In Cerebro Unveiling

Unconscious Mechanisms during Reading

Een wetenschappelijke proeve op het gebied van de
Sociale Wetenschappen

Proefschrift

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Chapter 1 General Introduction

Reading

Reading stands for the cognitive process of decoding symbols, or letters, into words and sentences that have a meaning to the individual. In order to read, one must follow a sequence of characters arranged in a particular spatial order. For example, English flows from left to right, Hebrew from right to left, and Chinese from top to bottom. Psychophysically speaking, it is performed as a series of eye fixations with saccades between them. Each fixation lasts for about a quarter of a second, in which more than one word is perceived and interpreted, so that a skilled reader may take in more than three words per fixation when reading easy material. Thanks to linguistic regularities, only some words are fixated during reading while contextual inference is used to fill in the missing information, resulting in a high reading speed. Depending on the rate of fixations and the difficulty of the material, an adult can read and understand anywhere from 200 to 1,000 words per minute.

Historically, human (oral) language has already appeared millions of years ago, whereas reading appeared only circa 4000 BC (the Sumerian logographs), which in evolutionary terms is extremely short time ago. Around 1500-2000 BC, the Phoenicians developed the first methods to represent sounds; however, this alphabet consisted entirely of consonants. In 1000 BC the Greeks added vowels to the alphabet, thus making it very similar to the modern alphabet of our time. This relatively short history of reading raises an interesting question: how a functioning mode which has appeared so late has become so specialized in such a short period of time? After all, these processes have become extremely automatic, fast, irrepressible and unconscious, and our visual system processes words so naturally as if the capacity to read has always existed. Brain-wise, to be able to recognize and process the written signs to their orthographic, phonological and semantic correspondences, the nervous system needs to attain a high degree of physiological and anatomical maturity. In the present dissertation, I probe (i) the recruitment and information routing within the neural network(s) for reading in general, and (ii) for each one of those automatic processes in particular, and finally, (iii) how the latter access perceptual consciousness. Thereby, I venture to better comprehend reading and its neural specialization along evolution.

Language processing in the brain – Background

Starting from the 19th century the scientific community gradually started dismissing the view of the brain as a single working unit and began assigning functions to different brain regions (Finger, 1994). Pioneering evidence appeared in the 19th century by Paul Broca and then by Carl Wernicke, who localized specific brain regions and attributed linguistic functions to them, which then has become widely accepted. Later on in the 1960s, Norman Geschwind refined Wernicke's model of language processing (see Geschwind, 1965); this so called Wernicke–Geschwind model still forms the basis of current investigations on normal and disturbed language function (Damasio & Geschwind, 1984). More recently, the model was revised by synthesizing the impressive amounts of data to develop new large-scale models (Posner et al., 1999; Price, 2000; Friederici, 2002; Indefrey and Levelt, 2004; Démonet et al., 2005; Hickok and Poeppel, 2007). With this regard, in the present thesis, I will present evidence that readily illustrates the importance of selective brain areas to the processing of rapid and unconscious mechanisms underlying reading.

As a grosser pinpointing of language areas, it is prevalently accepted that one hemisphere is predominantly involved in language activities; this is referred to as the concept of hemispheric specialization (also called predominance or lateralization) for language. Ninety percent of people have the left hemisphere predominant for language, although this predominance is not absolute and does not rule out the involvement of the other hemisphere (see Figure 1.1 for a nice instantiation of linguistic vs non-linguistic disentanglement). The degree of lateralization depends on several variables such as gender or handedness (Eviatar et al., 1997). This concept of hemispheric lateralization gained support thanks to the Nobel-winning work of Roger Sperry (Sperry, 1974), during the 1960s and 1970s. At present, there are many ways to assess hemispheric lateralization: behavioral procedures (e.g. divided visual field or dichotic listening), the well-known Wada procedure, or more recently, hemodynamic or magnetoencephalography neuroimaging measurements during linguistic tasks. It is interesting to note that, the Wada test, although dating since the middle of the last century (Wada, 1949; Wada and Rasmussen, 1960), is still up to now considered a gold standard for determining language dominance. Furthermore, neuroimaging technology and methodology have dramatically improved in the past decade, thereby successfully emulating the Wada test (fMRI and PET: Benson et al., 1999; Binder et al., 1996; Lehe´ricy et al., 2000; MEG: Kober et al., 2001; Hirata et al., 2004). The work in the present thesis will provide ample support also to the concept of hemispheric lateralization.

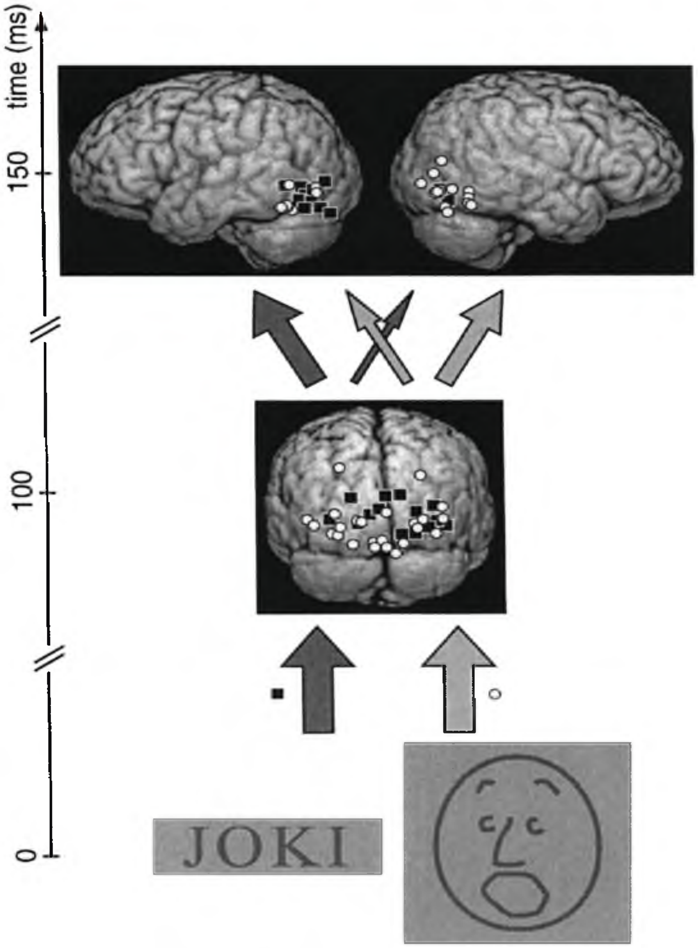

Figure 1.1. Early brain processing of linguistic (letter-string) and non-linguistic (face). Adapted from Tarkiainen et al., (2002). The first stage (~100ms) does not differ between the two categories and is restricted to the bilateral occipital cortex, whereas the second step proceeds to the occipito-temporal junction with a strong left-lateralization for linguistic stimuli and a slight right-hemispheric preponderance for non-linguistic stimuli.

Train of cerebral events during the visual recognition of a word

The first step taking place during reading, once the eye has fixated on the target word, is the processing of the visual features of the word per se. Light is captured by the retina, that is a light-sensitive membrane in the back of the eye, which produces neural impulses that are processed in a hierarchical fashion by different occipital areas (Young, 1992). In detail, the connection from the eye to the brain is done via the optic nerve. The majority of the axons in the optic nerve go to the lateral geniculate nucleus (LGN) in the thalamus. The LGN transfers information directly to the primary visual cortex, also termed striate cortex or V1, at the most posterior localization of the cortex. Visual information then hierarchically flows through the secondary visual areas, also called extrastriate visual cortex (V2, V3, V4 and V5/MT). After processing in V1 and V2, information is either forwarded via the ventral stream or via the dorsal stream (see Figure 1.2) (Mishkin and Ungerleider, 1982). The ventral stream, also known as the "what pathway", travels to the temporal lobe via V4, where it proceeds to visual identification (e.g. letter recognition). The dorsal stream ("where pathway") travels to the parietal lobe via V5 and processes spatial information. Thus, cerebral lesions in one of the two pathways may result in impaired reading: for damage in the ventral stream the identification of the letters could be defected, whereas for damage in the dorsal stream the ability to recognize the totality of the word may be altered. The completion of this first processing step is at 100 ms (Salmelin, 2007) and is probably common to all visual stimuli irrespective of their visual contents (Figure 1.1). Importantly, this rudimentary step does not exclude the occurrence of recurrent processes in the occipital lobe during later and more elaborate stages. In Chapter 2 I provide further support for the claim on the nature of this posterior early visual step, and in Chapter 3, on the implications of segments in the ventral and dorsal pathways during reading.

Secondly, follows orthographic processing, referring to the identification and translation of visual codes (letters). This step takes place circa 150 ms (Tarkiainen et al., 1999, 2002; Cohen et al., 2000, 2002; Martin et al., 2006) and disentangles between linguistic and non-linguistic stimuli (e.g. Tarkiainen et al., 1999; Pernet, Celsis and Démonet, 2005) (see Figure 1.1). However, this dissociation is still premature, i.e. it is restricted to low level linguistic processing (orthography), and is yet unable to process higher word information as it does not distinguish between words, pseudowords or letter strings (Salmelin et al., 1996; Cornelissen et al., 2003; Wydell et al., 2003). There is a long time and still ongoing debate on the plausible existence of a specialized or even exclusive area for the storage and processing of orthographic forms. The first candidate, the left angular gyrus, was raised by Joseph Déjerine in 1892 after he had observed patients with lesions in this area, which he then regarded as causal to their reading disability (Déjerine, 1892). Déjerine regarded this area as a center for storage of letter shapes. However, substantial neuroimaging evidence during the past two decades suggests this region to have a role in multimodal integration towards semantic (Jobard et al., 2003). The second candidate for an area dedicated to orthographic processing, the left medial extrastriate region, emerged from the princeps neuroimaging study of Petersen et al. (1990). This hypothesis followed the observation of an enhanced activation in this region following the visual presentation of words or pseudowords in contrast to that of consonant strings. Unfortunately, further neuroimaging experimentation has failed to establish this preliminary hypothesis, and this region is now considered as probably involved in low-level visual processing (Jobard et al., 2003). The third candidate was proposed more recently by Cohen and colleagues, who suggested that an area labeled the “visual word form area” (VWFA), situated at the anterior part of the left occipito-temporal junction (in the left fusiform gyrus), would underlie the abstract representations of letters in the visual modality (Cohen et al., 2000, 2002). However, it is debated whether this area is specific only to letters and only to the visual modality (Price and Devlin, 2003; Moore and Price, 1999). Substantial recent research is lending growing support to the possibility that this area reflects an operation common to the processing of words with regular (Kronbichler et al., 2007) or irregular (Bruno et al., 2008) orthographies, word sub-units (Binder et al., 2006), pictures (Starrfelt and Gerlach 2007), objects (Bar et al., 2001), or stored visual forms and structures in general (Joseph and Gathers, 2003). The fourth and last candidate is within the left parietal cortex, including neural patches in the left superior parietal lobule and perhaps also in the left supramarginal gyrus, which are often reported in studies that indicate activation in the left occipito-temporal junction (Price et al., 1996b; Puce et al., 1996; Longcamp et al., 2003; Pernet et al., 2004; Kuo et al., 2004; James et al., 2005) thus implying a role in letter processing. More recently, this area was found to be even more letter-selective than the left occipito-temporal junction is (Joseph et al., 2003, 2006; Levy et al., 2008). Together, the extensive research implies that some posterior/intermediate areas in particular in the left occipito-temporal junction and in left the temporo-parietal cortices significantly contribute to different aspects of brain processing of the letter visual forms, and as recently shown, also to logographic forms of alphabet (Chan et al., 2009). The present thesis attempts also to disambiguate the precise functional role of these areas during reading.

Thirdly, extending beyond posterior areas for lower level linguistic processing (Figure 1.1), the analysis of higher word information such as phonological and lexico-semantic processing takes place at 200-600 ms (Halgren et al., 2002; Helenius et al., 1998; Pylkkänen et al., 2002, 2006; Pylkkänen and Marantz, 2003; Simos et al., 1997; Wydell et al., 2003; Fiebach et al., 2002; Rodriguez-Fornells et al., 2002; Wilson et al., 2007) and recruits a large network including regions in the temporal and parietal cortices, and extending also to anterior (frontal) areas (see [Jobard et al., 2003] for a meta-analysis). At this stage the phonological and lexico-semantic properties of a word are processed, and therefore a clear distinction is made between words, pseudowords and letter strings (Salmelin et al., 1996; Wilson et al., 2005; Wydell et al., 2003). The work presented in the ensuing chapters highlights the significance and functionality of the parieto-frontal network for higher linguistic processing.

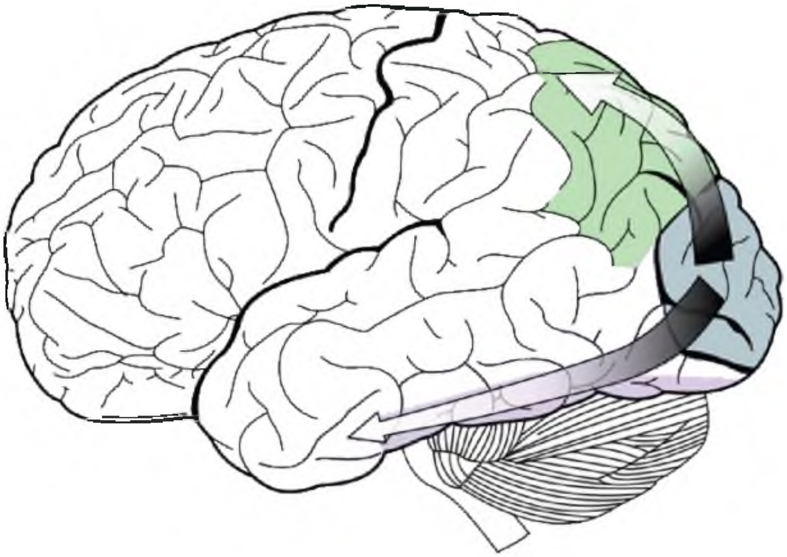

Figure 1.2 Ventral (purple) and dorsal (green) streams in the human brain visual system. Adapted from Wikimedia Commons (http://commons.wikimedia.org/wiki/Main_Page).

Neuronal oscillations during reading

As reviewed above, hemodynamic neuroimaging techniques such as PET and fMRI, with their excellent spatial resolution, are very successful in identifying the different brain areas that participate in the distributed brain network that is responsible for language. However, it has become evident over the years, that such one-to-one mapping between a brain area and a specific component of a cognitive function is very often far too simplistic. Alternatively, synchronous or neuronal activity corresponds to concurrent and repetitive firing of neurons, which facilitates the activation of functional networks because it increases the probability that neurons entrain one another in synchronous firing (e.g., Konig and Schillen, 1991). This firing occurs at a given frequency, specifically allowing the same neuron (or neuronal pool) to participate at different times in different representations. Synchronous oscillations in a wide range of frequencies are therefore considered to play a crucial role in linking areas that are part of one and the same functional network. The investigation of their patterns can therefore enable us to respond to questions that hemodynamic neuroimaging was unable to address so far, for instance, how the brain integrates the different types of linguistic processes (see [Bastiaansen and Hagoort, 2006] for a review). Moreover, the processing of more complex and higher level aspects of reading, such as the access to consciousness of its intrinsic processes, is particularly well accounted by synchronous oscillations (Dehaene and Naccache, 2001; Edelman, 2003). Hence, to accomplish this goal, Chapter 4 focuses on neuronal oscillatory patterns during consciousness access of reading processes.

Deos the bairn not raed ervey lteter by istlef, but the wrod as a wlohe? (title taken from Grill-Spector and Witthoft, 2009)

Given that in Chapter 4 we examine the perceptual consciousness access (CA) of either local (letters) or global (words) information, I reasoned it important to introduce here the two principal approaches in the literature vis-à-vis the nature of visual encoding of words: global and local. According to the first, the visual traits of word forms are probably encoded in memory. The main argument supporting this view is the existence of the "word superiority effect" (WSE) (Cattell, 1886) which postulates that a letter is better identified when it is presented within a word (Reicher, 1969; Wheeler, 1970) or within another stimulus with orthographical regularities, that is pseudoword (Gibson et al., 1962; Carr et al., 1979; Grainger et al., 2003; Jacobs and Grainger, 1992; McClelland, 1976) than within a randomly structured letter string or a letter in isolation. For instance, it is easier to distinguish 'b' from 'c' when they are presented in 'bar' vs 'car'. The WSE would therefore support the hypothesis that the physical characteristics, namely its form, of a word are encoded in memory, thus enhancing the recognition of its constituents, namely letters. More recently, it was shown that the WSE operates already during the processing of letters, i.e. the visual word form representations can constrain letter identification already at 200ms post stimulus (Martin et al., 2006). Another argument favoring the hypothesis of global encoding is the insensitivity of word recognition speed to the number of letters in (3–6-letter) words (Nazir et al., 1998). Longer words do not follow this rule as they involve more than one eye fixation (Legge et al., 1985). Finally, it is often that we read words with missing letters, without even having noticed the missing letters.

By contrast, local encoding postulates that words are recognized only if their letters and even letter features are separately recognizable. This view argues that in spite of our expertise from reading a hundred million words during our life (Pelli et al., 2006), we never learn to see a word as a feature; our efficiency is limited by the bottleneck of having to rigorously and independently detect simple features (Pelli et al., 2003). This bottleneck is explained by the fact that human vision squelches (suppresses) features, allowing them to pass only if they are well above the noise, namely the intrusion of countless false features. However, by blocking the intrusion of noise, this mechanism achieves reliability at the expense of efficiency, thus it impairs the recognition of more complex objects such as words. This phenomenon is best described by Pelli and colleagues who have shown that in identifying even the five most common three-letter English words, observers have the handicap predicted by recognition by parts: a word is unreadable unless its letters are separately identifiable (Pelli et al., 2003). This was explained by what the authors labeled the "word-length effect", according to which the efficiency of word recognition is inversely proportional to the word's number of letters. Therefore, efficiency for n-letter words is 1/n that for single letters. Surprisingly, this effect is valid not only for long words, which require more than one eye fixation (Legge et al., 1985), but also for short words and even single letters. Thus, despite reading for decades, a hundred million words, fluent readers identify even the most prevalent words with accuracy attainable through strictly letter-based identification. Interestingly, the authors claim that this effect is not at odds with the long-known WSE, but rather parallels (and over-powers) it: whereas the WSE increases a 5-letter word recognition by a factor of 1.3, the word length effect reduces it by a factor of 5. Despite the remarkable demonstration of such a plausible word length effect, it must be clear that the effect was obtained under very "unnatural" conditions (e.g. noise or contrast manipulation), which substantially differ from the every-day conditions of reading (e.g. excellent signal-to-noise ratio and maximal contrast). Hence, it is unclear whether such an effect also applies to the every-day realm, outside the laboratory. To summarize, the two approaches regarding word encoding could be taken as an indication that the two mechanisms operate in parallel, despite differences in spatio-temporal recruitment of the reading network. This note should be kept in mind when reading this thesis in general and Chapter 4 in particular.

Reading disability and skill

Literacy is the ability to read and write; illiteracy, however, is usually caused by not having had the opportunity to learn these functions. Dyslexia refers to a developmental disability in reading or spelling occurring despite normal intelligence, adequate environment and educational opportunities (see seminar by Démonet et al., 2004). Hence, it is a neurological deficiency which is distinct from reading disabilities resulting from other causes such as non-neurological audio, motor or visual impairment, from poor reading instruction, from mental retardation, emotional disturbance, or from environmental disadvantage. Many dyslexics never learn to read or write effectively, although they tend to show above average intelligence in other areas. From 10 to 15 percent of all children suffer from reading disability, i.e. they read significantly below their mental ability. In schools, students who are not mastering reading skills may be referred to either a remedial-reading or a learning-disabilities specialist, both of whom employ a similar procedure. They are given a series of diagnostic tests to determine how their strengths can be enhanced and their weaknesses overcome. A program based on the evaluation is developed for the student and followed by both the specialist and the classroom teacher. At the end of the term, the student will be retested to assess any progress and to update the program. Research has shown that with early and direct attention given to the reading program, greater improvement will occur. Many studies have indicated that remedial-reading instruction can lead to significant gains that are retained after many years. Although the present dissertation was based solely on findings from healthy participants who were mostly proficient readers, the results may have important implications on remedial reading instruction. This is also evidenced brain-wise since the remedial instruction is prone to alter brain activation in the dyslexic brain (Démonet et al., 2004). In particular, Chapter 3 elaborates on the link between dynamics within the reading neural network and reading performance. Tracing back the origins in time of this link, dyslexia was first recognized as a neurological impairment at the turn of the nineteenth century: neuropathological studies suggested a role of an atypical development of brain asymmetries to consist in the origin of dyslexia. To date, although dyslexia is usually considered of a constitutional origin, the actual mechanisms subtending it are still not univocal and currently remain the subject of intense research endeavor in various neuroscientific areas and along several theoretical frameworks (Habib, 2000). The large neuroimaging evidence points out that dyslexic patients fail to activate prominent reading areas in comparison to healthy subjects (see [Habib, 2000] for a review). Amongst the earliest and most posterior differences in the activation cascade during reading between healthy and dyslexic participants, emerges at the 150 ms post-stimulus activation in the the left occipito-temporal junction (LOT) (Figure 1.1). As previously mentioned, activation in this area is enhanced for letters; however, activation in this region is not enhanced as a response to letters, for dyslexics (Helenius et al., 1999; Paulesu, Démonet et al., 2001); and more recently, the correlational relationship between gray matter volumes in this region and reading skills which dissociate healthy from dyslexic participants (Pernet et al., 2009). Therefore, the findings in the coming chapter, which amply stress the importance of this region during reading, further allege the failure of dyslexics to activate prominent reading areas. In terms of long-brain communication (coherence), general tendencies for a reduced coherence can be found in dyslexic patients compared to healthy subjects during language processing (see [Weiss and Mueller, 2003] for a review).

In addition to the above mentioned developmental dyslexia, which is a learning disability, acquired dyslexia (alexia) is a reading disability following brain damage to prominent reading areas. Neuropsychological evidence has led to the dissociation between two sorts of acquired dyslexia: phonological and surface dyslexia (Coltheart, 1985). Patients with acquired phonological dyslexia are poor at reading pseudowords (unknown letter-strings following the internal structure of words) whereas their word reading is relatively spared (e.g. Funnell, 1983). This possibly results from impairment in grapheme-to-phoneme (G-P) conversion, which relies mainly on left infero-parietal and left infero-frontal regions (Jobard et al., 2003; Mechelli et al., 2003). By contrast, patients with acquired surface dyslexia present with left infero-temporal lesions and are very poor at reading irregular words (which are transformed by regularization) whereas their ability to read or spell pseudowords or regular words is unimpaired (e.g. McCarthy and Warrington, 1986). Semantic dementia patients who suffer from a loss of semantic knowledge also present with lesions to left temporal regions, and are also often poor at reading irregular words (Patterson and Hodges, 1992; for a review see Hodges and Patterson, 2007). Together, these evidences have converged to raise a conjecture of two anatomically distinct pathways underling reading

On the basis of this anatomical dissociation, Coltheart et al. (2001) have proposed the dual-route cascade (DRC) model, which is a computational model of visual word recognition and reading aloud, according to which reading is achieved via two major routes: the direct (also called lexical or orthographic) route and the indirect (also called non-lexical or phonological) route. As illustrated in Figure 1.3, whereas the lexical route has a direct access to semantics via the mental lexicon, the non-lexical route must first proceed to grapheme-to-phoneme conversion before retrieving semantics. The model is amongst the most successful of computational models in simulating reading, however, one should also note the other models having surged in the past decade, which can also complement the DRC model in better explaining reading (e.g. Harm & Seidenberg, 1999; Perry, Ziegler, & Zorzi, 2007; Plaut, McClelland, Seidenberg, & Patterson, 1996; Zorzi, Houghton, & Butterworth, 1998; Ans et al., 2001). Nevertheless, because brain lesions are often extensive and heterogeneous, it has been difficult to establish the precise functional anatomical correlates of the lexical (direct) and non-lexical (indirect) routes. In a similar vein, neuroimaging studies have not been more successful in establishing the neural correlates of these two routes (Jobard et al., 2003; Mechelli et al., 2003). In Chapter 3, we took on ourselves the enterprise to attempt and specify neuronal pathways underlying this remarkable computational model. Fortunately, we managed to isolate posterior neural pathways that provided a good account for the two routes. In view of the above, this endeavor could have noticeable consequences for diagnosing of dyslexic patients.

Extending beyond the advantage of the diagnosis of reading impairment, the DRC model allows one to make quantitative predictions about reading performance in normal (Coltheart et al., 2001; Castles, Bates and Coltheart, 2006; Coltheart, 2006) and dyslexic (Rapcsak et al., 2007) readers. Thus, it is suggestive of a reading style based on route reliance (lexical vs. non-lexical) in a skilled and poor population of readers. This single-word reading style should be distinguished from (i) strategies, which literally imply a certain conscious control, and may therefore be slightly misleading in the current context; and (ii) text-based strategies/styles, which are used in an automated manner to assist with meaning decoding, by, for instance, picking up morphemic, semantic, syntactic or contextual clues, to infer the meaning of the text, with minimum lower level processing (e.g. letters). The (single-word) reading style based on lexical/non-lexical processing, was already noted as early as in the seventies of the past century by Baron and Strawson, who have observed different degrees of such reliance patterns during reading (lexical vs. non-lexical) even in a population of skilled readers (Baron and Strawson, 1976). Such reliance differences are probably developed very early (or even pre-natally determined), as they are already observed in childhood (Treiman, 1984). Furthermore, these reliance patterns are performed in an automated/unconscious manner (Zevin and Balota, 2000), thus alluding to the possibility that they rely on shifts in neural pathways, which were recently found to unconsciously mediate the alternation of reading tasks (Nakamura et al., 2007). Chapter 3 thus expands upon the scope of understanding reading styles by providing a first and unique demonstration that such patterns are based on neural pathways and can predict reading skill. It also raises the novel idea of an efficient 'in cerebro' reading style depending on the fingerprint of the stimulus to be read and argues that individually unique reading styles may translate to either skilled or deficient reading ability, and could also be used in the future for improvement of reading skill in general, and for remedial reading instruction of dyslexics, in particular.

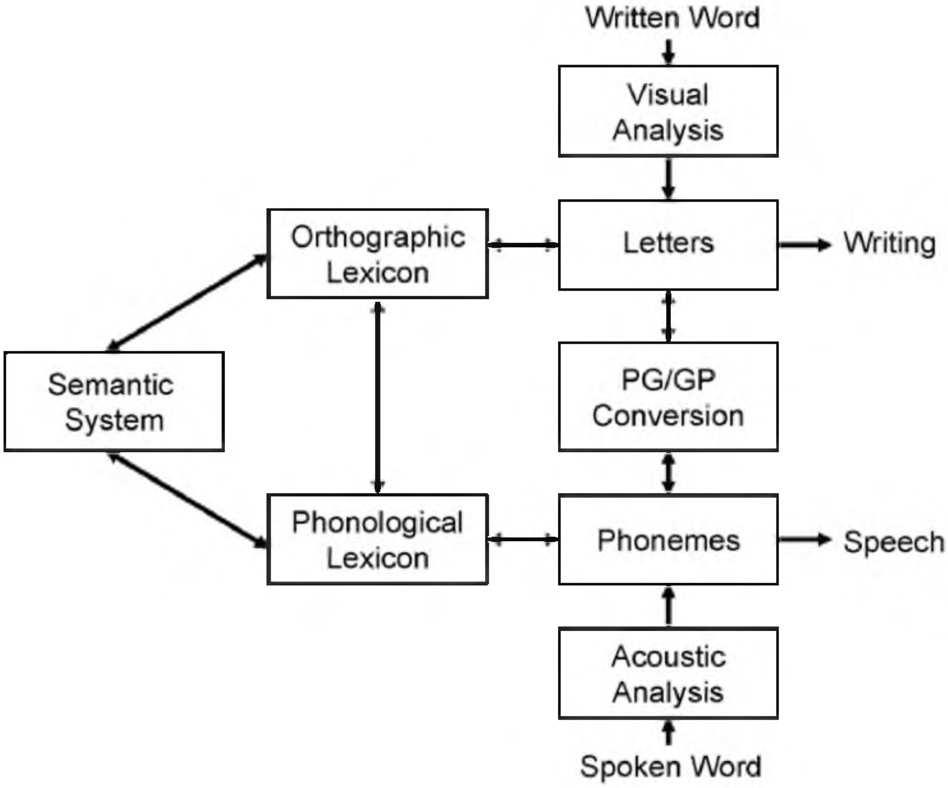

Figure 1.3 Dual-route cognitive model of reading and spelling. Adapted from Rapcsak et al. (2007). PG: phoneme–grapheme, GP: grapheme–phoneme conversion.

<u>Conscious and unconscious reading processes</u>

Reading is a complex function entailing the automatic execution of processes such as the (visual) decoding of letters (orthography) into pronunciations (phonology) that have a meaning (lexico-semantics). As previously described in this introduction, these processes are so automatic, rapid and irrepressible, that if we do not constantly maintain a firm intention to do so, they operate below the level of our consciousness. This irrepressible and unconscious automated function is well illustrated by the word interference effect in a standard color–word Stroop task (e.g., MacLeod, 1991). It is worth noting that additionally to the purely cognitive processes, other non-conscious processes occurring during reading entail other non-cognitive mechanisms such as visual fixations and saccades. For the cognitive orientation of this thesis, however, I will focus on the first type of mechanisms.

To realize the extent of non-conscious cognitive mechanisms during reading, studies mainly focus on the influence of the presentation of a word stated invisible, on thoughts, feelings, actions, learning or memory; this is referred to as subliminal perception. Words are usually made subliminal by the joint use of brief presentations and masking techniques. When presentation is brief enough and masking is strong enough, words stay below the threshold for consciousness access (CA) (see example in Figure 1.4). This masking technique has been used to show that unconscious, i.e. subliminal, word perception influences behavior. To this aim, the unconscious stimulus (prime) precedes a highly visible target, and it has been shown that the target is processed more efficiently when preceded by a related prime than by an unrelated prime. This technique is referred to as masked priming. Throughout the years the work of defining the limits of non-conscious perception has mainly relied on studies of semantic priming. This approach consists in testing the hypothesis that the meaning of a word (or another stimulus) is extracted while the subject cannot consciously identify it or even detect its presence. For instance, if an observer is asked to classify a letter string as either a word (e.g. *doctor*, *bread*) or a nonword (e.g. tocdor, dreab), a letter string such as the word *doctor* will be classified as a word faster when it follows a semantically related word (e.g. nurse) than when it follows a semantically non-related word (e.g. *butter*). A brief historical overview of studies on non-conscious word perception now follows (partly based on the review of Kouider and Dehaene, 2007).

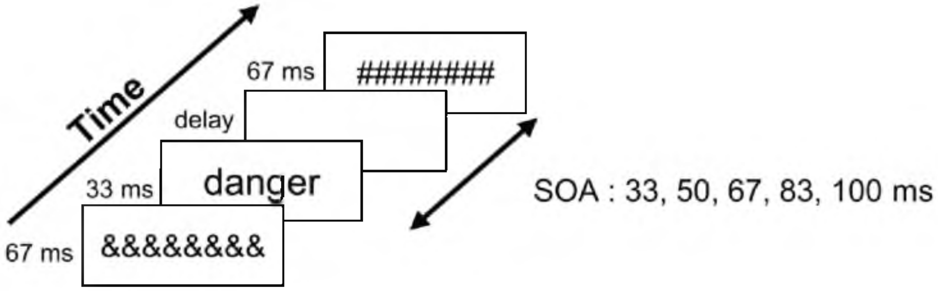

Figure 1.4 An example for a novel paradigm testing for semantic priming. Subjects were asked to name emotionally negative or neutral words flashed for 33 ms. Each target word was preceded by a 67-ms mask and followed by a variable blank and a 67-ms postmask. The interval (SOA) between the target and the subsequent mask varied from 33 to 100 ms. Adapted from Gaillard et al. (2006).

The study of non-conscious perception has appeared as early as the emergence of psychology and its separation from philosophy in the nineteenth century. Pioneering studies during that period and the beginning of the twentieth century were among the first to suggest that unconscious processing of stimuli presented below the level of conscious awareness can be detected in response to questions which require subjects to make decisions regarding the unperceived stimuli. In such studies, subjects were presented with indiscernible stimuli and asked to make guesses regarding the nature of the stimuli. For example, visual stimuli such as letters, numbers, or geometric shapes were presented at such a great distance from the subjects that they could not be seen clearly; or names of letters would be whispered so faintly that subjects could not hear them. Interestingly, it was shown that when asked to discriminate the stimulus (Pierce & Jastrow, 1884) or even to guess its identity (Sidis, 1898), subjects were able to do so with accuracy above chance level.

During the second half of the twentieth century, the power of subliminal perception has gained popularity with the appearance of claims of its effects on customer's choice. Perhaps the most widely known claim was made in 1957 by James Vicary, a market researcher. He claimed that over a six-week period, 45,699 patrons at a movie theater were shown two advertising messages, 'Eat Popcorn' and 'Drink Coca-Cola', while they watched a film. According to Vicary, a message was flashed for 3/1000 of a second once every five seconds. The duration of the messages was so short that they were never consciously perceived. Despite the fact that the customers were not aware of perceiving the messages, Vicary claimed that due to these subliminal messages the sales of popcorn rose 57.7% and the sales of Coca-Cola rose 18.1% over a six-week period. However, Vicary never released a detailed description of his study and there has never been any independent evidence to support his claims. Moreover, Vicary himself stated later on, that the original study was a fabrication, and that it had been no more than a marketing gimmick. For a critical review on these fallacious commercial studies see Pratkanis (1992). Later on in the 1970s, non-conscious influences during subliminal perception were studied under more controlled laboratory conditions. The classic studies were conducted by the British psychologist Anthony Marcel. These experiments were based on previous findings indicating that a decision regarding a stimulus is facilitated or primed when the stimulus follows a related stimulus. Marcel was able to demonstrate semantic priming, i.e. the facilitation of the processing of a visible target word by another semantically related invisible prime word (Marcel, 1980, 1983). Since the time of Marcel's original experiments, there have been many other studies that have used similar methods. Not only have these studies confirmed Marcel's original findings, but they have shown that other stimuli such as pictures, faces, and spoken words can also facilitate subsequent decisions when they are presented under conditions that make it difficult to discriminate one stimulus from another stimulus. Nevertheless, until the late 1980s the scientific community was extremely skeptical regarding the existence of subliminal perception, perhaps mainly due to the fallacious commercial studies described above, and to the critical positions of Eriksen (1960) and Holender (1986), who mainly argued against the use of introspection and for the need of methodological improvements, respectively. In the late 1980s, the improvements in subliminal priming paradigms, along with the emergence of great interest in implicit memory and implicit learning at that time (e.g. Kihlstrom 1987; Schacter 1987), have considerably helped reinstating the non-conscious processing from a cognitive rather than from a psychoanalytic perspective. As an example of the recent methodological improvements in demonstration of semantic priming, Gaillard et al. (2006) used a new approach by varying stimulus-mask interval, thereby illustrating that emotional words were more easily accessed than neutral words (Figure 1.4). For an exhaustive review of the many studies ever since and of the state of the art in non-conscious perception studies, refer to the critical review by Kouider and Dehaene (2007).

Despite the above mentioned ample evidence for non-conscious processes accompanying reading, studying how processes actually access consciousness has not been addressed until recently. Theoretical approaches (Chalmers, 2000; Koch, 2004; Block, 2007) contend that consciousness should be dissociated into two: (i) general (neural mechanisms for) consciousness, corresponding to an unspecific conscious experience such as the subcortical activity enabling wakefulness, and (ii) (specific neural mechanisms underlying) a specific conscious experience. Such concepts of "basic" versus "specific" "parcels" of consciousness have been borrowed and slightly re-adapted by neuro-scientific researchers interested in unveiling the neuronal mechanisms underlying consciousness. For instance: phenomenal vs. access consciousness (Block, 2005), unconscious (feedforward processing) vs. conscious (recurrent processing) (Lamme, 2006), or preconsciousness vs. consciousness (Dehaene et al., 2006) – are all used to attempt to account for the different states of consciousness that seem to be reported during neuro-cognitive experiments. Unfortunately, to date the neuronal mechanisms underlying consciousness access (CA) are far from being unequivocal; in a nutshell, whereas one group of researchers claims that consciousness emerges early and in posterior areas (ffytche and Zeki, 1996; Zeki and ffytche, 1998; ffytche et al., 1998; ffytche, 2000; Super et al., 2001; Pins and ffytche, 2003; Tse et al., 2005; Lamme, 2006; Melloni et al., 2007), another group argues that the latter corresponds to "a parcel of consciousness", that is, to partial consciousness, and that "full consciousness" is subtended by late and anterior brain activity (for review see Rees et al., 2002; or see Lumer et al., 1998; Beck et al., 2001; Dehaene et al., 2001, 2003, 2006; Rees et al., 2002; Marois et al., 2004; Dehaene and Changeux, 2005; Sergent et al., 2005; Del Cul et al., 2007; Vinckier et al., 2009). The core of the debate seems to ultimately emanate from the difficulty of isolating consciousness independently from its cognitive consequences, and from those related to the act of internally or externally reporting the CA (attention, working memory and language). This difficulty seems to be even more pertinent since the brain areas which are outlined above by the majority of the investigators to accommodate CA, namely the parieto-frontal network, is the same which underlies higher cognitive functions related to the act of "knowing" that one is conscious of something, even introspectively. Ostensibly, the authors who argue for posterior interactions as the basic correlates of consciousness (e.g. Lamme, 2006) cannot prove that the participant is aware, because there is no resorting to any kind of report. This difficulty is also reflected during the attentional blink, where evaluating CA is not certain because of the possibility of a momentary and fleeting CA, which is then rapidly forgotten and thereby cannot be reported (Luck et al., 1996). Attempting to solve this problem, Dehaene and colleagues defined a new nomenclature according to which this "basic" state of phenomenal consciousness without reporting should be addressed as "preconscious", whereas when reporting is present, it should be addressed as conscious. As described in the theoretical proposal by Dehaene and colleagues (2006), for a stimulus to reach consciousness, two factors are jointly needed: (i) strong enough bottom-up stimulation (which can be prevented by stimulus degradation or masking), and (ii) strong enough top-down resources allocated to the stimulus (which can be prevented by drawing the attention to another stimulus or task). Therefore, failure of CA due to poor bottom-up stimulation would lead to subliminal processing, whereas failure due to poor top-down access would result in preconscious processing. For the first, stimulus-induced activation is insufficient to allow information accessibility, in spite of all efforts of focused attention. For the second however, stimulus-induced activation is sufficient for CA, but the lack of top-down attentional amplification temporarily buffers the stimulus into a non-conscious store. This is also congruent with other proposals stipulating that CA is achieved only when the output representation is sufficient to trigger the correct behavior in the response pathway, and the perceptual and the response pathways are functionally interconnected (Colagrosso and Mozer, 2004); also alluding to the necessity of a report for the emergence of consciousness.

