2	**-5.0**	-0.2	**-5.0**	1.0	**-5.0**	1.0	**-8.6**	-0.2	**-5.0**	**-7.4**	**-5.0**	**-2.6**	**-6.2**	-0.2	-1.4	**-3.8**	**-7.4**
Phonological Pseudoword Forced-Choice (mean RT in msec)*	-1.0	0.2	**-1.8**	-0.6	-0.2	**-3.0**	0.8	**-4.2**	**-5.5**	**-6.9**	**-3.7**	**-2.0**	-1.4	0.0	-0.5	0.3	2.7	-0.7
Phonological Pseudoword Forced-Choice (% correct)*	0.4	0.4	-0.2	-1.1	0.7	1.1	-0.2	**-1.7**	-0.9	**-1.7**	**-1.8**	**-1.7**	0.0	**-2.0**	**-4.4**	**-2.9**	**-5.5**	**-3.3**
Phonological Awareness Composite	-0.5	**-3.4**	-1	**-3.1**	1.1	**-5**	0.6	**-7.6**	**-5**	**-10.6**	**-7.9**	**-5.9**	**-2.5**	**-4.5**	**-3.6**	**-3**	**-4.4**	**-5.8**
RAN Colour*	0.7	-0.1	-1.0	**-2.1**	0.5	0.2	**-2.3**	**-4.6**	-1.2	-1.2	-1.2	-0.4	-0.7	-1.5	**-3.7**	-0.7	-1.2	**-2.1**
RAN Picture*	0.8	0.2	-1.4	**-1.7**	0.5	-0.1	**-2.6**	**-4.0**	**-2.9**	-1.6	-0.5	-0.7	0.5	-1.3	**-4.9**	**-2.5**	-1.1	**-1.7**
RAN Digit*	0.3	**-2.3**	**-3.5**	**-2.7**	0.7	1.5	-1.4	-1.4	**-3.1**	**-5.2**	-0.6	-0.6	**-2.7**	-1.4	**-13.1**	-1.0	**-1.8**	**-1.8**
RAN Letter*	-0.4	**-2.1**	**-2.7**	**-1.4**	**-1.7**	-0.1	-1.4	-1.1	**-4.7**	**-8.7**	-0.4	**-1.7**	**-2.4**	**-1.7**	**-7.7**	-1.1	**-3.1**	**-1.7**
Phonological Fluency Composite	0.4	-1.3	**-2.7**	**-2.5**	0	0.5	**-2.4**	**-3.5**	**-3.7**	**-5.2**	-0.8	-1.1	-1.6	**-1.9**	**-9.2**	-1.6	**-2.3**	**-2.3**
Orthographic Word-Pseudohomophone Choice (% correct)*	1.3	0.0	1.3	0.0	1.3	-0.4	-0.9	0.4	**-2.2**	**-4.5**	0.9	0.0	-0.9	-0.9	**-7.1**	**-4.0**	**-2.7**	0.0
Orthographic Word-Pseudohomophone Choice test (mean RT in msec)*	-0.1	**-2.8**	**-1.8**	0.3	0.5	**-4.6**	0.2	**-1.7**	**-2.9**	**-3.6**	-0.9	-1.2	-1.1	**-6.7**	**-7.8**	**-1.8**	-0.1	-1.3
Orthography Composite	1.0	**-2.4**	-0.4	0.2	1.5	**-4.2**	-0.6	-1.0	**-4.2**	**-6.7**	0.0	-1.0	-1.6	**-6.3**	**-12.5**	**-4.8**	**-2.4**	-1.0

Note. * z-score (relative to the control group used in this study); Deviant scores (≤ -1.65) are marked in bold; Composite scores are marked in yellow.

Table 4.4 Performance of individual DPs on summary variables

Measures/ Participant number	*9*	*14*	*15*	*17*	*2*	*4*	*8*	*10*	*16*	*3*	*12*	*13*	*18*	*7*	*11*	*6*	*1*	*5*
Number of deficits	7/7 deficits				6/7 deficits					5/7 deficits				4/7 deficits	3/7 deficits		0/7 deficits	
Literacy measures																		
TOWRE Word Correct*	X	X	X	X	X	X	X	X	X	X	X	X	+	X	+	+	+	+
Pseudoword Reading Composite	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	+	+	+
Irregular Word Reading Composite	X	X	X	X	X	X	X	+	X	X	X	X	X	+	+	+	+	+
WRAT Spelling (% correct)*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	+	+
Phonological and orthographic measures																		
Phonological Awareness Composite	X	X	X	X	X	X	X	X	X	+	X	X	X	+	X	X	+	+
Phonological Fluency Composite	X	X	X	X	+	X	X	X	+	X	+	+	X	X	+	+	+	+
Orthography Composite	X	X	X	X	X	+	+	X	X	+	+	+	+	+	+	X	+	+

Note. X denotes deviant performance (≤ -1.65 SD below the mean of controls); + denotes non-deviant performance. * z-score (relative to the control group used in this study); Colour coding denotes number of deficits: light green=7/7, red =6/7 deficits,blue=5/7 deficits, magenta=4/7deficits, yellow =3/7 deficits, dark green =deficit0/7.

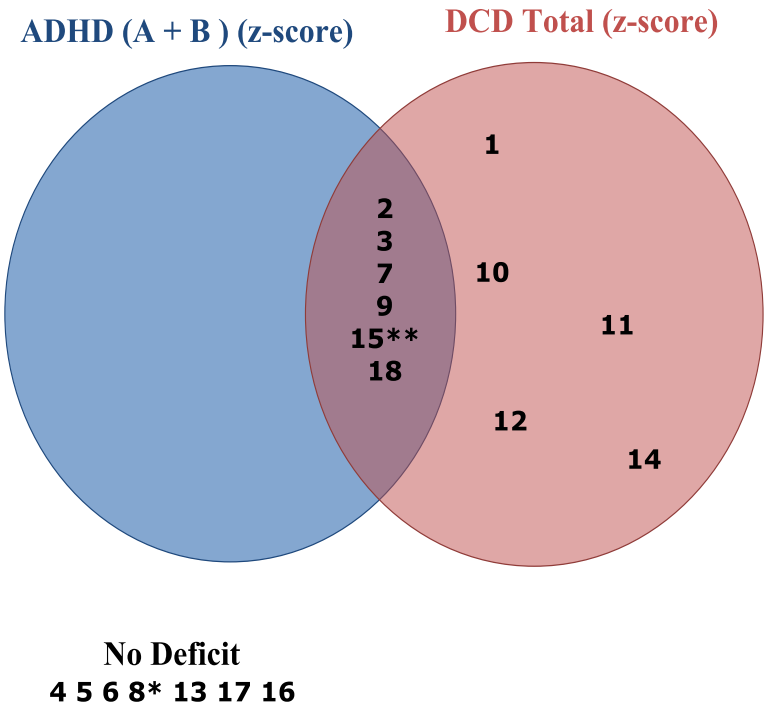

Figure 4.1 The distribution of ADHD (A+B) & DCD Total scores (z scores ≤ -1.65 SDs below the mean of controls). Numbers denote individual DPs. All the participants were screened for clinical ADHD and DCD (except, DP8 and DP15 on DCD, see below)

Note. * Although the number of DCD symptoms did not classify DP8 as 1.65 SDs below the mean of CPs, in the interview she said that DCD symptoms significantly interfere with her everyday life and work; **DP15's DCD symptoms classified him as 1.65 below the mean of the CPs and in the interview he said that DCD symptoms significantly interfere with his everyday life and work.

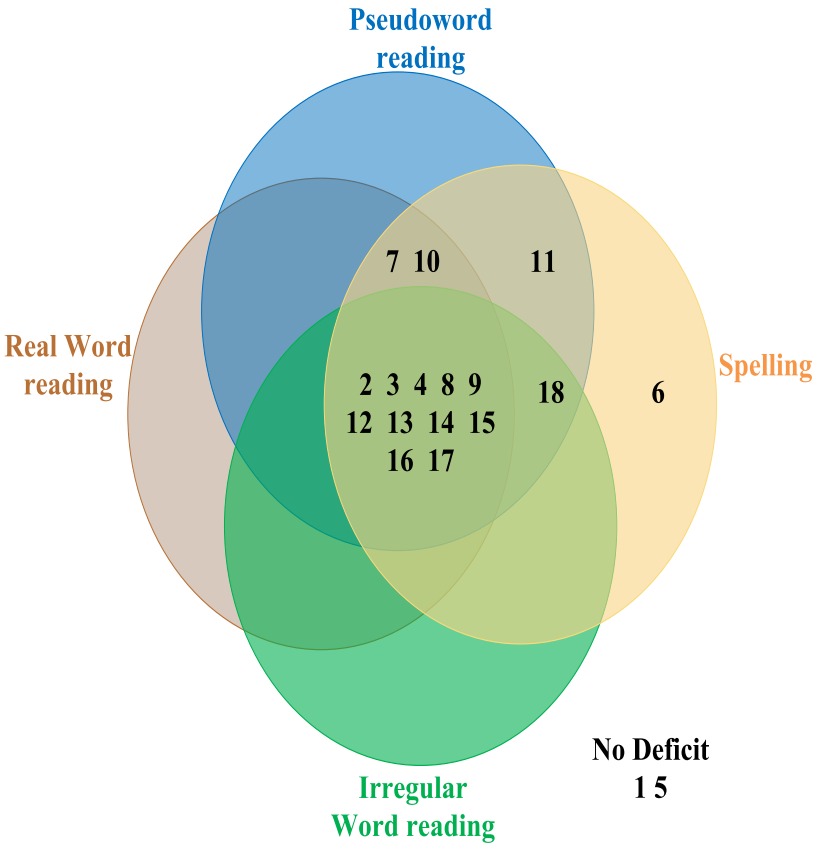

Figure 4.2 The distribution of composite scores for: pseudoword & irregular word reading, and z-scores for spelling (WRAT) and real word reading (TOWRE). All scores 1.65 SDs below the mean of CPs. Numbers denote individual DPs.

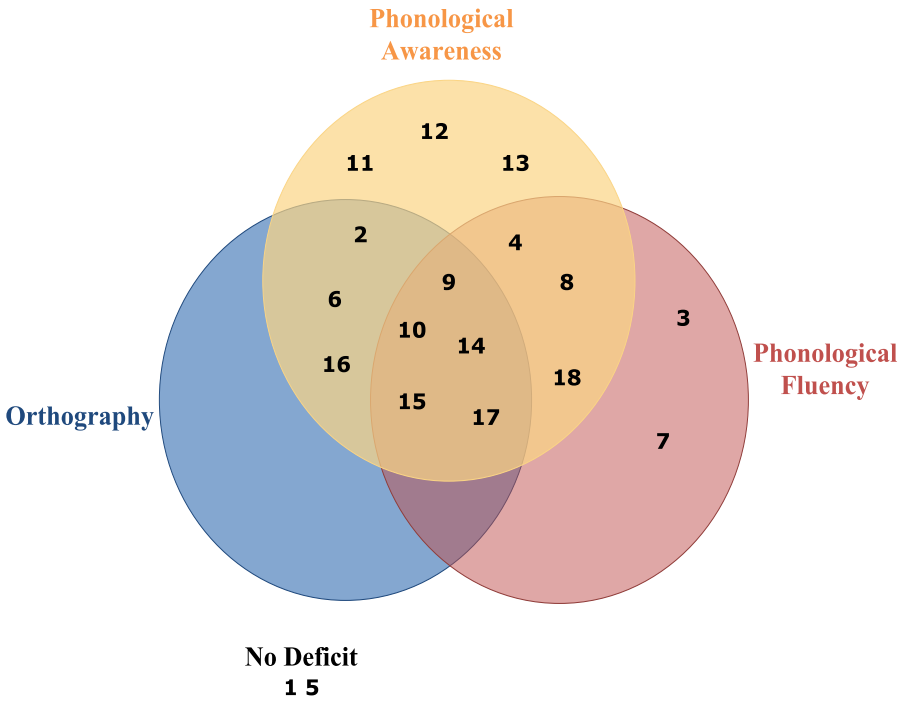

Figure 4.3 The distribution of: phonological awareness, phonological fluency & orthography composite scores (≤ - 1.65 SDs below the mean of controls). Numbers denote individual DPs.

4.3 Summary and Discussion

Focusing on the general psychometric measures, all but two DPs (DP5 & DP16) scored ≤ -1.65 on the Adult Dyslexia Check List (Vinegrad, 1994), indicating that they experienced significantly more dyslexia-related difficulties than CPs (see Table 4.1). The screening procedure for this study ensured that no DP had an FIQ score < 90; therefore only DPs with average or above FIQ scores were included in the study. Note that for WAIS, a test on which all DPs were tested, a score ≥ 130 denotes 'very superior', 120-129 denotes 'superior', 110-119 denotes 'high average', 90-109 denotes 'average', 80-89 denotes 'low average', 70-79 denotes 'borderline' and a score ≤ 69 denotes 'extremely low'. Most scores on FIQ were 'average', seven DPs (DP1, DP2, DP4, DP7, DP10, DP13 & DP16) were 'high average' and one DP5 was 'superior'. Similarly, most scores on PIQ were 'average', one DP16 was 'high average' and three DPs (DP5, DP7 & DP13) were 'superior'. The scores for VIQ were characterised by more variability, with DP17 exhibiting a 'borderline', DP14 the 'low average', eight DPs (DP3, DP6, DP8, DP9, DP11, DP13, DP15 & DP18) 'average', seven DPs (DP2, DP4, DP5, DP7, DP10, DP12 & DP16) 'high average' and one DP1 'superior' scores. Because the core deficits in dyslexia are in the language domain, scores on VIQ may be significantly lower in adult DPs than in the control group (Ramus, Rosen et al.,

2003), however this is not always the case, because some studies reported no significant difference between the groups (Reid et al., 2007). As IQ scores were taken from DPs' reports on their dyslexia diagnosis, it was not possible to calculate IQ Index Scores for all DPs because they were not provided in some reports (see Table 4.1). The lowest Index Scores were noted for 'Working Memory' and 'Processing Speed'. Three DPs (DP8, DP10 & DP18) scored 'low average' on 'Working Memory'. On Processing Speed, two DPs (DP2 & DP14) scored 'low average', two DPs (DP10 & DP15) 'borderline' and one DP9 'extremely low'.

'Working Memory' and 'Processing Speed' were reported to be deficient in DPs treated as a group (Hatcher et al., 2002; Paulesu et al., 2001; Ramus, Rosen et al., 2003). It should be noted, however, that in the sample tested here these deficits were exhibited by some DPs but not all. Therefore one should be cautious when making generalisations about DPs which are based on group analysis.

It is interesting to note that despite screening participants for 'being at risk of clinical ADHD', six (33%) DPs (DP2, DP3, DP7, DP9, DP15 & DP18) revealed ADHD (A+B) z-scores equal to or higher than 1.65 SD below the mean of CPs (see Figure 4.1). This means that although they did not meet the criteria for clinical ADHD, they did exhibit more ADHD characteristics than CPs. There was a relatively great overlap of symptoms, even when the diagnosis was controlled for, especially with regard to the symptoms of DCD. Furthermore, 11 (66.7%) DPs (DP2, DP3, DP7, DP9, DP15 & DP18 and DP1, DP10, DP11, DP12 & DP14) exhibited DCD Total z-scores equal to or more than 1.65 SD below the mean of the CPs. Two DPs (DP8 & DP15) were possibly in the 'at risk' category for a clinical diagnosis of DCD (see Figure 4.1). As is apparent from Figure 4.1, all six participants who had composite scores 1.65 SD below the mean of controls on ADHD were also impaired on DCD. The issue of the comorbidity of ADHD and DCD with dyslexia is an important one because it may be a potential confound in the analyses. Confounds could arise from the distinctive characteristics of a given disorder (e.g., an inappropriate and persistent pattern of inattention and/or hyperactivity and impulsivity (ADHD) and impairment in the development of motor coordination (DCD) (American Psychiatric Association, 1994)), as well as the overlapping characteristics (e.g., speed of processing deficits (ADHD and dyslexia (Shanahan et al., 2006; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005)) and the tendency to lose place while reading (DCD and dyslexia) (Dyspraxia Foundation, 2012; Reid et al., 2007).

This is the reason behind using analysis of covariance with ADHD and DCD scores as covariates in the between-group analysis in Chapter 3 and the neuroimaging analyses in Chapters 5, 6 and 7.

In the study reported in this thesis, six DPs (33.3%) exhibited ADHD (A+B) z-scores equal to or more than 1.65 SD below the mean of CPs. This is a lower occurrence than in Kaplan et al.'s (1998) study, however, it has to be borne in mind that in the study reported here, no DPs who were at 'risk' of clinical ADHD were included and that manifestations of DCD in adulthood and childhood may differ. Difficulty in recruiting dyslexics without ADHD characteristics may be due to the shared genetic risk factors that underlie both of these disorders (see the section 'Variability due to comorbidity with other developmental disorders' in Chapter 8).

There is growing evidence that reading-impaired individuals exhibit difficulties in motor control (Denckla, 1985; Fawcett & Nicholson, 1995; Haslum, 1989; Iversen et al., 2005; McPhillips & Sheehy, 2004; Miles, 1993; Wolff et al., 1984). Kaplan et al. (1998) reported that 63% of their reading-disabled children also met the criteria for DCD. In the current study, however, only two DPs (11.1%) were identified as possibly being 'at risk' of DCD. In contrast, ten DPs (55.6%) exhibited DCD-type difficulties of a 'sub-clinical' nature. To date no genetic overlap has been reported for dyslexia and DCD (Pennington & Bishop, 2009).

Regarding performance of DPs on real word, irregular word, and pseudoword reading and spelling, as revealed by the composite and z-scores summarised in Figure 4.2 and Table 4.4, 11 DPs (DP2, DP3, DP4, DP8, DP9, DP12, DP13, DP14, DP15, DP16 & DP17), (61%) exhibited a deficit across all the measures; two cases (DP7 & DP10) (11%) showed a deficit on real word reading, pseudoword reading, and spelling; one case (DP11) (5.6%) on pseudoword reading and spelling; one case (DP18) (5.6%) on irregular word and pseudoword reading and spelling; one case (DP6) (5.6%) just on spelling; finally two cases (DP1 & DP5) (11%) show no deficits on these summary variables.

All, but two DPs (88.9%) were impaired on spelling and all DPs, except three DPs (83.3%) on the pseudoword reading composite. Furthermore, DPs exhibited the largest impairments on these two measures. These findings are in line with previous reports on spelling (Bruck, 1990; Hanley, 1997; Rack, 1997; Reid et al., 2007) and pseudoword reading in DPs (Bruck, 1990; Reid et al., 2007). Seventy two percent (13) DPs and 66.7% (12) DPs exhibited deficits on real word reading and irregular word reading, respectively. Two DPs (11.1%), including DP5 who had an FIQ score within the superior range, did not show any deficit on any literacy

measures, despite the fact that they had a diagnosis of dyslexia and explained in the interview that they had been suffering from literacy problems all their life. These indicate that either they were well compensated, at least as far as the behavioural measures were concerned, or that the commonly used measures of literacy used here are not sensitive enough to detect their deficit.

Phonological awareness and phonological fluency are usually both treated as indices of phonological processing (e.g., Ramus & Szenkovits, 2008). If both measures are combined, then sixteen DPs (88.9%) in the sample, tested in this thesis, exhibited this deficit. This is similar to the findings of Reid et al. (2007), where 86.7% of DPs had a phonological deficit, but different to Ramus et al.'s (2003) results, where 100% of DPs showed this impairment and to White et al.'s (2006) findings, where only 52.2% of DPs had this disorder (when defined as performance ≤ 1.65 below the mean of the CPs). One must be cautious, however, when making a comparison with the results reported by White et al. (2006), as they refer to child DPs.

Eight DPs exhibited a deficit on the orthography composite based on the task, which although involves phonological processing, it biases towards orthographic processing through the stimulus design. One cannot decide which item: *'rane'* or *'rain'* is a real English word, on the basis of phonological form because it is the same for both items. One needs to access their orthographic lexicon to make this decision.

Summing up, the multiple case analysis of DPs' performance on psychometric tests revealed marked heterogeneity among DPs and this is in line with the previous findings (e.g., Ramus, Rosen et al., 2003; Reid et al., 2007; White et al., 2006).

5 Group fMRI analysis

The vast majority of neuroimaging studies involve only group analyses, therefore this chapter focuses on the within and between-group analyses. For detailed hypotheses, see the Introduction.

5.1 fMRI pilot study

The fMRI design, procedure and data analyses were piloted in two stages with seven CPs. It should be noted here that, as stated in Chapter 2, the words and pseudowords were pre-tested in a behavioural pilot experiment with five DPs and four CPs (both groups did not take part in the fMRI experiment); also the stimulus display time and ISI were determined to provide a comfortable reading task for both DPs and CPs. As a result of the fMRI pilot study the following changes and adjustments were made: 1) the vigilance task (with the star) was added to the design; 2) no adjustment (usually made in the behavioural experiments and initially made here) was made to the pseudorandom intermixing of stimuli; 3) instead of a pen and pencil post-test, a computer post-test was devised to assess participants' vigilance in the MRI scanner; the results of the post-test were entered into the neuroimaging analysis as *d Prime*; 4) To avoid confounding the BOLD response due to the 'Star' stimulus (which appeared during ISI) and 'Button Press' they were included in the design matrix as regressors; 5) usually realignment is run in the first step of the data preprocessing and slice timing correction in the second step, however, because at the Aston MRI Research Centre, each volume is acquired in slices in an interleaved fashion, starting from the bottom slice, the order of the two first steps of data preprocessing was swapped; 6) structural MRI data was acquired in the saggital plane at first, however, the protocol was changed to the axial plane; this was done to facilitate coregistration of structural MRI and fMRI; 7) Brain activations were initially labelled using the Talairach Daemon database (Lancaster et al., 1997; Lancaster et al., 2000) based on Talairach Atlas (Talairach & Tournoux, 1988), however, due to considerable problems with this atlas (see for discussion, e.g., Eickhoff et al., 2005) subsequent labelling was done with the Anatomy Toolbox (AT) V.1.7. (Eickhoff et al., 2005). The areas not available in the Anatomy Toolbox were labelled with the Automated Anatomical Labelling software (Tzourio-Mazoyer et al., 2002). Finally, the number of areas tested within the framework of the PDT was increased, in the light of the literature review (see

Introduction & Appendix A, Table 10.1; for the areas originally tested within the framework of the PDT see Appendix G, Table 16.1).

5.2 Materials and Methods of the main fMRI study

5.2.1 Participants

For details on the participants and group results on psychometric tests see Chapter 3; Thirty eight participants took part in the study. Three control participants (CPs) were excluded from the analysis because of high motion parameters due to movement in the MRI scanner. One DP was excluded from the study because she did not provide her dyslexia diagnosis and two DPs (DP8 and DP15) were excluded from the group analyses (but not from the multiple case study analysis) because they were possibly at risk of clinical DCD (see Chapter 3). Thirty two participants (16 DPs and 16 CPs) were entered into the within and between group analyses reported below.

5.2.2 Stimuli

There were three conditions in the fMRI experiment. Condition 1 consisted of 100 real English words (high familiarity, high imageability, high concreteness; two-syllable, five to seven letters, with regular spelling, as much as possible, selected using the rules on the structure of English orthography provided by Venezky (1970), and selected from the MRC Psycholinguistic Database (Coltheart, 1981) (see Appendix C, Table 12.1). Condition 2 contained 100 pseudowords created by the substitution of consonant/s in the onset or middle of real English words (used in Condition 1). They were all pronounceable pseudowords - in line with English orthography and phonology (see Appendix C, Table 12.2). Condition 3 (the control condition) consisted of 100 fixation crosses.

5.2.3 fMRI task – rationale and design

As discussed in the Introduction, each of the theories: the PDT, MDT and CDT make unique predictions about which brain areas would exhibit abnormal activation during a reading task in DPs, as compared to CPs. Additionally, the CDT predicts that a phonological deficit (in phonological awareness and in reading) can be caused by a cerebellar impairment (Nicolson et al., 2001). Hence, underactivation in the phonological areas in the DPs (as compared to the CPs) can be consistent with the CDT (and the PDT). Furthermore, the MDT postulates that the magnocellular system is important in the acquisition of ‘accurate visual

representations of the written, orthographic, form of words' and that this is essential in order to grasp their structure at the phonemic level. Therefore a deficient magnocellular system could be the underlying cause of deficient phonological representations and therefore of a phonological deficit (Stein, 2003). Hence it is possible that underactivation in phonological areas in DPs during reading in this study may be consistent with the visual MDT (and the PDT). Note, however, that these additional predictions hold if one takes the perspective of the CDT and MDT, but not the PDT, because according to this theory the underlying cause of reading impairment in dyslexia are abnormalities in the phonological brain areas and not in the cerebellum and/or magnocellular system. Also, it is possible that a given area was impaired and involved in reading acquisition, but it is not involved in adult reading.

It is argued here that the reading task is particularly suited, because it: 1) investigates an impairment which is a defining deficit of dyslexia (British Dyslexia Association, 2007; International Dyslexia Association, 2009; World Federation of Neurology, 1968); 2) involves areas hypothesized by all three theories of dyslexia (see Introduction), hence allows for contrasting the predictions of these theories (but see caveats in the paragraph above); 3) tests the predictions of the main theories of dyslexia, in contrast to the previous research, on one sample of DPs.

Inspection of the fMRI data collected from DPs and CPs, while carrying out a word or pseudoword reading task would reveal whether there is support for the hypothesis that the neural correlates of reading deficit in dyslexia are consistent with the predictions of the PDT and/or the visual MDT and/or the CDT.

The fMRI experiment had an event-related design with stimuli from all three conditions randomly intermixed, to avoid potential strategic effects (as discussed in Chapter 2). Each stimulus was displayed for 1000 milliseconds, with an SOA of 4000 milliseconds and an ISI 3000 milliseconds. See Figure 5.1 for the stimulus sequence in the fMRI task.

The stimulus display time was derived from behavioural pilot experiments (run with five DPs and four CPs who did not take part in this study), and was found to be at a comfortable reading presentation time for both groups. A comfortable reading speed in both groups is crucial for the task because then the potential differences in fMRI activation between CPs and DPs are less likely to be due to quantitative than qualitative differences in reading.

Within the scanning environment, the participants viewed the stimuli (words/pseudowords/fixation cross) presented in black letters on a white

background, through a mirror mounted on the head coil, placed for viewing a projection screen at the back of the MRI scanner. The participants were asked to keep their gaze fixed where the '+' sign was shown on the screen (this appeared at a fixed position in the centre of the field of view). They were asked to silently read words and pseudowords, but ensuring that they did not make any movement with their lips or mouth.

To ensure that participants did their best, they were asked to read every item as carefully as possible, because there would be a post-test after the experiment. It was explained to the participants that they should not try to memorise the words because careful reading would be sufficient for the test. The reason the silent reading task was chosen was twofold. First, there is evidence that the cerebellum is involved in reading aloud (Price, 2000; Turkeltaub et al., 2002), which, to at least a certain extent, could be accounted for by articulatory movements when pronouncing words. Here the aim was to test any other potential involvement of the cerebellum in reading. Second, it was desirable to avoid participants processing their own voice because it causes activation within the temporal areas; (the exact temporal areas depend on the nature of a baseline, for instance the primary temporal areas were activated when subjects generated the sounds of seen words relative to articulating the same words silently (Price, Moore, & Frackowiak, 1996). To monitor participants' vigilance in the scanner, they were required to press a response button (with their left index finger) when a black star (displayed during ISI) became red. This change occurred on 30 (10%) trials. The participants were also asked to stay as still as possible throughout the whole fMRI session.

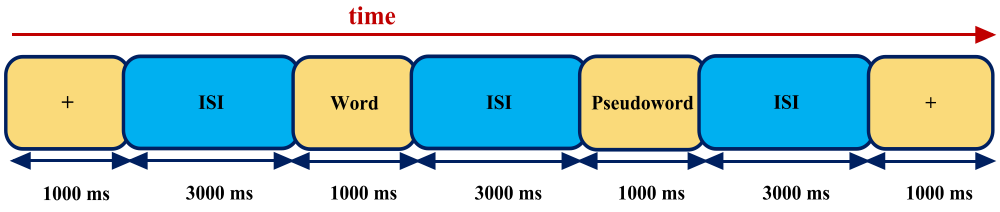

Figure 5.1 The stimulus sequence in the fMRI task. The stimuli (yellow boxes) for all conditions were randomized. They were displayed in the middle of the screen for 1000 ms. Participants had to silently read words and pseudowords and to keep their gaze fixed on the '+' . During the ISI a black star was presented, which on 10% of trials was red. The participants had to press the appropriate button when they saw the red star.

5.2.4 Procedure

The study was conducted with local ethics committee approval. All the participants gave written informed consent prior to taking part in the study. Before going into

the scanner, participants read instructions and completed a practice run of exactly the same task as they were going to do in the scanning environment, but with different stimuli, to avoid repetition effects. It was ensured that every participant understood and was able to do the task before they started the fMRI session.

Participants were positioned head first and supine in the scanner. Testing in the scanner involved first running seven dummy scans to obtain equilibrium, second - obtaining a structural high resolution MRI image, third running the reading experiment (approximately 20 minutes) and finally obtaining DTI data (not reported in this thesis). The whole MR scanning session took approximately 45 minutes.

Participants completed the post-test after they left the scanner. The post-test consisted of 64 items: 16 words which occurred in the fMRI experiment, 16 words which were not presented in the fMRI experiment, 16 pseudowords which occurred in the fMRI experiment and 16 pseudowords which were not presented during the fMRI experiment. Participants were asked to read every item and decide (by pressing an appropriate button) whether they saw a given item in the fMRI experiment. The words and pseudowords which were not present in the fMRI experiment had the same characteristics as the items presented in the experiment. The post-test was used to ensure that participants did their best at reading the stimuli. Their scores were summarised in a discriminability index - *d Prime* (see below) and entered as covariates into the 2nd level neuroimaging analysis.

Presentation of the stimuli for the practice, the experimental run in the scanner and the post-test was via Presentation software (version: 10.3: Neurobehavioural Systems). Both the practice and the post-test were run on a Dell Celeron laptop and the task in the scanner on a Dell Pentium 4 PC. The stimuli were displayed in the middle of the screen in black on a white background, one item per trial.

5.2.5 fMRI Data Acquisition

The fMRI data were acquired at the Aston University MRI Research Centre (located in Aston Day Hospital) using a 3T Trio Siemens Scanner equipped with echo planar imaging and a standard 8 channel head coil. Forty four (3 x 3 x 3 mm) slices, covering the whole brain, were acquired every 3 sec (*TR=3000 ms, TE=30, flip angle=90, FOVread=192, FOVphase=100*) for a total of 404 volumes.

5.2.6 fMRI Data Preprocessing and Analysis

5.2.6.1 Data preprocessing

SPM (Statistical Parametric Mapping) software was used to preprocess and analyse the fMRI data. It involved the following pre-processing steps: slice timing correction, realignment, coregistration, segmentation, normalisation and smoothing (Friston, 2002). (See Figure 5.2, please note that not all data preprocessing steps, described below, are presented in this figure).

5.2.6.1.1 Slice timing correction

The slice timing correction is needed due to differences in slice acquisition times. They differ because slices are acquired in a staggered order in echo-planar imaging. The correction makes the data on each slice match the same point in time, instead of 1/2 a TR removed from the next slice. It is possible if the data are considered as band-limited - having no significant information in the data at a frequency larger than the Nyquist (frequencies > 0.25 Hz) (The FIL Methods Group, 2006). Realignment, rather than slice timing correction, is usually the first step in the pre-processing of the data, however, because at the Aston MRI Research Centre each volume is acquired in slices in an interleaved fashion, starting from the bottom slice, it is advisable to run the slice timing correction in the first step, instead of realignment (John Ashburner, email communication, 4th of June, 2007).

5.2.6.1.2 Realignment

A serious confound, especially in fMRI studies, can arise from changes in signal intensity over time due to head motion. The 'realign' function removes these confounds from fMRI data. It realigns a time-series of images obtained from the same participant using a six parameter (three translations: x, y, z mm and three rotations: x, y, z degrees), rigid-body spatial transformation and a least squares approach (Friston, Frith, Frackowiak, & Turner, 1995). An image is chosen by the user (usually the first or the middle one, or the average of all scans), and all consecutive scans are realigned to it. In this study the middle slice was chosen as the reference image. Realignment parameters are saved for each participant for each session. At a later stage, they are incorporated into the design matrix as covariates, so one can account for confounds due to a participant's movement in the scanner (see the Results section).

5.2.6.1.3 Coregistration

This SPM function coregisters the functional and the structural data so as to maximise their mutual information. In SPM, coregistration is based on the work by Collignon, et al. (1995). However, in order to obtain a smoother cost function (a mathematical measure of the mismatch between two images, for which SPM uses the sum of the squared differences between the voxel intensity values), the original interpolation method (Collignon et al., 1995) was altered to obtain a cost function as smooth as possible. The images are smoothed a little to give faster convergence and a smaller probability of local maxima.

5.2.6.1.4 Segmentation

This SMP function segments the structural image according to tissue probability, using default maps, creating white and grey matter images and a bias-field corrected structural image. It can also be used to bias-correct and spatially normalise images within the same model (Ashburner & Friston, 2005). It uses a generative model, which involves three components: 1) a Gaussian mixture model, 2) a bias correction component and 3) a warping (non-linear registration) component.

5.2.6.1.5 Spatial normalisation

Spatial normalisation pools the data into the same anatomical space as if the acquired data had been caused by a canonical brain (identical for all participants). Because participants' brains vary slightly a spatial normalisation is then necessary to make the canonical brain assumption hold.

The spatial normalisation function in SPM, spatially normalises MRI images into a standard space defined by template images. There are two main uses for normalisation: 1) precise characterisation of functional anatomy and 2) averaging between participants (Ashburner & Friston, 1997). SPM provides the template images which correspond to the space defined by the International Consortium for Brain Mapping (ICBM), NIH P-20 project. They approximate the space as described in Talairach and Tournoux's co-planar stereotaxic atlas (Talairach & Tournoux, 1988). Normalisation algorisms work by minimising the sum of squares difference between a linear combination of one or more template images and the image which needs to be normalised. They involve three steps. Firstly, the optimum twelve parameter affine transformation is defined. Here the whole head (together with the scalp) is matched to the template. Secondly, the brains are matched together using weighting of the template voxels. This is done automatically by

using a Bayesian framework where the registration looks for the solution that maximises the a posteriori probability of it being correct (Ashburner, Neelin, Collins, Evans, & Friston, 1997). Thirdly, nonlinear deformations are estimated. Each of the deformation fields is characterised by 1176 parameters, which represent the coefficients of the deformations.

5.2.6.1.6 Smoothing

Generally this function limits the noise and effects caused by residual differences in gyral and functional anatomy when averaging across participants. It involves smoothing (or convolving) image volumes with a Gaussian kernel of a given width. More specifically, there are three reasons why data should be smoothed (Friston, 2002). Firstly, it makes the distribution of errors more normal and ensures a good basis for the validity of the inferential statistics. Secondly, within the SPM framework the inferences about regional effects are based on Gaussian random field theory which is based on a premise that the error terms are a plausible representation of a smooth Gaussian field. Therefore, voxels which are usually relatively large need to be smoothed. Finally, the data need to be smoothed when analysis requires inter-subject averaging, as is the case in this chapter, so the data were smoothed with an 8 mm smoothing Gaussian kernel.

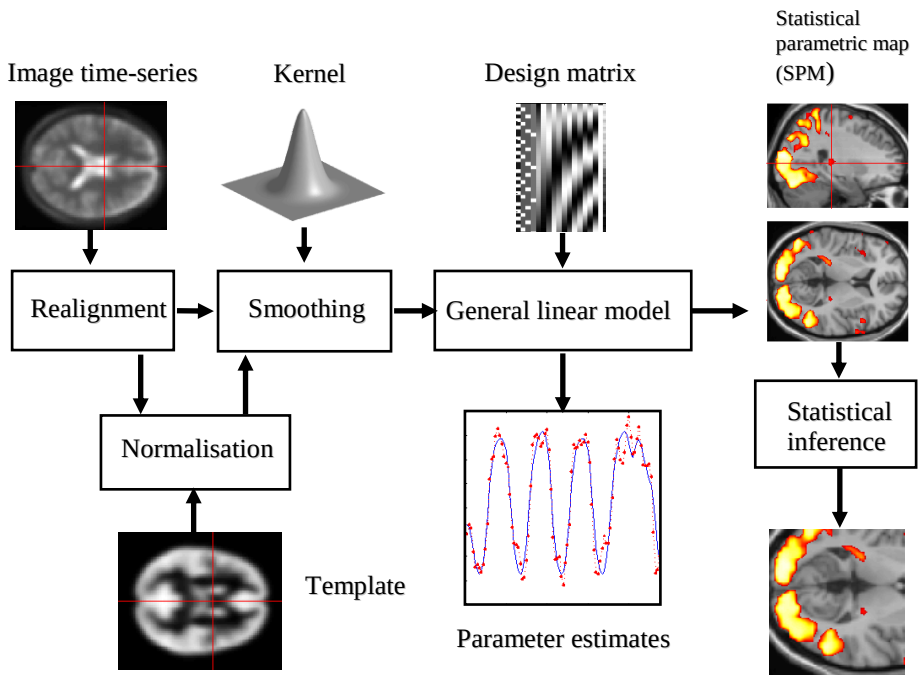

Figure 5.2 Data transformations and analysis in SPM. Realignment, normalisation and smoothing belong to the data pre-processing stage. The second stage consists of setting up a design matrix and parameter estimation using the general linear model (the fitted responses are in blue and the original data are in red). The third stage is characterised by creating a parametric map and making a statistical inference. Taken (& slightly modified) from Friston (2002).
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5.2.6.2 Data quality control

Following the recommendations by Poldrack et al. (2008), a data quality control procedure was employed. Head motion was assessed individually for each participant by examining the output from the Realignment procedure in the preprocessing stage. Three participants who had unusually large head movement (>5 mm for Translation and/or 5 degrees for Rotation) were excluded from the analysis. Despite spatial realignment, residual movement-related artefacts in the fMRI data can usually be found and concentrated near the edge of the brain (The FIL Methods Group, 2006). Therefore, the realignment parameters from this study were entered into the design matrix as multiple regressors, so that the residual participant's movement could be co-varied out, reducing the residual error, and improving statistics for the investigated effects.

As a further precaution fMRI data were also visually inspected for artefacts due to high signal loss. No participants were excluded on this criterion.

5.2.6.3 Data analysis

Broadly speaking, data analysis within SPM, involves setting up a design matrix and estimating model parameters (see Figure 5.2). A design matrix is essentially a set of explanatory variables (regressors) that try to explain the observed data in terms of a number of causes. Once the design matrix has been specified, SPM uses the general linear model to calculate the coefficients of the regressors. The regressors and corresponding parameters summarise the data in terms of their hypothesised cause/s. The model estimation (in SPM) involves SPM finding the parameter values (β1, β2 and β3) for the linear combination that best fits the data. The strength of this approach lies in the fact that one uses the same model for all the voxels (all the time-series) in the brain.

Analysis of data (in SPM) from multiple subjects proceeds in two stages, using models at two 'levels'. Therefore, two types of analysis were run: a first level (fixed effect) analysis and a second level-analysis (random effect analysis). The first level analysis uses 'first level' models which implement a within-subject analysis. There are as many first level models as there are subjects. This analysis results in estimated contrasts of parameters ('con images' – these are not statistical images, they are linear combinations of betas) for every participant for every contrast. In the random effect analysis the contrasts of parameters estimated in the first-level analysis for every individual participant are entered into an analysis. Therefore there is only one observation (contrast) for each participant and the error variance is calculated using the subject-to-subject variability of estimates from the first level. Such an analysis enables generalisations to be made from the findings to the population from which the subjects were sampled (Friston, 2002).

In the first level analysis, the Words (Condition 1) and the Pseudowords (Condition 2) were explicitly modelled in the design matrix. The Fixation Cross (Control Condition) was implicitly modelled in the design matrix (Glaser, 2006). To avoid confounding the BOLD response due to the 'Star' stimulus (which appeared during the ISI) and 'Button Press' they were included in the design matrix as regressors.

The shape of the canonical Haemodynamic Response Function (HRF) is in line with the haemodynamic response that is normally observed and this is the default in SPM. Further inclusion of the time and dispersion derivatives is necessary if one needs to account for variations in voxel-to-voxel and subject-to-subject responses. The time derivative allows for the variation in the peak response of plus or minus one second, whereas the dispersion derivative allows for the variation in the width

of the response by a similar amount (Friston, 2002) (Figure 2.5 in Chapter 2). As in the experiment reported in this thesis, there would be potentially more variability because the focus here is on DPs, who are usually characterised by marked heterogeneity with respect to behavioural and neuroimaging findings, canonical HRF, as well as, both time and dispersion derivatives were used as the basis functions in the model.

The following t-contrasts were probed in the 1st level analysis: Word > Fixation Cross and Pseudoword > Fixation Cross. The contrasts were the within participant contrasts. They resulted in con images which were used in the 2nd level analysis. Second level analysis involved comparison of DPs (treated as a group) and CPs (treated as a group). Data analysis involved within group comparisons and between group comparisons. There were the following within group comparisons, using a one-sample t-test: CPs - Word Effect, CPs - Pseudoword Effect, DPs - Word Effect and DPs - Pseudoword Effect. All four contrasts were relative to the control condition (fixation). The between group comparisons involved comparing CPs and DPs, using a two-sample t-test. Two contrasts were employed for the Word Effect (DPs<CPs and DPs>CPs) and two for the Pseudoword Effect (DPs<CPs, and DPs>CPs).

Although, as described in Chapter 3, the cases of DPs identified as 'at risk of clinical ADHD' were excluded from the study, a number of DPs exhibited elevated scores on ADHD and DCD measures, when compared to the CPs. None of these could be classified as being 'at risk' of the clinical form of these disorders however, except DP8 and DP15 who were possibly 'at risk' of clinical DCD. Therefore ADHD A+B and DCD Total were entered into the 2nd level analysis as covariates (Cyril Pernet, email communication, 1st of June 2008). Two DPs, possibly being at risk of clinical DCD were not included into the group analysis. Sixteen DPs and sixteen CPs were entered into the analysis.

To avoid confounds due to participants not paying attention to the stimuli, they were told that there would be a post-test after the scanning session. Their performance on the post-test was summarised in a discriminability index - *d Prime* which was calculated according to the following formula:

$$d\ Prime = Z\ FA - Z\ Hit,$$

Where *Z FA* stands for a Z score for false alarms (signal absent, response 'yes') and a *Z Hit* stands for a Z score for hits (signal present and response 'yes'). These

values were based on scores for both Words and Pseudowords to devise an overall measure of vigilance in the MRI scanner (see Appendix C, Table 12.3 for the *d Prime* score for individual participants); *d Prime* scores were entered into the 2nd level analysis as covariates.

5.2.6.4 Labelling of the activations

There is now growing evidence that different brain areas, such as BA44, BA45 are characterized by high inter-participant structural variability. This variability manifests in differences in: the sulcal pattern, shape and size of areas, as well as in the relationship of area borders to surrounding sulci (Amunts et al., 2004). See Figure 5.3 for examples of 3D reconstructions of 6 individual post-mortem brains with cytoarchitectonically mapped BA44 and BA45.

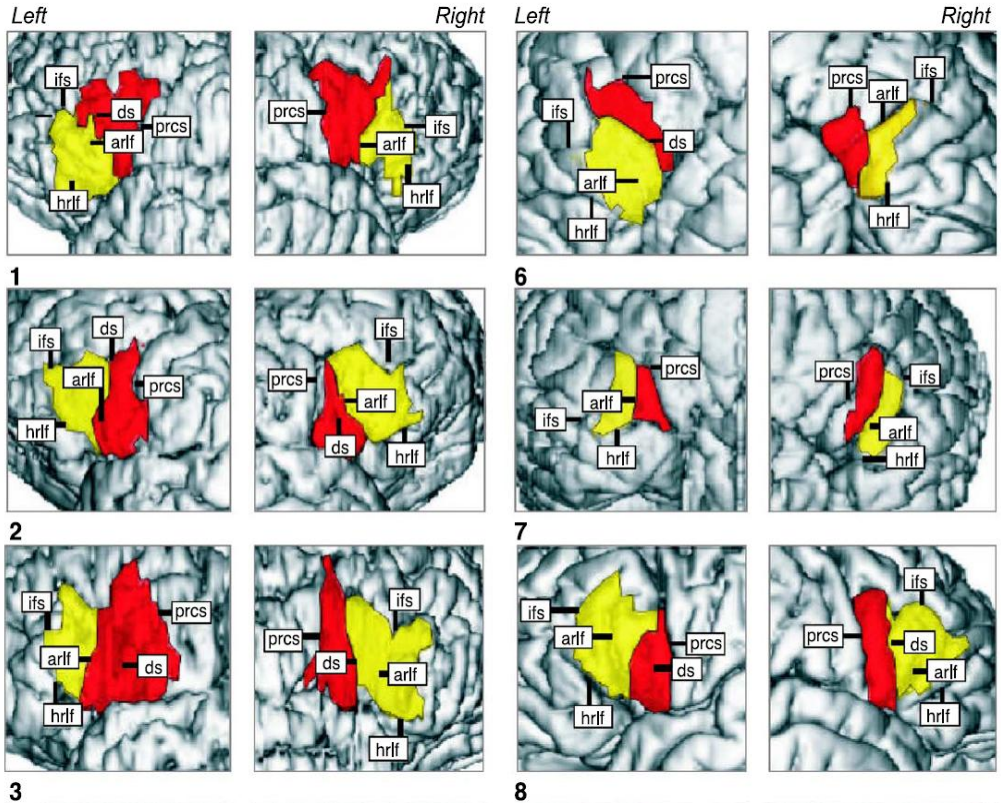


Figure 5.3 3D reconstructions of 6 individual postmortem brains (1, 2, 3, 6, 7 and 8). Red denotes BA44 and yellow denotes BA45. L and R hemispheres are presented after being cut into histological sections, stained for cell bodies, and given an observer-independent definition of cytoarchitectonic borders on serial histological sections; arlf = ascending branch of the lateral fissure; ds = diagonal sulcus; hrlf = horizontal branch of the lateral fissure; ifs = inferior frontal sulcus; prcs = precentral sulcus; Adapted from Amunts et al. (2004).

Bearing in mind this inter-participant variability of brain areas, labelling of activations in this study was done with the Anatomy Toolbox (AT) V. 1.7. AT enables the comparison of cytoarchitecture and function, providing a routine, standardized application of probabilistic cytoarchitectonic maps as an anatomical

reference for functional activations (Eickhoff et al., 2005). In contrast to classical cytoarchitectonic maps e.g., Brodmann's maps, probabilistic cytoarchitectonic maps provide stereotaxic information on the variability of cortical areas and the location in the MNI reference space (Amunts & Zilles, 2001; Zilles et al., 2002). Probabilistic cytoarchitectonic maps are based on the observer independent analysis of the cytoarchitecture in a sample of 10 human post-mortem brains, so 50% denotes that a given voxel was assigned to a given cytoarchitectonic area in 5 out of 10 brains. It should be noted, however, that some subsequent studies used more than 10 human post-mortem brains which influences probability calculations. See Figure 5.4 for steps involved in the generation of probabilistic cytoarchitectonic maps. Such maps have been published for various, but not all, brain regions. Because of the hypotheses put forward in the current study, the following cytoarchitectonic maps were of particular interest: Broca's region (Area 44/Area 45) (Amunts et al., 1999), the posterior insula (Areas Ig1, Ig2, Id1) (Kurth et al., 2009), the pre-motor cortex (Area 6) (Geyer, 2003), the inferior parietal lobule – (areas within BA40: PF, PFcm, PFm, PFop and PFt and areas within BA39: PGa and PGp) (Caspers et al., 2008), L Area TE3 in the lateral part of the superior temporal gyrus, perhaps homologous to BA22 (Wernicke's area) (Morosan, Schleicher, Amunts, & Zilles, 2005), the L hOC5 (V5/MT+) (Malikovic et al., 2007), V1/V2 (Amunts et al., 2000) and the cerebellum (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009). As the analyses presented in this thesis involved the whole brain, all probabilistic cytoarchitectonic maps currently included in the AT were also used. As no maps are available in AT for: the anterior insula, middle temporal gyrus, fusiform gyrus and the whole of BA22, these were labelled using Automated Anatomical Labelling software (Tzourio-Mazoyer et al., 2002) which relies on macroanatomically defined brain regions and therefore the results involving these areas can be less reliable.

The activations found in this study were labelled using the 'Local maxima labelling' option in AT. The anatomical location of a given maximum can be determined using AT by finding out: 1) whether it is assigned to a cytoarchitectonic area in the maximum probability map (MPM) and 2) what the probabilities of cytoarchitectonic areas at that position are. MPM is defined as a summary map which was computed by the AT from all currently available probabilistic maps. It defines the most likely cytoarchitectonic area at each voxel ('maximum probability map').

Figure 5.4 Steps involved in the generation of probabilistic cytoarchitectonic maps (taken from Eickhoff, Stephan et al. (2005)). Note that some subsequent studies used more than 10 human post-mortem brains.

It has to be borne in mind here that the resolution of the functional images (normally 2–4 mm voxel size after re-sampling during spatial normalization) is lower than the spatial resolution of the probabilistic maps (1 mm voxel size). Hence, it is possible that the directly corresponding voxel may underestimate or overestimate the anatomical probabilities. To increase the reliability of the anatomical labelling, the probability at the corresponding voxel and the probability range for the surrounding voxels are calculated by AT (Eickhoff et al., 2005).

In the group analysis, which involved DPs potentially characterised by considerable variability, activation in an area was considered as supporting a given hypothesis when the probability that a given voxel belonged to a given area was 10% or higher (Heim et al., 2010).

The cerebellar atlas (Diedrichsen et al., 2009) used in this study, via the interface of AT, differed from the one used in the meta-analysis by Stoodley and Schmahmann (2009). Therefore the local maxima in the cerebellum reported by Stoodley and Schmahmann (2009), were relabelled and for the same coordinates slightly different labels were used in this study (see Table 5.1 for details). It should be noted that in Diedrichsen et al.'s (2009) atlas, the vermis was not defined for the anterior cerebellar lobe (lobules I-V). This is because in the anterior lobe the vermis does not have a clear anatomical boundary with the cerebellar hemispheres (Schmahmann, Doyon, Toga, Petrides, & Evans, 2000). The term Crus I was used

to refer to Crus I hemispheric plus its corresponding vermal component - VIIaf and the term Crus II to refer to Crus II plus its vermal component - VIIat.

Table 5.1 Labels, obtained from the Anatomy Toolbox (Eickhoff et al., 2005) used in this study for coordinates provided by Stoodley and Schmahmann (2009)

MNI coordinates	Stoodley and Schmahmann's (2009) labels	Labels used in this study
36 -62 -28	R lobule VI	**R Lobule VIIa Crus I (Hem)** (probability: 66% (10-66%)) **R Lobule VI (Hem)** (probability: 34% (34-90%))
34 -82 -36	R Crus I	**R Lobule VIIa Crus I (Hem)** (probability: 89% (78-98%))
14 -86 -34	R Crus I/II	**R Lobule VIIa CrusII (Hem)** (probability: 60% (17-82%)) **R Lobule VIIa Crus I (Hem**) (probability: 38% (18-80%))
4 -82 -26	R lobule VIIAt	**R Lobule VI (vermis)** (probability: 88% (29-88%))
-42 -58 -26	L lobule VI	**L Lobule VI (Hem)** (probability: 32% (3-32%)) **L Lobule VIIa Crus I (Hem)** (probability: 44% (44-94%))

5.2.7 Underactivation, overactivation, fMRI, structural MRI and DTI

Usually underactivation is interpreted as a correlate of a deficit and it seems to be much more common than overactivation. Overactivation, as mentioned above, is less common in comparisons involving unimpaired samples. However, it is quite common in comparisons involving older and younger participants in studies of normal aging, in comparisons involving patients with brain damage and controls and in studies which contrast performance of DPs with CPs (see below).

Probably the most common interpretation of overactivation is compensation. For instance, in the neuroimaging literature on normal aging it has been hypothesised that the brain of an older person most likely has to work 'harder' (than that of a younger person) and overactivation allows older participants to better cope with a given cognitive task in a context of cognitive decline (Cabeza, 2002). Regarding brain damaged patients, overactivation, has been interpreted as an index of brain recovery following brain damage (Cao, Vikingstad, George, Johnson, & Welch, 1999). As described in the Introduction, overactivation in DPs has also been mostly interpreted as a compensatory mechanism (Brunswick et al., 1999; Shaywitz et al., 1998).

More recently, (Hoeft, Meyler et al., 2007) addressed the question of whether atypical activation (both underactivation and overactivation) is more related to the cause of dyslexia or the consequence of this disorder. DPs, while performing a visual rhyme judgment task (compared to a fixation cross and relative to age-matched controls) in an fMRI study, exhibited underactivation in: 1) the L fusiform/lingual gyri, 2) R fusiform/lingual gyri and 3) L inferior parietal lobule.

They also showed overactivation in two L frontal areas (the L inferior frontal gyrus and L middle frontal gyrus) and two sub-cortical regions (the L caudate and R thalamus). In contrast, DPs in comparison to the reading-matched controls, showed: 1) equal activation in all areas that had exhibited hyperactivation relative to age-matched controls and 2) underactivation in the L inferior parietal lobule and L fusiform/lingual gyri.

The subsequent voxel-based morphometry analysis revealed that in areas that showed atypical activation in DPs, only the L parietal lobule exhibited a reduction in grey matter volume in comparison to both control groups. On the basis of these results, the authors drew two conclusions. First, the areas of underactivation in dyslexia revealed functional deficits related to this disorder itself, independent of reading ability at the time of testing, and related to deficient brain morphology in dyslexia. Second, areas of overactivation in dyslexia revealed processes related to the level of current reading ability independent of dyslexia. In other words, according to the authors, underactivation is related to the cause of dyslexia, whereas overactivation is related to the consequence of this disorder. These results, if replicated with other samples of DPs, would further refine the interpretation of underactivation and overactivation in the neuroimaging literature on dyslexia.

It should be stressed that as functional underactivation was noted for DPs in the absence of structural abnormality in the L fusiform/lingual gyri (comparison with both control groups) and R fusiform/lingual gyri (comparison with age-matched CPs), the data suggest that the functional abnormality (as measured by BOLD) may arise in the absence of structural abnormality in grey matter volume (at least as measured in Hoeft, Meyler et al.'s (2007) study). However, as discussed above, this study also demonstrated underactivation in the L inferior parietal lobule in DPs and this area also exhibited a reduction in grey matter volume in DPs; both functional and structural comparisons were relative to age-matched and reading-matched CPs. The reduced grey matter volume in DPs in the L parieto-temporal area has also been reported in earlier studies (Brown et al., 2001; Eckert et al., 2005) (see also the section 'Neuroimaging studies investigating the cerebellum' in the Introduction for results on cerebellar areas in Brown et al.'s (2001) study). Furthermore, DTI studies (Deutsch et al., 2005; Klingberg et al., 2000) reported abnormalities in white matter microstructure in DPs in L parieto-temporal (see also Chapter 8 for further details).

Another two studies (Paulesu et al., 2001; Silani et al., 2005) investigated both functional and structural abnormalities in the same sample of DPs and CPs and

reported significant findings for different brain areas than reported by Hoeft et al. (2007). The results for Silani et al.'s (2005) study revealed that DPs exhibited increases and decreases in grey matter density compared to CPs in brain areas that showed underactivation during reading (Paulesu et al. 2001). Areas posterior to the L middle temporal gyrus were characterised by increases in grey matter density. Furthermore, the regions connecting the speech processing network, including Broca's area, were characterized by less dense white matter, suggesting that there was reduced connectivity within the temporo-parietal and frontal system involved in reading and phonological processing. Sumarising, there is not currently enough robust neuroimaging evidence to thoroughly assess the relationship between functional and structural abnormalities. Future studies need to systematically test functional and structural abnormalities in the same samples of DPs.

The PDT, CDT and MDT predict a deficit (which is causally related to dyslexia) in a given area/areas in a DP's brain (as specified in the Introduction). In contrast, the main theories are not concerned with compensatory mechanisms. Compensatory mechanisms arise when a system with a given deficit/s tries to master a given skill, e.g., reading. These compensatory mechanisms may be very variable and arise from many factors on many different levels of analysis. Therefore, it seems reasonable to interpret 'underactivation' in given area/areas (as specified in the Introduction) as a deficit and relate it as such to a given theory. On the other hand, given that most researchers have interpreted overactivation in DPs (as compared to CPs) as evidence of a compensatory mechanism and Hoeft's et al.'s (2007) findings, it seems reasonable not to use 'overactivation' to evaluate these theories. In this thesis overactivation is discussed in the homologous areas in the other hemisphere as well as in the areas hypothesised by a given theory to be underactivated. However, it is also possible that overactivation involves different areas. These regions, however, with some exceptions, are not discussed here.

Finally, it is important to mention some difficulties to do with interpreting BOLD (underactivation or overactivation) due to factors such as automatising a given task when one develops expertise, and so on. To a large extent this is addressed via a design with a carefully selected control group (matched to the DPs on: native language (English), years of education, age, gender, Performance IQ, Full Scale IQ and handedness) used in this thesis. Every contrast shown in this thesis is relative to the control group. The underlying assumption of such a design is that the control group is the golden standard and any significant differences in BOLD signal between the control group and the DPs' group are due to a deficit

(underactivation) and/or a compensatory mechanism (overactivation). Some differences in BOLD between the groups may originate from the developmental processes; however, as this study investigated adults at one point in time, it cannot explicitly address developmental issues. As discussed earlier, longitudinal studies starting with infants with familial risk of dyslexia are indispensable here (Goswami, 2003; Karmiloff-Smith, 1998; Ramus, 2004).

5.3 Results

The neuroimaging results for the within-group analyses are shown in Table 5.2 and Table 5.3 (for details see also Appendix C, Table 12.4 -12.7) and for the between-group analyses in Table 5.4 and Table 5.5 (for details see also Appendix C, Table 12.8 and Table 12.19). In Table 5.2 and Table 5.3 hyperactivations are shown relative to the control condition. In Table 5.4 and Table 5.5 hyperactivations are shown relative to the comparison group (either CPs, or DPs). The analyses reported here involve group comparisons, including the group with dyslexia characterised by considerable heterogeneity in terms of behavioural profiles (see Chapter 4) and fMRI profiles (see Chapter 6). Therefore activation in a given area was considered as supporting a given hypothesis when a voxel belonged to a cluster of 6 or more voxels (voxel threshold $k \geq 6$)(Pernet et al., 2009).

It needs to be underscored that because the results reported in this chapter are from the 2nd level (random effects) analysis they are robust. This is because, as discussed above, in this analysis the randomness of differential responses was accommodated by comparing the mean activation to the variability in activations from participant to participant (Friston, 2002). It should also be noted that the neuroimaging results are not confounded by ADHD or DCD. Firstly, because cases 'at risk' of the clinical form of these disorders were excluded from all between and within group comparisons (see Chapter 3 and Chapter 7) and, secondly, because ADHD and DCD scores were used as covariates in the neuroimaging analyses. Furthermore, the neuroimaging results are not confounded by the BOLD response due to the 'button press' and 'Star' stimulus because they were included in the design matrix as regressors. All results are reported at $p<0.001$, uncorrected for multiple comparisons, unless stated otherwise.

5.3.1 Within-group comparisons

5.3.1.1 CPs - Word Effect (relative to the control condition)

Inspection of Table 5.2 and Appendix C, Table 12.4 reveals that CPs (as a group) exhibited activation across the areas associated with the PDT (L Area 44, L Area 45 and L Area 6). Additionally, CPs exhibited activation in two RH areas: R Area 44 and R Area 6. Activation in the L insula (Ig1) and L IPC (PFcm (BA40) did not survive the correction for the number of voxels in a cluster ($k<6$). CPs also showed activation in areas associated with the MDT (the R Area 18 and R Area 17). Finally, the CPs exhibited activation in an area associated with the CDT (the R Lobule VI (Hem)).

It should be noted here that because these thresholds are arbitrary, they could turn out to be too conservative and could mask a real effect, especially where heterogeneous populations (with respect to fMRI and behavioural profiles) are involved. Therefore it is of value to lower them in some cases to ascertain whether there is an indication of an effect at a lower threshold.

When the statistical threshold was lowered to $p<0.05$, uncorrected for the multiple comparisons, CPs, as a group, exhibited activation in additional areas associated with the PDT (L (& R) TE 3, L (& R) middle temporal gyrus and L (& R) IPC (PF) (BA40). CPs, as a group, also showed activation in additional areas associated with the CDT (R Lobule VIIb (Hem) and R (& L) Lobule VIIa Crus I (Hem)).

5.3.1.2 CPs - Pseudoword Effect (relative to the control condition)

As a group, CPs exhibited activation across areas associated with the PDT (L (& R) Area 6, Area L 44 and L inferior frontal gyrus (p. triangularis)). CPs also showed activations in an area associated with the MDT (L Area 17). The activation in the area associated with the CDT (R Lobule VI (Hem) did not survive the correction for the number of voxels in a cluster ($k<6$). (See Table 5.2 and Appendix C, Table 12.5 for details).

When the statistical threshold was lowered to $p<0.05$, uncorrected for multiple comparisons, DPs, as a group, exhibited activation in the additional areas L TE 3, R Lobule VIIa Crus I (Hem) and R Lobule VIIb (Hem). Also, three additional areas associated with the PDT were activated in the RH: R Area 44, R Area 45 and R superior temporal gyrus (BA22).

5.3.1.3 DPs - Word Effect (relative to the control condition)

DPs exhibited activation across areas associated with the PDT (L Area 44, L Area 45 and L Area 6). DPs showed activations in areas associated with the MDT (L and R Area 18 and R Area 17). DPs did not exhibit any activation in the cerebellum (See Table 5.3 and Appendix C, Table 12.6 for details).

When the statistical threshold was lowered to $p<0.05$, uncorrected for multiple comparisons, DPs as a group, exhibited activation in additional areas associated with PDT: the L insula (Id1), L TE 3, L middle temporal gyrus (BA21) and L superior temporal gyrus (BA22). Activation was also observed in the additional areas, associated with the PDT, but in RH: R Area 44, R Area 45, R Area 6 and R Insula Lobe. Finally, there was activation in R Lobule VI (Hem), an area associated with the CDT.

5.3.1.4 DPs - Pseudoword Effect (relative to the control condition)

DPs, as a group, showed activation in areas associated with: the PDT (L Area 6, L Area 44, L Insula Lobe, L TE3 and L fusiform gyrus). DPs exhibited activation in areas associated with the MDT (L Area 17 and L Area 18). Finally, DPs exhibited activation in the area associated with the CDT (R Lobule VI (Hem)) (See Table 5.3 and Appendix C, Table 12.7 for details).

When the statistical threshold was lowered to $p<0.05$, uncorrected for the multiple comparisons, DPs, as a group, exhibited activation in additional areas associated with the PDT - L (& R) middle temporal gyrus. Other homologous areas in RH (associated with the PDT) were also activated (R Area 44, R Area 45 and R Area 6). Finally, R Lobule VIIb (Hem), an area associated with the CDT, was activated.

5.3.2 Between-group comparisons

5.3.2.1 Word Effect: DPs<CPs

DPs, as a group, exhibited significantly lower activation than CPs, as a group, in an area associated with the PDT (L IPC (PGp (BA39)). The activation in L IPC (PFm) (BA 40) did not survive the correction for the number of voxels in a cluster ($k<6$). DPs also showed significantly lower activation in one area associated with the MDT (L Area 17). The activation in L hOC5 (V5) did not survive the correction for the number of voxels in a cluster ($k<6$). No areas associated with the CDT were less activated by the DPs than by the CPs (See Table 5.4 and Appendix C, Table 12.8 for details).

5.3.2.2 Word Effect: DPs>CPs

DPs, as a group, exhibited significantly more activation than the CPs in one area, associated with the PDT - L Area 6 (See Table 5.4 and Appendix C, Table 12.8 for details).

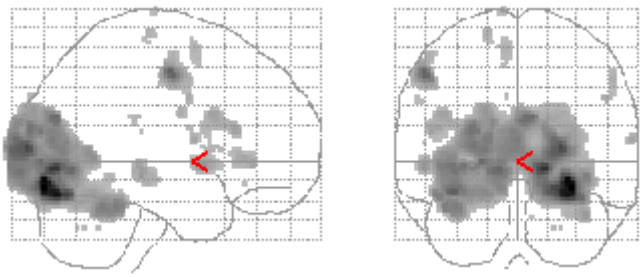
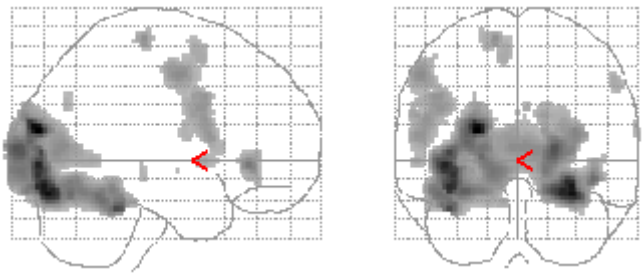
5.3.2.3 Pseudoword Effect: DPs<CPs

DPs, as a group, did not exhibit significantly lower activation than CPs in any areas associated with the PDT, MDT or CDT. The effect in R insula (Idl) did not survive the correction for the number of voxels in a cluster (k<6) (See Table 5.5 and Appendix C, Table 12.9 for details).

5.3.2.4 Pseudoword Effect: DPs>CPs

DPs, as a group, did not exhibit significantly higher activation than CPs in any areas associated with the PDT, MDT or CDT (See Table 5.5 and Appendix C, Table 12.19, for details).

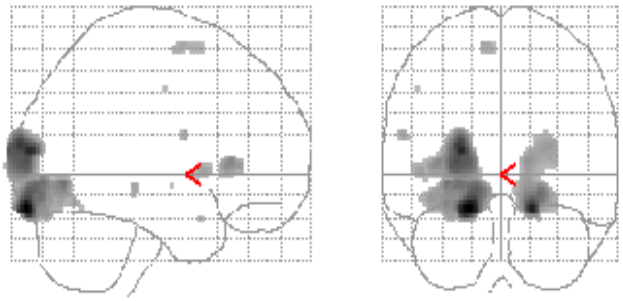
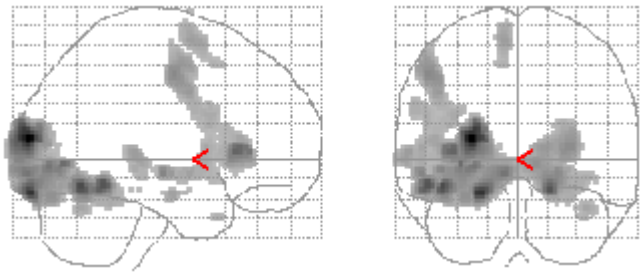
Table 5.2 Within-group comparisons (CPs)

Group	SPM maps	Areas Activated (p<0.001, uncorrected for multiple comparisons)
CPs (N=16): Word effect relative to fixation cross		**PDT:** Area L 44 (193) **Assigned to Area L 45 (193)** **Assigned to L Area 6 (211)** Corresponding areas in the RH: Area R 44 (33) **Assigned to R Area 6 (33)** **MDT:** **Assigned to R Area 18 (11156)** Area R 17 (11156) CDT: **Assigned to R Lobule VI (Hem) (122)**
CPs (N=16): Pseudo-word effect relative to fixation cross		**PDT:** **Assigned to L Area 6 (974)** **Assigned to Area L 44 (974)** L inferior frontal gyrus (p. triangularis) (BA45) (168) Corresponding areas in RH: **Assigned to R Area 6 (28)** **MDT:** **Assigned to L Area 17 (12)** **CDT:** No activation

Note. All activations shown are hyperactivations, relative to the control condition; This table represents only a summary of results. For instance, in some cases more than one peak of activation is found for a given area, but for brevity, only one peak is reported here, usually with the highest number of voxels (given in parenthesis);

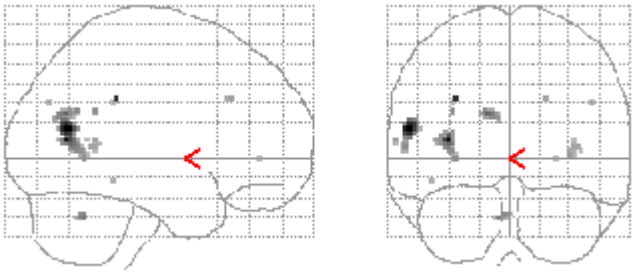
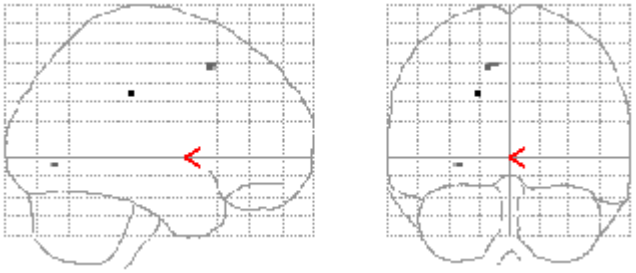
For a complete list of activated areas, please see Appendix C. In the column 'Areas Activated', **labels in bold** denote that a given activation was assigned by the Anatomy Toolbox (Eickhoff et al., 2005) to a labelled area; Non-bold labels denote that the probability of a given activation peak to be lying within a given area was 10% or more (See Appendix C for the exact values); All reported activations are at $p<0.001$, not corrected for multiple comparisons. See Appendix C, Note for Table 12.4 for Anatomy Toolbox labels.

Table 5.3 Within-group comparisons (DPs)

Group	SPM maps	Areas Activated (p<0.001, uncorrected for multiple comparisons)
DPs (N=16) Word effect relative to fixation cross		**PDT:** Area L 44 (34) **Assigned to Area L 6 (55)** Area L 45 (94) **MDT:** **Assigned to Area L 18 (1873)** Area R 18 (800) **Assigned to Area R 17 (800)** **CDT:** No activation
DPs (N=16) Pseudo-word effect relative to fixation cross		**PDT:** L fusiform gyrus (5498) L Insula Lobe (1756) L TE3 (1756) **Assigned to Area L 6 (198)** Area L 44 (43) **MDT:** Area L 17 (5498) **Assigned to Area L 18 (5498)** **CDT:** **Assigned to R Lobule VI (Hem) (47)**

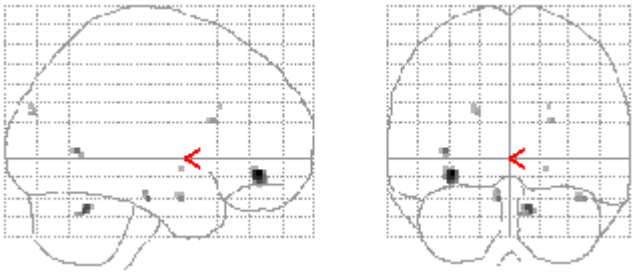
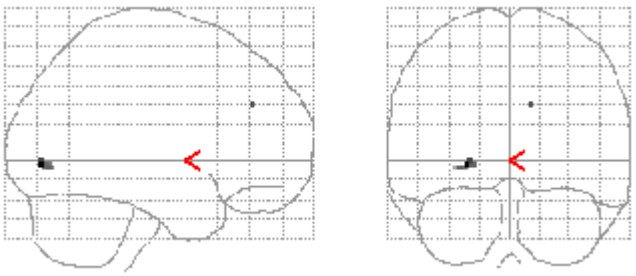
Note. Please see Note under Table 5.2.

Table 5.4 Between-group comparisons (Word Effect)

Group	SPM maps	Areas Activated (p<0.001, uncorrected for multiple comparisons)
Word effect DPs<CPs [DPs (N=16) CPs (N=16)]		**PDT:** L IPC (PGp) (BA39) (63) **MDT:** Area L 17 (51) **CDT:** Nothing significant
Word effect DPs>CPs [DPs (N=16) CPs (N=16)]		**PDT:** Area L 6 (6)

Note. Please see Note under Table 5.2.

Table 5.5 Between-group comparisons (Pseudoword Effect)

Group	SPM maps	Areas Activated (p<0.001, uncorrected for multiple comparisons)
Pseudo-word effect DPs<CPs [DPs (N=16) CPs (N=16)]		Nothing of interest
Pseudo-word effect DPs>CPs [DPs (N=16) CPs (N=16)]		Nothing of interest

Note. Please see Note under Table 5.2.

5.4 Discussion

It should be noted that some areas were considered to be activated when the statistical threshold was lowered (see Results section above). It may be important to consider these activations at the lower level of significance because there is much more variability in the group with dyslexia and therefore much more chance of false negatives at a more stringent level of significance. Also, it is worth emphasising that a less conservative significance level is more acceptable when the hypotheses are anatomically constrained, as in this thesis (see Introduction for details) than in a situation when they are anatomically opened (Friston, 2002). See also (Price & Mechelli, 2005).

5.4.1 Within group comparisons

The PDT, MDT and CDT make predictions about brain activation of DPs in relation to performance of CPs. However, before the between group comparisons are discussed, the within group results are discussed in the section below.

5.4.1.1 The control group

When silently reading words, relative to the control condition, CPs, as a group, activated a network of areas consisting of: anterior, dorsal and ventral systems associated with the PDT. Broadly speaking these results are in line with areas

associated with the PDT, as well as with neuroimaging studies on word reading (Fiez, Balota, Raichle, & Petersen, 1999; Hagoort et al., 1999; Howard et al., 1992; Jernigan et al., 1998; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Price, Moore et al., 1996; Price, Wise, Warburton et al., 1996). Four areas, listed in the Introduction as associated with the PDT – the L Insula, L supramarginal gyrus, the L angular gyrus (BA39) and L fusiform gyrus were not activated here. The activation in the first two did not survive the correction for the number of voxels in a cluster ($k<6$), therefore it is possible that a more robust effect would be noted with a bigger sample of CPs. Regarding, the L angular gyrus, it should be noted here that neuroimaging results on the involvement of this brain area in unimpaired reading in adults are inconsistent, with some authors reporting activation in the L angular gyrus (e.g., Horwitz et al., 1998) and some not (Fiez & Petersen, 1998). Furthermore, some studies (Ackermann, Wildgruber, & Grodd, 1997; Price, 2000) have reported an absence of activation in the left L angular gyrus during CPs' reading aloud. A similar picture emerges for the fusiform gyrus, with some studies reporting its involvement in normal adult reading (Fiez et al., 1999; Price, Moore et al., 1996) and others (Hagoort et al., 1999; Jernigan et al., 1998) not. There are many factors which differ between these studies and the study reported here: such as stimulus duration, stimulus rate, control condition and neuroimaging technique (e.g., PET or fMRI). Any of these factors (and the first three in particular) or factor combinations could potentially have contributed to the observed differences. For instance, Price et al. (1996) reported that for word reading, activity (measured by PET) decreased with increasing duration in regions associated with word recognition, whereas in regions associated with early visual analysis, activity increased with both rate and duration.

Although, the primary and secondary visual R hemisphere areas were activated by the CPs, no activation was exhibited in the crucial area (R & L hOC5 (V5)) associated with the MDT. This finding is unexpected, given the hypotheses and the supporting evidence on the role of these areas in image stabilization and/or letter localization in reading (Cornelissen, Hansen, Hutton, Evangelinou, & Stein, 1998; Liederman et al., 2003) and rapid triggering of attention to salient exogenous stimuli, such as words (Laycock, Crewther, Fitzgerald, & Crewther, 2009). This result may be due to the fact that individual variation in extent and location of area hOC5, in the standard space, is considerable (Malikovic et al., 2007). Furthermore, it is possible that activation within these areas is more transient and cannot be easily observed with a relatively long stimulus presentation time. Also, the effect in this

area could have been weakened due to image stabilization, needed also in the control condition – fixation on a cross, however, the effect due to letter localization should not have been weakened and therefore should be detectible (see Chapter 2 for a discussion on the choice of the baseline chosen in this study).

Finally, the CPs exhibited significant activation in the areas associated with the CDT - the R (& L) Lobule VIIa Crus I (Hem), R Lobule VI (Hem) and R Lobule VIIb (Hem). The activation in CPs was lateralized to the RH, except for the Lobule VIIa Crus I (Hem), which was activated in both hemispheres. The lateralization found here is congruent with the classical association of the R cerebellum with language functions because of its reciprocal connections with the L cerebral cortex (Desmond & Fiez, 1998). Significant activation in R (& L) Lobule VIIa Crus I (Hem) and R Lobule VI (Hem) is in line with Stoodley and Schmahmann's (2009) and Fulbright et al.'s (1999) findings, whereas significant activation in the R Lobule VIIb (Hem) is consistent with Fulbright et al.'s (1999) neuroimaging findings and with Finch et al.'s (2002) cerebellar histological results.