The nominal disentanglement between conscious and preconscious, however, does not solve the problem and does not provide any new way to empirically probe the "presence" of CA under a plausibly preconscious state. Nevertheless, we were yet inspired by the this nomenclature used by Dehaene et al. (2006), and in Chapter 4, we attempted to accommodate this proposal to the framework of reading: The cascade of processes during word reading entails the automatic execution of the (visual) decoding of letters (orthography) into pronunciations (phonology) that are mapped onto meaning (lexico-semantics). These processes are extremely automated, rapid, unconscious and irrepressible, almost like a "reflex", as nicely illustrated by the word interference effect in a standard color–word Stroop task (e.g., MacLeod, 1991). Hence, unless we constantly maintain a firm intention to be aware of these processes, they constantly operate below the level of our consciousness. Inspired by this synthesis, we conjectured that by maximizing attentional resources to different levels of CA, while maintaining bottom up stimulation at a certain equilibrium, it would be possible to report the oscillation between two levels of consciousness. However, as postulated by Dehaene and colleagues (2006), due to stimulation at the threshold of perception, efforts of focused attention cannot always result in CA. Thus, we introduced in Chapter 4, a novel approach according to which failure to access consciousness at the firstly intended task (semantic processing), would give in to a potential CA for a lower level task (orthographic processing). This approach presumes that, similarly to some meditation practices, voluntary sustained attention increases the mental processes that are accessible to conscious report (Lutz et al., 2008); a similar view was already held in the nineteenth century by the "father of experimental psychology", Wilhelm Wundt (Butler-Bowdon, 2007).

In summary, we found a way in Chapter 4, to circumvent the problem, which in our opinion, impedes consciousness investigation from advancing forward. This was done by addressing the issue differently: Instead of focusing on the effects of conscious versus unconscious processes, we employed a novel approach by focusing on the effects of contrasting two conscious processes, one higher (semantics) and the other lower (orthographic). Therefore, by contrasting the one to the other we obtain the correlates of moving from partial to full consciousness access (CA), thereby ruling out brain activations related to report-ability. This approach may at least partly, disambiguate the debate on the nature of consciousness: whether it can stand on itself without the need for a subjective report, or whether the latter is absolutely necessary for a full- (and not pre-) consciousness. Noteworthy, we are completely neutral, however, in regards to finding the "pure" neural correlates of consciousness as viewed previously (conscious vs unconscious) and thereby exempt ourselves from this perhaps impossible enterprise.

Outline of the thesis:

After giving an outlook of the thesis, and introducing the reader to some important information regarding automatic brain processes during reading, in Chpater 2 I outline the principal automatic processing steps sustaining reading, and illustrate their brain distribution and information routing. This work demonstrates the spatio-functional recruitment of reading areas and as a corollary, separates lower and higher reading processes.

In Chpater 3 I extended the scope of investigation by unraveling how automatic reading processes can predict reading skill. The chapter presents distinct anatomical pathways corresponding to the two routes for the processing of written language. It compares effective connectivity data during reading with out-of-scanner reading tests. Reliance on these neural pathways predicts reading skill. The chapter thus raises the novel idea of efficient ‘in cerebro’ reading styles depending on the word’s fingerprint.

In Chapter 4 I sought to understand how these automatic mechanisms access consciousness. To this aim, we used magnetoencephalography and a stair-case paradigm, to pinpoint the perceptual boundary between the consciousness access of lower and higher reading processes. The transition is reflected by localized neural oscillatory effects.

In Chapter 5 I outline the main findings described in this thesis, their implication to the domain of reading and consciousness, and reflect on interesting future follow-up studies or applications.

Chapter 2 Piecemeal Recruitment of Left-lateralized Brain Areas during Reading: a Spatio-functional Account

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Abstract

Neuro-imaging studies of reading converge to suggest that linguistically elementary stimuli are confined to the activation of bilateral posterior regions, whereas linguistically complex stimuli additionally recruit left hemispheric anterior regions, raising the hypotheses of a gradual bilateral-to-left and a posterior-to-anterior recruitment of reading related areas. Here, we tested these two hypotheses by contrasting a repertoire of eight categories of stimuli ranging from simple orthographic-like characters to words and pseudowords in a single experiment, and by measuring BOLD signal changes and connectivity while 16 fluent readers passively viewed the stimuli. Our results confirm the existence of a bilateral-to-left and posterior-to-anterior recruitment of reading related areas, straightforwardly resulting from the increase in stimuli's linguistic processing load, which reflects reading processes: visual analysis, orthographic encoding and phonological decoding. Connectivity analyses strengthened the validity of these observations and additionally revealed an enhancement of the left parieto-frontal information trafficking for higher linguistic processing. Our findings clearly establish the notion of a gradual spatio-functional recruitment of reading areas and demonstrate, to the best of our knowledge, the first evidence of a robust and staged link between the level of linguistic processing, the spatial distribution of brain activity and its information trafficking.

Introduction

The 19th century neurological model of language proposed that reading implicates a gradual posterior-to-anterior activation: starting with visual processing in the extrastriate cortex, then retrieving the visual word form in the left angular gyrus, proceeding to Wernicke's area for auditory word form conversion, and terminating in Broca's area and the motor cortex for speech articulation (see Geschwind, 1965); the model was later revised by refining the location and functional roles of the anatomical regions (Price, 2000), and by investigating their circuitry and plasticity (Posner et al., 1999). In a similar vein, over the past two decades there has been an extensive number of neuroimaging studies interested in unraveling the brain organization that sustains reading (reviewed in Price, 2000; Jobard et al., 2003; Démonet et al., 2005; Salmelin, 2007), altogether conveying an image of bilateral posterior activations which are induced by linguistically elementary stimuli, and of more left-hemispheric anterior activations induced by stimuli higher in terms of their linguistic contents. However, the bilateral-to-left and posterior-to-anterior activation-cascade which is progressively triggered by stimuli whilst increasing Linguistic Processing Load (LPL), has never been empirically tested in a single experiment. To this aim, rather than comparing the activation of letters to that of other non-linguistic stimuli (Gros et al., 2001; Polk et al., 2002; Flowers et al., 2004; Pernet et al., 2005) or of words to that of pseudowords or non-words (Howard et al., 1992; Price et al., 1994; Brunswick et al., 1999; Cohen et al., 2000, 2002), we contrasted a full range of hierarchically ordered stimuli ranging from simple orthographic-like elements to words and pseudowords: (a) *Single-pseudoletters*, (b) *5-pseudoletters*, (c) *Single-letters*, (d) *3-letter strings* (consonants), (e) *5-letter strings* (consonants), (f) *Syllables* (3- letters, single-syllable), (g) *Words* (5-letters, 2-syllables) and (h) *Pseudowords* (5-letters, 2-syllables) (see example of stimuli on Figure 2.1A).

There have already been a few studies that have applied a protocol with a hierarchical pool of linguistic stimuli. For instance, Tarkiainen et al. (1999) presented single-letters, two-letter syllables, four-letter words, as well as one-, two- and four-element symbol string, for which Gaussian-noise levels were manipulated. They measured the cortical dynamics induced by the perception of these stimulus-categories with magneto-encephalography and observed a left lateralized word/letter string-specific effect in the occipito-temporal cortex, the spatial focus of their investigation. An fMRI study by Tagamets et al. (2000) also used a pool of four stimulus-categories: false-fonts, letter-strings, pseudowords and words. Their results confirmed the presence of a bilateral-to-left lateralized shift from false-font to word but failed to observe a posterior-to-anterior recruitment which could be related to the particular working memory task they used (see Discussion). In addition to the visual complexity or other 'parametric' modulation, and given that the distributed brain network involved in reading is sensitive to several underpinning processing steps such as visual, orthographic, phonological and lexical-semantic analyses (Joubert et al., 2004; Price and Mechelli, 2005), one may wonder whether these steps could account for the converging observation of bilateral-to-left and posterior-to-anterior recruitment. Evidence from independent lines of research mirrors a serial organization of reading steps. First, visual perception of unfamiliar objects activates the extrastriate cortex with a right-hemispheric predominance (Gros et al., 2001) and progressively involves elaborated aspects of visual processing (Young, 1992). This first step related to feature processing would take place at 100 ms after stimulus onset (Salmelin, 2007). Second, encoding orthographic units, namely letters, additionally recruits intermediate regions such as the left fusiform and occipito-temporal (LOT) junction (Cohen et al., 2000, 2002; Polk et al., 2002; Joseph et al., 2003; Flowers et al., 2004; Pernet et al., 2005), the left parietal (LP) and the insula (Joseph et al., 2003). This second orthographic step would be sub-divided into letter specific encoding at about 150 ms post-stimulus (Tarkiainen et al., 1999) followed by, in the LOT junction at 180-200ms, a pre-lexical processing step specific to words and pseudowords but not to letter-strings nor to non-alphabetical stimuli (Cohen et al., 2000, 2002; Martin et al., 2006). Third, the processing of phonological units, i.e., syllables, involves the activation of more anterior regions (Posner et al., 1999; Démonet et al., 2005) such as superior temporal areas (mainly BA 22), the supramarginal gyrus (BA 40), and the opercular part of the inferior frontal gyrus (IFG, BA 44) at about 170-230 ms (Fiebach et al., 2002; Rodriguez-Fornells et al., 2002). Finally, the processing of meaningful units, i.e. sub-lexical or lexical units, additionally recruits after 250 to 600 ms (Helenius et al., 1998; Wilson et al., 2007) intermediate and anterior regions like the middle temporal gyrus, the posterior part of the inferior temporal gyrus and the triangular part of the L-IFG (see meta-analysis of Jobard et al., 2003). Altogether, these reports converge to raise the existence of a 'serial' recruitment of reading areas during the reading steps as specified above.

The investigation strategy used by some authors was to manipulate the stimuli's low- (e.g. length, Tarkiainen et al., 1999) or high-level (letter frequency, Vinckier et al., 2007) intrinsic properties. However, no neuroimaging study explicitly manipulated the piecemeal increasing number of orthographic (letter), phonological and/or semantic units. Here, by manipulating this gradual increase in linguistic processing while controlling for low level properties such as stimulus length, we could test whether the recruitment of brain areas as a function of linguistic complexity (referred here as Linguistic Processing Load - LPL) mirrored the 'serial' involvement of the aforementioned linguistic steps. Because the distributed brain network engaged by reading is sensitive to these processing steps (Price and Mechelli, 2005), we reasoned that the gradual increase in the number of these steps is likely to reflect an increment in the stimuli's LPL (Figure 2.1B). Finally, recent observations of task- (Bitan et al., 2005) or stimulus-dependent (Mechelli et al., 2005) shifts of effective connectivity have been observed between prominent sites for orthographic, phonological and/or semantic processing. Hence, if the nature of the stated recruitment of areas involved in reading is truly spatio-functional, their relationship (connectivity) should also be modified according to the LPL, i.e. the functional specialization of different areas would not be reflected via their level of activation only but also via the increase or decrease of connectivity according to the LPL (Pernet et al., 2007).

Here, we measured brain activity with fMRI while subjects fixated a cross and passively observed the alternating stimuli. Although passive viewing has some limitations, especially (i) the lack of subjects' responses which reduces the possibility of monitoring their behavior, and (ii) the inability to engage a specific process for stimuli like pseudoletters, it has the overall advantage of minimizing the engagement of task-related networks. The confound of task-related activations is often demonstrated: For instance, active tasks relative to passive viewing of the same stimulus array elicit a decrease of the blood flow for visual information processing (Shulman et al., 1997); reading aloud compared to silent reading implies the non-linguistic activation of motor and auditory regions (Bookheimer et al., 1995; Price et al., 1996a; Huang et al., 2001); silent and overt response conditions during word generation or semantic association elicit different activation patterns (Borowsky et al., 2005); and modifying the task instruction from discriminating to categorizing (Pernet et al., 2004), from rhyming to spelling (Bitan et al., 2005), or from lexical decision to pronunciation (Nakamura et al., 2006) – modulates the stimulus-driven activation and thereby engages different neural networks.

Materials and methods

Participants

Sixteen healthy individuals (eight males, eight females, mean age 27.2, sd 3.3 years), all university students with normal or corrected-to-normal vision participated in this experiment. All were right-handed on the Edinburgh handedness inventory, native French speakers, and free from any history of neurological or psychiatric illness or medical treatment. The Toulouse local ethics committee approved the experimental protocol and informed written consent was obtained from the subjects after the nature and possible consequences of the study had been explained to them.

Neuropsychological assessment

The subjects underwent a battery of neuropsychological tests in order to rule in average or higher than average IQ, phoneme awareness and meta-phonological aptitude, as well as to rule out reading disability, dyslexia or spatio-visual attention disorder (See Supplementary material: '*Neuropsychological assessment'* for details on the tests used).

Stimuli

Stimuli were all embedded in pseudo-characters so as to maintain a constant string length (seven characters), and displayed on a grey (RGB: 160, 160, 160) background to avoid visual fatigue (see example of stimuli on Figure 2.1A). Two hundred and eight stimuli were designed, twenty six per stimulus category, thus matching their frequency of appearance. Stimuli were matched (intra-category) and distinguished (inter-category) for their: angularity, visual surface and complexity, orthographic units in general and consonant and vowel structure in particular, phonological and lexical-semantic units, mean frequency of appearance for words, mean positional letter frequency (MPLF), mean positional bigram frequency (MPBF) and mental imagery score for words. It must be noted that pseudo-letters were easily distinguished from flankers (pseudo-characters) as they had clearly different (variable) shapes and were displayed at the center of fixation while pseudo-characters were always of the same shape and displayed in periphery.

The Linguistic Processing Load (LPL) ordering resulting from the stimulus construction was 1: *Single-pseudoletters, 2: Five-pseudoletters, 3: Single-letters, 4: Three-letter strings* (consonants)*, 5: Five-letter strings* (consonants), 6*: Syllables* (Three- letters, single-syllable*), 7-: Words* (Five-letters, two-syllables) and 8-*: Pseudowords* (Five-letters, two-syllables). This ranking followed a simple logic of ordered processes as reviewed in the Introduction: ranks 1 and 2 for visual feature extraction; ranks 3, 4 and 5 for orthographic processing (string assemblage); rank 6 for orthographic/phonological processing; and rank 7 and 8 for orthographic/phonological and semantic processing. Although the stimulus-ordering was mainly based on their intrinsic gradual involvement of reading steps (Figure 2.1B), it also reflected other factors like the visual 'load'. For instance, *Single-* and *5-pseudoletters* were ranked respectively 1 and 2 since *5-pseudoletters* were expected to require more processing. Noteworthy, this was based on the expected 'load' and not on stimulus complexity since stimuli were matched and flanked to ensure identical visual length. We also placed *Words* before *Pseudowords.* This may raise doubt given the lexical-semantic processing step, which can only be carried out by words and is, one could argue, the end goal of all language comprehension. The explanation to this apparent exception to the rule is that the concept of LPL is not utterly comparable to that of language comprehension, but rather reflects the heavier taxing of language-related areas. Indeed, orthographic and phonological similarities between pseudowords and neighborhood real words may not only cause activation of representations in lexical-semantic areas, but also increase the demands on lexical processing (Fiez et al., 1999; Price et al., 1996b), thereby taxing these areas to a greater extent (Mechelli et al., 2003) as a result of an automatic lexical-semantic ‘search’ for neighboring real words. This could additionally account for the longer RT and lower accuracy in lexical decision tasks (Ratcliff et al., 2004) observed for pseudowords in comparison to any other linguistic stimulus, including words.

Tasks and procedures

Subjects were briefly trained and familiarized with the procedures and stimuli prior to fMRI scanning. During the scanning, stimuli were displayed via a dual-display stereoscopic video projector (VisuaStimDigital, Resonance Technology Inc.) in synchrony with functional acquisition that duplicated the experimental computer screen with 500,000 pixels per 0.25 square inch resolution and a refresh rate of 85 Hz. In order to minimize ocular saccades and numerous fixations at different string positions, stimuli were presented with a horizontal visual angle of 4.2° for 200 ms. Additionally, the maximal number of letters was limited to five thus facilitating stimulus recognition in one fixation, although through the whole experiment the total length was always of 7 characters if one counts the pseudo-character flankers.

Participants were exposed to blocks of stimuli during five runs of five minutes each. Each run contained ten 17-s long blocks that alternated with 12.5-s long blocks of visual fixation (fixation-cross of 0.65° visual angle) necessary for the hemodynamic response relaxation. Such a blocked design maximizes the detection power of activity (Liu et al., 2001) and does not cause any attentional bias between lexical and non-lexical stimuli (Cohen et al., 2002). Subjects were simply instructed to fixate on the cross and to passively view the changing stimuli. Blocks were presented pseudo-randomly to increase condition alternation and avoid condition repetition among successive blocks. Each of the eight conditions was repeated in six different blocks among the five runs in such an order as to avoid interference with the low frequencies of scanner noise and physiological rhythms. In the fifth run, the last two blocks were used to equalize run-length, but discarded from analysis, so as to maintain an equal number (six) of blocks per condition. Each block contained twelve different stimuli of the same condition with a random inter-stimulus interval (ISI) ranging from 600 to 1100ms so as to avoid stimulus anticipation or rhythmic activity and to maximize the BOLD signal (Mechelli et al., 2000).

Data were sampled in a distributed way over the ISI, eschewing a possible bias of estimated activation (Price et al., 1999). This is particularly imperative for the signals within language regions, which are mostly phasic and transient (Price and Friston, 1997). At the end of each run, subjects could rest for 2-3 minutes and were asked to report stimulus visibility or any other difficulties or problems that could bias the experiment.

fMRI parameters

All subjects were scanned at the Neuroradiology service of Toulouse Purpan Hospital on a 1.5 Tesla Siemens Magnetom Vision scanner (Erlangen, Germany) equipped for multi-slice echo-planar imaging (EPI). For functional MRI studies, blood oxygen level-dependent (BOLD) imaging was performed using a T2*-weighted single-shot EPI sequence with a 60 ms echo time (TE), 2430 ms repetition time (TR), 90° flip angle, 250 mm field of view (FOV), 64 x 64 acquisition matrix with 16 interleaved slices parallel to the intercommissural plane (from z = -35 to z = 45), yielding a 3.91 x 3.91 x 5 mm voxel size. A high-resolution anatomical scan was acquired on the same plane at the end of the functional sessions using a 3D sequence: TE= 4 ms, flip angle= 8°, FOV=300 ms 5/8, 160 x 256 matrix, yielding a 1.17 x 1.17 x 1.18 mm voxel size.

Image processing

All functional images were pre-processed using techniques implemented in Statistical Parametric Mapping (SPM2, Welcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk). The functional scanning sessions contained 123 acquisition volumes, of which the first four were discarded for signal stabilization. A slice timing correction was performed with the fifteenth slice (the middle temporal one) as the reference. The sixtieth volume of the prior 3D-session was used as a reference for realignment of functional images to correct for head motion. T1-weighted anatomical images were coregistered to the reference image, and were used for the normalization of functional images onto the Montreal Neurological Institute T1-template with a resampling at $2mm^3$ (5th degree B-Spline interpolation).

Statistical analysis

Images were smoothed with a 6-mm-at-full-width-half-maximum Gaussian filter ensuring data normality. For each subject, the spatially normalized and smoothed images were used to create eight condition-type images per subject (general linear model with one regressor per condition and session convolved with a box car function). For the assessment of our first hypothesis, that is, the existence of a bilateral-to-left and posterior-to-anterior recruitment of reading areas, a random effect ANOVA model was set-up and a mean group image for each of the eight conditions compared to the fixation baseline (only positive activations were examined) corrected for multiple comparisons (FDR, $p < 0.05$, extended threshold $k > 30$ voxels, i.e., 240 mm^3) was obtained. Furthermore, a random effect regression analysis with a linear regressor coding for the increase in LPL across all 8 conditions was performed (FWE corrected, $p < 0.05$, $k > 30$ voxels). This analysis allowed us to look for areas that show a direct and linear relationship between activation levels and LPL. Results are reported in the Talairach space after transformation of the MNI coordinates using the Talairach Daemon Client (Lancaster et al., 2000). For figures, statistical parametric maps are overlaid on the individual 'inflated' Colin brain atlas anatomical images (Van Essen et al., 2001). Lateralization indices (LI) were also computed for each of the 8 conditions: Random effects maps were analyzed computing LI for increasing thresholds (LI curves) and bootstrapping voxels to create a sampling distribution of the LI and thus confidence intervals (Wilke and Schmithorst 2006). In short, LI curves were computed at regular intervals with a bootstrap (x100) for each hemisphere. The average of all 25% trimmed-means was then computed to obtain a single overall LI value. Weighted means were also reported and correspond to the average of all trimmed-means weighted by threshold value at each step of the LI curve. Computations were all performed using the Lateralization toolbox (Wilke and Lidzba 2007) excluding the 5 mm midline and stopping the bootstrap iterations for a cluster size of less than 30 voxels.

To assess our second hypothesis, i.e. that the gradual recruitment of left lateralized anterior areas reflects the progressive involvement of different reading processes, we performed three global null conjunctions (FWE corrected, $p < 0.05$, $k > 30$ voxels) that followed the increase in linguistic processing (Figure 2.1B). First we conjoined all conditions, therefore revealing areas involved in visual processing. Second, all conditions but single- and 5-pseudoletters were conjoined to look for areas involved in the processing of orthographic units. Third, syllables, words and pseudowords were conjoined to look for areas involved in phonological processing. It should be noted that a significant conjunction result does not mean that all the conditions were individually significant, but rather that activation levels for each condition were consistently high and jointly significant (Friston et al., 2005). In the aim of testing for individually significant activations, we used a more stringent approach by applying the conjunction null test. Correcting for multiple comparisons did not yield any significant activation in this case but similar results to the global null were obtained at $p < 0.005$ uncorrected ($k > 30$ voxels). Results of both conjunctions are reported in Table 2.1. Contrasts between conditions subsequently used the same uncorrected threshold. Contrasts were performed by pooling conditions and using an exclusive masking in case of 'double contrasts'. For instance, the '*Syllabic contrast'* tested for stronger activations related to phonological syllabic processing and was calculated as ((*Pseudowords* + *Syllables*) > (*5-letter strings* + *3-letter strings*)) while exclusively masking out -(*5-letter strings* + *3-letter strings*). Exclusive masking was performed with a threshold of $p < 0.05$ and ensured that stronger activations of pooled data were not spurious, e.g. stronger activation for syllabic conditions (*Pseudowords* + *Syllables*) in comparison to non-syllabic conditions (*5-letter strings* + *3-letter strings*) could not be related to deactivations of the latter. Likewise, inclusive masking ($p < 0.05$) ensured that differences were observed in regions where each of the main conditions was active (see Supplemental material '*Supplementary Analysis: contrast with inclusive masking*').

As further elaborated in the Results section, activation-clusters that were found selective for three processing steps (visual analysis, orthographic encoding/decoding and phonological encoding/decoding) were used for a supplemental region-of-interest (ROI) analysis. The analyses performed on these ROIs were orthogonal to the contrasts used to find the ROIs. The 1^{st} eigen values across voxels within a cluster and per subject were calculated and subjected to a repeated measures MANOVA with the different experimental conditions and ROI as independent variables. Post-hoc t-tests (Newman-Keuls, $p < 0.05$) were conducted to determine whether the difference among experimental conditions and ROIs was significant. Finally, for the purpose of testing the significance of the unilateral observations in the visual processing ROI (Results, p. 18, '*Posterior areas for visual processing*'), we also computed LI (lateralization indices) on masked random-effect maps.

Functional and effective connectivity

Functional MRI time series were extracted from each individual data set with spheres (3x3x3 mm) centered at cluster maxima-coordinates of the four left-hemisphere ROIs revealed in our analyses (thereby not taking into account the right occipital): (i) the left middle occipital gyrus (MOG) (-32 -91 10), (ii) the left lateral occipital-temporal area (LOT) (-46 -68 -5), (iii) the left parietal (precuneus, BA 7) (LP) (-24 -50 43), and (iv) the left inferior frontal gyrus (IFG) (-51 18 14). First, we looked at interregional functional connectivity: The temporal correlations of the fMRI signals across subjects within these four key areas were computed and compared across conditions. Here, we reasoned that some areas for reading should positively covary depending on the specific processing step of reading. If such co-variation among these areas was positively correlated to LPL, as defined here by the ordering of our stimuli (Figure 2.1A), it would predict the functional specialization of the connections between the areas we tested (Pernet et al., 2007). Second, for each individual, the segments of each regional time series corresponding to the different experimental conditions were extracted and multiplied by the first eleven time points of the hemodynamic response function. The segments of signal corresponding to each of the eight conditions were concatenated, resulting in a set of eight condition-specific series of 64 time points for each individual in each region. Finally, data were high-pass filtered (cut-off frequency 0.05Hz) to remove low-frequency concatenation-generated signals.

Effective connectivity was then assessed by means of structural equation modeling (SEM) implemented in LISREL software (version 8) (Jöreskog and Sörbom, 1996). Path models which provided a good account of the observed data were associated with both a small minima of the discrepancy function F and correspondingly large probabilities ($p > 0.05$) under the null hypothesis, as well as with low values ($p < 0.1$) for the root mean square error of approximation (RMSEA). Residual-variance and β-coefficient values of connection were estimated simultaneously using maximum likelihood methods implemented in LISREL. To define a path model that would account for the pattern of cortico-cortical associations during the passive viewing of all the eight conditions, we looked for paths (directed connections) and their coefficient values (path coefficients) which best accounted for the left hemispheric interregional associations captured by the correlations. The a priori model we used involved the four ROIs with the following directional connections: L-MOG to LOT, L-MOG to LP, LOT to LP, LOT to L-IFG and LP to L-IFG. Given that we also estimated residual variances, the number of connections between these areas was mathematically limited. Our starting hypothesis did not require defining feed-back connections, let alone that such operation would statistically render the model less robust. Finally, the model did not aim at investigating whole brain connectivity, feed-forward and -back projections, but rather to test the existence of the aforementioned recruitment of reading areas, and to expand the scope of functionality between these areas.

Table 2.1 Regions of activation revealed by the conjunction analyses

Region	BA	Hemisphere	Nb of voxels	z-score	x y z
<u>*Visual conjunction*</u>					
MOG/cuneus *	18/19	Right	2650	Inf	32 -91 12
		Left	2464	Inf	-32 -91 10
Precuneus	7	Right	168	7.17	24 -58 45
		Left	37	6.14	-22 -52 45

Orthographic conjunction					
MOG *		Right	2480	Inf	32 -91 12
		Left	3404	Inf	-32 -91 12
ITG/MOG (LOT) *†		Left	65	2.99	-46 -68 -5
Precuneus/SPL *		Left	227	7.09	-24 -60 47
MFG/IFG		Left	346	6.92	-38 50 -9
Precentral gyrus/IFG		Left	745	6.65	-48 2 37
STG		Left	37	6.36	-48 -50 10
Putamen		Left	42	5.96	-30 -16 -1
Phonological conjunction					
MOG/LG *	18/19	Right	1281	Inf	22 -96 16
MOG/cuneus *	18/19	Left	1884	Inf	-22 -97 12
SPL *	7	Left	124	6.58	-26 -52 43
Putamen *	-	Left	104	6.02	-18 4 5
IFG *	47/45	Left	405	5.95	-42 33 0
MFG *	11	Left	47	5.87	-38 46 -11
'Letter effect' conjunction					
SMG/STG *	40/13	Left	136	5.86	-53 -40 30

Results are reported for the conjunction global test at $p<0.05$ FWE corrected (extent threshold 30 voxels). Areas marked by a star (*) were also significant when testing for significant activations in each condition (conjunction null test $p<0.005$ uncorrected extent threshold 30 voxels). One area was present only in the conjunction null (and not global) and is marked by a **†**.

Inferior frontal gyrus (IFG); Inferior temporal gyrus (ITG); Left occipito-temporal (LOT); Lingual gyrus (LG); Left parietal (LP); Middle occipital gyrus (MOG); Middle frontal gyrus (MFG); Superior parietal lobule (SPL); Supramarginal gyrus (SMG); Superior temporal gyrus (STG).

Results

Progressive recruitment and reading gradients

In the first set of analyses, the eight conditions were contrasted to fixation to examine their cerebral correlates ($p < 0.05$ corrected, extent threshold $k > 30$ voxels) and test their left/right lateralization.

The recruitment of posterior visual areas

Both pseudoletter stimuli (*Single-pseudoletter* and *5-pseudoletters*) elicited significant posterior activations (Table S2.1 in Supplementary Material) and preferentially in the right hemisphere as revealed by lateralization index (LI - Figure 2.1C). *Single-letters* elicited a similar spatial pattern of activation, although more bilateral.

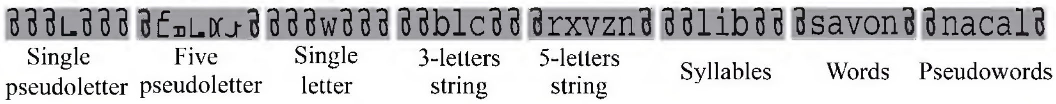
The recruitment of 'intermediate' areas

Increasing the LPL resulted in the recruitment of more dorsal and anterior regions, in addition to the posterior areas mentioned above (Table S2.1), together with a concurrent left hemispheric lateralization (Figure 2.1C). The activation maps for these three categories (*3-letter strings*, *5-letter strings*, *Syllables*) overlapped extensively in the occipital lobe. In addition, *3-letter strings* and *5-letter strings* overlapped in the left (-26 -58 43) and right (25 -61 43) superior parietal lobules (BA 7), the right cuneus (25 -80 33, BA 7) and the left precentral gyrus (-44 -3 37, BA 6).

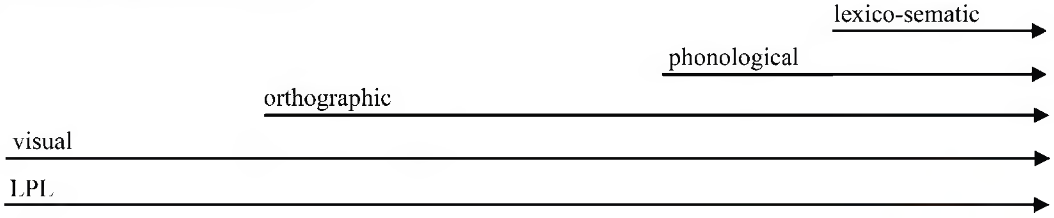
Expansion towards anterior visual reading areas and the recruitment of the frontal cortex

Finally, *Words* and *Pseudowords* not only activated all regions reported above to a larger extent, but also recruited additional areas (Figure 2.1C; Table S2.1): The left middle temporal gyrus (BA 37), the left fusiform gyrus (BA 19), the left supramarginal gyrus (BA 40), the bilateral inferior and middle frontal gyri (BA 9, 13, 44, 45, 46 and 47), the right precentral gyrus (BA 6) and the right thalamus. Noteworthy, two separate maxima were also observed within the LOT: *Words* more posterior (-36 -72 -8) and *Pseudowords* more anterior (-42 -60 -2; see Figure 2.1D). A ROI analysis with the locus (anterior, posterior) and stimulus type as repeated factors (repeated measure MANOVA) showed no difference between posterior and anterior LOT activations for all categories but *Pseudowords* (Figure 2.1D, right panel). In fact, the latter category elicited a significantly stronger anterior than posterior activation in addition to a stronger activation ($F(7, 105) = 3.56$, $p < 0.04$) than all other categories. In addition, *Pseudowords* also showed a significant stronger leftward lateralization than *Words* did (see Figure 2.1C: Confidence Intervals do not overlap).

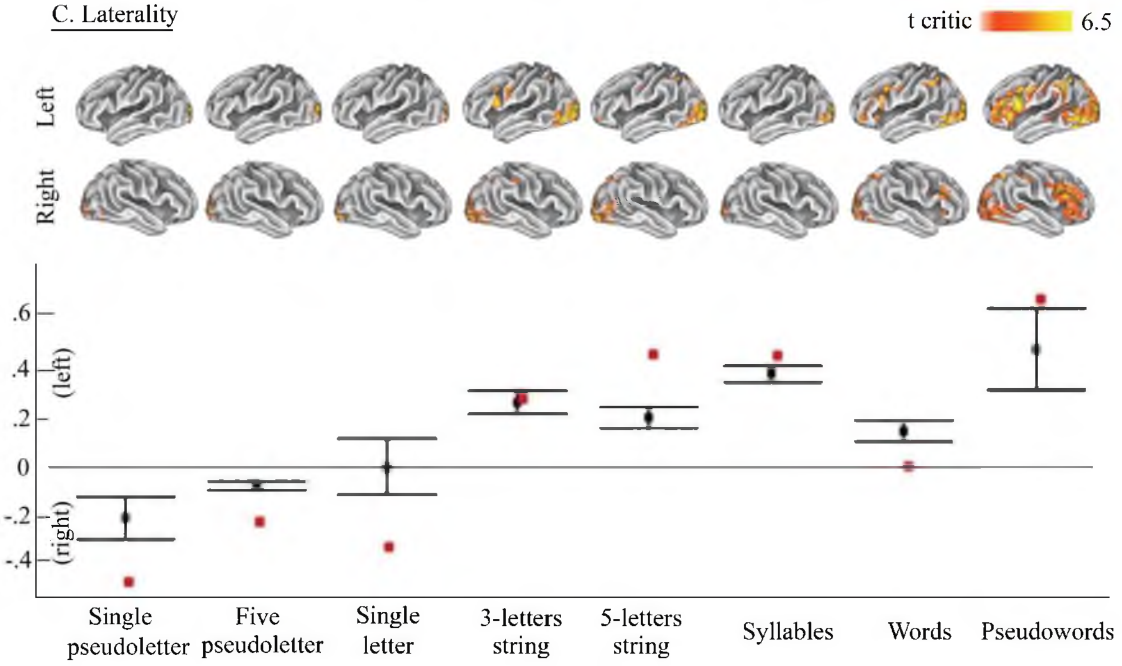
A. Stimuli



B. Linguistic processes and LPL



C. Laterality



D. LOT: words vs. pseudowords

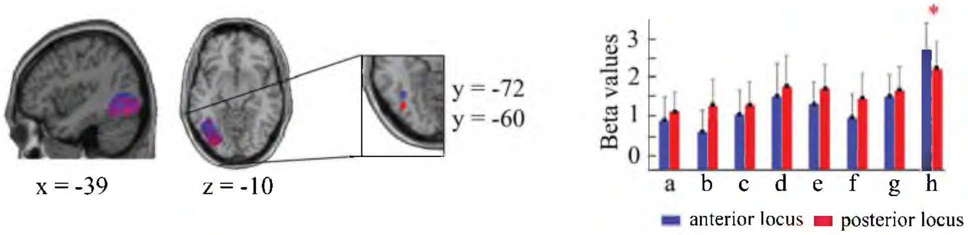


Figure 2.1 Examples of stimuli used for each of the eight experimental stimulus-categories (A), aligned to the involvement in reading processing steps (B), and the corresponding statistical parametric maps and lateralization indices (C). Color bar corresponds to the level of significance from T critic to 6.5. Critical T values from Single-pseudoletters to Pseudowords

were of respectively: 3.51, 3.29, 3.40, 2.78, 2.85, 3.29, 2.66, 2.20. Positive indices on the LI graph reflect left lateralization whereas negative indices reflect right lateralization. Black dots illustrate the average number of activated voxels whilst red dots illustrate the same average weighted by the regression (beta) coefficients (level of activation) for each category. Clusters within the LOT preferentially activated ($p < 0.05$ corrected) for Words (red), Pseudowords (blue) and both (purple) are also presented (D). The graphic presents the beta coefficient of these preferential clusters for each stimulus category. Pseudowords shows a significantly stronger (marked by a red star) anterior than posterior activation in addition to a stronger activation than all other categories in both preferential cluster sets. Error bars on both graphics (C and D) represent 95% confidence intervals.

Linear increase with the Linguistic Processing Load

While the above results suggest the existence of a bilateral-to-left and posterior-to-anterior recruitment of cerebral areas for the gradually increasing LPL of stimuli, a linear contrast with the LPL additionally provides a measure of the magnitude of this effect (increase in activation with increase in LPL). The linear regression ($p < 0.05$ corrected, $k > 30$ voxels) between activation levels and LPL throughout the whole brain revealed significant effects in the left precentral gyrus, the L-IFG, the left claustrum, the Left Parietal (LP), the right inferior and middle frontal gyri, the right insula, and the left superior temporal gyrus (Table S2.4). In particular, the strong involvement of the left parieto-frontal network (Figure 2.2D) is in line with the notion of a reading gradient in these areas. Peak-voxel activations in the LP and the L-IFG were robustly correlated with the increase in LPL (Spearman rank correlation, $p < 0.05$; $r = 0.78$ and $r = 0.9$, respectively – Figure 2.2D, right panel).

To summarize, the analysis of the pattern of activation revealed a right or bilateral-to-left lateralization through the whole brain while increasing the LPL. In addition, this left lateralization came with a gradient of activation (linear increase) in the left-parieto-frontal network.

Reading steps

Having scrutinized the different brain areas progressively involved by increasing LPL, we address whether the observed reading shifts/gradients reflect various reading processes.

Posterior areas for visual processing

Areas generally involved in processing visual input were obtained by conjoining contrasts of all eight conditions (conditions *a* to *h*). Significant activations ($p < 0.05$ corrected, $k > 30$) were observed in the bilateral middle occipital gyrus (MOG) and precuneus (Table 2.1), amongst which only the former was individually significant (marked by a star in Table 2.1). A region of interest (ROI) analysis on these two activation clusters (R/L-MOG) with the hemispheres and stimulus-category (conditions *a* to *h*) as repeated measures ($F(7, 105) = 0.45$, $p > 0.8$) did not exhibit reliable difference in activity across conditions (Figure 2.2A, right panel), therefore suggesting that the above regions process linguistic (or linguistic-like) categories of stimuli to the same extent. In a similar vein, lateralization index (LI) analysis on these occipital clusters failed to show any strong lateralization across stimuli (Table S2.3).

Posterior and intermediate areas for orthographic processing

To examine areas that selectively process orthographic units, we first conjoined all conditions that included letters (conditions *c* to *h*). The global null conjunction yielded significant activations ($p < 0.05$ corrected, $k > 30$) in the bilateral occipito-parietal cortices (bilateral MOG), but also in the left temporo-frontal cortices (Table 2.1), evidencing the recruitment of more anterior areas while additional linguistic processing is needed. Amongst these areas we further isolated four activation-clusters where all conditions were individually significant (marked by a star in Table 2.1): Bilateral MOG (two clusters), one cluster in the left inferior temporal gyrus (BA 37), and one cluster with maxima in the left precuneus and in the left superior parietal lobule (BA 7). Given that the first two clusters (bilateral MOG) were already obtained in the visual input conjunction (extensive overlap and almost identical maxima coordinates), we thereby reasoned that the latter two clusters (The first, in the left inferior temporal gyrus (LOT) and the second, in the left precuneus and the left superior parietal lobule (LP)) were preferentially involved in orthographic processing (see Figure 2.2B). A ROI analysis with these two clusters (LOT and LP) and the orthographic conditions (conditions *c* to *h*) as repeated measures showed a stronger activation for *Pseudowords* than for all other categories ($F(5, 75) = 5.61$, $p < 0.008$), suggesting a particularly strong implication of these regions during pseudoword reading (Figure 2.2B, right panel).

In addition to the conjunction of all conditions that included letters (conditions *c* to *h*), we also conjoined (global null, $p < 0.05$ corrected, $k > 30$) contrasts that tested for a letter effect, i.e. conjoined

(*Single-letters* - *Single-pseudoletters*) and (*5-letter strings* - *5-pseudoletter strings*) to further investigate the issue of letter-selectivity. This yielded one robust activation cluster in the left supramarginal / superior temporal gyri (BA 40) (Table 2.1). This activation cluster overlapped with that obtained in the left superior parietal lobule (see orthographic conjunction). In summary, the two sets of orthographic conjunctions led to the conclusion that the Left Parietal (superior parietal gyrus/supramarginal gyrus) has a selective role in the processing of orthographic units while LOT might have a more general role such as orthographic encoding.

Anterior areas for phonological and lexical processing

Areas involved in the processing of phonological units were studied by (i) conjoining the phonological conditions, namely stimuli containing syllables (*Syllables*, *Pseudowords*, *Words*), (ii) contrasting meaningless pronounceable stimuli with meaningless non-pronounceable letter-strings (*Syllabic* contrast = (*Pseudowords* + *Syllables*) > (*5-letter strings* + *3-letter strings*)) while exclusively masking ($p < 0.05$) out -(*5-letter strings* + *3-letter strings*) deactivations, and (iii) contrasting two- vs. one-syllable stimuli (*Supra-syllabic* contrast = (*Pseudowords* - *5-letter strings*) > (*Syllables* - *3-letter strings*)) while exclusively masking ($p < 0.05$) out (*3-letter strings* - *Syllables)*, in the aim of testing for a possible phonological length effect. To ensure that differences were observed in regions where each of the main conditions was active, we repeated the latter two contrasts while this time, inclusively masking ($p < 0.05$) with *Syllables* and *Pseudowords* (see '*Supplementary Analysis: contrast with inclusive masking*'). A drawback of these two contrasts, however, is that their effects could be driven entirely by *Pseudowords*, which showed very robust activations in comparison to the other conditions. Indeed, testing the same contrast, but instead of *Pseudowords* inserting *Words*, the contrast revealed mainly sub-cortical activations.

The phonological conjunction yielded significant left-lateralized parieto-frontal (and bilateral occipital) activations (Table 2.1). Given that the orthographic conjunctions did not extend to frontal areas whereas the phonological conjunction did (Figure 2.2C), we reasoned that the left frontal cortex (mainly IFG) is mainly involved in phonological processing. In agreement with this idea, the *Syllabic* contrast ((*Pseudowords* + *Syllables*) > (*5-letter strings* + *3-letter strings*)) yielded significant activations in the left parieto-frontal cortex, while the *Supra-syllabic* contrast ((*Pseudowords* - *5-letter strings*) > (*Syllables* - *3-letter strings*)) extended its activity to the right hemisphere (see Supplementary material Figure S2.1 and Table S2.2). Interestingly, the *Syllabic* contrast and the phonological conjunction overlapped in the left middle (-44 28 19, BA 46) and inferior (-50 17 14; -

38 32 0; BA 44/45) frontal gyri while the *Supra-syllabic* contrast and the phonological conjunction overlapped in the L-IFG (-50 17 15; -40 32 2; BA 44) but also in the L-MOG (-48 -67 -3) and the left precuneus (-24 -56 43, BA 7). These results suggest that left frontal areas participate in phonological processing to the same extent for both types of stimuli (mono- or bi-syllabic) while posterior areas are sensitive to this parameter (see Figure S2.1). To consider a ROI with a selective role in phonological processing, we pinpointed the only coordinate that overlapped all three phonological analyses (-51 18 14, L-IFG, BA 45). A ROI analysis on this cluster with the phonological conditions as repeated factors revealed a stronger activation for *Pseudowords* than for *Syllables* and *Words* (F(2, 30) = 6.15, $p < 0.01$).

Finally, we contrasted *Words* with *Pseudowords* to look for regions implicated in lexical-semantic processing. However, this yielded activation only in areas where there was greater deactivation for *Pseudowords* relative to all other conditions but *Single-pseudoletters* (MANOVA ROI*conditions: F(7,105) = 6.36, $p < 0.006$): inferior parietal lobules (BA 40/39), the left supramarginal gyrus (BA 40) and the right posterior cingulate (BA 23) (see Table S2.2). Hence, this contrast did not identify activations that were consistent with lexical-semantic processing.

To summarize, we first demonstrated a left lateralization of activations throughout the brain by increasing the LPL and a graded activation in the LP and L-IFG. We now additionally showed that the initial bilateral activation is related to feature processing and takes place, as expected, in the visual cortex (in particular the MOG). The left lateralization, in particular for LOT, comes with orthographic encoding. In parallel, the level of activation increases in the LP and the L-IFG (posterior-anterior gradient) with the LPL. Functionally speaking, this increase in activation levels may well reflect the reinforcement of orthographic-phonological decoding for the LP, and of phonological processing for the L-IFG. To further investigate this issue, functional-integration across those areas was explored by means of connectivity analyses.

Connectivity analyses

While previous analyses proved the existence of a spatio-functional activation-cascade during reading, we now consider in what way the increase in LPL/reading steps modulates information trafficking amongst these functional areas.

The former analyses revealed left-lateralized ROIs, with the exception of the bilateral MOG for visual processing; we thereby chose to focus on the left-MOG cluster for the connectivity measurements. Interregional functional connectivity was computed between spheres centered at the left middle occipital gyrus (L-MOG: -32 -91 10, BA 18 - visual analysis), the left occipito-temporal cortex (LOT: -46 -68 -5, BA 37 - visual/orthographic encoding), the left parietal (LP: -24 -50 43, BA 7 - orthographic/phonological decoding), and the left infero-frontal gyrus (L-IFG: -51 18 14, BA 45 - phonological processing). Spearman correlation coefficients were obtained (Table S2.5) for significant rank correlations ($p < 0.05$) between connectivity values and the pre-determined stimulus LPL ranking (see Materials and methods: ‘Stimuli’). Posterior (between L-MOG and LOT, L-MOG and LP, L-MOG and L-IFG) or intermediate (between LOT and LP, LOT and L-IFG) inter-regional co-variations did not significantly correlate with LPL, suggesting that posterior and intermediate activations within the above network co-varied to the same extent for all eight conditions. In contrast, the anterior (between LP and L-IFG) interregional co-variation rate produced a robust positive correlation ($r=0.79$) with the LPL. A model of effective connectivity among the four ROIs with the following directional connections L-MOG to LOT, L-MOG to LP, LOT to LP, LOT to L-IFG and LP to L-IFG has also been computed (see Figure 2.2E). The model has been proved to be significantly valid for all eight conditions as inferred by its high p-values and low RMSEA indices (Table S2.6), i.e. areas are connected in the way specified and levels of activations covary accordingly. In addition, the model illustrated that the LP → L-IFG connection participates in higher linguistic processing by revealing, again, a high positive correlation ($r = 0.81$) between the LPL and their connectivity level (Figure 2.2E, right panel).

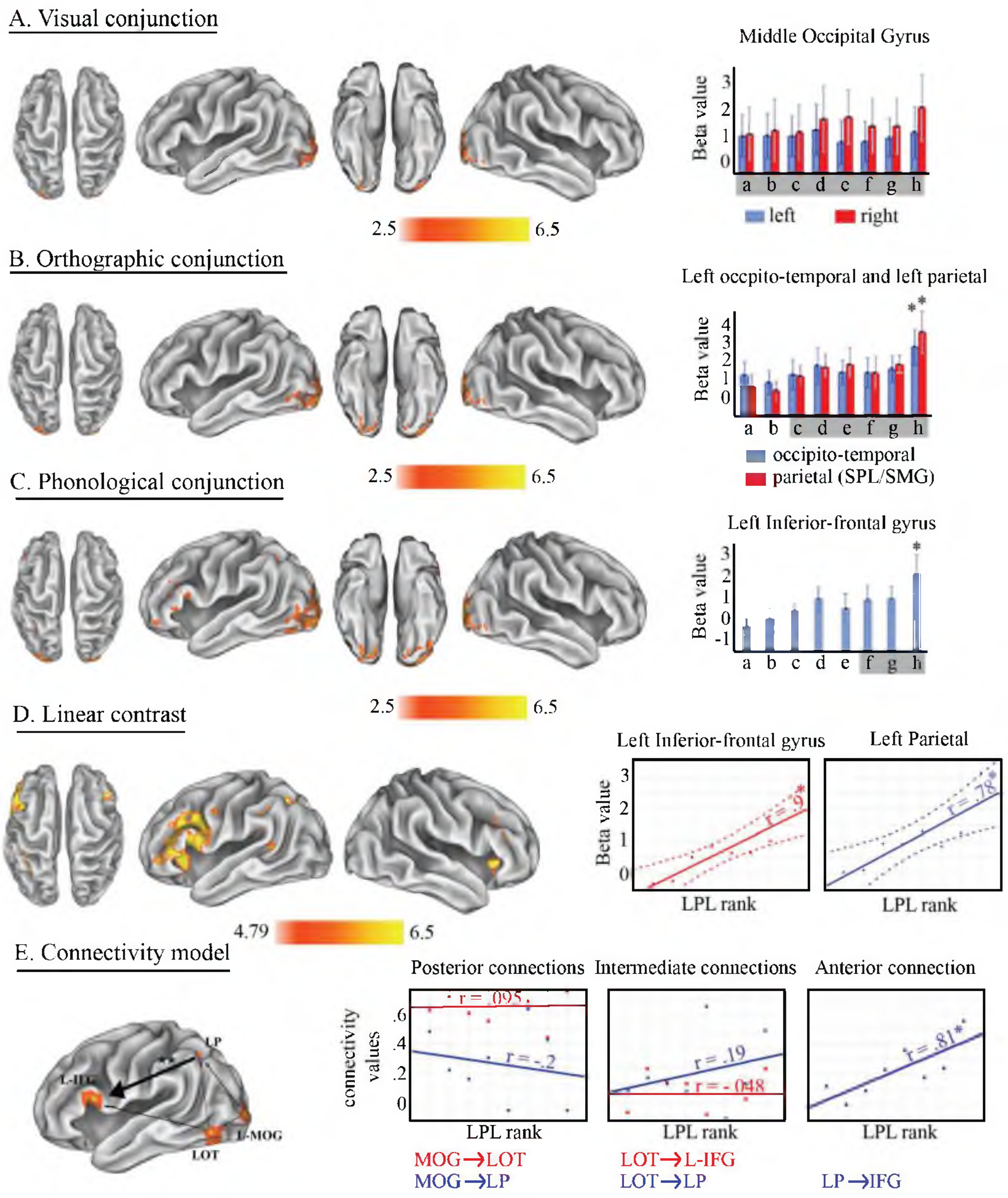


Figure 2.2 SPMs of the visual (A), orthographic (B) and phonological (C) conjunction null ($p <$ 0.005 uncorrected). The color bar corresponds to the level of significance from T=2.62 to 6.5. Histograms exhibit the amount of activation in selected ROI (reflected on histogram by the 1st eigen variate of the β-values ± 95% confidence intervals) for each category of stimuli: a: Single-pseudoletters, b: 5-pseudoletters, c: Single-letters, d: 3-letter strings, e: 5-letter strings, f: Syllables, g: Words and h: Pseudowords. Categories used for the ROI analyses are confined to gray rectangles. Categories whose activation significantly outscored all other tested categories were marked by a gray star (*). SPM from the linear contrast ($p <$ 0.05 corrected) is displayed

on D. The color bar corresponds to the level of significance from T=4.79 to 6.5. The regression lines with 95% confidence intervals illustrate the correlation between the LPL and the levels of activation in the IFG and the LP, respectively. The effective connectivity model with the four key areas (L-MOG, LOT, LP, L-IFG) is illustrated in E. Regression lines between effective connectivity values and the LPL rank are illustrated for posterior, intermediate and anterior connections. Significant correlations are marked with a star (*).

Discussion

The first purpose of the present study was to test the hypothesis of a right- or bilateral-to-left lateralized and a posterior-to-anterior recruitment of cerebral areas while increasing the Linguistic Processing Load. Contrasting a hierarchical repertoire of eight categories of stimuli with increasing LPL conformed to this observation, as illustrated by Figure 2.1C. The linear contrast extended this notion (Figure 2.2D) – showing a gradient of activation within the Left Parietal and Left Infero-Frontal Gyrus. The uniqueness of the findings is that they provide in a single experiment a demonstration of the converging evidence from a large body of neuroimaging studies over the years.

As mentioned in the Introduction, other studies provided such information but their results were restricted to some parts of the brain because of the smaller, specific, subset of stimuli used. For instance, Tarkiainen et al. (1999) proposed a posterior-to-anterior and bilateral-to-left activation recruitment from the occipital to the occipito-temporal junction. This, with other results, led to the Local Combination Detector (LCD) model (Dehaene et al., 2005). This model predicts that such a hierarchical ordering of linguistic stimuli activates a posterior-to-anterior ordering of neuron populations, although in that particular case the ordering is limited to the infero-temporal cortex. Our results therefore complement this model and further specify the role of the different areas (see below). In another study investigating linguistic stimulus hierarchy, Tagamets et al. (2000) observed a bilateral-to-left lateralized recruitment of activation similar to our results as a function of increasing the LPL of their stimuli. However, in contrast with our results, they reported stronger activation for false-fonts and letter strings than for words and pseudowords especially in the posterior-parietal cortex, whereas we observed a linear increase of activation from false-font to words/pseudowords in the left parieto-frontal cortex and an increase in connectivity from LP to the L-IFG. One possible explanation is that the lower activations observed in our data for say, *Single-pseudoletters*, were partly due to a repetition suppression effect. Because similar flankers were repeated during a block, the overall BOLD signal would be lower. However, the fact that the *5-pseudoletters* condition (minimum repetition suppression) yielded activations similar to those of the *Single-pseudoletters* or *Single-letters* conditions (maximum repetition suppression), rules out this explanation. More likely, the opposite false-font > word activation pattern would reflect an increase in working memory load since in Tagamets et al.'s (2000) study, participants had to perform a one-back matching task. This interpretation agrees with data showing that posterior-parietal cortex activations also correlate with working memory capacity limitation, which to some extent may vary with the familiarity of the stimuli (Linden, 2007). In a more recent space-time-frequency study by means of direct intracranial recordings, Mainy et al. (2007) presented to ten epileptic-patients: consonant strings, pseudowords and words, and performed a hierarchical paradigm contrasting visual, phonological and semantic processes. They revealed a left-hemispheric posterior-to-anterior activation-cascade resulting from the increase in processing steps. The authors also traced transient and local neural synchronization in the gamma frequency range among the areas corresponding to the functional reading steps. One inherent limitation in their investigation was that their methodology obliged them to leave large parts of the brain unexplored. Nonetheless, their findings are consistent with ours and additionally convey the prominence of high-frequency oscillations during the spatio-functional activation-cascade triggered by reading. Our investigation also partly overlaps with that of Vinckier et al. (2007). These authors collected fMRI data while subjects performed a low-level detection task on a hierarchically organized pool of stimuli (from false-fonts to words). Given the nature of their investigation, which was mainly restricted to the occipito-temporal cortex, most of their analyses were different than ours. Nevertheless, the linear contrasts computed in both our and their study yielded similar (mainly left anterior) activation patterns, with some distinctions possibly resulting from different tasks and stimulus design. Additionally, they revealed posterior-to-anterior activation gradients with an asymmetry in favor of the left hemisphere, lending further support to the findings in the present study. The authors' main spatial focus, however, was the LOT, which enabled them to observe a posterior-to-anterior gradient of selectivity through its entire span. Interestingly, they revealed a similar gradient within the left inferior frontoinsular cortex. The unraveling of reading gradients through the span of two prominent reading areas which concurrently revealed whole-brain functional gradients in the present study may not be a coincidence and may highlight a phenomenal neural tuning to stimulus properties, within (Dehaene et al., 2005) but also between these areas.

One may argue that the bilateral-to-left and posterior-to-anterior shift is not language specific and may relate to other mechanisms. Among others, the most likely candidates are visual complexity and attentional load. Regarding visual complexity, one must keep in mind that because of the use of flankers all our stimuli were of the same length. The complexity would therefore be related to the stimuli of interest (the categories), which by itself makes the argument of external visual complexity refutable. Referring to this as visual load related to the stimulus while ignoring its flankers, the new ordering would be 1: *Single-pseudoletters*, and *Single-letters, 2: Three-letter strings* and *Syllables, 3: Five-letter strings, Words* and *Pseudowords.* This ordering clearly does not follow the LI (Spearman r =0.33 vs. r =0.83 p<0.05 for the LPL) nor would agree with the activation levels observed in the IFG (Spearman r =0.56 vs. r =0.9 p<0.05 for the LPL) or the LP (Spearman r =0.54 vs. r =0.78 p<0.05 for the LPL). Similarly, one may think that attention would vary with the stimuli. For instance, one can think of a new ranking related to familiarity (or occurrence frequency); this would lead to 1. *Single-letters, 2. Syllables, 3. Words, 4. Pseudowords, 5. Three-letter strings and Five-letter strings 6. single and Five-pseudoletters.* Again this ordering does not follow LI (r =-0.4) or IFG (r =-0.36) and LP (r =-0.4) activation levels. The most likely is that the bilateral-to-left shift is driven by the linear increase in the LP and left IFG as a function of the LPL, in addition to a non linear shift in LOT for pseudowords in comparison with other categories. In turn, the LPL is mainly to be explained by the number of linguistic processes involved.

Reading steps and LPL

The second purpose of our experiment was to test whether the stated recruitment of reading areas reflected successive reading steps. The results indicate that bilateral activations corresponded to feature analysis and were restricted to the visual cortex. Left lateralization came with orthographic encoding in the LOT. Further left lateralization as well as dorsal (LP) and frontal (L-IFG) recruitment came with further orthographic-phonological decoding and phonological processing. In the present investigation we did not locate prominent temporal regions, notwithstanding their prominent implication in phonological and semantic processes (Démonet et al., 1992, 1994, 2005; Price, 2000; Gros et al., 2001; Polk et al., 2002; Jobard et al., 2003). However, this is not completely at odds with previous findings since (i) passive tasks do not activate this region as reliably as more active tasks do (Polk et al., 2002), and (ii) this region is mainly recruited by the processing of human voice and during other auditory tasks (Belin et al., 2000; Burton et al., 2005).

First, reproducing previous investigations (e.g., Cohen et al., 2000; Tarkiainen et al., 2002; Itier and Taylor, 2002), our results demonstrate the bilaterally-equal role of the MOG (BA 18/19) in stimulus-independent visual feature-processing (Figure 2.1C; Table S2.3). We also noted that the processing of novel items such as pseudoletters showed stronger right-hemispheric lateralization which could result from the increase in demand for on-line processing for feature extraction and shape analysis, predominantly corresponding to activations in the right extrastriate cortex (Gros et al., 2001).

Second, we observed stronger activations in response to orthographic units in the left occipito-temporal (LOT) junction and the left parietal (LP) cortex (Figure 2.2B). Previous reports (Tarkiainen et al., 1999; Cohen et al., 2000, 2002; Gros et al., 2001; Polk et al., 2002; Joseph et al., 2003; Flowers et al., 2004; Pernet et al., 2005) have already emphasized the important role of the LOT in letter and letter-string processing. Likewise, LP activation has been reported in the same studies that report LOT/extrastriate activation for letters (Joseph et al., 2006). However, the question of domain specificity for the LOT is under debate, and its activation might not be specific to words, but rather reflect an operation common to the processing of words with regular (Kronbichler et al., 2007) or irregular (Bruno et al., 2008) orthographies, word sub-units (Binder et al., 2006), pictures (Starrfelt and Gerlach 2007), objects (Bar et al., 2001), or stored visual forms and structures in general (Joseph and Gathers, 2003). Because LOT was activated in the orthographic conjunction but not in the conjunction testing for a 'letter effect' ((*Single-letters* - *Single-pseudoletters*) U (*5-letter strings* - *5-pseudoletter strings*) – Table 2.1), we contend that LOT is involved in orthographic encoding while LP is more 'letter-specific'. In particular, because the level of activation in LP increases linearly with the LPL, it might as well be involved in orthographic-phonological transcoding, or grapheme-to-phoneme conversion (Booth et al., 2002, 2003, Joseph et al., 2003). This idea is further supported by (i) the significant co-activation of the LP for both orthographic and phonological conjunction analyses, (ii) the fact that the supra-syllabic contrast revealed L-IFG and LP activation (more activation to process bi- vs. mono-syllabic stimuli), and (iii) the LP to L-IFG connectivity increment with the Linguistic Processing Load. In agreement with this reasoning, a recent report by Cao et al. (2008) provides evidence for a stronger modulating effect on the LP→L-IFG feed-forward connection in case of conflicting vs. non-conflicting orthographic and phonological information during a rhyming task. The present study elaborates upon this result by suggesting that the strength of information trafficking conveyed through this connection is manifested, not only through grapheme-phoneme conversion, but also as a function of the LPL of stimuli. A complementary and/or alternative explanation to the possibly distinctive roles of LOT and LP is a potential orthographic and phonological cortical-specialization of sub-regions within the LP. Given that our results revealed a stimulus-dependent dissociation pattern within the LOT (see Figure 2.1D) and thereby lent further support to prior similar reports (Hagoort et al., 1999; Paulesu et al., 2000; Xu et al., 2001; James et al., 2005; Dietz et al., 2005; Mechelli et al., 2005; Vinckier et al., 2007), it is possible that different sub-regions within the LP (BA 7 or 40) also selectively respond to orthographic and/or phonological units.

Third, alongside the implication of the LP in orthography-to-phonology translation, we also demonstrated the important role of the L-IFG in phonological processing, in particular for pseudoword reading. This result is in agreement with a large number of prior studies emphasizing the implication of the opercular part of the L-IFG in the subvocal rehearsal system (Démonet et al., 1992, 1994), in orthographic-to-phonological transformation (Fiez, 1999), in grapheme-to-phoneme conversion (Heim et al., 2005), in phonemic awareness (Katzir et al., 2005) and during rhyme judgment and discrimination tasks (Price and Mechelli, 2005) in both visual and auditory modalities (Burton et al., 2005).

Finally, contrasting *Words* with *Pseudowords* failed to locate specific components for lexical-semantic processing. In fact, the adequacy of this contrast to locate such processes is debatable given that no cluster is usually recruited more by word- than by pseudoword-reading (Jobard et al., 2003). On the contrary, our investigation showed that the above contrast yielded areas (see Table S2.2: the inferior parietal lobules, the left supramarginal gyrus and the right posterior cingulate) for which activation was significantly lower for *Pseudowords* than signals recorded not only for *Words* but also for all other conditions but *Single-pseudoletters*. These results are in line with Mechelli et al. (2003) who reported that contrasting words with pseudowords reveals areas which are mostly due to activation decreases for pseudowords rather than increases for words. In addition to these deactivations, we also observed greater activations for pseudowords than words in many other areas. In fact, both pseudowords and words activated a similar neural network (essentially, in the bilateral occipital and frontal cortices, in the LOT and in the LP) but pseudoword processing taxed the entire system to a greater extent; this was in agreement with previous studies (Mechelli et al., 2003; Price et al., 2003; Wilson et al., 2005). This was illustrated by the linear contrast and connectivity analyses which followed our LPL classification, therefore confirming that processing pseudowords is somehow ‘harder’ than that of words. A potential confounding factor is the high degree of similarity between *Pseudowords* and *Words*. This may have increased the attention demand during *Pseudowords* reading, eliciting in a higher BOLD signal. Although this explanation cannot be completely ruled out for our passive stimulation design, it seems unlikely to be the case since it has been demonstrated that there is no attentional bias between lexical and non-lexical stimuli in fMRI block design (Cohen et al., 2002).

The LPL-based ordering

As further elaborated in the Materials and methods section, the LPL-based ordering of our stimulus categories seems to make sense: Pseudoletters did not seem to have elicited linguistic activations (and hence corresponded to right or bilateral non-specific linguistic activations), then progressively increasing the number of letter units (from single-letter to three- then five-letters) increased the left lateralization and the LOT activation; and finally adding up the phonological and lexical-semantic components (higher order stimuli such as: *Syllables*, *Words* and *Pseudowords*) engaged the left fronto-parietal network. This ordering enabled us to observe consistent posterior-to-anterior and bilateral-to-left recruitment of reading areas. However, some findings countered our predictions: *Syllables* yielded lower activity (although more left-lateralized) than *5-letter strings* and even relative to *3-letter strings* (Figure 2.1C). This suggests that the number of orthographical units may, in some cases, over-power the effect of phonological units in terms of brain activity. In fact reordering the LPL ranking with *Syllables* before *5-letter strings* or even before *3-letter strings,* leads to a stronger correlation ($r = 0.88$ or 0.90, respectively) between the LPL and the effective connectivity values of LP → L-IFG (and still not with the other connections). By contrast to this result, our hypothesis that *Pseudowords* should be classified higher than *Words* in the LPL hierarchy was supported by the data: Beyond the theoretical argument mentioned (see 'Stimuli' in Materials and methods), (i) more robust and left-lateralized activity (see Figure 2.1C) was observed for *Pseudowords*, (ii) the *Pseudowords* > *Words* contrast revealed primarily left anterior activity (Table S2.2) and (iii) the *Words* > *Pseudowords* contrast revealed more posterior activity (Table S2.2) (left parietal). Higher LPL with *Pseudowords* on the top therefore corresponded well to higher left anterior recruitment. However, it is still unclear how words and pseudowords dissociate in terms of neural encoding/decoding since applying a reversed ordering and correlating connectivity values and LPL rank maintained the pattern of results, i.e. no significant correlation with posterior and 'intermediate' connections, but significant correlation with the anterior connection (LP → L-IFG ($r = 0.71$ for the functional and $r = 0.76$ for the effective connectivity).

Conclusion

The present study conveys two main findings: First, it provides an empirical evidence for the existence of a bilateral-to-left and posterior-to-anterior recruitment of reading areas with LPL, corroborating with a large body of converging independent neuroimaging observations over the years. Second, we show that this recruitment is likely to be reflected by the piecemeal increase in reading steps, which are intrinsically attributed to LPL. Connectivity analyses further strengthened the validity of these observations highlighting an enhancement of the left parieto-frontal branch that mediate the transition from 'peripheral' (visual/orthographic) to 'core' (phonological/semantic) linguistic processing. Our findings clearly establish the notion of a gradual spatio-functional recruitment of reading areas and demonstrate, to the best of our knowledge, the first evidence of a robust and staged link between the level of linguistic processing, the spatial distribution of brain activity and its information trafficking. Moreover, the results shed light on the recent controversy on the specificity of the role of the LOT relative to other language-related areas: LOT seems to process letter-strings for visual orthographic encoding while LP seems to participate not only in visual/orthographic encoding but also in orthographic-phonological transcoding (grapheme-phoneme conversion).

Supplementary material

Neuropsychological assessment

Subjects' reading skills were carefully screened with a battery including visual, phonological, lexical and attentional tests (Paulesu et al., 2001). Global reading abilities were assessed with the "*L'Alouette*" test (Lefavrais, 1967), while global visual reading abilities were evaluated with the "*Digit Naming Speed Test*". In addition**, "***nonword and irregular words naming tasks***"** was applied to assess phonological decoding ability and lexicon access. A "*spoonerism test*", which is a measure of the ability to manipulate phonemes in words presented orally, was also used to assess subjects' phonemic awareness. The "*d2 test of attention*" was used to assess processing speed, rule compliance, and quality of performance, allowing a cognitive estimation of individual attention and concentration performance. Because the paradigm of this current experiment required subjects to stay alert while passively viewing various stimuli, the "d2 test of attention" was of particular relevance. Finally, in order to rule in normal IQ, several subtests from the 3rd edition of Wechsler Adult Intelligence Test (WAIS-III; Wechsler, 1997) were included: "Vocabulary", measuring the degree to which the subject has learned, been able to comprehend and verbally express vocabulary; "Similarities", assessing abstract verbal reasoning; "Digit Span", evaluating the working memory; "Block Design", assessing spatial perception, visual abstract processing and problem solving; "Object Assembly", measuring visual analysis, synthesis and construction.

Construction of stimuli

Letters were presented in lower-case Courier font, resulting in an equal string length for all stimuli. Pseudoletters were conceived by reorienting and adjusting alphabetic letter-features, so that angularity, contour and visual surface or complexity, equaled those of alphabetic letters. This aimed at minimizing the difference between the processing of those two categories in terms of visual processing. *Single-pseudoletters* consisted of a pseudoletter embedded in other pseudo-characters. 5-*pseudoletter strings* were designed by replacing the letters of the *Words* stimuli with their corresponding pseudoletters.

3-letter strings contained three consonants lacking any semantic, nameable or acronymic value. In contrast, 3-letter syllables (*Syllables)* were conceived by replacing the middle consonant of *3-letter strings* with a vowel, resulting in a consonant-vowel-consonant structure lacking any semantic, name-like or acronymic value but with a phonological, nameable value. *Words* were made up of two syllables formed using five letters, containing no accents or capital letters. All words were of high-frequency (mean 17.0 sd 9.4), high MPBF and high mental imagery score (mean 6.2, sd 0.5). They were selected using the "text corpus" of the "*Lexique-III*" database, which constitutes a very good estimator of frequency of apparition compared to more traditional databases (New, B., Pallier, C. Manuel de *Lexique-III*. http://www.lexique.org/documentation.php). Each word belonged to one grammatical class, shared no homophone and was not semantically related to the other words, thus, excluding priming effect. *Pseudowords* stimuli formed two syllables out of five letters lacking any semantic, name-like or acronymic value, but orthographically regular. They were designed to be comparable with each other and with word stimuli (3777 vs. 3632) in terms of MPBF. Finally, non-words (*5-letter string)* contained five consonants lacking any semantic, nameable or acronymic value. They were conceived by exchanging the vowels of *Pseudowords* with consonants, thus maximizing the distinction between them in terms of orthographic and phonological processing while minimizing their visual differences.

Supplementary Analysis: contrast with inclusive masking

In addition to the exclusive masking used for the *Syllabic* and *Supra-syllabic* contrasts, we used an inclusive masking procedure. Whereas the analyses described in the manuscript allowed to make sure that effects were not related to deactivations, it did not ensure that differences were observed in regions where each of the main conditions was active. The *Syllabic* and *Supra-syllabic* contrasts were therefore re-computed but masking inclusively by *Syllables* and *Pseudowords*. Significant activations were observed again in the L-IFG region for both contrast as well as the LP and LOT for the *Supra-syllabic* contrast (see Fig S1).

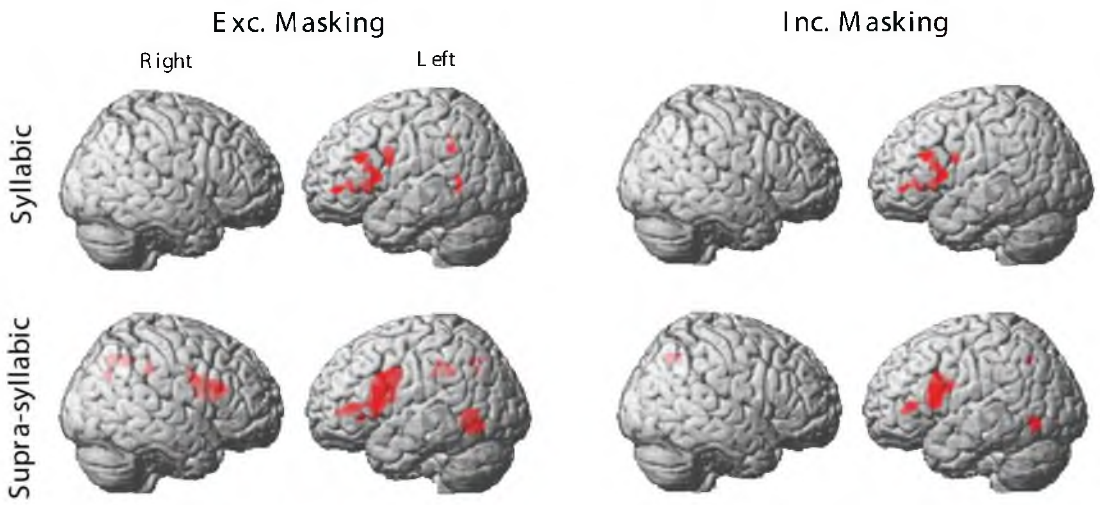


Figure S2.1 SPMs of the Syllabic (upper panel) and Supra-syllabic (lower panel) contrasts ($p < 0.005$ uncorrected, $k > 30$) masked ($p < 0.05$) exclusively (left panel) and inclusively (right panel).

Table S2.1 Regions of activations for the eight stimulus-categories vs. fixation

Region	BA	H	Voxels	z score	x	y	z
<u>Single-pseudoletters</u>							
MOG	18/19	R	346	5.46	30	-91	12
ITG	-	R	177	4.64	41	-66	-3
MOG	19	L	147	4.13	-34	-89	10
<u>5-pseudoletters</u>							
MOG/LG	18/19	R	767	5.54	35	-89	12
MOG/cuneus	18/30	L	633	5.19	-22	-99	5
MOG/MTG	19	L	36	3.92	-50	-77	9
<u>Single-letters</u>							
MOG/LG	18	R	564	5.51	30	-93	-3
MOG	19	L	400	4.38	-32	-91	10

3-letter strings							
MOG/LG	18	R	1976	5.79	30	-91	12
MOG	18	L	2595	5.55	-22	-86	-6
Precuneus	7	L	168	4.42	-24	-52	44
Precuneus	7/19	R	368	4.41	24	-60	47
IFG/precentral gyrus	44/6	L	1159	4.26	-55	7	24
IFG	46/47	L	115	3.65	-44	31	6
Postcentral gyrus/IPL	2/40	R	123	3.59	36	-27	42
Caudate body	-	L	48	3.58	-24	-18	29
IPL/postcentral gyrus	40/2	L	92	3.40	-38	-33	37
PHG	36	L	30	3.20	-38	-24	-12
5-letter strings							
Cuneus/MOG/IOG	19	L	2257	5.92	-20	-99	5
LG/MOG	19/18/1	R	2122	4.95	20	-84	-8
Precuneus/IPL	7	L	538	4.52	-24	-50	43
Precuneus/ SPL	7/40	R	417	3.95	26	-76	33
Putamen	19/7	L	89	3.67	-16	-6	2
Lentiform nucleus	-	R	53	3.61	18	-2	0
Precentral	6	L	62	3.57	-44	-2	37
MFG	11	L	40	3.23	-40	48	-7
Syllables							
MOG	19/18	R	381	5.24	34	-91	12
Cuneus/ MOG	18	L	886	5.12	-20	-99	10
LG/FG	18/19	R	84	4.29	20	-84	-8
Putamen	-	L	49	3.66	-26	18	3
Words							
FG/MOG/Cuneus	19/18	L	2627	5.27	-36	-72	-8
MOG/LG	18/19	R	3071	5.18	30	-91	12
Precuneus	7/19	L	413	4.49	-24	-50	43

MFG/IFG	46/45	R	438	4.22	50	25	25
IFG/MFG	47/46	L	2132	4.16	-40	31	4
PHG	-	L	218	3.92	-34	-24	-7
IFG/insula	47	R	244	3.62	34	27	-6
IPL	40	L	220	3.59	-46	-47	41
Putamen	-	L	161	3.44	-18	2	7
PHG	-	R	123	3.35	28	-16	-11
IFG	9	R	123	3.30	46	4	31
Pseudwords							
SPL/MTG/supramarginal gyrus	7/37/40	L	17217	Inf	-26	-56	45
IFG	9/44	L	9532	7.05	-42	5	25
Precentral gyrus/MFG	6/46/9	R	5507	6.07	44	1	28
Thalamus	-	R	313	4.16	24	-28	14

Clusters are presented with a threshold of FDR corrected p<0.05 (extent threshold of 30 voxels). Fusiform gyrus (FG); Inferior frontal gyrus (IFG); Inferior occipital gyrus (IOG); Inferior parietal lobule (IPL); Inferior temporal gyrus (ITG); Infinite (Inf); Lingual gyrus(LG); Middle occipital gyrus (MOG); Middle frontal gyrus (MFG); Middle temporal gyrus (MTG); Parahippocampal gyrus (PHG); Superior parietal lobule (SPL).