It should be emphasized that at present it is not clear what the specific role of these lobules is in language processing and/or reading, however, some interesting possibilities have started to emerge. For instance, Callan, Kawato, Parsons and Turner (2007), on the basis of a literature review on the perception and production of speech, put forward a hypothesis that Lobule VI in the posterior cerebellum (a region which contains the somatotopic representation of the tongue and lips), may instantiate models of vocal tract articulation that simulate learned phonological/articulatory associations - auditory mappings utilized for speech. The R and L Lobule VI (Hem) were also found to be involved in working memory (Stoodley & Schmahmann, 2009). Frings et al. (2006) found activation in the cerebellar R lobule VI/Crus I as a measure of verb generation. The authors emphasised that cerebellar activation related to verb generation may be explained by linguistic functions of the cerebellum or by its involvement in inner speech. Furthermore, Salmi et al. (2009), in an experiment designed to increase working memory load, found activation in the R (& L) Lobule VIIa Crus I (Hem) and R Lobule VIIb. Extension of this research showed that using the Lobule VIIa Crus I (Hem) or Lobule VIIb as a seed region in separate probabilistic tractography analyses, revealed tracts that linked the anterior prefrontal cortices (approximately BA10, BA11, and BA46/47) and the superior parietal lobule with the cerebellum (Salmi et al., 2009). As BA46 (part of the dorso-lateral prefrontal cortex) and BA10 are involved in working memory processes (Leung, Gore, & Goldman-Rakic, 2002;

Pochon et al., 2002), tractography results on cerebellar lobules suggest the involvement of Lobule VIIa Crus I (Hem) or Lobule VIIb in working memory, which is crucial for reading (Jerman & Swanson, 2005). It should be noted here that the result for the R & L Lobule VIIa Crus I (Hem) is consistent with the Stoodley and Schmahmann (2009) results, where they reported the involvement of the R Lobule VIIa Crus I (Hem) (probability: 94% (range 52-94%) and L Lobule VIIa Crus I (Hem) (probability: 82% (45-96%) in working memory. The result for the R Lobule VIIb being involved in working memory was also confirmed in Stoodley and Schmahmann's (2009) results, but with a much smaller probability of 7% and range from 0 to 43%.

Focusing on CPs' performance on pseudoword reading, relative to the control condition, CPs activated bilaterally anterior areas associated with the PDT (L (& R) Area 44, L (& R) Area 45 and L (& R) Area 6), as well as the dorsal area associated with the PDT (L TE3 (& R superior temporal gyrus (BA22)). Broadly speaking, they are in line with earlier findings on pseudoword reading (e.g., Burton, Locasto, Krebs-Noble, & Gullapalli, 2005; Herbster, Mintun, Nebes, & Becker, 1997). They are also congruent with the areas associated with the PDT. However, similar to Words, no activation was noted in the L angular gyrus (BA39) and additionally there was no activation in the L insula. These findings are consistent with other studies (Burton et al., 2005; Herbster et al., 1997). Also, similar to the profile found for Words, no activation here was observed in the L fusiform gyrus. This finding is not consistent with Burton et al.'s (2005) findings, nor with Herbster et al.'s (1997) results, however, it is in line with findings by Shaywitz et al.(1998). As stated above, these differences may stem from many factors, such as: differences in stimulus duration, stimulus rate, control condition and neuroimaging technique, or a combination of these.

Although CPs exhibited activation in the primary visual area (L Area 17), no activation was found in the crucial area (L & R hOC5 (V5)) associated with the MDT. This is most likely for the reasons stated above. Finally, cerebellar activation for Pseudowords was exhibited in the R Lobule VIIb and R Lobule VIIa Crus I (Hem) – the lobules which were also activated by the CPs for Words. The effect in the R Lobule VI (Hem), associated with the CDT, did not survive the correction for the number of voxels in a cluster ($k<6$).

5.4.1.2 The group with dyslexia

The DPs, as a group, similar to the CPs, activated a network of areas associated with PDT word reading. These included the bilateral anterior areas: (L (& R) Area 44, L (& R) Area 45 and L (& R) Area 6), bilateral insula and L lateralised dorsal areas (L superior temporal gyrus (BA22) and L TE 3). No ventral areas were activated. Primary and secondary visual areas (L & R Area 18 and R Area 17) were also activated, but the crucial areas (R & L hOC5 (V5)), associated with the MDT, were not activated. Similar to the CPs, this may be due to the fact that individual variation, in the extent and location of area hOC5 in the standard space, is considerable (Malikovic et al., 2007). It may be that the effects here are more transient and hence not easily observable with a relatively long stimulus presentation time. Furthermore, the effect in hOC5 could have been weakened due to image stabilization, needed also in the control condition, but, the effect due to letter localization should not have been weakened and therefore should be detectible. Finally, regarding areas associated with the CDT, DPs exhibited activation only in the R Lobule VI (Hem) which is probably the most commonly reported cerebellar lobule in reading studies (e.g., Brunswick et al., 1999; Fulbright et al., 1999; Turkeltaub et al., 2002). This result suggests that DPs, as a group, in contrast to the CPs, engaged only one cerebellar region during reading, whereas CPs activated two more regions – the R Lobule VIIa Crus I (Hem) and R Lobule VIIb (Hem). This result is suggestive of a cerebellar deficit in DPs for Word reading, however, it only can be definitely characterized in a direct comparison of the two groups (see the between group comparison section below).

Pseudoword reading of DPs (as a group) relative to the control condition, activated a network consisting of the L insula, anterior, dorsal and ventral areas associated with the PDT, similar to the CPs. These included: the bilateral Area 44, Area 6, R Area 45, L TE3, the bilateral middle temporal gyrus and L fusiform gyrus. It is important to note here that, in contrast to the Word reading condition, ventral areas were activated, implying that they are not characterised by a 'developmental lesion', but are utilised differently by the processing of different stimuli. DPs also elicited activation in the primary and secondary visual areas (L Area 17 and L Area 18), however no activation was found in the crucial areas - R & L hOC5 (V5) associated with the MDT. This is most likely for the reasons stated above. Finally, pseudoword reading elicited activation in two areas. One area was the same as for Word reading – the R Lobule VI (Hem) – additionally, DPs showed activation in the R Lobule VIIb (Hem) – a lobule which was activated for both

Word and Pseudowords by the CPs. The activation of the R Lobule VIIb (Hem) shows that lack of this activation for Word reading was not due to a 'developmental lesion'.

5.4.2 Between group comparisons

5.4.2.1 Words

Focusing on the between-group comparisons for the Word reading, DPs, as a group, exhibited significantly lower activation than CPs, as a group, in the L IPC (PGp (BA39). The effect in the L IPC (PFm) (BA40) did not survive the correction for the number of voxels in a cluster (k<6). The finding for L BA39 lends support to the PDT. DPs also exhibited significantly less activation in the R middle temporal gyrus.

As described in the Introduction, the L angular gyrus and L supramarginal gyrus are part of the dorsal system which is involved in reading as it was first suggested by Dejerine (1891, 1892, cited in Shaywitz et al., 2001). Subsequent literature on acquired reading deficit describes lesions centered about the angular gyrus as an area considered to be crucial in cross-modal mapping of graphemes on to phonemes (e.g., Damasio & Damasio, 1983; Friedman, Ween, & Albert, 1993; Geschwind, 1965). Regarding the developmental dyslexia literature, the findings of significantly less activation in DPs in the L (& R) angular gyrus and L supramarginal gyrus reported here are in line with the findings reported by others (e.g., Rumsey et al., 1997; Salmelin et al., 1996; Shaywitz et al., 1998) and Shaywitz et al. (1998), respectively. Furthermore, support for the dysfunction of the angular gyrus in dyslexia comes from two studies on functional connectivity (Horwitz et al., 1998; Pugh, Mencl, Shaywitz et al., 2000) discussed in the Introduction.

DPs also showed significantly lower activation than CPs in the primary visual area (L Area 17). The effect in the L hOC5 (V5/MT) did not survive the correction for the number of voxels in a cluster (k<6). Perhaps this effect would have been more robust with a larger sample of DPs.

Although there was suggestive evidence in the within group analysis that DPs, as a group, exhibited a cerebellar deficit, no cerebellar areas associated with the CDT, as defined in the Introduction, were significantly less activated by DPs than CPs. This result does not provide support for the CDT. Regarding the majority of studies which compare DPs and CPs on a reading task, it should be noted here that the vast majority of these studies, do not report results on the cerebellum. There are

at least two reasons why this may the case. Firstly, the vast majority of studies do not examine activation in the cerebellum (e.g., Shaywitz et al., 1998). Such an outcome is most likely due to the fact that most studies on reading were done within the theoretical framework of the PDT which focuses on classical language areas and therefore not on the cerebellum. Second, the typical human brain is bigger than the field of view of most PET scanners in the axial dimension. This limitation results in either failure to fully image the cerebellum or exclusion of this entire area (Fiez & Raichle, 1997). A very small subset of PET and fMRI studies (e.g., Brunswick et al., 1999; Flowers, Maisog, Einbinder, Curran, Jones, Cappell, et al., as cited in Maisong et al., 2008) reported differences between DPs and CPs in cerebellar involvement in reading, but relied on pronouncing words, as compared with a baseline without verbal output. Therefore, although significant differences between DPs and CPs in the involvement of the cerebellum in reading aloud were shown, this outcome could be due to differences in articulatory movements and not to the higher level processing of language.

The result of no difference between DPs and CPs in cerebellar areas is not in line with the predictions made within the CDT. In contrast, this finding is in agreement with the results of a recent meta-analysis of functional neuroimaging studies of dyslexia (Maisog et al., 2008) which revealed that activation likelihood estimate (ALE) maps provided no support for cerebellar dysfunction in dyslexia, suggesting that there is considerable variability in the spatial location and/or reproducibility of cerebellar findings.

A number of studies have reported increased activation in the frontal areas in DPs in comparison with CPs (e.g., Brunswick et al., 1999; Shaywitz et al., 1998). Shaywitz et al. (2001) put forward a hypothesis that DPs try to compensate for their disrupted reading system by shifting to anterior areas. These areas are important for articulating words (e.g., Fiez & Petersen, 1998) and they may facilitate development of an awareness of word sound structure. This in turn will facilitate reading, although the process will be slower than if the occipito-temporal word identification system was well-functioning.

In the study reported in this thesis the L BA6 was the only area which was significantly more activated by the DPs than the CPs in word reading. This finding is consistent with Brunswick et al.'s (1999) findings, but not with Shaywitz et al.'s results (1998) which revealed overactivation in DPs as compared to CPs in L (& R) BA 44 and L (&R) BA 45.

5.4.2.2 Pseudowords

Moving on to the between group comparisons for the Pseudoword reading, DPs as a group, did not exhibit significantly higher activation than CPs, as a group, in any areas associated with the PDT, MDT or CDT. Furthermore, DPs, as a group, did not show significantly lower activation than CPs in any areas associated with the MDT, CDT or PDT (the effect in the R posterior insula (Idl) did not survive the correction for the number of voxels in a cluster ($k<6$). No significant difference between the groups on Pseudoword reading in this study is perhaps surprising because studies usually report significant differences in this type of condition (Georgiewa et al., 1999; Grünling et al., 2004; Horwitz et al., 1998; Pugh, Mencl, Shaywitz et al., 2000; Rumsey et al., 1997; Shaywitz et al., 1998). This may be because these studies managed to balance the experimental parameters and stimulus characteristics, so that the differences between the DPs and CPs were maximised. However, it shoud be underscored here that there are inconsistencies in the results. For instance, whereas Shaywitz et al. (1998) reported underactivation in DPs (as compared to CPs) in Wernicke's areas (BA22), Georgiewa et al. (1999) reported overactivation in this area in DPs. Furthermore, while some studies (Grünling et al., 2004; Shaywitz et al., 1998) reported overactivation in DPs in frontal areas, others (e.g., Georgiewa et al., 1999) reported underactivation in DPs in these areas. Finally, while Georgiewa et al. (1999) reported underactivation in DPs in the L thalamus, Rumsey et al. (1997) reported overactivation of this brain structure in DPs.

There are several possible explanations for why the current study did not find significant differences between DPs and CPs on Pseudoword reading. First, it is possible that the Pseudoword reading network of DPs investigated in this study, did not significantly differ from the network of CPs'; in other words, the Pseudoword reading networks of DPs and CPs were almost the same, or very similar. Second, it may be the case that there are differences between the two groups, however they are indistinguishable with the experimental parameters used in this study, particularly with a relatively long stimulus presentation time (1000 ms) (please see Section 2.4 in Chapter 2 for the rationale behind the choice of stimulus presentation time in the current study). Third, it is possible that DPs' Pseudoword reading systems are significantly different than the ones used by CPs, however there is also considerable variability in this respect between DPs and therefore no consistent effects are observable on the group level. Regarding the first point, it seems that an explanation in terms of very similar networks for Pseudoword reading in DPs and

CPs is unlikely given the fact that there were significant differences for Word reading networks between the groups and Pseudoword reading is usually considered more demanding for the reading system, especially for DPs. Moving on to the second point, it is possible that the relatively long stimulus presentation time contributed to a lack of differences between the groups on Pseudowords. This may be because the between group differences in Pseudoword reading occur earlier in the time course of stimulus processing and need to be investigated using fMRI with different parameters, or be investigated using a neuroimaging technique, characterised by higher temporal resolution, such as MEG, which taps into the underlying cortical neuronal events in real time (10-100 msec). However, it is not clear why it would not affect the differences on Word reading too. Although Brunswick et al. (1999) also presented stimuli for 1000 ms, they used PET, rather than fMRI and the differences between groups were reported for Words and Pseudowords collapsed together, so the results reported here for Pseudowords cannot easily be compared with the results reported in their study. Finally, the third point which emphasises that the existing differences between the groups in the Pseudoword reading system are masked in the between group comparisons, due to considerable variability in the Pseudoword reading systems in individual DPs, is the most likely explanation. This possibility is further explored in the next chapter. It needs to be underscored that the approach and results presented in Chapter 6 are of main interest because they present a novel approach to dyslexia neuroimaging research.

6 fMRI individual case analysis

As stated in the Introduction, the main goal of this thesis is to investigate the neural correlates of reading impairment in dyslexia as hypothesised by the main theories, by contrasting their predictions. This study takes a broader ROI approach than has been used previously, and a case study approach to investigate individual differences in DPs. For detailed hypotheses, see the Introduction. This chapter presents a novel approach in dyslexia neuroimaging - individual case analyses of fMRI data, as compared to the control group.

6.1 Materials and Methods

6.1.1 Participants

Please see Chapter 3 for the details of the participants.

6.1.2 Stimuli, fMRI task design, Procedure, fMRI Data Acquisition and Preprocessing

These were the same as in Chapter 5.

6.1.3 Data analysis

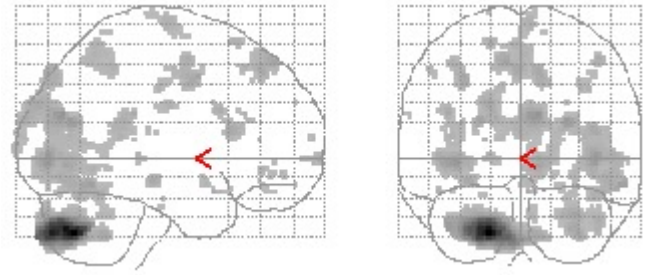
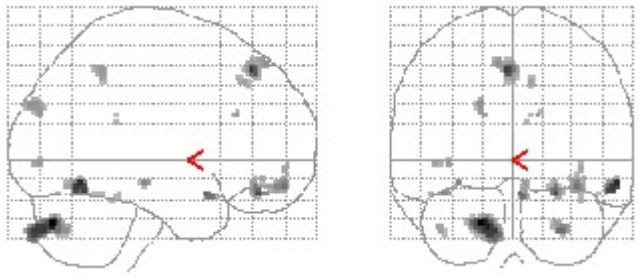
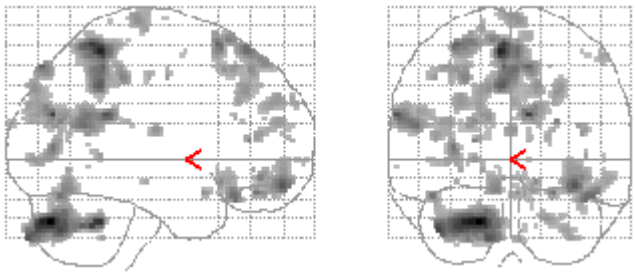
Con images obtained in 1st level analysis, described in Chapter 5, were entered into the 2nd level analysis (using SPM) which involved comparing every individual DP to the control group, using an unpaired t-test. The comparison involved the following contrasts: Word Effect: CPs>DP and DP>CPs and Pseudoword Effect: CPs>DP and DP>CPs. ADHD A+B, DCD Total and *d Prime* scores were entered into the 2nd level analysis as covariates (Cyril Pernet, email communication, 1st of June 2008), as described in Chapter 5.

The issue of the considerable variability between DPs does not arise in the analysis which involves a single DP. Therefore, more stringent criteria were used here than in Chapter 5 and activation in an area was considered as supporting a given hypothesis when a voxel belonged to a cluster of 20 or more voxels (Amunts et al., 2004) and there was at least a 20% probability that a given voxel belonged to a given area (Simon Eickhof, email communication, 9th of April 2010).

6.2 Results

The neuroimaging results for Word stimuli are shown in Table 6.1 and Table 6.2 (for details see also Appendix D) and for Pseudowords in Table 6.3 and Table 6.4 (see also Appendix E for details). The contrast CPs>DP show brain areas which were hypoactivated (underactivated) by a DP, as compared to the control group, during Word (or Pseudoword) reading, relative to a control condition. Hypoactivation in functional neuroimaging studies is usually assumed to reflect a functional disruption in a system (Shaywitz et al., 1998). In the context of the main theories of dyslexia, which assume deficits in particular brain areas, hypoactivation (underactivation) in these areas is interpreted as lending support for these theories. The contrast DP>CPs shows brain areas which were hyperactivated (overactivated) by a DP, as compared to the control group, during Word (or Pseudoword) reading, relative to fixating on a cross. Hyperactivation in the functional neuroimaging studies is usually interpreted as a correlate of a compensatory mechanism (Brunswick et al., 1999; Pugh, Mencl, Shaywitz et al., 2000; Shaywitz et al., 1998). Because the main theories of dyslexia are concerned with a deficit and not compensatory mechanisms, hyperactivation (overactivation) of the brain areas associated with these main theories is not interpreted as evidence of support for them.

Table 6.1 Word Effect CPs>DP

No	Word Effect (relative to fixation cross) CPs>DP (SPM map)	Word Effect CPs>DP Areas from ROI Activated
1		*PDT:* **L Area 44 (Broca's A.) (25)** L superior temporal gyrus (Wernicke's area) (45) L IPC (PFcm) (BA40) (45) **L Area 6 (98)** *MDT:* **R Area 17 (36)** **R Area 18 (211)** *L hOC5 (V5) (201)* *R hOC5 (V5) (2)* CDT: **R Lobule VIIa Crus I (Hem) (279)** **L Lobule VIIa Crus II (Hem) (2126)**
2		PDT: MDT: CDT: **R Lobule VIIa Crus I (Hem) (43)** **L LobuleVIIa Crus I (Hem) (225)** **L Lobule VIIa Crus II (Hem) (225)**
3		PDT: **L IPC (PFm) (BA40) (320)** **L IPC (PF) (BA40) (320)** **L IPC (PGp) (BA39) (29)** ***LTE3 (2)*** MDT: R Area 18 (99) CDT: **R Lobule VIIa Crus I (Hem) (59)** **R Lobule VI (Hem) (23)** **L Lobule VI (Hem) (58)** **L LobuleVIIa CrusI (Hem) (1436)**

Note. 'No' denotes the number of the participant with dyslexia (DP); Hyperactivations (DP>CPs) and hypoactivations (DP<CPs) are reported for L and R areas within the areas predicted by the main theories of dyslexia to be deficient; This table represents only a summary of results. For instance, in some cases more than one peak of activation is reported for a given area, for brevity only one peak is reported here, usually with the highest number of voxels (given in parenthesis); For a complete list of the activations please see Appendix D. For the labelling conventions and abbreviations, see Note under Table 12.4 in Appendix C. Labels in **bold** denote that a given activation was assigned by the Anatomy Toolbox (Eickhoff et al., 2005) to a labelled area; Non-bold denotes that the probability of a given activation peak to be lying within a given area was at least 20% or more (See Appendix D for the exact values); All reported activations are at $p<0.001$, not corrected for multiple comparisons; Naming conventions for brain areas given in columns DP>CPs and CPs>DP are as follows: first the hemisphere is given L= Left, R=Right; then the area name given by the Anatomy Toolbox (Eickhoff et al., 2005) is provided; where available this is followed by Brodmann's area name (e.g., BA44); the number in parentheses given on its own denotes the number of voxels in a given cluster; for the areas which are not included in the Anatomy Toolbox, a name assigned by the Automated Anatomical Labelling software (Tzourio-Mazoyer et al., 2002) is given.

Table 6.1 (continuation). Word Effect CPs>DP

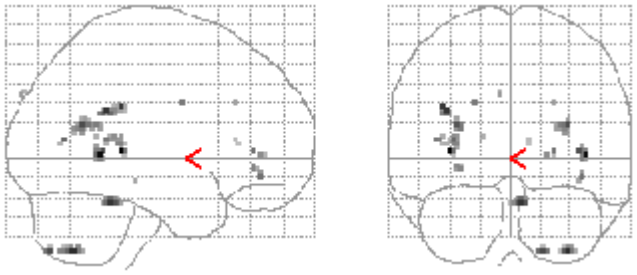
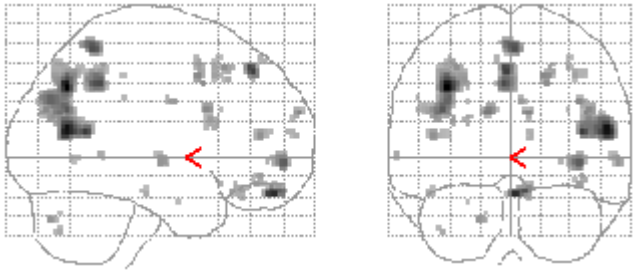
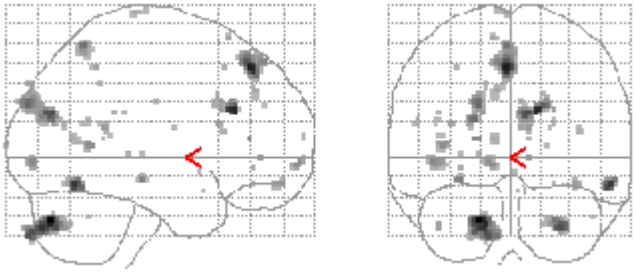
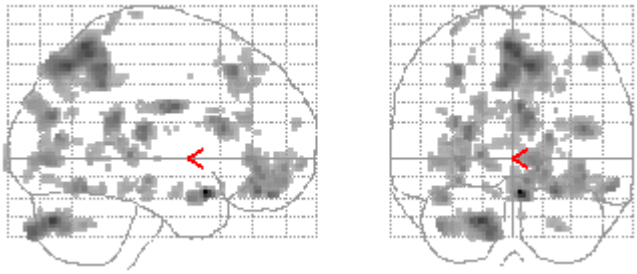
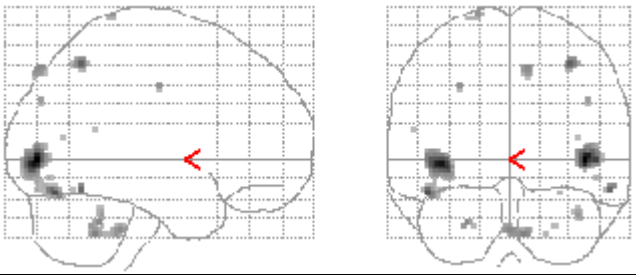
No	Word Effect (relative to fixation cross) CPs>DP (SPM map)	Word Effect CPs>DP Areas from ROI Activated
5		PDT: MDT: CDT: **R Lobule VIIb (Hem) (24)**
6		PDT: **L IPC (PGa) (BA39) (455)** **L IPC (PGp) (BA39) (455)** MDT: CDT:
7		PDT: MDT: R Area 18 (70) *R hOC5 (V5) (25)* CDT: **R Lobule VIIa Crus I (Hem) (74)** **L LobuleVIIa CrusI (Hem) (196)** **L LobuleVIIa CrusII (Hem) (196)**
9		PDT: L Insula Lobe (42) L superior temporal gyrus (Wernicke's area) (106) L fusiform gyrus **(106)** MDT: **R Area 17 (387)** **R Area 18 (387)** *R hOC5 (V5) (74)* CDT: **R Lobule VIIa Crus I (Hem) (29)** **L LobuleVIIa CrusI (Hem) (575)** **L LobuleVIIa CrusII (Hem) (575)**
10		PDT: MDT: *R hOC5 (V5) (1)* *L hOC5 (V5) (210)* CDT:
11		PDT: L Area 44 (61) L insula (61) MDT: **R Area 18 (23)** **L Area 18 (63)** L Area 17 (63) CDT: **R Lobule VIIa Crus I (Hem) (928)** **L Lobule VIIa Crus II (Hem) (360)**

Table 6.1 (continuation). Word Effect CPs>DP

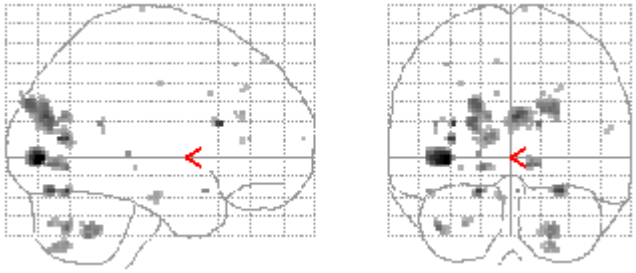
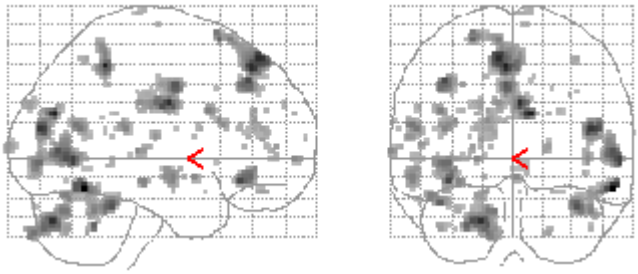
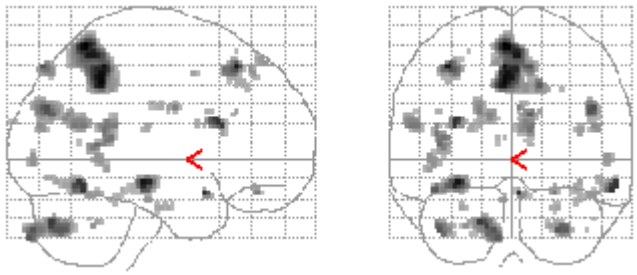
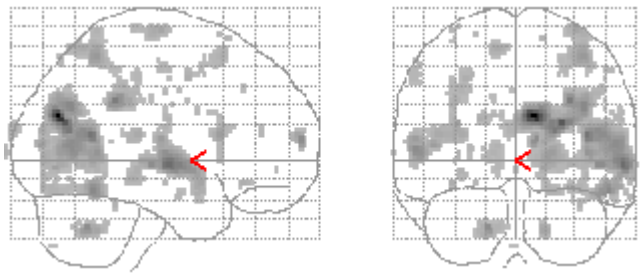
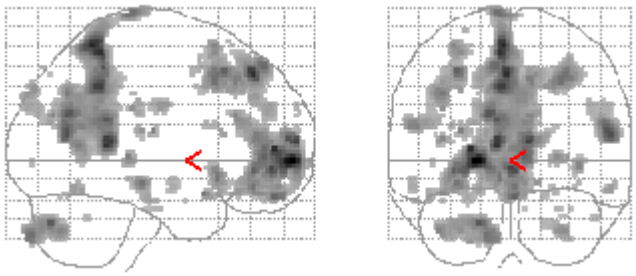
No	Word Effect (relative to fixation cross) CPs>DP (SPM map)	Word Effect CPs>DP Areas from ROI Activated
12		PDT: MDT: **L Area 17 (37)** **R Area 18 (97)** CDT: **R Lobule VIIb (Hem) (22)**
14		PDT: L Area 44 (38) L Area 6 (226) **L IPC (PGp) (BA39) (52)** L fusiform gyrus (36) ***LTE3 (17)*** L middle temporal gyrus (49) MDT: L Area 17 (91) **L Area 18 (91)** R Area 18 (91) *L hOC5 (V5) (85)* *R hOC5 (V5) (130)* CDT: L Lobule VI (Hem) (291) **L LobuleVIIa CrusI (Hem) (291)** **L LobuleVIIa CrusII (Hem) (291)**
15		PDT: L superior temporal gyrus (Wernicke's area) (61) L IPC (PGa) (BA39) (78) L middle temporal gyrus (BA21) (61) MDT: **R Area 18 (41)** *R hOC5 (V5) (41)* CDT: **R Lobule VIIa Crus I (Hem) (92)** **L LobuleVIIa CrusI (Hem) (170)** **L LobuleVIIa CrusII (Hem) (170)**
16		PDT: L insula (Ig1) (31) ***LTE3 (1)*** L middle temporal gyrus (341) MDT: **L Area 17 (22)** R Area 18 (2336) CDT:
18		PDT: L IPC (PFm) (BA40) (162) **L IPC (PGa) (BA 39) (125)** MDT: R Area 18 (27) *R hOC5 (V5)(12)* CDT: **R Lobule VIIa Crus I (Hem) (95)** **L LobuleVIIa CrusI (Hem) (490)** **L Lobule VIIa CrusII (Hem) (490)**

Table 6.1 (continuation). Word Effect CPs>DP

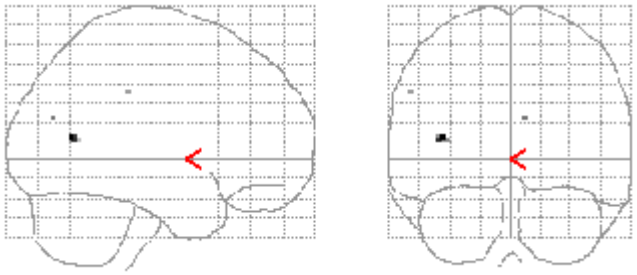
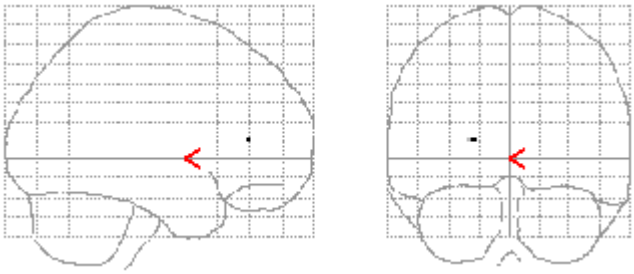
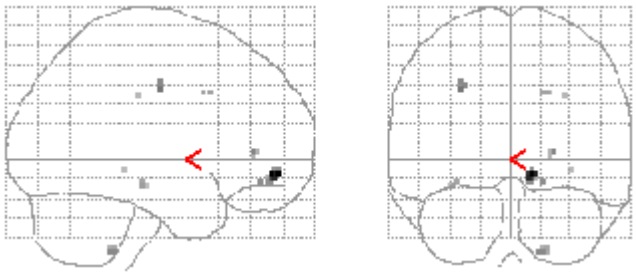
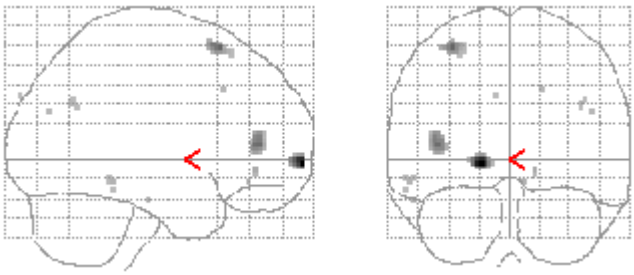
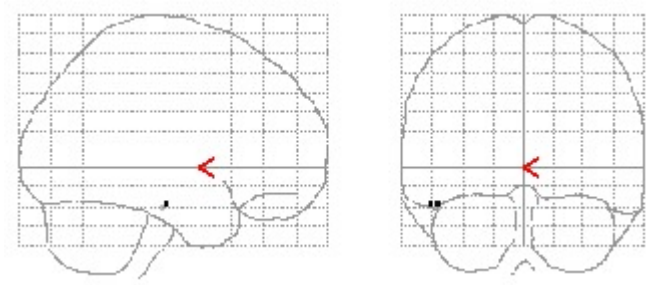
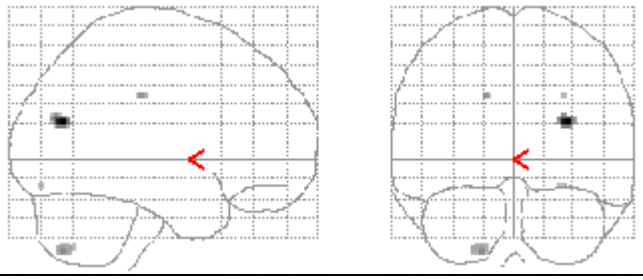
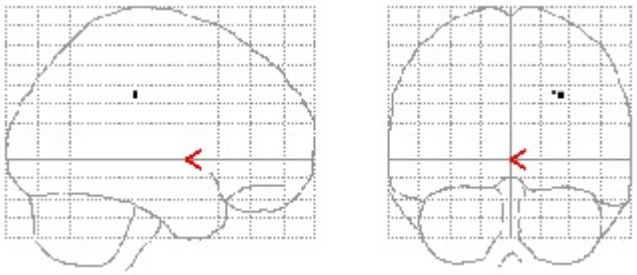
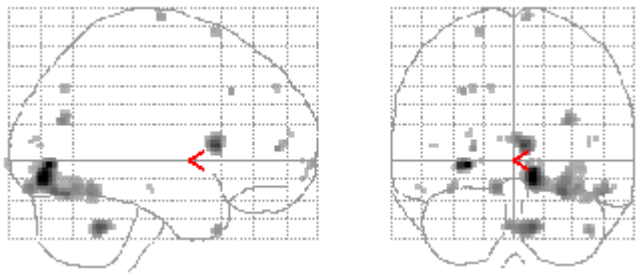
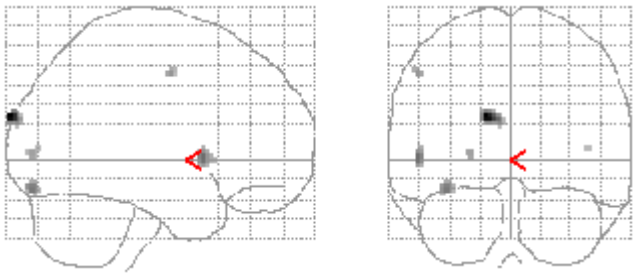
No	Word Effect (relative to fixation cross) CPs>DP (SPM map)	Word Effect CPs>DP Areas from ROI Activated
4		Nothing of interest
8		Nothing of interest R middle temporal gyrus (124)
13		Nothing of interest
17		Nothing of interest

Table 6.2 Word Effect DP>CPs

No	Word effect (relative to fixation cross) DP>CPs (SPM map)	Word effect DP>CPs Areas Activated
1		Nothing of interest
2		PDT: MDT: CDT: **L Lobule VIIb (Hem) (23)**
3		Nothing of interest
5		PDT: MDT: **L Area 17 (32)** **R Area 18 (522)** CDT:
6		PDT: L Area 44 (26) MDT: L Area 18 (57) CDT:

Note. See Note for Table 6.1.

Table 6.2 (continuation). Word Effect DP>CPs

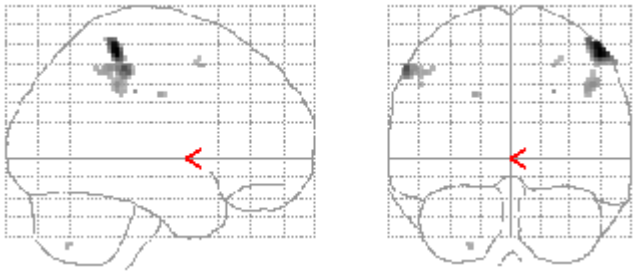
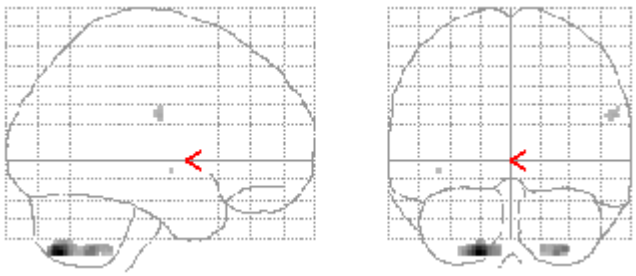
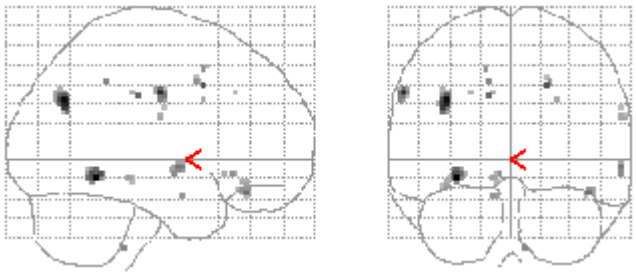
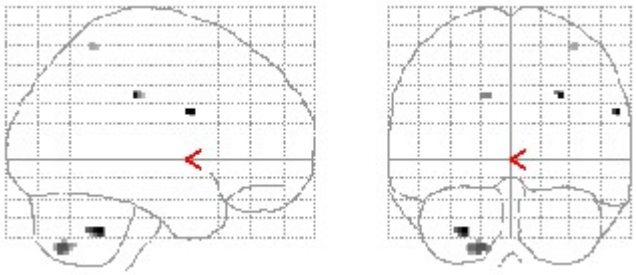
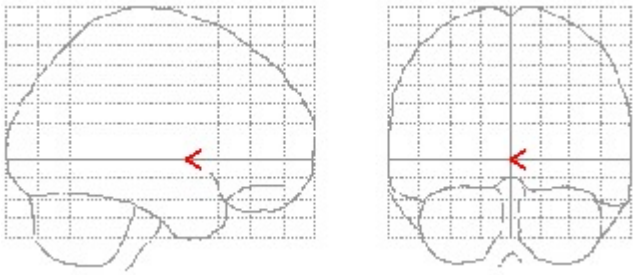
No	Word effect (relative to fixation cross) DP>CPs (SPM map)	Word effect DP>CPs Areas Activated
7		PDT: **L IPC (PF) (BA40) (50)** **R IPC (PFm) (BA40) (88)** MDT: CDT:
9		PDT: MDT: CDT: **L Lobule VIIb (Hem) (183)**
10		PDT: L IPC (PGa) (BA39) (37) L fusiform gyrus (34) ***RTE3 (10)*** MDT: CDT:
11		Nothing of interest
12		Nothing of interest

Table 6.2 (continuation). Word Effect DP>CPs

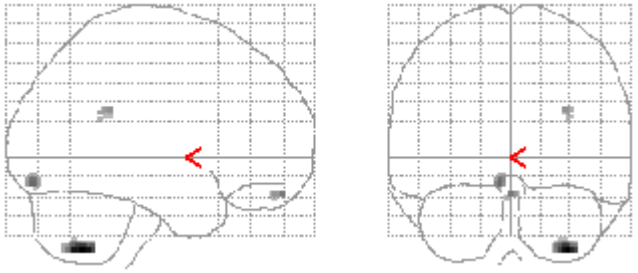
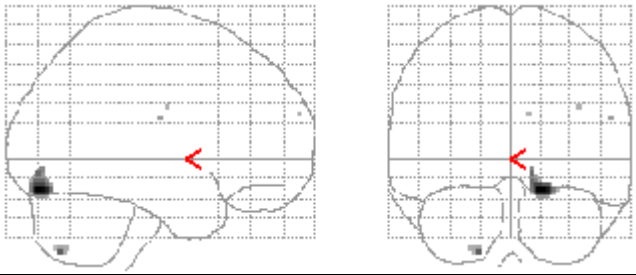
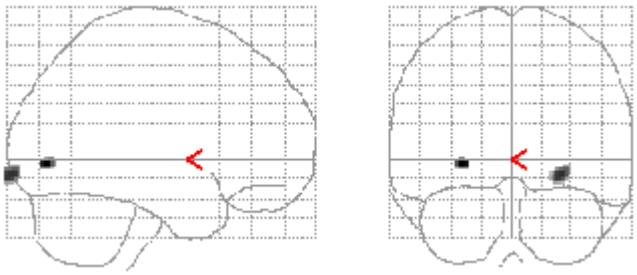
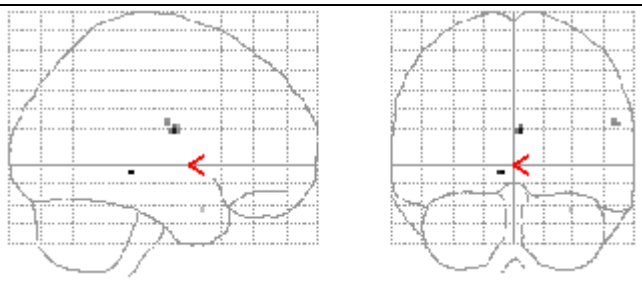
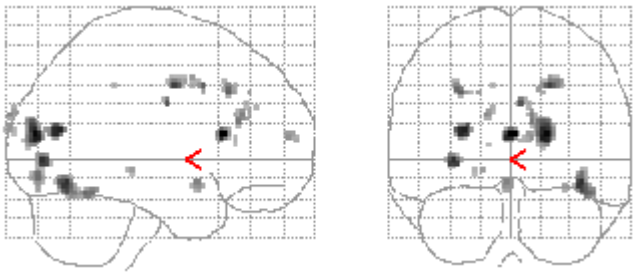
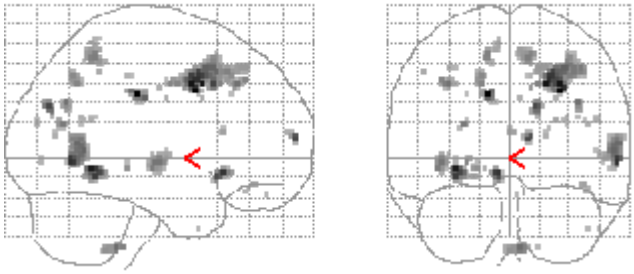
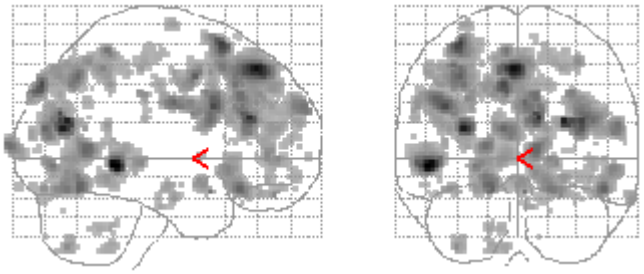
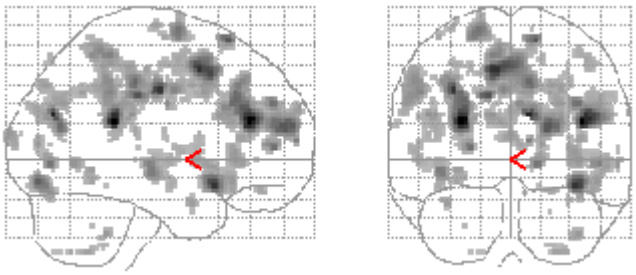
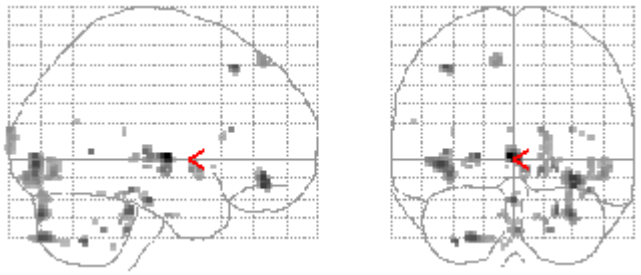
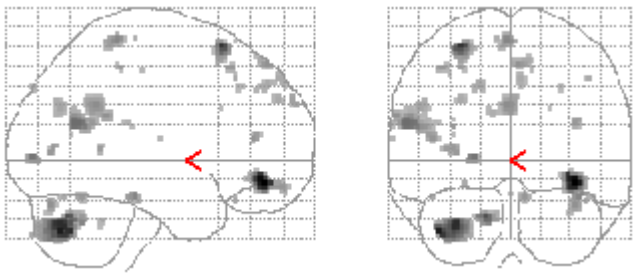
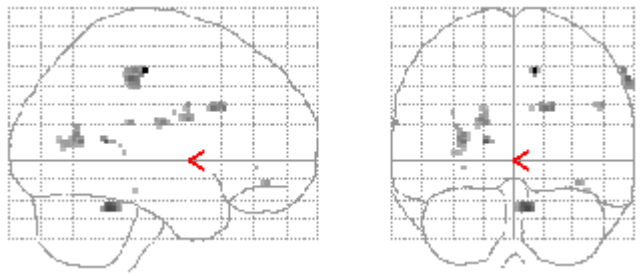
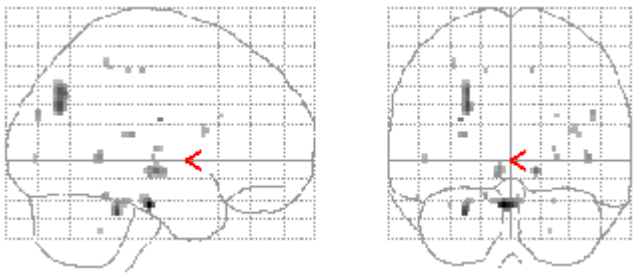
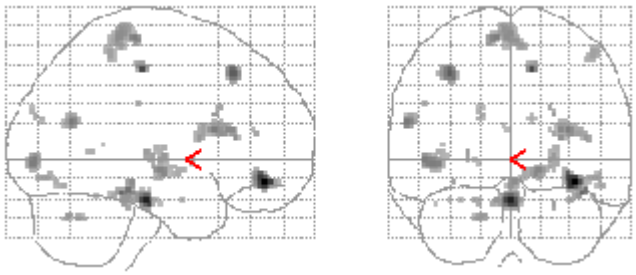
No	Word effect (relative to fixation cross) DP>CPs (SPM map)	Word effect DP>CPs Areas Activated
14		PDT: MDT: L Area 17 (26) CDT: R Lobule VIIb (Hem) (94)
15		PDT: MDT: **R Area 18 (105)** CDT:
16		PDT: MDT: **R Area 18 (40)** CDT:
18		Nothing of interest

Table 6.2 (continuation). Word Effect DP>CPs

No	Word effect (relative to fixation cross) DP>CPs (SPM map)	Word effect DP>CPs Areas Activated
4		PDT: R fusiform gyrus (97) MDT: CDT:
8		PDT: **L insula (Ig2) (47)** R middle temporal gyrus (124) MDT: CDT:
13		PDT: L Area 44 (751) R Area 44 (278) **R Area 45 (83)** L Area 45 (39) **L IPC (PGp) (BA39) (40)** **L IPC (PGa) (BA39) (304)** **R IPC (PGp) (BA39) (251)** L middle temporal gyrus (238) MDT: **R Area 17 (98)** **L Area 17 (350)** **L Area 18 (321)** R Area 18 (251) CDT: **L Lobule VIIa Crus II (Hem) (25)** **L Lobule VI (Hem) (321)** **R Lobule VI (Hem) (350)**
17		PDT: **L insula (Id1) (73)** **L Area 6 (125)** **(R Area 6 (45)** **L IPC (PFcm) (BA40) (76)** **L IPC (PFop) (BA40) (76)** **R IPC (PFcm) (BA40) (392)** **L IPC (PF) (BA40) (253)** ***LTE3 (5)*** MDT: **R Area 17 (66)** **L Area 17 (61)** **R Area 18 (66)** CDT:

Note. DP4, DP8, DP13 & DP17 exhibited significantly greater activation across many brain regions in comparison with CPs.

Table 6.3 Pseudoword Effect: CPs>DP

No	Pseudoword Effect (relative to fixation cross) CPs>DP (SPM map)	Pseudoword Effect CPs>DP Areas Activated
1		PDT: MDT: R hOC5 (V5) (47) **R Area 17 (27)** **R Area 18 (27)** CDT: **R Lobule VIIa Crus I (Hem) (92)** **L LobuleVIIa CrusII (Hem) (66)**
3		PDT: **L IPC (PGp) (BA39) (20)** L IPC (PGa) (BA39) (135) MDT: CDT: **L Lobule VI (Hem) (66)** **L LobuleVIIa CrusI (Hem) (332)**
5		PDT: MDT: L Area 18 (29) CDT:
6		Nothing of interest
9		PDT: L IPC (PGp) (BA39) (32) MDT: *R hOC5 (V5) (12)* CDT:

Note. For list of all the activations please see Appendix E; Labels in bold denote that a given activation was assigned by the Anatomy Toolbox (Eickhoff et al., 2005) to a labelled area; Non-bold denotes that the probability of a given activation peak to be lying within a given area was at least 20% or more (See Appendix E for the exact values); see also note under Table 6.1 above; Naming conventions are as in Table 6.1.

Table 6.3 (continuation). Pseudoword Effect: CPs>DP

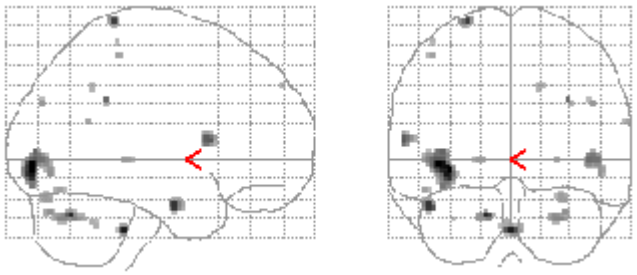
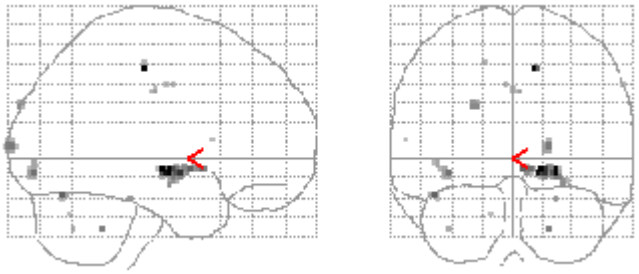
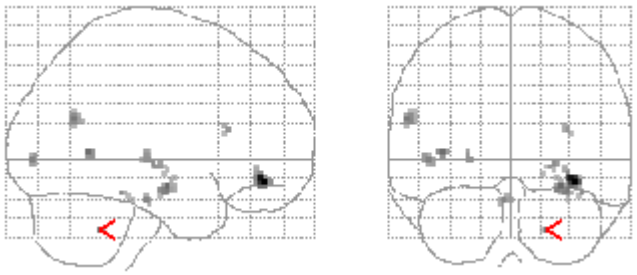
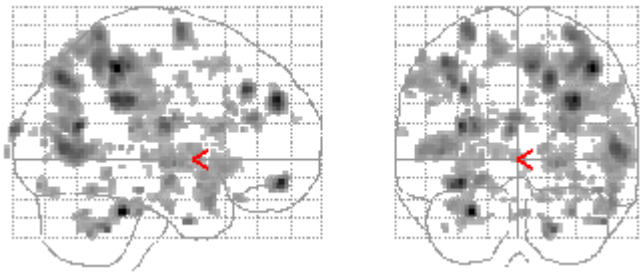
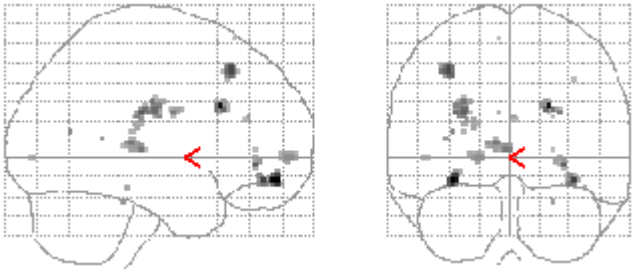
No	Pseudoword Effect (relative to fixation cross) CPs>DP (SPM map)	Pseudoword Effect CPs>DP Areas Activated
10		PDT: **L Area 44 (29)** L middle temporal gyrus (25) MDT: CDT: **R Lobule VIIa Crus I (Hem) (42)**
14		Nothing of interest
15		Nothing of interest
16		PDT: L insula (106) **L Area 6 (114)** L fusiform gyrus (139) L middle temporal gyrus (374) MDT: L hOC5 (V5) (374) *R hOC5 (V5) (307)* **L Area 17 (29)** CDT: **L Lobule VI (Hem) (139)**
18		PDT: L insula (51) MDT: CDT:

Table 6.3 (continuation). Pseudoword Effect: CPs>DP

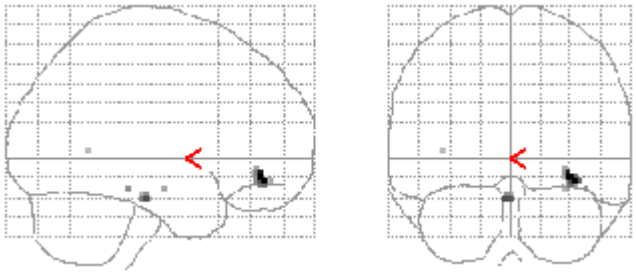
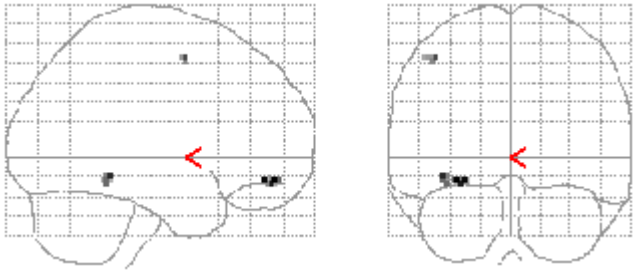
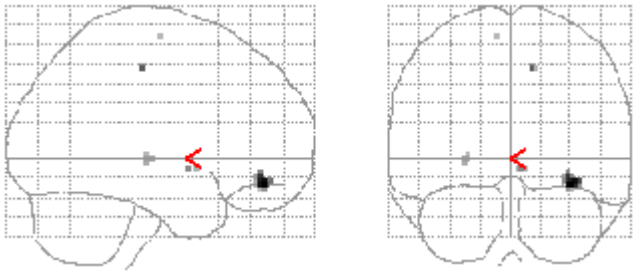
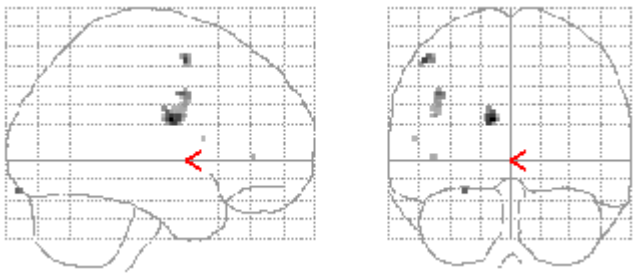
No	Pseudoword Effect (relative to fixation cross) CPs>DP (SPM map)	Pseudoword Effect CPs>DP Areas Activated
2		Nothing of interest
4		Nothing of interest
7		Nothing of interest
8		Nothing of interest

Table 6.3 (continuation). Pseudoword Effect: CPs>DP

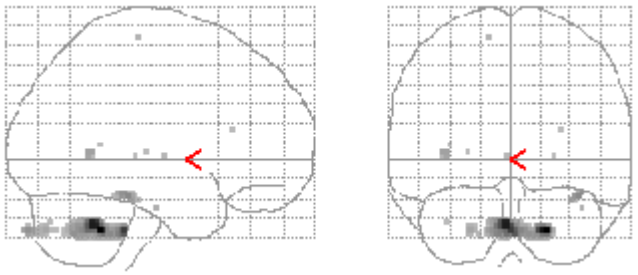
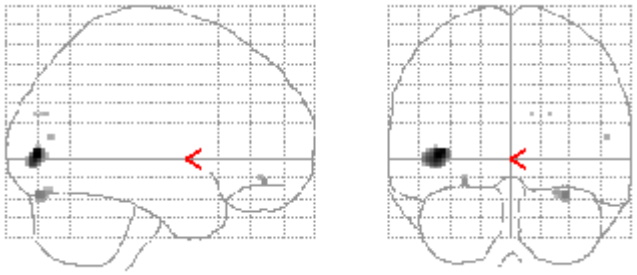
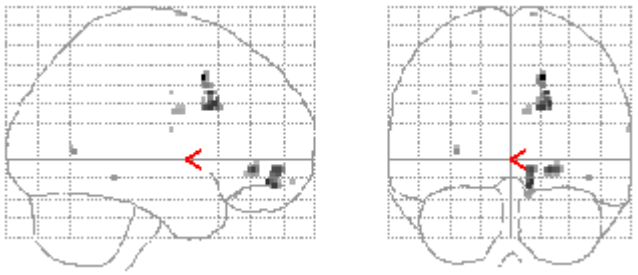
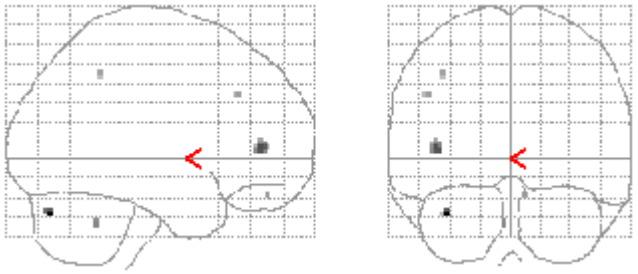
No	Pseudoword Effect (relative to fixation cross) CPs>DP (SPM map)	Pseudoword Effect CPs>DP Areas Activated
11		**L LobuleVIIa CrusII (Hem) (34)**
12		PDT: MDT: CDT: **R Lobule VIIa Crus I (Hem) (22)**
13		Nothing of interest
17		Nothing of interest

Table 6.4 Pseudoword Effect: DP>CPs

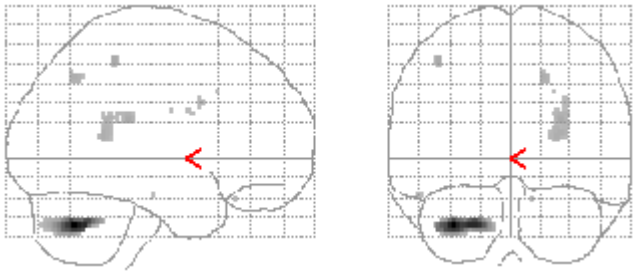
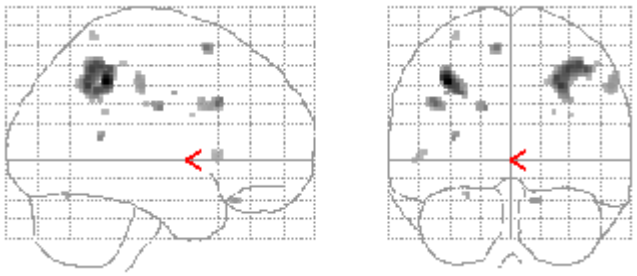
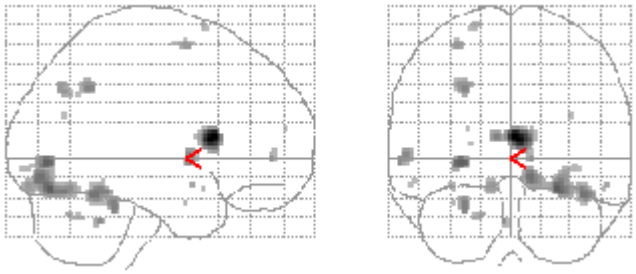
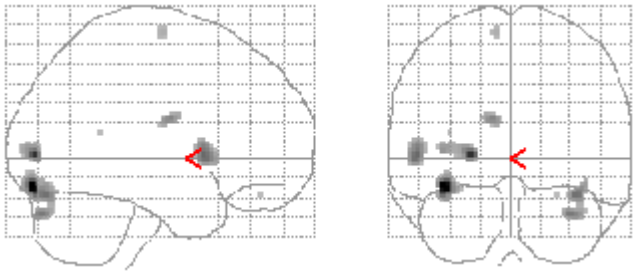
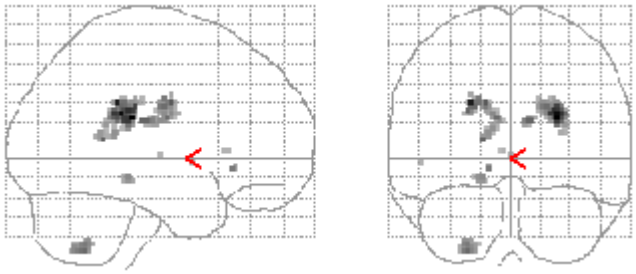
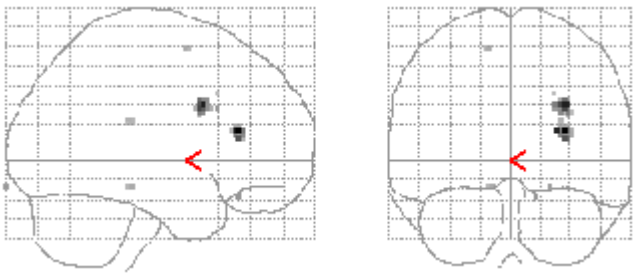
No	Pseudoword effect (relative to fixation cross) DP>CPs (SPM map)	Pseudoword effect DP>CPs Areas Activated
1		PDT: R insula (76) MDT: CDT: L Lobule VIIa Crus I (Hem) (346)
3		PDT: L Area 45 (44) MDT: CDT:
5		PDT: R fusiform gyrus (74) ***LTE3 (27)*** MDT: **L Area 17 (25)** **R Area 18 (283)** CDT: **L Lobule VI (Hem) (25)**
6		PDT: L Area 44 (102) MDT: CDT: **R Lobule VIIa Crus I (Hem) (95)**
9		PDT: R insula (137) MDT: CDT:
10		Nothing of interest

Table 6.4 (continuation). Pseudoword Effect: DP>CPs

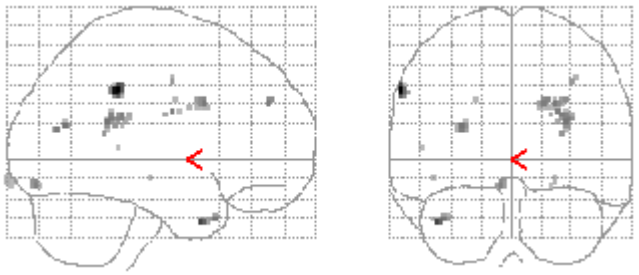
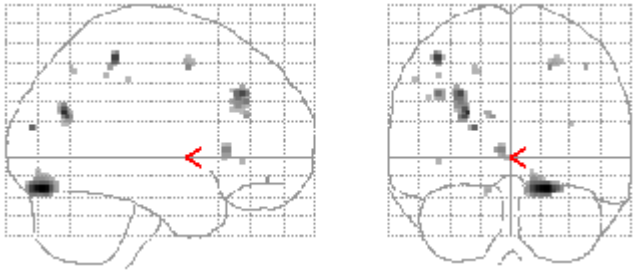
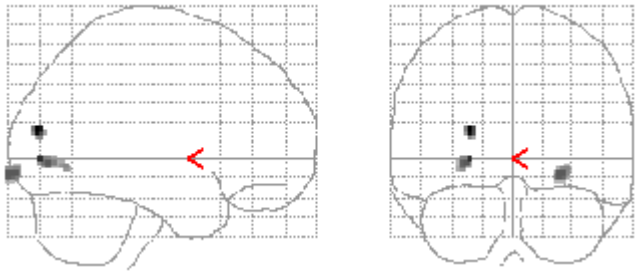
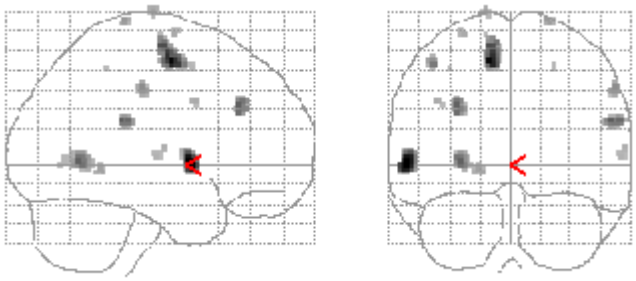
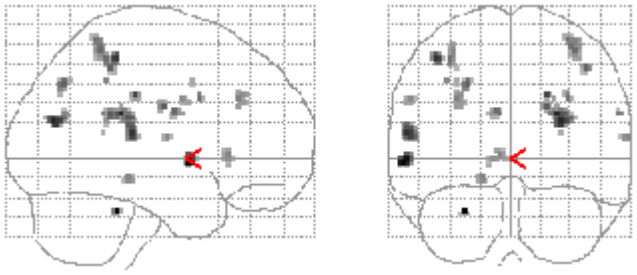
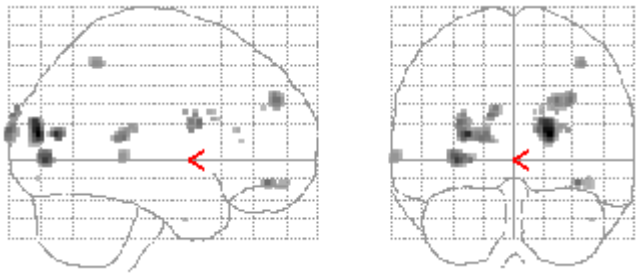
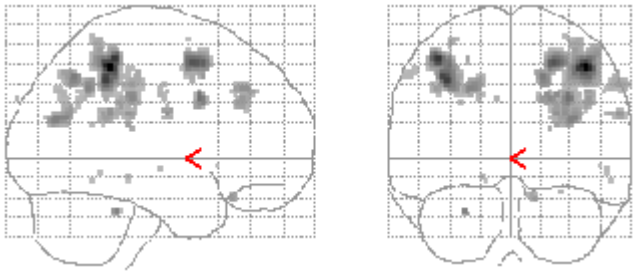
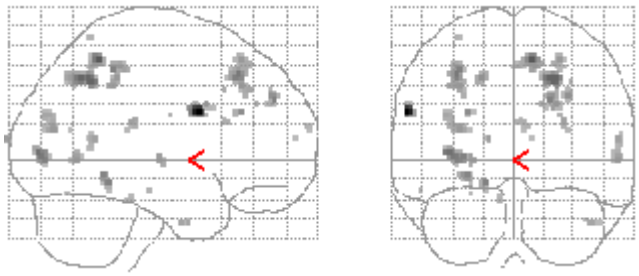
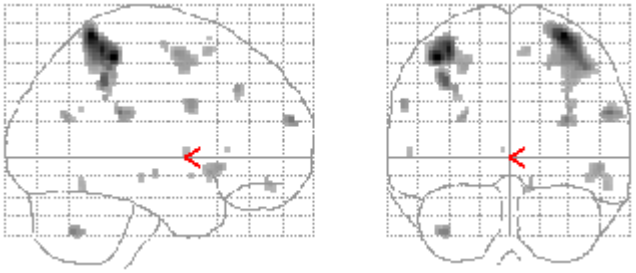
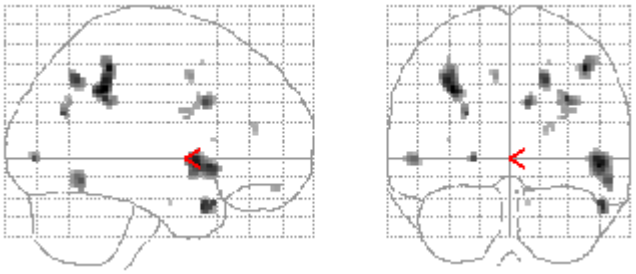
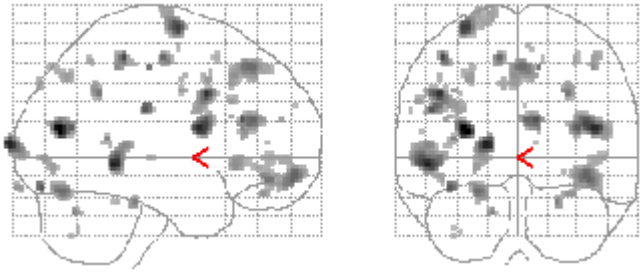
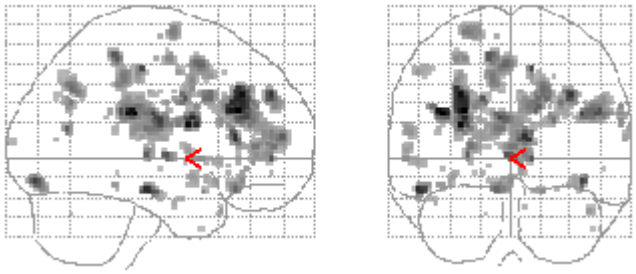
No	Pseudoword effect (relative to fixation cross) DP>CPs (SPM map)	Pseudoword effect DP>CPs Areas Activated
14		PDT: R insula (32) **L IPC (PF) (BA 40) (23)** MDT: CDT:
15		PDT: MDT: **R Area 18 (177)** CDT:
16		PDT: MDT: **R Area 18 (35)** CDT:
18		PDT: **L Area 6 (126)** **R IPC (PFcm) (BA 40) (43)** ***RTE3 (9)*** MDT: L Area 17 (56) CDT:

Table 6.4 (continuation). Pseudoword Effect: DP>CPs

No	Pseudoword effect (relative to fixation cross) DP>CPs (SPM map)	Pseudoword effect DP>CPs Areas Activated
2		PDT: ***LTE3 (26)*** R insula (67) MDT: CDT:
4		PDT: L insula (33) ***LTE3 (13)*** MDT: **L Area 18 (25)** *L hOC5 (V5) (59)* CDT:
7		PDT: **R IPC (PFcm) (BA40) (25)** **R IPC (PF) (BA40) (60)** **R IPC (PFt) (BA40) (60)** MDT: CDT:
8		PDT: **L Area 6 (26)** **L IPC (PGp) (BA39) (33)** MDT: *R hOC5 (V5)(12)* CDT:

Note. DP2, DP4, DP7, and DP8 exhibited significantly greater activation across many brain regions in comparison with the CPs.

Table 6.4 (continuation). Pseudoword Effect: DP>CPs

No	Pseudoword effect (relative to fixation cross) DP>CPs (SPM map)	Pseudoword effect DP>CPs Areas Activated
11		PDT: L Area 6 (86) **R IPC (PFcm) (BA40) (55)** MDT: CDT:
12		PDT: L Area 44 (26) R Area 44 (198) MDT: CDT:
13		PDT: **L Area 44 (100)** L Area 45 (62) R Area 45 (29) R insula (141) **L Area 6 (127)** L middle temporal gyrus (200) MDT: **L Area 18 (83)** CDT: **L Lobule VI (Hem) (59)**
17		PDT: L Area 44 (29) L insula (501) R insula (48) **L Area 6 (134)** **R IPC (PFcm) (BA40) (366)** ***RTE3 (11)*** L middle temporal gyrus (46) MDT: CDT:

Note. DP11, DP12, DP13, and DP17 exhibited significantly greater activation across many brain regions in comparison with the CPs.

6.2.1 Neuroimaging results for individual DPs

It is important to emphasise that the neuroimaging results, similar to the behavioural results, are not confounded by ADHD or DCD. Firstly, because cases at risk of the clinical form of these disorders were excluded from the study, except for DP8 and DP15, who were possibly at risk of clinical DCD (see Chapter 3) and secondly, because ADHD and DCD scores were used as covariates in the neuroimaging analyses. Furthermore, the neuroimaging results are not confounded by the BOLD response due to the 'button press' and 'Star' stimulus (used to monitor participants' vigilance in the scanner) because they were included in the design matrix as regressors.

An inspection of Tables 6.1, 6.2, 6.3 and 6.4, as well as Appendixes D and E reveals that individuals with dyslexia exhibited heterogeneous and complex patterns of hypoactivation (and hyperactivation) which involved the areas hypothesized by the three main current theories of dyslexia. The results for every individual DP are presented below in the context of the predictions made by the main theories. As the focus of this chapter is on the individual variability among DPs, activation of every DP is compared to activation of the CPs (treated as a group).

DP1 exhibited underactivation for Words (see Table 6.1, Table 6.2 & Appendix D, Table 13.1) of some areas predicted by: the PDT (L Area 44, L superior temporal gyrus (Wernicke's area), L Area 6 and L IPC (PFcm) (BA40) and the CDT (R Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)). DP1 showed hypoactivation for areas predicted by the MDT: R Area 17 and R Area 18; underactivation in R and L hOC5 was found only when the threshold for the probability that a given voxel belonged to a given area (probability threshold) was lowered to 10% (and in case of R hOC5 the threshold for the number of voxels in a cluster (voxel threshold) was lowered). Note that because these thresholds are arbitrary, they could turn out to be too conservative and could mask a real effect, therefore it is of value to lower them in some cases to ascertain whether there is an indication of an effect at a lower threshold. DP1 did not show any hyperactivation here in the areas associated with the main theories. For Pseudowords (see Table 6.3, Table 6.4 and Appendix E, Table 14.1), DP1 showed hypoactivation for areas predicted by the MDT (R hOC5, R Area 17 and R Area 18) and by the CDT (R Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)). Hyperactivation was

found in the R insula and L Lobule VIIa Crus I (Hem), areas associated with the PDT and CDT.

DP2 demonstrated underactivation for Words (see Table 6.1, 6.2 and Appendix D, Table 13.2) in the R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)), as predicted by the CDT and hyperactivation in L Lobule VIIb (Hem). For Pseudowords (see Table 6.3, Table 6.4 and Appendix E, Table 14.2), DP2 did not show any hypoactivation in the areas associated with the main theories. Hyperactivation was detected in the R insula and L TE3 (when the probability and voxel thresholds were lowered), areas associated with the PDT.

DP3 exhibited hypoactivations for Words (without any hyperactivations) (see Table 6.1, Table 6.2 and Appendix D, Table 13.3) across the areas predicted by the PDT (L IPC (PFm) (BA40), L IPC (PF) (BA40), L IPC (PGp) (BA39) and L TE3 (when the probability threshold and voxel threshold were lowered). Also, DP3 exhibited underactivation in four areas predicted by the CDT: the R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem), R Lobule VI (Hem) and L Lobule VI (Hem). Additionally there was hypoactivation of R Area 18, however, there was no hypoactivation in R and L hOC5, as predicted by the MDT (see Table 6.1, Table 6.2 & in Appendix D Table 13.3). Regarding Pseudowords, two areas predicted by the PDT were underactivated: the L IPC (PGa) (BA39) and L IPC (PGp) (BA39). Also, two areas predicted by the CDT were underactivated (L Lobule VI (Hem) and L Lobule VIIa Crus I (Hem)). Interestingly L Area 45 was overactivated for Pseudowords, an area associated with the PDT (see Table 6.3, Table 6.4 and Appendix E, Table 14.3.

DP4 shows no underactivation in any of the areas predicted by the main theories, for both Words and Pseudowords. However, DP4 exhibited hyperactivation of areas associated with the main theories. For Words, DP4 overactivated the R fusiform gyrus (see Table 6.1, Table 6.2 and Appendix D, Table 13.4). For Pseudowords, DP4 overactivated two areas associated with the PDT (L insula, L TE3 (when the probability and voxel thresholds were lowered)) two areas associated with the visual MDT (L Area 18 and L hOC5 (when the probability threshold was lowered)) (see Table 6.3, Table 6.4 and Appendix E, Table 14.4).

DP5 showed only underactivation for Words of the R Lobule VIIb (Hem), as predicted by the CDT and overactivation of L Area 17 and R Area 18 (see Table 6.1, Table 6.2 and Appendix D, Table 13.5). For Pseudowords only L Area 18 was underactivated. The overactivation for Pseudowords was noted in: one area

associated with the CDT (L lobule VI (Hem)), two areas associated with the PDT (R fusiform gyrus and L TE3 (when the probability threshold was lowered)) and two areas associated with the visual MDT (L Area 17 and R Area 18) (see Table 6.3, Table 6.4 and Appendix E, Table 14.5).

DP6 exhibited underactivation for Words in two areas predicted by the PDT (L IPC (PGa) and L IPC (PGp)) and overactivation in L Area 44 and L Area 18 (see Table 6.1, Table 6.2 and Appendix D, Table 13.6). No underactivation was noted for Pseudowords, however hyperactivation was noted here for L Area 44 and R Lobule VIIa Crus I (Hem), areas associated with the PDT and CDT, respectively (see Table 6.3, Table 6.4 and Appendix E, Table 14.6).