Table S2.2 Regions of activation for supplemental analyses

Syllabic contrast (excl.- (5-letter strings + 3-letter strings)							
Claustrum	*-*	*L*	*103*	*3.72*	*-30*	*20*	**3**
Insula	*13*	*L*	*430*	*3.40*	*-40*	*3*	**22**
SMG/IPL	*40*	*L*	*73*	*3.32*	*-36*	*-45*	**30**
Insula/MFG/Claustrum	*13/46*	*L*	*126*	*3.24*	*-36*	*20*	**16**
IFG	*47*	*L*	*81*	*3.03*	*-46*	*43*	**-2**
Precentral gyrus/IFG	*44/45*	*L*	*84*	*3.02*	*-52*	*14*	**7**
STG/MTG	*39/21*	*L*	*34*	*2.86*	*-51*	*-52*	**6**

Supra-syllabic contrast (excl.							
(3-letter strings – Syllables)							
Precentral gyrus/Cingulate gyrus	6/32	R	846	4.33	43	-1	26
IFG/Insula	9/44/13	L	1912	4.23	-53	7	25
Postcentral gyrus	2	R	156	3.94	40	-32	33
MTG/PHG/STG	37/4/39	L	502	3.81	-46	-62	-2
IPL	40	L	225	3.45	-38	-33	37
SPL/Precuneus	7	R	147	3.42	28	-50	47
Precentral Gyrus	6	L	35	3.27	-32	-8	34
Precuneus	7	L	113	3.08	-20	-60	36
Pseudowords > Words							
Precentral gyrus	44/6	L	1139	4.19	-51	10	12
SMG/IPL	40	L	983	4.15	-38	-39	31
MTG	39/22	L	182	3.75	-51	-54	6
MTG/MOG	37	L	132	3.35	-46	-60	-4
MFG	47	L	39	3.11	-44	39	0
Precentral gyrus/IFG	6/9	R	50	2.92	40	1	24
Words > Pseudowords							
IPL/SMG	40	L	102	3.60	-53	-54	41
Posterior Cingulate	23	R	31	3.27	10	-34	22
IPL	40/39	L	65	3.07	46	-62	47

Clusters are presented with a threshold of uncorrected $p<0.005$ (extent threshold of 30 voxels; masking with $p < 0.05$). Fusiform gyrus (FG); Inferior frontal gyrus (IFG); Inferior parietal lobule (IPL); Inferior temporal gyrus (ITG); Infinite (Inf); Lingual gyrus(LG); Middle occipital gyrus (MOG); Middle frontal gyrus (MFG); Middle temporal gyrus (MTG); Parahippocampal gyrus (PHG); Superior parietal lobule (SPL); Superior temporal gyrus (STG); Supramarginal gyrus (SMG).

Table S2.3 Lateralization indices (LI) in the BA 18/19 as a function of stimulus-category.

BA18/19	***Single-pseudoletters***	***5-pseudoletters***	***Single-letters***	***3-letter strings***	***5-letter strings***	***Syllables***	***Words***	***Pseudowords***
Mean +/- C.I.	-0.15+/- 0.016	-0.085+/- 0.012	-0.16+/- 0.015	-0.075+/- 0.011	-0.023 +/- 0.031	0.011+/- 0.046	-0.15+/- 0028	0.13+/- 0.082
Weighted mean	-0.3	-0.14	-0.29	-0.15	0.26	0.16	-0.24	0.39

Lateralization indices (LI) were based on the average (and 95% confidence intervals) of bootstrapped trimmed means for increasing threshold and/or weighted by the level of activation. Positive indices reflect left lateralization whereas negative indices reflect right lateralization.

Table S2.4 Whole-brain Linear contrast

Region	BA	H	Voxels	z score	x	y	z
Linear contrast							
Precentral gyrus/IFG/Claustrum	6/45	L	3064	6.17	-44	0	30
SMG/SPL	40/7	L	479	5.94	-36	-43	30
MFG	46/9	R	128	5.48	46	24	23
STG	22	L	64	5.33	-55	-48	12
IPL	40	L	37	5.21	-50	-37	31
Insula/IFG	47	R	136	5.11	34	19	-1

Clusters are presented with a threshold of FWE corrected $p < 0.05$ (extent threshold of 30). Inferior frontal gyrus (IFG); Inferior parietal lobule (IPL); Middle frontal gyrus (MFG); Superior parietal lobule (SPL); Superior temporal gyrus (STG). Supramarginal gyrus (SMG).

Table S2.5 Interregional correlation indices of functional connectivity for the stimulus-categories

	L-MOG & LOT	L-MOG & LP	LOT & LP	LOT & L-IFG	L-MOG & L-IFG	LP & L-IFG
Single-pseudoletters	0.62	0.57	0.46	0.08	0.23	0.13
5-pseudoletters	0.71	0.40	0.40	0.29	0.18	0.12
Single-letters	0.6	0.28	0.29	0.23	-0.02	0.15
3-letter strings	0.55	0.39	0.32	0.28	0.29	0.30
5-letter strings	0.83	0.54	0.67	0.26	0.11	0.37
Syllables	0.68	0.61	0.40	0.04	-0.01	0.17
Words	0.44	0.35	-0.01	0.11	0.07	0.24
Pseudowords	0.75	0.37	0.52	0.58	0.52	0.70
r-value	**0.095**	**-0.238**	**0.024**	**0.143**	**0.048**	**0.786**

Interregional correlation indices are presented according to stimulus-category. Spearman correlation coefficients (r) between these values and LPL are presented on the bottom row in light gray cells. Only interregional correlation indices between the LP and the L-IFG produced a significant positive correlation (marked in red) with the index of LPL.

Table S2.6 β-coefficient values of effective connectivity for the stimulus-categories

	L-MOG to LOT	L-MOG to LP	LOT to LP	LOT to L-IFG	LP to L-IFG	p- value	RMSEA
Single-pseudoletters	0.62	0.48	0.16	0.03	0.12	0.617	0
5-pseudoletters	0.71	0.23	0.24	0.29	0	0.999	0
Single-letters	0.6	0.17	0.2	0.21	0.09	0.694	0
3-letter strings	0.55	0.31	0.15	0.2	0.23	0.97	0

5-letter strings	0.83	-0.04	0.71	0.02	0.36	0.72	0
Syllables	0.68	0.63	-0.03	-0.03	0.18	0.895	0
Words	0.44	0.43	0.2	0.11	0.24	0.996	0
Pseudowords	0.75	-0.04	0.55	0.29	0.55	0.685	0
r-value	**0.095**	**-0.203**	**0.192**	**-0.048**	**0.810**	//	//

Path models which provided a good account of the observed data were associated with small minima of the discrepancy function F and correspondingly large probabilities ($p > 0.05$) under the null hypothesis as well as low values (< 0.1) for the root mean square error of approximation (RMSEA). Spearman correlation coefficients (r) between β-coefficient values and stimuli's positional rank are presented on the bottom row in light gray cells. Only β-coefficient values for the LP→L-IFG produced a significant positive correlation (marked in red) with the stimuli's positional rank.

Chapter 3 Testing for the dual-route cascade reading model in the brain: an fMRI effective connectivity account of an efficient reading style

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Abstract

Neuropsychological data about the forms of acquired reading impairment provide a strong basis for the theoretical framework of the dual-route cascade (DRC) model which is predictive of reading performance. However, lesions are often extensive and heterogeneous, thus making it difficult to establish precise functional anatomical correlates. Here, we provide a connective neural account in the aim of accommodating the main principles of the DRC framework and to make predictions on reading skill. We located prominent reading areas using fMRI and applied structural equation modeling to pinpoint distinct neural pathways. Functionality of regions together with neural network dissociations between words and pseudowords corroborate the existing neuroanatomical view on the DRC and provide a novel outlook on the sub-regions involved. In a similar vein, congruent (or incongruent) reliance of pathways, that is reliance on the word (or pseudoword) pathway during word reading and on the pseudoword (or word) pathway during pseudoword reading predicted good (or poor) reading performance as assessed by out-of-magnet reading tests. Finally, inter-individual analysis unraveled an efficient reading style mirroring pathway reliance as a function of the fingerprint of the stimulus to be read, suggesting an optimal pattern of cerebral information trafficking which leads to high reading performance.

Introduction

The theoretical framework of the dual-route cascade (DRC) model enables us to specify the preserved and damaged reading 'modules' of neurological patients, and allows us to make quantitative predictions about reading performance in normal readers (Castles et al., 2006; Coltheart et al., 2001, Coltheart, 2006). The model postulates the existence of two distinct but interactive routes for the processing of written language: the lexical (also called direct) route would process frequent and orthographically irregular words but would fail to do so for unfamiliar words or pseudowords. By contrast, the non-lexical/orthographic (also called indirect) route would process all pseudo- and real words that obey grapheme-to-phoneme (G-P) conversion rules but would fail to produce accurate responses to words that violate these rules, that is, irregular words. Acquired dyslexia, i.e. a selective reading impairment after brain damage in a previously skilled reader, provides direct evidence for these two routes. Patients with acquired surface dyslexia present with left infero-temporal lesions and are very poor at reading irregular words (which are transformed by regularization) whereas their ability to read or spell pseudowords or regular words is unimpaired (e.g. McCarthy and Warrington, 1986). Semantic dementia patients who suffer from a loss of semantic knowledge also present with lesions to left temporal regions, and are also often poor at reading irregular words (Patterson and Hodges, 1992; for a review see Hodges and Patterson, 2007). By contrast, patients with acquired phonological dyslexia are poor at reading pseudowords whereas their word reading is relatively spared (e.g. Funnell, 1983), possibly resulting from an impairment in G-P conversion which relies mainly on left inferior-parietal and left infero-frontal regions (Jobard et al., 2003; Mechelli et al., 2003).

This double dissociation between pseudoword reading and irregular word reading suggests that pseudoword reading depends more on the dorsal pathway (parietal cortex) whereas irregular word reading depends more on the ventral pathway (occipito-temporal cortex). In addition, frequent regular words would be processed via both the ventral and dorsal pathways (Coltheart et al., 2001). However, because brain lesions are often extensive and heterogeneous, it is difficult to establish the precise functional anatomical correlates of the lexical and non-lexical routes. Neuroimaging studies have not been more successful in establishing the neural correlates of these two routes (Jobard et al., 2003; Mechelli et al., 2003) as pseudowords and real-words recruit the same neural areas (Mechelli et al., 2003; Price et al., 2003; Wilson et al., 2005; Levy et al., 2008). Alternatively, making inferences on the effective connectivity between reading areas may circumvent this spatial overlap problem and be more suitable for revealing neuro-functional links underlying the DRC model while teasing apart different theoretical viewpoints (Pernet et al., 2007). In the present study, we focused on the connectivity between posterior reading areas during pseudoword-reading and highly frequent and imageable regular word-reading.

The first aim of this study was to compute effective connectivity between prominent reading areas and to look for plausible connective dissociations during word and pseudoword reading. The second aim of this study was to investigate whether the word/pseudoword dissociation in neural connectivity could account for reading performances.

To pinpoint the various processing stages (visual, orthographic, phonological) underlying the neural network of reading (Price and Mechelli, 2005), BOLD signal changes were previously measured using fMRI and connectivity values were computed from 15 subjects who passively viewed eight linguistic (and linguistic-like) stimulus-categories: (a) Single-pseudoletters, (b) 5-pseudoletters, (c) Single-letters, (d) 3-letter strings (consonants), (e) 5-letter strings (consonants), (f) Syllables (3-letters, single-syllable), (g) Words (5-letters, 2-syllables) and (h) Pseudowords (5-letters, 2-syllables) (see example of stimuli on Figure S2.1). This design allowed us to perform a series of conjunctions over these categories, thereby isolating the following processing stages: visual (all eight stimulus categories), orthographic (c-h) and phonological (f-h). Analyses brought up significant effects bridging brain areas with reading-related processing steps. Results were as follows: the middle occipital gyrus (MOG) activity was consistent with visual processing (left MOG, BA 19 at -32 -91 10), the left occipito-temporal junction (LOT) with letter-string (orthographic) processing (left MOG, BA 37 at -46 -68 -5), the left parietal cortex (LP) with orthographic-phonological transcoding (precuneus, BA 7 at -24 -50 43) and the left inferior frontal gyrus (IFG) with phonological processing (BA 45 at -51 18 14) (see Figure 2.1). In the current connectivity model, the four ROIs were defined by 3x3x3 mm spheres centered at the above coordinates. These prominent reading areas which were revealed by our own previous work (Levy et al., 2008) are consistent with many independent lines of research over the years that we reviewed. We previously demonstrated that a connectivity model based on these 4 areas that uses forward connections only, can account for all stimuli to be seen or read (Levy et al., 2008). Here, we focused on word and pseudoword reading only and tested for the differential use of the posterior paths. It is of importance to note the posterior localization of the LOT in this study (left MOG, BA 37 at -46 -68 -5) which reflects the initial sub-lexical analysis of written words (thus mainly of sub-word stimuli such as pseudowords) (Jobard et al., 2003; Mechelli et al., 2003; Booth et al., 2002; Mechelli et al., 2005; Dietz et al., 2005; Binder et al., 2005, 2006; Vinckier et al., 2007) whereas activation of more anterior parts of LOT reflects lexico-semantic processes

(Levy et al., 2008; Mechelli et al., 2005; Dietz et al., 2005; Vinckier et al., 2007; Moore and Price, 1999; James et al., 2005; Vigneau et al., 2006; Seghier et al., 2008). With respect to these considerations (for a more encompassed and detailed review c.f. the Discussion section) and the aforementioned double dissociation between surface and phonological acquired dyslexia, we hypothesized that (regular) word reading would rely equally on the MOG→LOT (ventral) and MOG→LP (dorsal) paths (for both sub-lexical and G-P conversion) whereas pseudoword reading would rely on the dorsal path, only after sub-lexical processing in the LOT (MOG→LOT→LP).

To investigate if connectivity values predict participants' reading skills, path coefficients during word and pseudoword reading were used to predict out-of-the scanner performances in (i) lexical (regular words) and non-lexical (pseudowords) reading, and in (ii) text reading. Furthermore, leaning on previous behavioral observations that showed that skilled readers shift between reading styles (non-lexical vs. lexical pathways) in an automated manner depending on the stimuli 'fingerprint' (lexicality, transparency, frequency, imageability; see Zevin and Balota, 2000), we hypothesized that the difference in connectivity values for the labeled 'pseudoword pathway' and 'word pathway' would predict the corresponding performances. The fact that explicit tasks during reading induce changes in the use of language neural pathways (Bitan et al., 2005; Nakamura et al., 2006, 2007) also supports the hypothesis that reading styles may be reflected by the preferential reliance on a neural pathway.

Here, connectivity results provide strong support to the little neuropsychological evidence suggesting an anatomical segregation of the lexical and non-lexical reading routes. However, at variance with previous brain models of reading pathways, our data suggest a more complex scheme for routing information such that the phonology-related 'dorsal' link between the parietal and the frontal nodes of the network can be directly accessed from the extrastriate lateral visual cortex by frequent regular words while a posterior ventral 'detour' pathway is accessed first during pseudoword reading. In addition, the results show that some subjects who relied inappropriately on the word pathway during pseudoword reading (i.e. incongruent reliance), and vice versa, show poor reading performance, whereas (congruent) reliance on the word pathway during word reading and likewise for pseudowords is predictive of high reading ability.

Table 3.1 Significance (p, χ^2) between the involvement (β) of paths during word reading.

vs.	**MOG→LOT**(β=0.44)	**MOG→LP**(β= 0.43)	**LOT→LP** (β= -0.20)	**LOT→IFG** (β= 0.11)	**LP→IFG** (β= 0.24)
MOG→LOT	-	p= 0.92 (χ^2= 0.01)	p=0.0002 (χ^2=14.14)	p= 0.047(χ^2= 3.93)	p=0.23 (χ^2= 1.44)
MOG→LP		-	p= 0.003 (χ^2= 8.54)	p= 0.068 (χ^2= 3.33)	p= 0.27 (χ^2= 1.19)
LOT→LP			-	p= 0.07 (χ^2= 3.19)	p= 0.01 (χ^2= 6.35)
LOT→IFG				-	p= 0.45 (χ^2= 0.57)

MOG, left middle occipital gyrus; LOT, left occipito-temporal junction; LP, left parietal cortex; IFG, left inferior frontal gyrus.

Results

Dissociating word and pseudoword reading

Estimated connectivity values provided an excellent account of the measured data for word ($p > 0.99$; RMSEA < 10^{-3}) and pseudoword ($p > 0.67$; RMSEA < 10^{-3}) reading, but also during the processing of the other categories (p-values in Table S3.1). Note that pseudoword reading data from one subject (number 15) did not fit the connectivity model ($p = 0.04$; Table S3.2) and were therefore discarded. To investigate the influence of stimulus-categories on the paths within the network, a stacked model approach was used. This approach consists in comparing a 'free' model in which all paths are allowed to vary between two conditions, to a 'restricted' model in which the tested path is forced to be equal across conditions.

Table 3.2 Significance (p, χ^2) between the involvement (β) of paths during pseudoword reading.

vs.	**MOG→LOT**(β=0.75)	**MOG→LP**(β=-0.04)	**LOT→LP** (β=0.55)	**LOT→IFG** (β= 0.29)	**LP→IFG** (β= 0.55)
MOG→LOT	-	p=0.0001(χ^2=18.95)	p=0.27(χ^2=1.2)	p= 0.0004(χ^2=12.76)	p=0.11 (χ^2=2.6)
MOG→LP		-	p= 0.05 (χ^2=3.8)	p= 0.077 (χ^2=3.13)	p= 0.002 (χ^2=9.53)
LOT→LP			-	p= 0.14 (χ^2=2.14)	p= 1 (χ^2=0)
LOT→IFG				-	p= 0.14 (χ^2=2.14)

MOG, left middle occipital gyrus; LOT, left occipito-temporal junction; LP, left parietal cortex; IFG, left inferior frontal gyrus.

For the first focus of the study, we applied a first analysis (between paths) in which, differences between path's coefficients were tested for each category. This allowed us to explore whether, for a given stimulus category (words or pseudowords) one path of the network was more involved than the other. For word reading, no difference could be observed between MOG → LOT and MOG → LP (p = .92). In addition, the MOG→LP, MOG→LOT and LP→IFG paths were all significantly more involved than the LOT→LP path (see Table 3.1), and a close-to-significant effect (p = .07) was observed between LOT → IFG and LOT → LP. These two sets of results thus suggest that during word reading, information traffics in parallel in the ventral and dorsal pathways. For pseudowords, significant differences were observed between MOG → LOT and MOG → LP, as well as between LOT → LP and MOG → LP (Table 3.2). By contrast to word reading, this suggests that information traffics first from MOG to LOT and then is transferred to the dorsal pathway (although LOT → IFG and LP → IFG do not differ).

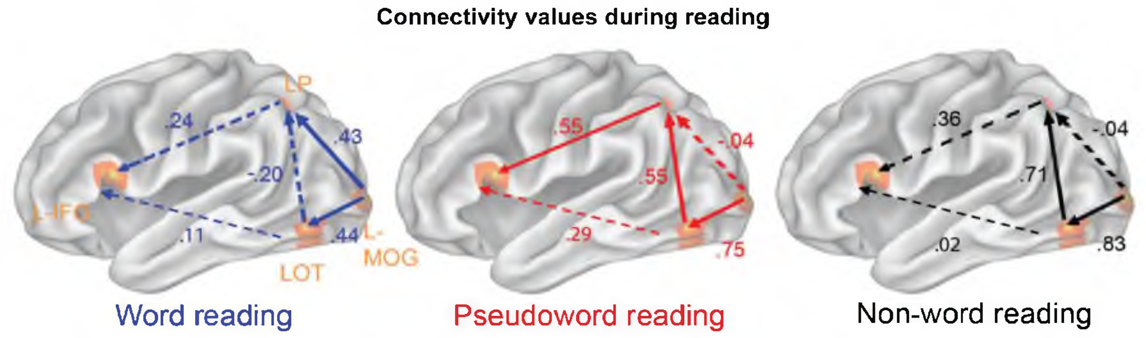

Figure 3.1 Connectivity values between prominent reading areas. Significant (full arrows) and non-significant (hashed arrows) connectivity values between prominent areas (overlaid on inflated Colin brain atlas anatomical images) during the reading of words (blue), pseudowords (red) and non-words (black). L-MOG, left middle occipital gyrus; LOT, left occipito-temporal junction; LP, left parietal cortex; L-IFG, left inferior frontal gyrus.

Furthermore, the DRC model postulates distinct routes for lexical and non-lexical reading. Hence, to pinpoint selective pathways as a function of stimulus category, we applied a second analysis (between conditions) to test for differences in connection strength between word and pseudoword reading. This analysis did not aim to control for exclusivity of paths as above, but rather to compare paths' contribution to the model between conditions. This analysis revealed a significantly stronger implication of MOG→LP during word reading than during pseudoword reading (β =0.43 vs. β =-0.04, χ^2 = 5.3, p = 0.02) (Figure 3.1). By contrast, connectivity coefficients of MOG→LOT, LOT→LP and LP→IFG were significantly more robust during pseudoword reading than during word reading (MOG→LOT β= 0.75 vs. β= 0.44, χ^2= 5.15, p= 0.02; LOT→LP β= 0.55 vs. β= -0.20, χ^2= 5.15, p= 0.0003; note however the χ^2= 3.83 and p= 0.05 for LP→IFG β= 0.55 vs. β= 0.24). No significant effect was observed for LOT→IFG (β= 0.29 vs. β= 0.11, χ^2= 1.33, p= 0.25). These results thus consolidate our interpretation of a 'detoured' route for pseudowords and also highlight the special role of MOG → LP in word vs. pseudoword processing.

In summary, the path MOG→LOT is preferentially used during pseudoword reading while the path LOT→LP is exclusively used during pseudoword reading. Thus, and for ease of explication MOG→LOT→LP is referred to hereafter as the 'pseudoword pathway'. By contrast, words revealed a preferential (and exclusive) direct connection to LP (MOG→LP), hereafter referred to as the 'word pathway', although the ventral (MOG → LOT → IFG) is also likely to be involved. We now focus on the posterior triangle (MOG – LOT – LP) since no difference between LOT → IFG and LP → IFG was observed for words and pseudowords.

Role of the posterior 'reading triangle'

Focusing on the posterior triangle MOG – LOT – LP which accounted for the strongest dissociation effects between word and pseudoword reading, we additionally tested for differences between paths during non-word reading (i.e. 5-consonant string) as well as for differences between categories for each path. This additional analysis allowed us to determine whether this 'mediator triangle' mirrored visual-orthographic or orthographic-phonological processing.

Overall, non-word (5-consonants without orthographic regularities, phonological units, and lexical entries) reading elicited the same pattern of connectivity as pseudowords did (i.e. 5-letters with orthographic regularities and phonological units but no lexical entries) and the same differences were observed in comparison to words (5-letters with orthographic regularities phonological units and lexical entries - Figure 3.1, right panel). In details, we observed that : (i) MOG→LOT and LOT→LP were equally involved in non-word processing (β =0.83 vs. β =0.71, χ^2= 0.50, p= 0.52), (ii) and both significantly more involved than MOG→LP (MOG→LOT β =0.83 vs. MOG→LP β =-0.04, χ^2= 26.55, p= 10^{-7}; LOT→LP β =0.71 vs. MOG→LP β =-0.04, χ^2= 6.41, p= 0.01); (iii) MOG→LP was significantly more engaged during word reading than during non-word reading (β =0.43 vs. β =-0.04, χ^2= 5.64, p= 0.02); (iv) as a corollary, connectivity coefficients in both MOG→LOT and LOT→LP were significantly more robust during non-word reading than during word reading (MOG→LOT β =0.83 vs. β= 0.44, χ^2= 8.85, p= 0.003; LOT→LP β= 0.71 vs. β= -0.20, χ^2= 20.33, p=10^{-6}). However, in contrast to pseudoword reading (words β= 0.24 vs. pseudowords β= 0.55, χ^2= 3.83, p= 0.05), connectivity in the LP→IFG path was modulated to the same extent by words and non-words (words β= 0.24 vs. non-words β= 0.36, χ^2= 0.40, p= 0.53). To summarize, the fact that non-word processing replicated the effects of pseudowords (vs. words) for the posterior connections only, suggests that the MOG→LOT→LP triangle is implicated in visual-orthographic analysis (but not necessarily in the processing of orthographic regularities) whereas the LP→IFG branch is more involved in orthographic-phonological transcoding, in agreement with previous reports (Levy et al., 2008; Booth et al., 2002; Cao et al., 2008).

In a nutshell, as hypothesized, results show that visual information accesses from MOG both the ventral path (to LOT) and the dorsal path (to LP), and that pseudoword reading engages strongly the anterior dorsal path (LP→IFG). However, we demonstrate that the latter involves a detour via the posterior ventral path (LOT) that is likely crucial to orthographic processing. In addition, although words engage both ventral and dorsal pathways, our data suggest a preference for the dorsal one (MOG→LP).

Predicting reading performances

For the second purpose of our study, we tested whether the above-described double dissociation in neural pathways could predict reading performance as measured outside the scanner. Spearman rank correlation coefficients ($p < 0.05$ - Table 3.3) were computed between on the one hand, z-scored (Table 3.4) Word Reading Test (WRT) and Pseudoword Reading Test (PWRT) accuracy scores (Paulesu et al., 2001), and "*Alouette-R*" CTL indices (Lefavrais, 2006), and on the other hand, BOLD-derived path coefficients for all modeled connections during word and pseudoword reading (Table 3.3). As elaborated in the Methods section, the first two tests are markers of impairment in word or pseudoword reading (Rapcsak and Beeson, 2004; Henry et al., 2007), whereas "*Alouette-R*" test is particularly conceived to assess proficiency at rapidly alternating between lexical and non-lexical processing during text reading (Lefavrais, 2006). For this second part of the study, we thus formulated two hypotheses: (i) scores in WRT and PWRT would negatively correlate with incongruent reliance of pathways, i.e. reliance on the word pathway during pseudoword reading and vice versa, and (ii) CTL ("*Alouette-R*") scores would positively correlate with congruent reliance of pathways, i.e. reliance on the word pathway during word reading and on the pseudoword pathway during pseudoword reading.

Testing for the correlations between path coefficients and reading performances, we observed that connectivity coefficients associated with pseudoword reading appraised during (on-line) word reading, negatively correlated with the performance on the *WRT* (**r = -0.70**, corrected for false discovery rate p= 0.002 for MOG→LOT and **r = -0.56**, corrected p= 0.015 for LOT→LP) and on the *PWRT* (**r= -0.50**, corrected p= 0.029 for MOG→LOT and **r = -0.60**, corrected p= 0.009 for LOT→LP) collected out of the scanner (Figure 3.2, blue hashed arrows). This shows that participants relying on the (posterior) pseudoword pathway (MOG→LOT, LOT→LP) during word reading had poorer performance in word and pseudoword reading. Conversely, connectivity coefficients of the word pathway (MOG→LP) measured during pseudoword reading, negatively correlated with the performance on the *PWRT* (**r = -0.52**, uncorrected p= 0.03) but not the *WRT* (r = -0.22, p= 0.22 - Figure 3.2, red hashed arrows). Overall, the findings allege that reliance on a neural pathway incongruent with the stimulus to be read predicts poorer reading performance as reflected by these tests.

As for reading skill per se (reflected by CTL index), reliance on the word pathway (MOG→LP) measured during word reading positively correlated (**r = 0.46**, uncorrected p= 0.04) with reading skill (CTL index) (Figure 3.2, full blue arrows). In a similar vein, reliance on the pseudoword pathway (MOG→LOT) measured during pseudoword reading positively correlated (**r = 0.58**, corrected p= 0.01) with reading skill (Figure 3.2, full red arrows). This set of findings confirmed the second hypothesis and cogently argues that reliance on a neural pathway congruent with the stimulus to be read predicts reading skill.

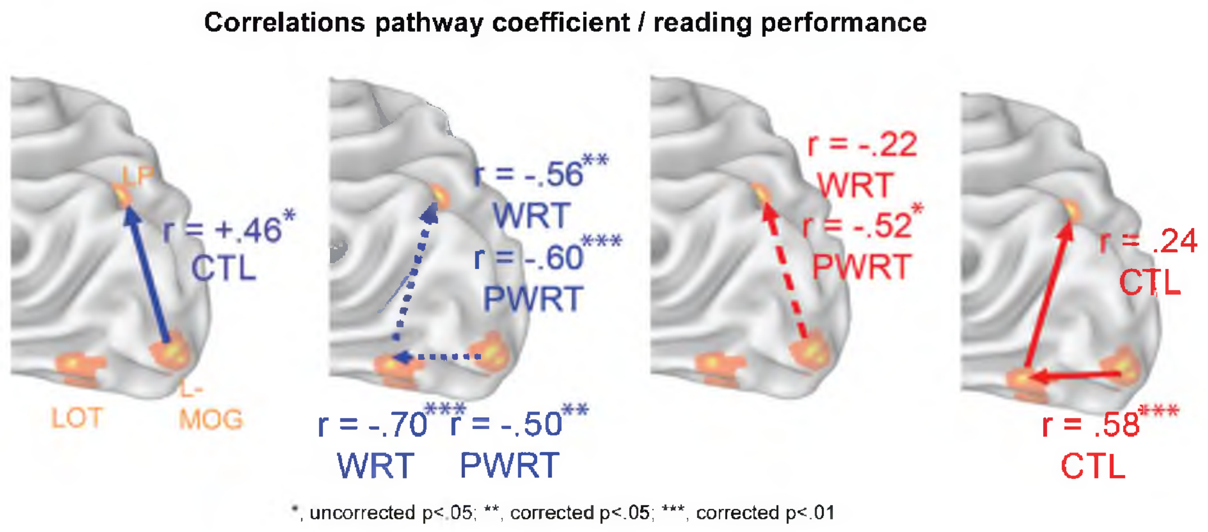

Figure 3.2 Correlations pathway coefficient / reading performance. Significant (FDR corrected or uncorrected) Spearman positive (full arrows) or negative (hashed arrows) correlation coefficients between off-line reading tests (WRT, PWRT, CTL) and effective connectivity values of on-line word (blue) and pseudoword (red) reading. WRT, Word reading Response Time test; PWRT, Pseudoword reading Response Time test; CTL, speed and precision index used in the "Alouette-R" test. L-MOG, left middle occipital gyrus; LOT, left occipito-temporal junction; LP, left parietal cortex; L-IFG, left inferior frontal gyrus.

Finally, we tested if the preferential use of one or the other pathway, i.e. MOG→LP vs. MOG→LOT, during on-line word vs. pseudoword reading predicted off-line text reading skill (how good one can alternate between reading frequent and infrequent (like pseudowords) words). To this aim, the difference (Delta) between connectivity values of MOG→LP and MOG→LOT during word and pseudoword reading respectively, were computed and correlated with reading skill (CTL indices). We reasoned that subjects with highly positive Delta values (i.e. subjects relying more on the word pathway) during word reading and highly negative Delta values (i.e. subjects relying more on the pseudoword pathway) during pseudoword reading would have the highest scores in reading performance, as evaluated by CTL indices. At first, Spearman correlations only showed a correlation of r = -.57 (p = 0.016) between CTL indices and delta Pseudoword and r = .39 (p = 0.08) between CTL indices and delta Word. Similarly, the multiple regression was not significant (R^2 = .28 F(2,11)=2.11 p=0.17). However, closer inspection showed that 2 subjects were outliers (see Methods and Supplementary Figure S3.2). Fitting the data again on the remaining 12 subjects revealed a rank correlation of **r = 0.60** (p= 0.04) for Delta Word/CTL and of **r = - 0.92**, p= 10^{-3} for Delta

Pseudoword/CTL. The regression analysis showed that a linear adjustment to the data explains 85% of the CTL variance (**R = 0.92**, F(2,9)= 25.8, p< 0.0002) with a significant contribution of the difference between paths for pseudoword reading (partial correlation t(9)= -5.36, p= 0.0004, R^2= -0.87) but not word reading (partial correlation t(9)= 1, p= 0.3, R^2= 0.30). A quadratic adjustment of the data explained up to 93% of the CTL variance (**R = 0.967**, F(5,6)= 17.63 p< 0.001) suggesting separate optima for each path but an optimal combination of their preferential recruitment depending on the lexicality of stimuli to be processed (Figure 3.3, left panel). To test if factors, other than connectivity measures in the two putative pathways could explain CTL variance, an augmented model was computed using demographic (age and gender) and educational variables (confidential data not shown here). The new model could explain 90% (F(5,6)=11.6 p=.004) of the CTL variance but this increase of 5% was not significant (full vs. reduced model, F(4,9)=1.63 p=.24). Overall, the results confirm our hypothesis that congruent pathway reliance as defined here, namely relying on the word pathway during word reading and on the pseudoword pathway during pseudoword reading, predicts high reading skill.

Table 3.3 Spearman correlation coefficients between off-line reading tests and β-values of effective connectivity.

	PW reading	**PW reading**	**PW reading**	**W reading**	**W reading**	**W reading**
	WRT	*PWRT*	*CTL*	*WRT*	*PWRT*	*CTL*
MOG → LOT	0.28	0.18	***0.58***	***-0.70***	***-0.50***	-0.42
MOG → LP	-0.22	***-0.52***	-0.04	0.27	-0.03	***0.46***
LOT → LP	0	0.10	0.24	***-0.56***	***-0.60***	-0.423
LOT → IFG	0.38	0.17	0.40	0.43	0.13	-0.2
LP → IFG	0.26	0.05	0.31	0.03	-0.03	0.21

Significant correlations are highlighted in ***italic bold****.* ***PW reading,*** *correlation with connectivity values during on-line pseudoword reading;* ***W reading,*** *correlation with connectivity values during on-line word reading;****MOG****, left middle occipital gyrus;* ***LOT****, left occipito-temporal junction;* ***LP****, left parietal cortex;* ***IFG****, left inferior frontal gyrus; WRT, correlation with the off-line Word reading Response Time test; PWRT, correlation with the off-line Pseudoword reading Response Time test; CTL, correlation with the off-line speed and precision index used in the "Alouette-R" test.*

Discussion

Dual route cascade model in the brain:

Comparing path coefficients between conditions (reading words vs. pseudowords) and between paths confirmed previous neuropsychological observations of reading impairment as proposed by the DRC model (Coltheart et al., 2001). Between path analyses lead to the following sketchy description of the main stages of information processing during reading (Figure 3.1): during regular word reading, visual information (MOG) is transmitted both to the ventral path (LOT) and to the dorsal path (LP) with a preference to the latter, information is then transferred to the left IFG. As for pseudoword reading, information is indeed processed via the dorsal path (LP→IFG), but this is done via the posterior ventral path first (MOG→LOT→LP). Additional testing with non-words suggests that the posterior reading triangle is involved in the visuo-orthographic component during reading while LP → IFG is involved in orthographic-phonologic decoding. In a similar vein, between conditions analyses showed that the pathways (originating at the visual cortex) to the posterior ventral and dorsal streams were selective for pseudoword (MOG→LOT→LP) and word (MOG→LP) reading respectively, thus strengthening neuropsychological evidence of the neuroanatomically distinct nature of the routes for pseudoword (non-lexical) and word (lexical) reading. Further consolidating this double dissociation, reliance on these pathways which was incongruent with the stimulus to be read predicts poorer reading performance, whereas congruent reliance on these pathways predicts higher reading skill (Figure 3.2). The main effects of our results therefore referred to this posterior reading triangle. Analyzing both the anterior dorsal (LP→IFG) and the anterior ventral (LOT→IFG) pathways of the model was less conclusive and therefore less discussed here. The findings allege that for pseudoword reading, LP→IFG is possibly more implicated than LOT→IFG, which is in accordance with its implication in G-P transcoding and phonological processing (Levy et al., 2008; Booth et al., 2002; Cao et al., 2008). It may be that words rely more on the anterior ventral path, but it is also possible that this path originates from a more anterior part of LOT (see further). For the rest of the discussion, we will focus on the posterior reading triangle and how our model fits with the literature.

Table 3.4 Individual delta PW, delta W values, as well as scores in the out-of-magnet reading tests.