DP7 showed underactivation for Words in: R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)), as predicted by the CDT, and R Area 18, as predicted by the MDT. However, underactivation for R hOC5 was noted only when the probability threshold was reduced to 10%. Hyperactivation was found for Words in two areas associated with the PDT (L IPC (PF) (BA40) and R IPC (PFm) (BA40)) (see Table 6.1, Table 6.2 and Appendix D, Table 13.7). For Pseudowords, there were no hypoactivations in the areas associated with the theories. Hyperactivation was found in three sub-areas of R Area 40: R IPC (PFcm), R IPC (PF) and R IPC (PFt). Note that these are different sub-areas of Area 40, than the areas hyperactivated by this DP for Words (see Table 6.3, Table 6.4 and Appendix E, Table 14.7).

DP8 – a participant possibly at risk of DCD; her profile will also be discussed in the context of DCD in Chapter 7. DP8 showed no underactivation in any of the areas predicted by the main theories for both Words and Pseudowords. However, DP8 exhibited hyperactivation of areas associated with the main theories. For Words DP8 overactivated L insula (Ig2) and R middle temporal gyrus (BA21) - areas associated with the PDT (see Table 6.1, Table 6.2 and Appendix D, Table 13.8). For Pseudowords, DP8 overactivated two areas associated with the PDT (L Area 6 and L IPC (PGp) (BA39)) and an area associated with the visual MDT (R hOC5, when the probability threshold and voxel threshold were lowered), (see Table 6.3, Table 6.4 and Appendix E, Table 14.8).

DP9 exhibited hypoactivation for Words in some areas predicted by the PDT (L insula Lobe, L superior temporal gyrus (Wernicke's area) and L fusiform gyrus) and in three areas predicted by the CDT (R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)). There was also underactivation in R Area 17 and R Area 18, but underactivation in R hOC5 was only noted when the

probability threshold and the voxel threshold were lowered. There was hyperactivation in L Lobule VIIb (Hem) (see Table 6.1, Table 6.2 and Appendix D, Table 13.9). For the Pseudowords, underactivation was found only in L IPC (PGp) (BA39), as predicted by the PDT. There was also underactivation in R hOC5, but only when the probability threshold and the voxel threshold were lowered. Hyperactivation was noted for the R insula (see Table 6.3, Table 6.4 and Appendix E, Table 14.9).

DP10 showed no underactivation for Words of any predicted areas, except for L and R hOC5 when the probability threshold and the voxel threshold were lowered. Hyperactivation was found for L IPC (PGa) (BA39) and L fusiform gyrus and R TE3 (when the probability threshold and the voxel threshold were lowered), areas associated with the PDT (see Table 6.1, Table 6.2 and Appendix D, Table 13.10). For Pseudowords two areas (L Area 44 and L middle temporal gyrus), predicted by the PDT and one area predicted by the CDT (R Lobule VIIa Crus I (Hem)) were underactivated. No areas associated with the theories were hyperactivated here (see Table 6.3, Table 6.4 and Appendix E, Table 14.10).

DP11 exhibited underactivation for Words in two areas predicted by the PDT (L Area 44 and L insula) and two areas predicted by the CDT (R Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)). As predicted by the MDT there was underactivation for R and L Area 18, and L Area 17, but not for the L and R hOC5 (see Table 6.1, Table 6.2 and Appendix D, Table 13.11). There were no areas overactivated here. For Pseudowords, only one area, as predicted by the CDT, was underactivated - L Lobule VIIa Crus II (Hem), however, two areas associated with the PDT were overactivated (L Area 6 and R IPC (PFcm) (BA40)), (see Table 6.3, Table 6.4 and Appendix E, Table 14.11).

DP12 exhibited no underactivation for Words, as predicted by the PDT. DP12 showed underactivation here for R Lobule VIIb (Hem), as predicted by the CDT and L Area 17 and R Area 18, as predicted by the MDT. However, there was no underactivation in L and R hOC5. No areas were hyperactivated here (see Table 6.1, Table 6.2 and Appendix D, Table 13.12). For Pseudowords only R Lobule VIIa Crus I (Hem) was underactivated, as predicted by the CDT. Note that this is a different cerebellar area from the one which was hypoactivated for Words by DP12. Two areas associated with the PDT were overactivated for Pseudowords (L and R Area 44) (see Table 6.3, Table 6.4 and Appendix E, Table 14.12).

DP13 showed no underactivation in any areas predicted by the main theories for both Words and Pseudowords. However, DP13 exhibited hyperactivation of areas

associated with the main theories. For Words, DP13 overactivated a multitude of areas. Eight areas were associated with the PDT (L and R Area 44, L and R Area 45, L and R IPC (PGp) (BA39), L IPC (PGa) and the L middle temporal gyrus (BA21); Four areas were associated with the MDT: L and R Area 17, L and R Area 18, without any hyperactivation in L and R hOC5. Furthermore, three areas were associated with the CDT: L Lobule VIIa Crus II (Hem), L Lobule VI (Hem) and R Lobule VI (Hem) (see Table 6.1, Table 6.2 and Appendix D, Table 13.13). For Pseudowords, DP13 overactivated six areas associated with the PDT: L Area 44, L and R Area 45, R insula, L Area 6 and the L middle temporal gyrus (BA21). Two other areas were hyperactivated, one associated with the MDT (L Area 18) and one with the CDT (L Lobule VI (Hem)) (see Table 6.3, Table 6.4 and Appendix E, Table 14.13).

DP14 exhibited underactivation for Words in six areas predicted by the PDT (Area 44, L IPC (PGp) (BA39), the L fusiform gyrus, L Area 6, L middle temporal gyrus (BA21) and in L TE3 (when the probability threshold and the voxel threshold were lowered)). There was also underactivation of L Area 17 and L Area 18, as predicted by the MDT, however there was underactivation of L and R hOC5, but only when the probability threshold was reduced to 10%. Surprisingly there was also overactivation here in L Area 17, an area associated with the visual MDT (see Table 6.1, Table 6.2 and Appendix D, Table 13.14). Finally, there was underactivation in three areas predicted by the CDT (L Lobule VI (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)) and overactivation of one area associated with the CDT (R lobule VIIb (Hem)). For Pseudowords, there was no underactivation in the predicted areas, but there was overactivation in two areas associated with the PDT (the R insula and L IPC (PF) (BA 40)) (see Table 6.3, Table 6.4 and Appendix E, Table 14.14).

DP15 – a participant possibly ‘at risk’ of DCD; his profile will also be discussed in the context of DCD in Chapter 7. DP15 showed underactivation for Words for three areas predicted by the PDT (the L superior temporal gyrus (Wernicke's area), L IPC (PGa) (BA39) and L middle temporal gyrus), three areas predicted by the CDT (R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)) and one area predicted by the MDT (R Area 18). There was underactivation in R hOC5 when the probability threshold was reduced to 10%. Surprisingly, there was also hyperactivation in R Area 18 (see Table 6.1, Table 6.2 and Appendix D, Table 13.15). For Pseudowords, there were no underactivations in the predicted areas, however, there was overactivation in the R

Area 18, an area associated with the visual MDT (see Table 6.3, Table 6.4 and Appendix E, Table 14.15).

DP16 exhibited hypoactivation in three areas predicted by the PDT – the L insula (Ig1), L middle temporal gyrus (BA21) and in L TE3 (when the probability and voxel thresholds were lowered). There was also hypoactivation in L Area 17 and R Area 18, as predicted by the MDT, however there was no underactivation in hOC5. Surprisingly, there was also overactivation here in R Area 18, an area associated with the visual MDT (see Table 6.1, Table 6.2 and Appendix D, Table 13.16). For Pseudowords, there was underactivation in four areas predicted by the PDT (L insula, L Area 6, L fusiform gyrus and L middle temporal gyrus (BA21)). Three areas (L and R hOC5 and L Area 17) predicted by the MDT were underactivated. Note, however, that R hOC5 was underactivated when the probability threshold was lowered to 10%. Also L Lobule VI (Hem) was underactivated, as predicted by the CDT. Overactivation was noted in R Area 18, an area associated with the visual MDT (see Table 6.3, Table 6.4 and Appendix E, Table 14.16).

DP17 shows no underactivation in any areas predicted by the main theories for both Words and Pseudowords. However, DP17 exhibited hyperactivation of areas associated with the main theories. DP17, for Words, overactivated a number of areas. Seven areas, associated with the PDT were overactivated (L insula (Id1), L and R Area 6, L and R IPC (PFcm) (BA40), L IPC (PFop) (BA40) and L IPC (PF) (BA40)). Additionally, L TE3 was overactivated (when the probability and voxel thresholds were lowered). Three hyperactivated areas (L and R Area 17, and R Area 18) were associated with the visual MDT (see Table 6.1, Table 6.2 and Appendix D, Table 13.17). For Pseudowords, DP17 did not show any underactivation in the areas predicted by the theories. In contrast, DP17 overactivated areas associated with the PDT (L Area 44, L and R insula, L Area 6, R IPC (PFcm), L middle temporal gyrus (BA21) and R TE3 (when the probability and voxel thresholds were lowered) (see Table 6.3, Table 6.4 and Appendix E, Table 14.17).

Finally, DP18 showed underactivation for Words for two areas predicted by the PDT (L IPC (PFm) (BA40) and L IPC (PGa) (BA39)), and three areas predicted by the CDT (R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)). Finally there was underactivation in R Area 18. Underactivation was also noted in R hOC5, but only when the probability and the voxel thresholds were lowered. No overactivation was found in any areas

associated with the main theories (see Table 6.1, Table 6.2 and Appendix D, Table 13.18). For Pseudowords there was underactivation in only one area (L insula), predicted by the PDT. There was hyperactivation in three areas associated with the PDT (L Area 6, R IPC (PFcm) (BA40) and R TE3 (when the probability and voxel thresholds were lowered)), and one area associated with the visual MDT (L Area 17) (see Table 6.3, Table 6.4 and Appendix E, Table 14.18).

6.3 Discussion

6.3.1 Findings with respect to the main causal theories of dyslexia

The main goal of this thesis was to investigate the neural correlates of reading deficit in dyslexia as predicted by the main theories of this disorder, with special emphasis on individual differences. The predictions of the main theories on the neural correlates of reading impairment in dyslexia were contrasted in the same individuals with dyslexia, as compared to the control group. Underactivation in a given area (as specified in the Introduction) in a given individual DP was interpreted as support for a given theory of dyslexia. Additionally, overactivation was interpreted as activation in response to a deficit and as such consistent with a compensatory mechanism, as described in some earlier publications on dyslexia (Brunswick et al., 1999; Shaywitz et al., 1998).

If the reading deficit in DPs is due to a phonological impairment, as predicted by the PDT, DPs should exhibit underactivation in comparison with CPs, in all or some areas within the phonological processing network, specified in the Introduction. As stated in the Introduction, underactivation only in the LH areas was interpreted as impairment, as all participants were right handed. RH phonological areas were considered only in the context of potential compensatory mechanisms (Pugh, Mencl, Shaywitz et al., 2000).

If reading impairment in dyslexia is due to magnocellular dysfunction, as predicted by the visual MDT, then DPs should exhibit underactivation, in comparison to CPs, in the areas within the magnocellular processing network (the magnocellular-dorsal pathway) (Wurtz & Kandel, 2000), as specified in the Introduction. Furthermore, the MDT postulates that the magnocellular system is important in the acquisition of ‘accurate visual representations of the written, orthographic, form of words’ and that this is essential in order to grasp their structure at the phonemic level. Therefore a deficient magnocellular system could be the underlying cause of deficient phonological representations and therefore of a phonological deficit (Stein, 2003). Hence it is possible that underactivation in

phonological areas (in the presence of underactivation in magnocellular areas) in DPs during reading in this study is consistent with the MDT (and with the PDT, as specified, earlier).

Finally, as described in the Introduction, the CDT makes clear predictions regarding the involvement of the cerebellum in reading acquisition. According to this theory, an impaired cerebellum in DPs who are acquiring reading will lead to difficulties with learning to read (Nicolson et al., 2001). However, the theory is less explicit regarding the involvement of the cerebellum in reading in adults. According to R. Nicolson (email communication, 1st of March 2013) the CDT would predict less cerebellar involvement in unimpaired adult reading, nevertheless it would predict some involvement of this brain structure in adult reading. Hence, it would predict underactivation of cerebellar areas during reading by adult DPs as compared to CPs. The CDT, however, does not make clear predictions on which cerebellar areas should be involved and therefore underactivated. Furthermore, because the cerebellum consists of 50% of the brain's neurons (Brodal, 1981), the predictions were narrowed here to the cerebellar areas which were found to be involved in: 1) language processing (Stoodley & Schmahmann, 2009), 2) silent reading (Fulbright et al., 1999), 3) four cerebellar areas (two in each hemisphere) where DPs exhibited the biggest difference in comparison with CPs in a histological study (Finch et al., 2002) and 4) one area which differentiated DPs and CPs in such a way that 100% of DPs fell outside the 95% confidence interval boundaries of CPs (Pernet et al., 2009). It should be noted that the majority of these areas overlapped with the areas identified in the meta-analysis (Stoodley & Schmahmann, 2009).

Additionally, the CDT (Nicolson et al., 2001) predicts that a phonological deficit (in phonological awareness and in reading) can be caused by a cerebellar impairment. Therefore it is possible that underactivation in phonological areas in DPs during reading (in the presence of underactivation in cerebellar areas, as specified above), in the study presented here, may also be consistent with the CDT. However, as pointed out above, the predictions of the MDT and CDT, regarding the phonological areas, hold if one takes the perspective advocated by these theories. They do not hold if one takes the perspective of the PDT.

Following these assumptions, the results which involved underactivation in the areas postulated by the main theories are summarized in Table 6.5 and Figure 6.1, below.

Focusing first on Words, the neural correlates of reading deficit in five (27.7%) DPs (DP1, DP9, DP14, DP15 and DP18) were consistent with the predictions of the PDT and CDT. It was not clear, however, whether their reading deficit was also consistent with the predictions of the visual MDT. The reading deficit of DP2 and DP5 (11.1%) were in agreement with the CDT. The reading deficit of a further two (11.1%) DPs (DP3 and DP11) was consistent with the PDT, CDT and VDT (Visual Deficit Theory - a hypothetical theory according to which the reading disorder in dyslexia is due to a visual (but not a magnocellular) processing problem. The results of another two DPs (DP6 and DP16) were consistent with the PDT. Note that from the current data it is unclear whether the reading disorder of DP16 was also in line with the VDT. The reading deficit of DP7 (5.6%) was consistent with the CDT, but it was not clear whether it was also in agreement with the visual MDT. DP10's reading deficit was not consistent with the PDT or with the CDT, and it was unclear whether it was consistent with the MDT. Finally, the reading deficit of a group of four DPs (DP4, DP8, DP13 and DP17) was not consistent with any of the three main theories.

Summarising, the neural correlates of Word reading deficit are consistent with the PDT in nine (50%) cases and with the CDT in eleven (61.1%) cases. It is not clear whether the reading deficit of seven (38.9%) cases is consistent with the MDT. The reading deficit of three (16.7%) cases are consistent with the VDT, but most likely not with the MDT, this is because in these cases, areas which receive input from both magno and parvo cells are underactivated, but not the V5/MT area which predominantly receives the magnocellular input. It is unclear whether the data for DP16 (5.6%) are consistent with the VDT, but not the MDT. Finally, the reading deficit of four (22.2%) cases is not consistent with any of the three main theories.

Taking into consideration the additional predictions of the CDT and the MDT, it is possible that the underactivation in phonological areas in DP1, DP3, DP9, DP11, DP14, DP15 and DP18 (38.9%) is also consistent with the CDT (as well as with the PDT), but this is only from the perspective of the CDT and not the perspective of the PDT. Furthermore, it is unclear whether the underactivation in phonological areas in DP1, DP9, DP14, DP15 and DP18 is also consistent with the MDT.

Table 6.5 Distribution of individual DPs for whom reading impairment is consistent with the predictions of the PDT and/or MDT and/or CDT; Reading impairment found in BOLD patterns (underactivation) in DPs for Word and Pseudoword reading

	Word Reading			Pseudoword Reading		
No	PDT	MDT	CDT	PDT	MDT	CDT
DP1	+	M?	+	-	+	+
DP2	-	-	+	-	-	-
DP3	+	- (V)	+	+	-	+
DP5	-	-	+	-	- (V?)	-
DP6	+	-	-	-	-	-
DP7	-	M?	+	-	-	-
DP9	+	M?	+	+	M?	-
DP10	-	M?	-	+	-	+
DP11	+	- (V)	+	-	-	+
DP12	-	- (V)	+	-	-	+
DP14	+	M?	+	-	-	-
DP15	+	M?	+	-	-	-
DP16	+	- (V?)	-	+	+	+
DP18	+	M?	+	+	-	-
DP4	-	-	-	-	-	-
DP8	-	-	-	-	-	-
DP13	-	-	-	-	-	-
DP17	-	-	-	-	-	-

Note. **'+'** denotes that the neural correlates of reading deficit in a DP are consistent with the predictions of a given theory (a DP needed to exhibit underactivation in one or more areas predicted by a given theory); **'-'** denotes that the neural correlates of reading deficit are not in agreement with the predictions of a given theory (a DP needed to exhibit no underactivation in the areas predicted by a given theory); **'M?'** denotes that on the basis of the data from the reported experiment it is unclear whether the neural correlates of the reading deficit are consistent with the predictions of the MDT; **'-(V)'** denotes that the neural correlates of reading impairment are not consistent with the predictions of the visual MDT, but the areas involved may be consistent with the VDT; this is because in these cases, areas which receive input from both magno and parvo cells are underactivated, but not the V5/MT - area which predominantly receives a magnocellular input (V5/MT); **'-(V?)'** denotes that the neural correlates of reading deficit are not in line with the MDT and it is unclear whether they are consistent with the VDT.

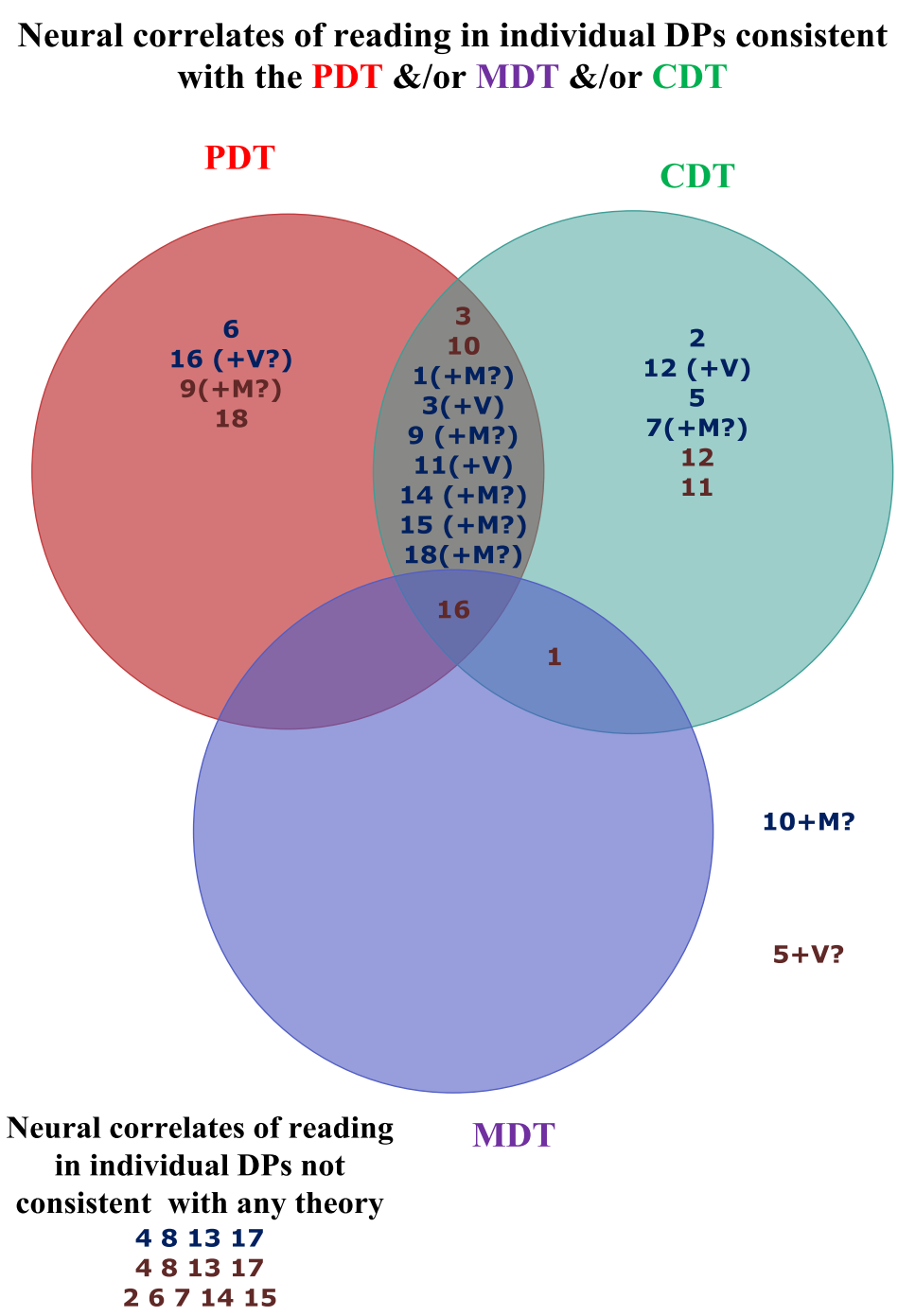


Figure 6.1 Distribution of individual DPs for who reading impairment is consistent with the predictions of the PDT and/or MDT, and/or CDT, as revealed by the neuroimaging data (underactivation) of Word and Pseudoword reading.

Note: Numbers represent individual DPs. Navy blue entries are for Words; Brown entries and for Pseudowords. '+M?' denotes that it is unclear whether the neural correlates of reading deficit for a given DP are consistent with the predictions of the MDT; '+V' denotes that the neural correlates of reading impairment are not consistent with the predictions of the visual MDT, but the areas involved seem to be consistent with the VDT. '+V?' denotes that the neural correlates of reading impairment are not consistent with the predictions of the visual MDT, and it is unclear whether the areas involved are in agreement with the VDT.

Moving on to Pseudowords, the neural correlates of reading of DP9 and DP18 (11.1 %) were consistent with the PDT and it was not clear whether the result for DP9 was also consistent with the MDT. The reading impairment of DP1 was consistent with the MDT and CDT. The results for DP10 and DP3 were consistent with the PDT and CDT. The reading deficits of DP11 and DP12 were in agreement with the CDT. DP16's results were consistent with all three theories (the PDT, MDT and CDT). Finally, the reading deficit of ten DPs (DP2, DP5, DP6, DP7, DP14, DP15, DP4, DP8, DP13 and DP17) (66.7%) was not consistent with any theory, except for DP5 whose reading deficit was possibly consistent with the VDT, but not the MDT. Taking into consideration the additional predictions of the CDT and the MDT, it is possible that the underactivation in phonological areas in DP3 and DP10 is also consistent with the CDT (as well as with the PDT) and in DP16 with the CDT and MDT (as well as with the PDT). However, these hold from the perspective of the CDT and MDT and not the perspective of the PDT. Summarising, the neural correlates of Pseudoword reading were in agreement with the predictions of the PDT in five (27.8%) cases, with the CDT in six (33.3%) cases and with the MDT in two (11.1%) cases. It is unclear whether the case of DP5 is consistent with the VDT, but not the MDT. Finally, the results for ten (55.6 %) cases are not consistent with the predictions of any of the three main theories.

It should be emphasized here that in cases where the neural correlates of reading deficit in a given DP are consistent with more than one of the main theories, it may be the case that an explanation offered by one theory is causal and the other is not. Hence it may be important to consider cases where reading deficit is consistent only with one of the main theories. DP6 is a case whose Word (but not Pseudoword) reading deficit is only consistent with the predictions of the PDT. DP2's Word (not Pseudoword) reading impairment is consistent with only the CDT. No DP demonstrated a reading impairment which is only consistent with the MDT.

If underactivation in a given DP is found in both phonological and cerebellar areas, as specified in the Introduction, the results are consistent with both the PDT and the CDT. It is consistent with PDT because phonological areas were underactivated. It is consistent with the CDT because the cerebellar areas were underactivated. Furthermore, the underactivation in phonological areas may also be consistent with the CDT because it predicts that a phonological deficit (in phonological awareness and in reading) can be caused by cerebellar underactivation. This interpretation, however, is inconsistent with the PDT

according to which the impaired phonological areas (not cerebellar areas) are the underlying cause of phonological impairment. It should be underscored that the methodology used in this study cannot easily tease apart the phonological from the cerebellar influences on underactivation within the phonological areas. The same is true for the cases which involve underactivation in phonological and magnocellular areas. For instance, DP16, underactivated phonological, magnocellular (and cerebellar areas), when reading Pseudowords. The results for DP16 are consistent with all three theories of dyslexia. They are consistent with the PDT, because phonological areas were underactivated; with the MDT, because magnocellular areas were underactivated and with CDT, because cerebellar areas were underactivated. Additionally, the underactivation in phonological areas could be consistent with the MDT, because the MDT postulates that the magnocellular system is important in the acquisition of 'accurate visual representations of the written, orthographic, form of words' and that this is essential in order to grasp their structure at the phonemic level. It could also be consistent with the CDT because it predicts that a phonological deficit (in phonological awareness and in reading) could be caused by a cerebellar underactivation (Nicolson et al., 2001). However, as pointed above, such interpretations are inconsistent with the PDT.

6.3.1.1 The combined results for Word and Pseudoword reading do not support an interpretation in terms of a 'developmental lesion'

An interesting issue, revealed by the results for Words and Pseudowords, is the finding that a given area in DPs is underactivated when they read Words, but not when they read Pseudowords, and vice versa. It shows that the underactivation in a given area does not indicate that there is a 'developmental lesion', and that the given area, although malfunctional in some tasks, is not deficient in others. It suggests that a given area in a DP may be functioning as well as in CPs in one task and be underactivated in a different task. This may indicate that the deficit lies in the pattern of connectivity within a network which specialises in a given function (i.e. reading Words). This area may also be a part of a different system which specialises in a different function, e.g. Pseudoword reading, but the connections within this network may be intact.

6.3.2 The nature of the neural correlates of reading impairment in DPs in the context of the main theories

It should be noted here that, as stated earlier, underactivation in DPs was interpreted as deficient brain activation, consistent with the predictions of the main theories of dyslexia, according to which the neural correlates of reading impairment would manifest as underactivation. Most likely, overactivation in brain areas arises in response to a deficit and as such may be conceptualised as a compensatory mechanism (see Table 6.6 for the summary of patterns of overactivation). Because of the limitations of the current study (only the age-matched control group, as commonly used with adult DPs, was employed) it is not possible to stringently check whether the underactivation and overactivation obtained in the current study is consistent with the interpretation put forward by Hoeft, Meyler et al. (2007). According to these authors underactivation is associated with the cause of dyslexia, whereas overactivation is related to the consequence of this disorder.

Table 6.6 Distribution of overactivation in Word or Pseudoword reading across individual DPs*

	Word Reading			Pseudoword Reading		
No	**PDT**	**MDT**	**CDT**	**PDT**	**MDT**	**CDT**
DP1	[-]	[-]	[-]	[-]	[-]	[+]
DP2	[-]	[-]	[+]	[?]	[-]	[-]
DP3	[-]	[-]	[-]	[+]	[-]	[-]
DP4	[-]	[-]	[-]	[+]	[?]	[-]
DP5	[-]	[-(V)]	[-]	[?]	[-(V)]	[+]
DP6	[+]	[-(V)]	[-]	[+]	[-]	[+]
DP7	[+]	[-]	[-]	[-]	[-]	[-]
DP8	[+]	[-]	[-]	[+]	[?]	[-]
DP9	[-]	[-]	[+]	[-]	[-]	[-]
DP10	[+]	[-]	[-]	[-]	[-]	[-]
DP11	[-]	[-]	[-]	[+]	[-]	[-]
DP12	[-]	[-]	[-]	[+]	[-]	[-]
DP13	[+]	[-(V)]	[+]	[+]	[-(V)]	[+]
DP14	[-]	[-(V)]	[+]	[+]	[-]	[-]
DP15	[-]	[(-V)]	[-]	[-]	[-(V)]	[-]
DP16	[-]	[-(V)]	[-]	[-]	[-(V)]	[-]
DP17	[+]	[-(V)]	[-]	[+]	[-]	[-]
DP18	[-]	[-]	[-]	[+]	[-(V)]	[-]

Note.***** denotes that overactivation only in the LH areas is shown in this table; **'[+]'** denotes overactivation in a DPs within Phonological areas and/or Magnocellular areas and/or Cerebellar areas, as defined in the Introduction for either Word or Pseudoword reading; '-' denotes lack of overactivation; **'[?]'** denotes that on the basis of the data from the reported experiment it is unclear whether there was an overactivation within area/s associated with a given theory; '[-(V)]' denotes that overactivation does not involve V5/MT, but V1 and/or V2; '[-(V?)]' denotes that overactivation does not involve V5/MT and it is unclear whether it involves V1 and/or V2.

Focusing more closely on the PDT, the data show that DPs have a remarkably heterogeneous pattern of underactivations and overactivations – see Table 6.5 and Table 6.6, as well as Figure 6.1 for summaries). For instance, DPs with

underactivation of the areas predicted by the PDT, exhibit a deficit for Word reading in the posterior parts of the brain (DP3, DP6, DP15 and DP18), posterior parts and insula (DP9), anterior and posterior parts (DP1 and DP14), anterior parts and insula (DP11) and just insula (DP16). This heterogeneity also holds for Pseudowords. Underactivation for only the posterior parts was noted for DP3 and DP9, for anterior parts for DP10 and anterior and posterior parts and insula for DP16.

As discussed above, a number of neuroimaging studies have reported that DPs use frontal areas (L and R Areas 44, 45 and 6) for compensation (Brunswick et al., 1999; Pugh, Mencl, Shaywitz et al., 2000; Shaywitz et al., 1998), although, as discussed earlier, a more recent meta-analysis (Maisog et al., 2008) revealed no support for hyperactivity in the L anterior areas in DPs, suggesting that neuroimaging results in these areas are likely to be more varied in their spatial location and their reproducibility. The claim that DPs tend to overactivate the anterior areas is supported here by eight (44%) cases (DP3, DP6, DP8, DP11, DP12, DP13, DP17 and DP18). All of these DPs overactivated frontal areas when reading Pseudowords, additionally DP6, DP13 and DP17 also exhibited hyperactivation in the frontal areas when reading Words.

As discussed earlier, Paulesu et al. (1996) put forward a hypothesis that the deficient phonological system of DPs is due to a dysfunctional L insula which acts as a connecting bridge between the anterior and posterior language areas. However, other researchers (e.g., Rumsey et al., 1997; Shaywitz et al., 1998) did not find evidence for a functionally impaired L insula in DPs. The study reported here found support for both, with some DPs exhibiting underactivation of the L insula and some not. Some DPs overactivated the L and/or R insula. For Words three DPs (DP9, DP11 and DP16) exhibited hypoactivation in the L insula, as predicted by the PDT. Another two DPs (DP8 and DP17) exhibited overactivation of the L posterior insula. For Pseudowords, two DPs (DP16 and DP18) underactivated the L insula, while six DPs (DP1, DP9, DP14, DP2, DP13 and DP17) overactivated the R insula and two DPs (DP4 and DP17) overactivated the L insula. Note, however, that hyperactivation/underactivation for Words was assigned using the cytoarchitectonic maps (Kurth et al., 2009) for only three DPs (DP8, DP16 and DP17), the remaining activations were labelled using Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002).

As discussed in the Introduction, the neuroimaging studies, which compare a group of DPs and CPs, revealed that DPs, as a group, when reading, show

underactivation, relative to CPs in the L dorsal sub-system (angular gyrus, supramarginal gyrus, Wernicke's area and the supramarginal gyrus) and the L ventral sub-system (inferior occipito-temporal fusiform area) (e.g., Brunswick et al., 1999; Paulesu et al., 2001; Pugh, Mencl, Jenner et al., 2000; Salmelin et al., 1996; Shaywitz et al., 1998). First, the focus here is on the results which have a bearing on the L dorsal sub-system.

For Words, five DPs (DP3, DP6, DP14, DP15 and DP18) demonstrated underactivation of the L angular gyrus, in line with the results reported above. However, two DPs (DP10 and DP13) showed overactivation of the L and bilateral angular gyrus, respectively. For Pseudowords, DP3 and DP9 underactivated the L angular gyrus, whereas DP8 hyperactivated the L angular gyrus. Note that the activations for the angular gyrus were assigned using cytoarchitectonic maps (Caspers et al., 2008). Regarding Wernicke's area, for Words, three DPs (DP1, DP9 and DP15) demonstrated underactivation and no DP showed overactivation in Wernicke's area. Note, nevertheless, that the reported activations were not assigned using the cytoarchitectonic maps, because only a portion of Wernicke's area (L Area TE3) was identified using these maps (Caspers et al., 2008). However, when the probability threshold and the voxel threshold were lowered, DP3, DP14 and DP16 exhibited underactivation in the L TE3. In contrast, DP10 and DP17 exhibited overactivation in the R TE3 and L TE3, respectively. There were no hypoactivations and hyperactivations for Pseudowords in Wernicke's area. However, when the probability threshold and the voxel threshold were lowered, three DPs (DP2, DP4 and DP5) showed hypoactivation in the L TE3, as predicted by the PDT, whereas DP17 and DP18 exhibited hyperactivation in the R TE3. It should be noted here that the activation in TE3 needs to be treated with caution as it does not fulfil the more stringent cut off point for the probability threshold and the voxel threshold.

In terms of another dorsal area - BA40, for Words two DPs (DP3 and DP18) showed underactivation in the L IPC (PFm), DP3 additionally demonstrated hypoactivation in the L IPC (PF), as predicted by the PDT. In terms of overactivation, DP7 exhibited hyperactivation in the L IPC (PF) and R IPC (PFm). DP17 also showed overactivation in the L IPC (PF) and additionally in the L IPC (PFcm), L IPC (PFop) and R IPC (PFcm). For Pseudowords no underactivation, but only overactivation was observed. DP14 showed overactivation in the L IPC (PF). Four DPs (DP18, DP7, DP11 and DP17) exhibited overactivation in the R IPC

(PFcm). DP7 additionally exhibited hyperactivation in the R IPC (PF) and R IPC (PFt).

The results from the current multiple-case study for the L dorsal sub-system show a picture that seems to be more complicated that the one which emerged from the studies employing only group (DPs vs CPs) comparisons. First, not all DPs exhibited underactivation in these areas. Second, seven DPs exhibited overactivation in one or more of these areas for Words; for Pseudowords, one DP showed overactivation in this system in the LH and six DPs exhibited overactivation in the RH counterparts within this system. Finally, the results of overactivation are not usually found in the L dorsal sub-system in adults with dyslexia in studies which only involve group comparisons (DPs vs CPs).

Focusing on the L ventral area (L BA37, L BA21 and VWFA), it was reported (Brunswick et al., 1999) that both during explicit and implicit reading DPs exhibited reduced activation in the L BA37 relative to CPs. The authors suggested that because of BA37 involvement in modality-independent naming, the reduced activation in DPs can be interpreted as a neural correlate of impairment in lexical retrieval. The data from the experiment reported in this thesis show that for Words, two DPs (DP9 and DP14) demonstrated underactivation of the L fusiform gyrus. In contrast, another two DPs (DP4 and DP10) exhibited overactivation of the R and L fusiform gyrus, respectively. For Pseudowords, DP16 showed underactivation of the L fusiform gyrus, whereas DP5 showed overactivation of the R fusiform gyrus. Note, however, that there are currently no probabilistic cytoarchitectonic maps of BA37.

Regarding the L middle temporal gyrus (BA21), the data show that for Words, three DPs (DP14, DP15 and DP16) exhibited underactivation of this area. In contrast, DP13 exhibited overactivation. DP8, on the other hand, showed underactivation in the R BA21. For Pseudowords the L middle temporal gyrus was underactivated by two DPs (DP10 and DP16) and overactivated also by two DPs (DP13 and DP17). Note that, as with BA37, there are no cytoarchitectonic maps currently available of BA21.

Finally, as discussed in the Introduction, Cohen, Lehericy et al. (2002) put forward a hypothesis stating that visual word form representations: "are subtended by a restricted patch of the L hemispheric fusiform cortex [average Talairach coordinates x=-43, y=-54, z=-12] which is reproducibly activated by reading" (p. 1054). These Talairach coordinates were transformed using Brett's (1999) formula which gave the following MNI coordinates: x=-43, y=-55, z=-17. The L VWFA

was underactivated in this study for Words in two DPs (DP9 and DP14) and in DP10 it was overactivated. There was underactivation in DP16 for this area for Pseudowords (the average coordinates were x=-35, y=-47, z=-15). See Appendix D and E for the exact coordinates.

Similar to the results for the L dorsal sub-system, the results for the L ventral sub-system from the current multiple-case study underscore the fact that the picture seems to be more complicated than the one which has emerged from the studies based only on group (DPs vs CPs) comparisons. First, not all DPs exhibited underactivation in the L dorsal sub-system, as one would predict from the group reports. For Words and Pseudowords, seven and four DPs, respectively, exhibited underactivation in the areas of the L dorsal sub-system (for Word reading, one DP showed underactivation in the RH homologous area). DPs also exhibited overactivation here (four DPs showed overactivation for Words and three for Pseudowords, including one DP in each category whose overactivation was located in the RH counterpart). The results on overactivation are not in agreement with the results of studies which reported only group comparisons.

6.3.2.1 The Cerebellar deficit theory

Heterogeneous patterns of underactivation (and overactivation) among DPs were also noted in the areas associated with the CDT. The results for Words are considered first. Five DPs (DP2, DP7, DP9, DP15 and DP18) (27.7%) exhibited underactivation in the R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem). Two DPs (DP1 and DP11) (11.1%) showed underactivation in the R Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus I (Hem). A further two DPs (DP5 and DP12) (11.1%) showed hypoactivation in the R Lobule VIIb (Hem). DP3 exhibited underactivation in R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem), R Lobule VI (Hem) and L Lobule VI (Hem). Underactivation in the L Lobule VIIa Crus I (Hem), L Lobule VIIa Crus II (Hem) and L Lobule VI (Hem) was noted for DP14.

Two DPs (DP2, DP9) overactivated the L Lobule VIIb (Hem) and DP14 overactivated the R Lobule VIIb (Hem). DP13 overactivated three cerebellar areas: the L Lobule VIIa Crus II (Hem), L Lobule VI (Hem) and R Lobule VI (Hem).

For Pseudowords, two DPs (DP10 and DP12) (11.1%) showed underactivation in only the R Lobule VIIa Crus I (Hem). DP1 exhibited underactivation in the R Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem). Underactivation in L Lobule VIIa Crus I (Hem) and L Lobule VI (Hem) was noted in DP3. DP16

exhibited underactivation only in the L Lobule VI (Hem). Underactivation in only L Lobule VIIa Crus II (Hem) was noted in DP11. In contrast, DP5 and DP13 showed overactivation in L Lobule VI (Hem), whereas DP1 and DP6 exhibited overactivation in the L Lobule VIIa Crus I (Hem) and R Lobule VIIa Crus I (Hem), respectively.

The data presented here on cerebellar involvement in the neural correlates of reading deficit in DPs shows that there is support for functional abnormality in the R Lobule VIIa Crus I (Hem). 44% and 17% of DPs showed underactivation in this lobule for Word and Pseudoword reading, respectively. However, one DP (5.6%) exhibited overactivation in this lobule for Pseudowords. R Lobule VIIa Crus I (Hem) was found to be functionally activated in language studies with CPs (Stoodley & Schmahmann, 2009), including silent reading (Fulbright et al., 1999).

Functional abnormality in the L Lobule VIIa Crus I (Hem) was noted in seven cases (38.9%) for Words and one case (5.6%) for Pseudowords. However, DP1 showed overactivation in the L Lobule VIIa Crus I (Hem) for Pseudowords. Similar to its RH counterpart, this area was found to be activated in language processing (Stoodley & Schmahmann, 2009), including silent reading (Fulbright et al., 1999).

One case (5.6%) supported the claim that there is functional abnormality in the R Lobule VI (Hem) for Words, but there was also one DP who exhibited overactivation of this lobule for Words. Two cases (11.1%) confirmed that there was functional abnormality in the L Lobule VI (Hem) for Words and for Pseudowords (DP3 exhibited underactivation for both types of stimuli). However, DP13 exhibited overactivation in this lobule for both Words and Pseudowords and DP5 just for Pseudowords. The R and L Lobule VI (Hem) were found to be functionally activated in language tasks with CPs (Stoodley & Schmahmann, 2009).

Eight cases (44.4%) in Word reading, and two cases (11.1%) in Pseudoword reading supported the claim that there is functional abnormality in L Lobule VIIa Crus II (Hem). But there was one DP who exhibited overactivation of this lobule for Words.

Finally, there is support in two cases (11.1%) for functional abnormality for the R Lobule VIIb (Hem) in Word reading, but one DP exhibited overactivation in this lobule. The R Lobule VIIb (Hem) has a representation of the whole body (Brodal, 1981) and within this lobule (and L Lobule VIIb (Hem)) the biggest significant difference was found between DPs' and CPs' brains in a histological study (Finch et al., 2002) (for more details see Introduction). Two DPs exhibited overactivation

of the L Lobule VIIb (Hem) for Words; there was no underactivation in this area for Words and Pseudowords.

The data presented in this study did not record underactivation in DPs (relative to CPs) in the L Lobule VIIb and R Lobule VIIa Crus II (Hem), which differentiated well between DPs' and CPs' (Finch et al., 2002). Furthermore, no underactivation in DPs was found in the R Lobule VI (vermis). As discussed above this was reported (Pernet et al., 2009) to differentiate (together with the R lentiform nucleus) DPs and CPs in such a way that 100% of DPs fell outside the 95% confidence interval boundaries of CPs. It was hypothesised (Pernet et al., 2009) that this lobule (in connection with other areas outside the cerebellum, such as the R lentiform nucleus) is important for the process of automatisation of skills. If this hypothesis is true, then this lobule would also be a good candidate to use when testing for deficits in automaticity, as specified in the ontogenetic causal chain (outside the main route) by Nicolson et al. (2001). However, this study did not find support for the claim that the R Lobule VI (vermis) is linked to reading deficit in dyslexia. It could be the case that the involvement of R Vermal Lobule VI in dyslexia may need to be investigated in a task other than reading.

Although the fMRI group comparisons (Chapter 5) showed no significant differences between DPs and CPs in the cerebellar areas, which was in line with a meta-analysis of functional neuroimaging studies of dyslexia (Maisog et al., 2008), the multiple case study reported here showed support for the predictions of the CDT in eleven (61.1%) cases for Word reading and in six cases (33.3 %) for Pseudoword reading. However, this study reveals a more complicated picture than one could expect on the basis of the neuroimaging literature involving exclusively between group comparisons (DPs vs CPs). This is because, although clear underactivation in cerebellar areas was found in Word and Pseudoword reading, some cases exhibited overactivation in the cerebellar areas hypothesised by the CDT to exhibit underactivation (four DPs (22.2%)) for Words and four DPs for Pseudowords). The results which involve overactivation suggest, in contrast to the CDT, that some areas of the cerebellum may be unimpaired and may be used for compensation.

The current study provides one of the most detailed insights into the differences between cerebellar involvement in reading impairment in dyslexia in a multiple-case study. The results from the current study also provide support for the hypothesis put forward by Maisog et al. (2008) that lack of cerebellar differences

between the DPs and CPs in studies which exclusively rely on group comparisons many be due to considerable variability in the spatial location of cerebellar effects.

6.3.2.2 The Magnocellular deficit theory

Focusing on the MDT, the Word reading deficit of seven DPs (38.9 %) might be consistent with the MDT, but it is not clear from the data obtained in this study. The Pseudoword reading deficit in two DPs (11.1%) was consistent with the predictions of the MDT; it was unclear whether the reading deficit of DP9 was in agreement with the predictions of the MDT.

It should be emphasised that the MDT turned out to be the most difficult to evaluate. This is because only one cortical area - the V5/MT - is thought to receive input predominantly from the magnocellular stream (Tootell & Taylor, 1995; Watson et al., 1993) and this area is characterised by considerable variation (between participants) in the extent and location of the standard space (Malikovic et al., 2007). Furthermore, the effect in the V5/MT could have been weakened due to the image stabilization, needed also in the control condition (i.e. fixating on the '+') which was necessary in this study and considered to be a better overall control condition than the 'rest condition' (see Chapter 2 for discussion). Nevertheless, it should be noted that the effect due to letter localization (needed in the experimental condition, but not in the control condition) should not have been weakened by the control condition and therefore should be detectible.

The other two areas R & L V1 and R & L V2 consist of partially separated magno and parvo cells (Wurtz & Kandel, 2000), therefore, underactivation in any of these areas may reflect underactivation of either magno cells, or parvo cells or a combination of the two. Hence, the approach taken in this thesis was to interpret underactivation in V1 and V2 as supporting the MDT, only if it was found jointly with the underactivation in V5/MT. A further complication occurs because in some cases both underactivation and overactivation for the L and R V1 and V2 were found. For instance, as described above, DP14 showed both underactivation and overactivation of the L Area 17 for Words. DP15 and DP16 showed underactivation and overactivation of the R Area 18 for Words and overactivation of this area for Pseudowords. It is not clear how such results can be reconciled. One possibility is that they reflect the fact that these areas consist of partially separated parvo and magno cells, and for a given stimulus the magno cell sub-area may be deactivated, whereas the parvo sub-area may be overactivated.

6.3.3 Neuroimaging results for individual DPs in the context of reading scores

6.3.3.1 Words

The neuroimaging and TOWRE results for Words divide DPs into three subgroups. The first sub-group consists of eight DPs (DP2, DP3, DP7, DP9, DP12, DP14, DP15 and DP16) who showed a clear deficit on Word reading (TOWRE) and also exhibited underactivation when reading real words, as predicted by one of the main theories. Despite the reading test in the scanner being most likely easier than TOWRE, the DPs in this sub-group exhibited a clear underactivation. These DPs are not compensated on the behavioural level, with respect to Word reading, and this is clearly reflected on the neural level. It is not clear whether DP10 belongs to this subgroup, as it is not clear whether he had a deficit on the neural level.

The second sub-group consists of five DPs (DP1, DP5, DP6, DP11 and DP18) who exhibited no reading deficit on TOWRE, but showed clear underactivation in the neuroimaging results on word reading, as predicted by at least one of the main theories. These DPs are clearly compensated on word reading on the behavioural level, however, the neuroimaging results uncovered a lack of compensation on the neural level, even on, the most likely easier reading test (than the behavioural test), administered in the MRI scanner.

Finally, the third sub-group consists of four DPs (DP4, DP8, DP13 and DP17), who, although exhibiting a reading deficit on TOWRE, showed no underactivation in any of the areas predicted by at least one main theory. Interestingly, most of these DPs exhibited hyperactivation of the areas associated with the main theories. These results are most difficult to interpret, because the reading test in the scanner was, most likely, easier than TOWRE. Therefore, it could be that hyperactivation (interpreted as a compensatory mechanism) of the areas associated with at least one main theory, was associated with fluent reading in the scanner. What is not clear is whether a similar pattern of neuroimaging results would be observed if these participants were to read items from TOWRE in the scanner.

6.3.3.2 Pseudowords

The neuroimaging and Pseudoword Reading Composite results divide DPs into four subgroups. The first sub-group consists of six DPs (DP3, DP9, DP10, DP12, DP16 and DP18) who exhibited a clear deficit on the Pseudoword Reading Composite and also showed underactivation while reading Pseudowords, as predicted by at least one of the main theories. These DPs are clearly not

compensated on the behavioural level, with respect to Pseudoword reading, and they are also clearly not compensated on the neural level.

The second sub-group consists of nine DPs (DP2, DP4, DP7, DP8, DP11, DP13, DP14, DP15 and DP17) who exhibited a clear deficit on the Pseudoword Reading Composite, but no underactivation, as predicted by at least one main theory. These results are difficult to interpret, because the pseudoword reading test in the scanner was most likely easier than the tests contributing to the Pseudoword Reading Composite score. Interestingly, most of these DPs exhibited hyperactivation of some areas predicted by at least one of the main theories, or their homologues in the other hemisphere. Therefore, it could be that hyperactivation (interpreted as a compensatory mechanism) of the areas associated with at least one main theory, was associated with fluent reading in the MRI scanner. It is not clear whether the same pattern of neuroimaging results would be noted if these participants were to read the more difficult tests in the MRI scanner, the results of which contributed to the Pseudoword Reading Composite score.

The third subgroup consists of DP6 who exhibited no deficit on the Pseudoword Reading Composite and no underactivation in the neuroimaging results, as predicted by at least one main theory. DP6, however, showed overactivation of areas associated with the PDT and CDT.

Finally, the fourth subgroup consists of DP1 who exhibited no deficit on the Pseudoword Reading Composite, but showed underactivation in the neuroimaging results, as predicted by at least one main theory. (It is possible that DP5 also belongs to this subgroup).

If one considers the results for Words and Pseudowords jointly, then a clear subgroup consists of the four DPs (DP4, DP8, DP13 and DP17) (see Tables 6.2 & 6.3). Interestingly all four of these DPs show no underactivation for both Words and Pseudowords in any of the areas predicted by the main theories. However, most of them exhibited hyperactivation of the areas associated with the main theories.

6.3.4 DPs' neuroimaging results in the context of psychometric summary variables

Looking from the broader perspective of literacy, phonological and orthographic measures and neuroimaging results, one can pose the question of whether DPs who have the same profile on behavioural measures also have a similar profile on their neuroimaging results. As shown in Table 6.7 below, there are five subgroups of DPs who exhibited the same profile on the behavioural measures. Subgroup 1 consists of: DP9, DP14, DP15 and DP17; DP4 and DP8 belong to Subgroup 2;

Subgroup 3 consists of DP2 and DP16; DP12 and DP13 belong to Subgroup 4. Finally, DP1 and DP5 belong to Subgroup 5. First the focus will be on Word results, then on Pseudoword results.

Putting behavioural results for the above defined subgroups in the context of the neuroimaging results for Word reading, half of DPs from Subgroup 1 (DP9 and DP14) exhibited similar patterns of neuroimaging results with the neural correlates of reading being consistent with the PDT and CDT. It was not clear in both cases whether the neuroimaging results were also consistent with the MDT. The other half of Subgroup 1 exhibited different profiles of neuroimaging results. The neural correlates of DP17's reading were not consistent with the predictions of any of the main theories. In contrast, DP15 showed underactivation consistent with the PDT, CDT and possibly the VDT, but not with the MDT.

The neural correlates of DP4 and DP8's reading (Subgroup 2) were not in agreement with predictions of any main theory. DP2 and DP16 from Subgroup 3 showed markedly different neural profiles; DP2 exhibited underactivation consistent with the CDT, whereas DP16 showed underactivation in agreement with PDT and possibly the VDT, but not the MDT. DP12 and DP13 (from Subgroup 4) also exhibited a very different profile on the neural level: underactivation consistent with the CDT and with the VDT, but not the MDT (DP12) and neural correlates of reading not consistent with any of the main theories (DP13). Finally, DP1 and DP5 exhibited very different profiles on the neuroimaging results. DP1 showed underactivation consistent with the PDT and CDT (it was not clear whether it was also consistent with the MDT), whereas DP5 showed underactivation consistent only with the CDT.

Focusing on Pseudowords, three (DP14, DP15 and DP17) out of four DPs from Subgroup 1 showed neural correlates of reading not consistent with the predictions of any of the main theories, whereas DP9 exhibited underactivation consistent with the PDT. DP4 and DP8 from Subgroup 2 both exhibited neural correlates of reading not consistent with the predictions of any of the main theories. Regarding Subgroup 3, DP16 showed underactivation consistent with all three main theories (the PDT, CDT and MDT), whereas DP2 exhibited neural correlates of reading not consistent with the predictions of any of the main theories. Moving on to Subgroup 4, DP12 exhibited underactivation consistent with the CDT and DP13 showed neural correlates of reading deficit not consistent with the predictions of any of the main theories. Finally, DP1 and DP5 (Subgroup 5) exhibited very different profiles. DP1 exhibited underactivation consistent with the CDT and MDT, whereas it was

not clear whether DP5 showed underactivation consistent with the VDT, but not the MDT.

It should be added that Subgroup 5 (DP1 and DP5) was of special interest because although both DPs reported problems with literacy acquisition and difficulties with literacy at the time of testing for this study, they did not show any deficits on behavioural literacy measures. Despite being relatively well compensated on the behavioural measures, they both exhibited underactivation on the neural level (see the details above). Their results suggest that although DPs can be compensated on the behavioural level, this does not mean that they are compensated on the neural level.

Summarising, DPs who have the same profile on behavioural measures can have similar profiles on the neural level, however in the subgroups examined above for Words and Pseudowords, a larger number of DPs with the same behavioural profile exhibited dissimilar, rather than similar, profiles on the neural level. It should be borne in mind that similar profiles on the neural level should be understood in the sense that they show underactivation consistent with a given theory, but do not necessary involve exactly the same brain areas. For instance, the neural correlates of DP9's and DP14's (Subgroup 1) Word reading were consistent with the predictions of the PDT and CDT, however, only one area associated with the PDT overlapped in both DPs. Furthermore, whereas two cerebellar areas overlapped in DP9 and DP14, another two cerebellar areas did not.

Table 6.7 Neuroimaging results for individual DPs in the context of the psychometric summary variables

Measures / number of an individual DP	*9*	*14*	*15*	*17*	*2*	*4*	*8*	*10*	*16*	*3*	*12*	*13*	*18*	*7*	*11*	*6*	*1*	*5*
Number of deficits (behavioural tests)	7/7 deficits				6/7 deficits					5/7 deficits				4/7 deficits	3/7 deficits		0/7 deficits	
Literacy measures																		
TOWRE Word Correct*	X	X	X	X	X	X	X	X	X	X	X	X	+	X	+	+	+	+
Pseudoword Reading Composite	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	+	+	+
Irregular Word Reading Composite	X	X	X	X	X	X	X	+	X	X	X	X	X	+	+	+	+	+
WRAT Spelling (% correct)*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	+	+
Phonological and orthographic measures																		
Phonological Awareness Composite	X	X	X	X	X	X	X	X	X	+	X	X	X	+	X	X	+	+
Phonological Fluency Composite	X	X	X	X	+	X	X	X	+	X	+	+	X	X	+	+	+	+
Orthography Composite	X	X	X	X	X	+	+	X	X	+	+	+	+	+	+	X	+	+
Neuroimaging - WORDS																		
[PDT]																X		
[MDT?]								X										
[CDT]					X													X
[PDT, +VDT?]									X									
[CDT, +MDT?]														X				
[CDT, +VDT]											X							
[PDT, CDT , +MDT?]	X	X											X				X	
[PDT, CDT, +VDT]										X					X			
[PDT, CDT, +VDT?]			X															
reading deficit inconsistent with any theory				X		X	X					X						
Neuroimaging - PSEUDOWORDS																		
[PDT]	X												X					
[CDT]											X							
[+VDT?]																		X
[PDT, CDT]								X		X								
[CDT, MDT]																	X	
[PDT, MDT, CDT]									X									
reading deficit inconsistent with any theory		X	X	X	X	X	X					X		X	X	X		

Note for Table 6.7. Abbreviations are the same as for Figure 6.1; Colour coding for the behavioural measures is the same as in Table 4.4; It should be noted that the following subgroups of DPs have the same profile on summary variables: Subgroup 1 (DP9, DP14, DP15 & DP17); Subgroup 2 (DP4 & DP8); Subgroup 3 (DP2 & DP16); Subgroup 4 (DP12 & DP13) and Subgroup 5 (DP1 & DP5); Colour Colour coding for the neuroimaging results marks all the cases which exhibit underactivation consistent with a given theory (e.g., PDT, e.g., Navy blue denotes 'reading deficit not consistent with any of the theories' for Words, etc.

7 The relationships between the psychometric and neuroimaging data

A considerable number of psychometric measurements were taken to ensure that the sample of DPs and the control group had desirable characteristics by satisfying inclusionary and exclusionary criteria for the main study presented in this thesis (see Chapter 3). The goal of this chapter is to examine the relationship between the psychometric and neuroimaging measures in the hope that further insights into their relationship can be gained.

The structure of this chapter is as follows. First, within group correlation analyses between the different psychometric data and the BOLD signal for Word and Pseudoword reading are presented. Second, analyses of two subgroups of DPs who significantly differed on *Orthography Composite* (and were both impaired on phonological processing, as revealed by *PA Composite* and *PF Composite* scores) are introduced and discussed. Third, the focus is on the question of whether there are within group associations between a score on *Purdue Pegboard Composite* and the BOLD signal for Words and Pseudowords in the cerebellar areas involved in reading and language, as defined in the Introduction.

The reason for focusing on the within group correlations is that it is very likely that the pattern of correlation within the group with dyslexia will differ from the pattern of correlation in the control group. Therefore the within group analyses will most likely reveal the most robust results.

7.1 Within group correlational analyses between the phonological, orthographic and literacy measures and the BOLD for Word and Pseudoword reading

Two sets of correlational analyses were performed. The first set focused on the correlation between the phonological and orthographic processing measures (*Phonological Awareness Composite (PA), Phonological Fluency Composite (PF), Digit Span* (z-score) and *Orthography Composite*) and the BOLD signal for Word or Pseudoword reading in CPs or DPs. The second set included correlational analyses between the literacy measures (*TOWRE* z-score (Words), *Pseudoword Composite*, *WRAT Spelling* (z-score) and *Irregular Word Composite*) and the BOLD signal for Word and Pseudoword reading in CPs or in DPs. The aim here was to uncover any covariance between the aforementioned measures and the patterns of BOLD signal for Word and Pseudoword reading.

It should be emphasised that although it is relatively straightforward to make predictions for the neuroimaging analyses, involving BOLD signal for Word and Pseudoword reading for a given group (e.g., DPs or CPs), it is considerably more difficult to make such predictions regarding the covariance between the behavioural measures and the BOLD signal for Word and Pseudoword reading. This is because the BOLD signal and behavioural scores are very different measures and each measure is potentially associated with different measurement errors and different amounts of variability between participants.

7.1.1 Within-group correlational analyses involving phonological and orthographic measures

Because measures of *phonological awareness, phonological fluency and digit span* are classic measures of phonological processing, and reading of Words and Pseudowords involves phonological processing, then it is reasonable to predict that there should be covariance between the aforementioned measures and the patterns of BOLD signal for Word and Pseudoword reading in some of the phonological processing areas, as defined in the Introduction. There should also be some overlap with the areas from the reading network discussed in the Introduction. These predictions should hold for both CPs and DPs. However, fMRI analyses (Chapter 6) revealed that there is considerable heterogeneity in patterns of BOLD (including underactivation and overactivation) in individual DPs' phonological areas (relative to the control group), hence on a group level the scores for BOLD in a given brain area and a given behavioural measure may not 'move together' (Starbird, 2006).

Orthography Composite consisted of accuracy and speed measures on the Orthographic Word-Pseudohomophone Choice Test (Olson et al., 1994) and participants had to decide whether the two items *'rane'* or *'rain'* had correct spelling. This decision required orthographic processing, because these items have identical phonological forms. Processing of orthographic information involves accessing the orthographic lexicon (a collection of neural representations which code for whole real word orthographic representation). Therefore it seems reasonable to predict that there should be correlations with BOLD for Word reading in areas which process orthographic information (and phonological areas, as defined in the Introduction). Again these predictions should hold for both CPs and DPs, but for the reason specified above the effects for DPs may be smaller, or even non-existent.

It needs to be emphasised here that currently there is no consensus on the localisation of the orthographic lexicon in the brain. As discussed in the

Introduction, some researchers have put forward a hypothesis according to which 'the Visual Word Form Area' (VWFA) is responsible for processing the orthographic forms of words (Cohen et al., 2000; Cohen et al., 2002; Cohen et al., 2003). However, some other investigators (e.g., McCrory et al. 2005; Price & Devlin, 2003) have questioned this conclusion and, on the basis of their research, have put forward a hypothesis that this area must be involved in a more general process of binding visual with phonological information (see Introduction for more details). Price and Devlin (2003) suggested that there may be no neural area in the brain that is specific to visual (orthographic) word processing, rather, activation specific to reading arises from interactions between language areas (involved in many different functions) and visual areas. The authors also emphasized that this hypothesis is in line with the claim made by Plaut, McClelland, Seidenberg, and Patterson (1996) and by Seidenberg and McClelland (1989) that knowledge of familiar grapheme combinations is a product of interactions between orthographic, phonological and semantic processing, and exists without explicit word form representations. A more recent study (Glezer, Jiang, & Riesenhuber, 2009), using fMRI rapid adaptation technique, have claimed however, that their results support the hypothesis that VWFA contains an orthographic representation of words based on neurons which are highly selective for individual real words.

A meta-analysis of 36 neuroimaging studies of reading (Taylor, Rastle, & Davis, 2012), using the quantitative activation likelihood estimation technique, identified a cluster in the L anterior fusiform gyrus (MNI coordinates: x=-22, y=-34, z=-14), part of the occipito-temporal visual processing stream, that responded more strongly to Words than Pseudowords. The authors suggested that it may contain the orthographic lexicon, as defined by, for instance, the Dual Route Cascaded (DRC) model (Coltheart et al., 2001). According to this model, the orthographic lexicon consists of form-independent and context-independent representations of the letter sequences which constitute familiar words. (For more details on the DRC model see also the sections: 'Development of the reading network' in Chapter 1 and 'Within-group correlational analyses involving literacy measures' below)**.** However, they pointed out that this result is also consistent with an alternative explanation that this area is involved in processing semantics, because this region was found to be sensitive to semantic variables such as imageability (Hauk, Davis, Kherif, & Pulvermüller, 2008) and because of the overlap between the cluster reported in Taylor et al.'s (2012) meta-analysis and a

cluster identified as being involved in semantic processing by Binder, Desai, Graves, and Conant (2009).

Furthermore, it was reported (Bitan et al., 2005) that areas showing task-specific activations for spelling were identified in the intra-parietal sulcus; the activation in the local maxima was identified in the L superior parietal lobule, and the L inferior parietal lobule. The results on the L inferior parietal lobule presented by Bitan et al. (2005) are congruent with Taylor et al.'s (2012) findings regarding spelling-to-sound conversion. Bitan et al. (2005) also reported activation in the L fusiform gyrus, but this area was engaged in both spelling and rhyming judgments on visually presented words.

On the basis of the literature review on orthographic processing, presented above, and the areas involved in the reading network as well as the phonological areas presented in the Introduction, it can be predicted that the correlation for *Orthography Composite* and BOLD signal for Word reading will involve: the VWFA (Cohen et al., 2000; Cohen et al., 2002; Cohen et al., 2003; Glezer et al., 2009), and L fusiform gyrus (Taylor et al., 2012), the L superior parietal lobule, L inferior parietal lobule (part of BA40) (Bitan et al., 2005), as well as the other phonological areas discussed in the Introduction. As Pseudowords by definition do not have lexical representations, there should be a correlation for *Orthography Composite* and BOLD signal for Pseudoword reading in sub-lexical processing of orthography (and phonology), and hence no correlation is predicted for the VWFA on the account proposed by Cohen and colleagues, and Glezer et al. (2009). However, the hypothesis put forward by McCrory et al. (2005), according to which this area must be involved in a more general process of binding visual with phonological information, would predict activation in VWFA for Pseudowords (and also for Words). These predictions should be applicable for both CPs and DPs. It must be born in mind, however, that for the reason specified above, the effects for DPs may be smaller, or even non-existent.

7.1.2 Within-group correlational analyses involving literacy measures

Both *TOWRE* (Words) and the BOLD for Words involve real word reading, therefore there should be significant correlations between these measures in the phonological areas and reading network areas (as defined in the Introduction). Similarly for *Pseudoword Composite* and BOLD for Pseudowords, because both measures involve Pseudoword reading, significant correlations should be found for these measures in the phonological areas and areas within the reading network (as defined in the Introduction). Significant correlations should be observed for CPs

and DPs. However, for the reason specified above, the effects for DPs may be smaller, or even non-existent.

Although both *Orthography Composite* and *WRAT Spelling* tap into orthographic processing, they differ on some characteristics. For instance, the latter involves recall of the whole word-form from the phonological representation (WRAT is presented in the auditory modality), whereas the former requires recognition and differentiation between different orthographic items (with the same phonological form), presented in the visual modality. Therefore, in the current study the outcome from these tests was investigated as separate measures in the correlation with BOLD for Word and Pseudoword reading. Predictions for the outcomes of the correlation analysis of *WRAT Spelling* with BOLD signal for Word reading are, regarding phonological and orthographic areas, the same as the predictions for the *Orthography Composite* (see the paragraph on *Orthography Composite* above, for details).

Finally the focus is on the correlation analysis for *Irregular Word Composite* and BOLD for Words and Pseudowords. One way of thinking about the predictions here is to use the framework of the DRC model (Coltheart et al., 2001). The DRC model consists of two routes for mapping orthography to phonology. The lexical route maps the orthographic form of a given word to its corresponding phonological form and is crucial for reading irregular words. The non-lexical route contains rules for converting graphemes into phonemes and is important for reading pseudowords. Regular words are pronounced correctly by both routes. It is important to emphasise here that both routes will be activated in parallel by all stimuli which contain familiar graphemes. As CPs' reading system is unimpaired, the DRC would predict some overlap in processing of regular and irregular words. Therefore it could be predicted that there would be a correlation between *Irregular Word Composite* and BOLD for Words in phonological areas and in reading network areas (as defined in the Introduction). A similar prediction would also hold for Pseudowords, but because Pseudowords do not have lexical representations, there should be no impact of lexical entries on the correlation between *Irregular Word Composite* and BOLD signal for Pseudoword reading. These predictions should hold for both CPs and DPs. However, for the reason specified above, the effects for DPs may be smaller, or even non-existent.

Because this chapter focuses on post-hoc correlations between behavioural and neuroimaging outcome measures, brain areas termed 'other areas' are also reported in the analyses, although they were not predicted (from the phonological areas or

reading network areas, as defined in the Introduction); some of them are explored in more detail in the Discussion section in this chapter. This also refers to cerebellar areas (labelled as such), beyond those characterised in the Introduction, as involved in language processing, and the L & R V5/MT+ (magnocellular areas), labelled as such.

7.1.3 Materials and Methods

7.1.3.1 Participants

Please see Chapter 3 for the details of participants.

7.1.3.2 Psychometric measurements

Please see Chapter 3 for the details of the psychometric measures.

7.1.3.3 Group correlational analysis (see Table 7.1)

'Con' images for each individual participant obtained in the 1st level analysis, described in Chapter 5, were entered into the 2nd level analysis using SPM. Following Hoeft et al.'s (2007) procedure (email communication with Fumiko Hoeft on the 9th and 11th of September 2012, and with Guillaume Flandin on the 8th of October 2012) this analysis involved whole brain voxel-by-voxel correlation of BOLD measure for Word reading or Pseudoword reading for DPs or CPs with each given behavioural measure, relating to: 1) phonological or orthographic processing (*Phonological Awareness*, *Phonological Fluency* and *Orthography Composites*, as well as *Digit Span*, and 2) literacy measures (*TOWRE* z-score (Words), *Pseudoword Composite* (Pseudowords only), *WRAT Spelling* z-score and *Irregular Word Composite*).

A second analysis (ROI analysis) was run with only the areas which belonged to the phonological processing network and which were possible to define in the Anatomy Toolbox (v 1.7). According to Poldrack, Mumford and Nichols (2011) the reason for this is that the best practice for ROI analysis (not based on ROI derived from one's own participants) is to use an atlas which is not based on a single-subject, such as the AAL atlas (Tzourio-Mazoyer et al., 2002), or the Talairach atlas (Talairach & Tournoux, 1988), but a probabilistic cytoarchitectural atlas, such as the one devised by Eickhoff et al. (2005).

The phonological areas defined by the Anatomy Toolbox (v 1.7) for the ROI analyses, included: L Area 44, L Area 45, L Area 6, L IPC (PF), L IPC (PFcm), L IPC (PFm), L IPC (PFop), L IPC (PFt), L IPC (PGa), L IPC (PGp), L Insula (Id1), L Insula (Ig1), L Insula (Ig2) and L TE3. It should be noted here that the following

phonological areas were not included in the ROI analysis because they are not available in the Anatomy Toolbox v.1.7: the L middle temporal gyrus, L fusiform gyrus, VWFA, Wernicke's area (except for TE3) and L insular cortex, except for the L insular areas specified above.

Because DPs are characterised by considerable heterogeneity in BOLD and behavioural measures, activation in a given area was considered as significant when 1) a voxel belonged to a cluster of 6 or more contiguous voxels (activation threshold = 6 voxels) (Pernet et al., 2009), as specified in Chapter 5; 2) activation was specified as $p<0.001$, uncorrected for multiple comparisons. Table 7.1 and Table 7.2 specify the analyses performed. The results are presented in Tables 7.3–7.6 and in Tables 15.1-15.28 (Appendix F).

7.1.3.3.1 ADHD and DCD - potential confounding variables

As described earlier in this thesis, the sample was screened for cases 'at risk' of clinical ADHD and DCD and such cases were not included in the group analyses. Despite screening participants for being 'at risk' of clinical ADHD and DCD, the groups significantly differed on ADHD (A+B) and ADHD Index (D) measures and all DCD measures (see Chapter 3 for details). Therefore to control for the potential confounds in the correlational analyses, the ADHD (A+B) measure and DCD Total measure were entered into the correlational analyses as covariates. The ADHD (A+B) measure was chosen because it is the most transparent measure and involves Inattention and Hyperactivity/Impulsivity measures, both of which could have an impact on reading and phonological processing. The DCD Total was chosen because it summarises all the DCD measurements. *d Prime* (on scores from the post-test on items read by the participants in the fMRI scanner) was also entered as a covariate (see Chapter 5 for details).

Table 7.1. Within-group correlation analyses between phonological processing measures (*PA, *PF* and *Digit Span* z-score) and the orthographic processing measure (*Orthography Composite*) and the BOLD signal for Words and Pseudowords**

CPs (N=16)		DPs (N=16)	
BOLD - Word reading	**BOLD - Pseudoword reading**	**BOLD - Word reading**	**BOLD - Pseudoword reading**
Correlation analysis 1 with *PA Composite*	Correlation analysis 5 with *PA Composite*	Correlation analysis 1 with *PA Composite*	Correlation Analysis 5 with *PA Composite*
Correlation analysis 2 with *PF Composite*	Correlation analysis 6 with *PF Composite*	Correlation analysis 2 with *PF Composite*	Correlation analysis 6 with *PF Composite*
Correlation analysis 3 with *Digit Span*	Correlation analysis 7 with *Digit Span*	Correlation analysis 3 with *Digit Span*	Correlation analysis 7 with *Digit Span*
Correlation analysis 4 with *Orthography Composite*	Correlation analysis 8 with *Orthography Composite*	Correlation analysis 4 with *Orthography Composite*	Correlation analysis 8 with *Orthography Composite*

Note: *PA = PHONOLOGICAL AWARENESS COMPOSITE; PF = PHONOLOGICAL FLUENCY COMPOSITE.

Table 7.2 Within-group correlational analyses between the literacy measures (*TOWRE* z-score (Words), *Pseudoword Composite* (Pseudowords only), *WRAT Spelling* z-score, *Irregular Word Composite*) and the BOLD signal for Words and Pseudowords

CPs (N=16)		DPs (N=16)	
BOLD - Word reading	**BOLD - Pseudoword reading**	**BOLD - Word reading**	**BOLD - Pseudoword reading**
Correlation analysis 1 with *TOWRE (Words)*	Correlation Analysis 4 with *Pseudoword Composite*	Correlation analysis 1 with *TOWRE (Words)*	Correlation analysis 4 with *Pseudoword Composite*
Correlation analysis 2 with *WRAT Spelling*	Correlation analysis 5 with *WRAT Spelling*	Correlation analysis 2 with *WRAT Spelling*	Correlation analysis 5 with *WRAT Spelling*
Correlation analysis 3 with *Irregular Word Composite*	Correlation analysis 6 with *Irregular Word Composite*	Correlation analysis 3 with *Irregular Word Composite*	Correlation analysis 6 with *Irregular Word Composite*

7.1.4 Results

The neuroimaging results for CPs are shown in Table 7.3 and Table 7.5 (for details see also Appendix F). The neuroimaging results for DPs are shown in Table 7.4 and Table 7.6 (see also Appendix F for details). The correlation results for the whole brain voxel-by-voxel analysis are reported first, they are followed by the results from the ROI analysis.

7.1.4.1 Control group

7.1.4.1.1 Correlation between Phonological Awareness (PA), Phonological Fluency (PF) and Orthography Composites, as well as Digit Span and BOLD (Table 7.3 below, and Appendix F).

The CPs did not show any significant correlation (all correlations at $p<0.001$, uncorrected for multiple comparisons, unless stated otherwise) between *PA Composite* and BOLD for Words or between *Orthography Composite* and BOLD for Words. In contrast, CPs exhibited significant correlations between *PF Composite* and BOLD for Words in a number of phonological areas (L Area 6, L Area 44 and L IPC (PFt) (and R insula (Id1)), one cerebellar area (L Lobule VI (Hem)) and some 'other areas' (L superior frontal gyrus, L (& R) hIP3, L Area 1 and L Area 4). A significant correlation was also found for *PF Composite* in the follow up ROI analysis in L Area 6 [local maxima, MNI coordinates: x=-22, y=-14, z=58, T=4.97, Z=3.53, $p<0.00001$; k=44; Probability=50%, Range=40-70%] (*p* denotes the chance of finding (under the null hypothesis) a voxel with this or a greater height (*T-statistic* or *Z-statistic*), corrected or uncorrected for search volume; *k* denotes the number of voxels in a cluster; *'Probability'* denotes the probability that a given voxel was assigned to a given cytoarchitectonic area (Eickhoff et al., 2005). To increase the reliability of the anatomical labelling, the probability at the corresponding voxel and the probability *'Range'* for the surrounding voxels were also calculated (Eickhoff et al., 2005) and are reported here. An effect in ROI analysis in L Area 44 did not survive the correction for the number of voxels ($k<6$).

Finally, there were significant correlations between the BOLD and *Digit Span* measures across many brain areas. These included phonological processing areas (L insula lobe, L Area 44 and L middle temporal gyrus, as well as some RH areas (R IPC (PGp), R IPC (PGa), R insula (Id1), R TE 3 and R angular gyrus); one cerebellar area (R Lobule IX (Hem)) and some 'other areas', including: the L superior occipital gyrus, L OP1, L SPL (7A), L Area 2, L superior temporal gyrus, L hIP2, L OP4, L superior medial gyrus, R Area 2, R superior frontal gyrus, R precuneus and R postcentral gyrus. A significant effect for *Digit Span* was also found in the follow-up ROI analysis in: L Area 44 [local maxima, MNI coordinates: x=-60 y=14, z=18, T=5.45, Z=3.72, $p<.00001$; k=13; Probability=50, Range=40-60%] and L IPC (PFcm) [local maxima, MNI coordinates: x=-44 y=-38, z=30, T=4.86, Z=3.48, $p<.00001$; k=6; Probability=30, Range=0-40%]; an effect in ROI analysis in L TE3 did not survive the correction for the number of voxels ($k<6$).

Moving on to the correlations of the above variables with BOLD for Pseudoword reading (see Table 7.3 below and Appendix F), CPs showed no significant correlations in the areas within the phonological processing network in the voxel-by-voxel analysis, except for *Digit Span*. There was a significant correlation between *PA Composite* and BOLD in two cerebellar areas (L Lobule VI (Hem) and L Lobule IX (Vermis)) and two 'other areas' (L SPL (7P) and R hIP1). For *PF Composite*, there was a significant effect in only one area – the L inferior temporal gyrus. There were also significant correlations for *Digit Span* in three phonological areas (L middle temporal gyrus, L Area 44 and L IPC (PFt)) and in several 'other areas', including: the L Area 4p, L posterior cingulate cortex, L middle frontal gyrus, RH hIP2, R SPL (7PC), R thalamus, R cuneus and R precunes. There was a significant effect for *Digit Span* in the follow-up ROI analysis in L Area 44 [local maxima, MNI coordinates: x=-48, y=10, z=40, [T=5.04, Z=3.55, p<.000001; k=7; Probability=40%, Range=20-50%] and L IPC (PFt) [local maxima, MNI coordinates: x=-52, y=-20, z=32, T=4.63, Z=3.38, p<.000001; k=10; Probability=70%, Range=60-70%].

Finally, there were significant correlations for BOLD and *PF* and *Orthography Composites* but only in the L inferior temporal gyrus and L SPL (7A), respectively.

7.1.4.1.2 Correlation between *TOWRE* z-score, *Pseudoword Composite*, *WRAT Spelling* and *Irregular Word Composite* with BOLD signal (Table 7.5 below and Appendix F)

The CPs, as a group, showed significant correlations between the BOLD for Word reading and *TOWRE*, and *WRAT Spelling* in numerous areas. In contrast, a significant effect for *Irregular Word Composite* involved only one area.

For *TOWRE*, areas with a significant correlation included: phonological areas (L Area 6, L IPC (PFcm), L Area 44 (as well as some RH areas, such as: R Area 6, R IPC (PGa), R IPC (PGp) and R middle temporal gyrus) and 'other areas' - LH areas (L SPL (7A), L hIP1, L middle frontal gyrus, L pallidum, L putamen and L thalamus), as well as RH areas (R middle frontal gyrus, R hIP3, R anterior cingulate cortex, R middle orbital gyrus, R superior orbital gyrus and R thalamus). A significant correlation was found for *TOWRE* in the follow-up ROI analysis in: L IPC (PFcm) [local maxima, MNI coordinates: x=-44 y=-38, z=30, T=5.23, Z=3.63, p<.00001; k=13; Probability=30, Range=0-40%] and L Area 44 [local maxima: x=-58 y=12, z=22, T=5.88, Z=3.87, p<.00001; k=11; Probability=50, Range=30-60%]. An effect in L Area 6, L TE 3 and L IPC (PGa) did not survive the correction for the number of voxels (all<6).

There were significant correlations between BOLD for Words and *WRAT Spelling* across many brain areas, including: phonological areas (L (&R) fusiform gyrus, R insula (Id1) and R insula (Ig2)), three cerebellar areas (L Lobules I-IV (Hem), L Lobule IX (Hem) and L Lobule V (Hem)), one magnocellular area (R hOC5 (V5)) and numerous 'other areas' (L inferior temporal gyrus, L (& R) OP3, L hippocampus, R Hipp (CA), L calcarine cortex, L middle occipital gyrus, R superior parietal lobule, R caudate and R amygdala (LB)). In contrast, a significant correlation for BOLD and the *Irregular Word Composite* measure was found only in the L middle orbital frontal gyrus.

Regarding correlations between BOLD signal and the behavioural measures for Pseudowords, there were no significant correlations for *Pseudoword Composite* in the phonological areas, however, there were significant correlations in two cerebellar areas (R Lobule IX (Hem) and Lobule X (Vermis)) and in two 'other areas' (L middle occipital gyrus and L SPL (7PC)).

Moving on to correlations with *WRAT Spelling*, there were significant correlations in the phonological areas (L Area 44, R inferior frontal gyrus (p. Orbitalis) and R insula Lobe), two cerebellar areas (L Lobules I-IV (Hem) and R Lobules I-IV (Hem)) and in L hOC5 (V5/MT+). 'Other areas', included LH areas, such as the L inferior temporal gyrus, L Hipp (FD), L middle occipital gyrus and L para-hippocampal gyrus, as well as, RH areas (R supra-marginal gyrus, R TE 1.0, R putamen and R middle frontal gyrus). A significant correlation for *WRAT Spelling* was also found in the follow-up ROI analysis in L Area 44 [local maxima, MNI coordinates: x=-50, y=8, z=30, T=4.91, Z=3.5, p<.00001; k=16; Probability=50, Range=30-50%]. An effect in ROI analysis in L IPC (PFop) did not survive the correction for the number of voxels (k<6).

Finally, a significant correlation between BOLD for Pseudowords and *Irregular Word Composite* was found in one cerebellar area (R Lobule VIIa Crus I (Hem)) and in two 'other areas' (L Hipp (CA) and L hippocampus).

7.1.4.2 The group with dyslexia

7.1.4.2.1 Correlation between Phonological Awareness (PA) Composite, Phonological Fluency (PF) Composite, Orthography Composite, and Digit Span with BOLD (see Table 7.4 below, and Appendix F).

Interestingly, for Words, DPs exhibited a significant correlation in the L middle temporal gyrus and L inferior temporal gyrus for all *PA, PF* and *Orthography Composites*. Additionally, a number of areas exhibited significant correlations. Two cerebellar areas (R Lobule IX (Hem) and Vermal Lobule X) and three 'other areas'

(L inferior temporal gyrus, R Area 17 and L Hipp (CA)) showed significant correlations for *PA Composite*. Only one other area (L superior temporal pole), exhibited a significant correlation for *PF Composite*. Finally, phonological areas showed significant correlations for *Orthography Composite* (L IPC (PGa) and L IPC (PFm) as well as, the R angular gyrus and R Area 6); and some 'other areas', including: the L inferior temporal gyrus, L hIP1, L Area 2 and R SPL (7A). A significant correlation was also found in the subsequent ROI analysis in L IPC (PGa) [local maxima, MNI coordinates: x=-42, y=-54, z=54, T=5.04, Z=3.55, p<.00001; k=18; Probability=30%, Range=0-30%] and in L IPC (PFm) [local maxima: x=-54, y=-56, z=44, T=4.34, Z=3.25, p=0.001; k=9; Probability=60%, Range=50-60%]. Finally, a significant correlation between BOLD and *Digit Span* was exhibited in the L temporal pole. A significant correlation for *Digit Span* was also found in the follow-up ROI analysis in L Area 44 [local maxima, MNI coordinates: x=24 y=-38, z=14, T=4.69, Z=3.41, p<.00001; k=24; Probability=10, Range=0-20%].

The correlations of the above composite variables with DPs' BOLD for Pseudowords were significant in the L middle temporal gyrus for all measures, except for *Digit Span*. Furthermore, two cerebellar areas (L Lobule IX (Hem) and R Lobule VIIIb (Hem)) and one 'other area' - L Hipp (CA) exhibited significant correlations for *PA Composite*. For the *PF Composite*, three additional areas showed significant correlations (R Area 6, L Lobule VIIa Crus I (Hem) and R superior frontal gyrus). Finally, the BOLD signal within a large number of areas was significantly correlated with *Orthography Composite*. This included, phonological areas (L (& R) Area 6, L IPC (PGa)), L fusiform gyrus and R IPC (PFm); one cerebellar area (L Lobule VIIa Crus I (Hem)) and some 'other areas' (L (& R) SPL (7P), L hIP2, R SPL (7P) and L (& R) SPL (7A). The significant effect was also found in the subsequent ROI analysis in L IPC (PGa) [local maxima, MNI coordinates: x=-46, y=-60, z=46, T=5.32, Z=3.67, p<.00001; k=14; Probability=70%, Range=60-70%]. Additionally, the ROI analysis revealed a significant effect, which was not revealed by the voxel-by-voxel analysis, in L IPC (PFm) [local maxima, MNI coordinates: x=-52, y=-58, z=44, T=4.11, Z=3.13, p=0.001; k=14; Probability=50%, Range=50-50%]. This is most likely due to the fact that an ROI analysis reduces the number of statistical tests to be controlled for, in contrast to a voxel-by-voxel analysis of the whole brain (Poldrack et al., 2011). Effects in L Area 44 and L Area 6 did not survive correction for the number of voxels (k<6).

No area showed a significant correlation between BOLD signal and *Digit Span* in the voxel-by-voxel analysis.

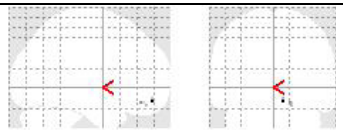
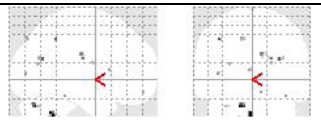
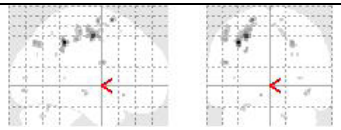
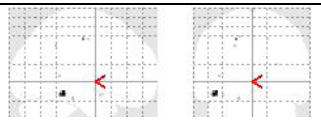
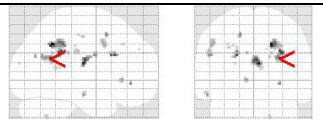
7.1.4.2.2 Correlations between TOWRE z-score, Pseudoword Composite (Pseudowords only), WRAT Spelling z-score and Irregular Word Composite with BOLD (see Table 7.6 below, and Appendix F)

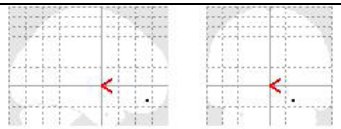
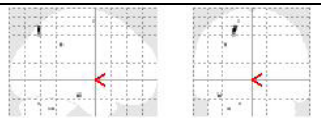
For the BOLD signal for Words, no brain area in the DPs group analysis showed a significant correlation with the *TOWRE* measure. The BOLD measure showed a significant correlation with *WRAT Spelling* in three brain areas, including: one phonological area (R IPC (PFm)), one cerebellar area (R Lobule IX (Hem)) and two 'other areas' (L inferior temporal gyrus and R middle frontal gyrus). There was a significant correlation between BOLD and *Irregular Word Composite* in only one phonological area (L IPC (PFm)) (see Table 7.6 below and Appendix F).

BOLD signal for Pseudowords and *Pseudoword Composite* showed a significant correlation in only L Area 3a (see Table 7.6 below, and Appendix F). BOLD signal and *WRAT Spelling* measure correlated in large number of areas, which included: phonological areas (L middle temporal gyrus and (R Area 6, R IPC (PFm), R IPC (PGp) and R angular gyrus)), three cerebellar areas (L Lobule VIIa Crus I (Hem), R Lobule VIIa Crus II (Hem), L Lobule VI (Hem)) and one other area (L inferior temporal gyrus). An effect in L IPC (PFop) did not survive the correction for the number of voxels ($k<6$) in the ROI analysis. The correlation for *WRAT Spelling* in L Area 6, in the follow-up ROI analysis, did not survive the correction for the number of voxels ($k<6$).

The BOLD signal correlated significantly with scores for *Irregular Word Composite* in one RH area, homologous to LH phonological area - R IPC (PFm) and two 'other areas' (L (& R) middle frontal gyrus).

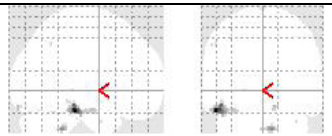
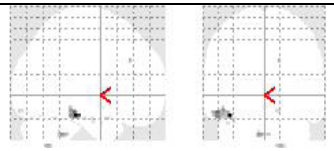
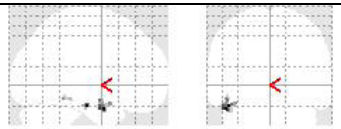
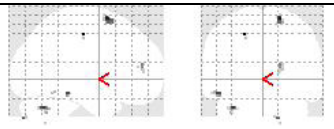
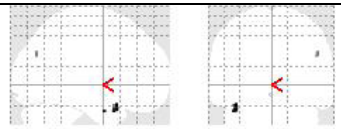
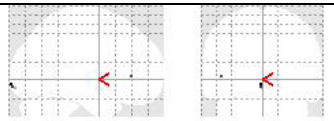
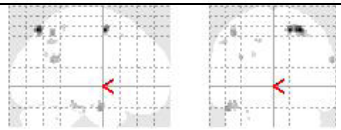
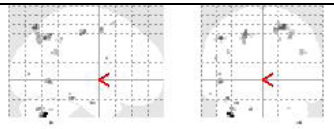
Table 7.3 CPs (N=16) Results for the within-group correlation analyses between *PA, *PF* and *Orthography Composites* and BOLD signal for Words and Pseudowords (whole brain voxel-by-voxel analysis)**

BOLD - Word reading (CPs, N=16)			**BOLD - Pseudoword reading (CPs, N=16)**		
correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001^, uncorrected for multiple comparisons)	correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001, uncorrected for multiple comparisons)
Correlation analysis 1 with **PA Composite**		No areas survived the voxel threshold	Correlation Analysis 4 with **PA Composite**		*Cerebellar areas* **Assigned to L Lobule VI (Hem) (13)** **Assigned to L Lobule IX (Vermis) (23)** *Other areas* [R hIP1 (9)] **Assigned to L SPL (7P) (10)**
Correlation analysis 2 with **PF Composite**		*Phonological network areas* **Assigned to L Area 6 (97)** L Area 44 (14) L IPC (PFt) (47) **[Assigned to R Insula (Id1) (7)]** *Cerebellar areas* **Assigned to L Lobule VI (Hem) (8)** *Other areas* L superior frontal gyrus (16) **Assigned to L hIP3 (36)** **[**R hIP3 (27)] **Assigned to L Area 4 (6)** **Assigned to L Area 1 (47)**	Correlation analysis 5 with **PF Composite**		*Other areas* L inferior temporal gyrus (26)
Correlation analysis 4: **with Digit Span (z-score)**		*Phonological network areas* L insula lobe (15) **Assigned to L Area 44 (13)** L middle temporal gyrus (34) L superior temporal gyrus (Wernicke's area) (34) [R IPC (PGp) (77)] [R IPC (PGa) (77)] [R Insula (Id1) (62)] [R TE 3 (62)]	Correlation analysis 8: **with Digit Span z-score**		*Phonological network areas* L middle temporal gyrus (6) **Assigned to L Area 44 (23)** **Assigned to L IPC (PFt) (10)** ***Other areas:*** **Assigned to L Area 4p (12)** L posterior cingulate cortex (15) L middle frontal gyrus (10) R precunes (105) R hIP2 (105)

		[R angular gyrus (28)] *Cerebellar areas* R cerebellum_9 (9) Other areas L superior occipital gyrus (23) L OP1 (16) **Assigned to L SPL (7A) (52)** **Assigned to L Area 2 (52)** L hIP2 (16) **Assigned to L OP 4 (12)** **[Assigned to R Area 2 (31)]** L superior medial gyrus (11) [R superior frontal gyrus (8)] [R precuneus (31)] [R postcentral Gyrus (31)]			R SPL (7PC) (105) R thalamus (59) R cuneus (54)
Correlation analysis 3 with **Orthography Composite**		No areas survived the voxel threshold	Correlation analysis 6 with **Orthography Composite**		*Other areas* **Assigned to L SPL (7A) (17)**

Note: ^ SPM doesn't report *'r'* values (Will Penny, email communication 25th of February 2013), therefore only *p* values are reported.

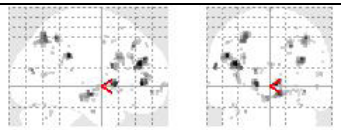
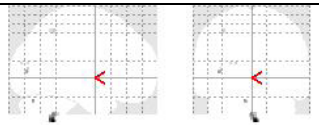
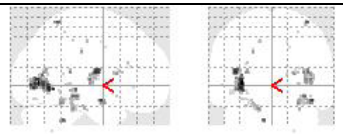
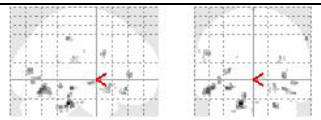
Table 7.4 DPs (N=16) Results for the within-group correlation analyses between *PA*, PF* and *Orthography Composites* and BOLD signal for Words and Pseudowords (whole brain voxel-by-voxel analysis)

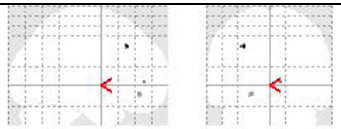
BOLD - Word reading (DPs, N=16)			**BOLD - Pseudoword reading (DPs, N=16)**		
correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001, uncorrected for multiple comparisons)	correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001, uncorrected for multiple comparisons)
Correlation analysis 1 with **PA Composite**		*Phonological network areas* L middle temporal gyrus (155) *Cerebellar areas* R Lobule IX (Hem) (42) Vermis_10 (42) ***Other areas:*** L inferior temporal gyrus (155) R Area 17 (6) L Hipp (CA) (21)	Correlation Analysis 4 with **PA Composite**		*Phonological network areas* L middle temporal gyrus) (87) *Cerebellar areas* L Lobule IX (Hem) (28) R Lobule VIIIb (Hem) (19) *Other areas* L Hipp (CA) (87)
Correlation analysis 2 with **PF Composite**		*Phonological network areas* L middle temporal gyrus) (49) Other areas L inferior temporal gyrus (14) L superior temporal pole (10)	Correlation analysis 5 with **PF Composite**		*Phonological network areas* L middle temporal gyrus (7) [R Area 6 (38)] *Cerebellar areas* **Assigned to L Lobule VIIa Crus I (Hem) (36)** *Other areas* [R superior frontal gyrus (10)]
Correlation analysis 4: **with Digit Span (z-score)**		Other areas L temporal pole (24)	Correlation analysis 8: **with Digit Span (z-score)**		No area survived the voxel threshold
Correlation analysis 3 with **Orthography Composite**		*Phonological network areas* L IPC (PGa) (L angular gyrus) (21) L middle temporal gyrus (33) **Assigned to L IPC (PFm) (9)** [R angular gyrus (22)] [R Area 6 (27)] *Other areas* L inferior temporal gyrus (21) L hIP1 (8) **Assigned to L Area 2 (6)**	Correlation analysis 6 with **Orthography Composite**		*Phonological network areas* L Area 6 (10) [R Area 6 (11)] **Assigned to L IPC (PGa) (14)** L fusiform gyrus (7) L middle temporal gyrus) (19) [R IPC (PFm) (14)] *Cerebellar areas* **Assigned to L Lobule VIIa Crus I (Hem) (9)** *Other areas*

		[Assigned to R SPL (7A) (75)]			**Assigned to L SPL (7P) (40)** **Assigned to L hIP2 (6)** **[Assigned to R SPL (7P) (33)]** L SPL (7A) (40) R SPL (7A) (22)

See Note for Table 7.3.

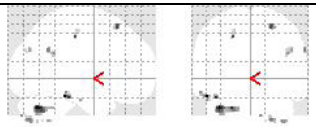
Table 7.5 CPs (N=16) Results for the within-group correlation analyses between literacy and neuroimaging (BOLD) measures (whole brain voxel-by-voxel analysis)

BOLD - Word reading (CPs, N=16)			**BOLD - Pseudoword reading (CPs, N=16)**		
correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001, uncorrected for multiple comparisons)	correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001, uncorrected for multiple comparisons)
Correlation analysis 1: **with TOWRE z-score (Words)**		*Phonological network areas* **Assigned to L Area 6 (6)** [R Area 6 (26)] L IPC (PFcm) (33) **Assigned to L Area 44 (49)** [R IPC (PGa) (61)] [R IPC (PGp) (14)] [R middle temporal gyrus (14)] *Other areas:* **Assigned to L SPL (7A) (71)** L hIP1 (33) L middle frontal gyrus (31) [R middle frontal gyrus (63)] L pallidum (12) [R anterior cingulate cortex (27)] **[Assigned to R hIP3 (32)]** [R middle orbital gyrus (9)] [R superior orbital gyrus (10)] L putamen (33) L thalamus (43) R thalamus (33)	Correlation Analysis 5: **with Pseudoword Composite**		***Cerebellar Areas*** **Assigned to R Lobule IX (Hem) (61)** **Assigned to Lobule X (Vermis) (61)** *Other areas* L middle occipital gyrus (6) **Assigned to L SPL (7PC) (6)**
Correlation analysis 2: **with WRAT Spelling (z-score)**		*Phonological network areas* L fusiform gyrus (211) [R fusiform gyrus (20)] [R insula (Id1) (24)] [R insula (Ig2) (48)] *Cerebellar areas* **Assigned to L Lobules I-IV (Hem) (33)** L Lobule IX (Hem) (8) L Lobule V (33)	Correlation analysis 6: **with WRAT Spelling z-score**		*Phonological network areas* L Area 44 (23) [R inferior frontal gyrus (p. Orbitalis) (9)] [R insula Lobe (7)] *Cerebellar areas* L Lobules I-IV (Hem) (62) **Assigned to R Lobules I-IV (Hem) (15)** Magnocellular areas: L hOC5 (V5) (30) *Other areas*

		Magnocellular Areas: R hOC5 (V5) (25) Other areas: L inferior temporal gyrus (211) **Assigned to L OP 3 (35)** **Assigned to R OP 3 (48)** L hippocampus (11) [R superior parietal lobule (12)] **[Assigned to R Hipp (CA) (24)]** [R caudate (10)] L calcarine cortex (7) L middle occipital gyrus (211) R Amyg (LB) (24)			L inferior temporal gyrus (110) **Assigned to L Hipp (FD) (15)** L middle occipital gyrus (30) L para-hippocampal gyrus (7) [R supra-marginal gyrus (8)] [R TE 1.0 (17)] [R putamen (7)] [R mid. frontal gyrus (22)]
Correlation analysis 3: **with Irregular Word Composite**		*Other areas* L middle orbital frontal Gyrus (12)	Correlation analysis 7: **with Irregular Word Composite**		*Cerebellar areas* R Lobule VIIa Crus I (Hem) (17) *Other Areas* L Hipp (CA) (12) L hippocampus (15)

See Note for Table 7.3.

Table 7.6 DPs (N=16) Results for the within-group correlation analyses between literacy and neuroimaging (BOLD) measures (whole brain voxel-by-voxel analysis)

BOLD - Word reading (DPs, N=16)			**BOLD - Pseudoword reading (DPs, N=16)**		
correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001, uncorrected for multiple comparisons)	correlation	SPM map	Areas where there is significant positive correlation between the measures (p<.001, uncorrected for multiple comparisons)
Correlation analysis 1: **with TOWRE z-score (Words)**		No area survived the voxel threshold	Correlation Analysis 5: **with Pseudoword Composite**		Other areas L Area 3a (8)
Correlation analysis 2: **with WRAT Spelling (z-score)**		*Phonological network areas* **Assigned to R IPC (PFm) (23)** *Cerebellar areas* R cerebellum_9 (13) Other areas L inferior temporal gyrus (58) R middle frontal gyrus (6)	Correlation analysis 6: **with WRAT Spelling z-score**		*Phonological network areas* L middle temporal gyrus (16) [R Area 6 (17)] [R IPC (PFm) (12)] **[Assigned to R IPC (PGp) (6)]** [R angular gyrus (6)] *Cerebellar areas* **Assigned to L Lobule VIIa Crus I (Hem) (223)** **Assigned to R Lobule VIIa Crus II (Hem) (20)** L cerebellum_6 (223) Other areas L inferior temporal gyrus (16)
Correlation analysis 3: **with Irregular Word Composite**		*Phonological network areas* **Assigned to L IPC (PFm) (7)**	Correlation analysis 7: **with Irregular Word Composite**	`	*Phonological network areas* **[Assigned to R IPC (PFm) (143)]** Other areas L middle frontal gyrus (47) [R middle frontal gyrus (23)]

See Note for Table 7.3.

7.1.5 Discussion

7.1.5.1 Results for *Phonological Awareness (PA), Phonological Fluency (PF)* and *Orthography Composites,* as well as for *Digit Span*

7.1.5.1.1 CPs' correlations with BOLD signal for Word reading

As predicted, for the CPs, there were significant correlations between BOLD for Word reading and *PF Composite* in phonological areas. These areas included the areas in the anterior reading system (L Area 6 and L Area 44), the R insula, and the dorsal reading system area L IPC (PFt) (L supra-marginal gyrus). There was also a significant correlation in the cerebellum (L Lobule VI (Hem)).

Broadly speaking, these results are similar to those reported for covert RAN for letters (Misra et al., 2004), less to those reported for covert RAN for objects (for further details see Misra et al. (2004)). Both studies found an effect in L Area 6, insula, L IPC and L hIP3. However, there were also differences. The study reported here found an additional effect in L Lobule VI (Hem), L superior frontal gyrus, L Area 4 and L Area 1. In contrast, Misra et al.'s (2004) study, found an additional effect in R middle temporal gyrus, L temporal pole, L anterior thalamus, L hOC3v (V3v) and R Area 17. These differences are most likely due to: 1) differences in the stimuli - Misra et al.'s (2004) study investigated letters, whereas this study relied on *PF Composite* scores which consisted of combined scores for RAN for pictures, colours, letters and digits; 2) this study showed correlation of the composite score and BOLD for Words, whereas Misra et al.'s (2004) presented the direct BOLD measurement during participants' performance on RAN for pictures or letters in the MRI scanner.

Interestingly there was also an effect here in 'other areas' (areas outside the ones which were defined as of interest in the Introduction) with the local maxima described by the following MNI coordinates; x=-34, y=-40, z=44. This area was labeled in Misra et al.'s (2004) study as L angular/supra-marginal gyrus, however, more recently, Scheperjans et al.'s (2008) study was the first to provide evidence for a distinct cytoarchitectonic area within this location, which the authors called - hIP3. At present it is not clear what the role of this area is, because to date, there have been only a few studies which have examined this area. For instance, Gillebert, Mantini, Peeters, Dupont, and Vandenberghe (in press) demonstrated that attentional selection between competing stimuli involves hIP3 (as well as hIP1). It was also reported (Uddin et al., 2010), using functional connectivity analysis, that L hIP3 exhibited connectivity with extra-striate visual areas (V3, V4 and V5/MT+),

and this result was confirmed with DTI analysis (Uddin et al., 2010). It is possible that the significant effect in this area for correlation between RAN tasks and BOLD for Words originates from shared demands on attentional processes in the visual domain. This is a post-hoc finding, involving an area which was not of primary interest in this study, nevertheless, it is of interest, especially in the context of connections with V5/MT+.

A significant correlation between BOLD for Words and *Digit Span* was found in a number of phonological areas, including the anterior, dorsal and ventral systems and the L insula. This result is consistent with the predictions and is similar to the one reported for *PA Composite*. Interestingly, there were significant effects in RH homologues of the LH phonological system, including areas from dorsal and ventral systems and the R insula. A significant effect was also observed (but only in the ROI analysis) in the L IPC (PFcm) - an area which has been suggested to be important (Paulesu et al., 1993) for verbal short term memory, and is also involved in the dorsal system of the reading network (Pugh, Mencl, Jenner et al., 2000; Sandak et al., 2004).

There was a significant correlation between *Digit Span* and BOLD for Words in some 'other areas', (for the full list of areas see Table 7.3 and Appendix F). These included, among others, the R cerebellar Lobule IX, L SPL (7A) and L hIP2. The significant effect in the R cerebellar Lobule IX is surprising because, one would expect to find it in some or all lobules which were reported to be activated in a meta-analysis (Stoodley & Schmahmann, 2009) in verbal working memory and language tasks. However, it was recently reported (Bernard et al., 2012) that the R cerebellar Lobule IX exhibits functional connectivity with the L Crus I and L Lobule VI and both lobules are involved in language and verbal working memory processing (Stoodley & Schmahmann, 2009). Furthermore, the activation in L SPL (7A), is particularly interesting in light of a recent report by Heim et al. (2012), which showed that this area is most likely involved in general aspects of motor sequencing, including the sequencing of speech. Finally, Gillebert et al. (in press) observed, using resting-state fMRI, that hIP3 (and hIP1) were highly correlated with PFm (part of the supra-marginal gyrus).

The lack of a significant effect for *PA Composite* and BOLD for Word reading, in CPs was unexpected for at least two reasons. First, phonological awareness is usually reported as a significant predictor of reading ability in children (e.g., Bradley & Bryant, 1983; Mann, 1984; Olson et al., 1989), see also Bowey (2005) for a review. However, it is less clear whether phonological awareness is a

significant predictor of literacy skills in adults who acquired reading in childhood. For instance, Ramus et al. (2003) reported that a phonology composite (which consisted of phonological awareness, phonological fluency and digit span variables, and therefore was not a pure measure of phonological awareness) was the main predictor of literacy and accounted for 76.1% of the variance in this variable. Reid et al. (2007) reported that phonological awareness accounted for unique variance in literacy, however, this result was not significant ($p<0.09$) with the relatively small sample. Second, CPs activated a network of areas consisting of the anterior, dorsal and ventral systems associated with the PDT, when reading Words, relative to the fixation cross (as reported in Chapter 5).

At present, a reason for the lack of significant correlation between *PA Composite* and BOLD for Word reading is not clear and warrants further research. It could be due to many factors, including the fact that the Word reading in CPs may be over-learnt and automatic, resulting in a BOLD signal with less fluctuation in the areas of interest. However, on its own this is an unlikely explanation, because CPs clearly exhibited correlations between BOLD for Words and other behavioural measures. Therefore, the outcome is most likely also to be due to the characteristics of *PA Composite*. For instance, *PA Composite* consisted of measures from the Spoonerism test and Phonological Pseudoword Forced-Choice test (Olson, et al., 1994) and perhaps a better predictive power would be found with a *PA Composite* which would consist of a larger number of *PA* measures, such as, word rhyming, pseudoword rhyming, alliteration, sound deletion and other measures.

Finally, there were no significant correlations for *Orthography Composite* and BOLD signal for Word reading in CPs, an outcome that is not in line with the predictions. Again it is not clear why this is the case and further research is needed to clarify this outcome. Potentially, it could be due to many factors, including, 1) the fact that Word reading in CPs may be over-learnt and automatic, resulting in a BOLD signal with less fluctuation and 2) the particular characteristics of the behavioural measure – the *Orthography Composite*. The *Orthography Composite* consisted of measures on the Orthographic Word Pseudo-homophone Choice Test (Olson et al., 1994) percent correct and time. It is possible that an *Orthography Composite* which consists of a larger number of orthographic measures (with different emphasis on orthographic processing) would exhibit better predictive power for BOLD signal for Word reading in CPs.

7.1.5.1.2 CPs' correlations with BOLD signal for Pseudoword reading

The results for Pseudowords, were broadly in line with the predictions. The most similar results to the results for Words, were for *Digit Span* and BOLD for Pseudowords. The significant effect was in the same areas of the anterior and ventral systems. Additionally a significant effect was found in L IPC (PFt). This is an area which was demonstrated (Paulesu et al., 1993) to be essential for verbal short term memory and is also a constituent part of the dorsal system of the reading network (Pugh, Mencl, Jenner et al., 2000; Sandak et al., 2004). Significant correlations were detected in different sub-parts of the L BA 40 for Words and Pseudowords - L IPC (PFcm) and L IPC (PFt), respectively. Currently it is not clear what the function of these cytoarchitectonic sub-areas of L BA40 in phonological processing is, hence this warrants future research. This is because these areas (till recently treated as one area – BA40) may differ significantly in their involvement in phonological processing.

There was a significant effect for *PF Composite* and BOLD for Pseudowords only in one 'other area' – the L inferior temporal gyrus. One caveat here is that currently there are no cytoarchitectonic data available for the inferior temporal gyrus that are three-dimensional, observer-independent and take into account inter-subject differences in brain architecture and macroscopy. It is likely that the L inferior temporal gyrus consists of several distinctive cytoarchitectonic sub-areas. This is because different studies have reported involvement of this area in different processes, such as: visual word identification, the mapping of phonology to semantics, lexical retrieval and sound-meaning interface (Cohen, Jobert, Le Bihan, & Dehaene, 2004; Hickok & Poeppel, 2004; Mechelli et al., 2005). Given the findings cited above, it is not clear why this effect was observed only for the correlation of the *PF Composite* with Pseudowords, but not for Words. However, neuroimaging studies (Fiez et al., 1999; Mechelli et al., 2003; Price, Wise, & Frackowiak, 1996) have demonstrated that Pseudowords tend to exhibit stronger activation than Words in the L inferior temporal gyrus. It is possible that this stronger effect for Pseudoword reading was more easily detected in the correlation analyses with *PF Composite* and BOLD signal for Pseudoword reading.

In contrast to the results for BOLD signal for Word reading, there was a significant effect in two cerebellar areas – the L Lobule VI and L Lobule IX for the correlation between BOLD signal for Pseudowords and *PA Composite*. As

discussed above the former area is involved in language processing, whereas the latter may be indirectly involved in linguistic processing.

In contrast to the results for Words, there was a significant relationship in the L SPL (7A) for the correlation between *Orthography Composite* and BOLD for Pseudowords. This finding is congruent with the predictions. However, it is not clear why there was no significant effect in the other brain areas specified in the introductory section for this chapter. It could be due to many factors and warrants further research. It is also worth noting here that L SPL, as discussed earlier, seems to be involved, among other functions, in the sequencing of speech (Heim et al., 2012). As both Pseudoword reading and orthographic processing involve sequencing, it may be the case that the observed correlation reflects the processes associated with this common characteristic.

7.1.5.1.3 A brief summary of the main results for CPs for Words and Pseudowords

Congruent with the predictions, there were significant correlations between BOLD for Words and Pseudowords and *PF Composite* and *Digit Span* in phonological areas. The BOLD signal in the L anterior and L dorsal areas consistently correlated with these behavioural measures, except for the *PF Composite* for Pseudowords, where the correlation was only noted in the ventral area. In contrast to the predictions, no significant correlations were noted between BOLD for Words and *PA* and *Orthography Composite*s. The reason for this result is unclear and further investigation is needed here. Finally, there were also significant correlations between BOLD for Words and Pseudowords and most behavioural measures in areas outside the ROI areas. The most consistent result was noted for L SPL.

7.1.5.1.4 DPs' correlations with BOLD signal for Word and Pseudoword reading

Consistent with the predictions there was a significant correlation between the *PA, PF and Orthography Composites* and the BOLD signal for Words and BOLD signal for Pseudowords in the L middle temporal gyrus in DPs. As discussed in the Introduction, the L middle temporal gyrus is typically activated in neuroimaging studies which tap into phonological and semantic processing (Lurito et al., 2000; McDermott et al., 2003; Moore & Price, 1999; Tivarus et al., 2008). The results reported here indicate the probable association in this area between BOLD and phonological and orthographic processing (on the behavioural level) in DPs. It is interesting to note here that the correlation in this area was consistent over different behavioural measures (except for *Digit Span*) for both Words and Pseudowords.

Perhaps a surprising result here is that DPs (in contrast to CPs) showed significant correlations for BOLD for Word and Pseudoword reading and *PA Composite* in a number of areas. These included, among other areas, the L middle temporal gyrus (already mentioned above) for both: Words and Pseudowords, two cerebellar areas for Words (R Lobule IX Hem and Vermal Lobule X), two cerebellar areas for Pseudowords (L Lobule IX (Hem) and R Lobule VIIIb (Hem)) and one hippocampal area (L Hipp (CA)) for both Words and Pseudowords. Vermal Lobule X and R Lobule IX Hem are functionally connected with the L (& R) IPC (PGp) and L (& R) angular gyrus (Bernard et al., 2012). These results suggest that cerebellar areas which exhibit correlations in the current study may be indirectly involved in language processing. Finally, it was reported (Cabeza, Dolcos, Graham, & Nyberg, 2002) that hippocampal regions were activated not only for episodic retrieval but also for working memory, a crucial skill for reading (Jerman & Swanson, 2005). Furthermore, resting-state functional connectivity analyses (Uddin et al., 2010) showed that the hippocampus is linked, among other areas, to IPC PGa (part of the angular gyrus). Therefore it is likely that it has some (indirect) involvement in language processing.

PF Composite and BOLD for Words, as well as *PF Composite* and BOLD for Pseudowords, correlated significantly in the L middle temporal gyrus, which is consistent with the predictions. Additionally, there was a significant effect in L inferior temporal gyrus and L superior temporal pole for Words. A similar effect was observed for Pseudowords in the L inferior temporal gyrus (see discussion regarding this area above) for CPs. The function of the temporal pole is not well understood (Olson, Plotzker, & Ezzyat, 2007). The results from various studies indicate that this area is involved in many diverse processes, including face recognition and theory of mind (Olson et al., 2007), retrieval of words for unique entities (Grabowski et al., 2001) and semantic processing (Tsapkini, Frangakis, & Hillis, 2011). A more recent study (Shim, Hurley, Rogalski, & Mesulam, 2012), which investigated spelling errors in the three subtypes of primary progressive aphasia, reported that atrophy in the L temporal pole correlated with errors in exception word spelling. It is possible that, given the list of processes for which this area was implicated, and because the effect in L temporal pole was noted for Words and RAN tasks, but not Pseudowords and RAN tasks, it reflects semantic processing in the study presented in this thesis. Finally, there was a significant effect in L Lobule VIIa Crus I (Hem) for Pseudoword reading. As this lobule is

involved in language processing, it is likely that the correlation here reflects both tasks requiring processing of linguistic information.

One of the most striking results for DPs, in the light of the results for the CPs, was the finding that there was a significant correlation between *Digit Span* and BOLD for Words in only the L temporal pole. Furthermore, no areas showed a significant correlation in this analysis with BOLD for Pseudowords. The role of the L temporal pole is not well understood and judging from the wide range of processes in which this structure is involved, it is most likely that it consists of sub-areas which can only be detected with a modern cytoarchitectonic analysis (Zilles et al., 2002). It remains to be seen which cytoarchitectonic sub-area of the L temporal pole will correlate with Digit Span. Correlations for *Digit Span* (for Words and Pseudowords) were the only correlations from the phonological and orthographic measures in DPs which did not show an effect in the L middle temporal gyrus. However, this finding is in the context of a result for DPs for *Digit Span*, which shows a significant correlation only in one area for Words and no areas for Pseudowords.

DPs exhibited significant correlations for the analysis involving the *Orthography Composite* variable and BOLD for Words and Pseudowords. In line with predictions, DPs showed correlation effects in the L IPC (PGa), L middle temporal gyrus (as already discussed above) and L IPC (PFm) for Words. Contrary to the predictions, there was no effect in VWFA for Words. This outcome could be due to many factors, for instance, the disfunction of VWFA in DPs, or considerable individual variation between DPs in the extent and location of this area in the standard space. Future studies would need to use an independent functional localizer scan to identify voxels in VWFA in every individual DP (Poldrack et al., 2011).

Congruent with the predictions, for Pseudowords, DPs exhibited correlations in L Area 6, L IPC (PGa) and L middle temporal gyrus (as discussed above). Interestingly there was a significant effect in the L fusiform gyrus with the local maxima with the following MNI coordinates: x=-38, y=-30, z=-20. VWFA, as defined by Cohen, Lehericy et al. (2002) had the following local maxima: x=- 43, y=-55, z=-17 (SD = ~ 0.5 cm) (MNI coordinates, transformed from the Talairach coordinates, using Brett's (1999) formula). Therefore VWFA is more posterior than the local maxima found here.

There was a significant effect for Pseudowords in L Lobule VIIa Crus I (Hem), an area that is implicated in language processing. Furthermore, significant

correlations were also found in 'other areas', including the L SPL (7A), which is involved in the sequencing of speech (Heim et al., 2012). The L SPL was also implicated in spelling (Bitan et al., 2005), however the cytoarchitectonic areas in the current study did not overlap with those of Bitan et al.'s (2005) study. Two 'other areas' were also implicated in the analysis for Pseudowords: L SPL (7P) and L hIP2. None of them, however, overlapped with the results reported by Bitan et al. (2005). L hIP2 exhibited strong functional connectivity with three language areas: the L inferior frontal gyrus, L insular cortex and L posterior middle temporal gyrus, supporting the involvement of these areas in language processing. L hIP2 connectivity with the frontal language areas was also confirmed by the DTI analysis (Uddin et al., 2010), revealing that L hIP2 can be indirectly involved in language processing.

The correlation analysis for the phonological and orthographic measures with BOLD for Word and Pseudoword reading revealed different profiles for CPs and DPs. Most notably, the groups consistently exhibited correlations in different brain areas for all measures. There were two exceptions here: 1) both groups exhibited correlations between BOLD for Pseudowords and the *Orthography Composite* in L SPL (7A), and 2) CPs did not exhibit significant correlations in any areas between *PA Composite* and BOLD for Words, and between *Orthography Composite* and BOLD for Words, whereas DPs did. Finally, DPs did not show any significant correlations between *Digit Span* and BOLD for Pseudowords, in contrast to CPs.

7.1.5.1.5 A brief summary of the main results for DPs for Words and Pseudowords

In agreement with the predictions, significant correlations between BOLD (for Words and Pseudowords) and *PA, PF* and *Orthography Composites* were noted. Interestingly, the BOLD signal in one L ventral area consistently correlated with all behavioural measures, except for *Digit Span*. In fact, no correlations within the predicted areas were noted for this behavioural measure. In contrast to the results for CPs, the BOLD signal for Words and Pseudowords correlated in a larger number of phonological areas for the *Orthography Composite*, including the ventral and dorsal areas. Significant correlations between BOLD for Words and Pseudowords and most behavioural measures were also noted in areas outside the ROI areas. For instance, the BOLD signal in L Hipp (CA) for Words and Pseudowords consistently correlated with *PA Composite*. Also, significant correlations between BOLD (for Words and Pseudowords) and the *Orthography Composite* were noted in R SPL.

7.1.5.2 Results for *TOWRE*, *Pseudoword Composite*, *WRAT Spelling* and *Irregular Word Composite*

7.1.5.2.1 CPs' correlations with BOLD signal for Word reading

As predicted, there was a significant correlation between BOLD for Word reading and *TOWRE* for Words in areas associated with phonological processing and areas from the cortical reading system in CPs (Pugh, Mencl, Jenner et al., 2000; Sandak et al., 2004). These included areas from the anterior reading sub-system (L Area 44 and L Area 6) and the dorsal reading sub-system (L IPC (PFcm)). There was also a correlation in the R angular gyrus (R IPC (PGa) and R IPC (PGp)). However, there was no correlation in the ventral reading-subsystem, but, there was a correlation in the R middle temporal gyrus. Some areas from the reading network, for which one would predict an effect, exhibited no significant correlations. For example, there was a lack of a significant effect in the L fusiform gyrus (including VWFA).

As discussed earlier, predictions are not put forward here for BOLD signal for just reading (Words or Pseudowords), but for a correlation between behavioural and neuroimaging measures. This is considerably more difficult because BOLD signal and behavioural scores are very different measures and each type of data point is potentially associated with different measurement errors and different amounts of variability between the participants. Therefore the observed effects could show the same trend, but be lower or exhibit a different trend, or even turn out to be undetectable.

Interestingly, there was a significant correlation for some 'other areas' not specified in the predictions, including L SPL (7A) and L hIP1. The L SPL (7A) is involved the sequencing of speech (Heim et al., 2012). Similar to hIP3, it is not clear, what the role of L hIP1 is. It was reported (Gillebert et al., in press) that hIP1 (together with hIP3, as discussed earlier) is involved in attentional selection between competing stimuli. Importantly, it was demonstrated, using resting-state functional connectivity analyses (Uddin et al., 2010) that hIP1 is connected with the insula. This result was also confirmed using DTI (Uddin et al., 2010). Therefore, it is possible that the correlations observed in the L hIP1 reflect (indirect) linguistic processes involved in reading.

The CPs exhibited a significant correlation between *WRAT Spelling* scores and BOLD for Words, in the L (& R) fusiform gyrus (and R insula (Id1) and R insula (Ig2)), in line with the predictions. The finding on the L fusiform gyrus is congruent with findings reported by Bitan et al. (2005). However, the L fusiform gyrus, reported by these researchers, was engaged in both spelling and rhyming

judgments on visually presented words. Perhaps surprisingly, especially in the light of findings by Bitan et al.(2005), there was no significant effect in the L inferior parietal lobule and L superior parietal lobule.

Interestingly, there were significant effects in the correlation involving *WRAT Spelling* in areas not predicted from the phonological and orthographic analysis of both tasks. First, there was a significant correlation in cerebellar areas (L Lobules I-IV (Hem), L Lobule IX and L Lobule V). It is interesting to note here that functional connectivity analysis (Bernard et al., 2012) showed that there is a functional connection between the R Lobules I-IV (Hem) and L IPC (PGp) (part of L angular gyrus), R Lobule IX and R IPC (PGp) (part of R angular gyrus). Therefore these lobules may be indirectly involved in language and spelling processing. Although no data were reported on the functional connectivity of the L cerebellar lobules it is possible that the connections are similar to those in R cerebellar hemisphere. Currently it is not clear why there was a significant correlation in L Lobules I-IV (Hem) and L Lobule V only for spelling. The involvement of R Lobule IX was less specific, because a significant correlation in this lobule was also found for BOLD for Pseudowords and *TOWRE (Words)* (CPs) and BOLD for Words and PA Composite (DPs). Second, there was a significant correlation in the R hOC5 (V5/MT+) which is in line with the predictions of the MDT, according to which good magnocellular function is hypothesised to be essential for high motion sensitivity and stable binocular fixation, and therefore for proper development of orthographic skills (Stein, 2001). However, it is not clear why there was no correlation in the L hOC5 (V5/MT+). It is possible that this is due to the fact that individual variation in extent and location of area L hOC5, in the standard space, in the CPs in the sample collected for the experiment reported in this thesis, is considerable (Malikovic et al., 2007).

Finally, contrary to the predictions, no significant correlations were found for *Irregular Word Composite* and BOLD for Words in the phonological areas and areas from the reading network, as defined in the Introduction. This could be due to many factors, including the fact that the Word reading in CPs may be over-learnt and automatic resulting in a BOLD signal with less fluctuation in the areas of interest. As underscored above, however, this on its own is an unlikely explanation, because CPs clearly exhibited correlations for BOLD for Words. Therefore, the outcome is most likely to be also due to some characteristics of the *Irregular Word Composite*. This composite consisted of a percent correct score and speed (in seconds) and for CPs it had a Mean=0 and SD=1. Perhaps the particular

characteristics of the *Irregular Word Composite* in combination with BOLD for over-learnt word reading resulted in the fact that these two scores did not 'move together' (Starbird, 2006) in areas of interest.

7.1.5.2.2 CPs' correlations with BOLD signal for Pseudoword reading

Regarding the results for Pseudoword reading in CPs, the most similar results to results for Word reading were for *WRAT Spelling* and BOLD for Pseudowords. Congruent with the predictions, significant correlations were found in one LH frontal area (L Area 44) and two RH areas (R inferior frontal gyrus and R insula). Perhaps surprisingly, and in contrast to the results for Words, there was no significant correlation in the L fusiform gyrus.

As for Words, there was a significant correlation in cerebellar lobules (L (&R) Lobules-IV (Hem)). There was also a significant correlation in L hOC5 (V5/MT+), providing some support for the MDT. It is not clear why there was no effect in the R hOC5 (V5/MT+), however, as stated in Chapter 5, one factor which could possibly contribute to this result may be that there is higher inter-subject variability (smaller maximal overlap) within hOC5 in the RH than in the LH (Malikovic et al., 2007).

Regarding the results for the *Pseudoword Composite* and BOLD for Pseudowords, there were no significant correlations within the phonological areas (as defined in the Introduction). This result is surprising, because both tasks tap into phonological processes. This outcome is unclear and warrants further investigation. However, there was significant effects in the R Lobule IX (Hem) and Vermal Lobule X. As described above R Lobule IX (Hem) is functionally connected to L (& R) IPC (PGp) (part of angular gyrus) (Bernard et al., 2012) and therefore this area may be involved (although indirectly) in the language processing network.

Finally, there was no significant correlation between *Irregular Word Composite* and BOLD for Pseudowords in the phonological and reading network areas, as specified in the Introduction. This result is not in line with the predictions and it is not clear why there were no significant effects here. One possibility (also relevant here) was discussed above in connection with BOLD for Words. However, the BOLD signal for Pseudowords in the R Lobule VIIa Crus I (Hem) significantly correlated with *Irregular Word Composite*. As described in the Introduction, this lobule was identified as an area involved in language, reading and working memory in other studies (see above) and therefore the correlation effect here is likely to reflect language and/or working memory processing.

7.1.5.2.3 A brief summary of the main results for CPs for Words and Pseudowords

In line with the predictions, there was a significant correlation between BOLD for Words and *TOWRE* in the phonological network, including anterior and dorsal areas. On the other hand, there was no significant correlation between BOLD for Words and this behavioural measure in the L fusiform gyrus (including VWFA). In contrast with the predictions there were no significant correlations between BOLD for Pseudowords and *Pseudoword Composite* in any of the phonological areas. Although there was a significant correlation for CPs between BOLD for Words and Pseudowords and *WRAT Spelling* in the phonological areas, ventral areas were implicated for Words and anterior for Pseudowords. No correlations in phonological areas were found for both behavioural measures and BOLD for Words and Pseudowords. These findings warrant further investigation. Finally, there were significant correlations between BOLD for Words and Pseudowords and the behavioural measures in areas outside the ROI areas. For instance, BOLD for Words and *TOWRE* and BOLD for Pseudowords and *Pseudoword Composite* significantly correlated in the L SPL. Furthermore, these behavioural and neuroimaging measures exhibited significant correlations also in the following areas: the cerebellar Lobules I-IV (Hem), L inferior temporal gyrus and L hippocampus.

7.1.5.2.4 DPs' correlations with BOLD signal for Word and Pseudoword reading

The most striking result for DPs was the lack of any correlation in phonological and reading network areas (as specified in the Introduction) for *TOWRE* and BOLD for Words, and *Pseudoword Composite* and BOLD for Pseudowords. One possible explanation here is that during reading, individual DPs (relative to the CPs) engage brain networks, which can differ, or partially differ from each other (See Chapter 6 for details). This, in combination with the particular behavioural scores could result in the outcome that the pairs of scores (BOLD and behavioural) did not 'move together' (Starbird, 2006), resulting in no significant correlation.

Moving on to the correlation between *WRAT Spelling* and BOLD for Word and Pseudoword reading, there was only one significant correlation which was in line with the predictions. It involved Pseudowords and the L middle temporal gyrus. There was also a significant correlation in the R IPC (PFm), part of the supra-marginal gyrus, for BOLD for Words and WRAT Spelling. This could reflect the existence of a potential compensatory mechanism for spelling. Furthermore, there were significant correlations here with the R Lobule IX (Hem), which as discussed above, has a functional connection with the R IPC (PGp) (part of R angular gyrus)

and hence observed activation may reflect indirect involvement in linguistic processing. Interestingly there was also a significant effect in the L inferior temporal gyrus, which may reflect involvement of this area in subserving the sound-meaning interface (Hickok & Poeppel, 2004).

Focusing on the correlation of *WRAT Spelling* and BOLD for Pseudoword reading, congruent with the predictions, there was a significant effect in the L middle temporal gyrus. This finding is interesting because this area was identified as being involved in the sound-meaning interface (Hickok & Poeppel, 2004). There were also significant effects in a number of RH areas, homologues of the LH language areas (R Area 6, R IPC (PFm), R angular gyrus and R IPC (PFm)). These may reflect a compensatory mechanism in DPs. DPs also exhibited a significant effect in three cerebellar areas implicated in language and reading (L Lobule VIIa Crus I (Hem), R Lobule VIIa Crus II (Hem) and L Lobule VI (Hem), hence a significant effect in these areas may reflect involvement in linguistic processing which is also important for spelling. There was a significant effect in the L inferior temporal gyrus, which as mentioned before, may be involved in subserving the sound-meaning interface (Hickok & Poeppel, 2004).

Finally, the focus is on the correlation between *Irregular Word Reading Composite* and BOLD for Words and Pseudowords. Regarding Words, the behavioural data indicate that DPs (as a group) were impaired on Word reading (*TOWRE*) and on Irregular Word Reading (speed) ($p<.01$), Irregular Word reading (accuracy) was significant at $p<0.05$. Furthermore, DPs, as a group were also impaired on Pseudoword reading speed ($p<.001$) (Pseudoword percent correct was significant at $p<0.05$). Hence the behavioural data suggest that both routes – the lexical and sub-lexical may be impaired. As was pointed out earlier, both routes will be activated in parallel by all stimuli which contain familiar graphemes, therefore there should be some overlap in the brain areas involved in reading both types of stimuli. It needs to be noted here that the extent of impairment of each route will probably influence the overlap. The results show that there was a significant effect in L IPC (PFm) (part of L angular gyrus). Currently it is not clear what the role of this particular cytoarchitectonic sub-area of the angular gyrus in language processing is. Studies which considered the L angular gyrus, as a whole, suggested that it is involved in the cross-modal mapping of graphemes to phonemes (Geschwind, 1965; Shaywitz et al., 1998). A recent meta-analysis (Taylor et al., 2012) suggest that this area is part of a lexical route and either serves as a phonological lexicon or is involved in semantic processing or both.

The predictions for the correlation between *Irregular Word Composite* and BOLD for Pseudoword reading in DPs are similar to those for Words. Both routes (sub-lexical and lexical) will be activated in parallel, therefore some overlap is predicted. In contrast to the predictions, there was no significant correlation in any of the phonological or reading network areas (as specified in the Introduction). However, one homologous area in the RH - R IPC (PFm) (part of R angular gyrus) exhibited a significant effect here. Two 'other areas' also showed significant effects here – the L and R middle frontal gyrus. Significant effects in these areas may indicate a compensatory mechanism in DPs.

DPs exhibited significant correlations for *TOWRE (Words), WRAT Spelling* and *Irregular Word Composite* in a smaller number of areas than the CPs. Particularly striking was the finding that DPs did not exhibit a correlation in any areas for *TOWRE* and BOLD for Word reading. There was overlap only in three areas for DPs and CPs: the R Lobule IX and L inferior temporal gyrus (*WRAT Spelling* and BOLD for Words) and the L inferior temporal gyrus (*WRAT Spelling* and BOLD for Pseudowords).

7.1.5.2.5 A brief summary of the main results for DPs for Words and Pseudowords

There were no significant correlations between BOLD for Words and *TOWRE*, and BOLD for Pseudowords and *Pseudoword Composite*. Also there were no significant correlations between BOLD for Words and *WRAT Spelling*, except in R IPC (PFm) which may reflect a compensatory mechanism. In line with the predictions, there was a significant correlation for BOLD for Pseudowords and *WRAT Spelling* in the L middle temporal gyrus. There were no correlations for these measures in any other areas in the phonological network, except four RH areas. There was a significant correlation between BOLD for Words and Pseudowords, and *Irregular Word Composite* in the L IPC (PFm) and R IPC (PFm), respectively. There were significant correlations for DPs between BOLD for Words, and Pseudowords and some behavioural measures in areas outside the ROI areas. For instance, a significant correlation for DPs between BOLD for Words and Pseudowords and *WRAT Spelling* was consistently found in the L inferior temporal gyrus. Finally, a significant effect was consistently found in cerebellar areas for the same measures.

7.2 Probing further questions on the level of two post-hoc sub-groups of DPs and on the level of individual DPs

The psychometric data, collected for the main study presented in this thesis, revealed that there are two sub-groups of DPs who significantly differ in their scores on *Orthography Composite*. However, they do not differ on the *PA* and *PF Composites* (both sub-groups are impaired on both phonological composites as compared to the CPs) (see Table 7.7 below and Table 7.17, Table 7.18 and Table 7.19 for details). These sub-groups can be used for probing two issues. First, the relationship between orthographic skills, reading and magnocellular processing can be tested. Second, the relationship between *PA* and *PF Composites* and under-engagement of the phonological areas during reading, can be investigated. However, it has to be emphasised that because these comparisons have post-hoc character the sub-groups are small (n<16) and therefore the neuroimaging analyses involving these sub-groups cannot be generalised to the population with dyslexia.

Regarding the first issue, as stated earlier, according to the MDT, good magnocellular function is essential for high motion sensitivity and stable binocular fixation, and therefore it has been hypothesized (Stein, 2001) that it is crucial for proper development of orthographic skills. Furthermore, as outlined in the Introduction, firstly, it was demonstrated (Liederman et al., 2003) that processing in V5/MT+ has an independent contribution to the reading process (most likely through image stabilization or letter localization) from the contribution of the areas responsible for phonological processing. Secondly, V5/MT+ is thought to receive a different input predominantly from the magnocellular stream (Tootell & Taylor, 1995; Watson et al., 1993) and therefore underactivation in this area (relative to CPs) can be interpreted as a manifestation of a magnocellular deficit. Therefore, the MDT would predict that there should be significant differences in BOLD in the V5/MT+ for Words and Pseudowords between DPs with impairment on *Orthography Composite* and CPs. In contrast, there should not be significant differences in BOLD in V5/MT+ for Words and Pseudowords between DPs with no impairment on *Orthography Composite* and CPs. The composite based on measures from the Orthographic Word-Pseudohomophone Choice test (Olson et al., 1994) was used here because it has been used in testing orthographic processing in the context of the MDT (e.g., Talcott et al., 2002; Talcott et al., 2000).

Focusing on the second issue, one can ask the question of whether DPs who are severely impaired on *PA* and/or *PF Composites* under-engage the areas from the

phonological network (as specified in the Introduction) during reading. Because phonological processing, measured on the behavioural level, is a good predictor of reading skills on the behavioural level, it may be also a good predictor of engagement of phonological areas, on the neural level, during reading. This question is asked on the level of the sub-group analysis and on the individual DP analysis.

Before proceeding with the neuroimaging analysis, required statistical analyses on behavioural data were carried out. These involved tests of normality for sub-group 1, sub-group 2 and the control group and statistical tests comparing the sub-groups on the following sets of measures: 1) age, handedness, IQ, ADHD and DCD; 2) *Orthography, PF* and *PA Composites* and 3) *Word reading (TOWRE), Pseudoword Composite* and *Irregular Word Composite*. The results from these analyses are presented below.

Table 7.7 Scores on *Orthography, PA* and *PF Composites* for individual DPs from sub-group 1 and sub-group 2

Individual DP	*Orthography Composite*	*PA Composite*	*PF Composite*
Sub-group 1: No orthographic deficit, but either PA or PF deficit [DPs - Orth Imp.], or both			
DP3	-0.4	-1	**-2.7**
DP4	0.2	**-3.1**	**-2.5**
DP7	-0.6	0.6	**-2.4**
DP11	0.0	**-7.9**	-0.8
DP12	-1.0	**-5.9**	-1.1
DP13	-1.6	**-2.5**	-1.6
DP18	-1.0	**-5.8**	**-2.3**
Subgroup 2: Orthographic deficit & either PA deficit or both PA and PF deficit [DPs + Orth. Imp.]			
DP2	**-2.4**	**-3.4**	-1.3
DP6	**-4.2**	**-5**	0.5
DP9	**-4.2**	**-5**	**-3.7**
DP10	**-6.7**	**-10.6**	**-5.2**
DP14	**-6.3**	**-4.5**	**-1.9**
DP16	**-4.8**	**-3**	-1.6
DP17	**-2.4**	**-4.4**	**-2.3**

Note: All scores are based on z-scores (as described in Chapter 4); DP1 and DP5 were excluded from the above subgroups because they were unimpaired on behavioural measures of phonological processing; DP8 and DP15 were also excluded from the subgroups due to the fact that they may be 'at risk' of clinical DCD.

7.2.1 Statistical Tests: Age, Handedness, IQ, ADHD and DCD

The descriptive statistics revealed that the distribution of PIQ scores departed from normality in sub-group 1 [DPs –Orth. Imp.] (Table 7.8). For the CPs, the distribution of scores for: age, handedness, ADHD A and DCD Total departed from normality (Table 7.9). Therefore for these variables, for the between group comparisons, a Mann-Whitney test was used. For the remaining variables an unpaired t-test was used, see Table 7.10 below, for the results.

Table 7.8 Test of normality for sub-group 1

	Shapiro-Wilk		
	Statistic	df	Sig.
age	.933	7	p=.573
handedness	.895	7	p=.304
PIQ	.769	7	p=.020*
FSIQ	.925	7	p=.513
VIQ	.819	7	p=.063
Digit Span	.888	7	p=.263
ADHD D	.905	7	p=.365
ADHD A	.918	7	p=.456
ADHD B	.913	7	p=.415
ADHD A+B	.894	7	p=.297
DCD Total	.906	7	p=.370

Table 7.9 Test of normality for CPs

	Shapiro-Wilk		
	Statistic	df	Sig.
age	.553	16^	p<.001**
handedness	.772	16	p=.001**
PIQ	.941	16	p=.357
FSIQ	.950	16	p=.485
VIQ	.965	16	p=.745
ADHD D	.967	16	p=.782
ADHD A	.872	16	p=.029*
ADHD B	.975	16	p=.911
ADHD A+B	.927	16	p=.218
DCD Total	.749	16	p=.001**

Note: ^as described in the section 'Participants' in Chapter 3.

The inferential statistics (Table 7.10) showed that there was a significant difference between sub-group 1 [DPs –Orth. Imp.] and the CPs on ADHD D [t(21)=2.512, p=.020], ADHD A [U=89, p=.027], ADHD A+B [t(21)=2.667, p=.014] and DCD Total [U=91, p=.018]. In contrast, there were no significant differences between sub-group 1 and CPs on age [U=60.5, p=.769], handedness [U=52, p=.820], PIQ [U=65, p=.579], FSIQ [t(21)=-1.052, p=.305] and VIQ [t(21)=-2.048, p=.060]. These results are very similar to the results presented in Chapter 3 on the comparisons between the DPs group (N=16) and the CPs (N=16).

Table 7.10 Sub-group 1 vs CPs (Mann-Whitney or unpaired samples t-test)

Variable	t or U value	DF	p value
age	U=60.5		p=.769
handedness	U=52		p=.820
PIQ	U=65		p=.579
FSIQ	t=-1.052	21	p=.305
VIQ	t=-2.048	21	p=.060
ADHD D	t=2.512	21	p=.020*
ADHD A	U=89		p=.027
ADHD B	t=1.651	21	. p=.114
ADHD A+B	t=2.667	21	p=.014*
DCD Total	U=91		p=.018*

Inspection of the data for subgroup 2 [DPs +Orth. Imp.] revealed that only age had a distribution which significantly differed from the normal distribution (see Table 7.11 for details). The between group comparisons (with the CPs) involving age, handedness, ADHD A+B and DCD Total were performed using a Mann-Whitney test (see Table 7.12 below). The between-group differences on the remaining variables were tested using an unpaired samples t-test (see Table 7.12).

Table 7.11 Test of normality for sub-group 2[DPs + Orth. Imp.]

	Shapiro-Wilk		
	Statistic	df	Sig.
age	.719	7	p=.006*
handedness	.917	7	p=.450
PIQ	.971	7	p=.904
FSIQ	.869	7	p=.183
VIQ	.871	7	p=.189
Digit Span	.922	7	p=.482
ADHD D	.878	7	p=.218
ADHD A	.925	7	p=.510
ADHD B	.867	7	p=.176
ADHD A+B	.934	7	p=.584
DCDTotal	.996	7	p=.999

The inferential statistics showed (Table 7.12) that there was a significant difference between sub-group 2 [DPs + Orth. Imp.] and the CPs on PIQ [T=-2.076, p=.05] and DCD Total [U=94, p=.01]. In contrast, no significant differences between the groups were noted on the remaining variables, including: age U=71.5, p=.308], handedness [U=44.5, p=.452], FSIQ [t(21)=-2.028, p=.060],

VIQ [t(6.994)=-1.181, p=.276], ADHD D [t(21)=.614, p=.546], ADHD A [U=68, p=.452], ADHD B [t(11.089)=1.151, p=.274] and ADHD A+B [t(21)=1.395, p=.178]. The results for PIQ, ADHD D and ADHD A+B differed from the between group comparison which involved the whole DPs group (N=16) (see Chapter 3 for details).

Table 7.12 Sub-group 2 [DPs + Orth. Imp.] vs the CPs (Mann-Whitney or unpaired samples t-test)

Variable	t or U value	DF	p value
age	U=71.5		p=.308
handedness	U=44.5		p=.452
PIQ	t=-2.076	20.974	p=.050*
FSIQ	t=-2.028	21	p=.060
VIQ	t=-1.181	6.994	p=.276
ADHD D	t=.614	21	p=.546
ADHD A	U=68		p=.452
ADHD B	t=1.151	11.089	p=.274
ADHD A+B	t=1.395	21	p=.178
DCDTotal	U=94		p=.01*

The inferential statistics revealed (Table 7.13) that there were no significant differences between sub-group 1 [DPs - Orth. Imp.] and sub-group 2 [DPs + Orth. Imp.] on all the variables (except for PIQ) tested in this section. These included: age [U=28, p=.710]; handedness [t(12)=.936, p=.368], FSIQ [t(12)=1.001, p=.336], VIQ [t(12)=.088, p=.931], ADHD D [t(12)= 1.014, p=.331], ADHD A [t(12)=.815, p=.431], ADHD B [t(12)=.424, p=.679], ADHD A+B [t(12)=.767, p=.458] and DCD Total [t(12)= t=-.519, p=.613]. The groups significantly differed on PIQ [U=9, p=.053].

Table 7.13 Sub-group 1 [DPs - Orth. Imp.] vs Sub-group 2 [DPs + Orth. Imp.] (Mann-Whitney or unpaired samples t-test)

Variable	t or U value	DF	p value
age	U=28		p=.710
handedness	t=.936	12	p=.368
PIQ	U=9		p=.053*
FSIQ	t=1.001	12	p=.336
VIQ	t=.088	12	p=.931
ADHD D	t=1.014	12	p=.331
ADHD A	t=.815	12	p=.431
ADHD B	t=.424	12	p=.679
ADHD A+B	t=.767	12	p=.458
DCDTotal	t=-.519	12	p=.613

7.2.2 Statistical Tests: *Orthography, PF* and *PA Composites*

Shapiro-Wilk test revealed that only the distribution of *PA Composite* scores departed from normality in sub-group 2 [DPs +Orth. Imp., + Phon. Imp.] (see Tables 7.14–7.16 below). Therefore an unpaired t-test was used for all the between group and sub-group comparisons, except those which involved *PA Composite* scores for sub-group 2. The comparisons, which involved the latter, were done using a Mann-Whitney test.

Table 7.14 Test of normality for sub-group 1 [-Orth. Imp., +Phon. Imp.]

	Shapiro-Wilk test		
	Statistic	df	Sig.
Orthography Composite	.968	7	p=.880
PA Composite	.964	7	p=.855
PF Composite	.885	7	p=.247

Table 7.15 Test of normality for sub-group 2 [+Orth. Imp., +Phon. Imp.]

	Shapiro-Wilk test		
	Statistic	df	Sig.
Orthography Composite	.909	7	p=.387
PA Composite	.733	7	p=.008*
PF Composite	.967	7	p=.880

Table 7.16 Test of normality for the control group

	Shapiro-Wilk test		
	Statistic	df	Sig.
Orthography Composite	.927	16	p=.220
PA Composite	.952	16	p=.517
PF Composite	.957	16	p=.600

As predicted (because neither sub-group 1 nor CPs were impaired on orthographic processing), the inferential statistics (Table 7.17) showed that there was no significant difference between DP sub-group 1 and CPs on *Orthography Composite* [t(21)=-1.507, p=.147]. There were, however, significant differences on *PF Composite* [t(21)= -4.656, p<.001] and *PA Composite* [t(6.520)=-3.145, p= .018].

Table 7.17 Unpaired t-tests – Sub-group 1 vs CPs

	t	DF	p value
Orthography Composite	-1.507	21	p=.147
PF Composite	-4.656	21	p<.001**
PA Composite	-3.145	6.520	p=.018*

Comparison of Sub-group 2 and CPs (Table 7.18) revealed, as predicted, that there were significant differences for every variable: *Orthography Composite* [t(21)=-7.878, p<.001], *PF Composite* [t(21)=-3.854, p=.001] and *PA Composite* [U=112, p<.000].

Table 7.18 Unpaired t-tests – Sub-group 2 vs CPs

	t or U value	DF	p value
Orthography Composite	t=-7.878	21	p<.001**
PF Composite	t=-3.854	21	p=.001**
PA Composite	U=112		p<.001**

Finally, as predicted, the between sub-group comparisons (Table 7.19) showed that the sub-groups with dyslexia significantly differed only on *Orthography Composite* [t(12)=5.579, p<.001] (one was selected as being impaired on *Orthography Composite*). There were no significant differences between the groups on *PF Composite* [t(12)= .404, p=.697] and *PA Composite* [U=19, p=.535].

Table 7.19 Sub-group 1 vs Sub-group 2

	t or U value	DF	p value
Orthography Composite	t=5.579	12	p<.001**
PF Composite	t=.404	12	p=.697
PA Composite	U=19		p =.535

7.2.3 Statistical Tests: Word reading (TOWRE), Pseudoword and Irregular Word Composites

The Shapiro-Wilk test (Tables 7.20-7.22) showed that the distribution of scores on the following measures: TOWRE (Words), *Pseudoword Composite* and *Irregular Words Composite* did not depart from normality in sub-group 1, sub-group 2 and CPs. Therefore, an unpaired t-test was used for all comparisons here.

Table 7.20 Normality Test for sub-group 1

	Shapiro-Wilk test		
	Statistic	df	Sig.
TOWRE (Words)	.948	7	p=.711
Pseudowords Composite	.872	7	p=.194
Irregular Words Composite	.858	7	p=.145

Table 7.21 Normality Test for the CPs

	Shapiro-Wilk test		
	Statistic	df	Sig.
TOWRE (Words)	.932	16	p=.259
Pseudowords Composite	.892	16	p=.060
Irregular Words Composite	.957	16	p=.607

Table 7.22 Normality Test for sub-group 2

	Shapiro-Wilk test		
	Statistic	df	Sig.
TOWRE (Words)	.866	7	p=.172
Pseudowords Composite	.869	7	p=.182
Irregular Words Composite	.862	7	p=.159

The inferential statistics (Table 7.23) showed that there was a significant difference between DP sub-group 1 and CPs on *TOWRE* (Words) [t(7.014)=-4.342, p=.003], *Pseudowords Composite* [t(6.914)=-5.650, p=.001] and *Irregular Words Composite* [t(6.760)= -2.435, p=.046].

Table 7.23 Sub-group 1 vs CP

	t	DF	p value
TOWRE (Words)	-4.342	7.014	p=.003*
Pseudowords Composite	-5.650	6.914	p=.001**
Irregular Words Composite	-2.435	6.760	p=.046*

Comparison of sub-group 2 and CPs (Table 7.24), similar to the comparison with the sub-group 1, revealed that there were significant differences for every variable: *TOWRE* (Words) [t(21)=-5.976, p<.001], *Pseudowords Composite* [t(6.184)=-3.127, p=.020] and *Irregular Words Composite* [t(8.839)=-5.054, p=.001].

Table 7.24 Sub-group 2 vs CP

	t	DF	p value
TOWRE (Words)	-5.976	21	p<.001**
Pseudowords Composite	-3.127	6.184	p=.020*
Irregular Words Composite	-5.054	8.839	p=.001**

Finally between the sub-group comparison (DP sub-group 1 vs DP sub-group 2) (Table 7.25) showed that the sub-groups did not significantly differ on any measure: *TOWRE* (Words) [t(11.672)=.469, p=.648], *Pseudowords Composite* [t(12)=.460, p=.653] and *Irregular Words Composite* [t(12)=.378 , p=.712].

Table 7.25 Sub-group 1 vs sub-group 2

	t	DF	p value
TOWRE (Words)	.469	11.672	p=.648
Pseudowords Composite	.460	12	p=.653
Irregular Words Composite	.378	12	p=.712

7.2.4 Neuroimaging analysis

Two types of analysis were performed. First, the comparisons which involved a whole brain voxel-by-voxel analysis, using an unpaired t-test in SPM were performed. This analysis probed two issues, as emphasised in the introductory section; the first issue, to do with magnocellular function and second issue to do with phonological processing. Four contrasts were tested for each comparison (see below). This type of analysis was chosen to characterise the differences between the groups across the whole brain, with particular interest in 'magnocellular areas' and phonological areas.

'Con' images for each individual participant obtained in the 1st level analysis, described in Chapter 5, were entered into the 2nd level analysis using SPM. DPs without impairment on the *Orthography Composite* and the CPs significantly differed on potential confounding variables, such as ADHD A+B and DCD Total (see Table 7.10, above), hence these two variables, as well as *d Prime* scores (described in Chapter 5), were entered to the neuroimaging analysis, as covariates. As DPs with impairment on the *Orthography Composite* and the CPs significantly differed on DCD Total and PIQ, but not on any measures of ADHD (see Table 7.12, above). DCD Total, PIQ and *d Prime* were entered into the neuroimaging analysis as covariates.

An ROI analysis which involved only the L and R hOC5 (V5/MT+) was run. The mask was prepared using Anatomy Toolbox V.1.7. (Eickhoff et al., 2005). The analysis was run in SPM, using an unpaired t-test, with the *SVC* (Small Volume Correction) option; SVC is usually used when one has an a priori anatomical hypothesis (The FIL Methods Group, 2006). Four contrasts were tested for each comparison (see below).

For the comparison involving DPs without impairment on the *Orthography Composite*, the following contrasts were tested: Words: DP[-Oth Imp]>CPs; Words: CPs>DP[-Oth Imp]; Pseudowords: DP[-Oth Imp]>CPs; Pseudowords: CPs>DP[-Oth Imp]. For the comparison involving DPs with impairment on the *Orthography Composite*, the following contrasts were tested: Words: DP[+Oth Imp]>CPs; Words: CPs>DP[+Oth Imp]; Pseudowords: DP[+Oth Imp]>CPs; Pseudowords: CPs>DP[+Oth Imp].

Additionally, follow-up analyses which directly compared the two sub-groups with dyslexia, were also run, to probe the patterns of activity within a given sub-group in comparison with the other sub-group. These involved the whole brain voxel-by-voxel analyses (with particular interest in magnocellular and visual areas, as well as in the phonological areas) and an ROI analysis with mask (constructed as described above) which consisted of the L and R hOC5 (V5/MT+). DPs without impairment on the *Orthography Composite* and DPs with impairment on the *Orthography Composite* significantly differed on PIQ (but not on ADHD A+B and DCD Total) (see Table 13, above). Therefore PIQ and *d Prime* scores were entered as covariates to the neuroimaging analyses. The analyses involved the following contrasts: Words: DPs [-Orth Imp]>DPs [+Orth Imp] and DPs [-Orth Imp]<DPs [+Orth Imp]; Pseudowords: DPs [-Orth Imp]>DPs [+Orth Imp] and DPs [-Orth Imp]<DPs [+Orth Imp].

7.2.4.1 Results from the neuroimaging analyses - comparisons with CPs (Table 7.26)

The results from the whole brain voxel-by-voxel analyses revealed that there were no significant differences between the CPs and DPs without impairment on *Orthography Composite* in three out of four contrasts (see Table 7.26, below, for summary of results and Tables 15.29-15.32 in Appendix F for detailed results). DPs without impairment on *Orthography Composite* exhibited a significantly stronger BOLD signal than CPs for Pseudowords in the frontal areas (L Area 44 and L Area 45) and in the L middle temporal gyrus. There were no significant differences between the groups in the L and R hOC5. The latter result was also confirmed in the ROI analysis.

There was significantly lower BOLD signal in DPs with impairment on *Orthography Composite* for Words than in the CPs in R hOC5 (V5) in both the whole brain voxel-by-voxel analyses and in the ROI analysis. The ROI analysis was performed using the *SVC* option and the significant effect had a local maximum at the following MNI coordinates: x=50, y =-66, z=8, T=4.08, Z=3.39, k=7, $p<0.000001$, search volume=image mask.

Interestingly, there were significant differences between a given sub-group and the CPs in some other visual areas. DPs, with no impairment on *Orthography Composite*, underactivated during Word reading the L Area 17 (V1); whereas DPs, with impairment on *Orthography Composite*, showed more complex results with underactivation of the R Area 17 (V1) and L Area 18 (V2) for Words, and overactivation of L hOCv4 (V4) for both Words and Pseudowords.

DPs, with impairment on *Orthography Composite*, also exhibited a significantly lower BOLD signal for Words and Pseudowords in phonological areas in the voxel-by-voxel whole brain analysis. For Word reading, these areas included several frontal areas (L Area 45, L Area 44 and L Area 6), L insula, L middle temporal gyrus and L IPC (PGa) (BA39)). For Pseudowords, the significant difference (underactivation) was only in the L IPC (PFop) (BA40). Finally, DPs with impairment on the *Orthography Composite* exhibited a significantly higher BOLD signal in L Area 44 when reading Pseudowords.

7.2.4.2 Results from the neuroimaging analyses - sub-group 1 vs sub-group 2 (Table 7.27)

There were significant differences between the sub-groups in brain activation in visual and phonological areas. For Words, DPs with impairment on *Orthography Composite* overactivated many areas in comparison with the DPs without impairment on *Orthography Composite* in the whole brain voxel-by-voxel analyses

(see Table 7.27). These included: 1) a phonological area - L IPC (PFcm, and 2) visual areas (L hOC4v (V4), L hOC3v (V3v), L Area 18, and R Area 17). In contrast, DPs without impairment on *Orthography Composite* did not overactivate any areas for Words, relative to the other group with dyslexia.

For Pseudowords, DPs with impairment on *Orthography Composite* overactivated (relative to DPs without impairment on *Orthography Composite*) one phonological area (L IPC (PGp)) and two visual areas (R Area 17 and L Area 18) (see Table 7.27). On the other hand, DPs without impairment on *Orthography Composite* (relative to DPs with impairment on *Orthography Composite*) overactivated two phonological areas, including one RH area – L Area 45 and R Area 44. Neither of the groups showed overactivation or underactivation (relative to each other) of V5/MT+ in either the whole brain voxel-by-voxel or in the ROI analyses.