	W RT	**PW RT**	**CTL**	**Delta PW**	**Delta W**
1	-0.17	0.20	683.48	-0.16	-0.27
2	-0.49	-0.05	372.96	-0.35	-0.23
3	0.93	0.98	594.68	-0.34	-0.25
4	2.62	1.61	622.9	-0.33	0.12
5	1.72	0.98	653.43	-0.51	0.18
6	2.44	1.92	625.26	-0.47	-0.04
7	0.60	1.36	510	0.18	-0.20
8	0.95	-0.5	491.61	0.18	0.02
9	0.91	0.85	572.93	-0.27	-0.30
10	-0.27	-0.09	436.67	0.34	-0.43
11	2.60	1.95	594	-0.41	-0.08
12	0.92	1.21	589.5	-0.45	-0.07
13	0.59	0.88	582.22	-0.16	-0.07
14	2.18	1.86	570.36	0.09	-0.30
15	1.60	1.32	685.59	0.14	0.14
Mean	1.14	0.97	572.37	-0.17	-0.12
Sd	1.03	0.77	87.44	0.28	0.18

***WRT**, Word reading Response Time test (off-line); **PWRT**, Pseudoword reading Response Time test (off-line); **CTL**, speed and precision index used in the "Alouette-R" test (off-line); Delta PW, the difference (delta) between connectivity values of MOG→LP and MOG→LOT during on-line pseudoword reading; Delta W, the same during on-line word reading.*

Our *a priori* model does not rule out the contribution of other (in between) regions to reading. Such spatial-temporal feed-forward cascade is supported by the extensive number of observations in neuroimaging, electro- and magneto-encephalography studies over the years (reviewed in Jobard et al., 2003; Price, 2000; Démonet et al., 2005; Salmelin, 2007). In short, we do contend that reading is a very complex task involving a very broad network with feed-forward and feed-back loops, yet, we reason that studying its main components during simple tasks using forward model should be enough to highlight main stream differences between conditions. Indeed, in accordance with the principle of parsimony, this forward model fitted well all eight categories of stimuli read or perceived, using the smallest number of parameters (paths) offering a good trade-off between bias and variance.

Although the findings support prior evidence (Coltheart et al., 2001), lexical reading is thought to involve more the left-hemispheric ventral pathway whereas non-lexical reading – the dorsal pathway (e.g. Pugh et al., 2000); this may appear counter-intuitive with respect to the above findings. A closer investigation of the precise location and functionality of the above regions may resolve this apparent contradiction. First, the ventral pathway is indeed involved in orthographic/lexical processing. Nevertheless, its specificity for lexical processing concerns a more anterior part of the pathway, which is assumed to gate lexico-semantic analysis (for a review see Jobard et al., 2003; Price and Mechelli, 2005). Previously, following irregular words presentation, effective connectivity between the anterior LOT (y = -42) and the left pars triangularis (IFG) was associated with increased activation in the latter, corroborating with the lexico-semantic role of this anterior pathway (Mechelli et al., 2005). Likewise, the Visual Word Form Area (VWFA) is thought to be attuned to orthographic regularities and thus to be more activated for words or pseudowords than for alphabetical consonant strings (Cohen et al., 2002). This is suggestive of the more lexico-semantic role of the VWFA and is therefore not surprising that this area is comprised in an anterior segment of the LOT (approximately: -43 -54 -12, in the left fusiform gyrus, BA 37).

Here, however, we isolated a more posterior part of the LOT (left MOG, BA 37 at -46 -68 -5) applying an analysis which isolated (alphabetical) letter-related activations. It is thus more likely that the region here is involved in the initial sub-lexical analysis of written words (see Dietz et al., 2005: y = -73) and in the processing of letters strings (sub-words) (see Booth et al., 2002: y = -60; Mechelli et al., 2005: y = -60; Binder et al., 2005: y = -63; Binder et al., 2006: y = -60; Vinckier et al., 2007: y = -56 to -64). This fits well with the higher activation of LOT usually observed during pseudoword reading (Mechelli et al., 2003; Price et al., 2003; Levy et al., 2008), which triggers an excess of sub-word processing relative to word reading. Indeed, pseudoword reading automatically triggers a process of recognition of familiar sub-word segments and a 'search' for their original real words, and is therefore slower than any other linguistic stimulus in lexical decision tasks (Ratcliff et al., 2004). In a similar vein, visual spelling task (match the spelling of two words from the first vowel onwards) which would probably involve similar processes to those during pseudoword reading, much more than during word reading, indeed yields stronger connectivity in MOG→LOT (y = -72) than in MOG→LP (Booth et al., 2008). As such, the posterior LOT is sensitive to 'low-level' linguistic stimuli (unfamiliar characters or infrequent letter-combinations), while activation becomes hierarchically more anterior for frequent letters, bigrams, quadrigrams, and the most anterior – for words (Vinckier et al., 2007). Overall, the literature is congruent with our findings if one is to look at sub-regions. It therefore contributes to the recently growing body of evidence of a functional dissociation inside the LOT depending on stimulus type (words, pseudowords, letter strings or unfamiliar characters) suggesting a more perceptual role for the posterior LOT and a more lexico-semantic role for the anterior LOT (Levy et al., 2008; Mechelli et al., 2005; Dietz et al., 2005; Vinckier et al., 2007; Moore and Price, 1999; James et al., 2005; Vigneau et al., 2006; Seghier et al., 2008).

Together, in terms of DRC, these observations imply that the ventral path implicated in lexical reading and associated with acquired surface dyslexia actually involves a more anterior segment than the one discussed here. Thus, reading regular words and pseudowords involves information trafficking to the posterior ventral path for letter/sub-word processing. However, this is much more substantial for pseudowords because of the necessity to process its sub-word components. Assuming a strict mapping between brain activation and functional involvement, pseudoword reading mainly relies on the assembling and processing of sub-word units. Information is then likely to be processed in the LP for subsequent G-P mapping (pseudowords), and in the anterior LOT for lexico-semantic access (words).

As for the dorsal path, the LP is often reported in the same studies that report LOT activation for letters (James et al., 2005; Price et al., 1996; Puce et al., 1996; Longcamp et al., 2003; Pernet et al., 2004; Kuo et al., 2004), thus implying a role in letter processing for both regions. However, in recent years more and more experimental evidence is gained over the more general role of the LOT (Levy et al., 2008) reflecting an operation common to the processing of words (Kronbichler et al., 2007), word sub-units (Binder et al., 2006), pictures (Starrfelt and Gerlach, 2007), objects (Bar et al., 2001), or stored visual forms and structures in general (Joseph and Gathers, 2003). Noteworthy, the coordinates of LP in the present study fall mainly in the left superior parietal lobule, which together with the left inferior parietal lobule yields greater letter-selectivity than does the LOT (Joseph et al., 2003; Joseph et al., 2006). Moreover, this letter-selective cluster in the LP also revealed (i) phonological selectivity (phonological null conjunction), and (ii) a positive activity gradient (linear contrast) as a function of the number of orthographic and phonological units (Levy et al., 2008). Likewise, a neighboring site within the LP (supramarginal gyrus) mediates G-P conversion, i.e. the retrieval of the phonological codes for the letters to be read (Booth et al., 2002; Pugh et al., 2000; Joseph et al., 2006), while acting as a bridge to phonological processing in the IFG (Cao et al., 2008). To be noted, we previously detected that the left supramarginal gyrus also yielded letter-selective activity during a passive viewing task (Levy et al., 2008). DRC speaking, literature and present findings suggest that first, regular words would feed to the dorsal path (LP) for letter-selective mapping into phonological representation and in parallel, to the (posterior) ventral path for letter/sub-word analysis, reflecting cooperative/competitive dorsal/ventral interactions (Coltheart et al., 2001). This view is in agreement with the DRC model arguing that regular words can be read in two ways. Despite parallel dorsal/ventral processing, only trafficking to the dorsal path (word pathway) is selective for words; this is further supported by the association between connectivity for this path (and not ventral path) and high reading performance (Figure 3.2, blue full arrow). Secondly, pseudowords would feed to the dorsal path for letter-selective mapping into phonological representation but not before the intervention of a substantial letter/sub-word analysis in the posterior ventral pathway (see Binder al., 2006; Vinckier et al., 2007) for the important role of the region in bi- tri- or quadri-gram processing). The prominence of this posterior ventral pathway during pseudoword reading receives further support by the correlation of its connectivity with high reading performance (Figure 3.2, red full arrows).

Limitations and alternative interpretations

Two points are to note about the words stimuli used here. First, we used regular words of high frequency and imageability thereby strengthening the reliance on the lexical vs. the non-lexical route (Zevin and Balota, 2000). However, irregular words are likely to rely on the lexical route to a higher extent; this should be interesting for further investigation. Second, it is important to note the relatively high degree of transparency in French. It would therefore make sense that words of a more opaque language (English) would rely more on the lexical (anterior LOT) pathway, and less on the dorsal G-P conversion (LP) as reported in the literature. It should be informative to address these points in the future using a similar design, but (i) between languages, and (ii) using irregular words.

We also note that our results could be interpreted by connectionist models (e.g. Seidenberg and McClelland, 1989) which represent orthography, phonology, and semantics as separate systems, presumably interacting via recurrent neural networks. This seems particularly pertinent given that our results point to a mechanism of parallel processing during reading. Nevertheless, there are several issues which led us to test our results rather according to the DRC model. First, the number of connections between the areas was mathematically limited and was thereby restricted to feed-forward connections given the posterior-to-anterior recruitment of the tested areas (Levy et al., 2008). Second, our experimental design did not allow us to directly pinpoint a region for semantic processing, which should be addressed to account for connectionist models. Instead, our investigation focused on early and more basic processing stages of reading. The analysis of letter-strings (non-words) replicated the connectivity effect of pseudowords (vs. words) for the posterior reading triangle MOG→LOT→LP, thereby supporting the idea that it is implicated in visual-orthographic analysis whereas more anterior connections would involve subsequent processing steps such as phonological and semantic analyses. Altogether, the simplistic and parsimonious nature of the neuronal modeling applied here, together with the straightforward pattern of results, led us to consider the DRC model particularly suitable for accommodating our results.

Previous effective connectivity (e.g. Mechelli et al., 2005) and magneto-encephalography (e.g. Wilson et al., 2007) accounts have reported distinct neuronal connections and dynamics during word and pseudoword reading. Given that these studies and ours used different tasks (e.g. oddball lexical decision vs. passive viewing) or applied the results on different anatomical models, they report different regions of interest, implying that word and pseudoword reading may in fact recruit a vaster neural network than the one reported in our study. In particular, because our connectivity model lacked a lexico-semantics ROI and focused on a restricted number of prominent regions during reading, it remains unclear which other regions participate in such complex process, and what recurrent loops and feed-back and -forward connections take place during reading. Nevertheless, the simplicity of our model is also its strength given that it straightforwardly reveals strong interactions between prominent (and serial) reading areas. In a similar vein, Seghier and colleagues (Seghier et al., 2008) showed that posterior- and anterior-LOT networks may correspond to lexical and non-lexical reading, respectively. The authors explained their counter-intuitive finding by suggesting that higher activation may reflect more effort, not more efficiency. Although such possibility cannot be excluded, with respect to other network suggestions in the literature, we would rather suggest that numerous neural networks mediate reading, depending on stimulus fingerprint, language properties/characteristics, task demands and probably other factors. At present, it may not be possible yet to provide a clear and complete picture encompassing the totality of the neural networks underlying reading. However, we do contend that investigating neural networks should be more informative than investigating a brain region in isolation (Reinke et al., 2008). Studying interactions within neural networks thus contributes to elaborate the ever growing scope of understanding the processes underlying reading, especially when correlated to off-line performances. The core of our investigation was, therefore, not only to highlight pathways for which activity is selectively modulated by words and pseudowords, but also to expand upon previous reports by locating those that are liable to predict reading performance.

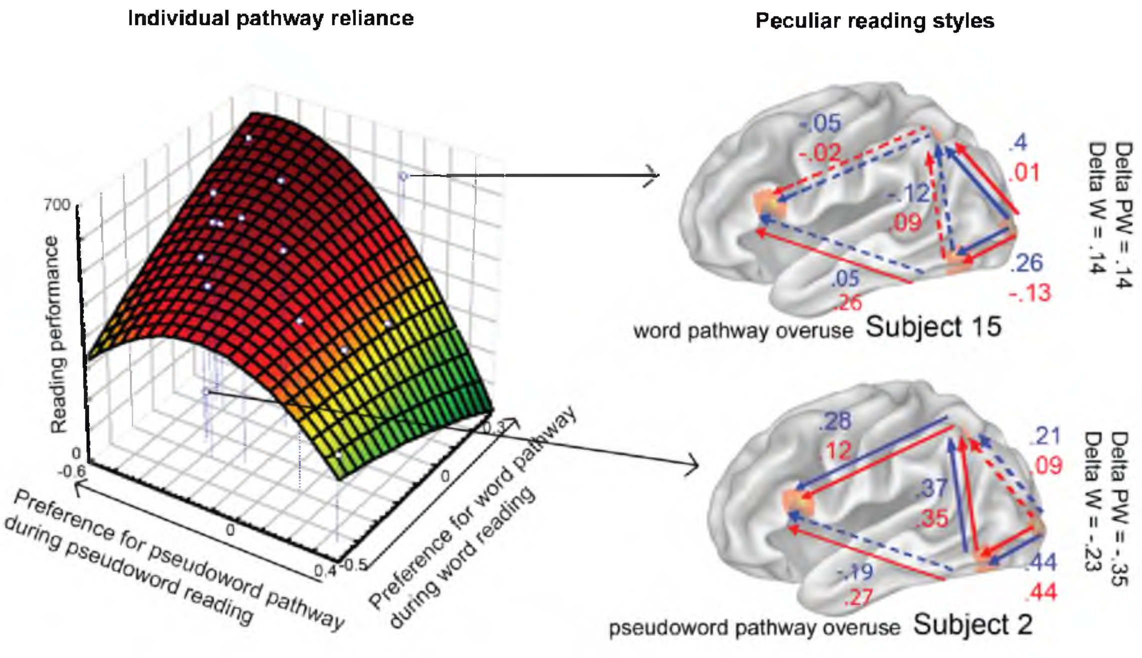

Figure 3.3 Group and individual pathway reliance. Left Panel: Group trade-off between preferences (delta values) for the word pathway vs. the pseudoword pathway resulting in efficient (dark-red) or deficient (yellow-green) reading performance outside the scanner (CTL index). Right Panel: Subjects with nonconformist reading styles during word (blue) and pseudoword (red) reading which predict their highly-efficient (subject 15) and inefficient (subject 2) reading performance.

Reading styles

Addressing the second point of our study, we found that (i) incongruent pathway reliance (word pathway vs. pseudoword pathway) as a function of the stimulus to be read predicts poorer reading performance (WRT/PWRT tests), (ii) congruent pathway reliance predicts higher reading skill (*"Alouette-R"* reading text reflecting skill in alternating pathway reliance), (iii) text reading was well predicted (85% to 93% of the variance) by an optimal combination of the preferential recruitment of the two pathways (especially the ability to use the pseudoword pathway). Overall, the results establish a firm link between reading performance and pathway reliance, in particular alluding to the prominent contribution of LOT, thereby lending support to (i) the recently observed correlations between LOT activation and reading performance in skilled readers (Bruno et al., 2008), to (ii) the stronger modulatory effect on the LOT→LP feed-forward connection observed in skilled vs. impaired (children) readers during an orthographic/phonological conflicting rhyming task (Cao et al., 2008), and even to (iii) the correlation between gray matter volumes in this region and reading skills (Pernet et al., 2009).

As a broader interpretation of the present results, we propose that the observed shifts in effective connectivity between word and pseudoword pathways are mediated through automatic mechanisms, which may rely on the extraction of the stimulus' global visual fingerprint and on a subsequent comparison with entries in the visual lexicon, so as to favor one of the routes. This idea was inspired by the early observation of reliance patterns (lexical vs. non-lexical) even in a population of skilled readers (Baron and Strawson, 1976). The particular nature of the text reading task used here, requiring high skill in rapidly alternating between lexical and non-lexical reading (Lefavrais, 2006), led us to formulate the following interpretation: the efficiency with which readers alternate between one path to another reflects individualized 'in cerebro reading styles' (pathway reliance) and could, in turn, determine reading speed and proficiency. Such automated shifts in (lexical and non-lexical) reading styles (Zevin and Balota, 2000) may be mediated through shifts in neural pathways (Bitan et al., 2005; Nakamura et al., 2006) on an unconscious level, as has been recently shown (Nakamura et al., 2007). With respect to this view, we analyzed the data to define the efficient 'in cerebro reading style', i.e. the reliance pattern, predicting high performance during text reading. A (non-linear) trade-off between the word vs. pseudoword pathways (dark red on Figure 3.3), i.e. relying on the word pathway during word reading and on the pseudoword pathway during pseudoword reading, accounted best for high reading performance.

However, not all subjects followed the 'efficient trade-off'. As an example of peculiar reading styles, subjects 1 and 2 were outliers in the multiple regression analysis (linear adjustment), and had highly negative Delta values (Table 3.4), i.e. they exhibited higher connectivity values for the non-lexical than the lexical route not only during pseudoword reading but also during word reading. Such an 'abnormal' connectivity pattern could be taken as an indication of an overuse of the non-lexical route regardless of stimulus-compliance to G-P conversion rules. Such a strategy has been recently observed in deaf readers (Aparicio et al., 2007) but seems to extend here, even to clinically normal readers. Interestingly, the other subject whose data did not conform to the model (discarded subject 15) also revealed a peculiar reading style, but this time reversed, i.e. this subject exhibited highly positive Delta values (Figure 3.3, right panel; Table 3.4). In this case, this indicates an overuse of the lexical route. Interestingly, although subject 15 did not fit the connective model during pseudoword reading ($p = 0.04$, Table S3.2), this subject's performance perfectly fit the connective model during word reading ($p = 1$, Table S3.3). This also indicates that our model relies more heavily on the non-lexical route: although outliers in the regression, subjects 1 and 2 did fit the overall model whereas subject 15 did not. Looking at the scores, subjects 15 and 1 were also the most skilled readers (highest CTL value; Table 3.4) whereas subject 2 had very poor reading skills (lowest CTL value). This suggests that the high performance is obtained with a (non-linear) trade-off between the lexical vs. non-lexical routes (dark red on Figure 3.3, subjects 4, 5 and 6, Table 3.4) but also that the 'quasi-exclusive' use of one route or the other can elicit highly-efficient (subjects 1 and 15) or inefficient (subject 2) performances. These peculiar reading styles did not conform to our model/regression and are illustrated in Figure 3.3 (right panel). In a nutshell, our findings are in agreement with data suggesting individual reading styles/profiles that can be accounted for by the DRC model (Ziegler et al., 2008). Furthermore, the observation of the 'quasi-exclusive' use of paths may suggest that subjects 1 and 15 may have relied on alternative pathways that are not included in our model, which would explain their excellent reading performance. By contrast, subject 2 may have not resorted to alternative pathways, thereby resulting in poor reading performance. Future research applying more complex connectivity models on reading data may reveal that different individuals rely on different pathways within a vast and complex neural network during reading.

Likewise, these observations raise the possibility that individualized reading styles may be explained by factors other than connectivity measures such as education, age and gender. To this aim, we found that the variance in reading skill could also be explained by the number of years of education (linear correlation: $r = .55$ with WRT, $r = .54$ with PWRT and $r = .61$ with CTL indices; $p<.05$) but not demographic data (age and gender). More importantly, the number of years of education did not correlate with delta word ($r = 0.02$) or delta pseudoword ($r = -0.29$), suggesting an independent contribution of the number of years of education (practice) and 'in cerebro' reading styles. This finding is of particular interest given that lexical/non-lexical reading styles are already observed in childhood (Treiman, 1984) and may be established during school time by individualized reading instruction methods (Connor et al., 2007). Hence, the present work may be used in future to elaborate the scope of understanding both early reading acquisition and the influence of various factors on reading skill.

Most recently, Seghier and colleagues (Seghier et al., 2008) showed that among a population of skilled readers, some rely more on lexical than sub-lexical reading and vice-versa (out-of-scanner assessment of irregular word and pseudoword reading), and that this correlated with the activation of two neural networks (fMRI for word reading). In the present study however, we directly focus on the lexical and sub-lexical pathways as assessed by connectivity during word and pseudoword reading in the scanner, and correlate it to reading tests outside the scanner. Although the studies applied different tasks and approach, and therefore investigated different neural networks, we contend that both are complementary in that they strengthen the idea that skilled readers differ by relying on different reading styles which in turn reflect activation of different neural networks.

To conclude, the results here reveal, for the first time, functional paths in the brain that are selectively involved in word and pseudoword reading in a manner consistent with the DRC model. Overall, the findings (i) confirm prior neuropsychological data by providing a remarkably good neural account of the early processing (visuo-orthographic) of the two routes in the DRC model, (ii) extend the knowledge about the non-lexical route, showing a mediation via the posterior LOT, (iii) demonstrate that incongruent or congruent reliance on these pathways predicts poor or skilled reading, (iv) raise the novel idea of efficient 'in cerebro' reading style depending on the stimulus to be read (known word vs. unknown word) and argue that individually unique reading styles may translate to either skilled or deficient reading ability, (v) and finally, introduce a link between individual reading styles and reading proficiency, which could be in part established during school time by individualized reading instruction methods (Connor et al., 2007). The findings here could also be considered as a first demonstration of the pattern of cerebral information trafficking which one 'should follow' in order to yield high reading performance. This may be of particular interest for applications already during school time for reading difficulties, such as in the case of developmental dyslexia.

Methods

In the present manuscript we extended the analyses performed on data from our previous experiment (Levy et al., 2008).

Participants

Fifteen healthy individuals (eight females, mean age 27.3, sd 3.4 years), all university students (5-8 years) with normal or corrected-to-normal vision participated in this experiment. All were right-handed on the Edinburgh handedness inventory, native French speakers, and free from any history of neurological or psychiatric illness or medical treatment.

Ethics Statement

The Toulouse INSERM (Institut national de la santé et de la recherche médicale) ethics committee approved the experimental protocol and informed written consent was obtained from the subjects after the nature and possible consequences of the study had been explained to them.

Out-of-scanner reading assessment

Subjects' reading ability was investigated outside the scanner by applying the Word reading Response Time (WRT) and the Pseudoword reading Response Time (PWRT) tests, that have been repeatedly used in our group for the diagnosis of developmental dyslexia in adults (e.g. Paulesu et al., 2001; Dufor et al., 2007, 2009). In these tests, four blocks of words and pseudowords (twenty each) were presented in an ABBA design on a computer screen; naming latency was recorded via a voice-key and reading correctness was registered. The words used were highly concrete and familiar nouns. Pseudowords maintained words' 'envelope' but with different internal consonants. Participants were asked to read each word/pseudoword as soon as it appeared on the screen. Once the subject had responded and the latency had been recorded via a voice key, the word disappeared; there was a 1-second interval before the next stimulus was presented. Voice onset time for single word/pseudoword reading was transformed into a z-score (z = -1*(vo – avg)/sd; 'vo' is voice onset, 'avg' and 'sd' are the average and the standard deviation of the population reference) while simple reaction times for a dot stimulus provided a baseline. Hence, positive z-values reflect higher performance whereas negative z-values reflect lower performance in comparison to the general population. Note that, spelling accuracy and voice onset in these two tests, both reflect reading impairment (Dufor et al., 2007). Furthermore, they convey an indirect estimation of the efficiency of the lexical and non-lexical routes, i.e. low scores in the first test (WRT) would point to a deficient utilization of the lexical route (Rapcsak and Beeson, 2004), whereas low scores in the second (PWRT) may reflect a damaged reliance on the non-lexical route (Henry et al., 2007). Thus, we expected negative correlation between scores in these tests and incongruent reliance of pathways, i.e. reliance on the 'word pathway' (posterior dorsal stream) during pseudoword reading and 'pseudoword pathway' (posterior ventral stream) during word reading. To expand our investigation to the reading circumstances closer to every-day life, we also used the "*Alouette-R*" test (Lefavrais, 2006), a standardized test for reading text in French which at variance with the former two tests, directly assesses text reading speed and precision (CTL index). This time-limited text involves both frequent words, and very rare words (making them appear as pseudowords to almost any subject), as well as words having low probability provided the sentence context in which they take place. The particular contents of this text requires the subject to alternate quickly between 'standard' text reading involving mainly the lexical route and the non-lexical route in order not to misprocess the ‘catch-up’ words hidden in the text from place to place. Note that whereas the first two tests are markers of impairment in word or pseudoword reading, i.e. predict negative correlation with pathway reliance, “*Alouette-R*” test assesses proficiency at dealing fluently with both routes during text reading. We therefore hypothesized a positive correlation between CTL scores and congruent reliance of pathways, i.e. reliance on the word pathway during word reading and vice versa.

fMRI stimuli

Stimuli were all embedded in pseudo-characters so as to maintain a constant string length (seven characters), and displayed on a grey (RGB: 160, 160, 160) background to avoid visual fatigue (see example of stimuli in Figure S3.1). Two hundred and eight stimuli were designed, twenty six per stimulus category, thus matching their frequency of appearance. Stimuli were matched (intra-category) and distinguished (inter-category) for their angularity, visual surface and complexity, orthographic units in general and consonant and vowel structure in particular, phonological and lexical-semantic units, mean frequency of appearance for words, mean positional letter frequency (MPLF), mean positional bigram frequency (MPBF) and mental imagery score for words.

Tasks and procedures

Subjects were briefly trained and familiarized with the procedures and stimuli prior to fMRI scanning. During the scanning, stimuli were displayed via a dual-display stereoscopic video projector (VisuaStimDigital, Resonance Technology Inc.) in synchrony with functional acquisition that duplicated the experimental computer screen with 500,000 pixels per 0.25 square inch resolution and a refresh rate of 85 Hz. In order to minimize ocular saccades and numerous fixations at different string positions, stimuli were presented with a horizontal visual angle of 4.2° for 200 ms. Additionally, the maximal number of letters was limited to five thus facilitating stimulus recognition in one fixation, although through the whole experiment the total length was always of 7 characters if one counts the pseudo-character flankers.

Participants were passively exposed to blocks of stimuli during five runs of five minutes each. Each run contained ten 17-s long blocks of stimuli that alternated with 12.5-s long blocks of visual fixation (fixation-cross of 0.65° visual angle). Blocks were presented pseudo-randomly to increase condition (stimulus category) alternation and avoid condition repetition among successive blocks.

Each of the eight conditions was repeated in six different blocks among the five runs in such an order as to avoid interference with the low frequencies of scanner noise and physiological rhythms. In the fifth run, the last two blocks were used to equalize run-length, but discarded from analysis, so as to maintain an equal number (six) of blocks per condition. Each block contained twelve different stimuli of the same condition with a random inter-stimulus interval (ISI) ranging from 600 to 1100ms so as to avoid stimulus anticipation or rhythmic activity and to maximize the BOLD signal (Mechelli et al., 2000). This also allowed us to sample data in a distributed way over the ISI, eschewing a possible bias of estimated activation (Price et al., 1999). At the end of each run, subjects could rest for 2-3 minutes and were asked to report stimulus visibility or any other difficulties or problems that could bias the experiment.

fMRI parameters

All subjects were scanned at the Neuroradiology service of Toulouse Purpan Hospital on a 1.5 Tesla Siemens Magnetom Vision scanner (Erlangen, Germany) equipped for multi-slice echo-planar imaging (EPI). For functional MRI runs, blood oxygen level-dependent (BOLD) imaging was performed using a T2*-weighted single-shot EPI sequence (60 ms echo time (TE), 2430 ms repetition time (TR), 90° flip angle, 250 mm field of view (FOV), 64 x 64 acquisition matrix with 16 interleaved slices parallel to the intercommissural plane (from $z = -35$ to $z = 45$), 3.91 x 3.91 x 5 mm voxel size). The high-resolution anatomical scan was acquired on the same plane as the EPI data at the end of the functional runs using a 3D MPRAGE sequence (TE= 4 ms, flip angle= 8°, FOV=300 ms 5/8, 160 x 256 matrix, 1.17 x 1.17 x 1.18 mm voxel size).

Image processing

All functional images were pre-processed using techniques implemented in Statistical Parametric Mapping (SPM2, Welcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk). The functional scanning sessions contained 123 acquisition volumes, of which the first four were discarded for signal stabilization. A slice timing correction was performed with the fifteenth slice (the middle temporal one) as the reference. The sixtieth volume of the prior 3D-session was used as a reference for realignment of functional images to correct for head motion. T1-weighted anatomical images were coregistered to the mean EPI image, and were used for the normalization of functional images onto the Montreal Neurological Institute T1-template with a resampling at $2mm^3$ (5th degree B-Spline interpolation).

fMRI data analysis

Images were smoothed with a 6-mm-at-full-width-half-maximum Gaussian filter ensuring data normality. For each subject, the spatially normalized and smoothed images were used to create eight condition-type images per subject (general linear model with one regressor per condition and session convolved with a box car function) and entered into an ANOVA model to inquire commonalities and differences between conditions (Levy et al., 2008). Figures illustrate statistical parametric maps overlaid on the individual 'inflated' Colin brain atlas anatomical images (Van Essen et al., 2001).

Functional MRI time points (TR = 2430 ms) were extracted from each individual data set with spheres (3x3x3 mm) centered at cluster maxima-coordinates of the four left-hemisphere ROIs revealed in our analyses: (i) the left middle occipital gyrus (-32 -91 10), (ii) the left lateral occipital-temporal area (-46 -68 -5), (iii) the left parietal (-24 -50 43), and (iv) the left inferior frontal gyrus (-51 18 14). Each condition was repeated in six functional blocks, each one consisting of twelve time points (seven for condition, five for fixation), thus resulting in 72 concatenated time points for most but not all conditions. Hence, to balance vector length among conditions, we selected 64 time points per condition for each individual in each region. Note that, each condition block was multiplied by the first eleven (out of twelve) time points of the hemodynamic response function so as to maximize signal extraction and to avoid interference with the subsequent block. Finally, data were high-pass filtered (cut-off frequency 0.05Hz) to remove low-frequency concatenation-generated signals.

Effective connectivity was then assessed by means of structural equation modeling (SEM) implemented in LISREL software (version 8) (Jöreskog and Sörbom, 1996). After averaging the observed data (BOLD signal) across subjects, covariance matrices were computed for both the observed data and for the estimates of the theoretical model. A robust estimator of maximum likelihood is achieved by an iterative procedure of adjusting the predicted values with the observed values, resulting in a β-coefficient value for each connection. Residual variance representing unmeasured influences from outside the model is also incorporated for each connection. It reinforces the statistical power and the precision of the calculated β-coefficient values. The null hypothesis postulates no difference between the predicted and the observed matrix. Thus, path models which provided a good account of the observed data were indicated by the impossibility of rejecting the null hypothesis ($p>0.05$); likewise a good fit of the model corresponded to low values ($p<0.1$) for the root mean square error of approximation (RMSEA). β-values reflect path strength; more precisely, for a given connection A→B, a positive β-value would mean that region A exerts a positive modulatory effect on region B, i.e. it increases the activity of region B. Alternatively, a negative β-value would mean that region A exerts a negative modulatory effect on region B, i.e. it decreases the activity of region B.

To define a path model that would account for the pattern of cortico-cortical associations during the passive viewing of all the eight conditions, we used our prior knowledge about prominent reading areas and the posterior-to-anterior fashion in which they are recruited (Levy et al., 2008). Following the principle of parsimony, we started by first testing an economical model (few connections) and then making it more complex by adding new ROIs, forward and backward connections. The objective was to retain the fewest ROIs (variables) and paths that explain as much as the variance in the phenomenon is possible (de Marco et al., 2009). Specifying paths and β-coefficient values (path strength), we retained the following explanatory variables (ROIs) and the most relevant paths between them which best accounted for the observed fMRI data: Left MOG to LOT, Left MOG to LP, LOT to LP, LOT to IFG and LP to IFG. Among different tested models which could represent simpler or more complex dynamics, this parsimonious and unidirectional model provided the best fit for observed data during the passive viewing of eight different pseudo-linguistic and linguistic stimulus categories (see high P-values in Table S3.1). Additionally to this, the chosen model consisted of four ROIs therefore allowing for the estimation of a maximum number of six (4x3/2) variables. Thus, we have here estimated five variables (paths). Finally, beside the fact that adding more connections than those already present would statistically render the model unstable, it is also known that adding double-sense connections in SEM is to be avoided at the risk of destabilizing the model's fit.

Hence, our choice of important connections had to be limited and was therefore inspired by the posterior-to-anterior fashion in which prominent reading areas are recruited {c.f. (Levy et al., 2008) for a direct or (Jobard et al., 2003; Price, 2000; Démonet et al., 2005; Salmelin, 2007) for an indirect demonstration}, thus retaining unidirectional forward paths in the model. It is important to note, however, that the potential contribution of feed-back connections and that of other reading areas is overlooked in the present account. Mitigating this concern, the temporal resolution of an fMRI measure, which is of about a couple of seconds, has for consequence that the weight of a directional path is in fact the net result of the time integral of all the millisecond-range information circulating (forwards and backwards) from within the duration of the measurement. In that sense, the weight of the oriented path depends on bi-directional information. Recapitulating upon bidirectional concerns, we argue that the more constrained the model, the more robust, powerful and interpretable the results are. Thus, investigating reading using a parsimonious, yet functionally robust, forward model should highlight important information trafficking during reading.

To test for differences between words and pseudowords on the paths within the network, a stacked model approach was used. This approach consists in comparing a ‘free’ model in which all paths are allowed to vary between two conditions, to a ‘restricted’ model in which the tested path is forced to be equal across conditions. In a first analysis, we compared pathways for each reading condition thus revealing which pathways are more ’engaged’ than others. In a second analysis, we compared reading conditions for each pathway, thus revealing which pathway is preferentially used during the reading of various stimuli.

To test for reading proficiency, Spearman rank correlation coefficients ($p < 0.05$ - Table 3.3) were computed between on the one hand, z-scored Word Reading Test (WRT) and Pseudoword Reading Test (PWRT) accuracy scores (Binder et al., 2005), and “*Alouette-R*” CTL indices (Lefavrais, 2006), and on the other hand, BOLD path coefficients during word and pseudoword reading (Tables 3.2,S3.2,S3.3 – Figure 3.2). P-values were adjusted for multiple comparisons by controlling the false discovery rate (FDR) (Benjamini and Hochberg, 1995). Voice onset and spelling errors in the first two tests (WRT and PWRT) constitute a valid criteria for the diagnosis of reading impairment (Rapcsak and Beeson, 2004; Henry et al., 2007; Dufor et al., 2007, 2009). Low performance in these tests for poor readers (dyslexics) but not for good readers (healthy subjects) (e.g. ref to (Dufor et al., 2007)) may be due to an erroneous reliance on the reading neural network, in particular in the parieto-temporal region (Meyler et al., 2007). These observations thus motivated the rationale hypothesizing that scores in WRT and PWRT tests should anti-correlate with incongruent reading pathway, which could in turn imply a tendency for reduced reading performance. Noteworthy, these observations could not rule out the possibility that these tests could also positively correlate with congruent reading pathway. Nevertheless, for the purpose of predicting reading skill (and not reduced reading performance) we reasoned the “*Alouette-R*” test more adequate. “*Alouette-R*” test is particularly conceived to assess proficiency at rapidly alternating between lexical and non-lexcial processing during text reading (Lefavrais, 2006). We formulated two working hypotheses: (i) scores in WRT PWRT should negatively correlate with incongruent reliance of pathways, i.e. reliance on the word pathway during pseudoword reading and vice versa, and (ii) CTL (“*Alouette-R*”) scores should positively correlate with congruent reliance of pathways, i.e. reliance on the word pathway during word reading and on the pseudoword pathway during pseudoword reading.

In addition to the above analysis, the difference (Delta) between connectivity values of MOG→LP and MOG→LOT were computed and correlated with reading skill (CTL indices) using Spearman rank correlation coefficients and multiple regression analyses. The latter analyses aimed at testing whether the 'preferential use' of the congruent route could predict individual's reading skill. A 1st analysis revealed that there were 2 outliers. These subjects were identified using absolute z-residues. Z-residues correspond to the absolute value of the standardized residuals, i.e. the ratio between the centered value of residuals (that is, the difference between the measured value and the estimated value) and its standard deviation; it is thus equivalent to a z-value. Subjects with z-residues (absolute values) greater than 2 reflect a deviation of approximately two standard deviations from the mean value of the population and are therefore considered as outliers (subjects 1 and 2) (see Figure S3.2). A second analysis was then performed using only 12 subjects. Finally, an augmented model was tested, using not only delta word and delta pseudoword but also age, gender and the number of years of education. The two models were compared using an F test to examine if those variables explained the data better.

Supporting Documents

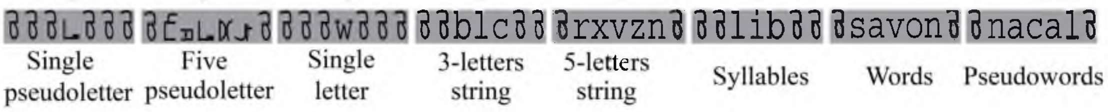

Figure S3.1 Examples of stimuli used for each of the eight experimental stimulus-categories. Stimuli were all embedded in pseudo-characters so as to maintain a constant string length.