Table 7.26 Results for neuroimaging analyses in two sub-groups of DPs, as compared to CPs

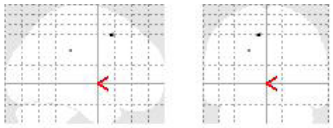
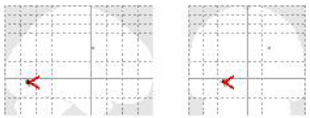
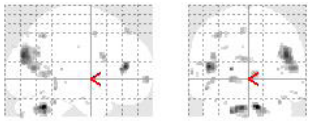
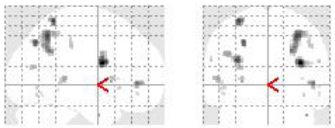
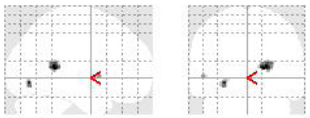
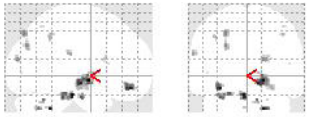
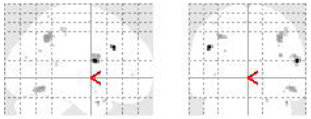
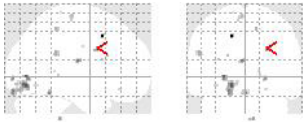
DPs (No Orthographic impairment) (N=7)		**DPs (Orthographic impairment) (N=7)**	
SPM map	Activated brain areas of interest (p<0.001, uncorrected for multiple comparisons)	SPM map	Activated brain areas of interest (p<0.001, uncorrected for multiple comparisons)
Word DPs>CPs 	L& R hOC5 (V5/MT) not significant Other Visual Areas not significant Phonological Areas not significant	Word DPs>CPs 	L& R hOC5 (V5/MT) not significant Other Visual Areas L hOC4v (V4) (17) Phonological Areas not significant
Word DPs<CPs 	L& R hOC5 (V5/MT) not significant Other Visual Areas L Area 17 (V1) (65) Phonological Areas not significant	Word DPs<CPs 	R hOC5 (V5/MT) (478) *(underactivation in this area was confirmed in the analysis with SVC)* Other Visual Areas R Arae 17 (V1) (43) L Arae 18 (V2) (49) Phonological Areas L Area 45 (97) L Insula (7) L Area 44 (25) L Area 6 (8) L middle temporal gyrus (18) L IPC (PGa) (BA39) (angular gyrus) (17)
Pseudoword DPs>CPs 	L& R hOC5 (V5/MT) not significant Other Visual Areas not significant Phonological Areas L Area 44 (76) L Area 45 (8) L middle temporal gyrus (30)	Pseudoword DPs>CPs 	L& R hOC5 (V5/MT) not significant Other Visual Areas L hOC4v (V4) (36) Phonological Areas L Area 44 (12)
Pseudoword DPs<CPs 	L& R hOC5 (V5/MT) not significant Other Visual Areas not significant Phonological Areas not significant	Pseudoword DPs<CPs 	L& R hOC5 (V5/MT) not significant Other Visual Areas not significant Phonological Areas Assigned to L IPC (PFop) (BA40) (11)

Table 7.27 Results for neuroimaging analyses directly comparing activation in DP with and without orthographic impairment

Words		**Pseudowords**	
SPM map	Activated brain areas of interest (p<0.001, uncorrected for multiple comparisons)	SPM map	Activated brain areas of interest (p<0.001, uncorrected for multiple comparisons)
DPs -Orth. Imp > DPs + Orth Imp 	nothing significant	DPs -Orth. Imp > DPs + Orth Imp 	<u>Phonological Areas</u> L Area 45 (13) [Assigned to R Area 44 (44)] <u>Magnocellular Areas</u> nothing significant <u>Visual Areas</u> <u>nothing significant</u>
DPs -Orth. Imp < DPs + Orth Imp 	<u>Phonological Areas</u> Assigned to L IPC (PFcm) (13) <u>Magnocellular Areas</u> nothing significant <u>Visual Areas</u> Assigned to R Area 17 (6) Assigned to L Area 18 (110) Assigned to L hOC3v (V3v) (110) Assigned to L hOC4v (V4) (110)	DPs -Orth. Imp < DPs + Orth Imp 	<u>Phonological Areas</u> Assigned to L IPC (PGp) (7) <u>Magnocellular Areas</u> nothing significant <u>Visual Areas</u> Assigned to R Area 17 (8) Assigned to L Area 18 (7)

7.2.5 Discussion

Before discussing the neuroimaging results it should be noted that the observed differences between sub-group 1 (DPs) and CPs, sub-group 2 (DPs) and CPs and sub-group 1 and sub-group 2 were not due to the following potential confounding variables: ADHD A+B, DCD Total, age, handedness, years of education, PIQ, FSIQ, and VIQ. Either there were no significant differences between the groups on these variables, or they were entered to the analyses as covariates. The other important point which needs to be made here is that because these are post-hoc analyses, which divide the original groups into sub-groups, the sub-groups consist of a small number of participants (N=7 in sub-groups with dyslexia) and therefore the results based on these sub-groups should be treated with caution.

7.2.5.1 The relationship between *Orthography Composite*, reading and magnocellular processing - comparisons of sub-groups with the CPs

As outlined in the introductory section above, according to the MDT, good magnocellular function is essential for high motion sensitivity and stable binocular fixation, and it has been hypothesized (Stein, 2001) that it is crucial for proper development of orthographic skills.

The results from the comparisons with the CPs suggest that there is some support for the magnocellular deficit associated with impairment measured on *Orthography Composite*. As predicted, DPs with no impairment on *Orthography Composite* did not exhibit significantly lower BOLD signal in R and/or L V5/MT+, in comparison to the CPs when reading Words and Pseudowords. However, this sub-group underactivated the L Area 17 (for Words), which suggests a deficit in the primary visual system for Word reading. As predicted on the basis of the MDT, DPs with impairment on *Orthography Composite* showed significantly lower BOLD signal in R V5/MT+ for Word reading. It is not clear why this also was not the case for the L V5/MT+. Furthermore, there was significant underactivation in the R Area 17 (V1) and L Area 18 (V2), for Words which taken together with underactivation in the V5/MT+, provides further support for the MDT.

In contrast to the predictions, there were no significant differences between the groups in the R and L V5/MT+ for Pseudoword reading. Significantly lower BOLD signal in R V5/MT+ for DPs with impairment on *Orthography Composite* during Word reading and lack of a significant difference in this area for Pseudowords, implies that this area does not exhibit the properties of a

'developmental lesion' ('functional lesion' due to a developmental disorder, not an acquired one). The finding of a significant difference for Words in this area and lack of such difference for Pseudowords warrants further investigation.

Interestingly, there was significant overactivation in the L hOCv4 (V4) for both Word and Pseudoword reading in the sub-group with impairment on Orthography. It is likely that DPs from this sub-group used this area to compensate for weaknesses in other parts of their visual system.

7.2.5.2 Direct comparisons between sub-group 1 and sub-group 2 on BOLD for Word and Pseudoword reading

The analyses which involved direct comparisons of the DPs without impairment on *Orthography Composite* and DPs with impairment on *Orthography Composite* revealed that the DPs with impairment on *Orthography Composite* overactivated for Words and Pseudowords (relative to DPs [-Orth Imp]) a number of visual areas. In contrast, DPs with no impairment on *Orthography Composite* did not overactivate any visual areas (relative to DPs [+Orth Imp]).

DPs with impairment on *Orthography Composite* overactivated for Words a number of visual areas. The overactivation in visual areas was mainly in LH (L Area 18, L hOC3v (V3v) and L hOC4v (V4)), except for R Area 17. This result is of particular interest because these areas were recently reported (Szwed et al., 2011) to exhibit (together with VWFA) greater BOLD responses to written words than to objects. DPs with impairment on *Orthography Composite* also overactivated the R Area 17 and L Area 18 for Pseudowords. It is possible that DPs with impairment on *Orthography Composite* compensated for potential weakness in their visual system, such as for instance underactivating (for Words) V5/MT+ (relative to CPs) by overactivation of other visual areas. The behavioural analysis reported earlier, revealed that there were no significant differences between the groups on reading measures (*TOWRE (Words)*, *Pseudoword Composite* and *Irregular Word Composite*) (see Table 7.25); whereas each sub-group significantly differed from the control group on these measures (see Table 7.23 and Table 7.24).

7.2.5.3 Phonological processing – sub-group 1 vs CPs and sub-group 2 vs CPs

A question can be asked here of whether DPs who are severely impaired on *PA* and/or *PF Composites* under-engage the areas from the phonological network during reading. The sub-groups of DPs consisted of individual DPs who were severely impaired on *PA* and/or *PF Composites* (see Table 7.7). The sub-groups did significantly differ from the CPs on these composites (see Tables 7.17 & 7.18, above), but the sub-groups did not differ between themselves on these composites

(see Table 7.19, above). Therefore, the prediction here was that both sub-groups would show under-engagement of some (or all) of the phonological areas (as defined in the Introduction) during reading of Words and Pseudowords in comparison to the CPs.

In contrast to this prediction, the DPs with no impairment on *Orthography Composite* did not show underactivation (relative to the CPs) in phonological areas both for Words and Pseudowords. For Pseudowords, they exhibited overactivation in anterior areas, including L Area 44 and L Area 45, as well as one ventral area - the L middle temporal gyrus. The results for this sub-group therefore do not support the hypothesis that DPs who are severely impaired on phonological processing, measured behaviourally, under-engage phonological areas during reading.

Interestingly, the results for DPs with impairment on the *Orthography Composite* were consistent with the predictions specified above. There was underactivation of phonological areas for both Words and Pseudowords. Three anterior areas (L Area 45, L Area 44 and L Area 6), L insula, and one ventral area (L middle temporal gyrus) were underactivated for Words. On the other hand, one dorsal area (L IPC (PGa) (BA39)) was underactivated for Pseudowords. However, L Area 44 was also overactivated for Pseudowords. Hence, the results for this sub-group do support the hypothesis that DPs who are impaired on phonological processing, measured behaviourally on *PA* and/or *PF Composites*, under-engage phonological areas during reading. However, they also exhibited overactivation of one anterior area (L Area 44) for Pseudoword reading, the same area which was underactivated for Word reading. This indicates that the area underactivated for Words is not characterized by a 'developmental lesion'.

Sumarising, these two sub-groups, which were both impaired on *PA* and *PF* exhibited different patterns of activation within in the phonological areas. Sub-group 1 did not show underactivation (relative to the CPs) in phonological areas, but exhibited overactivation. In contrast, subgroup 2 (as compared to the CPs) exhibited clear underactivation in phonological areas. As emphasized earlier, however, these results cannot be generalized onto the population of DPs (with appropriate characteristics) due to the low numbers of DPs involved in the sub-group post-hoc analysis.

The results for Words are interesting for several reasons. First, they differ from the results for BOLD for Word reading for the whole group of DPs, as compared with the CPs (see Chapter 5 for details). Those results showed that DPs significantly underactivated L IPC (PGp). Second, studies (e.g., Brunswick et al.,

1999; Shaywitz et al., 1998) usually report that DPs overactivate the anterior areas, (but see the meta-analysis by Maisog et al., 2008) whereas the comparison for sub-group 2 and CPs, reported above revealed that these areas were under-engaged by DPs for Word reading. Impairment in the L insula is in line with some reports (e.g., Paulesu et al., 1996), but not others (e.g., Rumsey et al., 1997; Shaywitz et al., 1998). Third, as described in the Introduction, it was reported (Shaywitz, Shaywitz, Pugh, et al., 2002) that children younger than ten and a half years of age, without reading difficulties, exhibit considerable engagement of the anterior and dorsal areas of the reading network during reading, with limited engagement of the ventral areas of the reading system. In contrast, children older than ten and a half years of age tend to exhibit increased engagement of the ventral areas of the reading system and this is associated with increasingly skilled reading. Therefore, one can speculate that proficient adult reading may be associated more with activation in the ventral areas than the anterior and dorsal areas. In this context, underactivation of a ventral area by DPs may suggest that DPs from sub-group 2 have not become proficient adult readers on the neural level.

Only one dorsal area (L IPC (PGp)) (part of the angular gyrus) was underactivated for Pseudowords in DPs from sub-group 2. As explained in the Introduction, the L angular gyrus has been linked to memories of visual word forms. However, more recently this area has been considered as a part of an association cortex which is involved in the cross-modal mapping of graphemes to phonemes (Geschwind, 1965; Shaywitz et al., 1998). In this study the angular gyrus was underactivated for Pseudowords, which require sub-lexical processing of mapping of graphemes to phonemes because they do not have lexical entries.

A further question can be asked here of how it is known that significantly lower activation in DPs from sub-group 2 (as compared to CPs), in areas from the phonological network is associated with poor reading. Although there was a significant difference between DPs in sub-group 2 and CPs on Word reading (*TOWRE*) and *Pseudoword Composite* (see Table 7.24), every effort was made (through extensive pilot work on Word and Pseudoword stimuli used in the experiment run in the MRI scanner (see Chapter 5 for further details)), to ensure that DPs were able to read the Words and Pseudowords well. As explained earlier, this was done to ensure that the potential differences in reading between the groups in BOLD were likely to be due to qualitative differences (due to different subsets of neuronal systems involved in each group), rather than quantitative differences (due to differences in the number of words read) (Brunswick et al., 1999). Clearly, this

argument does not hold for the *TOWRE* – a word reading test, in which words increase in difficulty, designed to differentiate between good and poor readers. Given the above facts, the assumption here is that the under-engagement of areas from the phonological network by DPs is not associated with their poorer reading (in the sense of being unable to read some items, or reading them with an error), but with perhaps different neural correlates (in comparison with the CPs), using the neuronal system which is impaired from birth and has developed in the presence of this impairment.

It is not clear why the two sub-groups of DPs, although both impaired on phonological processing measured on the behavioural level, showed different profiles on the neuronal level when compared with CPs. One possibility is that impairment on *Orthography Composite* is a marker for some deviation in the brain that influences phonological processing. The other option is that impairment on *Orthography Composite* may interact with phonological processing in such a way that underactivation is observed in phonological areas; For instance, interaction between orthography and phonology is an emerging property of connectionist models of reading and reading acquisition (Harm & Seidenberg, 1999). Finally, it could be the case that some protective factors (Pennington, 2006), which were not measured in this study, operated in sub-group 1, but did not in sub-group 2 (see Chapter 8 for further details).

7.2.5.4 Phonological processing – sub-group 1 vs sub-group 2

The follow-up analyses, which involved direct comparisons of the DPs without impairment on *Orthography Composite* and DPs with impairment on *Orthography Composite*, revealed that the latter significantly overactivated (relative to DP [-Orth Imp]) the phonological areas (L IPC (PFcm) and L IPC (PGp)) for Word and Pseudoword reading, respectively. It is likely that this reflects a compensatory mechanism for perhaps weaker engagement of the phonological areas, as compared with unimpaired participants (see Table 7.26). In contrast, DPs with no impairment on *Orthography Composite* did not overactivate any phonological areas for Word reading, but overactivated L Area 45 (and R Area 44) for Pseudoword reading, relative to the DP [+Orth Imp]. It is possible that these compensatory mechanisms have an impact on their reading measured on the behavioural level; there were no significant differences between the groups on reading measures (see Table 7.25).

7.2.6 Phonological processing – individual DPs case analyses

The analyses of the sub-groups showed a relatively straight-forward picture regarding phonological processing. However, as argued earlier in this thesis, the group analyses (and this is also relevant to the sub-group analyses) can obscure some effects because of between-subject variability. Therefore the same question, which was asked on the sub-group level, needs to be asked on the level of an individual DP; namely – do individual DPs, who are severely impaired on *PA* and/or *PF Composites*, under-engage the areas from the phonological network during reading, as compared to the CPs?

The remaining part of this section has the following structure. Firstly, the focus here is on the results for the individual DPs (as reported in Chapter 6) from sub-group 1; secondly, the results for individual DPs (as reported in Chapter 6) from subgroup 2 are discussed; thirdly, the results for two cases (unimpaired on behavioural measures of phonological processing) – DP1 and DP5 are presented; fourthly, the results for DP8 and DP15, who were excluded from group and sub-group analyses due to the fact that they may be 'at risk' of clinical DCD, are discussed. Finally, the focus is on the question of whether *TOWRE* scores and *Pseudoword Composite* scores are good predictors of underactivation in phonological areas during Word and Pseudoword reading, respectively, in individual DPs.

7.2.6.1 Results for individual DPs from sub-group 1 (as defined in Table 7.7)

All individual DPs from sub-group 1 were impaired on *PA* and/or *PF Composites* (see Table 7.28). The most impaired individual DPs were: DP11 (*PA*=-7.9; *PF*=-.8.0), DP12 (*PA*=-5.9; *PF*=-1.1), DP18 (*PA*=-5.8; *PF*=-2.3) and DP4 (*PA*=-3.1; *PF*=-2.5).

Do they, therefore, under-engage the areas from the phonological network during reading? The results are mixed – DP18 underactivated phonological areas for both Words and Pseudowords, DP11 underactivated phonological areas for Words, but not for Pseudowords, whereas DP4 and DP12 did not underactivate any phonological areas. The remaining DPs (DP7, DP13 and DP3) who were less severely impaired on *PA* and/or *PF* exhibited no underactivation of phonological areas, except for DP3 who did underactivate phonological areas for both Words and Pseudowords.

7.2.6.2 Results for individual DPs from sub-group 2 (as defined in Table 7.7)

Similar to sub-group 1, all DPs from sub-group 2 were impaired on *PA* and/or *PF Composites* (see Table 7.29, below). The most impaired DPs from sub-group 2 were: DP10 (*PA*=-10.6; *PF*=-5.2), DP9 (*PA*=-5; *PF*=-3.7), DP14 (*PA*=-4.5; *PF*=-1.9) and DP17 (*PA*=-4.4; *PF*=-2.3). Again, the results on under-engagement of phonological areas, similar to sub-group 1, are heterogeneous. Only one, DP9, under-engaged the phonological areas, as predicted, for both Words and Pseudowords. DP10 under-engaged phonological areas for Pseudowords, whereas DP14 under-engaged phonological areas for Words. In contrast, DP17 did not under-engage any phonological areas. The other DPs (from sub-group 2), who were also impaired on *PA* and/or *PF Composites* showed heterogeneous (inconsistent) profiles regarding the engagement of phonological areas as well. DP16 exhibited under-engagement of phonological areas for both Words and Pseudowords. DP6 showed under-engagement of phonological areas only for Words and DP2 exhibited no under-engagement of any phonological areas.

7.2.6.3 Results for two individual DPs who did not show impairment on PA and/or PF Composites

DP1 and DP5 did not show impairment on *PA* and/or *PF Composites* (see Table 7.30). If *PA* or *PF Composites* is a good predictor of engagement of phonological areas during reading, then one should expect to find that these DPs engage phonological areas during reading. According to this prediction DP5 did not show under-engagement of any phonological areas during reading. In contrast, DP1 did exhibit under-engagement of anterior and dorsal areas from the phonological network for Word reading.

7.2.6.4 Results for two individual DPs who were not included in the group and sub-group analyses because they may have been at risk of clinical DCD

DP8 and DP15 showed impairment on *PA* and/or *PF Composites* (see Table 7.31). In line with the predictions, DP15 exhibited underactivation of phonological areas during reading, but only for Words. In contrast, DP8 did not show any under-engagement of phonological areas during reading.

As stated, DP8 and DP15 were excluded from the group and sub-group analyses because they were identified in this study as possibly being at risk of a clinical form of DCD. Therefore their neuroimaging results were also inspected for potential underactivation (as compared to the controls) in the areas which have been reported to be deficient in participants with DCD. However, it needs to be born in mind that

similar to developmental dyslexia, there is no consensus regarding the underlying cause of DCD. Furthermore, it needs to be stressed that the BOLD signal in this study is from a reading task, and not from a task which is typically used to investigate DCD.

It was reported (Kashiwagi, Iwaki, Narumi, Tamai, & Suzuki, 2009) that participants with DCD (in comparison to CPs) exhibited significantly lower brain activation in the L posterior parietal cortex and L postcentral gyrus during a visuo-motor task. The authors concluded that the dysfunction of these areas could be the neural underpinnings of a deficit of motor skill in participants with DCD. The coordinates with significant differences between the groups, reported by Kashiwagi et al. (2009) labeled by Anatomy Toolbox (Eickhoff et al., 2005), had the following labels, probabilities and rages: [MNI: x=-40, y=-48, z=66 – L SPL (7PC), probability=10%, range=0-20%; MNI: x=-36, y=-52, z=50 – L SPL (7A), probability=30%, range=20-40% and hIP1, probability=20%, range=0-30%].

DP8 exhibited overactivation in R SPL (7PC) and L hIP1 (for Pseudowords) (see Appendix E, Table 14.8). Interestingly, this was in the context of DP8's overactivation (without any underactivation) in large number of areas for phonological areas, as described in Chapter 6. DP15 showed underactivation of L SPL (7A) only for Words (see Appendix D, Table 13.15).

There is now growing evidence that DCD may be associated with an impaired cerebellum (Brookes, Nicolson, & Fawcett, 2007; Ivry, 2003; Marien, Wackenier, De Surgeloose, De Deyn, & Verhoeven, 2010; O'Hare & Khalid, 2002). Furthermore, there is also evidence from animal models (Gramsbergen, 2003) which support this hypothesis. In this context, DP8 did not exhibit any underactivation or overactivation in the cerebellum during Word and Pseudoword reading. In contrast, DP15 showed significant underactivation in the R and L Lobule VIIa Crus I (Hem), as well as L Lobule VIIa Crus II (Hem).

Sumarising, the results for DP8 do not seem to be consistent with the neuroimaging results reported for DCD. Interestingly this participant exhibited only overactivation and no underactivation; her profile may be associated with a particular allelic variation that differs from the participants who exhibited underactivation (see Chapter 8 for further discussion). In contrast, DP15 exhibited a pattern of underactivation that seems to be consistent with the patterns of underactivation observed in participants with DCD.

7.2.6.5 Are *TOWRE* scores and *Pseudoword Composite* scores good predictors of underactivation in phonological areas during Word and Pseudoword reading, respectively, in individual DPs?

A further question (in the context of the results for individual DPs) can be asked of whether *TOWRE* scores can predict underactivation of phonological areas during Word reading in an individual DP. Inspection of the behavioural and neuroimaging data suggests that there are four sub-groups here. For two of these subgroups, *TOWRE* scores agree with the neuroimaging results, regarding the underactivation in phonological areas. Sub-group 2 (Words) (DP3, DP9, DP14, DP15 and DP16) is characterised by impairment on *TOWRE* scores and underactivation is noted in phonological areas. Furthermore, sub-group 3 (Words) (DP5) has *TOWRE* scores which are unimpaired and no underactivation is observed in phonological areas. In contrast, for two further sub-groups, *TOWRE* scores do not agree with the neuroimaging results. Subgroup 4 (Words) (DP1, DP6, DP11 and DP18) - *TOWRE* scores are unimpaired, however, underactivation is observed in phonological areas. Finally, Sub-group 1 (Words) (DP2, DP17, DP10, DP8, DP4, DP13 DP7 and DP12) - *TOWRE* scores are impaired, however, there is no underactivation in phonological areas. Summarising, for six DPs (33.3%) *TOWRE* scores agreed with the outcome of the neuroimaging analysis, regarding underactiation in phonological areas, whereas for twelve DPs (66.6%) they did not.

A parallel question can be asked regarding the scores on the *Pseudoword Composite* for a given individual DP and underactivation for the phonological areas during Pseudoword reading. Three sub-groups were identified here. For two of these subgroups, *Pseudoword Composite* scores agree with the neuroimaging results. Sub-group 2 (Pseudowords) (DP3, DP9, DP10, DP16 and DP18) is characterised by impaired scores on *Pseudoword Composite* and underactivation of the phonological areas and Sub-group 3 (Pseudowords) (DP1, DP5 and DP6) was not impaired on *Pseudoword Composite* scores and there was no underactivation of the phonological areas. In contrast, the score on *Pseudoword Composite* did not agree with the neuroimaging results in Sub-group 1 (Pseudowords) (DP2, DP4, DP7, DP8, DP11, DP12, DP13, DP14, DP15 and DP17). This sub-group was characterised by impaired scores on *Pseudoword Composite*, but no underactivation of the phonological areas. Summarising, for eight DPs (44.4%) *Pseudoword Composite* scores agreed with the outcome of the neuroimaging analysis, regarding underactivation of phonological areas, whereas for ten DPs (55.6%) they did not.

Table 7.28 Neuroimaging results and scores for *TOWRE* (Words) and *Pseudoword* and *Irregular Word Composites* for Individual DPs from sub-group 1

DP	Underactivation Words^	Underactivation Pseudowords	Overactivation Words	Overactivation Pseudowords	TOWRE Words (z-scores)	Pseudoword Comp.	Irreg. Comp.
3	PDT (L IPC (PFm) (BA40)** L IPC (PF) (BA40) L IPC (PGp) (BA39) L TE3	L IPC (PGa) (BA39) L IPC (PGp) (BA39)	-	L Area 45	**-5.1**	**-6.9**	**-8.1**
18	L IPC (PFm) (BA40) L IPC (PGa) (BA39)	L insula	-	L Area 6 R IPC (PFcm) (BA 40) R TE3*	-1.5	**-4.3**	**-1.7**
4	-	-	R fusiform gyrus	L insula L TE3*	**-3.1**	**-3.4**	**-1.9**
13	-	-	L & R Area 44 L & R Area 45 L & R IPC (PGp) (BA39) L IPC (PGa) L middle temporal gyrus (BA21)	L Area 44 L & R Area 45 R insula L Area 6 L middle temporal gyrus (BA21)	**-4.7**	**-8.1**	**-3.6**
7	- R Lobule VIIa Crus I (Hem) L Lobule VIIa Crus I (Hem) L Lobule VIIa Crus II (Hem)	-	L IPC (PF) (BA40) R IPC (PFm) (BA40)	R IPC (PFcm) (BA40) R IPC (PF) (BA40) R IPC (PFt) (BA40)	**-7.5**	**-2.4**	0
12	- R Lobule VIIb (Hem)	- R Lobule VIIa Crus I (Hem)	-	L & R Area 44	**-4.9**	**-8**	**-2.7**
11	L Area 44 L insula R Lobule VIIa Crus I (Hem) L Lobule VIIa Crus II (Hem)	- L Lobule VIIa Crus II (Hem)	-	L Area 6 R IPC (PFcm) (BA40)	-0.9	**-3.6**	-0.2

Note: * when the probability and voxel thresholds were lowered; ** phonological areas in black; cerebellar areas in green; ^the results are from the individual case analysis reported in Chapter 6; overactivation and underactivation is relative to the control group; $p<0.001$, uncorrected for multiple comparisons; Pseudoword Comp.=*Pseudoword Composite*; Irreg. Comp.=*Irregular Word Composite.*

Table 7.29 Neuroimaging results and scores for *TOWRE* and *Pseudoword* and *Irregular Word Composites* for Individual DPs from sub-group 2

DP	Underactivation Words^	Underactivation Pseudowords	Overactivation Words	Overactivation Pseudowords	TOWRE Words (z-scores)	Pseudoword Comp.	Irreg. Comp.
9	L insula Lobe L superior temporal gyrus (Wernicke's area) L fusiform gyrus R Lobule VIIa Crus I (Hem) L Lobule VIIa Crus I (Hem) L Lobule VIIa Crus II (Hem)	L IPC (PGp) (BA39)	- L Lobule VIIb (Hem)	R insula	**-8.1**	**-6.4**	**-3.7**
16	L insula (Ig1) L middle temporal gyrus (BA21) L TE3 (when the probability & voxel thresholds were lowered)	L insula L Area 6 L fusiform gyrus L middle temporal gyrus (BA21) L Lobule VI (Hem)	-	-	**-4.3**	**-3.9**	**-3.8**
2	- R Lobule VIIa Crus I (Hem) L Lobule VIIa Crus I (Hem) L Lobule VIIa Crus II (Hem) nothing	- nothing	- nothing	R insula L TE3* nothing	**-6.5**	**-3.6**	**-3.2**
17	-	-	L insula (Id1) L & R Area 6 L & R IPC (PFcm) (BA40) L IPC (PFop) (BA40) L IPC (PF) (BA40) L TE3 *	L Area 44 L & R insula L Area 6 R IPC (PFcm), L middle temporal gyrus (BA21) R TE3*	**-4.7**	**-12.5**	**-4**
6	L IPC (PGa) L IPC (PGp)	-	L Area 44	L Area 44 R Lobule VIIa Crus I (Hem)	0.7	-1	-0.6
10	-	L Area 44 L middle temporal gyrus R Lobule VIIa Crus I (Hem)	L IPC (PGa) (BA39) L fusiform gyrus R TE3*	-	**-4.7**	**-14.4**	-1.5
14	Area 44, L IPC (PGp) (BA39), L fusiform gyrus, L Area 6, L middle temporal gyrus (BA21) L TE3 (when the probability threshold & the voxel threshold were lowered) CDT (L Lobule VI (Hem) L Lobule VIIa Crus I (Hem)	-	- R lobule VIIb (Hem)	R insula L IPC (PF) (BA 40)	**-4.5**	**-1.9**	**-4.5**

	L Lobule VIIa Crus II (Hem)						

See 'note' under the Table 7.28.

Table 7.30 Neuroimaging results and scores for *TOWRE* (Words) and *Pseudoword* and *Irregular Word Composites* for DPs without Phonological Impairment, as revealed by *PA* and *PF Composites*

DP	Underactivation Words^	Underactivation Pseudowords	Overactivation Words	Overactivation Pseudowords	TOWRE Words (z-scores)	Pseudoword Comp.	Irreg. Comp.
1	L Area 44 L superior temporal gyrus (Wernicke's area) L Area 6 L IPC (PFcm) (BA40) R Lobule VIIa Crus I (Hem) L Lobule VIIa Crus II (Hem)	- R Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem)	-	R insula L Lobule VIIa Crus I (Hem)	-1.3	0.8	0.5
5	- R Lobule VIIb (Hem)	-	-	R fusiform gyrus and L TE3* L lobule VI (Hem)	0.7	0.4	0.6

See 'note' under the Table 7.28.

Table 7.31 Neuroimaging results and scores for *TOWRE* (Words) and *Pseudoword* and *Irregular Word Composites* for DPs who were not included in the group analysis because of being at risk of clinical DCD

DP	Underactivation Words^	Underactivation Pseudowords	Overactivation Words	Overactivation Pseudowords	TOWRE Words (z-scores)	Pseudoword Comp.	Irreg. Comp.
8	- nothing	- nothing	L insula (Ig2) R middle temporal gyrus (BA21) nothing	L Area 6 L IPC (PGp) (BA39) *R hOC5 (V5)*	**-2.3**	**-4.3**	**-6**
15	L superior temporal gyrus (Wernicke's area) L IPC (PGa) (BA39) L middle temporal gyrus R Lobule VIIa Crus I (Hem) L Lobule VIIa Crus I (Hem) L Lobule VIIa Crus II (Hem)	-	-	-	**-10.3**	**-15.7**	**-8.1**

See 'note' under the Table 7.28.

7.2.6.6 Discussion of results on phonological processing in individual DPs

Concluding, the results suggest that behavioural scores on *PA* and/or *PF* are not a sufficient predictor of whether a given individual DP will or will not under-engage

phonological areas during reading. Some DPs exhibit a phonological deficit on the behavioural level, but do not under-engage areas from the phonological network during reading compared to controls (e.g., DP4, DP13, DP7 and DP12 (subgroup 1) and DP2 and DP17 (sub-group 2)). How could this be the case? It may be that although there is a phonological deficit on the behavioural level it may not be due to a deficit in brain areas involved in phonological processing. For instance, it might be due to an underactivation in other brain areas, such as for instance, cerebellar areas (and possibly some other areas). The role of cerebellar areas in language processing is not currently clear, however it is clear that cerebellar areas do participate in language/reading processing, as discussed in the Introduction. It may therefore be possible that the phonological impairment as revealed by standardised measures observed in some cases (e.g., DP7 and DP12) is consistent with the CDT, which also has an impact on reading. DP7 underactivated for Words: R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem), L Lobule VIIa Crus II (Hem), whereas DP12 underactivated R Lobule VIIb (Hem) (Words) and R Lobule VIIa Crus I (Hem) (Pseudowords).

The other possibility here is that the phonological impairment in DP7 is possibly consistent with the MDT and in DP12 with the VDT. This is because DP7 underactivated R Area 18 and R hOC5 (V5/MT) (but only when the threshold was lowered) and DP12 underactivated L Area 17 and R Area 18. However, such explanations clearly do not apply to DP4 and DP13 who did not underactivate any cerebellar or magnocellular or visual areas. It is possible that processes with faster temporal resolution, which cannot be captured with fMRI, play some role here, but this would need to be investigated with MEG.

Moving onto DPs from sub-group 2, phonological deficit is consistent with the CDT in DP2 who underactivated several cerebellar areas, including the R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem), without any underactivation of magnocellular areas. On the other hand, the phonological impairment found on behavioural level in DP17 does not manifest on the neural level within phonological areas, nor within cerebellar or magnocellular areas.

In contrast, DP1 did not show impairment on *PA* and/or *PF Composites*, however, DP1 did exhibit under-engagement of anterior and dorsal areas from the phonological network for Word reading. The data suggest that DP1, although impaired on phonological processing on the neuronal level, is compensated on the behavioural level.

The results which involve *TOWRE* and *Pseudoword Composite* scores suggest that the behavioural scores on these variables are not a sufficient predictor of whether a given individual DP will exhibit underactivation or lack of underactivation during Word and Pseudoword reading. (However, it must be noted that, as described earlier, different reading tests were used in the behavioural testing from the fMRI testing, for the reasons specified earlier). For instance, some DPs exhibit a deficit on *TOWRE*, but do not underactivate areas from the phonological network during reading *Words* (DP2, DP17, DP10, DP8, DP4, DP13 DP7 and DP12) (Sub-group 1, Words). Also, DP5 (Sub-group 3, Words) was impaired on *TOWRE*, however, no underactivation was observed in phonological areas during DP5's Word reading. Furthermore, ten DPs (DP2, DP4, DP7, DP8, DP11, DP12, DP13, DP14, DP15 and DP17) (subgroup 1, Pseudowords) exhibit a deficit on *Pseudoword Composite*, but do not under-engage the phonological areas during reading.

It should be emphasised here that there are many factors which could potentially have an impact on the neural correlates of reading Words and Pseudowords in individual DPs and their relationship with behavioural measurements, such as *PA* and *PF Composites*. Furthermore, there are also most likely many factors which could potentially influence the neural correlates of reading Words and Pseudowords in individual DPs and their relationship with behavioural scores on *TOWRE* and *Pseudoword Composite.* Some of the factors, connected to the relationship of the neural correlates of reading and measurements on *PA*, *PF*, *TOWRE* and *Pseudoword Composite*, include: 1) the presence of genes implicated in dyslexia, 2) the age at which teaching instructions for reading started, 3) the method of teaching reading, 4) reading habits, 5) remediation, and many others. More generally, these factors include risk factors in terms of both biological and environmental influences, both of which have effects at different stages of development. Future studies need to take into account such factors in order to identify the significant influence of the various factors on the neural correlates of reading in individual DPs (see Chapter 8 for more details).

Finally it needs to be underscored that it is not possible to test the predictions of the DRC model (Coltheart et al., 2001) regarding the two potential sub-types of DPs, because, although measures of Pseudoword and Irregular reading were recorded, the vast majority of DPs exhibited impairment on both Pseudoword and Irregular Word reading. DP1, DP5 and DP6 were unimpaired on both measures. There were only three participants - DP7, DP11 and DP10 who were impaired on

Pseudoword reading and unimpaired on Irregular Word reading. There was no DP who was impaired on *Irregular Word Composite*, but not impaired on *Pseudoword Composite*.

7.3 Is there an association between a score on *Purdue Pegboard Composite* and BOLD signal for Words and Pseudowords in cerebellar areas involved in reading and language?

The behavioural and neuroimaging data collected in this thesis allow one to address the empirical question of whether there is an association between a score on *Purdue Pegboard Composite* and BOLD signal for Words and Pseudowords in the cerebellar areas involved in reading and language, as defined in the Introduction. It is perhaps an unusual question; most researchers would not look for an association between a motor skill (measured on the behavioural level) and BOLD for Word and Pseudoword silent reading.

As explained earlier, the Purdue Pegboard test was simply used in this study for screening for DCD. However, this test could be used to distinguish participants whose reading impairments co-occur with subtle motor impairment from those with normal motor function (Bishop, 2002). As discussed earlier, the cerebellum has been implicated in skilled motor movement and therefore a score on *Purdue Pegboard Composite* can be used to measure cerebellar processing on the behavioural level. The assumption here is that low scores on the sub-tests of this test are a proxy measure for poor cerebellar processing in general.

First, a possible association of a score on *Purdue Pegboard Composite* and BOLD signal for Words and Pseudowords in cerebellar areas involved in reading and language was probed in CPs. Second, the same association was tested for the DPs.

7.3.1 Control Participants

Table 7.32 Scores for Purdue Pegboard sub-tests and *Purdue Pegboard Composite* for individual CPs

CP	R Hand*	L Hand*	Both Hands*	Assembly*	*Purdue Pegboard Composite**
19	-1.1	-1.2	-0.4	-0.4	-1.0
20	-1.1	-0.7	-0.4	-0.4	-0.8
21	1.0	0.4	0.4	0.4	0.7
22	0.3	-0.2	0.4	0.2	0.2
23	-0.4	1.4	1.1	2.2	1.3
24	1.7	1.9	1.8	0.2	1.8
25	-0.4	-1.2	-0.4	-1.3	-1.0
26	1.0	1.4	-0.4	**-1.8**	0.1
27	1.0	0.4	0.4	1.1	0.9
28	-0.4	-0.2	0.4	0.4	0.1
29	-0.4	-0.7	-1.1	0.2	-0.6
30	-0.4	-1.2	**-1.8**	-0.2	-1.1
31	1.7	0.9	1.1	0.4	1.3
32	-0.4	0.4	1.1	0.9	0.6
33	-1.1	-0.7	-1.1	-1.3	-1.3
34	-1.1	-0.7	-1.1	-0.7	-1.1

Note: R Hand = Right Hand; L Hand = Left Hand

The data for the CPs is presented in Table 7.32 and show that no CP was impaired on *Purdue Pegboard Composite* - all scores <-1.65. Two CPs were, however, impaired on one measure; CP26 on the 'Assembly' measure (1.8 SD below the Mean of the CPs) and CP30 on the 'Both hands' measure (1.8 SD below the Mean of the CPs).

7.3.1.1 Neuroimaging analysis

'Con' images for every individual CP (N=16) obtained in the 1st level analysis, described in Chapter 5, were entered into the 2nd level correlational analysis using SPM. Separate analyses were run for Words and Pseudowords while controlling for ADHD A+B, DCD Total and *d Prime*. Volume search was limited to only cerebellar areas, as described in the Introduction. The mask was prepared using the Anatomy Toolbox V.1.7. (Eickhoff et al., 2005) and included the following cerebellar areas: the R and L Lobule VIIa Crus I (Hem), R and L Lobule VIIa Crus II (Hem), R and L H lobule VI, R and L H lobule VIIB (paramedian) and R Vermal lobule VI (R Vermal lobule VIIAt). The analysis (in SPM) was done using the *SVC* option.

The analyses revealed one cerebellar area (R Lobule VIIb (Hem), local maxima: MNI coordinates: x=14, y=-78, z=-48) where there was a significant correlation between BOLD for Word reading and scores on the *Purdue Pegboard Composite*,

however it did not survive the correction for the number of voxels in a cluster [T=4.1, Z=3.13, p=.001, k<6, Probability=66%, Range=40-83%]. The analysis involving BOLD for Pseudoword reading revealed a significant correlation between BOLD and scores on the *Purdue Pegboard Composite* in one cerebellar area (R Lobule VI (Hem), [local maxima: MNI coordinates: x=34, y=-46, z=-26, T=5.7, Z=3.81, p=0.00000; k=8, Probability=90%, Range=3-90%].

7.3.2 Participants with dyslexia

The data for the DPs in Table 7.33 show that four DPs (DP3, DP7, DP9 and DP10) were impaired on *Purdue Pegboard Composite*. Additionally, DP15, who was not impaired on the *Purdue Pegboard Composite*, had impairment on the 'R Hand' measure. This participant, similar to all other participants was right handed, but was identified as possibly being at risk of DCD. It is unclear why DP15's impairment was only manifested in the performance of his dominant hand. It is possible that he was distracted during performance on this task with the R hand and therefore did particularly badly. It is also possible that for some reason he was able to compensate for his impairment in all tasks, except for the task involving the dominant hand task. In the interview he reported that he had had considerable motor difficulties when trying to learn how to play the guitar. Certainly a more reliable measure here would be to include more (3-5) trials for each task. The case analysis of fMRI data, presented earlier in this Chapter revealed that he underactivated areas associated with the DCD. However, as stressed earlier, it needs to be born in mind that the BOLD signal in this study is from a reading task, and not from a task which is typically used to investigate DCD.

Table 7.33 Scores for *Purdue Pegboard Composite* for individual DPs

DP	RHand*	LHand*	Both Hands*	Assembly*	*Purdue Pegboard Composite**
3	**-1.9**	**-1.7**	**-1.8**	**-1.8**	**-2.2**
7	-1.1	-0.7	**-2.5**	**-2.7**	**-2.2**
9	**-2.6**	-0.2	-1.1	**-2.2**	**-1.9**
10	**-2.6**	-1.2	0.4	**-2.4**	**-1.8**
1	-0.4	0.4	1.1	-0.4	0.2
2	-0.4	-0.2	0.4	-1.6	-0.6
4	-1.1	-0.7	-0.4	-0.7	-0.9
5	1.0	0.9	1.1	2.0	1.6
6	-0.4	0.4	1.1	-0.9	0.0
8$	1.7	2.5	1.8	0.2	1.9
11	2.4	1.9	0.4	0.9	1.8
12	1.0	-0.7	-0.4	-0.7	-0.2
13	0.3	0.9	0.4	0.2	0.5
14	1.0	0.4	1.1	-1.6	0.3
15$	**-2.6**	0.4	0.4	-1.1	-0.9
16	-1.1	-0.7	-0.4	-1.3	-1.1
17	0.3	0.9	1.8	0.4	1.1
18	-0.4	-0.2	-0.4	-1.3	-0.7

Note: Z = Z-score (relative to the control group); $ - DPs not included in group analyses.

7.3.2.1 Neuroimaging analysis

The neuroimaging analysis for the DPs (N=16; excluding, DP8 and DP15, for consistency with the other analyses, presented in Chapter 5) revealed that there were no significant correlations with BOLD for Word reading. In contrast, there was significant correlation between BOLD for Pseudoword reading and scores on the *Purdue Pegboard Composite* in the L Lobule VI (Hem) [local maxima, MNI coordinates: x=-24, y=-60, z=-32, T=6.29, Z=4.01, p<.00001, k=28, Probability=100%, Range=13-100%] and the L Lobule VIIa Crus I (Hem) [local maxima, MNI coordinates: x=-32, y=-62, z=-30, T=4.65, Z=3.39, p<.00001, k=28, Probability=58%, Range=36-99%].

It should be noted here that the DPs group and the CPs group were the same as in Chapter 3, which presented the psychometric analysis for the between group comparisons (see Chapter 3 for details). Therefore the reported differences could not be accounted for by differences in age, handedness, VIQ, PIQ, FSIQ, years of education and gender differences (see Chapter 3 for details).

7.3.3 Discussion

Sumarising, the results show little association between BOLD for Word reading and performance on *Purdue Pegboard Composite* in the cerebellar areas involved in language and reading in either group (CPs and DPs). In contrast, the results show that there is an association between BOLD for Pseudoword reading and performance on this measure of motor control. However, different cerebellar areas,

in different cerebellar hemispheres, are involved for the CPs and DPs. BOLD for Pseudoword reading was significantly correlated with scores on *Purdue Pegboard Composite* in R Lobule VI (Hem) for CPs. In contrast for DPs, a significant correlation between BOLD for Pseudoword reading and scores on *Purdue Pegboard Composite* was found in L Lobule VI (Hem) and L Lobule VIIa Crus I (Hem).

These results pose some further questions. First, how does the association between BOLD for Pseudoword reading and a score on a *Purdue Pegboard Composite* arise? One possibility is that it arises through motor processing of inner vocalizations during Pseudoword reading and motor processing of hands; both of these actions involve motor processing. However, this explanation may be unlikely, given that there is increasing evidence of a division between overt motor control and language processing (Stoodley et al., 2012). The other possibility is that the observed correlation arises through motor processing of inner vocalizations during Pseudoword reading and inner vocalizations during performing the Purdue Pegboard tests (e.g., participants may keep repeating covertly the instructions to themselves). Yet another possibility is that the association is through the fact that scores on *Purdue Pegboard Composite* encompass not only the motor function of the cerebellum, but also more global functions, including also language and reading areas. This possibility needs to be addressed in future research.

Second, why is there an association with Pseudowords and not with Words? Perhaps, Pseudowords elicit stronger and more consistent inner vocalizations, because in contrast to Words, they do not have lexical representations, and their phonological form needs to be assembled from the constituent graphemes. (If this is the case, then one perhaps should also see larger pre-motor cortex activations for Pseudowords than Words).

Third, why are different cerebellar areas associated with BOLD for Pseudowords for CPs and DPs? Research shows that the cerebellum is one of the first brain structures to begin to differentiate, however it is one of the last brain structures to achieve maturity. This prolonged maturational process makes the cerebellum particularly susceptible to disruptions during the process of embryogenesis (Wang & Zoghbi, 2001). Furthermore the cerebellum exhibits considerable plasticity (e.g., Black, Isaacs, Anderson, Alcantara, & Greenough 1990; Klintsova, Goodlett, & Greenough, 2000; Schlang, 2001; Zheng & Raman, 2010) and can be influenced by many different factors during ontogenetic development (Bishop, 2002). Therefore, it is possible that the cerebellum was

influenced differently in CPs for whom the brain systems develop normally, than in DPs for whom the brain systems are impaired from birth and therefore have not developed in the same way as in CPs. However, it needs to be underscored here that differences in brain morphology between DPs and CPs are subtle, but nevertheless important.

8 Conclusions and future directions

8.1 Conclusions

Despite decades of research on dyslexia there is no consensus on the neural correlates of reading impairment in this developmental disorder. The main goal of this project was to shed more light on the neural correlates of reading deficit in adults with dyslexia, as hypothesised by the PDT, visual MDT and CDT, with special emphasis on individual differences. As reviewed in the Introduction, the majority of behavioural and neuroimaging studies, motivated by these theories, have three shortcomings. Firstly, they mostly tested one underlying cause of reading impairment in dyslexia. Secondly, they relied exclusively on group comparisons. Thirdly, a significant number of these studies focused on detecting a deficit, hypothesised by a given theory of dyslexia, without empirically demonstrating the relationship of this deficit to reading impairment (Eden et al., 1996; Nicolson et al., 1999).

The research reported in this thesis addressed these problems. First, by contrasting the predictions of the neural correlates of reading impairment in dyslexia, postulated by each of the theories, in one sample of DPs. Second by using a multiple case study to investigate BOLD for each DP in comparison to the BOLD of CPs, thereby detecting differences which otherwise would have been obscured in the between-group comparison, due to heterogeneity among DPs. Third, by demonstrating a possible relationship between reading impairment (on the behavioural level) and its neural correlates, hypothesised by the main theories of dyslexia, using fMRI and a reading task.

Despite relatively straightforward results from the fMRI between-group analysis (Chapter 5), the outcome from the fMRI multiple-case analyses (Chapter 6) showed remarkably complex results. The patterns of hypoactivation exhibited by all DPs were not consistent with one theory of dyslexia. Hence, the neural correlates of reading in dyslexia in all cases studied here are not in agreement with the predictions of a single theory of dyslexia. The underlying correlates of reading deficit in dyslexia are consistent with the predictions of one theory of dyslexia in some cases, for instance, DP6's neural correlates of Word reading are in agreement with the PDT, whereas DP2's neural correlates for Word reading are consistent with the CDT. No DP exhibited exclusively a magnocellular deficit.

It should be noted that the theories tested in this thesis (the PDT, visual MDT and CDT) have one important common feature – the assumption that one underlying deficit is necessary and sufficient to cause all symptoms of dyslexia: phonological or visual magnocellular, or cerebellar, respectively. However, as discussed before, one of the shortcomings of dyslexia research is that it has mostly tested one underlying cause, guided by one theoretical framework. The results reported in this thesis clearly show that if one tests the same sample of DPs, contrasting the predictions of the main theories of dyslexia, the neural correlates of reading for some DPs are consistent with more than one theory. In the sample studied here, the neuroimaging results for Word reading for: DP1, DP3, DP9, DP11, DP14, DP15 and DP18 are consistent with the PDT and CDT. The protagonists of the PDT (e.g., Ramus, Pidgeon, & Frith, 2003; Ramus, Rosen et al., 2003) would argue here that the neural correlates of reading in these cases are consistent with the core deficit in dyslexia, as hypothesised by the PDT, and that the underactivation in the cerebellum in these cases just co-occurs with this developmental disorder. (This argument works particularly well with results obtained in behavioural studies which demonstrate that DPs exhibit, for instance phonological and cerebellar deficits, but provide no data on the relationship of cerebellar deficit to reading). As emphasised above, in contrast to previous studies, this study, using fMRI, focused on the more direct relationship between reading deficit (the defining characteristic of dyslexia) and the predictions of the main theories on the neural level. It seems therefore that if some DPs exhibited underactivation in the areas hypothesised by the PDT and in the areas predicted by the CDT, during reading, it lends support to the claim that reading in these cases is consistent with the predictions of both theories and therefore both phonological areas and cerebellar areas contribute to the reading deficit in these DPs. Looking at these results from the perspective of the CDT, an additional interpretation is also possible, namely that the underactivation in phonological areas has been influenced by the cerebellum because the CDT predicts that a phonological deficit (in phonological awareness and in reading) can be caused by a cerebellar impairment. Hence, underactivation in the phonological areas in DPs (as compared to the CPs) can be consistent with the CDT (and the PDT). This interpretation, however, as pointed out earlier, is not consistent with the PDT. Furthermore, it may be that most cases are consistent with the predictions of more than two theories of dyslexia, as in a number of cases (the results for which were consistent with the PDT and/or CDT)

it is not clear whether the neural correlates of their reading are also in agreement with the MDT or VDT.

Looking from a broader perspective at the issue of the neural correlates of reading deficit in dyslexia, a single deficit model has been prevalent for many years in the research on this and other developmental disorders. However, a single deficit model, although parsimonious and straightforward to test, has limitations. It cannot readily explain cases which exhibit a single deficit, but do not have a reading disorder. Such cases have been reported in longitudinal studies involving children at risk of dyslexia (Pennington, 2011). Studies have also reported cases of CPs who, although exhibiting a phonological deficit, did not have a reading impairment (e.g., Reid et al., 2007). Furthermore, the single deficit model cannot account for comorbidities between dyslexia and some other developmental disorders which, as explained above, occur more frequently than would be expected by chance. Therefore a multiple deficit model has been formulated (Pennington, 2006). According to the multiple-deficit model, more than one cognitive deficit is necessary to create a developmental disorder. Disorders are correlated with each other and therefore comorbid. Comorbidity is explained by a disorder having a shared cognitive risk factor as well as some specific cognitive risk factors. Essentially the model is formulated within the same levels of explanation, as a single deficit model, such as the one proposed by Frith (1999), except that the biological level is split into two levels: the 'brain level' (neural systems) and the 'etiologic risk and protective factors level'. For more details on this model see 'The future of dyslexia research' section, below.

The neuroimaging results for reading revealed that DPs exhibited complex and very heterogeneous patterns of hypoactivation in the areas hypothesized by the three main theories of dyslexia. For instance, DP1 exhibited underactivation for Words in: L Area 44, L Area 6, L superior temporal gyrus, L IPC (PFcm) (BA40), R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus II (Hem), R Area 17 (V1) & 18 (V2). DP2 showed underactivation: in the R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem), whereas DP4 exhibited no underactivation in the areas of interest.

Furthermore, the neuroimaging data showed a high degree of individual differences. Even if the neural correlates of reading deficit in two DPs are consistent with the PDT, the neural correlates in those DPs can be very different. For instance, for Words, DP3 (within the framework of the PDT) showed underactivation in: L IPC (PFm) (BA40), L IPC (PF) (BA40) and L IPC (PGp)

(BA39) and L TE3 (reduced probability and voxel thresholds for the latter). DP11 exhibited underactivation in the L Area 44 and L insula, whereas DP12 showed no underactivation in any areas postulated by the PDT. This is also true about the neural correlates of reading which were in agreement with the CDT. For instance, DP2 showed underactivation in R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus I (Hem) and L Lobule VIIa Crus II (Hem); DP5 showed underactivation only in the R Lobule VIIb (Hem), whereas DP12 exhibited underactivation only in R Lobule VIIb (Hem). The results for Pseudowords are also characterised by heterogeneity (see Table 6.5, Table 6.6 and Figure 6.1). This could not have been uncovered with the traditional approach (as presented in Chapter 5) where only between-group differences (DPs versus CPs) are tested.

The results, showing considerable individual differences in patterns of underactivation (and overactivation) within the reading network among DPs, are certainly surprising in the context of the between-group comparison studies, which have dominated neuroimaging research on dyslexia. However, they are perhaps less surprising if one reflects that reading is a human invention, relatively new in evolutionary history. Reading involves areas, which evolved for vision, language and associative learning. Reading acquisition is an exercise in brain plasticity, the goal of which is to create an efficient reading network which enables the unimpaired reader to get from visual precept to meaning in approximately 250 milliseconds (Pugh, 2006). Because of the number of areas involved, which have to be 'adapted' for reading in the ontogenetic development of an individual DP, perhaps it is not surprising that in different individuals with dyslexia, different impaired components are found.

Somewhat unexpectedly, some DPs exhibited a given brain area as deficient in Pseudoword reading, but not in Word reading (e.g., R Lobule VIIa Crus I (Hem) in DP10) and vice versa (e.g., L Area 44 in DP1). If an area was deficient in both tasks, then one could draw the conclusion that it is characterised by a 'developmental lesion'. The fact that a given area appears deficient in one task, but not in another one, points to a different interpretation which has to do with the connections within different neural systems, e.g. a Word reading system and a Pseudoword reading system (cf. Pugh et al., 2000).

Some cases exhibited striking patterns of hyperactivation. A larger number of DPs exhibited hyperactivation for Pseudowords and those who exhibited overactivation for Pseudowords also exhibited hyperactivation for Words (DP8, DP13 & DP17). Perhaps the subgroup with striking patterns of hyperactivation is

characterised by some other feature, for instance the presence of a particular allele of a particular gene (cf. Bookheimer et al., 2000). Hyperactivation in some DPs in the areas hypothesised to exhibit underactivation in DPs by the PDT suggests that a compensatory network is not limited to the frontal areas, as suggested by a number of studies involving exclusively group comparisons (e.g., Shaywitz et al., 1998), but involves areas distributed throughout the entire phonological reading network. Furthermore, in some cases, there were areas overactivated in the cerebellum, which points to the presence of a compensatory network within this brain structure. It is likely that patterns of hyperactivation, interpreted as a compensatory mechanism, depend on DPs' individual characteristics.

Lack of a clear deficit on a behavioural test (e.g., *TOWRE*) does not necessarily mean that the neural correlates of reading are intact. For instance, despite having a history of reading difficulties and a diagnosis of dyslexia, DP1 and DP5 exhibited no deficits on all behavioural literacy measures, but their neural correlates of Word and Pseudoword reading, clearly showed underactivation. Furthermore, DPs who have the same profile on behavioural measures can have similar profiles on the neural level, but not necessarily - in the subgroups examined in this thesis for Words and Pseudowords, a larger number of DPs with the same behavioural profile exhibited dissimilar (rather than similar) profiles on the neural level.

8.1.1 Insights from additional analyses

Additional analyses were undertaken to examine the relationship between the psychometric and neuroimaging measures and were presented in Chapter 7. Three sets of analyses were performed. The first set involved the within-group correlations between the phonological, orthographic and literacy measures and BOLD for Words and Pseudowords run separately for CPs and DPs. The second set of analyses focused on: 1) investigating the relationship between *Orthography Composite*, reading and magnocellular processing in two subgroups of DPs who significantly differed on *Orthography Composite* and 2) testing the relationship between *PA* and *PF Composites* and under-engagement of the phonological areas during reading in between-group comparisons and on the level of individual DPs. Finally, the third set of analyses focussed on the question of whether there is an association between a score on *Purdue Pegboard Composite* and the BOLD signal for Words and Pseudowords in the cerebellar areas involved in reading and language.

The first set of analyses revealed interesting and complex results. Essentially, there were significant correlations in the predicted regions and some areas outside ROI, but there was also a lack of correlation in some predicted areas. One main point which needs to be emphasised again here is that although it is relatively straightforward to make predictions for the neuroimaging analyses, involving BOLD for Words and Pseudowords for DPs and CPs, it is considerably more difficult to make such predictions regarding the covariance between the behavioural measures and the BOLD for Words and Pseudowords. This is because the BOLD signal and behavioural scores are very different measures and each measure is potentially associated with different measurement errors and different amounts of variability between participants.

In line with the predictions, there were significant correlations for CPs (treated as a group) between BOLD for Words and Pseudowords and *PF Composite* and *Digit Span* in phonological areas. The BOLD signal in the L dorsal and L anterior areas consistently correlated with these behavioural measures, except for the *PF Composite* for Pseudowords, where the correlation was only in the ventral area. Also congruent with the predictions, there was a significant correlation in CPs (treated as a group) between BOLD for Words and *TOWRE* in the phonological network, including dorsal and anterior areas. Although there was a significant correlation for CPs between BOLD for Words and Pseudowords and *WRAT Spelling* in the phonological areas, ventral areas were implicated for Words and anterior areas for Pseudowords.

Consistent with the predictions, significant correlations for DPs between BOLD (for Words and Pseudowords) and *PA, PF* and *Orthography Composites* were noted here. Interestingly, the BOLD signal in one L ventral area consistently correlated with all behavioural measures, except for *Digit Span*. In contrast to the results for CPs, the BOLD signal for Words and Pseudowords for DPs correlated in a larger number of phonological areas for the *Orthography Composite,* including the dorsal and ventral areas. Congruent with the predictions there was a significant correlation for DPs between BOLD for Pseudowords and *WRAT Spelling* in the L middle temporal gyrus. Finally, there was a significant correlation for DPs between BOLD for Words and Pseudowords and *Irregular Word Composite* in L IPC (PFm) and R IPC (PFm), respectively.

Perhaps the most surprising result for CPs was the lack of significant correlations between BOLD for Words and *PA* and *Orthography Composite*s. The reason for these results is unclear. One possible explanation is to do with the

characteristics of behavioural measures. It is possible that a better predictive power would be found with the *PA* and *Orthography Composites* which would consist of a larger number of measures, or even different measures. The other factor which might have contributed here is that Word reading in CPs may be over-learnt and automatic, resulting in a BOLD signal with less fluctuation in the areas of interest. There were also two other surprising findings. First, in contrast with the predictions, there were no significant correlations for CPs between BOLD for Pseudowords and *Pseudoword Composite* in any of the phonological areas. Second, no correlations in phonological areas for CPs were found between *Irregular Composite* and BOLD for Words and Pseudowords. These results are surprising because all measures (behavioural and neuroimaging) involve phonological processing and they warrant further investigation.

Interestingly, there were also significant correlations between BOLD for Words and Pseudowords and behavioural measures in areas outside the ROI. The most consistent finding for CPs for phonological and orthographic measures was noted for the L SPL. The activation in L SPL (7A) is of particular interest because it has been shown recently (Heim, 2012) that this area is most likely involved in general aspects of motor sequencing, including sequencing of speech. CPs' BOLD for Words and *TOWRE* and BOLD for Pseudowords and *Pseudoword Composite* also significantly correlated in the L SPL. Furthermore, CPs' BOLD for Words and Pseudowords and *WRAT Spelling* significantly correlated in the cerebellar Lobules I-IV (Hem), L inferior temporal gyrus and L hippocampus. It needs to be added here that functional connectivity analysis (Bernard et al., 2012) showed that there is a functional connection between the R Lobules I-IV (Hem) and L IPC (PGp) (part of the L angular gyrus). Therefore it is possible that these lobules may be indirectly involved in language and spelling processes. Although no data were reported on the functional connectivity of the L cerebellar lobules it is possible that the connections are similar. Regarding the effect in the inferior temporal gyrus, as discussed above, many different studies have reported the involvement of this area in different processes, including: the mapping of phonology to semantics, lexical retrieval, the sound-meaning interface and visual word identification, (Cohen et al., 2004; Hickok & Poeppel, 2004; Mechelli et al., 2005). Hence, it is very likely that this brain area consists of several distinctive cytoarchitectonic sub-areas. Future research will need to establish which cytoarchitectonic sub-area will show a correlation here.

DPs'BOLD signal in L Hipp (CA) for Words and Pseudowords consistently correlated with *PA Composite.* It was reported (Cabeza, Dolcos et al., 2002) that hippocampal regions were activated not only for episodic retrieval but also for working memory, a crucial skill for reading (Jerman & Swanson, 2005); both measures correlated here involved reading. Furthermore, resting-state functional connectivity analyses (Uddin et al., 2010) demonstrated that the hippocampus is linked, among other areas, to IPC PGa (part of the angular gyrus). Therefore, it is likely that it has some indirect involvement in language processing. Also, significant correlations between BOLD (for Words and Pseudowords) and the *Orthography Composite* were noted in the R SPL (see the discussion above). A significant correlation for DPs between BOLD for Words and Pseudowords and *WRAT Spelling* was consistently found in the L inferior temporal gyrus (see the discussion regarding this brain area above). Finally, a significant effect was consistently found in cerebellar areas, for the same measures.

The second set of analyses focused on investigating the relationship between *Orthography Composite*, reading and magnocellular processing in two subgroups of DPs who significantly differed on *Orthography Composite*. The results showed some support for the MDT for Words (DPs with impairment on *Orthography Composite* showed significantly lower BOLD signal in R V5/MT+ for Word reading) but not for Pseudowords. The reason for the results for Pseudoword reading is unclear. The results suggest that the deficit is to do with the interconnections of the Word reading system and not to do with developmental lesions within the V5/MT.

Although both sub-groups were impaired on phonological processing, only the sub-group which was also impaired on *Orthography Composite* showed under-engagement of the phonological areas for Words and Pseudowords. The reason for this outcome is not clear and various explanations were discussed. Results from the subsequent case analysis suggest that scores from phonological behavioural tests are not a sufficient predictor of whether a given DP under-engages phonological areas during reading.

Finally, the third set of analyses focussed on the question of whether there is an association between a score on *Purdue Pegboard Composite* and the BOLD signal for Words and Pseudowords in the cerebellar areas involved in reading and language. The within-group correlation analyses demonstrated non-significant correlations for Words. In contrast, there was a significant correlation between BOLD for Pseudowords and performance on *Purdue Pegboard Composite*,

however, different cerebellar areas were involved for the CPs and DPs. BOLD for Pseudowords was significantly correlated with scores on *Purdue Pegboard Composite* in R Lobule VI (Hem) for CPs. On the other hand, a significant correlation between BOLD for Pseudowords and scores on *Purdue Pegboard Composite* for DPs, was found in L Lobule VI (Hem) and L Lobule VIIa Crus I (Hem). These results clearly ask further questions. One of the most interesting questions seems to be: why are different cerebellar areas associated with BOLD for Pseudowords for CPs and DPs? As discussed earlier, it is likely that the cerebellum was influenced differently in CPs for whom the brain systems develop normally, than in DPs for whom the brain systems are impaired from birth and therefore have not developed in the same way as in CPs. This explanation is particularly plausible in the light of current research findings which show that the cerebellum is characterised by a prolonged maturational process which makes this brain structure especially susceptible to disruptions during the process of embryogenesis (Wang & Zoghbi, 2001). It also shows considerable plasticity (e.g., Black et al., 1990; Klintsova et al., 2000; Schlang, 2001; Zheng & Raman, 2010) and can be influenced by many different factors during ontogenetic development (Bishop, 2002).

8.2 Shortcomings

It should be noted that historically, the main theoretical approaches to studying dyslexia (the PDT, the visual MDT and the CDT) were developed as separate and competing theories of dyslexia. Over the years different versions of these theories have been developed. For instance, a more recent version of the MDT (Stein, 2001), states that the cerebellum can be considered to be the most important part of the magnocellular timing system. Furthermore, the PDT could (but does not) argue that if there are areas within the cerebellum which participate in phonological/language processing, then they are a part of phonological/language processing network.

The focus of this thesis was on the well-established and most prominent versions of these theories, as described in the Introduction and this is both the strength and the weakness of the approach taken in this thesis. The strength of this approach lies in the fact that the predictions made on the basis of these versions are clear cut and differentiate the theories quite well. The weakness comes from the fact that the new theoretical developments within these theories may be omitted. However it is felt, that they are less well theoretically developed. For instance, it is

not clear how the cerebellum can be considered to be the most important part of the magnocellular timing system because strictly speaking there are no magnocellular neurons in the cerebellum. It should be underscored here that it is becoming increasingly apparent that the neural correlates of reading impairment in dyslexia involve more than just one system, including the visual processing system, the phonological processing system and cerebellum and in this new context, these theories can be viewed as complementary, rather than competing. The results from this thesis show that in the majority of cases the results are consistent with the predictions of more than one theory.

The shortcoming which is unavoidable at present is the fact that not all brain areas, and more importantly not all areas of interest, were labelled with the Anatomy Toolbox (AT) V.1.7. This is because probabilistic cytoarchitectonic maps have not yet been published for all brain areas. As a consequence some areas were labelled using the less reliable method (Tzourio-Mazoyer et al., 2002) which does not rely on probabilistic cytoarchitectonic maps. Future research will need to use probabilistic cytoarchitectonic maps, so that more precise localisation of brain activations can be obtained, especially in the regions of interest.

Another shortcoming is related to the role of brain areas in a given process. For instance, many brain areas have been implicated in phonological processing, as reviewed in the Introduction, but it is not clear whether some of them are crucial for phonological processing, or they are just co-activated with other brain areas which are indispensable for phonological processing. Furthermore, the list of areas crucial for a given process is open-ended and as the research progresses, it may be that new areas will be discovered. Therefore the evaluation of a given theory may need to be updated in future research.

Although a detailed history was taken from participants regarding potential impairments (including developmental disorders), and measures for ADHD and DCD, no measures were recorded for other developmental disorders, which also tend to co-occur with dyslexia, such as, SLI (Specific Language Impairment) and SSD (Speech Sound Disorder). It has been reported that dyslexia is comorbid with SLI (Catts, Adlof, Hogan, & Weismer, 2005; Riccio & Hynd, 1993), approximately 30% of individuals with dyslexia also have SLI (Riccio & Hynd, 1993). Extensive behavioural research has demonstrated that individuals who exhibited SSD in childhood are characterised by an increased risk of literacy difficulties (e.g., Aram, Ekelman, & Nation, 1984; Bishop & Adams, 1990; Catts, Fey, Tomblin, & Zhang, 2002; Hall & Tomblin, 1978; Scarborough & Dobrich, 1990; Snowling, Bishop, &

Stothard, 2000). These studies also showed that approximately 30% of children with SSD develop literacy difficulties. Therefore it is possible that some sub-threshold symptoms associated with SLI and/or SSD were present in the DPs tested in this study. The future studies on dyslexia will need to take measures of potential developmental disorders comorbid with dyslexia.

As for many studies on dyslexia, the study reported here is based on a relatively small sample which consists of university students and therefore cannot be treated as a representative sample of the population with dyslexia. There is an urgent need in future research to rely on representative samples of DPs (Hulme & Snowling, 2009).

The neuroimaging findings reported in this thesis add a new perspective on individual differences in dyslexia, however, it needs to be emphasized that the neuroimaging data provide a description of neurophenotypes in dyslexia, but do not provide an explanation of what causes such neurophenotypes. In this thesis the explanatory frameworks, from the main theories of dyslexia, were contrasted, however they do not take into account a deeper level of explanation at the genetic level. Genetics cannot be ignored nowadays, given the remarkable achievements of the Human Genome Project (Human Genome Project, 2011; Robbins & Stavroula, 2011) and will serve as an important branch of knowledge in future research on the underlying causes of reading impairment in dyslexia.

8.3 Future directions

Given the results reported in this thesis, there are three main issues which need to be resolved in future research. Firstly, further work is needed to establish the neural correlate of reading impairment in dyslexia in the cases which could not be accounted for by the main theories of this disorder. Secondly, there is a need to focus on individual DPs for whom a given area was underactivated in Word reading, but not in Pseudoword reading, and vice versa, suggesting that these areas are not characterised by a 'developmental lesion'. This is an important issue because it suggests that the observed deficits may be due to deficient connections between the brain regions, rather than the areas themselves. Third, dyslexia theories will need to account for the complexity and heterogeneity of individual DPs' patterns of underactivation and overactivation.

There are some specific approaches which may be taken in future research regarding these issues, as well as a more general approach, which is relevant to all three issues. The focus here is first on the more specific approaches and then on the more general approach.

It is possible that the cases, whose neural correlates of reading were not consistent with the predictions of any of the main theories of dyslexia, had more subtle and more transient deficits, not detectable with fMRI. A neuroimaging technique with higher temporal resolution, such as MEG which taps into the underlying cortical neuronal events in real time (10-100 msec) (Hämäläinen & Hari, 2002), as well as fMRI would be needed here. Furthermore, multimodal neuroimaging could enable integration of measurements of high spatial and temporal resolution, potentially providing better characterisation of deficits in dyslexia (Mathiak & Fallgatter, 2005). It should be noted that the study reported in this thesis was piloted using MEG with two unimpaired participants (see Appendix G for the preliminary results). However, due to time constraints on this project it was limited to fMRI and behavioural measurements.

The findings that a given area can be malfunctioning when Pseudowords are read, but exhibit a normal level of activation in Word reading and vice versa, suggests that a given area itself may be intact, but that a problem most likely lies in the connections within a given network, e.g., the Pseudoword reading network. Anatomical connectivity (*in vivo*) can be measured using Diffusion Tensor Imaging (DTI) (Mori, 2002) - a relatively new technique and future research needs to focus on characterising various networks in terms of their anatomical connectivity. See the section below, called 'Variability in structural connectivity' for further details.

To account for the complexity and heterogeneity of individual DPs' patterns of underactivation and overactivation, a first step would be to focus on a broader behavioural assessment of DPs and use of multivariate studies. Such studies provide analysis for the many dependent (and independent) variables which are correlated with each other to different degrees (Tabachnick & Fidell, 2001). The second step would be to enter potential confounding variables as covariates in the neuroimaging analysis.

Moving on to the more general approach, which is relevant to all three issues, and in particular to the third one, the essential need is to put variability between participants at the centre of the inquiry. These issues for future research are not easy to tackle, unless variability is taken into account. Variability between participants, which leads to individual differences in such a heterogeneous disorder as developmental dyslexia is present on every level of inquiry: biological, cognitive and behavioural, as well as on the environmental level which interacts with all the aforementioned levels. Essentially variability between participants is due to genetic variability, environmental variability and the interaction between the two.

Some developmental disorders were thought to be caused by environmental factors, for instance, until 1980s autism was defined as a disorder caused by brain damage or a cold unaffectionate parenting style. However, the picture has been changing and nowadays some of the most important discoveries involving behaviour point to genetic influence (it should be noted here that acknowledging genetic influence does not question the presence of environmental influence). As Plomin, DeFries, McClearn and McGuffin (2008) succinctly put it: "Genetic differences do not just make some of us abnormal; they contribute to differences among all of us in normal variation for personality and cognitive abilities" (p.2).

In the following sections, some different types of variability, particularly important for the future of dyslexia research, are discussed.

8.3.1 Variability due to risk and protective factors in ontogenesis

As discussed above, dyslexia manifests itself as difficulty with reading - a highly complex cognitive function which relies on many well integrated cognitive processes. It must be appreciated therefore, that the process of mastering such a skill is under the influence of a multitude of factors, some of which are risk factors (e.g., lack of reading instruction, the presence of genes implicated in dyslexia, etc.), and some of which are protective factors (e.g., good language skills, good naming skills, teaching tailored to individual needs, lack of a particular allele of a particular gene implicated in dyslexia, etc.).

Dyslexia research has focused mainly on the role of risk factors and not on the role of protective factors, nevertheless, the importance of protective factors should not be underestimated. For example, it has been established that smoking causes lung cancer. However, there are some people who smoke throughout their lives and do not get lung cancer. How this can be the case? Poisons from cigarette smoke are changed by the liver. In the majority of cases, these changes cause them to be more water-soluble and more able to cause DNA damage which could lead to lung cancer. It should be noted here that transformation of the majority of outside substances into more water-soluble forms is evolutionally advantageous because it allows for their excretion via the kidneys. If a person caries a genetic mutation (an allele) which leads to poisons being less acted upon by the liver system, there will be fewer poisons produced in their organism and hence less probability of DNA damage resulting in cancer (Sadava, 2008). Therefore the presence of this allele will act as a protective factor from lung cancer caused by smoking. Similarly, there may be genetic (and environmental) factors which act as protective factors from

dyslexia and it is likely that DPs will vary considerably across these factors and factor combinations.

8.3.2 Genetic variability

As discussed in the Introduction, molecular genetics has identified seventeen genes implicated in dyslexia, each of which can have several variants, some of which can be specifically associated with increased risk of developing dyslexia. For instance, *KIAA0319* has five variants: haplotype 1, haplotype 2, haplotype 3, haplotype 4 and haplotype 5, where haplotype 3 is the risk haplotype. It is likely (Williams, 2011) that there are hundreds of genes, still to be discovered, which could act together with non-genetic factors to influence an individual's risk of developing dyslexia, resulting in considerable variability among DPs.

8.3.3 Variability due to comorbidity with other developmental disorders

As discussed earlier, dyslexia co-occurs more frequently than would be expected by chance with ADHD (Pennington, 2006) and possibly with other developmental disorders, such as DCD, SLI and SSD. The implication here is that, for instance dyslexia and ADHD are not completely independent disorders. Results from cognitive, behavioural and molecular genetic studies lend some support for this view. Evidence was found for speed of processing being a cognitive risk factor which is shared by both ADHD and dyslexia (Shanahan et al., 2006). Behavioural genetic studies (Light, Pennington, Gilger, & DeFries, 1995; Stevenson, Pennington, Gilger, DeFries, & Gillis, 2006; Willcutt, Pennington, & DeFries, 2000) have reported bivariate heritability for reading disorder and ADHD. However, results from molecular genetic studies are less straightforward. For instance, a pioneering study on ADHD and reading comorbidity found that the dyslexia risk locus on chromosome 6p22 is also implicated in ADHD (Willcutt et al., 2002). Although, a more recent study (Couto et al., 2009) revealed a strong association for both inattention, as well as hyperactivity and impulsivity subtypes of ADHD for the markers in the 6p22 region, it found no overlap for ADHD and reading skills markers. This may be because only 31 individuals with ADHD, out of 264 probands and 55 siblings were diagnosed with reading disability. Loo et al. (2004) reported common loci on chromosome 16p, 17q and possibly on 10p contributing to both reading measures and ADHD. The findings for 16p and 17q replicated earlier findings for the same data set (Fisher, Francks, McCracken et al., 2002; Ogdie et al., 2003; Smalley et al., 2002). Finally, Doyle et al. (2008) reported

a region on chromosome 3 (3q13) which exhibited a suggestive linkage with the inattention subtype of ADHD and a range of neurocognitive traits. Interestingly, 3q13 overlaps with the region which contains the *ROBO1* gene associated with dyslexia (Nopola-Hemmi et al., 2001).

8.3.4 Variability due to neuronal migration and axon growth

Interestingly, molecular genetic findings point to abnormal connectivity in dyslexia. The roles of genes implicated in dyslexia were investigated, among others, in RAN interference (RANi) studies with animals. The results revealed that *DYX1C1* (Rosen et al., 2007; Wang et al., 2006), *KIAA0319* (Paracchini et al., 2006) and *DCDC2* (Burbridge et al., 2008; Meng et al., 2005) are involved in neuronal migration. *ROBO1* has been implicated in axon growth (Zhu, Li, Zhou, Wu, & Rao, 1999). More recently, six new genes (*KIAA0319L*, *S100B*, *DOCK4*, *FMR1*, *DIP2A* and *GTF2I*), implicated in dyslexia, have been reported to be involved in neuronal migration and neurite outgrowth (see Chapter 1).