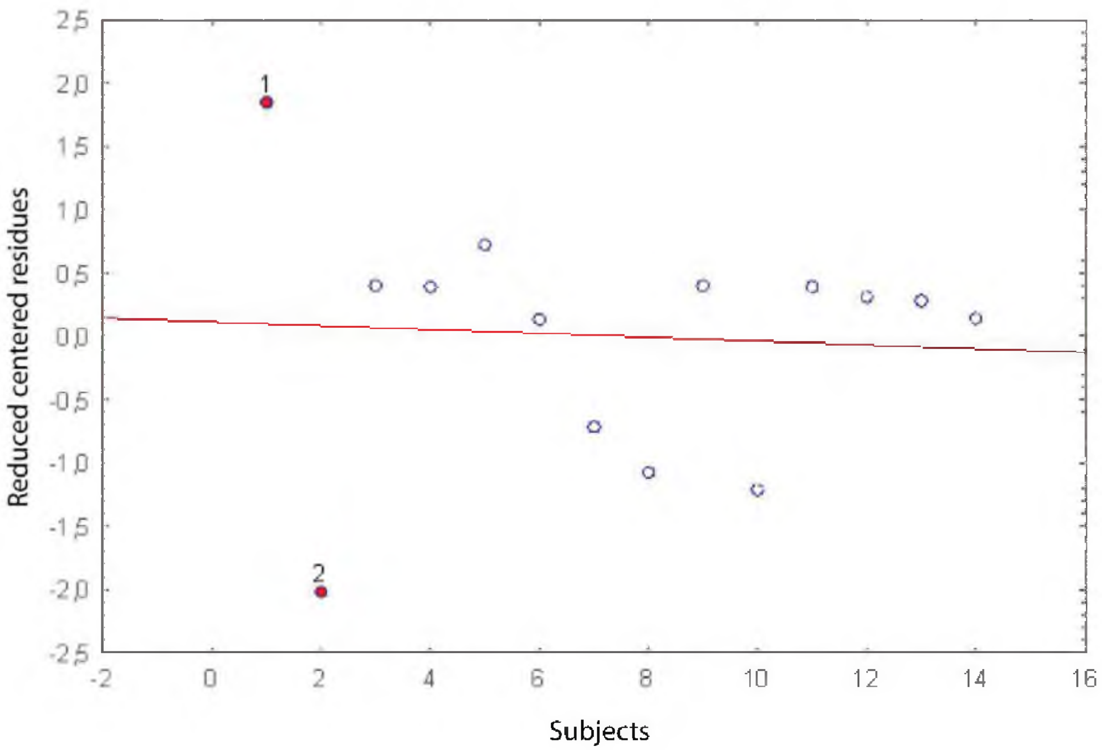

Figure S3.2 CTL z-residues as a function of subject number. Identified outliers are marked with filled circles.

Table S3.1 Group β-values of effective connectivity according to stimulus category.

	MOG → LOT	***MOG → LP***	***LOT → LP***	***LOT → IFG***	***LP → IFG***	***p- value***	***RMSEA***
Single-pseudoletters	0.62	0.48	0.16	0.03	0.12	0.617	0
5-pseudoletters	0.71	0.23	0.24	0.29	0	0.999	0
Single-letters	0.6	0.17	0.2	0.21	0.09	0.694	0
3-letter Strings	0.55	0.31	0.15	0.2	0.23	0.97	0

Non-words	0.83	-0.04	0.71	0.02	0.36	0.72	0
Syllables	0.68	0.63	-0.03	-0.03	0.18	0.895	0
Words	0.44	0.43	-0.2	0.11	0.24	0.996	0
Pseudowords	0.75	-0.04	0.55	0.29	0.55	0.685	0

Path models which provided a good account of the observed data were associated with small minima of the discrepancy function F and correspondingly large probabilities (p > 0.05) under the null hypothesis, as well as with low values (p < 0.1) for the root mean square error of approximation (RMSEA). Categories used for the present study are presented in bold. MOG, left middle occipital gyrus; LOT, left occipito-temporal junction; LP, left parietal cortex; IFG, left inferior frontal gyrus.

Table S3.2 Individual β-, p- and RMSEA values of effective connectivity during **pseudoword reading**.

	MOG → LOT	MOG → LP	LOT → LP	LOT → IFG	LP → IFG	p-value	RMSEA
1	0.40	0.24	0.33	0.19	0.37	1	0
2	0.44	0.09	0.35	0.27	0.12	0.83	0
3	0.50	0.16	0.12	0.14	0.40	0.98	0
4	0.47	0.14	-0.01	0.58	0.26	1	0
5	0.73	0.22	0.16	0.47	0.18	0.86	0
6	0.48	0.01	0.47	0.02	0.43	0.22	0.08
7	-0.05	0.13	0	-0.07	-0.17	0.93	0
8	0.32	0.50	0.07	0.09	0.53	0.29	0
9	0.22	-0.05	0.24	0.2	-0.11	0.79	0
10	0.24	0.58	-0.43	-0.21	0.12	1	0
11	0.52	0.11	0.15	0.38	0.19	0.10	0.12
12	0.34	-0.11	-0.04	0.1	0.31	0.68	0
13	0.64	0.48	0.15	0.04	0.61	0.96	0
14	0.02	0.11	0.27	0.14	0.37	0.84	0

15	-0.13	0.01	0.09	0.26	-0.02	0.04	0.14

MOG, *left middle occipital gyrus;* ***LOT***, *left occipito-temporal junction;* ***LP***, *left parietal cortex;* ***IFG***, *left inferior frontal gyrus;* ***RMSEA***, *root mean square error of approximation.*

Table S3.3 Individual β-, p- and RMSEA values of effective connectivity during **word reading**.

	MOG → LOT	**MOG → LP**	**LOT → LP**	**LOT → IFG**	**LP → IFG**	**P-value**	**RMSEA**
1	0.51	0.24	0.30	-0.01	0.52	0.26	0.07
2	0.44	0.21	0.37	-0.19	0.28	0.06	0.13
3	0.37	0.12	0.25	0.23	-0.02	0.83	0
4	0.25	0.37	-0.17	0.54	0.14	1	0
5	0.24	0.42	0.26	0.05	0.25	0.63	0
6	0.15	0.11	0.34	0.06	0.12	1	0
7	0.33	0.13	-0.01	0.14	-0.2	0.80	0
8	0.28	0.30	0.34	0.56	0.08	0.99	0
9	0.46	0.16	0.12	0.21	-0.05	1	0
10	0.46	0.03	0.43	0.17	-0.06	0.92	0
11	0.37	0.29	-0.02	0.09	0.24	0.60	0
12	0.36	0.29	-0.03	0.25	0.07	0.05	0.14
13	0.38	0.31	0.48	-0.04	0.37	1	0
14	0.38	0.08	0.14	0.27	0.20	1	0
15	0.26	0.40	-0.12	0.05	-0.05	1	0

MOG, *left middle occipital gyrus;* ***LOT***, *left occipito-temporal junction;* ***LP***, *left parietal cortex;* ***IFG***, *left inferior frontal gyrus;* ***RMSEA***, *root mean square error of approximation.*

Chapter 4 The neural oscillatory signature of leaps in linguistic consciousness

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In preparation for submission

Abstract

Neuroimaging studies have investigated the temporal and spatial dissociation between the different linguistic processes underlying word reading. In parallel, in recent years, there has been a surge of studies probing the neural correlates of consciousness (NCCs). Notwithstanding the progress in this field, it seems, unfortunately, as if the consciousness community has reached an impasse. To bridge between the opposing views, we raise here an alternative approach: to compare between levels of consciousness access, instead of between consciousness and non-consciousness, as done so far. To this end, we investigated the neural mechanisms enabling the leap from partial to full access to consciousness, or more precisely, from lower to higher level of linguistic processing. We used magnetoencephalography and focused on neuronal oscillations because they often correlate with conscious perception. We devised a (stair-case) paradigm while purposely fluctuating masking luminance in the aim of maintaining a constant bottom-up and top-down stimulation for every participant while each viewed masked words. Linguistic perception was successfully brought to the subtle boundary between partial (letters) and full (words) consciousness access (CA). This transition was mirrored as a left hemispheric occipito-parietal decrease in oscillatory activity in the alpha band (9-13 Hz) and in the beta band (17-20 Hz) starting at 650 ms post stimulus onset, and followed by a pre-response increase in gamma power (65-85 Hz) over left centro-frontal sensors. The results seem to reflect the transition from partial to full linguistic CA, while implications on the study of the NCCs are discussed. This endeavor thus introduces an important contribution to the semi-controversial field of consciousness study, and additionally links it to the domain of language.

Introduction

Over the years, an extensive number of observations in neuroimaging, electro- and magneto encephalography studies have investigated the temporal and spatial dissociation of the different linguistic processes underlying word reading (reviewed in Démonet et al 2005; Jobard et al 2003; Price 2000; Salmelin 2007). These processes can generally be distinguished as "lower" (visual features and letter extraction) and "higher" (phonological and lexico-semantic processing) in terms of their level of linguistic processing (Joubert et al., 2004; Price and Mechelli, 2005). Although not directly tested before, converging and indirect investigations allude that the transition from the first to the second level is characterized by a late spatial recruitment and increased functional connectivity to left-anterior reading areas (Levy et al., 2008); and in terms of neuronal oscillatory activity, it is associated with increased gamma power (Melloni et al., 2007; Mainy et al., 2008; Jung et al., 2008; Dalal et al., 2009) and decreased alpha and beta power (Klimesch et al., 1999, 1997, 2001; Roehm et al., 2001; Bastiaansen et al., 2005; Bastiaansen et al., 2008; Dalal et al., 2009). Nevertheless, a direct approach to address the neural mechanisms underlying the transition from partial to full access to consciousness of a written word remains to be established.

In the past decade there has been a surge of interest in the neural mechanisms underlying consciousness (Rees and Wojciulik et al., 2002; Rees et al., 2002; Rees and Heeger, 2003; Pins and Ffytche, 2003; Sergent et al., 2005; Dehaene et al., 2006; Lamme 2006; Melloni et al., 2007; Del cul et al., 2007; Gaillard et al., 2009). Theoretical approaches (Chalmers, 2000; Koch, 2004; Block, 2007) propose (i) general neural mechanisms for consciousness, corresponding to an unspecific conscious experience such as the subcortical activity enabling wakefulness, and (ii) specific neural mechanisms underlying a specific conscious experience, such as here, the neural oscillations sustaining a leap in linguistic consciousness. It is worth to note that, these two concepts of "basic" versus "specific" sorts of consciousness share similarities with other views in the neuro-scientific community focused on consciousness; for instance: phenomenal vs. access consciousness (Block, 2005), wakefulness vs. awareness (Laureys, 2005), unconscious (feedforward processing) vs. conscious (recurrent processing) (Lamme, 2006), or preconscious vs. conscious (Dehaene et al., 2006). In other words, these accounts seem to point to consciousness without vs. with the ability to report it. In this regard, what we refer to here as consciousness corresponds to the second definition advocated above, namely, specific consciousness, according to which a conscious experience is due to a given mental contents related or not to an external stimulation.

Despite substantial progress in the study of the NCCs, it is still controversial which brain structures underlie consciousness access (hereafter labeled CA), and in what time window it takes place. Some works postulate that activation of posterior (occipito/temporal) areas is sufficient for the induction of consciousness (ffytche and Zeki, 1996; Zeki and ffytche, 1998; ffytche et al., 1998; ffytche, 2000; Super et al., 2001; Pins and ffytche, 2003; Tse et al., 2005; Lamme, 2006). These authors and others claim that such activations take place early in brain processing (Zeki, 2003; Tong, 2003; Melloni et al., 2007). By contrast, other authors highlight the causal role of long distance interactions, in particular the fronto-parietal network, in generating CA (Lumer et al., 1998; Beck et al., 2001; Dehaene et al., 2001, 2003, 2006; Rees et al., 2002; Marois et al., 2004; Dehaene and Changeux, 2005; Del Cul et al., 2009). These anterior events having the causal role of gating CA take place late in brain processing (Sergent et al., 2005; Del Cul et al., 2007; Gaillard et al., 2009). In a nutshell, the second group of authors advocates the causal role of the parieto-frontal network in CA, and generally leans on the resorting to a subjective report of CA. In contrast, they do not fully agree with the first group of authors, who advocate the causal role of posterior activations as sufficient for conscious experience and independent of any cognitive function, such as report-ability. Instead, such a state is regarded by several members of the second group as "preconscious", that is, potentially accessible to consciousness (Dehaene et al., 2006). Unfortunately, since it is not possible to verify whether one has a conscious experience without resorting to cognitive functions such as attention, memory or inner speech (thus recruiting anterior areas), this debate remains to date unsolvable and scientifically non-addressable as stated by both Lamme (2006) and Dehaene et al. (2006). An alternative way to approach the study of consciousness, which receives here some consideration, is to compare between levels of CA.

Methodologically speaking, to investigate the effects of consciousness access (CA) studies mainly use tasks of (i) unmasked vs masked words (Melloni et al., 2007; Gaillard et al., 2009), (ii) perceived vs unperceived targets in the attentional blink design (Slagter et al., 2008; Sergent et al., 2005), (iii) detected vs undetected visual patterns (Super et al., 2001), (iv) varying the delay between the word and the backward mask (Gaillard et al., 2006; Del Cul et al., 2007), (v) binocular rivalry (Polonsky et al., 2000), and more (For a more exhaustive list c.f. [Lamme, 2006]). We will now summarize the methodological problems of these empirical approaches: the approaches that do not resort to subjective report tap into the problem described earlier, that is, the impossibility, at least to date, to empirically test whether a certain phenomenal experience was conscious or not without resorting to subjective report. As for methods of masked priming and forced-choice experiments: the first type of experiments (unmasked vs masked words) often uses very strong masking in order to reduce conscious perception, leading to chance-level forced choices. Even if unconscious perception is above chance level, these experiments do not control for the precise level of conscious perception (Merikle, 1992). Instead, they state an unconscious perception without pointing to the exact level. Recently, several experiments introduced new improvements by varying the delay between the word and the backward mask (Gaillard et al., 2006; Del Cul et al., 2007), thus achieving a more graded CA. Nevertheless, even this experimental approach still introduces several major problems: First, it is still unable to state and define the intermediate levels of CA; at best, one may state that condition A is more easily perceived than condition B. Second, it does not control for the large variance in conscious perception across individual subjects. It could be that one subject is able to recognize a word in one masking condition, whereas another subject is unable to do so. Third, it introduces a bottom-up confound, i.e. the experiments cannot guarantee whether the effect is due to a modulation in stimulation strength or to that of CA per se. Fourth, the studies often apply paradigms which compare the neural activity elicited respectively by a visible word and by an invisible word; this actually reflects the difference between the correlates of a conscious representation with those of a degraded non-conscious representation. Differences are therefore not guaranteed to isolate a neural signature of CA but rather that of processed or (quasi-) non-processed percepts.

To make things simpler, the theoretical proposal of Dehaene and colleagues (2006) states that two factors are jointly needed for a stimulus to reach consciousness,: (i) strong enough bottom-up stimulation (which can be prevented by stimulus degradation or masking), and (ii) strong enough allocation of top-down resources to the stimulus (which can be prevented by drawing the attention to another stimulus or task). Therefore, failure of CA due to poor bottom-up stimulation would lead to subliminal processing, whereas failure due to poor top-down access would result in preconscious processing. For the first, stimulus-induced activation is insufficient to allow information accessibility, in spite of all efforts of focused attention. For the second however, stimulus-induced activation is sufficient for CA, but the lack of top-down attentional amplification temporarily buffers the stimulus into a non-conscious store.

Here, we attempt to accommodate this proposal to the framework of reading: The cascade of processes during word reading entails the automatic execution of the (visual) decoding of letters (orthography) into pronunciations (phonology) that are mapped onto meaning (lexico-semantics). These processes are extremely automated, rapid, unconscious and irrepressible, almost like a “reflex”, as nicely illustrated by the word interference effect in a standard color–word Stroop task (e.g., MacLeod, 1991). Hence, unless we constantly maintain a firm intention to be aware of these processes, they constantly operate below the level of our consciousness. Inspired by this synthesis, we conjectured that by maximizing attentional resources to different levels of CA, while maintaining bottom up stimulation at a certain equilibrium, it would be possible to obtain fluctuations between two levels of consciousness. However, as postulated by Dehaene and colleagues (2006), due to stimulation at the threshold of perception, efforts of focused attention cannot always result in CA. Thus, we introduce here a novel approach according to which failure to access consciousness at the firstly intended task (semantic processing), would give in to a potential CA for a lower level task (orthographic processing). This approach presumes that, similarly to some meditation practices, voluntary sustained attention increases the mental processes that are accessible to conscious report (Lutz et al., 2008); note that a similar view was already held in the nineteenth century by the "father of experimental psychology", Wilhelm Wundt (Butler-Bowdon, 2007).

In the present paper, we introduce an alternative behavioral paradigm capable of isolating the boundary between two levels of perceptual consciousness. This is based on the observation that neural activity can reflect CA only in paradigms in which subjective perception changes whereas visual input remains constant (Pins and ffytche, 2003). Our choice to present different levels of CA was inspired by previous works leaning on intermediate levels of subjective reports (e.g. Summerfield et al., 2002; Sergent et al., 2005) rather than on all-or-none reports. To control for interference from unspecific parameters such as attention and stimulation strength, we maintained equilibrium of top-down and bottom-up resources by classifying conditions and varying masking strength on the basis of subjective visual perception of single words. In order to discard activations induced by the masking strength and thus assuring constant stimulation, we always subtracted from word-present conditions a corresponding blank condition (masking present). This subtraction allowed us to obtain one single condition in terms of stimulation (one level of top-down and bottom-up resources), and to classify this condition into two conditions based on the subjective report. The paradigm aims to pinpoint a subtle transition between two levels of (linguistic) conscious perception: orthographic (letter) and semantic (word). This was studied using magnetoencephalography by focusing on the (spatial-time-frequency) neural signature reflecting the transition between the first to the second level. We hypothesized that this transition to a higher level of linguistic processing would yield a qualitative signature of a parametric increase in CA in general, and of a higher linguistic CA in particular. Such signature does not reflect reportability, thus circumventing a highly debatable issue in the study of the NCCs.

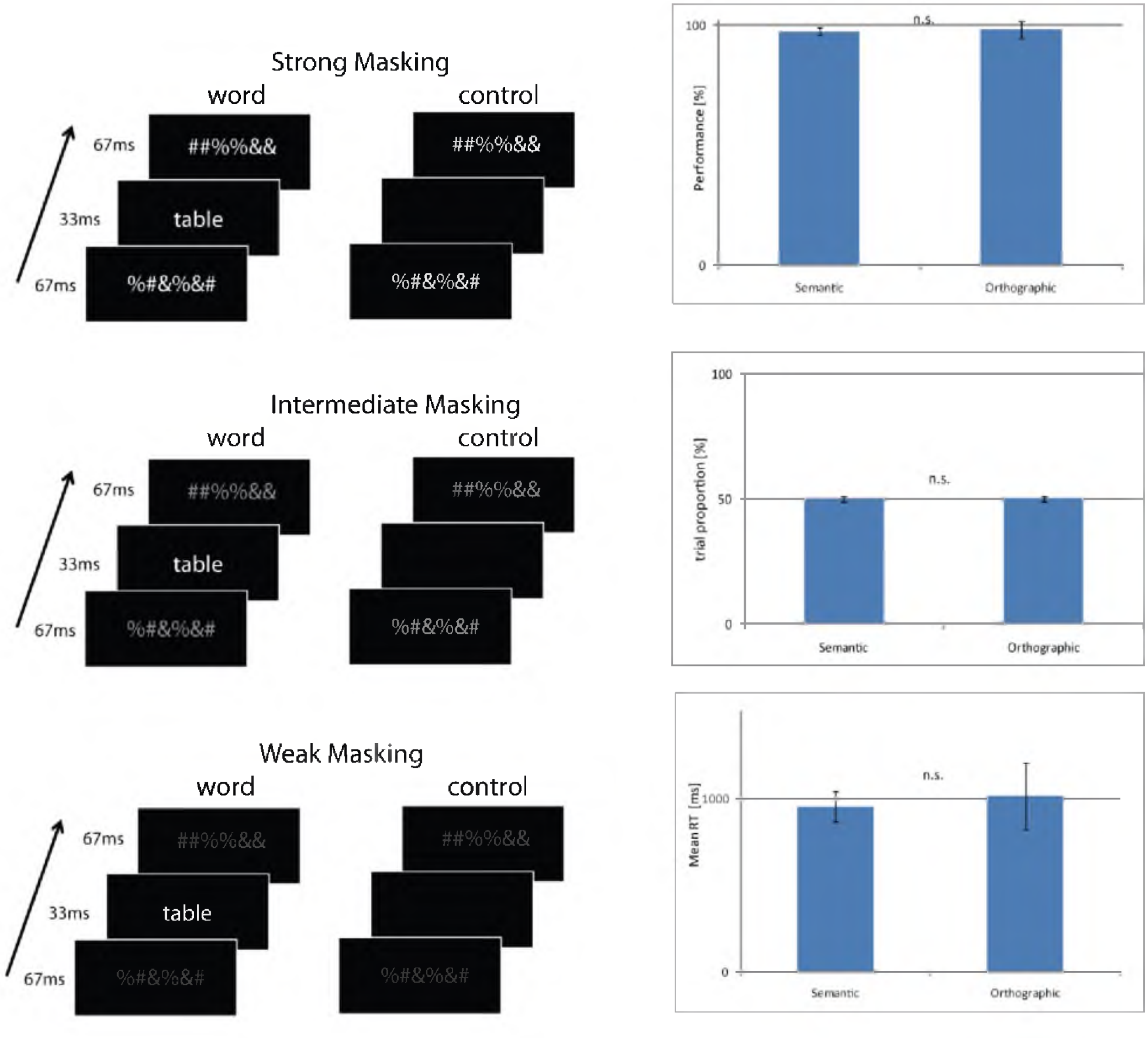

Figure 4.1 Design and behavioral results of the experiment. Left Panel: Stimulus sequence: stair-case design used to present words with piecemeal alteration of masking luminance, in the intention of alternating between high (semantic) and low (orthographic) level tasks. Control conditions were created to assess brain response to the mask stream. Right Panel: Behavioral performance: the stair-case resulted in two equal pools of trials for each task as shown in the middle histogram. Other histograms illustrate similar performance accuracy (upper) and response time (lower) in executing both tasks. Error bars represent ±1 SD.

Methods

Participants

Thirteen healthy native Dutch subjects (eight males, age, 23.92 ± 4.54 years, mean ± SD) participated in the experiment. None of the participants had a history of neurological or psychiatric disorders. All participants had normal or corrected-to-normal vision and were right-handed. The study was approved by the local ethics committee, and a written informed consent was obtained from the subjects according to the Declaration of Helsinki.

Stimuli

The experimental stimuli were Dutch nouns (300 animate, 300 inanimate) between 3 and 9 letters in length with a lemma frequency between 100 and 300 occurrences per million (c.f. CELEX lexical database: Baayen et al., 1993). Animate and Inanimate words were balanced with respect to their word frequency and number of letters. They were presented only once to prevent automatic stimulus–response learning or a repetition-suppression effect. The stimuli were presented using a PC running Presentation software (Neurobehavioral systems, Albany, USA). They were projected onto a screen that was positioned in front of the subject. The stimuli subtended a horizontal visual angle of ~2.5°.

Tasks and Procedures

To maximize and to balance attentional engagement, the subjects' task was to report (i) full or (ii) partial word recognition by semantically categorizing the word (animate/inanimate) or if failed to perceive the word, by orthographically categorizing the percept (letters/none), respectively. To achieve maximal sensitivity of the neural signal and the statistical tests, we needed to obtain approximately an equal number of trials for these two response categories. We thus used a modified "stair-case" version of the thereshold estimation procedure described by Levitt (Levitt, 1971). The "stair-case" effect (balanced distribution of fluctuations between the two tasks) was obtained by varying the contrast of the mask (RGB color: 70,70,70) every six trials based on the given subjective response: if a subject reported more than 50% full recognition (i) the masking contrast increased by 15 RGB units, whereas if a subject reported more than 50% partial recognition (ii) the masking contrast decreased by 15 RGB units. Note bene that in order to obtain optimal parameters resulting in a 50/50 distribution of the two perceptual tasks, prior to this study we conducted several pre-study pilots in which we obtained optimal stimulation/masking (i) latency and (ii) illumination, as well as (iii) optimal interval of illumination units (15 RGB units) for the stair-case.

The reports were through button presses that were counterbalanced across subjects between right/left hands and middle/index fingers, in the aim of controlling for differences in the motor representations of each finger. Stimuli were presented to the subjects in a random order. During MEG measurement, subjects engaged in six task blocks, each block consisting of 120 trials. Each trial started with a gray fixation cross, displayed for a random time of 599-933 ms (first presentation after pause presented for 2599-2933 ms), followed by the presentation of a forward mask (67 ms), a word (33 ms) and a backward mask (67 ms). The random time controlled for plausible anticipation of stimulus onset. In a portion of the trials we replaced the words with blank screens to avoid subject's habituation or anticipation and to subtract the effect of masking. This was followed by a larger fixation cross prompting the subject to make the response by pressing one of the buttons (max 2000ms), after which the cross turned smaller for 999ms until the next trial (Figure 4.1, left panel). In order to avoid guessing during the task, subjects were explicitly asked to categorize the word only when they had clearly recognized it, and were trained on the task with 90 training trials (different words than during the experiment) before measurement. Likewise, during the task, subjects received feedback if the semantic categorization was false, prompting a repetition of the objective of the task. In total, each subject performed 720 trials in a total measurement time of ~55 min.

MEG recordings

Ongoing brain activity was recorded (low-pass filter, 300 Hz; sampling rate, 1200 Hz) using a whole-head CTF MEG system with 275 DC SQUID axial gradiometers (VSM MedTech Ltd., Coquitlam, British Columbia, Canada). Head position was monitored using three coils that were placed at the subject's left ear, right ear, and nasion. Bipolar EEG channels were used to record horizontal and vertical eye-movements as well as the cardiac rhythm for the subsequent artifact rejection.

Data Analysis

All data analysis was performed using the FieldTrip toolbox developed at the Donders Centre for Cognitive Neuroimaging (http://www.ru.nl/neuroimaging/fieldtrip.) using Matlab 7 (MathWorks, Natick, MA, USA). We excluded incorrect trials from subsequent analysis. Partial artifact rejection was performed by rejecting segments of the trials containing eye-blink, muscle, and SQUID artifacts. By this procedure, smaller segments of a trial, rather than a whole trial, can be rejected. This is advantageous when calculating time frequency representations (TFR) because fewer full length trials have to be rejected. In the subsequent averaging, the number of segments applied was taken into account.

TFRs of power were calculated for each trial using a Fast Fourier Transform applied to short sliding time windows. Prior to applying the FFTs, one or more tapers were applied to each time window. The resulting power estimates were averaged across tapers. The power values were calculated for the horizontal and vertical component of the estimated planar gradient and then summed (Bastiaansen and Knösche, 2000). The horizontal and vertical components of the planar gradients were calculated for each sensor using the signals from the neighboring sensors thus approximating the signal measured by MEG systems with planar gradiometers. The planar field gradient simplifies the interpretation of the sensor-level data because the maximal signal typically is located above the source (Hämäläinen et al., 1993). The planar gradient power estimates were subsequently averaged over trials for a given condition.

Because the width of the frequency bands observed in physiological responses typically scales with the center frequency, we analyzed two frequency ranges separately: 2–40 and 40–150Hz. For the frequencies 2–40 Hz, we used a Hanning taper and applied a fixed time window of 0.5 s, resulting in a spectral resolution of 2 Hz. For the higher-frequency band (40–150 Hz), we applied multitapers (Percival and Walden, 1993) using a fixed window length of 0.2 s, resulting in a frequency smoothing of 15 Hz. To control for potential differences in reaction times in the observed TFRs, data was analyzed in alignment both to stimulus onset and to the button press response.

To solve the multiple comparisons problem, statistical significance was tested at the sensor level, using a nonparametric permutation test across subjects (Maris and Oostenveld, 2007). It was therefore not required that the tested power values were normally distributed. Z-scores representing the contrast between the conditions were computed for each subject for all channel-frequency-time points, resulting in a single number per subject. Subsequently, the significance at the group level was assessed by pooling the *z*-scores over all subjects. Testing the probability of this pooled *z*-score against the standard normal distribution would correspond to a fixed effect statistic. To be able to make statistical inference corresponding to a random effect statistic, we tested the significance of this group-level statistic by means of a randomization procedure. We randomly multiplied each individual z-score by 1 or by -1 and summed it over subjects. Multiplying the individual z-score with 1 or -1 corresponds to permuting the original conditions in that subject. This random procedure was repeated 1000 times to obtain the randomization distribution for the group-level statistic. The proportion of values in the randomization distribution exceeding the test statistic defines the Monte Carlo significance probability, which is also called a p-value (Nichols and Holmes, 2002; Maris and Oostenveld, 2007). When probing lateralization effect across all time-frequency bins, a dependent sample t-test was performed between power spectrum values averaged above all left- and then right-hemispheric sensors. The abovementioned randomization procedure was used to correct for multiple comparisons, thereby obtaining a Monte Carlo significance probability.

Results

Behavioral results

Subjects equally ($t(1,12) = -0.89$; $p = 0.39$) and efficiently reported their percepts of words (97.38 ± 1.55 % correct semantic categorization of perceived words) and letters (98.16 ± 3.60 % correct in letter detection) (Figure 4.1, right panel). The “stair-case” paradigm (see Tasks and procedures) efficiently managed to set linguistic perception at the subtle boundary between full (words) and partial (letters). This resulted in a fifty-fifty distribution ($t(1,12) = -0.08$; $p = 0.93$) of full (49.82 ± .49%) and partial (50.17 ± .74%) levels of linguistic consciousness for each subject (Figure 4.1, right panel). Response times (RTs) were not different for full and partial perception (full: 956.28 ms, partial: 1019.92 ms, $t(1,12) = -1.14$; p=0.27 – Figure 4.1, right panel) excluding the possibility that neural modulatory effects may be due to differences in reaction times or performance between reports of full and partial consciousness access (CA).

Occipito-Parietal alpha and beta oscillations are suppressed for full consciousness access (CA)

To test for the effect of increase from partial to full CA, we first looked at the low frequencies (2-40Hz). To maximize the specificity of the observed neuronal oscillations, i.e. to ensure pooling trials that reflect the perceptual boundary between full and partial CA, we pooled trials from the middle level of mask contrast, namely, Intermediate Masking (Figure 4.1). Contrasting full vs partial CA removed the effect of masks and crosses. Because we did not have a priori assumptions about the time-space-frequency of such plausible difference, we averaged across all sensors and searched for differences across both time and frequency while correcting for multiple comparisons. The complete TFR statistics (Figure 4.2A, corrected p = 0.007) of power difference for the full vs partial CA contrast illustrates t-values for all time-frequency bins. Low t-values are represented by cooler (blue) colors whereas higher values are represented by warmer (red) colors. T-values beaneath -1.96 represent time-frequency bins in which there was a significant activation effect for the tested contrast. Time (t) 0 s denotes word onset and (t) 1 s denotes the average response-time although this analysis was not response aligned. The TFR statistics reveals: (1) a strong and sustained peak of significance particularly between 9-13 Hz starting around 650 ms and lasting until 1000ms post stimulus onset (average response time); (2) a second peak, more transient, between 17-20 Hz starting from 700 ms and lasting until 900ms post stimulus onset. The sensors above which the two effects revealed significance are shown in Figure 4.2A (scalp topography): both first (alpha: p=0.01 corrected) and second (beta: p=0.02 corrected) effects revealed very similar spatial patterns.

As a corollary of isolating the significant time-frequency bins (9–13 Hz, [0.65 1] s after stimulus onset, and 17–20 Hz, [0.7 0.9] s after stimulus onset), we then plotted a scalp topography of the power changes of this contrast for both hemispheres, averaged across 2–40 Hz and -0.45 – 1.2 s relative to word onset (Figure 4.2C). We sought to investigate if the significant effect revealed in the TFR statistics could be reflected as power topography changes. Regions with warmer (red) colors indicate an increase of power resulting from this contrast, whereas regions with cooler (blue) color reflect a decrease of power. Topography shows a noticeable left-hemispheric power decrease for full vs. partial CA in the beta ($p=0$) but particularly in the alpha band ($p=0$). The sensors above which the two effects revealed significance are shown in Figure 4.2C (scalp topographies): alpha activation was concentrated in the left occipito-parietal cortex whereas beta activation restricted more to the left parietal. This confirmed that the two significant effects revealed in the TFR statistics corresponded to the abovementioned power topography changes.

To test whether these effects were trivial byproducts of potential differences in reaction times between reports of full and partial CA, we repeated the above analysis after temporally aligning each trial to the behavioral report; Time (t) 0 s denotes response-time and (t) -1 s denotes the average word onset although this analysis was not stimulus aligned. TFR statistics (p=0.001 corrected – Figure 4.2B, lower panel) shows (1) a noticeable and sustained peak of significance particularly between 9-

13 Hz starting around -350 ms pre-response time and lasting to response time and even after; (2) a second peak, more transient, between 17-21 Hz starting around -350 ms and lasting until -130 ms pre-response time. The sensors above which the two effects revealed significance are illustrated (Figure 4.2B, scalp topographies): both first ($p=0$) and second ($p=0$) effects revealed similar spatial patterns to the prior stimulus-aligned analysis, i.e. above left hemispheric and bilateral occipital sensors, but the second beta peak revealed a robust peak concentrated above the left anterior parietal sensors. Scalp topographies of the power changes were also essentially unchanged (Figure 4.2D): revealing an activation peak at 9-13 Hz [−0.35 0] s before response: $p=0$, and at 17-21 Hz [−0.35 – 0.13] s before response: $p=0$. Both effects were again above left occipito-parietal sensors, more posterior in the alpha band and slightly more anterior in the beta band (Figure 4.2D).

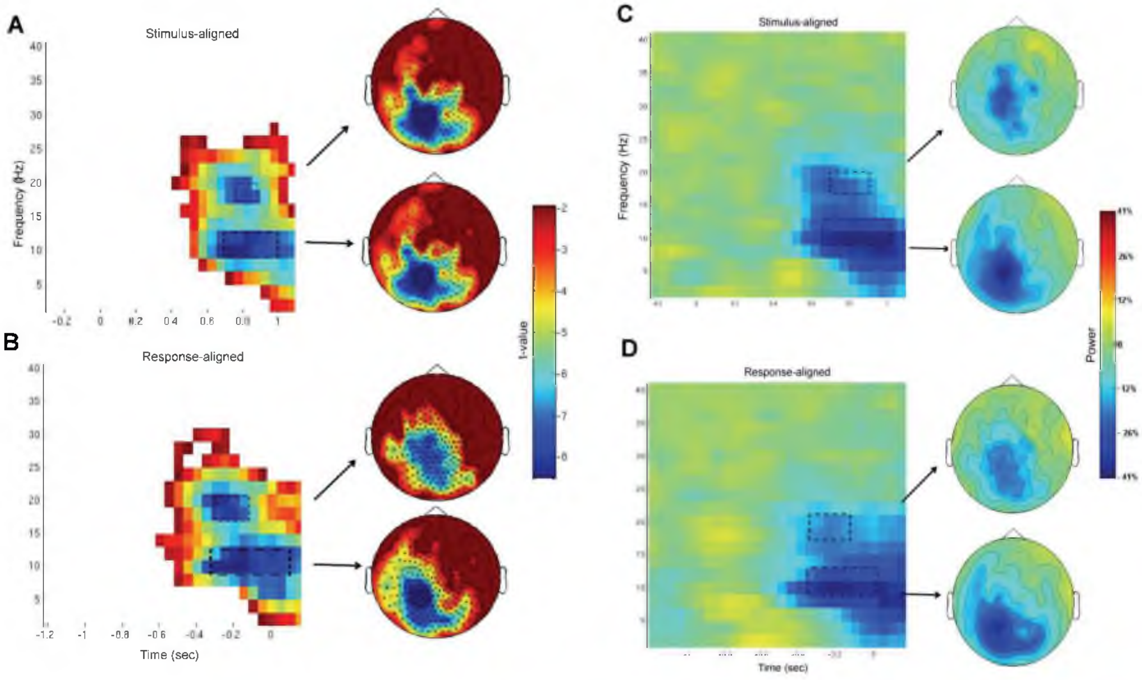

*Figure 4.2 Statistical and Power maps of the time-frequency representation in lower frequency bands pooled across hemispheres when contrasting full (semantic) vs partial (orthographic) consciousness access (CA). Color bars range from warmer (red) to cooler (blue) colors, highlighting significance (A, B) increase or power (C, D) decrease. Statistic maps (A, B) are masked thereby representing time-frequency windows in which a significant effect ($t<-1.96$) was observed across all collected data (corrected $p<0.05$ cluster-randomization statistics). Two peak-significance windows are delimited in rectangles in all four panels. * refer to clusters in which this effect was significant. Analysis was*

performed with stimulus-aligned data, time 0 denoting stimulus onset (upper panel); and repeated with response-aligned data, time 0 denoting the response (lower panel).

Left centro-frontal gamma oscillations are enhanced for increased CA

We also investigated activation in the higher frequencies (40-150Hz): after correcting for multiple-comparisons across all three dimensions (time-space-frequency) the data did not reveal any significant effect (p= 0.71). However, we observed a transient increase in gamma power over left centro-frontal sensors (Figure 4.3, right upper panel), concentrating at 65-80 Hz and 750-850 ms post word onset (Figure 4.3, left upper panel). At these time-frequency window above the left central cortex (sensors marked by asterisks) the effect was significant (p=0.008) in a post-hoc region of interest test. Testing the laterality of this effect, we pooled the right-hemispheric symmetrical sensors (marked by empty circles) at the same time-frequency window, this did not yield a significant effect (p=0.17). Excluding the possibility of potential different responses times between tasks, we again analyzed the data while aligning to the response. We again observed a very localized increase in power above the left central sensors, concentrated around 75-80 Hz and at t -120 ms to the response time (Figure 4.3, lower panel). The effect was significant (p=0.01) at that time-frequency window above the left central cortex (sensors marked by asterisks). Testing the laterality of this effect, we pooled the right-hemispheric symmetrical sensors (marked by empty circles) at the same time-frequency window, this did not yield significant effect (p=0.13). Furthermore, we found that the above mentioned power increase in high frequencies was correlated across subjects with the observed power decrease in the low frequencies (linear correlation, r = -0.72, p = 0.006). Although this was calculated without taking into account trials variability, the findings allude to a certain extent of coupling between posterior alpha/beta and centro-anterior gamma. This interesting coupling is further addressed in the Discussion.