A theory where neural migration deficit is the underlying cause of dyslexia has been proposed (Galaburda, 2005; Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006). According to this theory, impaired neuronal migration causes ectopias and microgyri which tend to agglomerate most densely within the L perisylvian cortex and this in turn causes dyslexia - a specific reading disorder. However, as the authors pointed out, the genes implicated so far in dyslexia appear to have a general function in neuronal migration and guidance, so are unlikely to restrict migration to these specific areas. Some additional mechanisms may be involved to restrict neuronal migration to certain brain areas, or the migration deficit may be more general in nature affecting many more areas throughout the brain, including for instance, the V5/MT and the cerebellum.

There is an indication that different DPs are carriers of different genes which are associated with dyslexia, therefore it is likely that these genes will influence brain development in different ways, hence the variability in the neurophenotype of DPs will be considerable.

8.3.5 Variability in structural connectivity

If genes associated with neuronal migration (together with the environment and gene by environment interaction) shape structural connectivity, DPs will vary in structural connectivity. As stated above, one could test structural (anatomical) connectivity in DPs, who are carriers of given genes associated with dyslexia, using DTI. This technique allows measurement of the micro-structural features of white

matter. The dependent measure is anisotropy which quantifies the degree to which diffusion of water differs in three dimensions. The lower anisotropy indicates lower coherence of white matter tracts (Mori, 2002). If, in agreement with the proposed theory (Galaburda, 2005; Galaburda et al., 2006), impaired neuronal migration affects mostly the L perisylvian cortex, then abnormal anatomical connectivity should be observed mainly within this area. If, on the other hand, the impaired neuronal migration is more general and affects many more areas, then abnormal anatomical connectivity should be observed within other areas, including areas from the magnocellular system and cerebellum.

Currently there is some support that there are differences between adult DPs and CPs in white matter microstructure, bilaterally in the temporo-parietal area (Klingberg et al., 2000). Furthermore, white matter diffusion anisotropy in the L temporo-parietal area is significantly correlated with reading scores in both groups. One shortcoming of this study is the small sample of six DPs; another is that the study focused only on group comparisons, hence nothing is known about DPs' individual differences in white matter microstructure.

8.3.6 Variability due to effective connectivity

In contrast to functional connectivity, as discussed in the Introduction, which describes patterns of statistical dependence, effective connectivity goes further by attempting to extract networks of causal influences of one brain area over another brain area, within a network of areas (Büchel & Friston, 2001). As reading is a highly complex cognitive function, which relies on many well integrated cognitive processes taking place within a complex reading network, effective connectivity should uncover another type of variability in DPs.

8.3.7 Summing up issues of variability

The sections above gave examples of different types of variability, which are of importance in shaping the future research on dyslexia. Some are on the phenotype level, some on genotype level and some on the neurophenotype level. Future research on dyslexia (and other developmental disorders), needs to focus on sophisticated designs where as much relevant variability as possible is, either controlled for by a selection process, e.g. presence/absence of a given gene associated with dyslexia, or measured and entered into the behavioural and/or neuroimaging analyses as covariates.

Variability (due to various factors) not accounted for, will confound the results. For instance, as mentioned in the section on shortcomings, the study reported in this

thesis did not collect any measures on SLI and/or SSD. Therefore, some variability in the neurophenotypes of DPs may be due to these potential confounds. Furthermore, the study reported here did not have any genetic data on whether a given participant had genes associated with dyslexia and if so which ones. Hence some variability in the neuroimaging results presented in this thesis is due to genetic factors and is not accounted for.

8.4 The future of dyslexia research

Although these are early days, some studies have already started to address the variability due to genotype (e.g., Bookheimer et al., 2000; Lesch et al., 1996). For instance, Bookheimer et al. (2000) showed in an fMRI study that the extent and the magnitude of activation during memory tasks in areas affected by Alzheimer's disease were significantly greater in the carriers of the *APOE €4* allele (a known genetic risk factor for Alzheimer's disease) than in participants with the *APOE €3* allele (who served as CPs). This difference occurred without any statistically significant behavioural differences on this task between the groups. However, these are early days and the majority of studies leave many important variables unquantified.

The complexity and multitude of factors involved in dyslexia has been addressed in a recent multiple-deficit model (Pennington, 2006) introduced above. The model accommodates the fact that there are multitudes of environmental and genetic risk factors and that they do not act independently. It may be that they are correlated with each other, or that they share effects of gene-by-environment interaction, or genes may interact with each other because they are part of the genetic system. Future research within this model, using neuroimaging and other research techniques, promises important insights into dyslexia and its comorbid disorders.

Undoubtedly, this is an exciting time, when considerable technological, behavioural, neuroimaging and genetic advancements promise deeper clarity into the mechanisms underlying the reading disorder in dyslexia upon which this thesis began to venture - glimpsing the tip of the iceberg of this widely heterogeneous disorder.

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10 Appendix A - Tables for Introduction

Table 10.1 Results from the neuroimaging studies of phonological awareness, naming & short term memory in CPs and DPs

Study	Task	Imaging method	Results/Regions	Coordinates (x y z)	Z score
Phonological awareness, a sample from the unimpaired population					
Paulesu et al. (1996)	Covert consonant rhyming: "Does *'p'* rhyme with *'t'* ?"	PET	L SMA (BA6) L inferior frontal gyrus - BA44/45/46 (including Broca's area) PMC (BA6) L insula L insula L posterior superior temporal gyrus – BA22 (Wernicke's area) L caudate L caudate L cerebellum R insula R striatum R cerebellum	-14 8 56 -36 32 12 -46 12 12 -38 6 32 -34 -6 -4 -38 14 0 -46 -26 4 -44 -32 12 -6 18 8 -22 22 12 -12 -58 -12 34 12 4 18 -12 4 18 -64 -16 (Talairach)	3.7 6 6.5 7.4 3.3 3.8 6.1 3.9 4.9 2.9 3.3 3.7 4.5 3.5
Booth, Wood, Lu, Houk, & Bitan (2007)	Word rhyming task with 3 words, e.g., 'hold – milk – cold', Ps were asked to indicate whether the final word rhymed with either of the previous two; which two items rhyme? Control task: line matching with three sets: '// - \\ - //'; Ps had to indicate whether the final set of lines was the same as either of the previous two.	fMRI	L Inferior/middle frontal gyri (BA 46/45/9) L Fusiform gyrus (BA 19/37) L Superior/middle temporal gyri (BA 21/22) L Putamen Cerebellum (VI/Crus I)	-51 30 21 -45 -60 -21 -66 -36 -3 -30 -15 -6 12 -75 -30 (not clear whether MNI or Talairach)	5.15 4.72 3.71 4.86 4.25
Xu et al. (2001)	Word rhyming relative to colour matching with letters	PET	L mid-temporal gyrus L inferior temporal occipital junction (BA37) L Posterior-prefrontal cortex	-48 -40 0 -44 -56 -16 -42 4 30	unclear whether given

			R Cerebellum	10 -72 -34 (not clear whether MNI or Talairach)	
Xu et al. (2001)	Pseudoword rhyming relative to colour matching with letters	PET	L inferior temporal occipital junction (BA37) L Posterior-prefrontal cortex R Cerebellum L supramarginal gyrus (BA40)	-48 -54 -14 -44 4 28 32 -68 20 -34 -50 38 (not clear whether MNI or Talairach)	unclear whether given
Covert object naming, the unimpaired population					
Lurito et al. (2000)	Covert naming of simple line drawings of common objects, relative to covert naming of abstract line drawings	fMRI	L inferior frontal gyrus (Broca area) L posterior superior temporal gyrus (Wernicke area) L posterior fusiform gyrus L middle temporal gyrus L middle temporal gyrus L premotor cortex L superior cerebellum R premotor cortex R superior cerebellum R supplementary motor area	-48 7 8 -50 -39 17 -45 -55 -17 -55 -43 -3 -53 -28 -4 -44 -6 34 -32 -50 -20 51 -7 32 35 -50 -21 2 -6 49 (Talairach)	Not given
Moore & Price (1999)	Overt object naming, compared to saying 'yes' or 'okay yes' in response to nonsense shapes; Object naming compared to object viewing; Object naming compared to word naming;	PET	All comparisons elicited activation in: L anterior fusiform (BA20) L posterior fusiform (BA37)	 -38 -34 14 -40 -50 -12	 3.3 3.4
Misra et al. (2004)	covert RAN of objects (experimental task) passive viewing of matrix of plus signs (control task);	fMRI letter naming > object naming	L inferior parietal lobule L angular gyrus L superior frontal gyrus L medial occipital gyrus	-48 -42 57 -57 -45 30 -24 51 36 -3 -72 9 (unclear whether MNI or Talairach)	6.59 (t) 6.56 (t) 4.85 (t) 4.77 (t)
Misra et al. (2004)	covert RAN of letters (experimental task) passive viewing of matrix of plus signs (control task);	object naming > letter naming	L inferior temporal gyrus (fusiform gyrus)	-33 -54 -15 (unclear whether MNI or Talairach)	8.19 (t)
Verbal short term					

memory, the unimpaired population					
Paulesu et al. (1996)	Ps were instructed to remember sequences of 6 consonants and 2 s later to make a judgement whether a target consonant was previously displayed.	PET	SMA (BA6) L IFG (BA6/44) (Broca's area) L IFG (BA6/44) (Broca's area) PMC (BA6) L insula L STG (BA22) (Wernicke's area) L STG (BA22) (Wernicke's area) L supramarginal gyrus (BA40) L lingual gyrus (BA18) L cerebellum R IFG (BA6/44) R PMC (BA6) R insula R STG (BA20)/SMG (BA40) R cuneus (BA19) R cerebellum	-2 2 56 -46 -2 20 -42 10 16 -52 0 16 -36 -8 36 -30 0 0 -46 -38 16 -44 -34 24 -14 -68 -8 -12 -68 -12 50 2 16 46 -8 36 38 0 4 54 -42 20 4 -84 32 14 -58 -16 (Talairach)	3.3 9.7 4.3 4.2 6.1 5.2 6.5 6.7 3.5 3.7 5.9 4.8 5.5 4.3 4.8 4.7
Paulesu et al. (1993)	Experiment 1: Ps were required to remember a string of English letters (experimental task) and a string of Korean letters (control task); Experiment 2: Ps were required to make rhyming judgements for English letters;	PET	Combined results for Experiment1 & Experiment 2: L SMA (supplementary motor area) L BA44 (Broca's area) L supramarginal gyrus (BA40) L BA 22/42 (includes Wernicke's area) L BA18 L insula L cerebellum R SMA R BA44 R BA40 R BA 22/42 R insula R cerebellum	 -6 6 56 -46 2 16 -44 -32 24 -46 -32 16 -12 -66 -8 -34 2 4 -18 -54 -16 4 4 48 48 4 12 54 -32 24 50 -28 16 40 4 4 14 -60 -16 (Talairach)	 4.7 9.0 6.4 6.6 4.8 6.4 4.1 4.8 6.4 4.5 4.9 6.9 5.5
Phonological awareness, DPs vs CPs					
Paulesu et al. (1996)	Covert consonant rhyming: "Does *'p'* rhyme with *'t'* ?"	PET DPs < CPs	L prefrontal motor cortex (BA 6) L superior temporal gyrus (BA21/22) L insula R SMA (BA6) R striatum	-32 2 40 -44 -22 4 -34 -14 4 6 -6 52 18 -6 8	2.7 1.9 3.3 1.7 2.4

			R striatum	34 6 4 (Talairach)	2.5
Shaywitz et al. (1998)	Covert single letter rhyming: "Does *'t'* rhyme with *'v'* ?"	fMRI DPs<CPs DPs>CPs	L & R posterior superior temporal gyrus (BA22) L & R angular gyrus (BA39) L & R Inferior frontal gyrus (pars opercularis) (BA44) & pars triangularis (BA45) L & R BA 17	-53/53 -43 11 -47/47 -45 33 -47/47 18 18 -8/8 -89 3 (Talairach)	Not reported
Overt object naming, DPs vs CPs					
McCrory et al. (2005)	Overt object naming, compared to saying 'yes' or 'okay yes' in response to nonsense shapes; (also reading aloud, compared to saying 'yes' or 'okay yes' in response to false fonts).	PET DPs<CPs	L occipito-temporal region L occipito-temporal region	-48 -54 -16 -46 -52 -16 (unclear whether MNI or Talairach)	4.8 5.4
Short term memory, DPs vs CPs					
Paulesu et al. (1996)	Ps were instructed to remember sequences of 6 consonants and 2 s later to make a judgement whether a target consonant was previously displayed.	DPs<CPs	L SMA (BA6) L inferior frontal gyrus (BA6/44) L PMC (BA6) L insula L SMG (BA40) L cerebellum R IFG (BA6/44) R insula	-8 0 56 -38 -4 20 -40 -6 32 -34 0 12 -46 -44 24 -16 -48 -16 44 0 12 38 2 4 (Talairach)	2.2 4.2 2.2 3.9 2.8 2.4 3.3 3.8

Note. Ps = Participants; the macro-anatomical labels as specified in the cited papers.

Table 10.2 Results from the neuroimaging studies of V5/MT and other areas sensitive to magnocellular processing in CPs and DPs

Study	Task	Imaging method	Results/Regions	Coordinates (x, y, z)	Z score
V5/MT investigated in the unimpaired population					
Liederman et al. (2003)	Non-word reading with rTMS stimulation (experimental task) vs non-word reading with no rTMS stimulation (control task)	rTMS	Significantly more visual errors during the rTMS stimulation of V5/MT+ during nonword reading as compared to the control task	Not given	Not given
V5/MT investigated in DPs vs CPs					
Eden et al. (1996)	Ps viewed coherently moving, low-contrast random dots (Magno, experimental, stimulus) & a high-contrast, patterned stimulus (Parvo, control stimulus)	fMRI	All CPs exhibited bilateral motion sensitivity in volume search surrounding V5/MT No DPs (except for one) exhibited activation in the same volume search; All Ps exhibited similar responses to the control stimulus in the posterior occipital cortex (V1/V2) & extrastriate visual areas (inferior temporal/fusiform gyrus);	L V5/MT: –52 ± 11, –75 ± 8, 8 ± 5; R V5/MT: 50 ± 9, –70 ± 8, 5 ± 4; (Talairach)	Not given
Demb et al. (1997) & Demb et al. (1998)	Ps responded to moving visual grating stimuli presented at a low mean luminance, which stimulate magnocellular inputs to the cortex (Experimental condition); Ps responded (in the Control Condition) to contrast-reversing grating stimuli presented at a higher mean luminance.	fMRI	DPs significantly impaired in the following areas: V5/MT+ , V1,V2, V3, V3a, V4v DP not impaired on the control condition.	Not given	Not given
Vanni et al. (1997)	'Magno task': the height contrast foveal stimulus, oblique black-white sinusoidal grating projected on the black background; It jumped abruptly to the right and then back once per 1.6 s; Ps were asked to fixate on a stationary dot presented in the centre of the display;	MEG	No sig. difference between the groups	LH: -33 ±6, -79±9, 9±7; RH: 34±9, -76±11, 9±10;	Not given

Table 10.3 Results from the neuroimaging studies which targeted the cerebellum in CPs and/or DPs

Study	Task	Imaging method	Results/Regions	Coordinates (x, y, z)	Z score
a sample from the unimpaired population					
Fulbright et al. (1999)	Rhyming judgement for pseudoword pairs	fMRI	R & L H lobule VI (simple lobule) R & L H lobule Crus I (superior semilunar lobule) R & L H Crus II & lobule VIIb (inferior semilunar lobule)	No coordinates given	Not given
Fulbright et al. (1999)	Semantic category judgement for real words	fMRI	the same areas as for rhyming judgement (see above) R deep nuclear region the inferior vermis	No coordinates given	Not given
Stoodley and Schmahmann (2009)	Language tasks (meta-analysis)	fMRI & PET	R H. lobule VI R Crus I R Crus I/II R Vermal lobule VIIAt L H. lobule VI	36 -62 -28 34 -82 -36 14 -86 -34 4 -82 -26 -42 -58 -24 (MNI)	12.18* 6.95* 9.91* 5.86* 6.36*
DPs vs CPs					
Nicolson et al. (1999)	Pre-learned sequence of finger movements *vs* rest	PET	CPs > DPs the R cerebellum	34^ -40 34 (not clear whether MNI or Talairach coordinates)	3.75
Nicolson et al. (1999)	New sequence of finger movements *vs* rest	PET	CPs > DPs the R cerebellum	34^ -46 34 (not clear whether MNI or Talairach coordinates)	4.38
Baillieux et al. (2009) (child DPs & child CPs)	A noun-verb association paradigm	fMRI	*Activation in CPs, absent in DPs:* R Anterior: H. lobule V (anterior quadrangular lobule) R Posterior: H. lobule VI (lobulus simplex) L Posterior: H. lobule VI (lobulus simplex) L Posterior: H. lobule VIIIA (biventral lobule)	 25 -49 -22 29 -64 -19 -29 -60 -19 -24 -60 -40	Not given
Baillieux et al. (2009) (child DPs & child CPs)	A noun-verb association paradigm	fMRI	*Activation in DPs, absent in CPs:* R Anterior: V. lobule I & II/lingual R Posterior: V. lobule VIIAt,VIIAf/tuber, folium R Anterior: V lobule III/centralis R Posterior: Crus II (inferior semilunar lobule) L Anterior: V. lobule V/culmen L Posterior: H. lobule VI (lobulus simplex) L Posterior: Crus I (superior semilunar lobule)	 2 -37 -20 5 -75 -28 7 -49 -25 30 -63 -38 - 13 -54 -17 -42 -50 -23 -51 -55 -26	Not given

Rae et al. (1998)	n/a	MRS (Magnetic Resonance Spectroscopy)	Cho/Na ratio (choline-containing compounds/N-acetylaspartate) sig. lower in DPs than in CPs	-	-
Laycock et al. (2008)	n/a.	MRS (Magnetic Resonance Spectroscopy)	DPs exhibited a higher ratio of Cho/Cr (creatine) in the L cerebellar hemisphere accompanied by a lower ratio of Na/Cho in the R cerebellar hemisphere	-	-
Laycock et al. (2008)	n/a	volumetric MRI	DPs had a larger volume of white matter in L and R cerebellar hemispheres;	-	-
Kronbichler et al. (2008) (teenage DPs & teenage CPs)	n/a	CPs > DPs Voxel Based Morphometry with T1 weighted MR images to investigate grey matter volume	R anterior cerebellum	27 -54 -33 46 -46 -33 (MNI)	4.88 4.22
Kronbichler et al. (2008)	n/a	As above	L anterior cerebellum	-34 -41 -31 -28 -51 -30 (MNI)	3.35 3.08
Brown et al. (2001) (adult men DPs & CPs)	n/a	Voxel Based Morphometry, comparing grey matter volume CPs > DPs	R & L semilunar lobules of cerebellum	18/-18 -74 -38 -18 -74 -50	 4.30
Eckert et al. (2005) (child DPs & CPs)	n/a	Voxel Based Morphometry, comparing grey matter volume CPs > DPs	R cerebellar anterior lobe	-10 -71 -8 39 -73 -50 (MNI)	5.68 (t) 6.37 (t)
Eckert et al. (2005) child DPs & CPs	n/a	Voxel Based Morphometry, comparing white matter volume CPs > DPs	Cerebellar anterior lobe (analysis with white matter volume co-varied)	0 -72 -6 (MNI)	4.23 (t)
Pernet, Poline, Demonet, and Rousselet (2009) adult DPs & CPs	n/a	CPs' brains were used to build a 'typical' brain using bootstrapped confidence intervals. Each DP's grey matter was classified at each voxel as being outside or within the normal range.	R cerebellar declive (vermal lobule VI)	26 -64 -28 (MNI)	
Finch, Nicolson, and Fawcett (2002) 4 adults (except for one teenager) DPs' brains & 5 adult CPs' brains from the Orton Society brain bank;	n/a	Analysis of the size and density of cerebellar Purkinje cells; samples taken systematically from anterior, posterior and flocculonodular lobes;	***Cell size analysis:*** Purkinje cells significantly larger in DPs than in CPs in the posterior cerebellar cortex; No significantly differences in anterior and flocculonodular lobes; ***Distributional analysis:*** Significant differences in posterior and anterior lobes due to DPs having more large Purkinje cells and fewer small cells of this type; The dentate nucleus: no significant differences;	-	-

			Inferior olive: significant difference in distribution of cell sizes (due to fewer small cells & more large cells in DPs, when compared with CPs);		

Note. R= right; L=left; H=hemispheric; *Activation Likelihood Estimate (ALE) values (10 to the power of -3, significant on a FDR ($p<0.001$); ^ X coordinate in the original paper is negative, indicating L cerebellum, but the label in Table 2 states 'R cerebellum'; the first author confirmed that the R cerebellum was involved (personal communication – 29th of January 2010), therefore the negative X coordinate was changed into positive X coordinate; However, subsequently it was found that these coordinates do not lie in the cerebellum; When labelled with the Anatomy Toolbox (AT) (Eickhoff et al., 2005), the voxel with the following coordinates x=34, y=-40, z=34 was Assigned to R hIP1 (probability=50%, range=20-60%) and the other voxel with the following coordinates: x=34, y=-46 , z=34 was not assigned, (probability for hIP3=20%, range=10-30%);

11 Appendix B - Tables for Chapter 3

Table 11.1 ADHD & DCD as covariates in ANCOVA for Psychometrics & Literacy

DV	Covariate	F (df)	p
General Psychometrics			
PIQ	ADHD	F(1, 28)=.114	p=.738
PIQ	DCD	F(1, 28)=1.413	p=.244
FIQ	ADHD	F(1, 28)=.001	p=.981
FIQ	DCD	F(1, 28)=.04	p=.842
VIQ	ADHD	F(1, 28)=.139	p=.712
VIQ	DCD	F(1, 28)=.574	p=.455
Digit Span	ADHD	F(1, 28)=.0.951	p=.0.339
Digit Span	DCD	F(1, 28)=1.334	p=.259
ADC	ADHD	F(1, 28)=.332	p=.569
ADC	DCD	F(1, 28)=9.343	p=.005**
Purdue Pegboard RH	ADHD	F(1, 28)=.128	p=.723
Purdue Pegboard RH	DCD	F(1, 28)=.662	p=.423
Purdue Pegboard LH	ADHD	F(1, 28)=.839	p=.368
Purdue Pegboard LH	DCD	F(1, 28)=.600	p=.445
Purdue Pegboard BH	ADHD	F(1, 28)=6.24	p=.019*
Purdue Pegboard BH	DCD	F(1, 28)=.019	p=.892
Purdue Pegboard RH + LH + BH	ADHD	F(1, 28)=1.79	p=.192
Purdue Pegboard RH + LH + BH	DCD	F(1, 28)=.541	p=.468
Purdue Pegboard Assembly	ADHD	F(1, 28)=3.132	p=.088^
Purdue Pegboard Assembly	DCD	F(1, 28)=1.381	p=.250
Literacy tests			
number of words read correctly (TOWRE)	ADHD	F(1, 28)=.151	p=.701
number of words read correctly (TOWRE)	DCD	F(1, 28)=2.198	p=.149
% correctly read words (WRAT)	ADHD	F(1, 28)=.074	p=.787
% correctly read words (WRAT)	DCD	F(1, 28)=3.961	p=.056^
irregular word reading (Castles & Coltheart, 1993) (% correct)	ADHD	F(1, 28)=1.859	p=.184
irregular word reading (Castles & Coltheart, 1993) (% correct)	DCD	F(1, 28)=.453	p=.506^
words read (WRAT) (time)	ADHD	F(1, 28)=2.735	p=.109
words read (WRAT) (time)	DCD	F(1, 28)=.504	p=.484
irregular word reading (Castles & Coltheart, 1993) (time)	ADHD	F(1, 28)=1.738	p=.198
irregular word reading (Castles & Coltheart, 1993) (time)	DCD	F(1, 28)=.475	p=.496
words reading (SS) (WRAT)	ADHD	F(1, 28)=.049	p=.826
words reading (SS) (WRAT)	DCD	F(1, 28)=4.944	p=.034*
number of pseudowords read correctly (TOWRE)	ADHD	F(1, 28)=1.227	p=.277
number of pseudowords read correctly (TOWRE)	DCD	F(1, 28)=.000	p=.990
pseudoword reading (% correct) (Castles and Coltheart's (1993)	ADHD	F(1, 28)=.018	p=.894
pseudoword reading (% correct) (Castles and Coltheart's (1993)	DCD	F(1, 28)=.399	p=.533
pseudoword reading (time) (Castles & Coltheart's (1993)	ADHD	F(1, 28)=1.757	p=.196
pseudoword reading (time) (Castles & Coltheart's (1993)	DCD	F(1, 28)=.036	p=.850
WRAT spelling (% correct)	ADHD	F(1, 28)=.767	p=.389
WRAT spelling (% correct)	DCD	F(1, 28)=.679	p=.417
WRAT spelling (SS)	ADHD	F(1, 28)=2.295	p=.141
WRAT spelling (SS)	DCD	F(1, 28)=5.897	p=.022*

Note. The order of tests the same as in the main text in Chapter 3; ^ $p \leq 0.1$, * $p \leq 0.05$, ** $p \leq 0.01$.

Table 11.2 ADHD & DCD as covariates in ANCOVA for Phonology & Orthography

DV	Covariate	F (df)	p
Phonological Awareness			
Spoonerisms (% correct)	ADHD	F(1, 28)=.158	p=.694
Spoonerisms (% correct)	DCD	F(1, 28)=3.652	p=.067^
Spoonerisms (time)	ADHD	F(1, 28)=3.132	p=.088
Spoonerisms (time)	DCD	F(1, 28)=1.664	p=.208
Phonological Force Choice (% correct)	ADHD	F(1, 28)=4.184	p=.050*
Phonological Force Choice (% correct)	DCD	F(1, 28)=.017	p=.898
Phonological Force Choice (mean RT)	ADHD	F(1, 28)=.090	p=.766
Phonological Force Choice (mean RT)	DCD	F(1, 28)=.604	p=.444
Phonological Fluency			
RAN digits	ADHD	F(1, 28)=.185	p=.670
RAN digits	DCD	F(1, 28)=.038	p=.847
RAN letters	ADHD	F(1, 28)=.084	p=.775
RAN letters	DCD	F(1, 28)=7.263	p=.012*
RAN colours	ADHD	F(1, 28)=.109	p=.744
RAN colours	DCD	F(1, 28)=.882	p=.356
RAN pictures	ADHD	F(1, 28)=.015	p=.902
RAN pictures	DCD	F(1, 28)=.702	p=.409
Orthographic processing measures			
Olson's pseudo-homophone (mean RT)	ADHD	F(1, 28)=.043	p=.838
Olson's pseudo-homophone (mean RT)	DCD	F(1, 28)=.200	p=.658
Olson's pseudo-homophone (% correct)	ADHD	F(1, 28)=1.335	p=.258
Olson's pseudo-homophone (% correct)	DCD	F(1, 28)=.229	p=.636

Note. The order of tests the same as in the main text in Chapter 3; ^ $p \leq 0.1$, * $p \leq 0.05$.

12 Appendix C - Tables for Chapter 5

Table 12.1 Word Stimuli and their characteristics

Number	Word	Code	CNC	FAM	KFSMP	IMG	KFFRQ	NLET	NSYL
1	hotel	w_1	591	565	60	597	126	5	2
2	cottage	w_2	593	543	15	607	19	7	2
3	apple	w_3	620	598	6	637	9	5	2
4	capsule	w_4	540	505	4	594	5	7	2
5	gutter	w_5	498	467	1	506	1	6	2
6	party	w_6	496	619	87	596	216	5	2
7	story	w_7	427	578	80	491	153	5	2
8	corner	w_8	533	556	64	556	115	6	2
9	cattle	w_9	600	511	20	619	97	6	2
10	tulip	w_10	619	546	4	641	4	5	2
11	village	w_11	576	524	45	578	72	7	2
12	contact	w_12	456	543	37	449	63	7	2
13	metal	w_13	582	559	39	541	61	5	2
14	angle	w_14	467	518	18	503	51	5	2
15	pencil	w_15	617	598	14	607	34	6	2
16	rumble	w_16	407	476	2	494	2	6	2
17	witness	w_17	459	496	25	467	28	7	2
18	saddle	w_18	603	436	12	578	25	6	2
19	belly	w_19	630	486	12	576	23	5	2
20	painter	w_20	568	575	14	565	21	7	2
21	lobby	w_21	532	420	13	462	20	5	2
22	essay	w_22	527	578	13	564	19	5	2
23	canal	w_23	598	464	3	588	3	5	2
24	vessel	w_24	571	461	10	525	16	6	2
25	tennis	w_25	574	528	8	634	15	6	2
26	gospel	w_26	403	437	6	440	13	6	2
27	puppy	w_27	623	522	2	635	2	5	2
28	lady	w_28	564	573	42	571	80	4	2
29	margin	w_29	472	499	9	494	10	6	2
30	tunnel	w_30	555	541	5	578	10	6	2
31	berry	w_31	573	470	6	551	9	5	2
32	blossom	w_32	559	507	5	618	7	7	2
33	cable	w_33	544	492	6	469	7	5	2
34	maple	w_34	534	518	6	511	7	5	2
35	trumpet	w_35	608	490	6	628	7	7	2
36	buckle	w_36	568	474	5	587	5	6	2
37	coral	w_37	572	425	3	561	5	5	2
38	kitten	w_38	612	517	4	639	5	6	2
39	trolley	w_39	579	449	5	585	5	7	2
40	flannel	w_40	574	499	4	520	4	7	2
41	pupil	w_41	570	547	7	572	20	5	2
42	beaver	w_42	589	470	3	612	3	6	2
43	dummy	w_43	551	478	2	562	3	5	2
44	jelly	w_44	560	521	3	590	3	5	2
45	magnet	w_45	550	526	3	543	3	6	2
46	slipper	w_46	585	494	3	595	3	7	2
47	fable	w_47	459	477	2	477	2	5	2
48	gallon	w_48	488	519	4	525	6	6	2
49	tailor	w_49	535	417	2	499	2	6	2
50	piping	w_50	538	451	3	491	5	6	2

Table 12.1 (continuation). Word Stimuli and their characteristics

Number	Word	Code	CNC	FAM	KFSMP	IMG	KFFRQ	NLET	NSYL
51	record	w_51	558	609	83	591	137	6	2
52	battle	w_52	564	537	58	597	87	6	2
53	temple	w_53	565	450	19	547	38	6	2
54	pony	w_54	611	524	6	642	10	4	2
55	helmet	w_55	602	528	1	620	1	6	2
56	market	w_56	551	518	57	583	155	6	2
57	letter	w_57	577	610	70	595	145	6	2
58	pattern	w_58	472	555	68	453	113	7	2
59	dinner	w_59	542	621	61	570	91	6	2
60	winter	w_60	499	615	53	621	83	6	2
61	valley	w_61	575	515	34	600	73	6	2
62	message	w_62	459	557	39	438	64	7	2
63	signal	w_63	464	507	32	513	63	6	2
64	uncle	w_64	580	557	27	574	57	5	2
65	cotton	w_65	608	521	19	562	38	6	2
66	supper	w_66	563	593	25	590	37	6	2
67	blanket	w_67	622	563	19	582	30	7	2
68	lesson	w_68	404	559	23	446	29	6	2
69	mirror	w_69	605	593	21	627	27	6	2
70	barrel	w_70	590	487	15	602	24	6	2
71	marble	w_71	611	436	15	605	21	6	2
72	border	w_72	444	489	18	453	20	6	2
73	timber	w_73	578	440	10	553	19	6	2
74	candy	w_74	602	559	11	601	16	5	2
75	clover	w_75	554	486	1	606	16	6	2
76	jury	w_76	540	498	22	580	67	4	2
77	insect	w_77	593	542	9	586	14	6	2
78	pepper	w_78	591	554	7	587	13	6	2
79	ferry	w_79	580	458	6	592	11	5	2
80	harness	w_80	563	421	7	513	10	7	2
81	navy	w_81	472	465	25	562	37	4	2
82	hammer	w_82	605	515	6	618	9	6	2
83	bucket	w_83	594	506	6	586	7	6	2
84	cradle	w_84	587	478	4	592	7	6	2
85	rocket	w_85	645	525	6	612	7	6	2
86	cherry	w_86	611	514	5	582	6	6	2
87	glitter	w_87	420	440	5	503	5	7	2
88	soda	w_88	600	536	2	544	3	4	2
89	convent	w_89	537	458	4	559	4	7	2
90	wire	w_90	585	556	29	564	42	4	2
91	velvet	w_91	580	515	4	569	4	6	2
92	blister	w_92	573	462	3	616	3	7	2
93	hurdle	w_93	572	437	3	600	3	6	2
94	kettle	w_94	602	551	3	594	3	6	2
95	napkin	w_95	585	495	3	582	3	6	2
96	canteen	w_96	587	490	1	540	2	7	2
97	fiddle	w_97	582	465	1	555	2	6	2
98	herring	w_98	617	425	2	524	2	7	2
99	carrot	w_99	622	539	1	577	1	6	2
100	hero	w_100	428	510	31	483	52	4	2

Note. Code=Code in the experiment; CNC=Concreteness rating (scale from 100 to 700), FAM=Familiarity rating (scale from 100 to 700), IMG=Imagability rating (scale from 100 to 700) KFFRQ=Kucera-Francis written frequency, NLET= Number of letters, NSYL= Number of syllables.

Table 12.2 Pseudoword Stimuli and their characteristics

Number	Pseudoword	Code	NSYL	Change	Baseword
1	fecord	n_1	2	1	record
2	dattle	n_2	2	1	battle
3	gemple	n_3	2	1	temple
4	vony	n_4	2	1	pony
5	melmet	n_5	2	1	helmet
6	darket	n_6	2	1	market
7	lemmer	n_7	2	2	letter
8	passern	n_8	2	2	pattern
9	hinner	n_9	2	1	dinner
10	cinter	n_10	2	1	winter
11	palley	n_11	2	1	valley
12	mettage	n_12	2	2	message
13	gignal	n_13	2	1	signal
14	unble	n_14	2	2	uncle
15	cosson	n_15	2	2	cotton
16	hupper	n_16	2	1	supper
17	clanket	n_17	2	1	blanket
18	leccon	n_18	2	2	lesson
19	hirror	n_19	2	1	mirror
20	warrel	n_20	2	1	barrel
21	marfle	n_21	2	2	marble
22	bormer	n_22	2	2	border
23	tirber	n_23	2	2	timber
24	nandy	n_24	2	1	candy
25	blover	n_25	2	1	clover
26	mury	n_26	2	1	jury
27	inbect	n_27	2	2	insect
28	pemmer	n_28	2	2	pepper
29	feddy	n_29	2	2	ferry
30	larness	n_30	2	1	harness
31	ravy	n_31	2	1	navy
32	fammer	n_32	2	1	hammer
33	mucket	n_33	2	1	bucket
34	pradle	n_34	2	1	cradle
35	gocket	n_35	2	1	rocket
36	cheggy	n_36	2	2	cherry
37	plitter	n_37	2	1	glitter
38	noda	n_38	2	1	soda
39	ronvent	n_39	2	1	convent
40	bire	n_40	2	1	wire
41	velmet	n_41	2	2	velvet
42	plister	n_42	2	1	blister
43	nurdle	n_43	2	1	hurdle
44	keffle	n_44	2	2	kettle
45	narkin	n_45	2	2	napkin
46	lanteen	n_46	2	1	canteen
47	fimmle	n_47	2	2	fiddle
48	hebbing	n_48	2	2	herring
49	cassot	n_49	2	2	carrot
50	dero	n_50	2	1	hero
51	hokel	n_51	2	2	hotel
52	cossage	n_52	2	2	cottage
53	affle	n_53	2	2	apple

Table 12.2 (continuation). Pseudoword Stimuli and their characteristics

Number	Pseudoword	Code	NSYL	Change	Baseword
54	camsule	n_54	2	2	capsule
55	tutter	n_55	2	1	gutter
56	garty	n_56	2	1	party
57	stoly	n_57	2	2	story
58	dorner	n_58	2	1	corner
59	jattle	n_59	2	1	cattle
60	mulip	n_60	2	1	tulip
61	dillage	n_61	2	1	village
62	montact	n_62	2	1	contact
63	wetal	n_63	2	1	metal
64	antle	n_64	2	2	angle
65	wencil	n_65	2	1	pencil
66	cumble	n_66	2	1	rumble
67	ritness	n_67	2	1	witness
68	naddle	n_68	2	1	saddle
69	relly	n_69	2	1	belly
70	painser	n_70	2	2	painter
71	loffy	n_71	2	2	lobby
72	erray	n_72	2	2	essay
73	tanal	n_73	2	1	canal
74	veddel	n_74	2	2	vessel
75	hennis	n_75	2	1	tennis
76	hospel	n_76	2	1	gospel
77	fuppy	n_77	2	1	puppy
78	pady	n_78	2	1	lady
79	marsin	n_79	2	2	margin
80	junnel	n_80	2	1	tunnel
81	bemmy	n_81	2	2	berry
82	bloccom	n_82	2	2	blossom
83	dable	n_83	2	1	cable
84	raple	n_84	2	1	maple
85	brumpet	n_85	2	1	trumpet
86	wuckle	n_86	2	1	buckle
87	cocal	n_87	2	2	coral
88	killen	n_88	2	2	kitten
89	trossey	n_89	2	2	trolley
90	fladdel	n_90	2	2	flannel
91	mupil	n_91	2	1	pupil
92	neaver	n_92	2	1	beaver
93	duggy	n_93	2	2	dummy
94	jeddy	n_94	2	2	jelly
95	zagnet	n_95	2	1	magnet
96	vlipper	n_96	2	1	slipper
97	nable	n_97	2	1	fable
98	dallon	n_98	2	1	dallon
99	lailor	n_99	2	1	tailor
100	viping	n_100	2	1	piping

Note. Code=Code in the experiment; NSYL=Number of syllables; Change=substitution of consonant/s in the real English word (baseword), 1=substitution at the onset, 2=substitution in the middle.

Table 12.3 *d Prime* scores for individual participants

Participant Number*	DPrime**
DP1	1.61
DP2	0.56
DP3	1.54
DP4	1.89
DP5	0.82
DP6	0.67
DP7	1.25
DP8^	3.77
DP9	0.60
DP10	2.26
DP11	0.98
DP12	1.16
DP13	0.92
DP14	1.31
DP15^	0.53
DP16	0.55
DP17	1.22
DP18	0.66
CP1	0.58
CP2	1.44
CP3	0.56
CP4	1.17
CP5	1.78
CP6	1.62
CP7	0.56
CP8	1.12
CP9	1.08
CP10	0.98
CP11	1.82
CP12	1.16
CP13	1.54
CP14	0.82
CP15	1.63
CP16	0.89

Note. * Letters denote group membership: CP – control participant; DP – participant with dyslexia; ***d Prime* = 0 (chance); *d Prime* = 0.5 to 1 (moderate performance), *d Prime* = 1.5 to 2 (pretty good performance) and *d Prime* >2.5 (nearly perfect performance); ^ - not included in the group analysis.

Table 12.4 Local maxima for within group comparisons: CPs Word > Control Condition

				MNI			CPs Word > Control Condition	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with anatomy toolbox) or AAL***		
							Phonological Deficit Theory		
5.79	3.93	0	193	-40	12	26	L Area 44	30	20-60
4.67	3.46	0	193	-36	20	18	L Area 44	20	10-30
6.65	4.23	0	86	-52	6	-2	L Area 44	10	0-20
3.94	3.1	0.001	1	-52	10	10	L Area 44	30	20-40
5.72	3.9	0	193	-48	24	16	**Assigned to L Area 45**	40	40-70
							L Area 44	20	20-20
5.58	3.85	0	84	-32	34	-2	L Inferior Frontal Gyrus (BA45)		
5.32	3.74	0	84	-38	30	2	L Inferior Frontal Gyrus (BA45)		
9.87	5.06	0	211	-52	-10	46	**Assigned to L Area 6**	70	30-80
							L Area 1	30	20-50
							L Area 4a	30	20-60
4.67	3.46	0	38	-8	2	62	L Area 6	60	40-80
4.68	3.46	0	13	-16	-24	70	**Assigned to L Area 6**	70	60-80
							L Area 4a	50	40-60
4.41	3.34	0	5	-8	-20	80	L Area 6	30	0-80
							L Area 4a	20	0-30
4.09	3.18	0.001	3	-54	-2	32	**Assigned to L Area 6**	40	0-70
							L Area 4a	30	10-30
4.13	3.2	0.001	1	-30	-28	16	L Insula (Ig1)	50	0-70
							L TE 1.1	30	10-30
3.95	3.1	0.001	1	-40	-34	24	L IPC (PFcm) (BA40)	20	0-60
							L OP 1	20	10-30
							Homologous areas in the RH		
5.09	3.65	0	33	50	-2	34	R Area 44	10	0-10
4.93	3.58	0	33	54	-2	44	**Assigned to R Area 6**	90	50-90
4.38	3.32	0	122	38	-58	-18	R Fusiform Gyrus		
							Magnocellular Deficit Theory		
13.26	5.65	0	11156	14	-76	-4	**Assigned to R Area 18**	60	50-90
							R hOC3v (V3v)	40	30-60
11.72	5.41	0	11156	24	-92	8	R Area 18	20	20-30
							R Area 17	10	10-50
17.21	6.15	0	11156	30	-82	-14	**Assigned to R hOC4v (V4)**	60	40-60
							R hOC3v (V3v)	60	40-70
							R Area 18	20	10-30
							Cerebellar Deficit Theory		
6.24	4.09	0	122	38	-46	-30	**Assigned to R Lobule VI (Hem)**	96	44-98
4.61	3.43	0	122	28	-52	-26	**Assigned to R Lobule VI (Hem)**	100	95-100
							Other areas		
6.19	4.07	0	54	-24	-28	-8	**Assigned to L Hipp (FD)**	30	10-70
							L Hipp (SUB)	20	0-50
5.28	3.73	0	54	-20	-30	0	L Thalamus		
4.18	3.22	0.001	54	-30	-20	-12	**Assigned to L Hipp (CA)**	40	30-70
							L Hipp (FD)	30	0-50
5.91	3.97	0	119	20	-28	-4	R Hippocampus		
4.92	3.57	0	119	28	-26	-8	R Hipp (FD)	20	0-60

Table 12.4 (continuation). Local maxima for within group comparisons: CPs Word > Control Condition

				MNI			CPs Word > Control Condition	P$	R$
T	Z	p	k	x	y	z	Area (labelled with anatomy toolbox) or AAL		
5.57	3.84	0	15	64	2	12	Area R 3b	20	0-20
4.34	3.3	0	33	54	-12	48	**Assigned to R Area 1**	50	40-60
							Area R 4a	40	30-60
							Area R 6	40	10-70
							Area R 3b	20	0-30
4.82	3.53	0	9	4	-6	28	R Mid Cingulum**		
4.66	3.46	0	5	18	12	6	R Caudate**		
4.51	3.38	0	5	-42	-30	24	L OP 1	40	20-50
4.45	3.35	0	6	-28	8	6	L Putamen		
4.28	3.27	0.001	4	-42	0	16	L Rolandic Operculum		
4.23	3.25	0.001	3	-6	-90	36	**Assigned to L SPL (7P)**	30	10-30
							Area L 18	10	0-10
3.99	3.12	0.001	1	-24	6	8	L Putamen		
3.95	3.1	0.001	1	-36	30	-12	L Inferior Frontal Gyrus		
4.58	3.42	0	13	10	-46	-8	**Assigned to R Lobule V**	60	3-87
4.24	3.25	0.001	1	20	-60	-36	R Cerebellum 8**		
4.23	3.24	0.001	1	24	-52	-36	R Cerebellum 6**		
4	3.13	0.001	1	20	-64	-36	R Cerebellum 8**		
4.01	3.13	0.001	1	8	-56	-30	Cerebellar Vermis		

Note. Areas were labelled with the Anatomy Toolbox (AT) (Eickhoff et al., 2005) or with the Automated Anatomical Labeling (AAL) software (Tzourio-Mazoyer et al., 2002). The Anatomy Toolbox (AT) (Eickhoff et al., 2005) uses probabilistic cytoarchitectonic maps. In contrast to classical cytoarchitectonic maps, probabilistic cytoarchitectonic maps provide stereotaxic information on the variability of cortical areas and the location in the MNI reference space (Amunts & Zilles, 2001; Zilles et al., 2002). Probabilistic cytoarchitectonic maps are based on the observer independent analysis of the cytoarchitecture, usually in a sample of 10 human post-mortem brains, so 50% denotes that a given voxel was assigned to a given cytoarchitectonic area in 5 out of 10 brains. To increase the reliability of the anatomical labelling, the probability at the corresponding voxel (P$) and the probability range for the surrounding voxels (R$) are calculated by AT (Eickhoff et al., 2005). For more information see Chapter 5; **Bold typeface** denotes that a given activation peak was assigned to a given area (by the Anatomy Toolbox). 'T' and 'Z' (SPM output) – T and Z statistics; 'p' – (SPM output), denotes significance level at $p \leq 0.001$, uncorrected for multiple comparisons; 'k' – (SPM output), denotes number of voxels in a cluster; 'L' denotes left hemisphere and 'R' denotes right hemisphere; ** denotes that the activation peak was assigned to a brain area using the Automated Anatomical Labeling (AAL) software (Tzourio-Mazoyer et al., 2002) which relies on macroanatomically defined brain regions and therefore the results involving these areas may be less reliable. The lack of values for 'probability' and 'range' reflects the fact that this is work in progress and therefore cytoarchitectonic maps are not yet available for all brain areas; Area X denotes a cytoarchitectonic equivalent to Brodmann's area X;
Abreviations used by Anatomy Toolbox: **Areas associated with the PDT:** Area 44/Area 45 equivallent to Broca's region (BA44 & BA45) (Amunts et al., 1999); Posterior Insula (Areas: Ig1 (granular area 1), Ig2 (granular area 2) and Idl (dysgranular region) (Kurth et al., 2009); Premotor cortex (Area 6) - equivallent to Broca's region BA6 (Geyer, 2003); Inferior Parietal Lobule (5 individual areas): IPC PFop, IPC PFt, IPC PF, IPC PFm, and IPC PFcm; They approximately cover the region of BA40 on the supramarginal gyrus with extension into the depth of the Sylvian fissure (Caspers et al., 2008); Inferior Parietal Cortex (2 individual areas): IPC PGa and IPC PGp (Caspers et al., 2006); These areas are located approximately at the position of BA 39 on the angular gyrus; TE3 (Morosan et al., 2005) equivalent to part of BA22; **Areas associated with the visual MDT:** Area 17 and Area 18 equivalent to BA17 and BA18, respectively (Amunts et al., 2000); hOC5 equivallent to V5/MT+ (Malikovic et al., 2007); **Areas associated with the CDT:** see Table 5.1; **Other areas** (please note that these are all other areas in the Anatomy Toolbox, not necessarily all of these areas were activated in the study reported here): Amygdala - Amygdala superficial, Amygdala laterobasal and Amygdala centromedial complex (Amunts et al., 2005); Hippocampus - Hippocampus DG, Hippocampus CA1-3, Hippocampus Subiculum and Hippocampus HATA (Amunts et al., 2005); Entorhinal cortex - Entorhinal cortex (Amunts et al., 2005); Intraparietal sulcus (IPS) (two areas): hIP1 (the intraparietal area 1) and hIP2 (the intraparietal area 2) (Choi et al., 2006); Parietal operculum (4 areas): OP1, OP2, OP3 and OP4 (Eickhoff, Amunts, Mohlberg, &

Zilles, 2006; Eickhoff, Schleicher, Zilles, & Amunts, 2006); Primary motor cortex (2 areas were mapped): Area 4a and Area 4p (Geyer et al., 1996); Primary somatosensory cortex: Area 3a, Area 3b and Area 1 (Geyer, Schleicher, & Zilles, 1999; Geyer, Schormann, Mohlberg, & Zilles, 2000); Primary somatosensory cortex: Area 2 (Grefkes, Geyer, Schormann, Roland, & Zilles, 2001); Primary auditory cortex: Area TE 1.0, Area TE 1.1 and Area TE 1.2 (Morosan et al., 2001). Ventral Visual Cortex: Area V3v and Area V4 (Rottschy et al., 2007).

Table 12.5 Local maxima for within group comparisons: CPs PWord > Control Condition

				MNI			CPs PWord > Control Condition	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with anatomy toolbox) or AAL**		
							Phonological Deficit Theory		
6.36	4.13	0	974	-50	8	22	**Assigned to L Area 44**	50	50-60
6.33	4.12	0	974	-42	4	28	Area L 44	10	10-30
8.22	4.68	0	168	-40	32	-2	L Inferior Frontal Gyrus (BA45)		
6.94	4.32	0	974	-54	-8	46	**Assigned to L Area 6**	80	60-90
							L Area 1	40	0-50
							L Area 4a	20	20-50
6.63	4.22	0	65	-12	-26	66	**Assigned to L Area 6**	50	40-60
							Area L 4a	30	30-60
4.28	3.27	0.001	65	-20	-22	66	**Assigned to Area L 6**	90	0-90
							Area L 4a	30	30-60
5.14	3.67	0	87	-6	6	56	**Assigned to Area L 6**	50	30-70
							Homologous areas in the RH		
5.19	3.69	0	28	54	-2	44	**Assigned to Area R 6**	90	
							Magnocellular Deficit Theory		
5.62	3.86	0	12	-2	-98	16	**Assigned to Area L 17**	60	30-70
							Area L 18	40	40-60
3.99	3.12	0.001	1	-18	-68	8	**Assigned to Area L 17**	70	40-70
							Area L 18	20	10-20
							Cerebellar Deficit Theory		
4.08	3.17	0.001	1	36	-42	-28	R Lobule VI (Hem)	27	2-76
							Other areas		
16.09	6.02	0	8764	-22	-86	16	L Middle Occipital Gyrus		
14.58	5.83	0	8764	30	-80	-18	**Assigned to R hOC4v (V4)**	30	10-50
							R hOC3v (V3v)	20	10-40
							R Lobule VIIa Crus I (Hem)	4	0-4
13.49	5.69	0	8764	-40	-86	-2	L Middle Occipital Gyrus		
5.1	3.65	0	6	4	-2	28	R Mid Cingulum**		
4.69	3.47	0	15	68	-2	12	**Assigned to R OP 4**	30	10-60
							Area R 3b	20	0-30
4.35	3.31	0	1	-20	-28	-2	L Thalamus		
4.06	3.16	0.001	1	16	-8	-6	R Thalamus**		
3.95	3.1	0.001	1	0	-4	26	R Mid Cingulum**		
5.27	3.72	0	13	-8	-34	-22	L Lobules I-IV (Hem)	1	0-90

Table 12.6 Local maxima for within group comparisons: DPs Word > Control Condition

				MNI			DPs Word > Control Condition	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with anatomy toolbox) or AAL**		
							Phonological Deficit Theory		
4.79	3.52	0	34	-46	10	2	Area L 44	30	20-40
5.8	3.93	0	94	-36	26	6	Area L 45	10	0-10
4.7	3.48	0	55	-8	-2	64	**Assigned to Area L 6**	60	40-80
							Magnocellular Deficit Theory		
5.23	3.7	0	800	16	-96	6	**Assigned to Area R 17**	80	70-90
							Area R 18	20	10-40
10.42	5.17	0	1873	-18	-92	-16	**Assigned to Area L 18**	40	30-50
							L hOC3v (V3v)	30	0-40
							Area L 17	20	20-40
							L hOC4v (V4)	20	20-30
7.38	4.45	0	1873	-22	-102	12	Area L 18	20	0-40
9.16	4.91	0	800	18	-92	-16	Area R 18	10	0-70
6.5	4.18	0	800	22	-84	-10	**Assigned to R hOC3v (V3v)**	60	40-70
							Area R 18	50	20-70
							Cerebellar Deficit Theory		
							Other areas		
4.71	3.48	0	7	-56	0	20	**Assigned to Area L 3a**	30	0-30
							Area L 44	10	10-10
4.71	3.48	0	10	-20	-28	-8	**Assigned to L Hipp (SUB)**	50	10-70
4.01	3.14	0.001	1	20	-8	-6	R Amyg (SF)	40	0-70
4	3.13	0.001	1	-48	-12	42	**Assigned to Area L 4a**	50	40-60
							Area L 4p	40	10-60
							Area L 3b	40	20-60
							Area L 6	20	10-30

Table 12.7 Local maxima for within group comparisons: DPs PWord > Control Condition

				MNI			DPs PWord > Control Condition	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with anatomy toolbox) or AAL**		
							Phonological Deficit Theory		
4.78	3.51	0	43	-58	2	26	**Assigned to L Area 6**	50	30-50
							Area L 3b	20	10-20
							Area L 44	10	10-20
5.76	3.92	0	198	-8	0	64	**Assigned to Area L 6**	60	50-80
4.49	3.37	0	198	-8	12	52	Area L 6	20	10-40
7.27	4.42	0	1756	-54	-16	-8	L TE 3	10	10-10
9.21	4.92	0	1756	-36	24	4	L Insula Lobe		
10.65	5.22	0	5498	-42	-62	-14	L Fusiform Gyrus		
							Magnocellular Deficit Theory		
15.6	5.96	0	5498	-26	-92	12	Area L 17	10	0-10
							Area L 18	10	0-30
3.98	3.12	0.001	3	-10	-74	8	**Assigned to Area L 17**	80	60-80
							Area L 18	20	0-30
12.11	5.47	0	5498	-20	-90	-18	**Assigned to Area L 18**	40	20-40
							L hOC4v (V4)	30	10-40
							L hOC3v (V3v)	20	0-30
							Cerebellar Deficit Theory		
5.37	3.76	0	47	38	-62	-26	**Assigned to R Lobule VI (Hem)**	66	21-66
							R Lobule VIIa Crus I (Hem)	34	22-68
							Other areas		
6.95	4.32	0	1756	-50	-10	46	**Assigned to Area L 4a**	50	30-70
							L Area 6	50	40-80
							L Area 1	20	20-40
5.59	3.85	0	38	-16	-10	-18	**Assigned to L Amyg (SF)**	50	30-70
							L Hipp (HATA)	30	20-40
							L Hipp (SUB)	30	10-40
							L Hipp (EC)	20	10-30
							L Hipp (CA)	20	0-40
4.6	3.43	0	23	-22	-28	-10	**Assigned to L Hipp (SUB)**	60	30-90

Table 12.8 Local maxima for between group comparisons: Word Effect

				MNI			Word Effect CPs>DPs	P$	R$
T	Z	p	k	x	y	z	Area (labelled with anatomy toolbox) or AAL		
							Phonological Deficit Theory		
3.59	3.22	0.001	2	-64	-50	10	L IPC (PFm) (BA 40)	30	0-30
4.71	3.99	0	63	-56	-66	16	L IPC (PGp) (BA39)	30	30-40
3.73	3.32	0	63	-58	-62	6	L IPC (PGp) (BA39)	20	0-20
							Homologous areas in the RH		
3.48	3.14	0.001	1	46	-76	30	**Assigned to R IPC (PGp)**	90	80-90
3.5	3.15	0.001	1	36	-48	8	R Mid Temporal**		
3.45	3.11	0.001	1	36	-54	10	R Mid Temporal**		
							Magnocellular Deficit Theory		
3.51	3.16	0.001	1	-42	-70	10	L hOC5 (V5)	30	20-40
4.58	3.9	0	51	-34	-66	10	Area L 17	10	0-10
							Cerebellar Deficit Theory		
							other areas		
3.73	3.32	0	51	-30	-56	0	L Lingual**		
4.39	3.78	0	1	-30	-38	32	L hIP1	10	0-10
4.01	3.52	0	42	-12	-66	24	L Cuneus		
3.73	3.32	0	2	-32	-50	26	L hIP1	20	10-40
							L hIP2	10	0-10
3.63	3.25	0.001	6	34	-56	2	R Lingual**		
3.6	3.23	0.001	2	20	26	32	R Superior Frontal Gyrus		
3.5	3.15	0.001	1	-44	-40	-12	L Inf Temporal**		
3.42	3.09	0.001	1	26	42	0	R Mid Frontal**		
3.42	3.09	0.001	1	-32	-40	30	L hIP2	10	0-10
							L hIP1	10	0-10
3.86	3.41	0	11	-6	-56	-32	L Lobule VIIIb (Vermis)	5	0-5
							L Lobule IX (Vermis)	0	0-23
							Word Effect: DPs>CPs		
							Phonological Deficit Theory		
3.69	3.29	0	6	-12	14	48	Area L 6	10	10-20
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas		
3.95	3.48	0	1	-18	-30	34	L SPL (5Ci)	10	0-30
3.69	3.29	0	2	-28	-72	-4	L hOC4v (V4)	30	0-50

Table 12.9 Local maxima for between group comparisons: PWord Effect

				MNI			PWord Effect: CPs > DPs	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with anatomy toolbox) or AAL**		
							Phonological Deficit Theory		
							Homologous areas in the RH		
3.69	3.29	0.001	5	42	-2	-22	R Insula (Id1)	20	10-30
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas		
							R Amyg (LB)	10	0-10
4.47	3.83	0	32	-32	42	-8	L Middle Orbital Gyrus		
3.86	3.42	0	6	-6	-20	-22	L ParaHippocampal**		
3.85	3.41	0	3	-36	-60	4	L Mid Occipital**		
3.6	3.23	0.001	2	24	16	20	R Caudate**		
3.59	3.21	0.001	5	-18	-84	24	L Superior Occipital Gyrus		
3.48	3.13	0.001	1	20	-2	-6	R Pallidum	20	0-30
3.45	3.11	0.001	1	22	20	28	R Sup Frontal**		
4.03	3.54	0	16	12	-56	-28	R Lobule V	0	0-0
							PWord Effect: DPs>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas		
3.75	3.34	0	14	-24	-80	-2	L hOC4v (V4)	20	10-40
							L hOC3v (V3v)	10	10-30
3.61	3.23	0.001	1	12	38	30	R Middle Cingulate Cortex		

13 Appendix D - Tables for Chapter 6 (Local maxima for Word reading)

Table 13.1 Local maxima for DP1 - Word Contrasts

				MNI			Contrast - Word: CPs>D1P	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with anatomy toolbox) or AAL**		
							Phonological Deficit		
5.49	3.81	0	25	-40	14	26	**Assigned to L Area 44**	**50**	**20-60**
5.29	3.73	0	45	-38	-42	12	L Superior temporal gyrus (Wernicke's area)**		
5.45	3.79	0	98	-38	-6	52	**Assigned to L Area 6**	**50**	**40-50**
6.05	4.02	0	45	-40	-34	24	L IPC (PFcm) (BA40)	20	0-60
							L OP 1	20	10-30
							Visual magnocellular theory		
4.68	3.46	0	36	18	-100	4	**Assigned to Area R 17**	**70**	**60-90**
							Area R 18	30	10-40
4.57	3.41	0	36	20	-98	12	**Assigned to Area R 18**	**60**	**30-70**
6.6	4.21	0	211	10	-72	-4	**Assigned to Area R 18**	**80**	**50-90**
							R hOC3v (V3v)	50	40-50
8.7	4.8	0	783	10	-74	24	Area R 18	30	20-40
4.4	*3.33*	*0*	*2*	*60*	*-64*	*-2*	*R hOC5 (V5)*	*10*	*0-10*
8.3	*4.7*	*0*	*201*	*-36*	*-82*	*-2*	*L hOC5 (V5)*	*10*	*10-10*
4.69	*3.47*	*0*	*23*	*-36*	*-62*	*8*	*L hOC5 (V5)*	*10*	*10-10*
							Cerebellar Deficit theory		
6.57	4.2	0	279	30	-84	-30	**Assigned to R Lobule VIIa Crus I (Hem)**	**100**	**97-100**
5.8	3.93	0	279	30	-78	-36	**Assigned to R Lobule VIIa Crus I (Hem)**	**84**	**77-94**
6.61	4.21	0	279	32	-70	-40	**Assigned to R Lobule VIIa Crus I (Hem)**	**84**	**46-98**
23.89	6.73	0	2126	-20	-80	-40	**Assigned to L Lobule VIIa Crus II (Hem)**	**91**	**56-98**
							Other areas (not predicted by theories)		
5.7	3.89	0	31	44	-4	54	**Assigned to Area R 6**	**40**	**40-40**
4.33	3.29	0	76	6	-26	78	**Assigned to Area R 6**	**60**	**0-70**
							Area R 4a	50	0-70
5.27	3.72	0	76	6	-16	72	**Assigned to Area R 6**	**100**	**90-100**
4.06	3.16	0.001	76	2	-6	66	**Assigned to Area R 6**	**100**	**90-100**
9.86	5.06	0	2126	-2	-76	-46	**Assigned to L Lobule VIIIa (Vermis)**	**90**	**30-90**
5.09	3.65	0	211	6	-58	-6	**Assigned to R Lobule V (Vermis)**	**83**	**49-89**
6.43	4.15	0	89	12	-82	44	**Assigned to R SPL (7P)**	**40**	**30-50**
5.7	3.89	0	204	-4	-46	50	SPL (5M)	20	10-40
6.18	4.07	0	33	-30	-24	-12	**Assigned to L Hipp (FD)**	60	30-80
							L Hipp (CA)	50	30-80
5.34	3.75	0	25	34	-20	38	**Assigned to R Area 3a**	**90**	**50-90**
							R Area 4p	30	20-60
4.18	3.22	0.001	25	38	-14	42	R Area 4p	40	10-70
							R Area 4a	30	20-50

Table 13.1 (continuation) Local maxima for DP1 - Word Contrasts

				MNI			Word: CPs>DP1 (continuation)	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with anatomy toolbox) or AAL**		
5.34	3.75	0	204	-4	-56	62	**Assigned to L SPL (7A)**	**50**	**30-50**
							L SPL (5L)	20	10-40
							L Area 3a	20	10-20
							L SPL (5M)	20	10-30
5.04	3.62	0	204	2	-56	56	**Assigned to R SPL (7A)**	**50**	**10-50**
6.6	4.21	0	201	-44	-86	-2	L hOC4v (V4)	20	10-20
4.42	3.34	0	108	6	-50	4	(Cerebellar Vermis)		
5.58	3.85	0	108	8	-40	20	R Posterior Cingulate Cortex		
5.23	3.71	0	27	-16	24	64	L Superior Frontal Gyrus		
6.6	4.21	0	220	-8	44	52	L Superior Medial Gyrus		
6.17	4.06	0	220	-2	36	48	L Superior Medial Gyrus		
4.73	3.49	0	220	0	36	56	L Superior Medial Gyrus		
8.52	4.76	0	838	42	-82	0	R Middle Occipital Gyrus		
6.65	4.23	0	783	-22	-74	20	L Superior occipital gyrus**		
7.29	4.42	0	838	58	-58	-14	R Inferior Temporal Gyrus		
							Word: DP1>CPs		
							Nothing to report		

Note. See Note under Table 11.5.

Table 13.2 Local maxima for DP2 - Word Contrasts

				MNI			Contrast - Word: CPs>DP2	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Area (labelled with Anatomy Toolbox) or AAL**		
							Phonological Deficit Theory		
							Visual Magnocellular Theory		
							Cerebellar Deficit Theory		
5.28	3.73	0	43	26	-72	-38	**Assigned to R Lobule VIIa Crus I (Hem)**	**57**	**47-82**
							R Lobule VIIa Crus II (Hem)	28	0-50
7.37	4.45	0	225	-18	-76	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	**68**	**51-77**
6.22	4.08	0	225	-14	-82	-38	**Assigned to L Lobule VIIa Crus II (Hem)**	**94**	**58-94**
							Other areas (not predicted by theories):		
5.93	3.98	0	28	24	40	-18	R Middle Orbital Gyrus		
5.18	3.68	0	38	36	54	-14	R Middle Orbital Gyrus		
4.17	3.21	0.001	38	38	46	-14	R Middle Orbital Gyrus		
6.18	4.07	0	69	-4	36	48	L Superior Medial Gyrus		
4.69	3.47	0	69	-8	44	52	L Superior Medial Gyrus		
4.51	3.39	0	27	0	-48	48	L SPL (5M)	20	10-40
6.45	4.16	0	30	58	-60	-12	R Inferior Temporal Gyrus		
							Contrast- Word: DP2>CPs		
							Phonological Deficit Theory		
							Visual Magnocellular Theory		
							Cerebellar Deficit Theory		
5.16	3.67	0	23	-18	-70	-50	**Assigned to L Lobule VIIb (Hem)**	**68**	**11-84**
							L Lobule VIIIa (Hem)	26	7-84
							Other areas (not predicted by theories):		
8.64	4.79	0	46	30	-70	20	R Middle Occipital Gyrus		

Table 13.3 Local maxima for DP3 - Word Contrasts

				MNI			Contrast - Word: CPs>DP3	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labeled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
6.02	4.01	0	208	-10	24	64	L SMA		
6.33	4.12	0	320	-60	-56	22	**Assigned to L IPC (PFm) (BA40)**	**30**	**30-50**
							L IPC (PGa)	20	0-50
							L IPC (PF)	20	0-30
7.6	4.52	0	320	-64	-44	24	**Assigned to L IPC (PF) (BA40)**	**50**	**50-70**
							L IPC (PFm)	40	0-40
4.76	3.5	0	29	-50	-72	26	**Assigned to L IPC (PGp) (BA39)**	**70**	**60-70**
							L IPC (PGa)	20	0-30
4.33	3.3	0	29	-42	-76	20	L IPC (PGp) (BA39)	30	20-40
4.27	*3.27*	*0*	*2*	*-66*	*-32*	*20*	*L TE3*	*30*	*0-50*
							Magnocellular Deficit Theory		
8.37	4.72	0	99	10	-74	24	R Area 18	30	20-40
							Cerebellar Deficit Theory		
5.11	3.66	0	59	20	-70	-32	**Assigned to R Lobule VIIa Crus I (Hem)**	**56**	**37-66**
4.68	3.46	0	59	32	-70	-40	**Assigned to R Lobule VIIa Crus I (Hem)**	**84**	**46-98**
4.06	3.16	0	59	34	-80	-40	**Assigned to R Lobule VIIa Crus I (Hem)**	**60**	**57-94**
							R Lobule VIIa Crus II (Hem)	40	5-43
4.41	3.34	0	23	12	-66	-18	**Assigned to R Lobule VI (Hem)**	**94**	**94-100**
5.8	3.93	0	58	-8	-68	-16	**Assigned to L Lobule VI (Hem)**	**94**	**85-94**
10.89	5.26	0	1436	-18	-76	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	**68**	**51-77**
9.37	4.95	0	1436	-26	-80	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	**92**	**86-100**
							Other areas (not predicted by theories)		
4.68	3.46	0	98	54	24	-12	R Area 45	20	0-20
7.09	4.37	0	755	-4	-46	50	L SPL (5M)	20	10-40
5.3	3.73	0	94	4	-26	76	**Assigned to Area 4a**	**60**	**30-70**
							Area 6	60	40-70
6.91	4.31	0	63	10	-80	50	**Assigned to R SPL (7P)**	**40**	**30-70**
							R SPL (7A)	20	10-30
5.75	3.91	0	43	-26	-36	44	L Area 3a	20	10-30
9.35	4.95	0	755	-6	-48	58	**Assigned to L SPL (5M)**	**40**	**30-70**
							L Area 3a	30	10-40
							L Area 4p	20	10-20
5.37	3.76	0	227	-12	-68	22	L Cuneus)		
5.95	3.98	0	211	40	42	-10	R Inferior Frontal Gyrus (p. Orbitalis)		
6.64	4.23	0	98	42	28	-22	R Inferior frontal gyrus, orbital part **		
7.02	4.34	0	208	-30	18	62	L Middle Frontal Gyrus		
5.03	3.62	0	59	-28	52	32	L Middle Frontal Gyrus		
4.95	3.58	0	56	-34	52	20	L Middle Frontal Gyrus		
7.35	4.44	0	211	36	54	-14	R Middle Orbital Gyrus		
6.4	4.15	0	26	24	40	-18	R Middle Orbital Gyrus		
5.27	3.72	0	55	26	34	36	R Middle Frontal Gyrus		
5.46	3.8	0	214	-4	36	48	L Superior Medial Gyrus		
6.72	4.25	0	214	4	34	58	R Superior Medial Gyrus		
5.61	3.86	0	214	4	42	54	R Superior frontal gyrus, medial**		
5.3	3.73	0	227	-20	-76	20	L Superior occipital gyrus**		
4.02	3.14	0	99	22	-78	26	R Superior Occipital Gyrus		
5.2	3.69	0	20	2	-16	16	R Thalamus**		
							Contrast - Word: DP3>CP		
							Nothing to report		

Table 13.4 Local maxima for DP4 - Word Contrasts

				MNI			Contrast - Word: CPs>DP4	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
							Contrast - Word: DP4>CPs		
							Phonological Deficit Theory		
5.4	3.77	0	97	44	-56	-18	R Fusiform Gyrus		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.62	4.22	0	40	-26	-70	16	L Calcarine fissure & surrounding cortex**		
7.08	4.36	0	115	20	-84	14	R Calcarine Gyrus		
7.31	4.43	0	34	2	22	14	R Anterior Cingulum**		
6.36	4.13	0	97	40	-66	-12	R Inferior Occipital Gyrus		
5.34	3.75	0	24	40	-82	-10	R hOC4v (V4)	20	20-60

Table 13.5 Local maxima for DP5 - Word Contrasts

				MNI			Contrast - Word: CPs>DP5	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
5.18	3.69	0	24	32	-62	-50	**R Lobule VIIb (Hem)**	**25**	2-30
							Other areas (not predicted by theories)		
5.1	3.65	0	25	6	-42	-24	R Lobules I-IV (Hem)	70	3-70
							Contrast - Word: DP5 >CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
6.08	4.03	0	32	-10	-88	-14	**Assigned to L Area 17**	**20**	**10-20**
							L hOC4v (V4)	20	10-30
							L hOC3v (V3v)	20	10-50
10.1	5.12	0	522	10	-82	-10	**Assigned to R Area 18**	**80**	**60-90**
							R Area 17	40	10-80
							R hOC3v (V3v)	20	10-20
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.62	3.86	0	109	-2	-48	-36	**Assigned to L Lobule IX (Vermis)**	**56**	**15-58**
							L Lobule X (Vermis)	27	27-77
7.18	4.39	0	109	10	-50	-36	**Assigned to R Lobule IX (Hem)**	**74**	**40-82**
6.86	4.3	0	522	28	-70	-18	R hOC4v (V4)	30	0-50
7.84	4.58	0	105	6	16	8	R Caudate nucleus**		
5.7	3.89	0	29	30	-70	20	R Middle Occipital Gyrus		
5.89	3.96	0	522	50	-54	-18	R Inferior Temporal Gyrus		

Table 13.6. Local maxima for DP6 - Word Contrasts

				MNI			Contrast - Word: CPs>DP6	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
8.36	4.72	0	455	-36	-66	38	**Assigned to L IPC (PGa) (BA39)**	**40**	**30-40**
							L IPC (PGp)	20	0-20
6.19	4.07	0	455	-38	-66	26	**Assigned to L IPC (PGp) (BA39)**	**40**	**20-50**
							L IPC (PGa)	30	10-30
5.91	3.97	0	455	-36	-76	30	L IPC (PGp) (BA39)	20	20-70
							Magnocellular Deficit theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.15	3.67	0	355	42	-72	24	R IPC (PGp) (BA39)	30	0-50
7.82	4.58	0	355	54	-66	16	**Assigned to R IPC (PGp) (BA39)**	**50**	**40-50**
4.69	3.47	0	142	-4	-46	50	L SPL (5M)	20	10-40
5.49	3.81	0	36	-12	-66	24	L Cuneus		
6.12	4.05	0	63	38	56	-2	R Middle Orbital Gyrus		
4.14	3.2	0.001	21	24	10	50	R Middle Frontal Gyrus		
6.79	4.27	0	50	-2	38	46	L Superior Medial Gyrus		
5.1	3.65	0	21	18	8	44	R Superior frontal gyrus**		
3.96	3.11	0.001	142	-6	-58	46	L SPL (7A)	20	20-40
							L SPL (7P)	20	10-30
6.39	4.14	0	80	2	-52	58	**Assigned to R SPL (5M)**	**40**	**20-60**
							R SPL (5L)	20	10-30
7.23	4.41	0	62	2	50	-20	R Rectal Gyrus		
4.61	3.43	0	21	6	26	-18	R Rectal Gyrus		
4.22	3.24	0.001	21	10	32	-22	R Rectal Gyrus		
							Contrast - Word: DP6>CPs		
							Phonological Deficit Theory		
5.58	3.84	0	26	-52	10	2	L Area 44	30	20-30
							Magnocellular Deficit theory		
7.95	4.61	0	57	-14	-98	24	L Area 18	20	0-60
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.28	3.73	0	21	-36	-86	-16	**Assigned to L hOC3v (V3v)**	**30**	**20-40**
							L hOC4v (V4)	20	0-50

Table 13.7 Local maxima for DP7 - Word Contrasts

				MNI			Contrast - Word: CPs>DP7	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
5.96	3.99	0	70	10	-74	24	R Area 18	30	20-40
6.38	*4.14*	*0*	*25*	*56*	*-62*	*-14*	*R hOC5 (V5)*	*10*	*0-10*
							Cerebellar Deficit Theory		
5.91	3.97	0	74	28	-72	-38	**Assigned to R Lobule VIIa Crus I (Hem)**	**88**	**50-88**
7.5	4.49	0	196	-18	-76	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	**68**	**51-77**
5.93	3.98	0	196	-14	-86	-40	**Assigned to L Lobule VIIa Crus II (Hem)**	**77**	**77-94**
4.3	3.28	0.001	196	-22	-84	-44	**Assigned to L Lobule VIIa Crus II (Hem)**	**92**	**86-100**
							Other areas (not predicted by theories)		
4.88	3.55	0	27	-44	-86	-2	L hOC4v (V4)	20	10-20
5.28	3.73	0	44	-2	-56	60	**Assigned to L SPL (5L)**	**20**	**0-20**
							L SPL (5M)	20	0-30
							L SPL (7A)	20	10-50
6.73	4.25	0	39	14	28	24	R Anterior Cingulate Cortex		
4.81	3.53	0	20	-10	62	-4	L Mid Orbital Gyrus		
6.85	4.29	0	139	-2	36	48	L Superior Medial Gyrus		
4.92	3.57	0	139	-8	44	52	L Superior Medial Gyrus		
5.35	3.76	0	81	-20	-74	20	L superior occipital gyrus**		
							Contrast - Word: DP7>CPs		
							Phonological Deficit Theory		
5.3	3.74	0	50	-58	-34	48	**Assigned to L IPC (PF) (BA40)**	**80**	**0-90**
							L Area 2	20	0-30
4.48	3.37	0	50	-54	-42	48	**Assigned to L IPC (PF) (BA40)**	**60**	**50-70**
							L IPC (PFm)	50	30-50
							L hIP2	30	10-50
6.42	4.15	0	88	50	-38	56	**Assigned to R IPC (PFm) (BA40)**	**30**	**20-30**
							R Area 2	30	20-60
							R IPC (PFt)	30	0-40
							R hIP2	20	10-20
							R Area 1	20	0-40
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.53	3.4	0	34	46	-38	40	R hIP1	20	0-20

Table 13.8 Local maxima for DP8 - Word Contrasts

				MNI			Contrast - Word: CPs>DP8	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Contrast - Word: DP8>CPs		
							Phonological Deficit Theory		
5.13	3.66	0	47	-38	-16	-2	**Assigned to L Insula (Ig2)**	**30**	**20-60**
5.41	3.78	0	124	58	-56	4	R Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.59	4.21	0	66	-30	-52	-6	L Lingual Gyrus		
4.35	3.3	0	66	-20	-46	-10	L Lingual Gyrus		
6.17	4.07	0	28	-6	22	-8	L Anterior Cingulate Cortex		
7.17	4.39	0	28	-12	-26	34	L Middle cingulum**		
5.84	3.95	0	22	14	-76	28	R Cuneus		
5.18	3.69	0	22	-34	30	40	L Middle Frontal Gyrus		
5.43	3.79	0	365	30	12	48	R Middle Frontal Gyrus		
6.71	4.25	0	365	20	10	40	R Superior frontal gyrus**		
4.54	3.4	0	30	16	32	48	R Superior Frontal Gyrus		
5	3.61	0	45	10	-50	54	**Assigned to R SPL (5M)**	40	30-50
							R SPL (5L)	30	20-30