Hemispheric Lateralization

Moreover, probing the extent of hemispheric lateralization of the oscillatory patterns underlying the increase in CA, we found: (i) The alpha effect (delimited time-frequency rectangle in Figure 4.2AB) was significant (p = 0.012) when averaging the left hemispheric sensors, but not when averaging the right hemispheric sensors (p = 0.068); (ii) the beta effect (delimited time-frequency rectangle in Figure 4.2AB) was significant when averaging both the left (p=0.013) and the right (p=0.034) hemispheric sensors; (iii) as for the gamma effect, as mentioned above, only the left hemispheric sensors yielded a significant effect. Secondly, since the extent of lateralization is prone to alter along the posterior-anterior axis readily from the increase in linguistic processing (Levy et al., 2008), we tested whether power spectrum differed between the full and partial CA, across all time-frequency bins and across trials. While a significant difference was obtained above both posterior hemispheres (right occipito-parietal, p = 0.003 corrected; left occipito-parietal, p = 0 corrected), only left anterior sensors yielded a significant effect (right temporal-central-frontal, p = 0.32 corrected; left temporal-central-frontal, p = 0.006 corrected). This suggests that power spectrum is modulated between partial and full CA in both posterior hemispheres, but only in the anterior left hemisphere. Finally, to probe the extent of hemispheric lateralization when contrasting full vs partial CA, power spectrum values in all time-frequency bins and above all right hemispheric sensors were compared with those above all left hemispheric sensors. Power values above the left hemispheric sensors were significantly lower than over right hemispheric sensors (corrected p=0.025, clusterstat=108.16), therefore pointing to a strong left desynchronization effect, independently of time or frequency window, readily resulting from the transition from lower to higher CA.

Discussion

In the present study, we investigated the shift from partial to full linguistic consciousness. We expected to isolate brain regions that are specific to the transition to higher linguistic functions and are independent of the report-ability bias which often hurdles the endeavour of localizing the NCCs (for a review see [Lamme, 2006]). The findings illustrate significant power suppressions in the alpha (9--13 Hz) and beta (17--20 Hz) bands in the occipital lobe and in most of the left hemisphere. This took place relatively late, that is, starting at 350ms prior to the report of perception, and was followed 200ms later by a power enhancement in the gamma band (65--80 Hz) above left pre-motor sensors. Activation was sustained in the alpha band and more transient in the beta and gamma bands. This conjoint oscillatory pattern underlying CA was (a) more substantial above the left hemispheric sensors, and (b) more prominent above left anterior and bilateral posterior sensors, thereby providing new support to the recent demonstration of a bilateral-to-left and posterior-to-anterior activation gradient with the piecemeal increase in linguistic processing (Levy et al., 2008). Moreover, the conjoint pattern of gamma increase concurrently with alpha and beta suppressions was often observed in the literature (Crone et al., 1998a,b; Lachaux et al., 2005, 2006; Mainy et al., 2007), although the converse (gamma decrease and alpha/beta increase) is not necessarily true (Dalal et al., 2009). Likewise, as observed here, gamma responses tend to be spatially localized whereas alpha/beta responses are widespread (Dalal et al., 2009). Moreover, such gamma increase and alpha/beta decrease coupling has already been observed in our group during tasks involving enhanced attention and perceptual decision making (e.g. Bauer et al., 2006; Vidal et al., in preparation). We thus propose that these neuronal markers subtend the transition from partial to full CA, and the (neuro-) cognitive (linguistic) consequences that follow. The results are now broadly discussed and compared with respect to (a) the current literature on the NCCs, (b) the neural dynamics during reading, and (c) the various automatic and unconscious processes during reading. Furthermore, we elaborate upon possible follow-up directions of prospective research.

Accounts of CA

The findings are in agreement with the recent study that investigated the oscillatory signatures of CA (Gaillard et al., 2009): The authors reported that local spectral power increases in the gamma band and decreases in the alpha and beta bands are putative oscillatory markers of CA. Similar reports also emerge from the attentional blink paradigm when contrasting detected with undetected items, that is, this yields reduced occipito-parietal alpha power (though increased beta) and enhanced midline gamma power (Kranczioch et al., 2007). Kranczioch et al.'s findings further suggest that these local oscillatory patterns for CA apply not only to linguistic functions, since the attentional blink paradigm they used did not contain words as items. Additionally, Gaillard et al. (2009) argue that such effects are most noticeable in anterior areas, whereas non-conscious processing is restricted to posterior areas. In the present work, we also show that the transition between two levels of consciousness concentrates in left parietal and frontal areas. This corroborates prior studies of the neural correlates of binocular rivalry and other bi-stable perception, showing that activity in parietal and frontal areas correlates with fluctuations in reports of (visual) CA (for review see Rees et al., 2002; or see Lumer et al., 1998; Beck et al., 2001; Dehaene et al., 2001, 2003, 2006; Rees et al., 2002; Marois et al., 2004; Dehaene and Changeux, 2005; Sergent et al., 2005; Del Cul et al., 2007). Other studies (ffytche and Zeki, 1996; Zeki and ffytche, 1998; ffytche et al., 1998; ffytche, 2000; Super et al., 2001; Pins and ffytche, 2003; Tse et al., 2005; Lamme, 2006) seem to point to a more "basic" sort of consciousness which is not implicating subjective report, thereby yielding activation in more posterior areas.

Latency-wise, Gaillard and colleagues replicated prior reports by showing evidence for the temporal divergence between unconscious and conscious processing (Sergent et al., 2005; Del Cul et al., 2007; Gaillard et al., 2009): the former would restrict to an early time window whereas the latter would expand to later processes (>300ms). Other studies (e.g. Pins and ffytche, 2003; Tong, 2003; Zeki, 2003; Melloni et al., 2007), however, argue that the temporal divergence occurs much earlier, at approximately 100ms, followed by the same later divergence (>300ms). According to the latter view, the early divergence reflects CA whereas the later does not contribute directly to perception. Our study is exempted from this debate given that it does not compare conscious to unconscious, but rather higher conscious with lower conscious. Hence, the results observed here make sense: the increase in CA yielded effects later than 600 ms post stimulus. However, access of more rudimentary processes to consciousness (words vs blanks) resulted in earlier effects (*data not shown*). These findings could be taken as an indication that the partial to full CA is translated by late oscillatory activity (> 600 ms), corroborating the notion that early neural activity does not correlate with conscious perception (Del Cul et al., 2007; Hayens, 2009). This is in line with previous reports of late temporal divergence in cortical activity as a signature of CA (Dehaene et al., 2003; Dehaene et al., 2005; Sergent et al., 2005; Del Cul et al., 2007; Gaillard et al., 2009). These authors reported divergence at a time window of 250 – 500 ms, whereas here we report an even later divergence (> 600 ms). This can be explained by the different nature of these studies which focused on conscious vs unconscious effect. It has been suggested that visual processing of words initiates two sequential processes: first, an information fast-forward sweep, and second, recurrent feedback-driven processes (Pammer et al., 2004). The later the MEG component is in time, the more likely it is to be indicative of the second type recurrent processes. Here, we contrasted fully vs partially conscious access, thereby plausibly removing the effect of the first information sweep, and instead highlighting recurrent processes, which are believed to be essential for conscious processes (e.g. Lamme, 2006). Alternatively, it could well be that the task-cueing-hand type of design used here highlighted effects at relatively late stage of stimulus processing. This is congruent with another such task-cueing-hand design in which lateralized readiness potential started peaking only after 600-750ms post stimulus onset (van Turennout et al., 1998). Our findings thus corroborate such observations which state that full vs (almost) null CA is marked by late temporal divergence, and further elaborate upon them by demonstrating that full vs partial CA translates to even later temporal divergence.

As introduced at the beginning of the manuscript, the endeavor of localizing the NCCs has been exhaustively addressed in the past decade, but nonetheless, the putative correlates are certainly not univocal, and this topic remains highly controversial. The core of the debate seems to ultimately emanate from the difficulty of isolating consciousness independently from its cognitive consequences and those related to the act of internally or externally reporting the CA (attention, working memory and language). On the one hand, the authors claiming for the parieto-frontal network as a necessary condition for the emergence of consciousness and not preconsciousness (see Dehaene et al., 2006), cannot preclude that that network underlies such other cognitive functions related to the act of “knowing” that one is conscious of something, even introspectively. In other words, how to be certain that in the absence of any subjective report, there is no form of consciousness at all? It should be considered that the neural mechanisms putatively deemed indispensable for consciousness are in fact only required for interconnecting a number of cognitive functions such as memorizing and reporting (see Colagrosso and Mozer, 2004). Thus, an absence of any subjective report may be caused by a lack of neuronal interconnectedness rather than by the lack of any sort of consciousness. This doubt is also reflected during the attentional blink, where evaluating CA is not certain because of the possibility of a momentary and fleeting CA, which is then rapidly forgotten and thereby cannot be reported (Luck et al., 1996). Furthermore, by modulating the depth of general anaesthesia, participants show different sorts of conscious experience on the basis of sometimes with or without the ability to recall or to report, thereby suggesting that CA is not only subtended in the case of subjective report (Zeman, 2002). On the other hand, the authors who argue for posterior interactions as the basic correlates of consciousness (e.g. Lamme, 2006) cannot prove that the participant is aware under such a state, because there is no resorting to any kind of report. Attempting to solve this problem, Dehaene and colleagues defined a new nomenclature according to which this "basic" state of phenomenal consciousness without reporting should be addressed as "preconscious", whereas when reporting is present, it should be addressed as conscious. Preconscious would allegedly refer to a state when information is visible, yet not seen, but with the potential to be seen under enough attentional resources (Dehaene et al., 2006). However, this nominal disentanglement does not solve the problem and does not provide any new way to empirically probe the "presence" of CA under this condition.

Mitigating part of the problem, Tse et al. (2005), have done well in minimizing the task-specific contamination following CA by employing inattention toward the percept. More recently, Kouider et al. (2007) have employed a similar strategy by using a semantic decision task on highly visible target words, while studying the neural correlates of primes which did not receive task-related attention. The authors emphasize that despite the visibility of the primes (above threshold stimulation) they are preconscious, that is, non-consciously accessed because of inattention or irrelevance to the task. Their findings revealed that non-conscious perception yielded posterior activity, which is independent of the cognitive consequences of non-conscious perception. Notwithstanding the tenability of these findings, it is still impossible to know whether there was any phenomenal awareness in that state or not. The authors conclude that given the current lack of scientific criterion for defining conscious processing without report-ability, the dissociation between access and phenomenal consciousness remains largely speculative and even possibly immune to scientific investigation (Kouider et al., 2007).

Noteworthy, it may be that what hampers the study of the neuro-dynamics of consciousness is what is referred to as "the hard problem of consciousness" (Chalmers, 1995). Essentially, the latter problem is not theoretically answerable via traditional empirical scientific inquiry, in contrast to (easy) cognitive problems such as report-ability or the ability to discriminate. Thus, consciousness studies cannot be approached solely on a materialistic base, but should also heuristically rely on first-person data (Varela, 1996). Here, we found a way to circumvent this ostensibly complex problem, but also to address it differently. Instead of focusing on the effects of conscious versus unconscious processes, we employed a novel approach by focusing on the effects of two conscious processes, one higher and the other lower. Therefore, by contrasting the one to the other we obtain the correlates of proceeding from partial to full CA, thereby ruling out brain activations related to report-ability. We are completely neutral, however, in regards to the endeavor of localizing the "pure" NCCs as viewed previously (conscious vs. unconscious) and thereby exempt ourselves from that perhaps impossible enterprise.

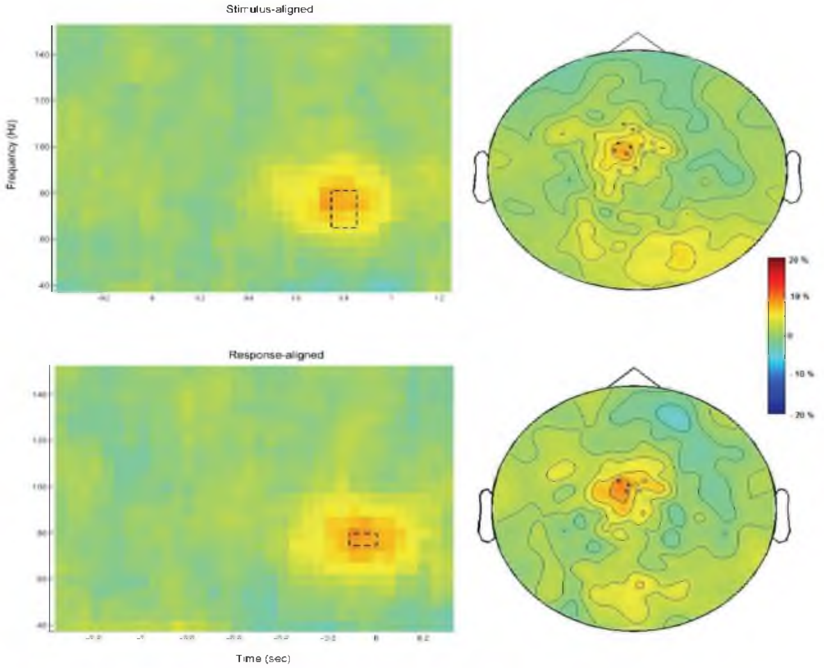

*Figure 4.3. Power topography changes in higher frequency bands pooled across hemispheres when contrasting full (semantic) vs partial (orthographic) consciousness access (CA). Cooler (bluer) colors correspond to power decrease whereas warmer (redder) colors correspond to power increases in percentage (color bar). We selected sensors (marked with *) and a time-frequency window for which a significant effect was detected for both stimulus-aligned (uncorrected p=0.008) and response-aligned (p=0.01) data. Time 0 denotes stimulus onset in the stimulus-aligned topography (upper panel) and response press in the response-aligned data (lower panel).*

Lower Oscillations underlying the transition in CA

With respect to the above postulation, the reported neuronal events convey of a transition from partial to full CA, but more accurately, the transition from lower to higher linguistic processes accessing consciousness. We therefore found it necessary to examine the state-of-the-art literature on the neuronal oscillations accompanying such linguistic processes (see [Bastiaansen and Hagoort, 2006] for a review). In a nutshell, the emerging image implies that: memory retrieval operations are mostly accompanied by increased neuronal synchronization in the theta frequency range; unification operations, in contrast, induce high-frequency neuronal synchronization in the beta and gamma frequency bands; and upper alpha frequency band (about 10.5-13 Hz) desynchronization may reflect the behavioral consequences of language comprehension. In the present study, we contrasted the CA of two levels of linguistic processing, mainly mirroring the transition from low (orthographic) to high (phonological-semantic) linguistic processes. We thus expect some of the above converging and emerging image from the review of the literature, to match the oscillatory patterns observed here. This will now be reviewed and discussed in more detail.

Alpha is the dominant oscillation in the human scalp EEG of awake adults, known since the pioneering research of Berger (e.g., Berger, 1929). These oscillations are most noticeable at posterior recording sites and can be observed primarily during a cognitive state usually described as “relaxed wakefulness”. It has been demonstrated repeatedly (particularly on the basis of band power analyses) that alpha power decreases (desynchronizes) during task performance (Klimesch et al., 2005). Posterior alpha activity used to be considered an idling rhythm (Adrian and Matthews, 1934); however, there is a growing body of evidence in recent years, demonstrating a stimulus specific alpha decrease of the specific visual stream engaged in covert attention and working memory tasks (Thut et al., 2006; Jokisch and Jensen, (2007); Medendorp et al., (2007); Rihs et al., (2007); Romei et al., (2008a, 2008b)), which reflects the wavering of visual stream inhibition. However, alpha not only decreases, but also increases, if visual information is not required for the task, thus inhibiting task-irrelevant cortical areas. More specifically, it may be that alpha inhibits posterior areas in order to reduce the flow of visual information in order to increase the gain of cognitive functions in anterior areas. This could be inferred by observations of increased alpha power during working memory retention execution of control processes (e.g., rehearsal or focused attention) (Klimesch et al., 1999; Jensen et al., 2002; Schack and Klimesch, 2002; Sauseng et al., 2005; Tuladhar et al., 2007). With respect to this view, since there was no need to reduce the flow of visual information in the present paradigm, but on the contrary, to maximize it, the observed alpha deactivation could indicate an increase in the flow of visual information in order to maximize perceptual gain. Furthermore, recent findings demonstrate that pre-stimulus alpha deactivation is correlated with enhanced stimulus perception or task performance (Ergenoglu et al., (2004); Linkenkaer-Hansen et al., (2004); Thut et al., (2006); van Dijk et al., (2008); Zhang et al., (2008)). Together, these lines of research converge to indicate that alpha increase reflects functional inhibition for task irrelevant areas (for instance), whereas alpha decrease reflects enhanced cortical excitability to maximize perceptual gain, and in the current study, to spur visual/linguistic CA.

As described above, the functional meaning of alpha can sometimes appear to be of a heterogeneous nature. This could be due to the differentiation within the alpha range, namely, in the lower (about 8-10.5 Hz) and in the upper (about 10.5-13 Hz); the first generally shows a widespread topography during desynchronization, whereas the second is more localized (see Pfurtscheller & Lopes da Silva, 1999 for a review). In strong support of this dissociation, it has been demonstrated that event-related power changes in the lower and the upper alpha frequency bands increasingly dissociate as task demands increase (Fink et al., 2005). Functionally speaking, findings from numerous studies unequivocally argue that desynchronization in the first reflects attentional processes whereas desynchronization in the second reflects semantic processes (Klimesch et al., 1999, 1997, 2001; Roehm et al., 2001). In another study, Ihara and Kakigi (2006) observed consistently more noticeable upper alpha desynchronization (less consistent for lower alpha desynchronization) for linguistic (letters) vs. non-linguistic (pseudoletters) visual items. Upper alpha desynchronization was also observed during the visual processing of “open class” and “closed class” words (Bastiaansen et al., 2005), whereas upper and lower alpha (8-12 Hz) desynchronization was observed following a visual lexical decision task (Bastiaansen et al., 2008). Taken together, the literature supports the notion that higher, and perhaps also lower, alpha desynchronization is remarkably associated with lexico-semantic, and perhaps also with orthographic, processing of written words. In the present study, the (desynchronization) effect in the alpha band was significant in the frequency window of 9-13 Hz (Figure 4.2CD), thus with respect to these two ranges, is most likely to reflect the semantic processing involved in the increase from the lower level to the higher level of linguistic access. More precisely, the trigger for such desynchornization may be linked to the process of (word) meaning retrieval from long-term memory storage for the purpose of a transient decision making as has already been pointed out before (see Ruchkin et al., 2003 for a review; Klimesch et al., 2005).

Furthermore, in a semantic task, such desynchornization is enhanced for more intelligent than for less intelligent subjects (Doppelmayr et al., 2005). This enhancement is largest over the left hemisphere (at centro-parietal regions) for good performers but reverses at posterior sites of the right hemisphere for bad performers. This data conforms to most recent findings showing how information trafficking from visual areas to the left parietal cortex (or to the left occipito-temporal cortex) can completely reverse between good and poor readers (Levy et al., 2009). Doppelmayr et al. (2005) assume that this observed modulation primarily reflects semantic search and comparison processes, not retrieval processes, nor task difficulty. This could be interpreted as an indication that efficient semantic processing is associated with upper alpha event related desynchoronization above left centro-parietal sensors. Assuming a mapping between brain activity modulation and functional involvement, the reports above thereby agree with our finding that CA from orthographic to lexico-semantic level is primarily characterized with a noticeable desynchoronization in the upper alpha band over left centro-parietal sensors, suggesting that our observed effect was primarily related to the transition to the semantic processing involved in the higher level task.

Likewise, despite the concentration of the significant desynchronization in the upper alpha band, a similar effect was also observed in the lower beta band (17-21 Hz) (Figure 4.2CD). Desynchronization in the lower beta band was previously observed above parieto-frontal sensors and was suggested to reflect the graphemic-phonetic encoding during word reading (Klimesch et al., 2001). Similarly, beta desynchronization was also observed during the visual processing of words (Bastiaansen et al., 2005). As for long-range synchrony (coherence), a task of semantic categorization/integration similar to that (the higher level task) applied in the present paradigm, was found to strikingly modulate coherence at the lower beta band (Weiss and Mueller, 2003) and within the left temporo-parietal network (von Stein et al., 1999). Also long-range synchronization in the alpha band should be noted, since it is yielded in the left-hemisphere cerebro-cerebellar network during reading (Kujala et al., 2007). To summarize, global synchrony in frequencies higher than 10 Hz seems to predominantly reflect higher level cognitive-linguistic differences related to word type, whereas synchrony under 10 Hz tends to reflect non-specific components of word processing such as sensory, attentional, mnemonic and basic semantic parts of the task (see [Weiss and Mueller, 2003] for a review). We reason it important to note that, to date, the attribution of linguistic processes to frequency bands has not seemed to differ much between local and global synchrony (see [Bastiaansen and Hagoort, 2006] for a review), thereby allowing us to compare our finding to those investigating coherent interactions during reading. Taken altogether, the literature supports the role of specific narrow ranges in the alpha and beta bands in higher level processes during word perception. Hence, it agrees with our observed findings and provides a more functional interpretation to the nature of transition from lower to higher CA.

Sub-regions within the left parietal cortex are known to play a causal role in underlying grapheme-to-phoneme conversion (Booth et al., 2002), namely, the first step in phonological processing. More recently, this region was found to mediate the transition from orthographic to phonological processing, possibly functioning as a gate to more substantial phonological processing in the left inferior frontal gyrus (Cao et al., 2008; Levy et al., 2008). In the present study we found that sensors above the left occipito-parietal region showed a noticeable negative modulation (suppression) in activity resulting from the increase from low (orthographic) to high (phonological and lexico-semantic) reading processing. As elaborated above, prior reports also yielded such oscillatory pattern, readily due to higher linguistic processes. Assuming a certain matching between direct (electrical activity) and indirect (hemodynamic) markers of brain processing, this finding could converge to corroborate the prior evidence showing an increased blood flow in the left parietal region. Indeed, combined EEG and PET recordings have indicated that posterior alpha suppression corresponds to blood flow increases in the occipito-parietal region (Sadato et al., 1998). Assuming that this is also the case here, this joint evidence further highlights the importance of the left parietal in mediating the transition from lower to higher levels of linguistic processing. Furthermore, it provides a nice convergence between oscillatory and hemodynamic data, two complementary but unrelated sets of functional descriptions of the human brain, and thus contributes to the rising enterprise of linking the two approaches (Lachaux et al., 2007).

Higher Oscillations for the transition

Furthermore, not only synchronous oscillations in the alpha frequency negatively correlate with perception gain of shortly presented stimuli, but synchronous oscillations in higher frequencies also positively correlate with perception gain (Hanslmayr et al., 2007). Originally, we expected gamma band oscillations to enhance in the present paradigm since they often correlate with conscious perception (e.g. Summerfield et al., 2002; Lutz et al., 2002; Meador et al., 2002; Melloni et al., 2007). However, a closer look at the emerging view from the literature suggests that gamma oscillations are hardly detected as a result of the retrieval and the processing of the linguistic information encoded during single word reading. Instead, they seem to underlie unification processes (see [Bastiaansen and Hagoort, 2006] for a review), i.e. the integration of such information (orthographic, phonological, lexico-semantic) at the sentence and discourse level into a meaningful whole, in order to yield a coherent interpretation of the linguistic input (Hagoort, 2005). However, despite the lack of unification processes which could emerge under the conditions of the present paradigm, the findings here point to a gamma-band enhancement in left anterior areas resulting from the increase in CA. This is not at odds with the statement raised in the abovementioned literature review, since the gamma burst was probably confined to sensory cortices. Indeed, there is very little evidence of gamma activity in higher level areas of the reading network. The little evidence that exists could only be demonstrated using invasive electrophysiological recordings, which are sensitive enough to detect such an effect (Sinai et al., 2005; Tanji et al., 2005; Jung et al., 2008).

The gamma response emerged shortly before (button) response and ended at the time of the response. This modulation in activity is most likely not owing to motor related activity given that both lower and higher CA involved the same motor (finger) movement, because the latter was counterbalanced across subjects. By contrast, it could be due to differences in decision processes as motor and pre-motor regions are recruited not only for motor planning and execution but also for decision making (Romo et al., 2004; Heinen et al., 2006). Other studies also suggested that late gamma (though at 40 Hz) enhancement may reflect response-related information in preparation for response requirements (Gruber et al., 2001, Kranczioch et al., 2006; Kranczioch et al., 2007). If this is the case here, (higher) semantic vs (lower) perceptual decision making would translate to anterior gamma modulation shortly before response. Not only high-frequency enhancement but low-frequency decrease may also be related to the decisional process and motor response preparation. This is first implied by their late latency (above 650 ms), and would corroborate the notion that deactivation in the alpha and beta frequency ranges in general (Pfurtscheller et al. 1998; Pfurtscheller and Lopes da Silva 1999; Stancak et al. 2000; Taniguchi et al. 2000; Kaiser, Ulrich, et al. 2003), and beta deactivation above central sensors in particular (Kaiser et al., 2007) are closely related to decisional processes and the preparation of motor responses in perceptual tasks. Additionally, this would make sense given the left lateralization of the power modulations observed in our study, which may be attributed to the language hemispheric dominance resulting in left-lateralized modulations in activity during linguistic tasks (see [Hirata et al., 2004] for a demonstration in MEG).

Alternatively, one could argue for instance that the perceptual orthographic task was more difficult to perform because it always occurred when subjects have already failed at detecting the percept (word), in comparison to the semantic task which occurred when subjects were certain of their percept. Most likely, subjects may have attended primarily to word perception, but if this was not possible, they may have then resorted to letter perception. With respect to this view, our finding of enhanced frontal gamma would reflect the effect of task difficulty. In line with this interpretation, Kaiser and colleagues have recently found that frontal gamma (60-80 Hz) is enhanced to a larger extent for easy than for difficult decisions (Kaiser et al., 2007). The search for perceptual alternatives may thus be involving less high frequency oscillations than when the decision to be made is straightforward. This is also supported by the notion that communication between regions in the decision-making network may be globally enhanced via coherent oscillations in the gamma band (Fries, 2005). To test whether the observed effects could be due to differences in decisional processes, we first compared between difficulty of performing the semantic and orthographic tasks, i.e. we measured variations in response time during both tasks. Response time was found slightly longer (ΔRT = 63.64 ms) during the orthographic task, although without any significant difference ($p = 0.27$). Additionally, we have re-performed our analyses response-aligned which were essentially similar in comparison to the stimulus-aligned patterns (Figures 4.2, 4.3). Hence, it is unlikely that differences related to the time necessary for the execution of the tasks may have largely influenced the observed oscillatory pattern. We reason that if the gamma response pattern was response-driven then the effect would not be re-produced in the stimulus-aligned analysis. Nevertheless, we cannot completely rule out the potential influence of decision making processing in the observed results since although both tasks lasted equally, it could still be that their difficulty was unequal. Unfortunately, it is a major challenge for researchers to evaluate and compare the phenomenal experience of “difficulty” in different cognitive tasks; we remain open to the possibility that further research may succeed in measuring, to some extent, such introspective experience.

Noteworthy, despite the fact that our data failed to reveal an ample gamma response in anterior reading areas (e.g. inferior frontal gyrus), this does not necessarily exclude its existence as MEG (compared to fMRI) may be less prone to revealing left frontal activations during linguistic tasks (Liljeström et al., 2009). For instance, Jung et al. (2008) and Mainy et al. (2008) recently observed gamma in prominent reading areas during attentive word reading. However, this was done using invasive electrophysiological recordings, which are sensitive enough to detect such an effect. As elaborated by Dalal et al. (2009), failure to detect gamma power in noninvasive recordings can be due to: (i) contamination of the gamma band by biological noise such as muscle activity; (ii) limited spatial extent of the gamma response over the cortical surface and lack of synchrony between gamma sources; (iii) source characteristics (the gamma band signal is generally 1–2 orders of magnitude smaller than the dominating content in lower frequencies); (iv) gamma power decrease would partially cancel, at the scalp level, gamma band enhancements; (v) it is commonly stated that the skull and scalp effectively act as a lowpass filter, thereby passing lower frequency signals with more gain than higher frequency signals; and (vi) subject’s low position in the MEG helmet; or, as elaborated by Hoogenboom et al. (2006), due to (vii) the use of transient static stimuli non-optimal for generating gamma response; (viii) paradigms which do not require the subject's sustained attention; or (ix) inadequate spectral analysis methods or recording apparatus. By contrast, alpha and beta power spectrum does not suffer from most of these constraints: it has a much better signal to noise ratio; the spectrum of muscular artifact rarely extends below the gamma band; it extends over wider cortical areas. Dalal et al. (2009) used the same paradigm as Jung et al. (2008) and Mainy et al. (2008), that is, attentive word reading, but this time in addition to intracranial measurement, applied simultaneous MEG recording. The resulting findings of Dalal et al. were: (a) a gamma response, only in the invasive data, (b) accompanied by alpha and beta suppression, detected in both the invasive and the non-invasive data. This supports our findings and suggests that alpha and beta suppression may be coupled as a marker of word reading. Furthermore, it alludes to the possibility that gamma may not only mediate response related information, but may also sustain the CA of word reading processing as tested here. However, unless methodological improvements are made, the detection of such gamma response is probably bound to remain undetected by non-invasive recordings.

Broadly speaking, one may reflect on the origins of the gamma oscillations to better capture their functionality. It has been shown recently, that each cycle in the gamma frequency band is framed by synchronized spiking of inhibitory interneurons, which receive their excitatory drive from pyramidal cells (Fries et al., 2007). As Fries et al. describe in detail, after excitatory input, the network of inhibitory interneurons generates rhythmic synchronized activity and imposes rhythmic inhibition onto the entire local network. Pyramidal cells will be able to respond to excitatory input only during the time window of fading inhibition. Because pyramidal cells provide the major excitatory drive to the interneurons, the interneurons will discharge with some phase delay relative to the pyramidal cells and the resulting network inhibition terminates the firing of both the pyramidal cells and the interneurons. The whole network is inhibited and the next gamma cycle starts anew. Tracing the origins of this cycle, the Acetylcholine neurotransmitter (ACH) probably plays a major role in its maintenance since it induces a persistent increase in the excitability of pyramidal cells (McCormick and Prince, 1986; Kirkwood et al., 1999; Gulledge and Stuart, 2005), or as recently stated, it inhibits layer 4 of the spiny neurons, the main targets of thalamocortical inputs, while excitating of pyramidal cells in layers 2/3 and layer 5 (Eggermann and Feldmeyer, 2009). This filters out weak sensory inputs in layer 4 and amplifies inputs that reach the layers 2/3 and layer 5 excitatory microcircuits. As a result, these layer-specific effects of ACH might operate to improve the signal noise ratio of cortical processing (Eggermann and Feldmeyer, 2009), and thus subtend the gamma cycle, which is also a mechanism for enhancing cortical processing (Fries et al., 2007). In the present study we observed frontal gamma enhancement as a result of higher linguistic processing access, i.e. word detection. In view of the above information, this gamma enhancement could be broadly related to ACH release, as the latter has an important role in the enhancement of sensory perception (Himmelheber et al., 2000), and as more recently shown, its release in the (pre-)frontal cortex controls cue detection (Parikh et al., 2007).

Fine-tuning to Linguistic Properties

One concern about our double-task design was that cuing hand-laterality for response based on task alteration may introduce alterations in the dynamics of language processing and decision making. However, a previous design (van Turennout et al., 1998) cueing for hand response based on two different linguistic processes (syntactic and phonological) lead to similar RTs (approximately 900-1000ms after stimulus onset). To tap into RTs involved in the two processes used in our task (semantic vs orthographic), prior evidence using very similar tasks on visual single-words in a single experiment (see Mari-Beffa et al., 2005), namely, semantic categorization (animate vs inanimate) and orthographic decision (A/E letter search), yielded very similar RTs to those observed here, that is, 830.16 ms and 881.43 respectively. It is also worth noting the slightly shorter RTs for the semantic task, as observed here (956.28 ms vs 1019.92 ms), thereby suggesting that task alteration, cuing hand-laterality for respons does not dramatically alter performance and processing of the two taks, as can be evaluated by RTs.

The task used here was based on the assumption that word recognition proceeds from the processing of lower to higher traits, i.e. the visual system first identifies elementary letter features, then the global form of letters and finally words themselves (Selfridge, 1959; McClelland & Rumelhart, 1981). This view may be subject to criticism given the well-established “word superiority effect” (WSE) (Cattell, 1886) which postulates that a letter is better identified when it is presented within a word (Reicher, 1969; Wheeler, 1970) or within another stimulus with orthographical regularities, that is pseudoword (Gibson et al., 1962; Carr et al., 1979; Grainger et al., 2003; Jacobs and Grainger, 1992; McClelland, 1976) than within a randomly structured letter string or a letter in isolation. For instance, it is easier to distinguish ‘b’ from ‘c’ when they are presented in ‘bar’ vs ‘car’. The WSE would therefore support the hypothesis that the physical characteristics of a word, namely its form, are encoded in memory, thus enhancing the recognition of its constituents, namely letters. Furthermore, seminal papers pointed out already a decade ago, the existence of semantic processing even when the word is invisible (Greenwald et al., 1996; Luck et al., 1996; Dehaene et al., 1998). These findings provided experimental neuro-cognitive support for the existence of the WSE, and as a corollary, for the possibility of the subliminal recognition of words even when a subject is able to report having seen only letters, or nothing at all. More recently, Martin and colleagues found that the WSE operates already during the processing of letters, i.e. they showed that the visual word form representations can constrain letter identification already at 200ms post stimulus (Martin et al., 2006).

Altogether, these lines of evidence could be taken as an indication that while subjects were reporting letters in our experiment, still word representations were subliminally accessing their mind.

By contrast, research on the temporal brain dynamics of visual word recognition conveys a slightly conflicting view: comparing the event-related potential (ERP) waveforms generated by letters and pseudo-letters (false-fonts) reveals that these categories diverge as early as 145 ms post-stimulus onset (Rey et al., 2008) or slightly after (Wong et al., 2005). However, ERP waveforms generated by words and randomly organized letter strings (non-words) diverge much later, namely, in the time window of 200-600 ms (Salmelin et al., 1996; Wydell et al., 2003). This temporal divergence seems also to match a spatial divergence (e.g. Mainy et al., 2008) along the posterior-to-anterior axis, with letters recruiting more posterior areas whereas words recruiting more anterior areas (Levy et al., 2008). These findings suggest that the major cognitive processes underlying letter (orthographic) and word (phonological and lexico-semantic) perception markedly differ spatio-temporally, and that letter processing comes first. Also psycholinguistic research supports this view: Pelli and Tillman (2007) indicated lately that, letter information explains about 62% of the variance in reading speed, whereas word shape explains about 16% of the variance. For instance, changing the letters in a word while preserving its shape (e.g., changing ‘‘this’’ to ‘‘tbis’’) impedes reading more than changing the word shape (changing ‘‘this’’ to ‘‘tHis’’). Likewise, previous work showed that despite our expertise from reading a hundred million words during our life (Pelli et al., 2006), we never learn to see a word as a feature; our efficiency is limited by the bottleneck of having to rigorously and independently detect letters and its sub-features (Pelli et al., 2003). This was explained by what Pelli et al. labeled the “word-length effect”, according to which the efficiency of word recognition is inversely proportional to the word’s number of letters (efficiency for n-letter words is 1/n that for single letters). Surprisingly, this effect is valid not only for long words, which require more than one eye fixation (Legge et al., 1985), but also for short words and even single letters. This, however, does not exclude the WSE, but rather parallels (and over-powers) it: whereas the WSE increases a 5-letter word recognition by a factor of 1.3, the word length effect reduces it by a factor of 5. It should also be noted that the so-called word length effect may not apply to the standard (every-day) conditions of reading (with an excellent signal-to-noise ratio and maximal contrast), since it was obtained under very “unnatural” conditions (noise or contrast manipulation).

Recent empirical evidence challenged the view that unperceived words exert an influence at the word level, and posit instead, that the influence is exerted at the sub-word level (Abrams and Greenwald, 2000). In their intriguing study, subjects extensively practiced a relatively small set of words that were then used and recombined to form primes. For example, the word *tumor* was composed of the two word fragments that were derived from the words *tulip* and *humor*. Both those words were extensively studied at the first part of the experiment, but not the word *tumor*. The behavioral results indicated that *tumor* was subliminally processed by the two fragments that compose it and not as a unitary entity. From a neural-network point of view, the prior rehearsal of those words (e.g. *tulip* and *humor*) must have facilitated the activation of the pathways associated with those two words compared to that of a very frequent word such as *tumor*, which was not rehearsed beforehand. Ample support for this view comes even from experiments using subliminal number primes instead of word primes (Greenwald et al., 2003), thereby broadly positing that subliminal priming involves stimulus parts and not whole-stimulus meaning. A follow-up study by Abrams further expanded the findings by ruling out the possibility that such sub-word analysis is limited to operating on individual letters (Abrams, 2005); this was done by designing the word as such that no individual letter contained a diagnostic piece of information about a word's evaluative valence, that is, letter's identity and position could not facilitate subject's inference on the word's evaluative valence. The authors then repeated the experiment, this time removing any diagnostic information on bigrams and trigrams (two and three consecutive letters respectively) and replicated their findings, namely, the information captured by bigrams or trigrams was not critical for the subliminal priming. These findings are compatible with other studies; for instance, Kouider and Depoux (2004) have shown a similar effect during the Stroop test, namely, subjects extracted word fragments and reconstructed the incompletely perceived stimulus, which also resulted in a semantic priming effect.