Table 13.9 Local maxima for DP9 - Word Contrasts

				MNI			Contrast - Word: CPs>DP9	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
4.53	3.39	0	42	-26	24	14	L Insula Lobe		
4.99	3.6	0	97	-26	36	4	L Insula**		
5.4	3.78	0	106	-36	-44	8	L Superior temporal gyrus (Wernicke's area)**		
4.85	3.54	0	106	-34	-54	-2	L Fusiform gyrus**		
							Magnocellular Deficit Theory		
6.09	4.04	0	387	20	-72	12	**Assigned to R Area 17**	**40**	**0-70**
4.85	3.54	0	20	14	-102	-2	**Assigned to R Area 17**	**100**	**50-100**
							R Area 18	20	0-30
6.13	4.05	0	387	12	-78	-2	**Assigned to R Area 18**	**80**	**70-90**
							R Area 17	20	0-60
							R hOC3v (V3v)	20	10-40
6.9	4.31	0	387	8	-76	22	R Area 18	30	30-50
							R Area 17	20	0-20
4.88	*3.56*	*0*	*74*	*52*	*-68*	*-14*	*R hOC5 (V5)*	*10*	*0-10*
							Cerebellar Deficit Theory		
5.01	3.61	0	29	26	-72	-38	**Assigned to R Lobule VIIa Crus I (Hem)**	**57**	**47-82**
							R Lobule VIIa Crus II (Hem)	28	0-50
8.49	4.75	0	575	-18	-76	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	**68**	**51-77**
6.14	4.05	0	575	-40	-68	-38	**Assigned to L Lobule VIIa Crus I (Hem)**	**53**	**53-92**
7.41	4.46	0	575	-14	-86	-40	**Assigned to L Lobule VIIa Crus II (Hem)**	**77**	**77-94**
							Other areas (not predicted by theories)		
5.94	3.98	0	46	46	-52	52	**Assigned to R IPC (PFm) (BA 40)**	**50**	**30-70**
7.43	4.47	0	1305	-4	-46	50	L SPL 5M	20	10-40
4.4	3.33	0	20	-16	-4	-14	**Assigned to L Amyg (SF)**	**70**	**30-90**
4.71	3.48	0	24	4	-28	78	**Assigned to R Area 4a**	**60**	**0-70**
							R Area 6	30	0-50
4.65	3.45	0	21	-18	-38	78	**Assigned to L SPL (5L)**	**30**	**10-30**
							L Area 6	20	10-20
8.25	4.69	0	1305	-2	-56	60	**Assigned to L SPL (5L)**	**20**	**0-20**
							L SPL (5M)	20	0-30
							L SPL (7A)	20	10-50
8.26	4.69	0	1305	10	-66	50	**Assigned to R SPL (7A)**	**30**	**20-40**
							R SPL (7P)	20	10-40
5.21	3.7	0	57	4	34	22	R Anterior Cingulate Cortex		
5.19	3.69	0	57	12	32	22	R Anterior Cingulate Cortex		
4.45	3.35	0	104	-6	-26	26	L Middle cingulum**		
7.23	4.41	0	104	4	-6	28	R Middle cingulum**		
4.96	3.59	0	47	8	28	36	R Middle Cingulate Cortex		
6.92	4.31	0	147	10	-40	22	R Posterior Cingulate Cortex		
5.19	3.69	0	147	10	-44	14	R Posterior Cingulate Cortex		
6.29	4.11	0	625	40	42	-10	R Inferior Frontal Gyrus (p. Orbitalis)		
5.31	3.74	0	36	-14	64	-4	L Mid Orbital Gyrus		
6.74	4.26	0	86	-30	26	46	L Middle Frontal Gyrus		
4.15	3.21	0.001	86	-28	24	36	L Middle Frontal Gyrus		
6.15	4.06	0	97	-28	38	-6	L Middle frontal gyrus, orbital part**		
7.33	4.44	0	625	24	40	-18	R Middle Orbital Gyrus		
4.34	3.3	0	128	32	20	20	R Middle frontal gyrus**		
5.3	3.73	0	43	-2	36	48	L Superior Medial Gyrus		
4.16	3.21	0.001	43	4	34	58	R Superior Medial Gyrus		
4.96	3.59	0	47	10	28	44	R Superior Medial Gyrus		
5.31	3.74	0	106	-30	-38	10	L Hippocampus**		

Table13.9 (continuation). Local maxima for DP9 - Word Contrasts

				MNI			Contrast - Word: CPs>DP9	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
5.32	3.74	0	67	-40	-86	-2	L Middle Occipital Gyrus		
5.25	3.71	0	85	-18	-86	30	L Superior Occipital Gyrus		
4.49	3.38	0	85	-20	-76	20	L Superior occipital gyrus**		
11.2	5.32	0	61	4	10	-18	R Olfactory cortex**		
4.77	3.5	0	20	-10	-6	-20	L ParaHippocampal Gyrus		
4.71	3.48	0	28	38	-34	-16	R ParaHippocampal Gyrus		
5.18	3.69	0	21	-32	-44	70	L Superior parietal gyrus**		
4.18	3.22	0.001	86	-28	-22	8	L Putamen		
4.81	3.52	0	61	12	20	-14	R Rectal Gyrus		
7.06	4.36	0	625	4	46	-20	R Rectal Gyrus		
5.21	3.7	0	20	-42	-26	-18	L Inferior Temporal Gyrus		
6.24	4.09	0	74	56	-58	-16	R Inferior Temporal Gyrus		
4.76	3.5	0	74	48	-48	-18	R Inferior Temporal Gyrus		
6.16	4.06	0	65	-38	4	-22	L Temporal Pole		
6.86	4.3	0	86	-24	-24	16	L Thalamus**		
6.34	4.13	0	24	-18	-32	2	L Thalamus		
							Contrast - Word: DP9>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
9.58	**5**	**0**	**183**	-18	-70	-50	**Assigned to L Lobule VIIb (Hem)**	**68**	**11-84**
							L Lobule VIIIa (Hem)	26	7-84
							Other areas (not predicted by theories)		
6.04	4.02	0	64	30	-52	-48	**Assigned to R Lobule VIIIa (Hem)**	**17**	**0-27**
4.69	3.47	0	64	18	-42	-48	**Assigned to R Lobule VIIIb (Hem)**	**38**	**3-47**
							R Lobule X (Hem)	21	5-82
4.44	3.35	0	64	28	-60	-50	R Lobule VIIIa (Hem)	22	20-77

Table 13.10 Local maxima for DP10 - Word Contrasts

				MNI			Contrast - Word: CPs>DP10	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
3.94	*3.1*	*0.001*	*1*	*38*	*-68*	*12*	*R hOC5 (V5)*	*10*	*10-10*
7.53	*4.49*	*0*	*210*	*-38*	*-84*	*-2*	*L hOC5 (V5)*	*10*	*0-10*
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.18	3.69	0	51	8	-50	-40	**Assigned to R Lobule IX (Hem)**	**90**	**87-97**
5.85	3.95	0	30	34	-58	52	R SPL (7A)	20	10-50
4.05	3.16	0.001	210	-40	-80	-16	L hOC4v (V4)	30	20-50
5	3.61	0	20	10	-80	50	**Assigned to R SPL (7P)**	**40**	**30-70**
							R SPL (7A)	20	10-30
6.19	4.07	0	210	-46	-72	-18	L Inferior Occipital Gyrus)		
8.08	4.65	0	103	42	-82	0	R Middle Occipital Gyrus)		
							Contrast - Word: DP10>CPs		
							Phonological Deficit Theory		
5.6	3.85	0	37	-36	-68	32	L IPC (PGa) (BA39)	20	10-30
5.77	3.92	0	34	-30	-50	-10	L Fusiform Gyrus		
4.6	*3.43*	*0*	*10*	*62*	*-4*	*-4*	*R TE3*	*20*	*10-40*
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.29	3.73	0	22	-60	-14	36	**Assigned to L Area 1**	**50**	**40-70**
							L IPC (PFt)	30	0-30
							L Area 3b	30	10-40

Table 13.11 Local maxima for DP11 - Word Contrasts

				MNI			Contrast - Word: CPs>DP11	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
5.51	3.82	0	61	-40	12	26	L Area 44	30	20-60
5.22	3.7	0	61	-32	14	20	L Insula**		
							Magnocellular Deficit Theory		
4.52	3.39	0	63	-10	-64	10	L Area 17	20	10-40
							L Area 18	20	0-40
4.86	3.55	0	23	12	-72	-2	**Assigned to R Area 18**	70	60-80
							R hOC3v (V3v)	40	20-50
							R Area 17	20	0-30
5.14	3.67	0	63	-14	-96	20	**Assigned to L Area 18**	60	30-60
6.08	4.03	0	46	10	-74	24	R Area 18	30	20-40
							Cerebellar Deficit Theory		
8.88	4.84	0	928	28	-72	-40	**Assigned to R Lobule VIIa Crus I (Hem)**	**81**	12-88
8.37	4.72	0	360	-20	-80	-40	**Assigned to L Lobule VIIa Crus II (Hem)**	91	56-98
6.42	4.15	0	360	-14	-76	-36	**Assigned to L Lobule VIIa Crus II (Hem)**	78	11-78
							Other areas (not predicted by theories)		
9.23	4.92	0	928	22	-56	-42	R Cerebellum		
8.85	4.84	0	928	28	-62	-44	R Cerebellum		
5.99	4	0	83	-4	-46	50	L Middle Cingulate Cortex		
							L SPL (5M)	20	10-40
5.18	3.68	0	63	-12	-66	24	L Cuneus		
4.84	3.54	0	63	-16	-84	24	L Superior Occipital Gyrus		
4.26	3.26	0.001	63	-20	-74	20	L Superior occipital gyrus**		
5.62	3.86	0	39	0	6	-12	L Olfactory cortex**		
4.55	3.4	0	22	10	-50	8	R Precuneus		
6.35	4.13	0	24	-18	-32	2	L Thalamus		
							Contrast - Word: DP11>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.7	3.47	0	38	-16	-68	-46	**Assigned to L Lobule VIIIa (Hem)**	79	24-79

Table 13.12 Local maxima for DP12 - Word Contrasts

				MNI			Contrast - Word: CPs>DP12	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
4.95	3.58	0	37	-14	-66	10	**Assigned to L Area 17**	**40**	**20-50**
							L Area 18	30	10-50
5.51	3.82	0	97	4	-78	22	**Assigned to R Area 18**	**50**	**10-70**
5	3.61	0	27	14	-76	-4	**Assigned to R Area 18**	**60**	**50-90**
							R hOC3v (V3v)	40	30-60
							Cerebellar Deficit Theory		
4.26	3.26	0	22	20	-76	-50	**Assigned to R Lobule VIIb (Hem)**	**90**	**56-90**
							Other areas (not predicted by theories)		
4.87	3.55	0	30	22	-54	-42	R Cerebellum		
5.17	3.68	0	83	-20	-76	20	L Superior occipital gyrus**		
5.01	3.61	0	45	22	-78	26	R Superior Occipital Gyrus		
5.59	3.85	0	35	28	-76	-18	**Assigned to R hOC4v (V4)**	**60**	**0-60**
							R hOC3v (V3v)	30	0-40
							Contrast - Word: DP12>CPs		
							nothing to report		

Table 13.13 Local maxima for DP13 - Word Contrasts

				MNI			Contrast - Word: CPs>DP13	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
							Contrast - Word: DP13>CPs		
							Phonological Deficit Theory		
8.45	4.74	0	751	-40	12	28	L Area 44	30	20-60
4.89	3.56	0	39	-48	22	-2	L Area 45	20	10-30
4.88	3.55	0	40	-44	-72	26	**Assigned to L IPC (PGp) (BA39)**	**70**	**60-70**
							L IPC (PGa)	20	20-20
4.69	3.47	0	40	-48	-74	34	L IPC (PGp)	70	0-80
							L IPC (PGa)	20	0-20
7.16	4.39	0	304	-34	-64	44	**Assigned to L IPC (PGa) (BA39)**	**40**	**0-40**
5.39	3.77	0	304	-30	-74	44	**Assigned to L IPC (PGp) (BA39)**	**40**	**0-50**
7.05	4.35	0	278	36	10	24	R Area 44	30	20-30
6.7	4.24	0	83	56	30	18	**R Assigned to Area 45**	**90**	**70-90**
5.04	3.62	0	83	48	30	16	**R Assigned to Area 45**	**60**	**40-60**
6.1	4.04	0	278	30	8	36	R Inferior frontal gyrus, opercular part**		
4.8	3.52	0	251	46	-82	18	**Assigned to R IPC (PGp) (BA39)**	**50**	**0-50**
12.2	5.49	0	238	-50	-44	-4	L Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
4.98	3.6	0	98	16	-78	16	**Assigned to R Area 17**	**30**	**10-50**
7.19	4.4	0	115	-8	-82	16	**Assigned to L Area 17**	**40**	**40-60**
							L Area 18	20	10-30
8.46	4.74	0	98	10	-74	24	R Area 18	30	20-40
7.25	4.41	0	350	10	-60	4	**Assigned to L Area 17**	**60**	**50-70**
							R Area 18	60	40-80
5.3	3.73	0	321	-8	-66	0	**Assigned to L Area 18**	**70**	**40-80**
							L Area 17	40	20-50
6.88	4.3	0	73	-18	-102	6	**Assigned to L Area 18**	**70**	**50-90**
							Cerebellar Deficit Theory		
6.42	4.15	0	350	18	-70	-16	**Assigned to R Lobule VI (Hem)**	**54**	**0-94**
5.49	3.81	0	25	-34	-70	-48	**Assigned to L Lobule VIIa Crus II (Hem)**	**68**	**60-82**
							L Lobule VIIb (Hem)	20	1-28
7.37	**4.45**	**0**	**321**	-14	-64	-16	**Assigned to L Lobule VI (Hem)**	**95**	**94-95**
							Other areas (not predicted by theories)		
6.53	4.19	0	321	-24	-78	-4	L hOC4v (V4)	40	30-70
							L hOC3v (V3v)	20	10-40
5.54	3.83	0	26	34	-58	52	R SPL (7A)	20	10-50
8.44	4.74	0	107	-8	-84	40	L SPL (7P)	30	20-40
5.77	3.92	0	350	24	-76	-16	**Assigned to R hOC4v (V4)**	**50**	**0-70**
							R hOC3v (V3v)	40	0-50
4.86	3.55	0	25	24	-28	48	R Area 3a	50	30-60
							R Area 4p	20	0-30
5.03	3.62	0	153	-40	-2	44	L Area 6	20	10-20
4.85	3.54	0	153	-46	-8	42	**Assigned to L Area 4a**	**30**	**20-60**
							L Area 6	20	0-40
6.58	4.2	0	157	-6	-48	58	**Assigned to L SPL (5M)**	**40**	**30-70**
							L Area 3a	30	10-40
							L Area 4p	20	10-20
5.98	4	0	157	-4	-50	48	L SPL (5M)	30	0-40
4.83	3.53	0	157	-12	-44	54	**Assigned to L Area 3a**	**30**	**20-40**
							L SPL (5M)	30	20-40
							L Area 4p	20	10-30
							L Area 3b	20	0-20

Table 13.13 (continuation). Local maxima for DP13 - Word Contrasts

				MNI			Contrast - Word: CPs>DP13	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
5.08	3.64	0	29	-10	44	16	L Anterior Cingulate Cortex		
9.72	5.03	0	1247	12	32	22	R Anterior Cingulate Cortex		
5.7	3.89	0	30	10	42	2	R Anterior Cingulate Cortex		
6.88	4.3	0	1247	10	28	34	R Middle Cingulate Cortex		
7.15	4.38	0	105	4	-10	30	R Middle Cingulate Cortex		
5.85	3.95	0	105	2	-2	30	R Middle Cingulate Cortex		
4.55	3.4	0	105	8	-16	34	R Middle Cingulate Cortex		
7.37	4.45	0	180	48	26	-16	R Inferior Frontal Gyrus (p. Orbitalis)		
8.95	4.86	0	751	-32	16	62	L Middle Frontal Gyrus		
7.08	4.36	0	751	-32	26	46	L Middle Frontal Gyrus		
4.95	3.58	0	51	-38	48	16	L Middle Frontal Gyrus		
4.7	3.47	0	51	-28	40	10	L Middle frontal gyrus**		
11.2	5.32	0	1247	-2	36	48	L Superior Medial Gyrus		
6.61	4.22	0	153	6	62	28	R Superior Medial Gyrus		
10.64	5.22	0	125	-30	-72	16	L Middle occipital gyrus**		
8.8	4.83	0	251	36	-74	20	R Middle occipital gyrus**		
5.34	3.75	0	35	2	4	-12	L Olfactory cortex**		
6.64	4.23	0	35	4	10	-18	R Olfactory cortex**		
5.69	3.89	0	20	22	-28	-2	R Thalamus**		

Table 13.14 Local maxima for DP14 - Word Contrasts

				MNI			Contrast - Word: CPs>DP14	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
5.39	3.77	0	38	-40	12	26	L Area 44	30	20-60
5.08	3.64	0	38	-36	20	18	L Area 44	20	10-30
6.37	4.14	0	266	-4	-8	40	L Area 6	20	0-20
5.6	3.85	0	52	-56	-62	18	**Assigned to L IPC (PGp) (BA39)**	**40**	**30-40**
6.15	4.06	0	36	-40	-42	-24	L Fusiform Gyrus		
5.14	*3.67*	*0*	*17*	*-68*	*-28*	*4*	***Assigned to L TE3***	***50***	***40-90***
4.42	*3.34*	*0*	*17*	*-62*	*-22*	*6*	*L TE3*	*20*	*0-50*
5.35	3.76	0	49	-56	-8	-10	L Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
4.23	3.25	0	91	-4	-74	20	**Assigned to L Area 18**	**40**	**10-50**
							L Area 17	30	20-40
7.79	4.57	0	91	10	-74	24	R Area 18	30	20-40
5.03	3.62	0	91	-14	-78	20	L Area 17	20	0-30
5.86	*3.95*	*0*	*85*	*-36*	*-82*	*-2*	*L hOC5 (V5)*	*10*	*10-10*
6.98	*4.33*	*0*	*130*	*60*	*-64*	*0*	*R hOC5 (V5)*	*10*	*0-20*
6.42	*4.15*	*0*	*130*	*56*	*-72*	*4*	*R hOC5 (V5)*	*10*	*0-30*
							Cerebellar Deficit Theory		
5.55	3.83	0	291	-10	-70	-28	L Lobule VI (Hem)	27	4-76
7.34	4.44	0	291	-18	-76	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	**68**	**51-77**
5.68	3.88	0	291	-14	-86	-40	**Assigned to L Lobule VIIa Crus II (Hem)**	**77**	**77-94**
							Other areas (not predicted by theories)		
7.15	4.38	0	90	44	-82	16	**Assigned to R IPC (PGp) (BA39)**	**30**	**0-50**
7.76	4.56	0	155	-4	-46	50	L SPL 5M	20	10-40
4.59	3.42	0	155	-8	-50	62	**Assigned to L Area 3a**	**30**	**0-30**
							L SPL (5L)	20	20-40
							L Area 4p	20	10-20
							L Area 3b	20	10-30
							L SPL (7A)	20	10-30
5.26	3.72	0	25	-38	-34	16	**Assigned to L TE 1.1**	**40**	**20-70**
4.65	3.45	0	55	-18	42	10	L Anterior cingulum**		
4.5	3.38	0	55	-10	44	14	L Anterior Cingulate Cortex		
7.31	4.43	0	266	4	-10	30	R Middle Cingulate Cortex		
5.1	3.65	0	266	6	-20	28	R Middle cingulum**		
6.75	4.26	0	65	-36	30	-12	L Inferior Frontal Gyrus (p. Orbitalis)		
5.19	3.69	0	65	-32	38	-6	L Inferior Frontal Gyrus (p. Orbitalis)		
6.63	4.22	0	73	-38	34	42	L Middle Frontal Gyrus		
7.44	4.47	0	330	-4	36	48	L Superior Medial Gyrus		
7.4	4.46	0	330	-8	40	54	L Superior Medial Gyrus		
4.78	3.51	0	55	-14	38	20	L Superior Medial Gyrus		
5.07	3.64	0	90	42	-82	0	R Middle Occipital Gyrus		
8.68	4.8	0	163	56	-58	-16	R Inferior Temporal Gyrus		
							Contrast - Word: DP14>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
6.06	4.03	0	26	-6	-86	-14	L Area 17	20	10-20
							L Area 18	20	10-40
							Cerebellar Deficit Theory		
8.89	**4.85**	**0**	**94**	32	-58	-50	R Lobule VIIb (Hem)	20	11-35
							Other areas (not predicted by theories)		
							nothing to report		

Table 13.15 Local maxima for DP15 - Word Contrasts

				MNI			Contrast - Word: CPs>DP15	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
5.5	3.83	0	61	-38	-42	12	L Superior temporal gyrus (Wernicke's area)**		
5.4	3.77	0	78	-54	-58	18	L IPC (PGa) (BA39)	30	20-30
5.7	3.9	0	61	-40	-50	8	L Middle temporal gyrus**		
5	3.62	0	61	-42	-48	18	L Middle temporal gyrus**		
							Magnocellular Deficit Theory		
6	3.99	0	41	10	-76	24	**Assigned to R Area 18**	**40**	**30-40**
4.6	*3.4*	*0*	*41*	*52*	*-68*	*-14*	*R hOC5 (V5)*	*10*	*0-10*
							Cerebellar Deficit Theory		
6.1	4.05	0	92	26	-72	-38	**Assigned to R Lobule VIIa Crus I (Hem)**	**57**	**47-82**
							R Lobule VIIa Crus II (Hem)	28	0-50
6.7	4.25	0	170	-18	-76	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	**68**	**51-77**
6.1	4.03	0	57	-40	-70	-38	**Assigned to L Lobule VIIa Crus I (Hem)**	**72**	**72-91**
6.2	4.09	0	170	-10	-86	-38	**Assigned to L Lobule VIIa Crus II (Hem)**	**82**	**66-93**
4.1	3.18	0	170	-22	-82	-40	**Assigned to L Lobule VIIa Crus II (Hem)**	**83**	**73-94**
							Other areas (not predicted by theories)		
6.3	4.1	0	87	46	-78	28	**Assigned to R IPC (PGp) (BA39)**	**80**	**80-80**
5	3.58	0	87	46	-82	18	**Assigned to R IPC (PGp) (BA39)**	**50**	**0-50**
4.2	3.21	0	23	36	-40	-24	R Fusiform Gyrus		
7.8	4.56	0	928	-4	-46	50	L SPL (5M)	20	10-40
7.6	4.52	0	121	-30	-24	-12	**Assigned to L Hipp (FD)**	**60**	**30-80**
							L Hipp (CA)	50	30-80
4.5	3.39	0	23	38	-28	-12	R Hipp (CA)	30	10-80
6.2	4.06	0	52	10	-80	50	**Assigned to R SPL (7P)**	**40**	**30-70**
8.2	4.68	0	928	-4	-56	62	**Assigned to L SPL (7A)**	**50**	**30-50**
							L SPL (5L)	20	10-40
							L Area 3a	20	10-20
							L SPL (5M)	20	10-30
5.1	3.66	0	29	-12	-66	24	L Cuneus		
7.6	4.51	0	94	-36	28	50	L Middle Frontal Gyrus		
5.6	3.85	0	94	-30	22	48	L Middle Frontal Gyrus		
4.2	3.24	0	94	-36	30	42	L Middle Frontal Gyrus		
4.3	3.26	0	41	48	-76	-10	R Inferior Occipital Gyrus		
5.2	3.71	0	48	-18	-82	26	L Superior Occipital Gyrus		
5.6	3.83	0	74	10	-46	16	R Precuneus		
6.1	4.04	0	121	-42	-24	-16	L Inferior temporal gyrus**		
6.9	4.31	0	41	58	-58	-14	R Inferior Temporal Gyrus		
							Contrast - Word: DP15>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
6	4	0	105	18	-82	-16	**Assigned to R Area 18**	**30**	**0-60**
							R hOC3v (V3v)	30	0-40
4.8	3.52	0	105	12	-82	-8	**Assigned to R Area 18**	**90**	**70-100**
							R Area 17	20	10-30
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
							nothing to report		

Table 13.16 Local maxima for DP16 - Word Contrasts

				MNI			Contrast - Word: CPs>DP16	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
5.5	3.82	0	31	-30	-28	14	L Insula (Ig1)	40	0-80
							L TE 1.1	20	0-30
4.2	*3.23*	*0.001*	*1*	*-68*	*-24*	*4*	***Assigned to L TE3***	***100***	***0-100***
8.2	4.69	0	341	-56	-66	6	L Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
5	3.59	0	22	-4	-98	16	**Assigned to L Area 17**	**50**	**30-60**
							L Area 18	30	20-60
22	6.57	0	2336	10	-74	24	R Area 18	30	20-40
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.6	4.2	0	77	46	16	14	R Area 44	20	0-40
							R Area 45	20	10-20
6	4	0	44	34	-16	70	**Assigned to R Area 6**	70	0-100
9.7	5.02	0	207	30	-42	32	R Angular gyrus**		
4.9	3.57	0	143	36	-60	-16	R Fusiform Gyrus		
4.6	3.44	0	155	42	-44	50	**Assigned to R hIP2**	**50**	**30-50**
							R hIP3	30	10-40
							R SPL (7PC)	20	10-40
6.9	4.31	0	155	38	-52	56	**Assigned to R hIP3**	**40**	**0-50**
							R SPL (7A)	30	20-60
							R SPL (7PC)	20	10-60
4.7	3.47	0	155	30	-52	70	**Assigned to R SPL (7PC)**	**70**	**20-80**
5.5	3.83	0	93	-10	-60	60	**Assigned to L SPL (7A)**	**50**	**50-70**
							L SPL (7P)	20	10-20
5	3.62	0	207	44	-34	36	R hIP2	20	10-20
6.6	4.21	0	79	-56	-16	12	**Assigned to L OP 1**	**40**	**30-60**
							L OP 4	20	20-50
4.8	3.5	0	31	-12	-66	24	L Cuneus		
5.4	3.78	0	50	32	18	56	R Middle Frontal Gyrus		
4.4	3.34	0	50	28	6	48	R Middle Frontal Gyrus		
8	4.63	0	42	12	62	12	R Superior Medial Gyrus		
6.2	4.07	0	341	-32	-64	20	L Middle occipital gyrus**		
5.4	3.75	0	31	-20	-74	22	L Superior occipital gyrus**		
4.2	3.25	0.001	31	-34	-38	14	L Rolandic Operculum**		
8.5	4.76	0	143	52	-54	-16	R Inferior Temporal Gyrus		
5.4	3.77	0	42	66	-32	-10	R Middle Temporal Gyrus		
6.2	4.06	0	583	58	4	-8	R Temporal Pole		
11	5.3	0	583	60	-12	-2	R Superior Temporal Gyrus		
							Contrast - Word: DP16>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
5.5	3.82	0	40	28	-98	-8	**Assigned to R Area 18**	**70**	**50-90**
							R Area 17	30	30-70
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
							Nothing to report		

Table 13.17 Local maxima for DP17 - Word Contrasts

				MNI			Contrast - Word: CPs>DP17	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.7	4.25	0	41	-32	20	60	L Middle Frontal Gyrus		
10	5.13	0	49	-16	66	-2	L Superior Medial Gyrus		
							Contrast - Word: DP17>CPs		
							Phonological Deficit Theory		
6.6	4.22	0	73	-40	-18	-6	**Assigned to L Insula (Id1)**	**100**	**50-100**
							L Insula (Ig2)	30	0-102
4.7	3.47	0	73	-40	-8	-14	**Assigned to L Insula (Id1)**	**50**	**0-70**
4.7	3.47	0	98	-40	6	-2	L Insula Lobe		
6.9	4.31	0	125	-18	-4	70	**Assigned to L Area 6**	**80**	**70-80**
9.8	5.05	0	792	-8	8	48	L Area 6	30	20-50
4.8	3.52	0	76	-42	-36	18	**Assigned to L IPC (PFcm) (BA40)**	**60**	**40-80**
5.7	3.89	0	76	-46	-30	24	**Assigned to L IPC (PFop) (BA40)**	**30**	**10-40**
							L OP 1	20	10-60
6.3	4.1	0	253	-50	-42	36	**Assigned to L IPC (PF) (BA40)**	**40**	**20-70**
9.7	5.03	0	301	36	16	-14	R Insula Lobe		
5.6	3.85	0	132	38	28	0	R Insula Lobe		
4.9	3.54	0	45	42	-4	54	**Assigned to R Area 6**	**40**	**30-40**
5.2	3.68	0	392	50	-34	30	**Assigned to R IPC (PFcm) (BA40)**	**50**	**30-60**
							R hIP2	20	10-20
							L hIP2	20	0-70
4.6	3.4	0	138	-22	-6	48	L Area 6	20	10-30
4.3	*3.26*	*0.001*	*5*	*-66*	*-30*	*18*	***Assigned to L TE3***	***40***	***0-50***
4.6	*3.42*	*0*	*3*	*66*	*-32*	*26*	***Assigned to R IPC (PF) (BA40)***	***80***	***70-90***
							R IPC (PFcm)	*20*	*10-40*
							R TE3	*10*	*0-10*
							Magnocellular Deficit Theory		
5.1	3.67	0	66	18	-82	8	**Assigned to R Area 17**	**100**	**80-100**
5.3	3.74	0	61	0	-98	14	**Assigned to L Area 17**	**60**	**40-70**
							L Area 18	40	30-50
10	5.16	0	326	10	-74	24	R Area 18	30	20-40
7	4.34	0	66	14	-76	-2	**Assigned to R Area 18**	**70**	**50-90**
							R hOC3v (V3v)	30	0-60
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.6	3.43	0	392	46	-40	36	R hIP1	20	10-30
5	3.6	0	20	26	-54	-50	**Assigned to R Lobule VIIIa (Hem)**	**56**	**15-63**
5	3.59	0	113	-8	-22	48	**Assigned to L Area 4a**	**40**	**10-40**
							L Area 6	40	20-50
7.4	4.47	0	208	10	-28	42	**Assigned to R SPL (5Ci)**	**40**	**10-50**

Table 13.17 (Continuation) Local maxima for DP17 - Word Contrasts

				MNI			Contrast - Word: CPs>DP17	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							R Area 6	20	10-20
5.2	3.68	0	208	2	-32	50	**Assigned to R Area 4a**	**50**	**30-60**
							R SPL (5M)	20	0-50
7.8	4.57	0	73	40	-82	-12	**Assigned to R hOC4v (V4)**	**40**	**20-60**
							R hOC3v (V3v)	30	10-50
9.6	5.01	0	138	-32	-14	38	L Area 4p	20	0-40
6.4	4.16	0	278	-10	-42	56	**Assigned to L SPL (5M)**	**40**	**20-50**
							L Area 3a	40	20-50
							L Area 4a	30	0-40
5.9	3.97	0	278	4	-52	56	**Assigned to R SPL (5M)**	**50**	**10-60**
							R SPL (5L)	20	0-30
5.3	3.74	0	278	2	-46	50	**Assigned to R SPL (5M)**	**30**	**20-50**
4.8	3.51	0	98	-54	-2	4	Assigned to L OP 4	40	20-50
							L TE 1.2	30	10-40
							L Area 44	20	10-30
4.8	3.53	0	80	54	-10	0	**Assigned to R TE 1.0**	**60**	**40-80**
							R TE 1.2	40	20-70
12	5.49	0	392	40	-40	20	R Superior temporal gyrus**		
5.3	3.72	0	27	-30	-52	-6	L Lingual Gyrus		
5.6	3.87	0	125	-10	24	24	L Anterior cingulum**		
4.4	3.31	0	125	-2	32	22	L Anterior Cingulate Cortex		
6.3	4.12	0	60	12	28	26	R Anterior Cingulate Cortex		
8.3	4.71	0	113	-12	-26	34	L Middle cingulum**		
4.7	3.49	0	125	-6	18	36	L Middle Cingulate Cortex		
6	3.99	0	792	4	-10	30	R Middle Cingulate Cortex		
4.6	3.41	0	60	8	22	34	R Middle Cingulate Cortex		
5.4	3.77	0	301	48	26	-12	R Inferior Frontal Gyrus (p. Orbitalis)		
12	5.47	0	619	-28	36	20	L Middle Frontal Gyrus		
7.5	4.48	0	619	-26	28	32	L Middle Frontal Gyrus		
7.1	4.38	0	45	38	48	30	R Middle Frontal Gyrus		
7.1	4.37	0	619	-22	50	6	L Superior Frontal Gyrus		
4.7	3.47	0	125	-16	-4	78	L Superior Frontal Gyrus		
5.4	3.76	0	381	6	64	28	R Superior Medial Gyrus		
8.2	4.68	0	381	20	54	18	R Superior Frontal Gyrus		
5.3	3.73	0	28	-20	-74	22	L Superior Occipital Gyrus		
5	3.61	0	98	-52	8	0	L Temporal Pole		
5.3	3.73	0	301	54	14	-4	R Temporal pole: superior temporal gyrus**		

Table 13.18 Local maxima for DP18 - Word Contrasts

				MNI			Contrast - Word: CPs>DP18	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
5	3.62	0	162	-46	-52	22	L IPC (PFm) (BA40)	20	0-20
6.7	4.23	0	125	-38	-66	36	**Assigned L IPC (PGa) (BA 39)**	**30**	**20-50**
							L IPC (PGp)	20	0-30
4	3.13	0.001	125	-44	-58	32	**Assigned L IPC (PGa) (BA39)**	**40**	**20-40**
							L IPC (PFm)	30	20-30
							L hIP1	20	10-30
6.2	4.08	0	162	-52	-58	18	L IPC (PGa) (BA39)	30	30-40
							Magnocellular Deficit Theory		
6.1	4.04	0	27	10	-74	24	R Area 18	30	20-40
5.2	*3.69*	*0*	*12*	*56*	*-62*	*-14*	*R hOC5 (V5)*	*10*	*0-10*
							Cerebellar Deficit Theory		
5.8	3.92	0	95	30	-74	-38	**Assigned R Lobule VIIa Crus I (Hem)**	**80**	**75-94**
7.9	4.58	0	490	-18	-76	-34	**Assigned L Lobule VIIa Crus I (Hem)**	**68**	**51-77**
6.1	4.05	0	490	-40	-70	-38	**Assigned L Lobule VIIa Crus I (Hem)**	**72**	**72-91**
6.9	4.3	0	490	-14	-86	-40	**Assigned L Lobule VIIa Crus II (Hem)**	**77**	**77-94**
							Other areas (not predicted by theories)		
4.5	3.36	0	280	44	-70	30	**Assigned R IPC (PGp) (BA39)**	**70**	**60-80**
4.4	3.35	0	280	54	-68	28	**Assigned R IPC (PGp) (BA39)**	**90**	**70-90**
8.2	4.68	0	280	56	-66	14	**Assigned R IPC (PGp) (BA39)**	**40**	**0-50**
6.8	4.28	0	75	-30	-24	-12	**Assigned L Hipp (FD)**	**60**	**30-80**
							L Hipp (CA)	50	30-80
4.9	3.56	0	75	-24	-20	-20	L Hipp (SUB)	90	80-100
							L Hipp (CA)	60	20-60
							L Hipp (FD)	50	0-70
9.9	5.06	0	3307	-4	-52	62	**Assigned L SPL (5M)**	**30**	**10-30**
							L SPL (7A)	30	20-40
							L SPL (7PC)	20	20-20
							L SPL (5L)	20	20-40
							L Area 3a	20	10-30
5.4	3.76	0	46	-18	42	10	L Anterior cingulum**		
4.8	3.52	0	46	-18	34	12	L Anterior cingulum**		
5.3	3.75	0	29	4	-12	30	R Middle Cingulate Cortex		
7.6	4.52	0	249	-30	22	48	L Middle Frontal Gyrus		
6.1	4.02	0	249	-32	16	62	L Middle Frontal Gyrus		
5.3	3.73	0	249	-28	24	38	L Middle Frontal Gyrus		
6.2	4.08	0	34	38	56	-4	R Middle Orbital Gyrus		
7	4.32	0	1198	28	16	44	R Middle Frontal Gyrus		
5.8	3.92	0	29	26	44	2	R Middle frontal gyrus**		
12	5.42	0	2421	-20	60	0	L Superior Frontal Gyrus		
9.7	5.03	0	2421	-22	50	6	L Superior Frontal Gyrus		
9.6	5.01	0	1198	-2	38	46	L Superior Medial Gyrus		
7.2	4.41	0	1198	-8	44	50	L Superior Medial Gyrus		
8.8	4.82	0	2421	10	62	10	R Superior Medial Gyrus		
6.8	4.27	0	70	-6	18	-10	L Olfactory cortex		
6.2	4.09	0	26	-18	-32	2	L Thalamus		
							Contrast - Word: DP18>CPs		
							nothing to report		

14 Appendix E for Chapter 6 (Local maxima for Pseudoword reading)

Table 14.1 Local maxima for DP1 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP1	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
4.39	3.32	0	47	50	-78	0	R hOC5 (V5)	20	20-10
4.3	3.28	0.001	27	18	-100	6	**Assigned to R Area 17**	**60**	**50-80**
							R Area 18	30	30-50
4.71	3.48	0	27	16	-100	16	**Assigned to R Area 18**	**50**	**40-70**
							R Area 17	40	30-50
							Cerebellar Deficit Theory		
5.69	3.89	0	92	32	-82	-30	**Assigned to R Lobule VIIa Crus I (Hem)**	**100**	**96-100**
5.59	3.85	0	66	-22	-82	-42	**Assigned to L Lobule VIIa Crus II (Hem)**	**83**	**73-92**
4.27	3.27	0.001	66	-14	-88	-42	**Assigned to L Lobule VIIa Crus II (Hem)**	**91**	86-100
							Other areas (not predicted by theories)		
							Assigned to R hOC3v (V3v)	**40**	**20-70**
							R hOC4v (V4)	30	10-30
							R Area 18	30	20-50
							R Area 17	20	10-20
4.42	3.34	0	47	42	-84	-2	R hOC4v (V4)	20	0-30
5.82	3.94	0	89	-40	-86	-2	L Middle Occipital Gyrus		
6.99	4.34	0	41	-2	-12	2	L Thalamus		
4.87	3.55	0	92	30	-90	-10	R Inferior Occipital Gyrus**		
4.88	3.56	0	47	50	-76	-8	R Inferior Occipital Gyrus		
5.97	3.99	0	41	34	42	-10	R Middle Orbital Gyrus		
							Contrast - Pseudoword: DP1>CPs		
							Phonological Deficit Theory		
5.24	3.71	0	76	28	-32	20	R Insula**		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
19.5	6.37	0	346	-32	-62	-36	L Lobule VIIa Crus I (Hem)	25	12-86
							Other areas (not predicted by theories)		
5.06	3.63	0	76	26	-46	12	R Precuneus**		
4.64	3.44	0	76	30	-44	20	R Precuneus**		

Note. See Note for Table 12.4.

Table 14.2 Local maxima for DP2 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP2	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.87	3.96	0	27	36	44	-12	R Middle Orbital Gyrus		
							Contrast - Pseudoword: DP2>CPs		
							Phonological Deficit Theory		
5.47	3.8	0	67	26	-36	24	R Insula**		
5.82	*3.94*	*0*	*26*	*-60*	*2*	*-2*	*L TE3*	*10*	*0-20*
5.34	*3.75*	*0*	*44*	*-58*	*-30*	*14*	***Assigned to L OP 1***	***30***	***20-50***
							L IPC (PFcm)	*20*	*0-30*
							L TE3	*10*	*10-10*
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.34	3.75	0	44	-58	-30	14	**Assigned to L OP 1**	**30**	**20-50**
							L IPC (PFcm)	20	0-30
4.72	3.48	0	57	34	-68	22	R Middle occipital gyrus**		
5.5	3.82	0	57	28	-74	20	R Superior Occipital Gyrus		
4.82	3.53	0	42	36	-48	58	**Assigned to R SPL (7PC)**	**40**	**30-60**
							R Area 1	30	0-30
							R Area 2	20	10-50
							R hIP3	20	0-30
4.59	3.42	0	67	24	-46	24	R Precuneus**		

Table 14.3 Local maxima for DP3 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP3	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
4.5	3.38	0	20	-50	-70	28	**Assigned to L IPC (PGp) (BA39)**	**80**	**70-80**
							L IPC (PGa)	20	20-30
6.06	4.02	0	135	-58	-60	20	L IPC (PGp) (BA39)	30	0-30
							L IPC (PFm)	20	0-30
4.26	3.26	0.001	135	-46	-50	22	L IPC (PGa) (BA39)	20	10-30
4.18	*3.22*	*0*	*3*	*-66*	*-32*	*20*	***Assigned to L IPC (PF) (BA40)***	***50***	***0-70***
							L TE3	*30*	*0-50*
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
6.79	4.27	0	66	-14	-66	-30	**Assigned to L Lobule VI (Hem)**	**34**	**0-68**
8.29	4.7	0	332	-40	-70	-38	**Assigned to L Lobule VIIa Crus I (Hem)**	**72**	**72-91**
7.87	4.59	0	332	-30	-70	-34	L Lobule VIIa Crus I (Hem)	38	32-88
							Other areas (not predicted by theories)		
4.66	3.46	0	21	56	-24	40	**Assigned to R IPC (PFt) (BA40)**	**70**	**50-80**
							R Area 2	40	20-60
5.37	3.76	0	51	-2	-38	64	**Assigned to L Area 4a**	**80**	**0-80**
5.24	3.71	0	79	-2	-50	30	L Posterior Cingulate Cortex		
7.6	4.52	0	75	-28	20	62	L Middle Frontal Gyrus		
9.2	4.92	0	152	36	44	-12	R Middle Orbital Gyrus		
4.85	3.54	0	152	36	54	-14	R Middle Orbital Gyrus		
5.06	3.63	0	23	4	46	52	R Superior frontal gyrus, medial**		
							Contrast - Pseudoword: DP3>CPs		
							Phonological Deficit Theory		
5.51	3.82	0	44	-42	18	30	L Area 45	30	20-30
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.29	4.11	0	284	28	-54	40	R hIP3	40	20-40
							R hIP1	20	10-30
7.53	4.49	0	99	-34	-44	42	**Assigned to L hIP1**	**30**	**10-40**
							L SPL (7PC)	20	0-20
							L hIP2	20	20-20
							L hIP3	20	10-40
5.91	3.97	0	99	-30	-50	38	**Assigned to L hIP1**	**30**	**20-40**
							L hIP3	20	10-20
6.19	4.07	0	284	32	-52	48	**Assigned to R hIP3**	**40**	**30-70**
5.91	3.97	0	284	42	-42	48	**Assigned to R hIP2**	**40**	**30-50**
							R hIP3	30	20-30
							R SPL (7PC)	20	0-40

Table 14.4 Local maxima for DP4 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP4	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
							Contrast - Pseudoword: DP4>CPs		
							Phonological Deficit Theory		
5.62	3.86	0	33	-30	6	20	L Insula**		
4.78	*3.51*	*0*	*13*	*-66*	*-36*	*2*	*L TE3*	*10*	*0-10*
							Magnocellular Deficit Theory		
5.44	3.79	0	25	-16	-102	14	**Assigned to L Area 18**	80	30-90
							L Area 17	20	10-30
6.72	*4.25*	*0*	*59*	*-32*	*-80*	*0*	*L hOC5 (V5)*	*10*	*0-20*
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
8.15	4.66	0	104	20	-84	14	R Calcarine Gyrus		
5.59	3.85	0	66	32	48	32	R Middle Frontal Gyrus		
5.53	3.83	0	66	24	50	32	R Middle Frontal Gyrus		
5.55	3.83	0	51	-18	-36	12	L Hipp (CA)	20	0-20
7.02	4.34	0	34	-26	-74	14	L Middle occipital gyrus**		

Table 14.5 Local maxima for DP5 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP5	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
5.19	3.69	0	29	-28	-60	10	L Area 18	20	10-30
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.54	3.4	0	29	-32	-62	18	L Middle occipital gyrus**		
5.45	3.79	0	29	64	-32	44	R SupraMarginal Gyrus		
4.34	3.3	0	29	60	-26	50	R SupraMarginal Gyrus		
							Contrast - Pseudoword: DP5>CPs		
							Phonological Deficit Theory		
6.17	4.06	0	74	40	-50	-20	R Fusiform Gyrus		
5.5	*3.81*	*0*	*27*	*-58*	*2*	*2*	*L TE3*	*10*	*0-10*
							Magnocellular Deficit Theory		
5.01	3.61	0	25	-10	-88	-14	**Assigned to L Area 17**	20	10-20
							L hOC4v (V4)	20	10-30
							L hOC3v (V3v)	20	10-50
6.27	4.1	0	283	12	-80	-10	**Assigned to R Area 18**	90	70-100
							R Area 17	20	10-40
							R hOC3v (V3v)	20	10-50
							Cerebellar Deficit Theory		
5.74	**3.91**	**0**	**25**	**-26**	**-40**	**-24**	**Assigned to L Lobule VI (Hem)**	**47**	**18-69**
							L Lobule V	46	19-74
							Other areas (not predicted by theories)		
6.94	4.32	0	283	26	-76	-16	**Assigned to R hOC4v (V4)**	60	50-80
							R hOC3v (V3v)	30	30-40
							R Area 18	20	0-20
5.65	3.87	0	39	-26	-54	38	L hIP1	20	10-30
							L hIP3	20	10-40
6.87	4.3	0	54	-28	-78	-2	L hOC4v (V4)	20	10-40
5.85	3.95	0	214	-8	10	12	L Caudate Nucleus		
10.1	5.11	0	214	4	14	10	R Caudate nucleus**		

Table 14.6 Local maxima for DP6 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP6	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.87	4.3	0	30	-4	-20	-24	L ParaHippocampal gyrus**		
							Contrast - Pseudoword: DP6>CPs		
							Phonological Deficit Theory		
6.89	4.3	0	102	-52	10	2	L Area 44	30	20-30
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
6.34	4.13	0	95	34	-80	-30	**Assigned to Lobule R VIIa Crus I (Hem)**	**100**	**96-100**
							Other areas (not predicted by theories)		
5.82	3.94	0	32	-10	-8	22	L Caudate nucleus**		
10.9	5.27	0	73	-38	-86	-14	L hOC4v (V4)	40	20-60
							L hOC3v (V3v)	30	10-30
5.31	3.74	0	86	-38	-84	4	L Middle Occipital Gyrus		
6.62	4.22	0	95	36	-78	-20	R hOC4v (V4)	20	0-50

Table 14.7 Local maxima for DP7 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP7	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.23	4.09	0	35	34	44	-14	R Middle Orbital Gyrus		
							Contrast - Pseudoword: DP7>CPs		
							Phonological Deficit Theory		
5.15	3.67	0	25	60	-32	24	**Assigned to R IPC (PFcm) (BA40)**	60	40-60
							R IPC (PF)	50	20-70
4.92	3.57	0	60	60	-30	40	**Assigned to R IPC (PF) (BA40)**	80	40-90
							R IPC (PFop)	30	0-40
							R IPC (PFt)	30	0-40
4.07	3.16	0.001	60	52	-26	36	**Assigned to R IPC (PFt) (BA40)**	40	30-80
							R OP 1	20	0-20
							R IPC (PFop)	20	10-30
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
7.92	4.6	0	216	-36	-44	42	Assigned to L hIP1	40	20-60
							L hIP2	30	20-30
							L SPL (7PC)	20	10-20
10.2	5.14	0	526	42	-42	50	Assigned to R SPL (7PC)	40	10-40
							R hIP2	30	30-50
							R hIP3	30	10-30
8.19	4.67	0	216	-40	-40	54	**Assigned to L Area 2**	**40**	**30-50**
							L SPL (7PC)	20	10-30
5.26	3.72	0	526	30	-42	24	R Precuneus**		
6.02	4.01	0	44	18	-62	44	R Precuneus		
5.63	3.87	0	526	22	-30	32	R Middle cingulum**		
4.98	3.6	0	45	44	32	32	R Middle Frontal Gyrus		
5.83	3.94	0	128	36	-72	22	R Middle Occipital Gyrus		
4.59	3.42	0	128	28	-76	20	R Superior Occipital Gyrus		

Table 14.8 Local maxima for DP8 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP8	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.66	3.88	0	41	-10	-8	22	L Caudate nucleus**		
4.31	3.29	0.001	31	-42	-2	24	L Precentral Gyrus		
							Contrast - Pseudoword: DP8>CPs		
							Phonological Deficit Theory		
7.6	4.52	0	26	-60	6	26	**Assigned to L Area 6**	**40**	**20-50**
							L Area 44	30	30-40
4.37	3.32	0	33	-38	-80	24	**Assigned to L IPC (PGp) (BA39)**	**40**	**30-50**
							Magnocellular Deficit Theory		
4.56	*3.41*	*0*	*12*	*58*	*-62*	*0*	*R hOC5 (V5)*	*10*	*0-20*
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.17	3.68	0	43	-32	28	46	L Middle Frontal Gyrus		
4.38	3.32	0	43	-30	34	38	L Middle Frontal Gyrus		
5.34	3.75	0	43	-36	-84	4	L Middle Occipital Gyrus		
5.05	3.63	0	43	-28	-82	2	L Middle Occipital Gyrus		
4.54	3.4	0	33	-30	-76	16	L Middle Occipital Gyrus		
5.05	3.63	0	25	-30	-42	48	**Assigned to L Area 2**	**30**	**10-50**
							L SPL (7PC)	20	10-30
							L Area 1	20	0-20
4.49	3.37	0	25	-32	-42	40	**Assigned to L hIP1**	**30**	**20-40**
							L hIP2	20	0-20
							L hIP3	20	20-40
4	3.13	0.001	64	28	-52	50	**Assigned to R SPL (7PC)**	**40**	**10-40**
							R SPL (7A)	30	20-40
4.72	3.48	0	23	-18	-64	44	L SPL (7A)	20	10-40
5.77	3.92	0	42	10	-50	54	**Assigned to R SPL (5M)**	**40**	**30-50**
							R SPL (5L)	30	20-30

Table 14.9 Local maxima for DP9 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP9	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
5.7	3.89	0	32	-58	-64	20	L IPC (PGp) (BA39)	40	0-40
							Magnocellular Deficit Theory		
4.4	*3.33*	*0*	*12*	*52*	*-68*	*-14*	*R hOC5 (V5)*	*10*	*0-10*
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.6	3.87	0	100	32	16	16	R Insula**		
5.3	3.71	0	100	28	26	16	R Insula**		
7	4.35	0	21	12	-24	48	**Assigned to R Area 6**	**20**	**10-30**
6.1	4.05	0	30	40	-36	-18	R Fusiform Gyrus		
6.5	4.19	0	52	-34	26	46	L Middle Frontal Gyrus		
9.2	4.91	0	88	36	44	-12	R Middle Orbital Gyrus		
5.6	3.86	0	62	-44	-86	-2	L hOC4v (V4)	20	10-20
4.9	3.55	0	26	24	-12	2	R Pallidum**		
4.2	3.22	0.001	26	24	-10	-6	R Amyg (CM)	50	30-80
							R Amyg (SF)	30	0-60
5.6	3.87	0	148	-8	-28	66	**Assigned to L Area 4a**	**60**	**40-70**
							L Area 6	30	20-60
5.2	3.7	0	148	-2	-36	66	**Assigned to L Area 4a**	**70**	**0-80**
							L Area 3a	20	0-30
							L Area 4p	20	0-30
							L SPL (5M)	20	10-40
4.9	3.57	0	148	6	-36	62	**Assigned to R Area 4a**	**80**	**60-80**
5.4	3.76	0	50	16	-14	-6	R Thalamus**		
4.4	3.32	0	50	8	-4	-8	R Thalamus**		
							Contrast - Pseudoword: DP9>CPs		
							Phonological Deficit Theory		
6.5	4.19	0	137	26	-30	22	R Insula**		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.1	**3.63**	**0**	**67**	-24	-56	-50	**Assigned to L Lobule VIIIa (Hem)**	**70**	**37-81**
							L Lobule VIIIb (Hem)	29	3-50
4.2	3.23	0.001	50	-22	-8	34	L Caudate nucleus**		
5	3.59	0	26	20	-12	28	R Caudate nucleus**		
6.1	4.03	0	26	-22	-38	30	L Middle cingulum**		
5.3	3.72	0	50	-14	-8	30	L Middle cingulum**		
4.4	3.32	0	137	20	-28	30	R Middle cingulum**		
5.7	3.89	0	137	22	-40	24	R Posterior cingulum**		
5	3.6	0	50	-8	-10	22	L Thalamus**		
5.1	3.66	0	25	10	-22	20	R Thalamus**		
4.6	3.41	0	25	8	-14	20	R Thalamus**		

Table 14.10 Local maxima for DP10 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP10	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
5.49	3.81	0	29	-60	14	10	**Assigned to L Area 44**	**40**	**0-60**
							L Area 45	20	0-30
6.06	4.02	0	25	-46	-6	-24	L Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
4.8	3.52	0	42	28	-70	-32	**Assigned to R Lobule VIIa Crus I (Hem)**	**94**	**54-97**
							Other areas (not predicted by theories)		
5.06	3.64	0	155	-38	-86	-14	L hOC4v (V4)	40	20-60
							L hOC3v (V3v)	30	10-30
4.62	3.44	0	48	50	-76	-8	R Inferior Occipital Gyrus		
6.96	4.33	0	155	-40	-86	-2	L Middle Occipital Gyrus		
5.18	3.68	0	48	44	-82	0	R Middle Occipital Gyrus		
							Contrast - Pseudoword: DP10>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.09	4.04	0	28	30	30	16	R Middle frontal gyrus**		

Table 14.11 Local maxima for DP11 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP11	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
5.6	3.86	0	34	-8	-88	-38	**Assigned to L Lobule VIIa Crus II (Hem)**	**79**	**79-97**
4.8	3.51	0	21	-22	-78	-38	**Assigned to L Lobule VIIa Crus II (Hem)**	**98**	**52-98**
							Other areas (not predicted by theories)		
10	5.15	0	514	-2	-52	-36	**Assigned to L Lobule IX (Vermis)**	**88**	**81-93**
5.9	3.97	0	25	38	-32	-20	R Fusiform Gyrus		
							Contrast - Pseudoword: DP11>CPs		
							Phonological Deficit Theory		
5	3.61	0	86	-36	-4	56	L Area 6	30	20-30
6	3.99	0	55	56	-36	24	**Assigned to R IPC (PFcm) (BA40)**	60	40-60
							R IPC (PFm)	20	0-20
							R IPC (PF)	20	0-60
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.7	3.48	0	58	26	2	54	R Superior Frontal Gyrus		
6.5	4.18	0	255	-36	-46	42	**Assigned to L hIP1**	**60**	**30-60**
							L hIP2	20	10-30
							L hIP3	20	0-30
6.1	4.06	0	520	42	-42	50	**Assigned to R SPL (7PC)**	**40**	**10-40**
							R hIP2	30	30-50
							R hIP3	30	10-30
8.2	4.69	0	255	-34	-46	58	**Assigned to L SPL (7PC)**	**60**	**40-80**
							L Area 2	40	30-50
							L Area 1	20	10-40
							L hIP3	20	0-30
							L SPL (7A)	20	10-30
8.8	4.82	0	520	30	-52	66	**Assigned to R SPL (7PC)**	**70**	**20-80**
							R SPL (5L)	20	0-20
							R Area 2	20	0-20
							R SPL (7A)	20	0-50
7	4.35	0	520	36	-48	58	**Assigned to R SPL (7PC)**	**40**	**30-60**
							R Area 1	30	0-30
							R Area 2	20	10-50
							R hIP3	20	0-30
4.3	3.29	0	58	36	4	50	R Pre-central Gyrus		
9.1	4.89	0	255	-40	-40	54	**Assigned to L Area 2**	**40**	**30-50**
							L SPL (7PC)	20	10-30

Table 14.12 Local maxima for DP12 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP12	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
4.95	3.59	0	22	30	-82	-20	**Assigned to R Lobule VIIa Crus I (Hem)**	**36**	**3-36**
							Other areas (not predicted by theories)		
7.03	4.35	0	87	-40	-82	2	L Middle Occipital Gyrus		
							Contrast - Pseudoword: DP12>CPs		
							Phonological Deficit Theory		
5.08	3.64	0	26	-54	8	0	L Area 44	20	10-30
6.43	4.16	0	198	50	8	-4	R Area 44	20	0-30
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
6.64	4.22	0	110	-32	-44	38	**Assigned to L hIP1**	**30**	**20-50**
6.4	4.15	0	50	42	-42	48	**Assigned to R hIP2**	**40**	**30-50**
							R hIP3	30	20-30
							R SPL (7PC)	20	0-40
5.78	3.92	0	33	20	-60	42	R Precuneus**		
5.35	3.75	0	32	56	-58	-12	R Inferior Temporal Gyrus		
5.91	3.97	0	29	52	10	-26	R Medial Temporal Pole		

Table 14.13 Local maxima for DP13 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP13	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.34	3.75	0	26	18	14	28	R Middle cingulum**		
5.33	3.74	0	26	20	14	36	R Middle cingulum**		
5.25	3.71	0	27	22	38	-6	R Inferior frontal gyrus, orbital part**		
5.43	3.79	0	34	12	46	-12	R Mid Orbital Gyrus		
5.16	3.68	0	34	12	52	-6	R Mid Orbital Gyrus		
							Contrast - Pseudoword: DP13>CPs		
							Phonological Deficit Theory		
7.35	4.44	0	100	-44	8	34	**Assigned to L Area 44**	**40**	**30-50**
5.12	3.66	0	62	-50	24	-4	L Area 45	30	20-40
7.07	4.36	0	127	-30	-8	70	**Assigned to L Area 6**	**50**	**30-50**
4.67	3.46	0	127	-22	-12	78	**Assigned to L Area 6**	**80**	**0-80**
4.28	3.27	0.001	127	-20	-14	70	**Assigned to L Area 6**	**90**	**80-90**
6.01	4.01	0	24	-10	-16	54	**Assigned to L Area 6**	**40**	**30-70**
							L Area 4a	20	0-30
5.04	3.63	0	29	50	30	14	R Area 45	70	40-80
7.7	4.54	0	141	42	4	16	R Insula**		
7.9	4.6	0	200	-50	-44	-4	L Middle Temporal Gyrus		
5.27	3.72	0	200	-50	-38	6	L Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
7.86	4.59	0	83	-18	-102	8	**Assigned to L Area 18**	**60**	**20-90**
							Cerebellar Deficit Theory		
5.95	3.98	0	59	-22	-74	-18	**Assigned to L Lobule VI (Hem)**	**78**	**0-86**
							Other areas (not predicted by theories)		
5.6	3.85	0	22	28	-52	34	R hIP1	30	30-30
6.61	4.21	0	108	10	28	20	R Anterior Cingulate Cortex		
4.61	3.43	0	62	-42	48	-12	L Inferior Frontal Gyrus (p. Orbitalis)		
5.71	3.9	0	41	40	42	-12	R Inferior Frontal Gyrus (p. Orbitalis)		
4.93	3.58	0	41	30	40	-20	R Inferior Frontal Gyrus (p. Orbitalis)		
6.14	4.05	0	130	40	56	-12	R Middle Orbital Gyrus		
4.38	3.32	0	130	42	54	-2	R Middle Orbital Gyrus		
5.98	4	0	186	2	34	48	L Superior Medial Gyrus		
4.98	3.6	0	186	-2	24	44	L Superior Medial Gyrus		
8.89	4.85	0	75	-28	-74	14	L Middle occipital gyrus**		
6.39	4.14	0	61	34	-68	16	R Middle occipital gyrus**		
4.71	3.48	0	23	-26	-70	44	L SPL (7A)	20	10-20
5.08	3.64	0	23	42	-42	48	**Assigned to R hIP2**	**40**	**30-50**
							R hIP3	30	20-30
							R SPL (7PC)	20	0-40
6.92	4.31	0	25	-42	-38	54	**Assigned to L Area 2**	**50**	**40-60**
							L SPL (7PC)	20	10-30
							L hIP3	20	10-20
6.5	4.18	0	30	-48	-26	26	**Assigned to L OP 1**	**30**	**20-50**
							L IPC (PFop)	30	20-50
4.85	3.54	0	23	-18	-82	0	L hOC3v (V3v)	30	10-60

Table 14.14 Local maxima for DP14 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP14	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.75	3.91	0	67	24	-10	-6	R Amyg (CM)	50	30-80
							R Amyg (SF)	30	0-60
5.74	3.91	0	67	16	-14	-6	R Thalamus**		
							Contrast - Pseudoword: DP14>CPs		
							Phonological Deficit Theory		
5.95	3.99	0	23	-62	-38	38	**Assigned to L IPC (PF) (BA 40)**	90	0-90
4.6	3.43	0	32	28	-36	24	R Insula**		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.65	3.45	0	32	30	-44	20	R Precuneus**		

Table 14.15 Local maxima for DP15 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP15	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.03	3.62	0	27	-58	-62	22	**Assigned to R IPC (PGp) (BA39)**	**40**	**0-50**
							R IPC (PGa)		
7.09	4.37	0	32	36	44	-12	R Middle Orbital Gyrus		
5.31	3.74	0	31	28	-10	-14	**Assigned to R Amyg (LB)**	**40**	**30-70**
							R Hipp (CA)	40	10-70
							R Amyg (CM)	20	20-50
							R Amyg (SF)	20	0-20
							Contrast - Pseudoword: DP15>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
6.36	4.13	0	177	20	-80	-16	**Assigned to R Area 18**	**30**	**0-50**
							R hOC3v (V3v)	30	0-70
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
3.94	3.1	0	49	-30	26	26	L Middle frontal gyrus**		
5.38	3.77	0	49	-28	32	34	L Superior Frontal Gyrus		
5.7	3.89	0	30	-24	-68	24	L Superior Occipital Gyrus		

Table 14.16 Local maxima for DP16 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP16	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
5.2	3.69	0	106	-32	8	-8	L Insula**		
7.42	4.46	0	114	-28	-6	70	**Assigned to L Area 6**	**60**	**30-60**
5.55	3.83	0	139	-36	-40	-24	L Fusiform Gyrus		
5.93	3.98	0	374	-52	-70	6	L Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
6.61	4.21	0	374	-42	-66	4	L hOC5 (V5)	20	0-40
3.99	*3.12*	*0.001*	*1*	*48*	*-80*	*2*	*R hOC5 (V5)*	*20*	*0-20*
4.24	*3.25*	*0.001*	*1*	*38*	*-68*	*2*	*R hOC5 (V5)*	*10*	*0-20*
7.34	*4.44*	*0*	*307*	*60*	*-64*	*2*	*R hOC5 (V5)*	*10*	*0-20*
7.39	4.46	0	29	-4	-100	16	**Assigned to L Area 17**	**70**	**50-70**
							L Area 18	50	30-60
							Cerebellar Deficit Theory		
5.05	3.63	0	139	-30	-48	-34	**Assigned to L Lobule VI (Hem)**	**77**	**77-98**
							Other areas (not predicted by theories)		
5.47	3.8	0	51	50	4	2	R Area 44	20	10-30
							R OP 4	20	20-30
5.99	4	0	67	32	16	18	R Insula**		
4.58	3.42	0	67	32	6	20	R Insula**		
4.61	3.43	0	22	60	-30	22	**Assigned to R IPC (PFcm) (BA40)**	**50**	**50-50**
							R IPC (PF)	30	0-40
							R OP 1	20	0-40
4.92	3.57	0	307	44	-82	16	**Assigned to R IPC (PGp) (BA39)**	**30**	**0-50**
5.74	3.91	0	388	38	-74	32	**Assigned to R IPC (PGp) (BA39)**	**40**	**0-50**
8.82	4.83	0	1237	30	-42	32	R Angular gyrus**		
10.73	5.23	0	139	-26	-38	-28	**Assigned to L Lobule V**	**68**	**65-80**
							L Lobule VI (Hem)	29	15-35
4.44	3.35	0	20	-14	-46	-20	**Assigned to L Lobule V**	**79**	**69-82**
7.44	4.47	0	197	-24	-16	18	L Caudate nucleus**		
5.22	3.7	0	197	-14	-8	20	L Caudate Nucleus		
6.39	4.14	0	25	24	-10	22	R Caudate nucleus**		
6.73	4.25	0	80	0	36	22	L Anterior Cingulate Cortex		
4.91	3.57	0	21	12	-2	40	R Middle Cingulate Cortex		
8.56	4.77	0	56	-30	30	38	L Middle Frontal Gyrus		
9.6	5.01	0	84	-32	50	-12	L Middle Orbital Gyrus		
10.1	5.11	0	204	32	48	32	R Middle Frontal Gyrus		
4.98	3.6	0	84	28	16	52	R Middle Frontal Gyrus		
4.72	3.48	0	84	26	6	50	R Middle Frontal Gyrus		
5.3	3.74	0	204	24	36	18	R Superior frontal gyrus**		
6.31	4.11	0	64	-22	-14	-12	**Assigned to L Hipp (CA)**	**60**	**40-70**
							L Hipp (HATA)	30	0-40
							L Hipp (FD)	20	10-40
4.71	3.48	0	64	-26	-20	-20	**Assigned to L Hipp (SUB)**	**80**	**30-100**
							L Hipp (FD)	60	10-90
							L Hipp (CA)	60	40-90
9.01	4.87	0	374	-32	-64	18	L Middle occipital gyrus**		
4.65	3.45	0	106	-20	4	-2	L Pallidum		

Table 14.16 (Continuation) Local maxima for DP16 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP16	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
4.55	3.4	0	80	-12	-2	4	L Pallidum**		
5.22	3.7	0	217	20	-2	-4	R Pallidum		
8.14	4.66	0	392	8	-36	50	**Assigned to R SPL (5M)**	**50**	**40-70**
							R SPL (5Ci)	50	20-60
							R Area 4a	30	10-50
4.75	3.5	0	392	16	-44	52	R Area 2	30	10-30
							R SPL (5L)	20	0-20
							R SPL (5M)	20	0-40
							R SPL (5Ci)	20	0-30
7.81	4.57	0	455	-40	-40	52	**Assigned to L Area 2**	**30**	**30-50**
							L hIP3	30	10-30
7.17	4.39	0	455	-36	-44	42	**Assigned to L hIP1**	**40**	**20-60**
							L hIP2	30	20-30
							L SPL (7PC)	20	10-20
5.62	3.86	0	455	-50	-26	42	**Assigned to L Area 2**	**90**	**50-100**
							L IPC (PFt)	50	40-60
11.07	5.3	0	1237	42	-42	48	**Assigned to R hIP2**	**40**	**30-50**
							R hIP3	30	20-30
							R SPL (7PC)	20	0-40
7.22	4.41	0	1237	36	-52	54	**Assigned to R hIP3**	**40**	**0-60**
							R SPL (7A)	30	20-50
							R SPL (7PC)	30	10-60
5.43	3.79	0	278	26	-72	54	**Assigned to R SPL (7A)**	**30**	**0-30**
5.96	3.99	0	163	-10	-64	58	**Assigned to L SPL (7A)**	**70**	**20-80**
							L SPL (7P)	30	20-40
5.9	3.97	0	163	-14	-56	64	**Assigned to L SPL (7A)**	**50**	**40-70**
							L SPL (5L)	50	30-50
8.69	4.8	0	278	18	-74	44	R SPL (7A)	20	0-20
							R SPL (7P)	20	0-40
6.14	4.05	0	392	10	-50	54	**Assigned to R SPL (5M)**	**40**	**30-50**
							R SPL (5L)	30	20-30
4.89	3.56	0	197	-26	-18	6	L Putamen		
5.4	3.78	0	50	32	6	-8	R Putamen		
4.09	3.17	0.001	50	22	6	-10	R Putamen		
6.85	4.29	0	28	48	-2	-34	R Inferior Temporal Gyrus		
5.21	3.7	0	25	46	-14	-26	R Inferior Temporal Gyrus		
7.85	4.58	0	307	56	-72	6	R Middle Temporal Gyrus		
6.28	4.1	0	271	52	10	-22	R Temporal Pole		
5.59	3.85	0	271	54	4	-14	R Superior Temporal Gyrus		
4.8	3.52	0	80	0	-6	2	L Thalamus**		
6.37	4.14	0	217	22	-10	-2	R Thalamus**		
5.18	3.68	0	217	28	-26	2	R Thalamus**		
							Contrast - Pseudoword: DP16>CPs		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
5.41	3.78	0	35	28	-98	-8	**Assigned to R Area 18**	**70**	**50-90**
							R Area 17	30	30-70
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.85	3.54	0	38	-26	-74	-2	L hOC4v (V4)	40	10-60
6.82	4.28	0	21	-24	-84	16	L Middle Occipital Gyrus		

Table 14.17 Local maxima for DP17 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP17	P$	R$
T	Z	p	k	x	y	z	Areas labelled with Anatomy Toolbox or AAL		
							Phonological Deficit Theory		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
							Contrast - Pseudoword: DP17>CPs		
							Phonological Deficit Theory		
4.9	3.56	0	29	-58	8	0	L Area 44	20	10-20
4.32	3.29	0	61	22	4	34	R Inferior frontal gyrus, opercular part**		
7.65	4.53	0	501	-28	2	18	L Insula**		
6.54	4.19	0	501	-26	-14	20	L Insula**		
4.62	3.44	0	48	30	-10	30	R Insula		
5.29	3.73	0	56	-26	-8	68	**Assigned to L Area 6**	**60**	**50-60**
4.94	3.58	0	56	-18	-6	68	**Assigned to L Area 6**	**70**	**40-80**
5.76	3.92	0	134	-4	8	50	**Assigned to L Area 6**	**60**	**40-70**
4.98	3.6	0	35	-26	-10	54	L Area 6	30	20-40
6.2	4.08	0	366	50	-36	26	**Assigned to R IPC (PFcm) (BA40)**	**40**	**30-70**
4.5	*3.37*	*0*	*11*	*64*	*-12*	*10*	*R TE3*	*20*	*10-50*
6.96	4.33	0	46	-52	-22	-16	L Middle Temporal Gyrus		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
4.92	3.57	0	58	0	32	-12	R Mid Orbital Gyrus		
5.54	3.83	0	48	24	-14	20	R Caudate**		
6.37	4.13	0	673	-6	34	22	L Anterior Cingulate Cortex		
6.84	4.29	0	673	8	28	12	R Anterior cingulum**		
6	4	0	108	-12	-38	54	**Assigned to L Area 3a**	**30**	**10-50**
							L Area 3b	20	0-20
							L SPL (5M)	20	20-30
5.33	3.75	0	108	-10	-34	42	L SPL (5M)	20	10-40
							L SPL (5Ci)	20	10-30
5.61	3.86	0	61	16	12	32	R Middle cingulum**		
7.91	4.6	0	265	-26	30	26	L Middle frontal gyrus**		
5.39	3.77	0	265	-30	38	20	L Middle Frontal Gyrus		
6.71	4.25	0	45	34	48	34	R Middle Frontal Gyrus		
7.52	4.49	0	265	-28	32	34	L Superior Frontal Gyrus		
5.42	3.78	0	30	-22	50	6	L Superior Frontal Gyrus		
5.12	3.66	0	37	-18	50	30	L Superior Frontal Gyrus		
6.13	4.05	0	673	12	48	0	R Superior Medial Gyrus		
6.54	4.19	0	31	40	-84	-12	**Assigned to R hOC4v (V4)**	**50**	**20-60**
							R hOC3v (V3v)	50	20-50
5.76	3.91	0	58	-8	28	-16	L Rectal Gyrus		
4.32	3.29	0	29	-60	0	6	**Assigned to L OP 4**	**50**	**40-50**
6.41	4.15	0	366	40	-18	24	L OP 3	20	20-40
5.15	3.67	0	366	48	-22	24	R OP 3	40	20-40
							R IPC (PFcm)	20	0-30
							R OP 1	20	10-30
							R IPC (PFop)	20	0-30
4.35	3.31	0	48	12	-18	18	R Thalamus		

Table 14.18 Local maxima for DP18 - Pseudoword Contrasts

				MNI			Contrast - Pseudoword: CPs>DP18	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Areas labelled with Anatomy Toolbox or AAL**		
							Phonological Deficit Theory		
5.24	3.71	0	51	-26	-24	24	L Insula**		
							Magnocellular Deficit Theory		
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.04	3.62	0	51	-26	-16	26	L Caudate nucleus**		
5.5	3.82	0	36	-34	26	46	L Middle Frontal Gyrus		
5.59	3.85	0	20	36	44	-12	R Middle Orbital Gyrus		
4.55	3.4	0	20	-18	60	0	L Superior Frontal Gyrus		
4.85	3.54	0	39	-2	-24	4	L Thalamus**		
4.82	3.53	0	39	-8	-30	8	L Thalamus		
							Contrast - Pseudoword: DP18>CPs		
							Phonological Deficit Theory		
5.9	3.97	0	126	-12	-12	64	**Assigned to L Area 6**	**80**	**50-100**
7.17	4.39	0	126	-12	-8	56	L Area 6	40	30-50
5.63	3.87	0	43	56	-36	24	**Assigned to R IPC (PFcm) (BA 40)**	**60**	**40-60**
							R IPC (PFm)	20	0-20
							R IPC (PF)	20	0-60
4.18	*3.22*	*0*	*9*	*64*	*-12*	*10*	*R TE3*	*20*	*10-50*
							Magnocellular Deficit Theory		
4.01	3.13	0	56	-26	-68	4	L Area 17	30	20-30
							Cerebellar Deficit Theory		
							Other areas (not predicted by theories)		
5.57	3.84	0	33	-30	30	32	L Middle Frontal Gyrus		

15 Appendix F for Chapter 7

CPs correlation analysis for BOLD signal for Words

CPs correlation analysis for Words

Table 15.1 CPs – Word; PA covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**
T	**Z**	**p**	**k**	**x**	**y**	**z**	
							Areas with too low voxel threshold
4.58	3.35	0	3	10	52	-14	(Right Middle Orbital Gyrus)**
4.27	3.21	0.001	1	18	40	-16	(Right Superior Orbital Gyrus)**
4.19	3.17	0.001	2	20	46	-18	(Right Middle Orbital Gyrus)**

Note. See note under Table 14.4.

Table 15.2 CPs – Word; PF covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological areas		
6.59	4.11	0	97	-24	-10	50	L Area 6	20	20-40
4.97	3.53	0	97	-22	-14	58	**Assigned to L Area 6**	50	40-70
5.9	3.88	0	12	-18	12	68	L Area 6	10	0-20
							Assigned to L Area 6	50	40-70
4.39	3.27	0.001	5	16	-12	52	Area 6	10	10-30
5.07	3.57	0	14	-48	0	24	L Area 44	10	10-20
4.59	3.36	0	7	40	-18	-8	Assigned to R Insula (Id1)	90	30-90
							R Insula (Ig2)	10	0-50
5.06	3.56	0	47	-48	-26	48	Assigned to L Area 2	70	50-90
							L IPC (PFt)	20	0-40
							L Area 1	40	20-70
							L Area 3b	20	0-30
							L Area 4p	10	10-20
							Cerebellar areas		
4.32	3.24	0.001	8	-30	-58	-24	**Assigned to L Lobule VI (Hem)**	100	94-100
							Other areas		
5.16	3.6	0	16	-20	-4	66	(Left Superior Frontal Gyrus)**		
7.75	4.44	0	36	-34	-40	44	**Assigned to L hIP3**	40	30-50
							L SPL (7PC)	10	0-20
4.67	3.4	0	6	-32	-16	50	**Assigned to L Area 4p**	30	10-40
							L Area 6	30	20-30
							L Area 4a	20	10-30
							L SPL (5L)	10	0-10
							L Area 2	10	0-20
							L hIP1	10	0-20
5.07	3.57	0	27	24	-72	44	R SPL (7A)	10	0-10
							R SPL (7P)	10	0-30
							R hIP3	10	0-10
4.94	3.51	0	47	-48	-24	56	**Assigned to L Area 1**	90	60-100
							L Area 2	10	10-30
							L Area 4a	10	0-20
							L Area 3b	10	0-60
							Areas with too low voxel threshold		
4.13	3.15	0.001	1	-32	0	46	L Area 6	10	10-10
4.29	3.22	0.001	1	4	6	62	**Assigned to R Area 6**	80	60-80

Table 15.2 (continuation) CPs – Word; PF covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**T**	**Z**
4.29	3.22	0.001	4	12	-2	58	R Area 6	10	10-60
4.13	3.14	0.001	1	6	4	64	**Assigned to R Area 6**	70	60-90
4.04	3.1	0.001	1	18	-8	48	R Area 6	20	10-20
4.11	3.13	0.001	3	16	-62	-32	R Lobule VI (Hem)	1	0-48
4.66	3.39	0	4	42	-84	-6	R hOC4v (V4)	20	0-40
							R hOC3v (V3v)	10	0-20
4.41	3.28	0.001	3	14	-64	68	**Assigned to R SPL (7A)**	80	30-80
							R SPL (5L)	20	10-40
							R SPL (7PC)	10	0-10
4.26	3.21	0.001	2	32	-84	8	(Right Middle Occipital Gyrus)**		
4.22	3.19	0.001	1	22	-36	44	R hIP1	20	0-30
4.17	3.16	0.001	1	24	-50	32	R hIP3	10	0-10
4.1	3.13	0.001	1	30	-70	32	(Right Middle Occipital Gyrus)**		
4.06	3.11	0.001	1	14	-54	54	R SPL (5L)	20	0-30
							R SPL (5M)	10	0-20
4.03	3.09	0.001	1	-32	20	56	(Left Middle Frontal Gyrus)**		
4.03	3.09	0.001	1	-38	-40	8	L TE 1.1	10	0-10
							L OP 1	10	0-10

Table 15.3 CPs – Words; Digit Span (z-scores) covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.68	3.8	0	15	-40	2	-4	(Left Insula Lobe)**		
5.45	3.72	0	13	-60	14	18	**Assigned to L Area 44**	50	40-60
							L Area 45	20	10-30
4.79	3.45	0	34	-50	-40	4	(Left Middle Temporal Gyrus)**		
5.1	3.58	0	21	-62	-36	-8	(Left Middle Temporal Gyrus)**		
8.6	4.65	0	77	60	-62	12	R IPC (PGp)	20	20-30
4.95	3.52	0	77	52	-56	14	R IPC (PGa)	30	0-40
7.18	4.29	0	62	46	-20	-6	R Insula (Id1)	10	0-50
5.33	3.67	0	62	56	-16	-6	R TE 3	10	0-20
4.53	3.33	0	6	46	-50	4	R IPC (PGp)	10	0-10
4.99	3.53	0	28	62	-58	34	(Right Angular Gyrus)**		
							Cerebellar Areas		
5.43	3.71	0	9	14	-42	-36	R Cerebellum_9**		
							Other Areas		
7.25	4.31	0	23	-22	-84	34	(Left Superior Occipital Gyrus)**		
7.05	4.25	0	16	-60	-20	4	L OP 1	10	0-10
5.24	3.63	0	52	-26	-50	62	**Assigned to L SPL (7A)**	60	20-70
							L Area 2	40	0-40
							L SPL (7PC)	30	20-40
							L Area 1	20	0-30
							L SPL (7P)	10	0-10
							L SPL (5L)	10	10-40
5.21	3.62	0	52	-22	-48	54	**Assigned to L Area 2**	50	30-50
							L SPL (5L)	40	20-50
							L Area 1	20	10-20
							L SPL (7A)	10	0-30
5.23	3.63	0	34	-52	-44	12	(Left Superior Temporal Gyrus)**		
5.07	3.57	0	16	-44	-40	30	L hIP2	30	20-30
							L hIP1	10	0-10
5.05	3.56	0	12	-58	-12	14	**Assigned to L OP 4**	50	40-80
							L OP 1	30	10-40
							L OP 3	20	0-30
							L IPC (PFop)	20	0-20
							L TE 1.2	10	10-10
							L TE 1.0	10	0-10
							L Area 3b	10	0-10
4.9	3.5	0	31	28	-40	50	**Assigned to R Area 2**	100	70-100
							R SPL (7PC)	10	10-40
							R Area 4p	10	10-10
							R Area 3b	10	10-30
							R hIP3	10	10-20
4.72	3.42	0	8	14	60	20	(Right Superior Frontal Gyrus)**		
4.66	3.39	0	6	4	14	-6	(Right Olfactory cortex)**		
5.23	3.63	0	11	-8	34	44	(Left Superior Medial Gyrus)**		
5.03	3.55	0	31	22	-42	42	R Precuneus**		
4.12	3.14	0.001	31	24	-34	40	R Postcentral**		
							Areas with voxels with too low threshold number		
4.91	3.5	0	5	-50	-30	-12	(Left Middle Temporal Gyrus)**		
4.56	3.34	0	1	-54	0	30	L Area 6	10	0-30
							L Area 44	10	10-20
							L Area 4a	20	10-20
4.25	3.2	0.001	1	20	32	46	R Area 6	10	0-10
4.41	3.28	0.001	1	-42	40	-6	(Left Inferior Frontal Gyrus (p. Orbitalis))**		
4.09	3.12	0.001	1	-54	-32	-12	(Left Middle Temporal Gyrus)**		
4.03	3.09	0.001	1	-64	-44	4	(Left Middle Temporal Gyrus)**		
4.47	3.31	0	3	-30	-56	-12	(Left Fusiform Gyrus)**		

Table 15.3 CPs – Words; Digit Span (z-scores) covariance with BOLD – continuation

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
4.57	3.35	0	1	64	-12	-20	(Right Middle Temporal Gyrus)**		
4.45	3.3	0	2	20	-56	-42	(Right Cerebellum)**		
4.39	3.27	0.001	1	16	-38	-16	**Assigned to R Lobule V**	40	5-77
							R Lobules I-IV (Hem)	9	0-27
4.37	3.26	0.001	1	52	-38	14	R IPC (PFm)	10	0-10
							R IPC (PF)	10	10-20
4.03	3.09	0.001	1	12	-40	-14	**Assigned to R Lobule V**	70	32-83
							R Lobules I-IV (Hem)	26	2- 57
4.13	3.14	0.001	1	30	0	52	(Right Middle Frontal Gyrus)**		
4.83	3.47	0	3	26	-46	56	**Assigned to R Area 2**	70	30-100
							R SPL (7PC)	40	30-50
							R SPL (5L)	20	0-20
							R Area 1	20	10-20
							R SPL (7A)	20	10-20
4.51	3.33	0	1	24	-42	52	**Assigned to R Area 2**	80	60-100
							R SPL (7PC)	50	20-60
							R SPL (5L)	10	0-60
							R Area 4p	10	0-60
							R Area 1	10	10-60
							R Area 3b	10	10-60
4.44	3.29	0	4	8	60	6	(Right Superior Medial Gyrus)**		
4.41	3.28	0.001	1	28	2	50	(Right Middle Frontal Gyrus)**		
4.37	3.26	0.001	1	-24	-12	-26	**Assigned to L Hipp (CA)**	90	50-100
							L Hipp (FD)	70	60-70
							L Hipp (SUB)	70	30-100
							L Amyg (LB)	50	20-70
4.34	3.24	0.001	2	-54	-16	0	L TE 1.2	20	10-30
							L TE 1.0	20	10-30
4.3	3.23	0.001	1	-24	-40	42	L hIP1	10	0-10
4.21	3.18	0.001	1	-26	-62	-2	L Area 17	20	10-20
							L hOC3v (V3v)	10	10-10
4.17	3.16	0.001	1	12	62	14	(Right Superior Medial Gyrus)**		
4.15	3.15	0.001	1	-26	-38	44	L SPL (5L)	10	0-10
							L Area 2	10	0-10
							L Area 3a	10	0-30
							L hIP3	10	0-10
4.06	3.11	0.001	1	14	54	16	(Right Superior Medial Gyrus)**		
4.06	3.11	0.001	1	-18	-76	-2	**Assigned to L hOC4v (V4)**	40	30-70
							L hOC3v (V3v)	40	10-50
							L Area 18	10	0-20

Table 15.4 CPs – Word; Orthography covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**
T	**Z**	**p**	**k**	**x**	**y**	**z**	
4.36	3.25	0.001	2	26	50	-16	(Right Middle Orbital Gyrus)**
4.19	3.17	0.001	1	-30	6	-30	L Sup. Temporal Pole**

CPs correlation analysis for Pseudowords

Table 15.5 CPs – Pseudoword; PA covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological areas		
							Cerebellar areas		
6.18	3.98	0	13	-14	-70	-30	**Assigned to L Lobule VI (Hem)**	86	25-95
							L Lobule VIIa Crus I (Hem)	4	1-54
6.5	4.09	0	23	-2	-52	-38	**Assigned to L Lobule IX (Vermis)**	81	72-93
							L Lobule X (Vermis)	11	5-12
							L Lobule IX (Hem)	6	0-17
							Other areas		
5.49	3.73	0	9	32	-62	24	R hIP1	10	0-10
4.68	3.4	0	10	-12	-80	48	**Assigned to L SPL (7P)**	50	20-50
							L SPL (7A)	10	10-30
							Areas with too low voxel threshold		
4.71	3.41	0	1	40	-36	-18	(Right Fusiform Gyrus)**		
4.41	3.28	0.001	3	-30	-66	-30	**Assigned to L Lobule VIIa Crus I (Hem)**	98	78- 99
5.45	3.72	0	3	-38	-46	46	**Assigned to L hIP2**	30	20-40
							L hIP1	30	30-50
							L hIP3	30	0-40
							L SPL (7PC)	20	10-20
							L SPL (5L)	10	0-10
							L Area 2	10	0-10
							L Lobule VI (Hem)	2	0-22
4.07	3.11	0.001	1	-16	-44	-42	L Lobule IX (Hem)	2	0-13
							L Lobule X (Hem)	1	0-8
4.81	3.46	0	3	-40	-82	6	L hOC5 (V5)	10	0-20
4.07	3.11	0.001	1	-12	0	18	(Left Caudate Nucleus)**		
4.7	3.41	0	1	10	56	-14	(Right Mid Orbital Gyrus)**		

Table 15.6 CPs – Pseudoword; PF covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological areas		
							Language processing areas		
7.02	4.24	0	26	-44	-38	-14	(Left Inferior Temporal Gyrus)**		
							Areas with too low voxel threshold		
4.25	3.2	0.001	1	-14	-14	50	L Area 6	20	10-40
4.23	3.19	0.001	1	18	-8	48	R Area 6	20	10-20
4.24	3.2	0.001	3	-34	6	-16	L Insula**		
4.1	3.13	0.001	1	28	-14	20	R Insula**		
4.48	3.31	0	2	-16	-26	-18	**Assigned to L Hipp (SUB)**	90	0-90
							L Lobules I-IV (Hem)	1	0-4
4.37	3.26	0.001	1	-20	-46	40	L SPL (7A)	10	0-10
							L SPL (5Ci)	10	0-10
4.35	3.25	0.001	1	-38	-42	6	L Sup. Temporal **		

Table 15.7 CPs – Pseudowords; Digit Span (z-scores) covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.21	3.62	0	6	-54	-14	-16	(Left Middle Temporal Gyrus)**		
5.04	3.55	0	23	-48	10	40	**Assigned to L Area 44**	40	20-50
4.63	3.38	0	10	-52	-20	32	**Assigned to L IPC (PFt)**	70	60-70
							L Area 2	20	10-20
							L Area 1	10	10-10
							L OP 4	10	10-10
							L OP 1	10	0-20
							L Area 3b	10	10-30
							Other Areas		
6.79	4.17	0	105	32	-42	30	R hIP2	10	0-10
6.22	3.99	0	105	24	-38	40	R SPL (7PC)	10	0-20
7.39	4.35	0	59	6	-14	18	(Right Thalamus)**		
5.27	3.65	0	54	26	-62	26	(Right Cuneus)**		
5.47	3.73	0	12	-50	-2	28	**Assigned to L Area 4p**	30	10-30
							L Area 4a	20	0-20
							L Area 3a	10	0-30
							L Area 44	10	10-10
4.4	3.27	0	15	-2	-50	20	(Left Posterior Cingulate Cortex)**		
4.21	3.18	0	6	8	-46	14	(Right Precuneus)**		
8.17	4.55	0	105	20	-50	40	R Precunes**		
7.12	4.27	0	54	30	-52	24	R Precunes**		
6.6	4.12	0	10	-20	22	28	L Mid. Frontal Gyrus**		
							Areas with voxel number threshold too low		
5.55	3.76	0	4	-16	12	50	L Area 6	10	0-10
4.7	3.41	0	2	-16	-14	48	L Area 6	10	0-20
4.41	3.28	0	3	18	-58	-40	(Right Cerebellum)**		
5.23	3.63	0	3	-22	-70	26	(Left Superior Occipital Gyrus)**		
4.46	3.3	0	2	-28	-50	36	L SPL (7A)	10	0-10
							L hIP1	10	10-20
							L hIP3	10	0-20
4.33	3.24	0	1	-18	-20	50	L Area 4p	10	10-10
							L Area 6	10	0-10
4.25	3.2	0	1	-22	-88	18	L Area 18	10	0-30
4.22	3.19	0	2	-30	30	40	(Left Middle Frontal Gyrus)**		
4.08	3.12	0	1	14	50	34	(Right Superior Frontal Gyrus)**		

Table 15.8 CPs – Pseudoword; Orthography covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Other areas		
5.3	3.66	0	17	-20	-66	58	**Assigned to L SPL (7A)**	50	20-90
							L SPL (7P)	30	10-40
4.23	3.19	0.001	17	-22	-66	50	**Assigned to L SPL (7A)**	50	20-60
							L hIP3	10	0-20
							Areas with too low voxel threshold		
4.23	3.19	0.001	2	-16	-2	66	**Assigned to L Area 6**	40	40-70
4.55	3.34	0	3	-26	-50	-34	L Lobule VI (Hem)	22	0-71
4.37	3.26	0.001	1	-14	-66	-28	**Assigned to L Lobule VI (Hem)**	34	10-75
4.03	3.09	0.001	1	30	-64	-50	**Assigned to R Lobule VIIb (Hem)**	38	2-40
							R Lobule VIIa Crus II (Hem)	7	0-11
							R Lobule VIIIa (Hem)	3	0-50
4.7	3.41	0	4	-38	-20	-18	**Assigned to L Hipp (CA)**	40	30-60
							L Hipp (FD)	30	10-30
4.67	3.4	0	5	-30	-40	40	**Assigned to L hIP1**	20	0-20
							L hIP3	20	10-20
							L SPL (7PC)	10	0-20

DPs correlation analysis for Words

Table 15.9 DPs – Word; PA covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
8.03	4.52	0	155	-46	-28	-14	L Mid. Temporal **		
							Cerebellar Areas		
6.82	4.18	0	42	10	-42	-38	R Lobule IX (Hem)	0	0-34
4.85	3.47	0	42	0	-38	-38	Vermis_10**		
							Other areas		
11.65	5.24	0	155	-52	-26	-20	(Left Inferior Temporal Gyrus)**		
7.39	4.35	0	155	-44	-24	-22	(Left Inferior Temporal Gyrus)**		
5.19	3.62	0	6	14	-90	-16	R Area 17	10	0-20
							R Area 18	10	0-30
5	3.54	0	21	-34	-8	-18	L Hipp (CA)	30	0-30
							L Amyg (LB)	20	0-50
							Areas with too low voxel threshold		
4.16	3.16	0.001	1	-56	-54	44	**Assigned to L IPC (PFm)**		
							L IPC (PFm)	60	0-60
							L IPC (PGa)	30	0-40
							L IPC (PF)	20	0-30
4.1	3.13	0.001	2	-52	-54	46	**Assigned to L IPC (PFm)**	70	50-70
							L IPC (PGa)	50	40-50
							L IPC (PF)	30	0-30
4.19	3.17	0.001	1	38	2	-30	R Amyg (LB)	20	0-40
4.15	3.15	0.001	1	-20	-30	0	(Left Thalamus)		

Table 15.10 DPs – Word; PF covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**
T	**Z**	**p**	**k**	**x**	**y**	**z**	
							Phonological Areas
5.74	3.83	0	49	-48	2	-24	(Left Middle Temporal Gyrus)**
4.97	3.53	0	49	-46	-2	-16	(Left Middle Temporal Gyrus)**
4.41	3.28	0.001	7	-46	-34	-14	L Middle Temporal Gyrus**
							Other Areas
5.9	3.88	0	14	-44	-16	-22	(Left Inferior Temporal Gyrus)**
4.63	3.38	0	7	-48	-42	-14	(Left Inferior Temporal Gyrus)**
4.67	3.4	0	10	-36	8	-18	L Superior Temporal Pole **

Table 15.11 DPs – Words; Digit Span (z-scores) covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
4.69	3.41	0	24	-38	14	-22	(Left Temporal Pole)		
							Areas with too small number of voxels		
4.57	3.35	0	3	-42	0	-28	(Left Middle Temporal Gyrus)**		
4.32	3.23	0.001	4	50	-72	32	R IPC (PGp)	90	80-90
4.06	3.11	0.001	3	-2	-98	-10	**Assigned to L Area 17**	30	0-70
							L Area 18	10	0-10

Table 15.12 DPs – Word; Orthography covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological areas		
7.01	4.24	0	27	18	2	58	R Area 6	20	10-40
5.04	3.55	0	21	-42	-54	54	L IPC (PGa) (L Angular Gyrus)	30	0-30
							L hIP1	30	20-30
							L hIP3	20	10-20
							L SPL (7PC)	10	10-20
							L IPC (PFm)	10	0-30
							L IPC (PF)	10	0-10
5.11	3.58	0	33	-50	-4	-22	(Left Middle Temporal Gyrus)**		
4.34	3.25	0	9	-54	-56	44	**Assigned to L IPC (PFm)**	60	50-60
							L IPC (PGa)	40	40-50
							L IPC (PF)	10	0-20
4.92	3.51	0	22	64	-54	26	(Right Angular Gyrus)**		
							Other areas		
4.77	3.44	0	21	-42	-32	-16	(Left Inferior Temporal Gyrus)**		
4.51	3.32	0	21	-48	-24	-22	(Left Inferior Temporal Gyrus)**		
4.77	3.44	0	8	-34	-48	30	L hIP1	30	20-50
7.57	4.4	0	75	28	-70	58	**Assigned to R SPL (7A)**	40	30-60
4.23	3.19	0	6	-42	-42	60	**Assigned to L Area 2**	60	40-60
							L Area 1	30	20-50
							L SPL (7PC)	20	10-30
							L SPL (5L)	10	0-10
							Areas with too low voxel threshold		
4.06	3.11	0	1	-26	-50	-34	L Lobule VI (Hem)	22	0-71
4.17	3.16	0	1	38	20	52	(Right Middle Frontal Gyrus)**		
4.05	3.1	0	1	-42	-20	-24	(Left Inferior Temporal Gyrus)**		
4.46	3.3	0	1	-28	-20	-26	**Assigned to L Hipp (EC)**	30	0-40
							L Hipp (SUB)	20	0-70
							L Hipp (CA)	10	0-30
4.37	3.26	0	5	-18	-56	48	L SPL (7P)	10	10-20
							L hIP3	10	0-10
4.22	3.19	0	1	-42	-12	-20	L Inf. Temporal Gyrus**		
4.13	3.14	0	4	-20	-60	32	L Mid. Occipital Gyrus**		

DPs correlation analysis for Pseudowords

Table 15.13 DPs – Pseudoword; PA covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
6.26	4.01	0	87	-52	-30	-16	(Left Middle Temporal Gyrus)**		
							Cerebellar areas		
5.27	3.65	0	28	-6	-44	-36	L Lobule IX (Hem)	23	12-58
							L Lobule X (Hem)	0	0-9
4.92	3.51	0	19	18	-58	-46	R Lobule VIIIb (Hem)	28	14-48
							R Lobule IX (Hem)	20	1-29
							Other areas		
8.18	4.55	0	87	-38	-28	-18	L Hipp (CA)	10	0-40
							Areas with too small voxel number		
4.37	3.26	0.001	1	-50	-18	-22	(L Middle Temporal Gyrus)**		
4.07	3.11	0.001	2	-42	0	-26	L Middle Temporal Gyrus**		
4.23	3.19	0.001	3	-34	-8	-24	L Fusiform Gyrus**		
4.3	3.23	0.001	2	-44	8	-22	(Left Temporal Pole)**		
4.23	3.19	0.001	4	16	-90	-14	**Assigned to R Area 18**	30	10-70
							R Area 17	20	0-50
4.4	3.27	0.001		4	-38	-36	R Vermis_10**		

Table 15.14 DPs – Pseudoword; PF covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.12	3.59	0	38	20	8	68	R Area 6	10	0-20
4.85	3.48	0	7	-50	-34	-16	Left Middle Temporal Gyrus**		
							Cerebellar Areas		
4.95	3.52	0	36	-32	-62	-32	**Assigned to L Lobule VIIa Crus I (Hem)**	82	58-99
							L Lobule VI (Hem)	18	0-42
4.36	3.25	0.001	36	-36	-58	-38	L Lobule VIIa Crus I (Hem)	11	11-58
							Other areas		
4.52	3.33	0	10	20	48	16	R Sup. Frontal Gyrus**		
4.15	3.15	0.001	10	18	50	8	R Sup. Frontal Gyrus**		
							Areas with too low voxel threshold		
5.28	3.65	0	2	-20	-18	50	L Area 6	30	10-60
							L Area 4p	10	0-10
4.67	3.4	0	4	16	-84	-44	**Assigned to R Lobule VIIa Crus II (Hem)**	92	56-99
4.15	3.16	0.001	1	20	-60	-50	**Assigned to R Lobule VIIIb (Hem)**	45	35-57
4.28	3.22	0.001	3	-54	-50	-14	(Left Inferior Temporal Gyrus)**		

Table 15.15 DPs – Pseudowords; Digit Span (z-scores) covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Areas with too small number of voxels		
4.26	3.21	0.001	1	-46	36	4	L Area 45	10	0-20
4.07	3.11	0.001	1	-30	-42	-22	(Left Fusiform Gyrus)**		
4.38	3.26	0.001	2	-2	-98	-6	Assigned to L Area 17	70	60-80
							L Area 18	50	10-60
4.14	3.15	0.001	1	0	-94	-10	Assigned to Area 17	60	40-80
							Area 18	40	10-80

Table 15.16 DPs – Pseudoword; Orthography covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.32	3.67	0	14	-46	-60	46	**Assigned to L IPC (PGa)**	70	60-70
							L IPC (PFm)	50	30-50
							L hIP1	20	10-30
5	3.54	0	10	-18	-18	52	L Area 6	30	10-40
							L Area 4p	10	0-10
							L Area 4a	10	0-10
4.92	3.51	0	7	-38	-30	-20	(Left Fusiform Gyrus)**		
4.88	3.49	0	19	-46	-56	-2	(Left Middle Temporal Gyrus)**		
4.77	3.44	0	11	16	2	56	R Area 6	10	10-20
4.39	3.27	0	14	44	-46	30	R IPC (PFm)	10	0-20
							R hIP1	30	0-30
							R hIP2	10	0-20
							Cerebellar Areas		
6.15	3.97	0	28	-36	-58	-38	L Lobule VIIa Crus I (Hem)	11	11-58
4.65	3.39	0	9	-36	-66	-32	**Assigned to L Lobule VIIa Crus I (Hem)**	95	95-100
							L SPL (7P)	10	0-20
							L hIP3	10	10-10
							Other Areas		
4.61	3.37	0	22	30	-68	48	R SPL (7A)	20	10-20
							R SPL (7P)	10	0-20
							R hIP3	10	10-10
5.32	3.67	0	33	24	-70	60	**Assigned to R SPL (7P)**	60	30-80
							R SPL (7A)	40	20-70
							R hIP3	10	10-10
5.02	3.54	0	40	-20	-54	50	**Assigned to L SPL (7P)**	20	0-20
							L SPL (7A)	10	0-20
							L SPL (7PC)	10	10-10
							L SPL (5L)	10	0-10
							L hIP3	10	0-30
4.47	3.31	0	40	-20	-68	42	L SPL (7A)	10	10-40
							L hIP3	10	0-10
4.37	3.26	0	6	-44	-42	46	**Assigned to L hIP2**	30	10-40
							L hIP3	20	10-30
							L SPL (7PC)	10	10-10
							L SPL (5L)	10	0-10
							L Area 2	10	0-30
							Areas with the voxel number threshold too low		
4.27	3.21	0	1	-58	-32	-16	(Left Middle Temporal Gyrus)		
4.26	3.2	0	2	18	16	64	R Area 6	30	0-30
4.03	3.09	0	1	-54	-48	44	**Assigned to L IPC (PFm)**	60	60-60
							L IPC (PGa)	10	10-30
							L IPC (PF)	30	20-40
4.52	3.33	0	1	-52	8	24	**Assigned to L Area 44**	60	50-60
							L Area 3b	10	10-10
4.07	3.11	0	2	28	-66	-32	**Assigned to R Lobule VIIa Crus I (Hem)**	75	74-98
							R Lobule VI (Hem)	24	0-24
5.03	3.55	0	4	42	-54	-48	**Assigned to R Lobule VIIa Crus I (Hem)**	46	36-62
							R Lobule VIIa Crus II (Hem)	42	6-57

Table 15.16 DPs – Pseudoword; Orthography covariance with BOLD - continuation

				MNI			Area (labelled with anatomy toolbox) or AAL**	P$	R$
T	**Z**	**p**	**k**	**x**	**y**	**z**			
4.19	3.17	0	3	-32	-54	-34	L Lobule VI (Hem)	84	25-98
							L Lobule VIIa Crus I (Hem)	16	2-74
4.66	3.39	0	5	-12	-70	-34	(Left Cerebellum)**		
4.44	3.29	0	2	-48	-78	6	L hOC5 (V5)	20	10-40
4.29	3.22	0	2	20	-56	44	R hIP1	10	0-20
4.28	3.22	0	3	-38	-52	30	L hIP1	30	20-40
							L hIP2	10	0-10
							L hIP3	10	0-20
4.08	3.12	0	3	-10	-60	50	L SPL (7A)	50	30-50
							L SPL (7P)	20	10-30
4.08	3.12	0	1	16	18	62	(Right SMA)	30	0-30
4.74	3.43	0	2	-28	-8	-26	**Assigned to L Hipp (CA)**	80	0-80
							L Amyg (LB)	70	0-80
							L Hipp (SUB)	30	0-50
							L Hipp (FD)	20	0-30
							L Amyg (SF)	10	0-10

Correlations with Literacy measures
CPs correlation analysis for BOLD for Words

Table 15.17 CPs – Words; TOWRE z-scores covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.72	3.82	0	26	22	34	42	R Area 6	10	10-10
4.48	3.31	0	6	-46	2	46	**Assigned to L Area 6**	40	20-70
6.95	4.22	0	33	-46	-36	32	L IPC (PFcm)	30	0-30
							L IPC (PF)	10	0-30
5.38	3.69	0	49	-48	18	30	**Assigned to L Area 44**	60	20-70
							L Area 45	50	10-50
5.88	3.87	0	11	-58	12	22	**Assigned to L Area 44**	50	30-60
							L Area 45	20	10-30
							L Area 3b	10	10-10
5.24	3.64	0	61	38	-64	46	R IPC (PGa)	10	0-20
							R SPL (7P)	10	0-10
							R hIP3	10	0-20
4.54	3.34	0	14	56	-62	12	R IPC (PGp)	20	0-30
4.25	3.2	0.001	14	54	-52	14	(Right Middle Temporal Gyrus)**		
							Other areas		
7.26	4.31	0	111	-36	42	22	(Left Middle Frontal Gyrus)**		
4.13	3.14	0.001	33	-42	-42	28	L hIP2	20	10-20
							L hIP1	20	10-20
6.93	4.22	0	27	8	44	2	(Right Anterior Cingulate Cortex)**		
6.31	4.02	0	63	34	46	28	(Right Middle Frontal Gyrus)**		
4.55	3.34	0	63	30	42	22	(Right Middle Frontal Gyrus)**		
6.02	3.92	0	32	40	-50	50	**Assigned to R hIP3**	40	10-40
							R hIP2	30	10-30
							R SPL (7PC)	20	0-30
							R hIP1	20	10-30
							R SPL (7A)	10	0-20
6	3.92	0	71	-26	-62	52	**Assigned to L SPL (7A)**	30	30-60
							L hIP3	20	10-30
5.14	3.59	0	31	-36	48	10	(Left Middle Frontal Gyrus)**		
4.39	3.27	0.001	31	-32	42	4	(Left Middle Frontal Gyrus)**		
5	3.54	0	14	-28	32	30	(Left Middle Frontal Gyrus)**		
4.78	3.45	0	10	2	18	22	(Right Anterior Cingulate Cortex)**		
4.62	3.37	0	12	-18	-4	0	(Left Pallidum)**		
4.58	3.36	0	9	12	64	-2	(Right Mid Orbital Gyrus)**		
4.53	3.33	0	10	18	60	-6	(Right Superior Orbital Gyrus)**		
6.41	4.06	0	33	-14	14	0	L Putamen**		
6.28	4.01	0	33	10	-12	-8	R Thalamus**		
4.75	3.43	0	33	16	-18	-8	R Thalamus**		
5.07	3.57	0	43	-4	-22	-12	L Thalamus**		
4.74	3.43	0	43	10	-20	-10	R Thalamus**		
							Areas with the voxel number threshold too low		
4.17	3.16	0.001	3	34	22	-4	(Right Insula Lobe)**		
4.22	3.19	0.001	1	-40	14	28	**Assigned to L Area 44**	50	20-70
4.1	3.13	0.001	1	58	20	26	**Assigned to R Area 45**	80	60-80
							R Area 44	30	30-50
4.47	3.3	0	4	52	12	0	**Assigned to R Area 44**	50	20-50
							R Area 45	10	0-10
4.22	3.19	0.001	2	-36	34	-20	(Left Inferior Frontal Gyrus (p. Orbitalis))**		

Table 15.17 CPs – Words; TOWRE z-scores covariance with BOLD - continuation

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
4.07	3.12	0.001	1	-38	16	16	(Left Inferior Frontal Gyrus (p. Opercularis))**		
4.42	3.28	0.001	3	-40	-62	-20	(Left Fusiform Gyrus)**		
4.04	3.1	0.001	1	58	-54	36	**Assigned to R IPC (PFm)**	70	30-80
							R IPC (PGa)	60	50-90
							R IPC (PGp)	10	0-10
4.29	3.22	0.001	5	-34	-56	-28	**Assigned to L Lobule VI (Hem)**	77	65-94
							L Lobule VIIa Crus I (Hem)	23	6-35
4.33	3.24	0.001	1	-42	-60	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	100	73-100
4.18	3.17	0.001	1	-66	-20	4	**Assigned to L TE 3**	100	60-100
							L OP 1	10	0-10
4.7	3.41	0	1	10	24	22	(Right Anterior Cingulate Cortex)**		
4.58	3.36	0	1	-34	-32	16	Assigned to L TE 1.1	40	20-60
							L OP 1	20	10-30
4.54	3.34	0	3	34	-74	-20	**Assigned to R hOC4v (V4)**		
							R hOC4v (V4)	30	0-60
4.43	3.29	0.001	1	-40	-44	26	L hIP1	20	0-20
4.39	3.27	0.001	1	28	22	60	(Right Superior Frontal Gyrus)**		
4.34	3.24	0.001	2	14	-52	40	(Right Precuneus)		
4.32	3.24	0.001	1	22	50	42	(Right Superior Frontal Gyrus)**		
4.32	3.24	0.001	1	26	20	-4	(Right Putamen)**		
4.31	3.23	0.001	1	-30	32	38	(Left Middle Frontal Gyrus)**		
4.28	3.22	0.001	3	32	-8	-14	**Assigned to R Amyg (LB)**	50	20-80
							R Amyg (CM)	40	10-60
							R Hipp (CA)	10	0-40
4.25	3.2	0.001	2	30	4	52	(Right Middle Frontal Gyrus)**		
4.22	3.19	0.001	3	46	14	48	(Right Middle Frontal Gyrus)**		
4.19	3.17	0.001	1	20	48	44	(Right Superior Frontal Gyrus)**		
4.18	3.17	0.001	4	-8	-76	16	**Assigned to L Area 17**	50	40-60
							L Area 18	20	10-40
4.15	3.15	0.001	1	12	6	12	(Right Caudate Nucleus)**		
4.15	3.15	0.001	1	30	44	14	(Right Middle Frontal Gyrus)**		
4.08	3.12	0.001	1	26	-44	48	Assigned to R Area 2	50	20-70
							R SPL (7PC)	30	20-60
							R SPL (5L)	10	0-30
							R Area 1	10	10-10
							R hIP3	10	0-30
4.06	3.11	0.001	2	32	-6	-10	**Assigned to R Amyg (CM)**	40	0-60
							R Area 6	10	0-10
4.7	3.41	0	5	-26	-10	-26	**Assigned to L Hipp (CA)**	80	70-80
							L Amyg (LB)	60	30-90
							L Hipp (FD)	50	20-70
							L Hipp (SUB)	40	10-100
5.29	3.66	0	5	-16	-76	16	L Area 17	20	20-40
5.26	3.64	0	5	38	54	-6	(Right Middle Orbital Gyrus)**		

Table 15.18. CPs – Words; WRAT Spelling z-scores covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.85	3.87	0	24	44	-2	-16	R Insula (Id1)	30	10-50
5.12	3.59	0	48	42	-14	6	R Insula (Ig2)	20	10-50
6.18	3.98	0	211	-34	-58	-2	L Fusiform Gyrus**		
4.95	3.52	0	20	28	-46	-18	(Right Fusiform Gyrus)**		
							Cerebellar Areas		
5.01	3.54	0	33	-14	-32	-24	**Assigned to L Lobules I-IV (Hem)**	45	0-96
5.46	3.72	0	8	-8	-44	-36	L Lobule IX (Hem)	13	13-58
4.59	3.36	0	33	-20	-34	-18	L Lobule V	8	0-27
							Magnocellular Areas		
4.94	3.51	0	25	38	-70	6	R hOC5 (V5)	10	0-10
							Other areas		
4.22	3.19	0.001	211	-44	-60	-8	(Left Inferior Temporal Gyrus)**		
5.98	3.91	0	35	-38	-8	14	**Assigned to L OP 3**	60	40-80
							L OP 4	20	10-20
5.29	3.66	0	48	40	-10	14	**Assigned to R OP 3**	80	50-90
							OP 4	20	10-30
							R Insula (Ig2)	20	0-20
4.39	3.27	0.001	24	36	-2	-18	R Amyg (LB)	10	0-40
							R Amyg (SF)	10	0-10
5.41	3.7	0	12	38	-50	66	(Right Superior Parietal Lobule)**		
5.34	3.67	0	24	36	-32	-12	**Assigned to R Hipp (CA)**	50	20-100
							R Hipp (FD)	10	0-30
4.86	3.48	0	10	24	14	12	R Caudate**		
4.85	3.47	0	7	-28	-64	14	L Calcarine**		
6.63	4.13	0	211	-32	-70	2	L Mid Occipital Gyrus**		
5.39	3.69	0	11	-34	-30	-4	L Hippocampus**		
							Areas with voxels with too low threshold number		
4.49	3.32	0	3	-12	-18	46	**Assigned to Area 6**	30	20-40
							SPL (5Ci)	10	0-10
							Area 4a	10	0-10
4.04	3.1	0.001	1	16	-2	46	Area 6	20	0-20
4.07	3.11	0.001	1	-36	-2	18	(Left Insula Lobe)**		
4.25	3.2	0.001	1	42	14	-12	(Right Insula Lobe)**		
4.1	3.13	0.001	1	24	-56	-48	**Assigned to Lobule VIIIb (Hem)**	33	5-59
							Lobule VIIIa (Hem)	15	0-39
4.45	3.3	0	5	30	-40	0	**Assigned to R Hipp (CA)**	80	40-100
4.23	3.19	0.001	5	-30	-74	-14	**Assigned to L hOC4v (V4)**	40	40-50
5.31	3.66	0	1	-32	-66	10	L Area 17	10	10-10
5	3.54	0	2	34	-36	14	R TE 1.1	10	0-20
4.71	3.41	0	2	30	-20	-24	**Assigned to R Hipp (SUB)**	90	30-100
							R Hipp (FD)	10	0-40
							Hipp (CA)	10	0-50
4.59	3.36	0	1	-28	-22	-22	**Assigned to Hipp (SUB)**	60	30-90
							Hipp (FD)	20	0-70
4.43	3.29	0.001	1	22	20	14	(Right Caudate Nucleus)		
4.27	3.21	0.001	1	62	-32	48	(Right SupraMarginal Gyrus)**		
4.24	3.2	0.001	1	28	-42	56	**Assigned to Area 2**	100	70-100
							SPL (7PC)	20	10-30
							SPL (7A)	10	0-10
							SPL (5L)	10	10-10
							Area 4p	10	10-10
							Area 3b	10	10-30
4.24	3.2	0.001	2	16	-60	12	**Assigned to Area 17**	30	10-70
							Area 18	20	10-50
4.22	3.19	0.001	1	-28	-48	-6	(Left Lingual Gyrus)		
4.21	3.18	0.001	1	-54	0	0	TE 1.2	20	0-30

Table 15.18 CPs – Words; WRAT Spelling z-scores covariance with BOLD - continuation

				MNI			Area (labelled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
4.21	3.18	0.001	1	-26	-46	-8	(Left Lingual Gyrus)		
4.13	3.14	0.001	1	6	32	-2	(Right Anterior Cingulate Cortex)**		

Table 15.19 CPs – Words; Irregulars Composite scores covariance with BOLD

				MNI			Area (labelled with anatomy toolbox) or AAL**
T	**Z**	**p**	**k**	**x**	**y**	**z**	
							Other areas
4.42	3.28	0.001	12	-20	40	-10	L Mid. Orb. Frontal Gyrus**
							Areas with voxels with too low threshold number
5.34	3.68	0	5	-28	28	40	(Left Middle Frontal Gyrus)**
4.59	3.36	0	1	12	46	4	(Right Superior Medial Gyrus)**

CPs correlation analysis for BOLD for Pseudowords

Table 15.20 CPs – Pseudowords; Pseudoword Composite scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
							Cerebellar Areas		
6.94	4.22	0	61	4	-50	-50	**Assigned to R Lobule IX (Hem)**	97	62-100
5.21	3.62	0	61	0	-48	-42	**Assigned to Lobule X (Vermis)**	52	11-52
							Lobule IX (Vermis)	26	11-70
							Lobule IX (Hem)	18	17-56
							Lobule X (Hem)	0	0-3
							Other areas		
4.82	3.46	0	6	-38	-80	6	(Left Middle Occipital Gyrus)**		
4.24	3.2	0	6	-34	-48	52	**Assigned to L SPL (7PC)**	50	20-60
							L hIP3	40	30-50
							L Area 2	30	10-50
							L SPL (7A)	30	10-40
							L SPL (5L)	10	0-10
							L Area 1	10	0-20
							Areas with voxel number threshold too low		
4.91	3.5	0	3	-8	-72	-26	Assigned to L Lobule VI (Hem)	64	35-87
4.19	3.17	0	1	-18	-86	16	L Area 17	10	0-10

Table 15.21 CPs – Pseudowords; WRAT Spelling z-scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.02	3.55	0	23	-52	8	30	L Area 44	20	10-50
							L Area 6	10	0-10
							L Area 3b	10	10-10
5.11	3.58	0	9	48	32	-16	(Right Inferior Frontal Gyrus (p. Orbitalis))**		
4.78	3.44	0	7	40	14	-12	(Right Insula Lobe)**		
							Cerebellar Areas		
7.45	4.36	0	62	-14	-32	-28	L Lobules I-IV (Hem)	0	0-10
5.47	3.72	0	62	-10	-32	-18	L Lobules I-IV (Hem)	18	0-88
5.38	3.69	0	62	-12	-42	-32	L Lobules I-IV (Hem)	1	0-2
5.52	3.75	0	15	26	-28	-30	**Assigned to R Lobules I-IV (Hem)**	56	0-79
							R Lobule V	14	0-36
							Magnocellular areas		
4.89	3.49	0	30	-40	-68	2	L hOC5 (V5)	20	10-50
							Other areas		
6.14	3.96	0	110	-52	-64	-12	(Left Inferior Temporal Gyrus)**		
4.99	3.53	0	110	-56	-54	-16	(Left Inferior Temporal Gyrus)**		
6.03	3.93	0	15	-30	-30	-10	**Assigned to L Hipp (FD)**	100	20-100
							L Hipp (CA)	80	60-90
5.46	3.72	0	8	62	-32	48	(Right SupraMarginal Gyrus)**		
5.36	3.68	0	22	-28	-78	10	(Left Middle Occipital Gyrus)**		
5.14	3.6	0	7	-24	-42	-8	(Left ParaHippocampal Gyrus)**		
4.99	3.53	0	17	50	-8	-4	R TE 1.0	20	0-30
4.95	3.52	0	30	-40	-76	-2	(Left Middle Occipital Gyrus)**		
4.86	3.48	0	7	24	16	-6	(Right Putamen)**		
5.37	3.69	0	22	34	38	4	R Mid. Frontal Gyrus**		
							Areas with voxel number threshold too low		
4.4	3.27	0	2	-56	-22	20	**Assigned to L OP 1**	60	40-60
							L IPC (PFop)	50	30-60
							L OP 4	10	0-10
4.23	3.19	0	1	-62	-14	32	**Assigned to L Area 1**	40	30-50
							L IPC (PFt)	30	0-40
							L Area 2	20	10-30
							L OP 4	20	10-40
							L IPC (PFop)	20	0-20
							L IPC (PF)	10	0-10
							L Area 3b	10	10-20
4.12	3.14	0	2	36	-28	22	R TE 1.1	20	0-20
							R OP 1	20	0-30
							R IPC (PFcm)	10	0-30
4.1	3.13	0	1	40	0	-16	R Insula (Id1)	10	0-20
5.17	3.61	0	4	34	34	-10	(Right Inferior Frontal Gyrus (p. Orbitalis))**		
4.47	3.31	0	1	30	-28	20	R OP 1	10	0-10
4.2	3.18	0	2	20	26	-14	(Right Superior Orbital Gyrus)**		
4.19	3.17	0	2	36	-22	26	R OP 3	20	0-20
4.15	3.15	0	1	38	-24	-10	R Hipp (CA)	20	0-60
4.13	3.14	0	1	12	38	2	(Right Anterior Cingulate Cortex)**		
4.11	3.13	0	1	44	-16	-24	(Right Inferior Temporal Gyrus)**		
4.03	3.09	0	1	18	20	-6	(Right Caudate Nucleus)**		

Table 15.22 CPs – Pseudowords; Irregulars Composite scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
							Cerebellar Areas		
4.87	3.48	0	17	38	-68	-22	R Lobule VIIa Crus I (Hem)	11	0-13
							R hOC4v (V4)	10	0-10
							R Lobule VI (Hem)	1	0-1
							Other areas		
5.23	3.63	0	12	-38	-20	-14	L Hipp (CA)	40	10-60
							L Hipp (FD)	20	0-20
8.62	4.66	0	15	-22	-36	14	L Hippocampus**		
							Areas with voxel number threshold too low		
4.39	3.27	0	5	-40	-68	-20	L hOC4v (V4)	10	0-20
							L Lobule VIIa Crus I (Hem)	3	0-7
4.09	3.12	0	1	26	-58	30	R SPL (7A)	10	0-10
							R hIP1	10	0-10
4.05	3.1	0	1	36	-46	50	**Assigned to R hIP3**	40	30-60
							R SPL (7PC)	40	30-40
							R Area 2	20	0-30
							R hIP1	10	0-20
8.61	4.66	0	2	42	-30	-18	(Right Fusiform Gyrus)**		
4.41	3.28	0	3	42	-2	-32	(Right Inferior Temporal Gyrus)**		

DPs correlation analysis for BOLD for Words

Table 15.23 DPs – Words; TOWRE z-scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Areas with too small number of voxels		
4.1	3.13	0.001	1	-38	12	-18	L Sup. Temporal Pole**		

Table 15.24 DPs – Words; WRAT Spelling z-scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
5.01	3.54	0	23	64	-50	26	**Assigned to R IPC (PFm)**	50	0-60
							R IPC (PGa)	30	0-60
							Cerebellar Areas		
5.66	3.8	0	13	10	-40	-36	R Cerebellum_9**		
							Other areas		
6.85	4.19	0	58	-48	-22	-22	(Left Inferior Temporal Gyrus)**		
5.34	3.67	0	58	-46	-30	-20	(Left Inferior Temporal Gyrus)**		
4.72	3.42	0	58	-54	-32	-20	(Left Inferior Temporal Gyrus)**		
4.3	3.23	0.001	6	40	20	52	(Right Middle Frontal Gyrus)**		
							Areas with too small number of voxels		
4.6	3.36	0	3	42	-82	32	**Assigned to R IPC (PGp)**	80	0-90
4.24	3.2	0.001	2	22	10	62	R Area 6	10	10-10
4.17	3.16	0.001	1	34	-70	54	**Assigned to R IPC (PGp)**	20	10-30
							R hIP3	20	0-20
							R SPL (7A)	20	0-40
							R SPL (7P)	20	0-20
4.99	3.53	0	4	-34	-52	28	L hIP1	30	0-40
							L hIP2	10	0-10
4.23	3.19	0.001	1	28	-70	58	**Assigned to R SPL (7A)**	40	30-60
							R SPL (7P)	30	30-40
							R hIP3	20	10-20
4.13	3.15	0.001	1	-58	-36	-20	(Left Inferior Temporal Gyrus)**		

Table 15.25 DPs – Words; Irregulars Composite scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological Areas		
4.59	3.36	0	7	-64	-54	20	**Assigned to L IPC (PFm)**	40	0-40
							L IPC (PGa)	20	0-30
							Areas with too small number of voxels		
4.47	3.31	0	3	-22	68	4	(Left Superior Frontal Gyrus)**		
4.2	3.18	0.001	1	-2	-70	-30	**Assigned to L Lobule VIIb (Vermis)**	40	19-40
							L Lobule VI (Vermis)	23	3-23
							L Lobule VIIIa (Vermis)	22	20-75
4.12	3.14	0.001	1	40	-48	64	R SPL (7PC)	20	0-20
4.03	3.09	0.001	1	20	42	-20	(Right Middle Orbital Gyrus)**		

DPs correlation analysis for BOLD for Pseudowords

Table 15.26 DPs – Pseudowords; Pseudoword Composite scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
5.41	3.7	0	8	-20	-20	46	L Area 3a	10	0-10
							Areas with too small number of voxels		
4.47	3.3	0	1	-32	10	-28	(Left Temporal Pole)		
4.34	3.24	0.001	2	16	52	-18	(Right Middle Orbital Gyrus)		
4.23	3.19	0.001	1	8	42	-18	(Right Rectal Gyrus)		

Table 15.27 DPs – Pseudowords; WRAT Spelling z-scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological areas		
4.73	3.42	0	16	-58	-32	-16	(Left Middle Temporal Gyrus)**		
5.36	3.68	0	17	24	26	58	R Area 6	10	0-20
4.64	3.38	0	12	44	-46	28	R IPC (PFm)	20	10-30
							R hIP1	20	0-20
4.56	3.35	0	6	48	-76	32	**Assigned to R IPC (PGp)**	90	0-90
4.86	3.48	0	6	64	-54	32	R Angular Gyrus**		
							Cerebellar Areas		
5.97	3.91	0	223	-36	-64	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	77	58-99
5.6	3.77	0	223	-22	-62	-34	**Assigned to L Lobule VIIa Crus I (Hem)**	54	0-54
							L Lobule VIIa Crus I (Hem)	6	0-6
4.93	3.51	0	20	24	-76	-46	**Assigned to R Lobule VIIa Crus II (Hem)**	39	39-67
							R Lobule VIIb (Hem)	5	2-20
4.72	3.42	0	10	40	-74	-50	**Assigned to R Lobule VIIa Crus II (Hem)**	96	84-99
4.54	3.34	0	223	-22	-48	-34	L Cerebellum_6**		
							Other areas		
6.08	3.95	0	16	-50	-34	-20	(Left Inferior Temporal Gyrus)**		
5.52	3.74	0	13	-40	-30	-22	(Left Inferior Temporal Gyrus)**		
							Areas with too small number of voxels		
4.12	3.14	0.001	2	42	-82	32	**Assigned to R IPC (PGp)**	80	0-90
4.82	3.46	0	2	12	-84	-42	**Assigned to R Lobule VIIa Crus II (Hem)**	84	71-95
							R Lobule VIIb (Hem)	5	0-15
4.65	3.39	0	3	-50	-16	-24	(Left Middle Temporal Gyrus)**		
4.61	3.37	0	4	40	-52	-48	**Assigned to R Lobule VIIa Crus II (Hem)**	55	6-63
							R Lobule VIIa Crus I (Hem)	34	20-62
							R Lobule VIIb (Hem)	5	0-6
4.26	3.21	0.001	2	28	-66	-50	**Assigned to R Lobule VIIb (Hem)**	59	18-59
							R Lobule VIIa Crus II (Hem)	8	0-8
							R Lobule VIIIa (Hem)	4	0-48
4.18	3.17	0.001	2	-18	-20	54	Assigned to L Area 6	40	10-50
							L Area 4p	10	10-10
							L Area 4a	10	0-30
4.1	3.13	0.001	1	22	-80	-42	**Assigned to R Lobule VIIa Crus II (Hem)**	76	74-96
4.06	3.11	0.001	1	18	-60	-48	**Assigned to R Lobule VIIIb (Hem)**	56	14-56
							R Lobule IX (Hem)	7	2-29
							R Lobule VIIIa (Hem)	4	0-7
5.35	3.68	0	4	-20	-22	48	L Area 3a	10	10-10
							L Area 4p	10	0-20

Table 15.28 DPs – Pseudowords; Irregulars Composite scores covariance with BOLD

				MNI			Area (labeled with anatomy toolbox) or AAL**		
T	**Z**	**p**	**k**	**x**	**y**	**z**		**P$**	**R$**
							Phonological areas		
6.17	3.97	0	143	58	-56	42	**Assigned to R IPC (PFm)**	80	0-80
							R IPC (PGa)	60	0-80
5.74	3.83	0	143	52	-52	36	**Assigned to R IPC (PFm)**	50	0-80
							R IPC (PGa)	50	40-50
							Other areas		
6.03	3.93	0	23	40	6	58	(Right Middle Frontal Gyrus)**		
5.98	3.91	0	47	-32	58	18	(Left Middle Frontal Gyrus)**		
5.58	3.77	0	47	-32	48	30	(Left Middle Frontal Gyrus)**		
5.41	3.7	0	15	26	30	34	(Right Middle Frontal Gyrus)**		
							Areas with too small number of voxels		
4.86	3.48	0	5	-30	-80	-28	Assigned to L Lobule VIIa Crus I (Hem)	99	97-100
4.11	3.13	0.001	2	-28	-70	-32	Assigned to L Lobule VIIa Crus I (Hem)	73	38-92
4.19	3.17	0.001	1	-10	-76	-34	L Lobule VIIa Crus II (Hem)	18	0-59
							L Lobule VIIa Crus I (Hem)	8	5-62
							L Lobule VIIb (Hem)	2	0-2
							L Lobule VI (Hem)	0	0-12
4.16	3.16	0.001	1	-56	-58	-12	(Left Inferior Temporal Gyrus)**		
4.12	3.14	0.001	2	-24	62	-2	(Left Superior Orbital Gyrus)**		
4.3	3.22	0.001	2	18	44	-16	(Right Superior Orbital Gyrus)		
4.06	3.11	0.001	1	4	60	-16	(Right Rectal Gyrus)**		

Table 15.29 Local maxima for comparisons (involving BOLD for Word reading) between DPs without impairment on Orthography Composite and CPs

T	Z	p	k	MNI			Contrast Word: DP [-Orth Imp] >CPs	P$	R$
							Nothing to report		
							Contrast Word: DP [-Orth Imp] <CPs		
							Areas of Interest		
3.8	3.23	0.001	65	-30	-62	2	L Area 17	10	0-30
							Phonological Areas		
							Other Areas		
5.6	4.2	0	65	-36	-62	10	L Middle Occipital Gyrus **		
4.3	3.51	0	1	42	-16	-24	R Hipp (CA)	30	0-50
4.3	3.5	0	7	-30	-24	-12	Assigned to L Hipp (FD)	60	30-80
							L Hipp (CA)	50	30-80
							L Hipp (SUB)	10	0-20
4.3	3.49	0	8	-14	-42	78	Assigned to L SPL (5M)	10	0-20
							L Area 2	10	0-10
							L Area 1	10	0-30
							L Area 6	10	0-20
							L Area 3b	10	0-10

Table 15.30 Local maxima for comparisons (involving BOLD for Pseudoword reading) between DPs without impairment on Orthography Composite and CPs

T	Z	p	k	x	y	z	Contrast Pseudoword: DP [-Orth Imp] >CPs	P$	R$
							Areas of Interest		
							Other Areas		
							Phonological Areas		
4.25	3.49	0	76	-42	4	32	L Area 44	20	10-30
3.78	3.2	0.001	8	-46	24	-4	L Area 45	20	10-30
							L Area 44	10	10-20
4.31	3.53	0	30	-52	-36	6	(Left Middle Temporal Gyrus)**		
3.73	3.17	0.001	30	-48	-42	2	(Left Middle Temporal Gyrus)**		
5.31	4.06	0	76	-34	4	26	(Left Inferior Frontal Gyrus (p. Opercularis))**		
3.69	3.14	0.001		48	10	22	Assigned to R Area 44	60	50-60
4.77	3.79	0	32	50	42	2	(Right Inferior Frontal Gyrus (p. Triangularis))**		
3.94	3.3	0	16	46	-30	42	Assigned to R IPC (PFt)	60	40-70
							R Area 2	50	10-60
							Other Areas		
6.19	4.47	0	92	36	4	22	R Inferior Frontal Operculum**		
5.39	4.11	0	45	-30	-48	66	Assigned to L Area 1	20	0-30
							L SPL (7A)	10	0-40
							L SPL (7PC)	10	10-30
							L SPL (5L)	10	0-40
							L Area 2	10	0-10
5.32	4.07	0	226	32	-54	50	Assigned to R hIP3	60	40-70
							R SPL (7A)	40	10-40
							R IPC (PGa)	10	0-10
4.9	3.86	0		26	-52	36	R hIP1	30	20-30
							R hIP3	10	10-20
4.25	3.49	0		40	-48	54	Assigned to R SPL (7PC)	30	20-40
							R hIP2	20	0-30
							R hIP3	20	20-40
							R SPL (7A)	10	0-20
							R Area 2	10	0-10
							R hIP1	10	0-20
5.15	3.98	0	29	-26	-68	44	L SPL (7A)	20	10-20
							L SPL (7P)	10	0-20
							L hIP1	10	0-20
4.25	3.49	0	8	-28	14	4	L Putamen**		
4.2	3.46	0	15	-30	-70	20	L Middle Occipital Gyrus**		
							Contrast Pseudoword: DP [-Orth Imp] < CPs		
							Areas of Interest		
							Phonological Areas		
							Other Areas		
4.25	3.49	0	23	-16	50	-12	(Left Superior Orbital Gyrus)**		

Table 15.31 Local maxima for comparisons (involving BOLD for Word reading) between DPs with impairment on Orthography Composite and CPs

				MNI					
T	Z	p	k	x	y	z	Contrast Word: DP [+Orth Imp] >CPs	P$	R$
							Areas of Interest		
							Phonological Areas		
							Other Areas		
4.36	3.55	0	17	-28	-72	-4	L hOC4v (V4)	30	0-50
							L hOC3v (V3v)	10	0-10
							Contrast Word: DP [+Orth Imp] < CPs		
							Areas of Interest		
5.17	3.99	0	478	52	-66	12	R hOC5 (V5)	10	0-20
							R IPC (PGp)	30	0-40
4.39	3.57	0	49	-6	-70	22	L Area 18	30	30-30
4.37	3.56	0	43	8	-56	4	Assigned to R Area 17	60	50-80
							R Area 18	50	20-80
							R hOC3v (V3v)	10	0-10
							Phonological areas		
6.42	4.57	0	97	-44	40	14	L Area 45	20	20-40
5.34	4.08	0	7	-20	36	10	L Insula**		
4.53	3.65	0	25	-40	14	24	L Area 44	30	10-40
							L Area 45	10	0-20
4.26	3.5	0	8	-32	4	50	L Area 6	20	0-20
4.52	3.65	0	18	-48	-42	-12	L Middle Temporal Gyrus**		
4.35	3.55	0	7	-64	-48	6	(Left Middle Temporal Gyrus)**		
4.03	3.36	0	17	-52	-58	16	L IPC (PGa) (BA39) (Angular Gyrus)	20	0-40
							RH Homologues of Phonological Areas		
6.21	4.48	0	478	46	-78	26	Assigned to R IPC (PGp) (BA39)	80	80-80
4.7	3.75	0	478	52	-72	18	Assigned to R IPC (PGp) (BA39)	50	50-60
3.91	3.28	0.001	8	42	-56	-22	(Right Fusiform Gyrus)**		
							Other Areas		
							Cerebellar areas		
7.23	4.89	0	130	10	-56	-32	R Lobule IX (Hem)	1	0-1
4.56	3.67	0	130	18	-60	-34	R Cerebellum_6**		
6.13	4.45	0	198	-8	-58	-32	Lobule L IX (Hem)	0	0-0
5.49	4.15	0	198	-20	-54	-36	L Cerebellum_8**		
3.86	3.25	0.001	198	-14	-48	-34	L Cerebellum_9**		
4.37	3.56	0	8	36	-42	-26	R Lobule VI (Hem)	0	0-27
4.18	3.45	0	17	-4	-82	-40	Assigned to L Lobule VIIa Crus II (Hem)	61	55-77
							L Lobule VIIb (Hem)	38	20-43
							L Lobule VIIIa (Vermis)	0	0-1
							Various areas		
4.67	3.73	0	19	-36	-56	48	Assigned to L hIP1	30	10-50
							L SPL (7A)	20	10-30
							L hIP3	10	0-20
4.57	3.67	0	40	-20	64	0	(Left Superior Frontal Gyrus)**		
4.34	3.55	0	18	-40	-42	0	L ParaHippocampal Gyrus**		
4.24	3.48	0	16	-8	44	52	(Left Superior Medial Gyrus)**		

Table 15.32 Local maxima for comparisons (involving BOLD for Pseudoword reading) between DPs with impairment on Orthography Composite and CPs

				MNI					
T	Z	p	k	x	y	z	Contrast Pseudoword: DP [+Orth Imp] >CPs	P$	R$
							Areas of Interest		
							Phonological Areas		
4.14	3.42	0	12	-50	10	2	L Area 44	30	20-30
							Other Areas		
4.91	3.86	0	36	-26	-72	-6	Assigned to L hOC4v (V4)	50	30-70
5.2	4.01	0	125	20	-42	10	R Precunes**		
4.42	3.59	0	125	28	-46	16	R Precunes*8		
							Contrast Pseudoword: DP [+Orth Imp] < CPs		
							Areas of Interest		
							Phonological areas		
4.1	3.4	0	11	-62	-24	26	Assigned to L IPC (PFop) (BA40)	50	40-80
							L OP 1	30	10-50
							L IPC (PFt)	30	0-40
							L IPC (PF)	20	0-20
4.44	3.6	0	37	-34	-30	-22	(Left Fusiform Gyrus)**		
							Other areas		
							Cerebellar Areas		
5.24	4.03	0	13	20	-48	-38	R Cerebellum_9**		
4.69	3.74	0	64	-4	-32	-24	L Cerebellum_3**		
4.62	3.71	0	37	-20	-30	-20	L Hipp (EC)	20	0-20
							L Lobules I-IV (Hem)	1	0-1
4.47	3.62	0	8	12	-56	-28	R Lobule V	0	0-0
4.45	3.61	0	10	26	-62	-38	R Lobule VI (Hem)	8	0-8
							R Lobule VIIa Crus I (Hem)	7	0-28
4.25	3.49	0	21	20	-86	18	(Right Superior Occipital Gyrus)**		
5.11	3.97	0	63	-30	46	-14	(Left Middle Orbital Gyrus)**		
4.63	3.71	0	19	-30	-12	-24	Assigned to L Hipp (CA)	90	70-100
							L Hipp (FD)	50	30-70
							L Amyg (LB)	30	30-40
							L Hipp (SUB)	20	10-60
							L Amyg (SF)	10	0-10
4.33	3.54	0	22	-24	-78	48	Assigned to L SPL (7P)	20	0-30
							L SPL (7A)	10	10-20
							L IPC (PGp)	10	0-20
							L IPC (PGa)	10	0-20
							L hIP3	10	0-10
4.29	3.51	0	20	-24	-76	34	L SPL (7A)	10	0-10
4.01	3.35	0	7	-36	-48	44	L hIP1	40	30-60
							L hIP2	20	10-20
							L SPL (7PC)	10	10-20
							L Area 2	10	0-10
							L hIP3	10	0-30
3.96	3.31	0	7	42	-46	48	Assigned to R hIP2	40	30-50
							R IPC (PFm)	30	0-40
							R hIP3	20	20-30
							R SPL (7PC)	10	0-20
							R hIP1	10	0-20
5.41	4.12	0	192	20	-2	-6	R Amyg (SF)	20	0-30
5.09	3.96	0	192	14	-12	-8	R Thalamus**		
4.27	3.5	0	192	22	-10	-2	R Thalamus**		
5.2	4.01	0	64	-4	-22	-22	L ParaHippocampal Gyrus**		

Table 15.33 Local maxima for comparisons (involving BOLD for Word reading) between DPs [-Oth Imp] with DPs [+Oth Imp]

				MNI					
T	Z	p	k	x	y	z	**Contrast Word: DPs [-Orth Imp] >DPs [+Orth Imp]**	P$	R$
							nothing significant		
							Contrast Word: DPs [+Orth Imp] >DPs [-Orth Imp]		
							Phonological Areas		
4.88	3.41	0	13	-54	-40	26	Assigned to L IPC (PFcm)	40	40-60
							L IPC (PF)	40	0-50
							L IPC (PFm)	30	30-30
							L TE 3	20	0-20
							Magnocellular areas		
							Cerebellar areas		
5.42	3.62	0	14	2	-48	-18	Assigned toR Lobules I-IV (Hem)	84	15-95
5.05	3.48	0	7	10	-36	-48	R Lobule X (Hem)	1	0-1
							Visual areas		
6.05	3.84	0	110	-16	-76	-10	Assigned to L hOC4v (V4)	60	
							L hOC3v (V3v)	60	
							L Area 18	20	
5.49	3.65	0		-18	-90	-16	Assigned to L hOC3v (V3v)	50	20-50
							L Area 18	40	20-40
							L hOC4v (V4)	30	20-40
							L Area 17	10	10-20
4.56	3.28	0.001		-10	-88	-8	Assigned to L Area 18	60	50-70
							L hOC3v (V3v)	40	40-60
							L Area 17	10	10-30
5.9	3.79	0	15	-24	-76	0	L hOC3v (V3v)	10	0-10
5.18	3.53	0	6	24	-90	-2	Assigned to R Area 17	40	30-60
							R Area 18	20	10-40
							R hOC3v (V3v)	20	10-30
							Other areas		
5.54	3.66	0	9	-4	-14	18	Left Thalamus*		

Table 15.34 Local maxima for comparisons (involving BOLD for Pseudoword reading) between DPs [-Oth Imp] with DPs [+Oth Imp]

				MNI					
T	**Z**	**p**	**k**	**x**	**y**	**z**	**Contrast Pseudoword: DPs [-Orth Imp] > DPs [+Orth Imp]**	**P$**	**R$**
							Phonological areas		
6.85	4.08	0	13	-44	26	34	L Area 45	20	10-20
6.84	4.08	0	44	58	6	18	Assigned to R Area 44	30	30-50
4.77	3.37	0	7	38	2	26	R Area 44	10	0-20
							Magnocellular areas		
							Cerebellar areas		
							Other areas		
5.02	3.47	0	66	38	-50	44	R hIP1	40	10-50
							R hIP2	20	10-20
							R hIP3	20	20-40
							R SPL (7PC)	10	0-10
4.97	3.45	0	35	52	-58	-12	Right Inferior Temporal Gyrus**		
4.59	3.29	0		54	-66	-14	Right Inferior Occipital Gyrus**		
4.96	3.45	0	27	-32	-50	46	Assigned to L hIP3	40	30-40
							L SPL (7PC)	40	10-50
							L SPL (7A)	20	0-20
							L SPL (5L)	10	0-10
							L hIP1	10	10-20
4.33	3.18	0.001		-24	-48	44	L SPL (7A)	10	0-10
							L SPL (5L)	10	0-10
4.39	3.2	0.001	7	44	-34	54	Assigned to R Area 2	100	70-100
							R Area 1	40	10-60
							R IPC (PFt)	10	10-30
T	Z	p	k	x	y	z	**Contrast Pseudowords: DP [+Orth Imp] > DPs [-Orth Imp]**	P$	R$
							Phonological areas		
4.8	3.38	0	7	-46	-70	32	Assigned to L IPC (PGp)	70	70-80
							L IPC (PGa)	30	20-40
							Magnocellular areas		
							Cerebellar areas		
							Visual areas		
7.5	4.26	0	8	24	-90	-2	Assigned to R Area 17	40	30-60
							R Area 18	20	10-40
							R hOC3v (V3v)	20	10-30
5.54	3.66	0	7	-8	-92	-8	Assigned to L Area 18	60	60-80
							L Area 17	40	20-40
							L hOC3v (V3v)	10	0-40

16 Appendix G - MEG pilot

16.1 Participants

Two postgraduate students from Aston University participated in the pilot MEG experiment. They were right handed, with English as native (and dominant) language and had no reading and/or spelling difficulties. Each participant gave informed consent to participate in the study. The study was approved by the local ethics committee.

16.2 Experimental Design for MEG

The same as described in Chapter 5

16.3 Data Acquisition

Data were collected in the Welcome Trust Laboratory for MEG Studies at Aston University, using a 275-channel CTF Omega system (CTF Systems, Port Coquitlam, Canada) at a sampling rate of 600 Hz. Before MEG data acquisition was initiated, the shape of the participants head and the relative position of the headcoils for the nasion, left and right ears on the headset were digitised using a 3-D digitiser (Polhemus Isotrack). *Lucky coregistration* (Matlab program developed at Aston University) was used to match this surface to that extracted from the participant's anatomical MRI, so that the MEG data obtained from each participant was coregistered with their anatomical MRI scan.

16.4 Measurements and Analysis

16.4.1 MEG

MEG measures weak magnetic fields outside a participant's head which are created by electrical neuronal activity (Hämäläinen & Hari, 2002). Data were inspected for eye blinks. They occurred randomly and therefore they were not excluded from the data set. The Powerline Filter (freq=50Hz and width=3.5) was applied to the data. Data were analysed using an adaptive beam-former technique known as Synthetic Aperture Magnetometry (SAM) (Vrba & Robinson, 2001). The main assumption of this technique is that no two distant cortical areas generate coherent local field potentials over a long time period. It has been shown empirically (Singh, Barnes, Hillebrand, Forde, & Williams, 2002) that this is a reasonable assumption. SAM provides continuous 3-D images of the cortical oscillatory power changes related to the experimental task (Hillebrand & Barnes, 2005; Singh et al., 2002). Increases or decreases in power changes can either be evoked (phase-locked to the stimulus), or

induced by the presence of the stimulus (without phase-locking). In SAM each voxel in the brain is linked to a detection array by using an optimal spatial filter for a given voxel. The MEG data were then projected through this filter to obtain a measure of current density as a function of time in a given voxel. The voxel time series was calculated as a weighted sum of all MEG sensors and therefore it had the same time resolution as the original voxel. This time series was then divided into active and passive epochs (passive = viewing a cross; active = reading words or pseudowords) and Fourier analysis was used to calculate the total amount of power within each active and passive epoch. The resulting SAM images were normalised using SPM and foci of activation were identified in MNI space using *mri3dX* software (Singh, undated). SAM is particularly suitable for the investigation of higher level cognitive processes (e.g., language processes) because they are poorly phase-locked to the stimulus across trials (Michalewski, Prasher, & Starr, 1986).

First, data were analysed using a relatively long time window (0-1sec) with broad frequency bands (1-20 Hz; 10-30 Hz and 20-70 Hz), these analyses resulted in relatively small pseudo-t values (<1) in ROI. Second, data were analysed in 0.0-0.2 sec; 0.1-0.3 sec; 0.2-0.4 sec; 0.3-0.5 sec; 0.4-0.6 sec; 0.5-0.7 sec; 0.6-0.8 sec; 0.7-0.9 sec and 0.8-1.0 sec time windows within the classical frequency bands: 8-13 Hz (alpha), 14-30 Hz (beta) and 30-50 Hz (gamma). The data were additionally analysed in the 10-20 Hz frequency band because Pammer et al. (2004) reported that they obtained the best results for their lexical decision task in this frequency band. The analysis for 14-30 Hz is presented here as it revealed the most salient activations. For this frequency range the time window of 200 ms seemed reasonable because 4.4 cycles were probed on average. Note also that the 200 ms time window was successfully used with SAM by Pammer et al. (2004).

16.5 Results

The results, which consist of the SAM analysis of changes of oscillatory power in two participants P1 and P2, revealed a complex picture (see; Table 14.1, Table 14.2 and Table 14.3, below). First, all ROI were activated by both participants for Words and Pseudowords (except P2 did not activate BA44/45 for Pseudowords, however, areas BA46/47 were activated). It should be noted here that the pilot experiment focused on a smaller number of ROI than the main fMRI study reported in this thesis. Second, generally slightly more increase than decrease in power was noted, except for Pseudowords (P1). The pseudo-t values (SAM) were relatively small, with the highest value of |3|, however they occurred in the predicted areas. Third, there were differences between P1 and P2 (for both stimulus types) in the

spatiotemporal evolution of cortical activity and in the patterns of increase and decrease of power in the ROI (see Table 14.1 and Table 14.2). It should be noted that it is not clear how to interpret the spatiotemporal evolution of cortical activity for Word versus Pseudoword contrast (see Table 14.3, below) and further analyses involving spectrograms are necessary.

Table 16.1 Spatiotemporal evolution of cortical activity for Words (14-30 Hz)

Participant 1																				Participant 2																			
	STG (BA 22)*				**IFG (BA 44/45)***				**insula**				**V5/MT***				**cerebellum**				**STG (BA 22)***				**IFG (BA 44/45)***				**insula**				**V5/MT***				**cerebellum**			
time (s)	peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates		
		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z
0.0-0.2													1L	-46	-70	2																	1L	-46	-70	2				
																																	R	46	-66	-1				
0.1-0.3									1L	-48	3	3	-1L	-44	-77	2									1R	50	4	16					1L	-49	-60	1				
0.2-0.4	2L	-65	-15	1					1R	42	-9	-6									2L	-53	-6	3																
	2R	62	-9	0																	2L	-62	-49	11													-1L	-37	-80	-21
0.3-0.5									-1R	42	-9	-6																												
0.4-0.6	-2R	53	-32	7																	-1R	62	-32	7					-1L	-57	-36	18								
0.5-0.7	-1L	-50	-49	14	1L	-39	38	1									-2R	42	-69	-27									1L	-42	9	0	-1L	-47	-78	2	1L	-36	-78	-33
	-2R	65	3	-5													1R	6	-78	-27																				
0.6-0.8					1L	-59	10	16					-1L	-46	-70	2									-1L	-48	4	30					-1L	-46	-70	2				
																									-2R	53	7	13												
0.7-0.9	1L	-68	-18	-2	1R	56	23	-6					1L	-45	-65	2																								
	-1L	-59	-40	8									1R	46	-66	-1																	1R	46	-66	-1				
0.8-1.0					-2R	36	17	-3													-1L	-50	-43	10																

Note. Blue=Decrease of Power; Red=Increase of Power; L=Left; R=Right; *=Talairach coordinates (Talairach & Tournoux, 1988) (calculated using Brett's formula - http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach), otherwise MNI coordinates.

Table 16.2 Spatiotemporal evolution of cortical activity for Pseudowords (14-30 Hz)

Participant 1 = HL																																		
Participant 2 = EF																																		
Participant1																			Participant 2														
	STG (BA 22)*				**IFG (BA 44/45)***				**insula**				**V5/MT***				**cerebellum**				**STG (BA 22)***				**IFG (BA 44/45)***				**insula**				**V5/MT***				**cerebellum**			
time (s)	peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates		
		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z		x	y	z
0.0-0.2					2R	46	35	4	-1L	-27	30	0					-1L	-54	-54	-27	2L	-48	-26	1											-1L	-28	-63	-41
																	1L	-6	-93	-27																				
0.1-0.3	-2R	50	-12	1					-1L	-42	12	0	1L	-50	-63	1	-2L	-36	-54	-27	-1L	-50	14	-6									1L	-50	-64	1				
0.2-0.4	1L	-62	-34	18													-1L	-29	-34	-45					-1L	-50	35	9^									1L	-42	-81	-27
					1R	53	27	7													-2R	59	-38	7																
0.3-0.5					1L	-56	29	4									1L	-6	-84	-24	1L	-59	-23	1	-1L	-48	38	4^					-1R	46	-66	-1				
	-2L	-56	-3	-2	2R	56	14	5					-1R	46	-66	-1																								
0.4-0.6													1R	46	-66	-1					-1R	59	-35	7	-1L	-56	36	12^					1R	46	-66	-1				
																									-1L	-18	22	-21^												
0.5-0.7									1L	-42	-6	18					-1L	-24	-63	-48																	1R	38	-39	-45
																	1R	15	-33	-12					1R	48	35	-7^												
0.6-0.8	-1R	62	-38	7	-1L	-56	24	7					-1L	-39	-72	2																								
																																	-1R	41	-63	-1				
0.7-0.9	-3L	-59	-12	-2																	-2L	-60	-59	14					1L	-37	-16	16	1L	-42	-66	1				

Note. Blue=Decrease of Power; Red=Increase of Power; L=Left; R=Right; *=Talairach coordinates (Talairach & Tournoux, 1988) (calculated using Brett's formula - http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach), otherwise MNI coordinates.

Table 16.3 Spatiotemporal evolution of cortical activity for Words versus Pseudowords (14-30 Hz)

Participant 1																	Participant 2														
	STG (BA 22)*				**IFG (BA 44/45)***				**insula**				**cerebellum**				**STG (BA 22)***				**IFG (BA 44/45)***				**insula**				**cerebellum**			
time	peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates			peak	coordinates		
		x	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**
0-0.2									2.1L	-36	9	-3					1.7R	56	-46	11												
																	-1.7L	-48	-29	4												
0.1-0.3	-1.1L	-56	-35	7									1.1L	-33	-60	-36	1.1L	-65	-40	16	2.0R	53	4	16					1R	59	-60	-43
													1.1R	36	-33	-27																
0.2-0.4	-1.2L	-65	-40	16	-1.7L	-42	20	-4^									1.4L	-48	0	-5	2.1R	50	1	22					-1.2L	-60	-69	-42
																													1.1L	-24	-54	-24
0.3-0.5													-1.5L	-21	-75	-27													-1.2L	-45	-75	-45
0.4-0.6					-1.0L	-59	20	-6^					-1.5R	48	-63	-27													1.3R	42	-81	-27
													-1.1L	-21	-78	-27													-1.1L	-41	-60	-47
																													1.1R	42	-66	-48
0.5-0.7													1.3R	9	-90	-27	-1.2R	62	-26	7	-1.2R	27	29	-6^					1.7L	-39	-78	-24
													1.3L	-6	-84	-21													-1.3L	-54	-57	-33
									-1.2L	-42	12	-3	1.1R	42	-90	-33																
0.6-0.8									-1.1L	42	-15	3	1.2L	-6	-84	-21					1.2L	-15	31	-17^								
													1.1L	-18	-66	-27					-1.4R	48	27	10								
0.7-0.9	1.2L	-59	12	-1	1.3L	-30	22	-21^									1.1R	56	-20	4	-1.2R	50	47	-2^								
0.8-0.10													1.0R	54	-63	-39					1.1R	33	20	-16^					1.5L	-12	-81	-36

Note. Blue=Decrease of Power; Red=Increase of Power; L=Left; R=Right; *=Talairach coordinates (Talairach & Tournoux, 1988) (calculated using Brett's formula -http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach), otherwise MNI coordinates.

16.6 Discussion

In SAM analysis for Words, P1 and P2 exhibited increases and decreases in oscillatory power (across defined time windows) for all predicted areas of interest. SAM results for Pseudowords revealed that both P1 and P2 showed increases and decreases of oscillatory power, except P2 did not exhibit any power changes in BA44/45 and, in the insula, showed only increases of oscillatory power. It should be underscored here that it is not currently clear how to interpret decreases and increases in oscillatory power in the MEG results. Decrease in oscillatory power (event related desynchronisation) has been shown to be a correlate of neuronal activation (Pfurtscheller & Lopes da Silva, 1999). On the basis of literature (e.g., Pammer, et al., 2004; Pfurtscheller & Lopes da Silva, 1999; Singh et al., 2002) it is assumed here that both decreases and increases in oscillatory power are equally meaningful correlates of stimulus processing. The analysis needs to be refined in future work. SAM analysis needs to be corrected for multiple comparisons.