The abovementioned findings deserve serious consideration in regards to our study. Here, when subjects failed to perceive the presented word and thereby to perform the first task (semantic categorization), they were indicated to resort to a secondary task, that is, to report the absence or presence of letter(s). However, our experimental setup did not allow us to distinguish between perception of a single letter (orthographic level) and that of sub-word segments (pre-lexical level). This may allude to the possibility that the neuronal oscillations observed here during the secondary task, may ostensibly corresponded to pre-lexical processing and not to orthographic processing. This would actually mean that the transition in CA described here may correspond to even subtler a boundary between two levels (pre-lexical and lexico-semantic) that are very close to each other, as can be inferred from the temporal similarity in the onset of their ERFs (Salmelin et al., 1996; Cornelissen et al., 2003; Wydell et al., 2003). Hence, in prospective research, it would be challenging to develop a similar paradigm exploiting the uniqueness of the present paradigm, and at the same time expanding its scope by isolating more specific levels of reading processes, such as orthographic or pre-lexical processing. Perhaps even phonological processing could apply, although it has been recently posited that during word recognition, phonological priming can only emerge during supraliminal perception, that is, for visible words, because heavy masking and brief word presentation impedes the propagation of visual activity to anterior phonological areas (Kouider et al., 2007). However, Kouider et al. do not rule out the possibility that phonological priming can occur under the condition that participants are engaged in a phonological task. Hence, this additionally introduces the possibility that under an appropriate experimental paradigm taking into account the above considerations, it could even be feasible, in the future, to investigate how phonological processing accesses consciousness.

One should not restrict its investigation to only noticeable reading processes. The scope of our understanding of reading can be expanded if we pinpoint the CA of even subtler processes such as morphological processing, i.e. the processing of the internal units within words, which are bound by syntactical rules (e.g. play-er). Morphological processing, if independently existing at the brain level (see Devlin et al., 2004), would temporally precede, during brain activation dynamics, higher processes, such as phonological and semantic processing (Pylkkänen et al., 2004). Thus, it seems to be an intermediate process occurring between orthographic and higher processes. Another option would be to probe how even lower level analyses access our perception during reading; for example, from letter features to letters. Interestingly, Ihara and Kakigi (2006) tested the oscillatory difference between lower levels of linguistic processes, namely, letters contrasted to pseudoletters (false fonts), and found consistently stronger and longer lasting (upper) alpha desynchronization. Although their study was not particularly conceived to investigate differences in CA between different levels of linguistic processing, their findings in conjunction with ours and another recent report (Dalal et al., 2009) could imply that alpha/beta desynchronization may be a marker of increase in, lower- or higher-level, linguistic processing. This novel conjecture and the many possible prospective directions of research should be interesting to be addressed in the future.

To summarize, we hold the view that even under subliminal visual conditions leading to absence of perception, a word, or more precisely, its sub-segments, are processed to a certain extent. However, such processing markedly differs from the processing that accompanies conscious word perception. It is worth to note that, in the present study we did not aim at studying subliminal word processing, but instead, partial and full supraliminal word processing. Our results thus, only focus on conscious processing, whether partial or full. By training subjects to voluntarily sustain their attention towards two distinct levels of perception while concurrently stimulating at threshold, the probability for a transition from a "preconscious" to a conscious state increases (Dehaene et al., 2006). As previously stated, this is inspired by meditation practices in which voluntary sustained attention increases the mental processes that are accessible to conscious report (Lutz et al., 2008). Hence, when subjects reported word percept we are sure that high linguistic processes accessed their consciousness (97.38 ± 1.55 % correctness), whereas when they reported letter percept, we are sure that low linguistic processes accessed their consciousness (98.16 ± 3.60 % correctness).

Neuronal Coherence for CA

Despite the interest of our reported findings which solely focused on local synchrony, there is every possibility that we overlooked an important point: neuronal coherence and its implications in the emergence of CA. This idea is born from data suggesting that conscious perception is related to coordinated dynamical states of the cortical network, rather than to the activation of specific brain regions (Fries et al., 1997, 2002; Engel and Singer, 2001; Thompson and Varela, 2001; Lamme, 2006). Neuronal coherence is the pattern of phase-locking among oscillations, mechanistically sub-serves neuronal communication (Fries, 2005). More precisely, activated neuronal groups oscillate and thereby undergo rhythmic excitability fluctuations that produce temporal windows for communication. Only coherently oscillating neuronal groups can interact effectively, because their communication windows for input and for output are open at the same times; accordingly, the absence of neuronal coherence prevents communication. Thus, a flexible pattern of coherence defines a flexible communication structure, which sub-serves our cognitive flexibility. Access to consciousness probably leans on such a mechanism for neuronal communication by means of long-distance synchronized/connected activity (Dehaene and Naccache 2001; Dehaene and Changeux, 2005). Another outlook of long distance processing refers to reentry interactions, and explains their importance for the emergence of consciousness. As argued by Edelman (2003): Reentry is an ongoing process of recursive signaling among neuronal groups taking place across massively parallel reciprocal fibers that link mapped regions such as those found in the cortex. It is a selectional process occurring in parallel; it differs from feedback, which is instructional and involves an error function, which is serially transmitted over a single pathway. As a result of the correlations that reentry imposes on the interactions of competing neuronal groups, synchronously active circuits across widely distributed brain areas are selectively favored.

The importance of coherence as a marker for the study of consciousness is further supported by the observation that only perceived words, in comparison to unperceived words, induced a transient long-distance synchronization of gamma oscillations across widely separated regions of the brain (Melloni et al., 2007). The authors then inferred that it is likely that the early long-distance synchronization of neural assemblies in the gamma band is the key event mediating access to consciousness. Their findings can also be strengthened by the observation of long-range gamma synchrony when comparing between detected and undetected items during the attentional blink (Nakatani et al., 2005). By contrast, different results were reported by the informative and encompassing intracranial study attempting to link CA and phase coherence (Gaillard et al., 2009). The authors observed a late (300-500ms) increase in beta phase synchrony, not in the gamma band, for full CA of words (unmasked) compared to the lack of CA of words (strongly masked), the authors then concluded that the (full) CA of words is characterized by a massive increase in long-distance beta, not gamma, coherence. Their findings can also be strengthened by the observation of long-range beta synchrony when comparing between detected and undetected items during the attentional blink (Gross et al., 2004; Kranczioch et al., 2007), although the two latter papers will not be discussed here because they lean on a very different paradigm, which does not guarantee that all consciously accessed stimuli are reported; this may occur due to the fleeting nature of the accessed representations (Wolfe, 1999). This lack of consistence between studies can be explained by two arguments: First, despite the interest of the effects observed by Gaillard et al. (2009), they were limited by the number of available electrodes and could only analyze coherences between electrodes within a given patient. Unfortunately, electrodes within subject tended to be regrouped within a cortical area, thus preventing a thorough analysis of how coherence evolves across distant anatomical sites, e.g. posterior to anterior. It is therefore likely that the lack of observed gamma coherence in their study reflected this methodological constraint. Second, the hypothesis of Melloni and colleagues was restricted to the higher frequency, thus their investigation may have over-looked potential long-range synchrony in lower bands. In a similar vein, the above reported beta (Gaillard et al., 2009) and gamma (Melloni et al., 2007) phase synchrony associated with CA probably do not directly relate to the influence of reading on the brain. This could be inferred from the convergence of the above reports with the recent finding that reading employs the left-hemispheric cerebro-cerebellar network in the alpha band (Kujala et al., 2007; see however the arguments of Palva and Palva in the second next to come paragraph). Hence, the findings of Gaillard et al. and Melloni et al. are critically informative since they argue that beta and gamma coherence underlies a particularly crucial aspect of CA, probably independently from the phase coherence underlying word reading.

It is also of particular importance to note the limitations of the above studies: First, just like in many other intracranial studies, the effects observed by Gaillard et al. (2009) are solely restricted to the location of the implanted depth electrodes as part of a pre-surgical evaluation of the epileptic participants. Therefore, they represent only a minute proportion of the brain in general, and of the reading/consciousness network, in particular. This is noteworthy especially due to the little number of implanted electrodes covering the parieto-frontal cortices, which are argued mainly by the same authors, to constitute the network for CA (Lumer et al., 1998; Beck et al., 2001; Dehaene et al., 2001, 2003, 2006; Rees et al., 2002; Marois et al., 2004; Dehaene and Changeux, 2005). Second, both the studies by Melloni et al. (2007) and of Gaillard et al. (2009) present findings of neuronal signatures associated with conscious perception that could be taken as reflection of more extensive processing rather than reflecting mechanisms specifically associated with awareness. In other words, when comparing the neural activity elicited respectively by a visible word and by an invisible word, one is actually comparing the correlates of a conscious representation with those of a degraded non-conscious representation. Differences may therefore isolate a neural response to two very different states of word perception (full vs. quasi-null), not to mention the ample differences in between a task being performed (in the conscious condition), and a task not being performed (in the unconscious condition). In the present study, this aspect was controlled by isolating and specifying precise and intermediate levels of processing. To the credit of Melloni and colleagues, it should be said that they attempted to control for this limitation by conducting a behavioral control experiment to evaluate the depth of processing of the unperceived word. The authors clearly observed semantic priming for the unperceived words and thus concluded that the unconsciously perceived words are processed despite their invisibility. Despite the lack of doubt concerning the existence of semantic priming during subliminal word perception (see [Kouider and Dehaene, 2007] for a review), their additional control raises new concerns: First, if both seen and unseen stimuli evoke semantic activations, what is the difference between the two? Second, how would one know what processes are accessed for the first in comparison to the second? A third problem related to the two discussed studies, is that they do not control for the large variance in conscious perception across individual subjects. Fourthly, bottom-up stimulation and top-down resources are not properly balanced, thus “contaminating” CA correlates with unspecific factors. As explained in the introduction, we contend that the present paradigm circumvents these serious limitations, thereby disentangling unspecific activation from CA. In the future, in addition to the local synchrony patterns presented here, measuring global synchrony along the reading network may reveal novel findings that could shed more light on the neuronal mechanisms underlying CA between two specific mechanisms, although so far the attribution of linguistic processes to frequency bands has not seemed to differ much between local and global synchrony (see [Bastiaansen and Hagoort, 2006] for a review).

Not only beta or gamma phase synchrony, but also alpha phase synchrony seems to contribute to the neuronal underpinnings of CA (Palva and Palva, 2007). Ongoing alpha oscillations in human sensorimotor, as well as frontoparietal regions, which are known to be relevant for consciousness

(Rees et al., 2002; Dehaene et al., 2006), often selectively phase lock to weak somatosensory stimuli that become consciously perceived (Palva et al., 2005). Thus, perception-selective alpha phase-locking in sensori-fronto-parietal networks indicates a direct role for alpha phase correlations in neuronal processes supporting consciousness (Palva and Palva, 2007). As further discussed by Palva and Palva, alpha oscillations that are phase locked to the synchronous fronto-parietal network – underlie CA. By contrast, if they are not phase locked to that network, they may be associated with subliminal/non-conscious perception, thereby possessing different functional roles, perhaps idling or inhibition. Furthermore, the joint cooperation of top-down modulation induced by alpha synchrony, and the bottom-up processing induced by gamma synchrony may be crucial for inducing CA (von Stein et al., 2000). Such cross-frequency rhythmicity could thereby contribute to recurrent processing (Lamme, 2006) as a neuronal mechanism for CA. Likewise, cross-frequency phase synchrony between the "fronto-parietal alpha network" and locally synchronous gamma assemblies underlies the selection and inclusion of neuronal object representations into sensory awareness (Palva and Palva, 2007). To summarize, despite the relatively concomitant and late appearance of these three frequency bands in our findings which already allude to a certain functional linkage, it should be even more informative in the time to come, to further investigate cross-frequency phase synchrony between the three synchronous frequency bands, as a plausibly additional marker underlying CA.

Conclusion

To conclude, the present study probed for the first time the neural signature of a 'leap' in the level of (visual) linguistic consciousness. It introduced a paradigm which controlled for bottom-up and top-down biases, and pinpointed the boundary between two consciousness levels for each individual. This did not aim to isolate brain activity that is putatively specific to the induction of consciousness per se, as extensive evidence accumulates to point out that such endeavor is perhaps ill-posed. Instead, the study reveals a left-hemispheric neuronal oscillatory pattern underlying a transition between lower to higher level of CA. This pattern seems to mirror a qualitative signature of a parametric increase in CA in general, and of a higher linguistic CA in particular. Such signature does not reflect reportability nor other unspecific processes (e.g. attentional variability between conditions, stimulation strength variability) thus circumventing a highly debatable issue in the study of the NCCs. The observed pattern suggests that the fronto-parietal network is probably not specificly engaged in the parametric increase in CA but rather may be a by-product of reportability. Instead, centro-posterior oscillations seem to indicate the "upgrading" of consciousness to a higher linguistic process. This enterprise thus introduces an important contribution to the semi-controversial study of the NCCs and additionally links it to the domain of language.

Chapter 5 Discussion and Prospective

While you are now reading this text, you are unaware of a complex series of extremely rapid processes which is taking place: Within less than 250 ms of viewing a written word, the visual system extracts the information needed to identify its linguistic significance, and this, despite wide variations in print, script, font, size and retinal position (McCandliss, Cohen and Dehaene, 2003). This is orchestrated by a network of specialized brain regions constantly communicating and trafficking information to and from each other, by discharging electrical pulses at various frequencies. On the surface, because the processes are so automated, it is underneath our level of consciousness. Notwithstanding the advantageousness of such simple, automated and efficient mechanism, we would benefit a lot from understanding the mechanisms that subtend it. The aim of the present thesis was to bring these unconscious processes onto the surface of our knowledge, to disambiguate some problematic notions, and to propose novel outlooks for future ensuing research.

Reading processes prefer left and anterior

Over the past two decades there has been an extensive number of neuroimaging studies interested in unraveling the brain organization that sustains reading (reviewed by: Price, 2000; Jobard et al., 2003; Démonet et al., 2005; Salmelin, 2007), altogether conveying an image of bilateral posterior activations which are induced by linguistically elementary stimuli, and of more left hemispheric anterior activations induced by stimuli, higher in terms of linguistic processing. Despite this converging unequivocal notion of a gradient of left anteriority for linguistic processing, it is intriguing that a proper investigation was never conducted to empirically prove a notion which is so internalized, even outside of the scientific community.

In Chapter 2, we undertook the enterprise of demonstrating the above converging view in a single experiment. This was done by contrasting a large repertoire of eight categories of stimuli ranging from simple orthographic-like characters to words and pseudowords (Figure 2.1). BOLD activation patterns and connectivity measurements confirmed our prediction, namely, the existence of a bilateral-to-left and posterior-to-anterior recruitment of reading related areas, straightforwardly resulting from the increase in linguistic processing. The results illustrate an unambiguous image: First, unfamiliar shape forms which possess as identical visual complexity (ink area) as letters, i.e. “pseudoletters”, recruited only visual areas when passively viewed (activation peak in the left middle occipital gyrus [MOG], BA 19). These areas were unequivocally non-linguistic since they were recruited to the same extent among all eight linguistic and non-linguistic stimulus-categories ($F(7,105) = 0.45$, $p > 0.8$). Second, progressively increasing the number of linguistic units (letters, syllables, meaning) straightforwardly recruited more anterior and more left-hemispheric areas. More precisely, this piecemeal increase in linguistic units triggered two noticeable effects: (i) a non-linear increase in the left occipito-temporal junction (anterior part of the middle occipital gyrus, BA 37) (LOT), particularly for the sub-lexical analyses during pseudowords reading, and (ii) a linear increase in the left parietal (precuneus, BA 7) (LP) and in the left inferior frontal gyrus (IFG). The second part of the study illustrated that this gradient-like pattern reflects reading processes in a piecemeal manner: from visual, through orthographic, and to phonological processing (Figure 2.2). Of particular tenability we found the role of the left parieto-frontal network which was particularly activated for the highest processes (phono-lexico-semantic) during reading, thereby once more emphasizing the posterior-to-anterior and bilateral-to-left activation cascade as a function of increasing linguistic processing. When expanding our analyses to probe information trafficking (connectivity) between regions, we were not only able to replicate the existence of the spatio-functional gradients, but also to again point out the enhancement of the left parieto-frontal branch as a mediator of transiting from ‘peripheral’ (visual/orthographic) to ‘core’ (phonological/semantic) linguistic processing. In a nutshell, the two focuses of the study converge to reveal a spatio-functional piecemeal recruitment while increasing linguistic processing. In Chapter 4, we followed up these data by focusing on the transition between the two main processes: peripheral (visual/orthographic) to core (phonological/semantic) linguistic processing. We then investigated the neural mechanisms underlying the transition between both, as they perceptually and conceptually access consciousness, respectively.

Recent findings corroborate our results and further expand it to completely different language systems such as the logographic alphabet in Chinese (Chan et al., 2009). Intriguing was the overlap between their and our findings, namely, the tuning of the left occipito-temporal and the left parietal cortices to the increase in linguistic processing, i.e. from unknown letters, through pseudo-characters (with Chinese radicals), to real Chinese characters. Additionally, the effect in increase from lower (pseudo-characters) to higher (real-characters) linguistic processing was mostly pronounced in the left parietal and left frontal cortices. Similarly to our investigation, this points out the higher linguistic (phonological-semantic) role of the latter two regions in comparison to the lower linguistic (orthographic) role of the left occipito-temporal cortex. Such converging unambiguous findings between two completely different language systems (alphabetic and logographic) lead us to venture that posterior-to-anterior piecemeal recruitment of reading areas resulting from the increase in linguistic processing level may constitute an innate characteristic of a “universal” neuronal language network. This yet immature proposal remains to be strengthened and established by empirically testing it for other language systems.

As introduced in Chapter 1, the concept of hemispheric lateralization of language is widely accepted already since four decades ago. Our work provides an elaborated illustration of the contribution of linguistic units to the pattern of left lateralization. It is readily evident that the prevalent characteristic to the processing of various visual patterns of all kinds is their recruitment of both posterior (occipital) hemispheres (e.g. Cohen et al., 2000; Tarkiainen et al., 2002; Itier and Taylor, 2002). We also know that novel items, which may resemble letters in their visual features (pseudoletters), generally recruit slightly more the right hemisphere (e.g. Gros et al., 2001; Figures 1.1 and 2.1). Figure 2.1 conveys this notion by illustrating the right lateralization for non-linguistic stimuli (pseudoletters), and how the balance from right to left noticeably reverses with the parametrical increase of orthographic (letter) units, and then even more complex, phonological (syllable) and lexical (meaning) units. However, when focusing on higher linguistic stimuli, this mounting lateralization suffers from a sudden bilateral recruitment for words. This may at first appear counter intuitive given that the lexical-semantic processing step, which per se can only be carried out by words and is, one could argue, the end goal of all language comprehension. However, since there was no task involved (passive viewing), words may have yielded not as much “linguistic effort” as other unknown stimulus categories have induced. This is particularly tenable for pseudowords, whose orthographic and phonological similarities to words activates representations in lexical–semantic areas, and increases the demands on lexical processing (Fiez et al., 1999; Price et al., 1996b), thereby taxing these areas to a greater extent (Mechelli et al., 2003) as a result of an automatic lexical–semantic ‘search’ for neighboring real words. An alternative, yet parallel interpretation may additionally explain why the processing of words was only weakly left lateralized, in contrast to other linguistic stimuli that possess less linguistic properties (e.g. meaningless syllables or consonant strings). First, weaker left-lateralization for words does not appear in complete surprise since lexicality also relies to some extent on the right hemisphere (Zaidel, 1986). Second, prior neuroimaging and divided visual field studies revealed significantly more left hemispheric lateralization during phonological than during semantic processes (Baciu et al., 2001; Kareken et al., 2000; Lurito et al., 2000). This would explain why in our fMRI data, unknown phonological stimuli (e.g. syllables and pseudowords) yielded the most noticeable lateralization patterns (Figure 2.1).

Additionally, given that in our paradigm syllables and pseudowords were novel phonological items, we contend that our findings agree with the recent demonstration of the importance of left hemispheric language processing in the formation of novel phonological entries in the mental lexicon (Paulesu et al., 2009). Finally, in addition to Chapters 2 and 3, Chapter 4 also contributed importantly to the language hemispheric lateralization: significant activations underlying the reported effects were predominantly found above the left, not right hemispheric sensors. Moreover, this lateralization was found to be significant when taking into account trial variability and independent from time and frequency of the collected data. Therefore, the oscillatory patterns underlying the leap to full linguistic CA are subtended by neural areas mainly in the left hemisphere. This also contributes to the observation that oscillatory brain patters are a good predictor for hemispheric language dominance in contrast to handedness for instance (Hirata et al., 2004).

It may be intriguing in the future to probe even subtler processes such as morphological processing, i.e. the processing of the internal units within words, which are bound by syntactical rules (e.g. play-er). There is currently a debate regarding the holistic (see Devlin et al., 2004) or local (see Rastle et al., 2004) nature of this process. The advocates of the first approach argue that brain signature for this process would result from orthographic and semantic effects (Martin and Thierry, 2008), whereas advocators of the second approach argue that it is probably an intermediate process between orthographic and higher processes, which would temporally precede higher processes, such as phonological and semantic processing (Pylkkänen et al., 2004). Newer accounts suggest, however, that the answer lies in the nature of the task (e.g. Gold and Rastle, 2007; Kouider and Dupoux, 2009) or depends on the morphological characteristics of the tested language (e.g. Bick et al., 2008). Prior evidence confirms that this processing step, if should be endowed with its own neural correlates, the latter would be left lateralized, although it is not certain whether this should be in the LOT (Gold and Rastle, 2007), in the LP (Bick et al., 2008) or in the left frontal cortex (Bozic et al., 2007; Bick et al., 2008). To elaborate our understanding of morphological decomposition, I contend it to be of interest to insert and test this process in future follow-ups of the presented work. For instance: (i) to determine the contribution of morphological processing to the posterior-to-anterior and bilateral-to-left hypothesis as tested in Chapter 1, that is, what are the regions that morphological processing recruits along that axis? (ii) And even more interesting in my opinion, would be to probe the exact boundary to which CA occurs for this processing step, and examine its neuronal signature. This may be particularly pertinent to possibly shed light on the present controversy vis-à-vis the local or holistic nature of the processing of internal units during word recognition, and could more over, elaborate the scope of our understanding of reading.

Same Reading, different Networks

In the work presented in Chapters 2 and 3, we present a model including four regions of interest (ROIs) for reading. Selecting these areas was not based on prior data from the literature, but was exploratory. As described in detail in the two Chapters, the areas were readily obtained by a series of conjunctions isolating three important processes during reading: visual, orthographical and phonological processing. To form a model, we applied the approach of parsimony, that is, we first tested an "economical" model (few connections, and only uni-directional) and then made it more complex by adding new ROIs, forward and backward connections. The objective was to retain the fewest ROIs (variables) and paths that explain the most successfully the variance. We then retained the presented model because it provided the best fit for the observed data during the passive viewing of all eight different pseudo-linguistic and linguistic stimulus categories (high fit values).

Notwithstanding the prominence of these areas to reading, the model does not rule out the contribution of other (in between) regions to reading. In fact, often research investigates activation and connectivity for regions from a model that had been previously determined by other studies (e.g. Mechelli et al., 2005; Vinckier et al., 2007; Seghier et al., 2008). I do not overlook the advantage of such an approach, and particularly not when the ROIs have been prevalently reported over the years by different research groups. However, I still think it is necessary to pay careful attention to the underlying conditions of the experiment. For example, in Chapters 2 and 3 we used (i) passive viewing in (ii) French. The first condition would ostensibly minimize the implications of unspecific areas for reading (task-related networks). This confound of task-related activations is often demonstrated: For instance, active tasks relative to passive viewing of the same stimulus array elicit a decrease of the blood flow for visual information processing (Shulman et al., 1997); reading aloud compared to silent reading implies the non-linguistic activation of motor and auditory regions (Bookheimer et al., 1995; Price et al., 1996a; Huang et al., 2001); silent and overt response conditions during word generation or semantic association elicit different activation patterns (Borowsky et al., 2005); and modifying the task instruction from discriminating to categorizing (Pernet et al., 2004), from rhyming to spelling (Bitan et al., 2005), or from lexical decision to pronunciation (Nakamura et al., 2006) – modulates the stimulus-driven activation and thereby engages different neural networks. The second condition, it is important to note the relatively high degree of transparency in grapheme-to-phoneme conversion in the French language (pronunciation is straightforwardly inferred by spelling). It would therefore make sense that words from a language with different degrees of transparency would recruit reading areas differently (see Paulesu, Démonet et al., 2001). For instance, words from English, which is an opaque language would rely more on the lexical (anterior LOT) pathway, and less on the dorsal G-P conversion (LP). The dissociation in activation patterns between lexical and non-lexical stimuli is elaborated in detail in the second next section.

Keeping the above in mind should be valuable for different research groups when comparing between results that at first glance may appear contradictory or intriguing. It should also be noted that individual variability is an important factor, for some individuals neuronal dynamics can even completely reverse, as reported in Chapter 3. Also behaviorally, reading proficiency (Chapter 3) and even the threshold for single word perception (Chapter 4) may amply vary between individuals. This adds credit to the approach applied in Chapters 2 and 3, namely, determining ROIs from the data of the same experiment. Finally, it is most probable that, reading recruits much vaster a neural network than those prevalently tested in the literature. At present, it may not be possible yet to provide a clear and complete picture encompassing the totality of the neural networks underlying reading. However, this should not impede the motivation of future research for understanding the neuronal network underlying reading. Instead, we should evaluate what has been achieved up to now, and seek to elaborate the range of our investigation. In the end, we will probably not obtain a static image, but an ever-changing and developing one, since the brain is endowed with the gift of plasticity, fortunately.

As noticed, our work revealed a network for reading processes, except for perhaps the most important one – meaning extraction. We attempted to do so by contrasting Words with Pseudowords. However, the adequacy of this contrast to locate such processes is debatable given that no cluster is usually recruited more by word- than by pseudoword-reading (Jobard et al., 2003). Instead, our investigation showed that the above contrast yielded areas for which activation was significantly lower for Pseudowords than signals recorded not only for Words but also for all other conditions but Single-pseudoletters. These results are in line with Mechelli et al. (2003) who reported that contrasting words with pseudowords reveals areas which are mostly due to activation decreases for pseudowords rather than increases for words. In addition to these deactivations, we also observed greater activations for pseudowords than words in many other areas. In fact, both pseudowords and words activated a similar neural network (essentially, in the bilateral occipital and frontal cortices, in the LOT and in the LP) but pseudoword processing taxed the entire system to a greater extent; this observation is in agreement with previous studies (Mechelli et al., 2003; Price et al., 2003; Wilson et al., 2005). This pattern was also illustrated by the linear contrast and connectivity analyses which followed our linguistic processing load (LPL) classification, therefore confirming that processing pseudowords is somehow ‘harder’ than that of words. To summarize, the advantage of using a passive viewing task revealed itself to be efficient for most reading processes, but was ineffective for isolating areas for lexico-semantic processing. I hope a novel approach would be able to overcome this limitation, while maintaining the advantages of the passive viewing paradigm.

When inspecting the findings from Chapters 2 and 3, an interesting image emerges vis-à-vis the reading network that we isolated: it could actually be divided into two sub-networks, the first, (i) intermediate-posterior areas (occipito-temporo-parietal) which are involved in predicting reading skill (thereby confirming prior reports which tested it indirectly), and the second, (ii) anterior areas (parieto-frontal), which account a correlational measure of the linear increase in linguistic processing. As addressed in much detail in Chapter 2, the second network was found to be of prime importance for the increasing linguistic processing, but not the first (posterior). However, the first, in contrast to the second, revealed to be implicated in visual-orthographic analysis, not in higher processes such as phono-lexico-semantic. This was readily observed when in Chapter 3, additionally to comparing connectivity for words and pseudowords, we also added an important control – (consonant) letter-strings, that is, non-words. This was an important control since non-words were actually 5-consonants without orthographic regularities, phonological units, and lexical entries, whereas pseudowords were 5-letters with orthographic regularities and phonological units but no lexical entries, and words were 5-letters with orthographic regularities, phonological units and lexical entries. Thus, if non-words would elicit similar connectivity patterns as pseudowords did, then it would mean that phonology does not play an important role in the network. However, if it elicited a different connectivity pattern, then phonology would be prominent for the selected network. The results emphasized the posterior-anterior disentanglement of two sub-networks, i.e. connectivity was the same for non-words as for pseudowords (particularly vis-à-vis words connectivity pattern) for the posterior, but not for the anterior sub-network. This should be interpreted as an indication for the visuo-orthographic role of the posterior sub-network, in contrast to the phono-lexical role of the anterior sub-network. Additionally, in Chapter 4, although we were yet unable to investigate the precise localization of the neuronal network underlying the transitional CA (consciousness access) from low to high linguistic processing, it seems to concentrate mainly above the left parietal cortex, but also above more anterior left hemispheric areas. Assuming a certain mapping between these data and cortical functionality, the results again highlight the prominent role of the left parieto-frontal sub-network in the transition from low to high linguistic processing. I contend that this functional dissociation between posterior and anterior networks is an interesting emerging finding from our different lines of work, and should be kept in mind for future research to consider.

Beside the posterior-anterior functional disentanglement, there is of course a ventral-dorsal dissociation. As revealed in Chapter 3, the posterior ventral pathway (MOG→posterior LOT) is mainly endowed with the function of transferring visual information for sub-word analysis; the latter will be detailed in the second next underlined heading. By contrast, the posterior dorsal pathway (MOG→(precuneus)LP) is in charge of trafficking visual information for letter encoding and seubsequently phonological transcoding, i.e. grapheme-to-phoneme conversion. Ensuing with the second sub-network (parieto-frontal), the anterior dorsal pathway (precuneus(LP)→IFG) is in charge of routing the orthographically encoded information for phonological processing. As detailed in Chapters 2 and 3, this pathway was found crucial for the execution of higher linguistic processes, and more in particular, for phonological processing, thereby conforming to prior studies (Booth et al., 2002; Cao et al., 2008). This is why pseudoword reading, which implies heavy phonological processing (see next heading for more detail), recruited this path significantly more than during word reading. Despite this interesting dissociation, information trafficking in this pathway during word or pseudoword reading did not predict reading skill. Additionally, other contrasts involving this pathway as well as the other anterior (ventral) pathway (posteriorLOT→IFG), were much less conclusive than for the posterior connections, thus leading us in Chapter 3 to focus on the functionality of the posterior sub-network.

In our model, the functionality of the anterior ventral pathway revealed to be less conclusive since the involvement of this pathway was prevalently weak for all the three tested stimulus-categories in Chapter 3 (words, pseudowords, non-words). This may appear at odds with prior literature since the ventral axis from the LOT to Broca area is prevalently believed to sustain lexico-semantic analysis (see meta-analysis of Jobard et al., 2003). As I will soon elaborate in the next outlined heading, I reason that such axis strongly depends on the originating coordinates particularly along the y-axis. Thus, it may be that words rely more on the anterior ventral path, but it is also possible that this path originates from a more anterior part of LOT. In convergence with our findings in Chapter 3, information is then likely to be processed both for orthographic encoding in the LP, and in parallel for lexico-semantic access in the anterior LOT, that is, the posterior temporal cortex. Furthermore, this dissociation should also apply for Broca area, that is, its posterior part (pars opercularis) for phonological processing (as revealed in Chapters 2 and 3), and its anterior part (pars triangularis) for semantic processing (Jobard et al., 2003; Price and Mechelli, 2005), as unfortunately could not be addressed under our paradigm's constraints as previously commented, due to the impossibility of isolating lexical areas. Remarkably, this prediction has already been confirmed by showing that during irregular words presentation, effective connectivity between the anterior LOT (y = -42) and the left pars triangularis (IFG) was associated with increased activation in the latter

(Mechelli et al., 2005). Finally, the emerging picture here also conforms to the most recent report of the precise neural connectivity of Broca's region in macaque monkeys using the autoradiographic method to achieve a level of detail impossible in the human brain (Petrides and Pandya, 2009). The authors identified two major streams of connections feeding into Broca's area (IFG): a ventral stream from the temporal region, and a dorsal stream originating from the inferior parietal lobule. Whereas the dorsal pathway feeds to both posterior and anterior parts of the IFG, the ventral pathway connected particularly amply from the temporal lobe to the anterior IFG. Vis-à-vis the aspect of posterior-anterior and dorsal-ventral disentanglement, I contend our findings to be complementary to prior reports by emphasizing aspects that were previously overlooked, and thereby unveiling a clearer image on the neural mechanisms subtending word reading.

In cerebro reading styles

In Chapter 3, we expanded our scope of study to explore neural pathways during reading; we were originally intrigued to comprehend if and how such 'in cerebro' dynamics predict reading skill. The chapter presents distinct anatomical pathways corresponding to the two routes for the processing of written language. It compares effective connectivity data during reading with out-of-scanner reading tests. Reliance on these neural pathways predicts reading skill. The findings of this Chapter could be summed up as follows: (i) they confirm prior neuropsychological data by providing a remarkably good neural account of the early processing (visuo-orthographic) of the two routes in the dual-route cascade model (Coltheart et al., 2001), (ii) extend the knowledge about the non-lexical route by unraveling that the latter is substantially mediated via the posterior LOT, (iii) demonstrate that incongruent or congruent reliance on these pathways predicts poor or skilled reading. Most importantly, the data (iv) raises the novel idea of efficient 'in cerebro' reading style depending on the stimulus to be read (known word vs. unknown word) and argue that individually unique reading styles may translate to either skilled or deficient reading ability.

I would like to elaborate upon the last raised point, namely, the possibility of an efficient 'in cerebro' reading style, which could also be considered as a first demonstration of the pattern of cerebral information trafficking which one 'should follow' in order to yield high reading performance. What is even more intriguing is the existence of outlier readers who did not follow the "efficient trade-off" of pathway reliance; instead, they may have resorted (or not) to alternative pathways, resulting in skilled (or poor) reading performance. In view of the above observations, we were intrigued whether differences in reading skill would depend on other individual factors such as age, gender or years of education, and whether these would also affect the individual pathway reliance. It could indeed be that such demographical/educational factors would exert the most amble influence on reading skill, much more than neural dynamics exert alone. Furthermore, it could also be that such factors would predict even neural dynamics. Interestingly, we found that the only factor to significantly predict reading skill in our study was the years of education (practice) of the participants. More importantly, we found that none of these three demographic factors could predict (explain the variance) pathway reliance. These broad and interesting findings could suggest that the neural network for reading is malleable particularly during school time and may therefore be immune to significant life-time plasticity as a result of age or practice. However, practice may on the contrary improve reading skill, but perhaps without major malleability of the neural network. Taken altogether, these results may be of particular interest for future applications of individualized reading instruction methods (Connor, 2007) already during school time for potentially good readers as well as for children suffering from developmental dyslexia; this notion is particularly to note and possibly to apply as well, since the reading network is highly plastic during school time (Parviainen et al., 2006). Another possibility for future application, although still far-fetched to date, could be for brain-computer-interface research to apply these findings, by starting up novel implications for improving reading performance for both skilled and dyslexic readers, particularly in view of the changes in brain activity after remedial intervention for dyslexics (Démonet et al., 2004).

Another noteworthy point is the reading tests used in Chapter 3. The first tests, namely, WRT and PWRT, mimicked to a certain extent an “artificial” and laboratory-like reading of single words. Notwithstanding the interest of studying this reading style, it is however, not prevalently used in our daily life, since we commonly read more than a single word, i.e. text reading. Nevertheless, the WRT and PWRT tests, which measure voice onset and spelling errors, consist in a valid criteria for the diagnosis of reading impairment (Rapcsak and Beeson, 2004; Henry et al., 2007; Dufor et al., 2007, 2009). As such, these tests predict erroneous pathway reliance, not successful reliance. By contrast, to expand our investigation to the reading circumstances closer to every-day life, we also used the “Alouette-R” test (Lefavrais, 2006), a standardized test for reading text in French which at variance with the former two tests, directly assesses text reading speed and precision (CTL index). This time-limited text involves both frequent words, and very rare words (making them appear as pseudowords to almost any subject), as well as words having low probability provided the sentence context in which they take place. The particular contents of this text requires the subject to alternate quickly between ‘standard’ text reading involving mainly the lexical route and the non-lexical route in order not to misprocess the ‘catch-up’ words hidden in the text from place to place. Thus, contrary to the former two “artificial” tests, which are markers of reading impairment, “Alouette-R” test assesses proficiency at dealing fluently with both lexical and non-lexical routes during text reading. We therefore hypothesized a positive correlation between scores in this test and congruent reliance of pathways, i.e. reliance on the word pathway during word reading and on the pseudoword pathway during pseudoword reading. The results conformed to our conjecture; further more interesting, there was no correlation between scores in this test and erroneous reliance, such as was the case for the former two tests. This could point out to the importance of using such "daily-life" tests more often, since they may convey more pertinent information in general, and such as the reading skill shown here in particular. Nonetheless, our on-line task still used such an "artificial" task, therefore rendering our interpretations valid with respect to the neural network underlying (single) word reading. However, when referring to "more natural" reading, that is, text reading, it would certainly be more pertinent to isolate the neural network underlying unification processing. The latter refers to the information processing of many single-words, and to its integration into a representation of multi-word units (Hagoort, 2005). Hence, future applications could address the even more challenging endeavor of probing the dynamics within a unification network, and whether it is prone to predict reading skill.

Moreover, the findings in Chapter 3 revealed a very significant anti-correlation ($r = -0.92$, $p= 0.001$) between preference for the lexical route during (on-line) pseudoword reading and (off-line) text reading skill (CTL index), therefore highlighting that strong reliance on the non-lexical route when processing unknown words that abide to orthographical regularities, predicts reading skill. Similarly, the regression analysis showed that a linear adjustment to the data explains 85% of reading skill (CTL variance) ($R = 0.92$, $F(2,9)= 25.8$, $p< 0.0002$) with a significant contribution of the difference between paths for pseudoword reading (partial correlation $t(9)= -5.36$, $p= 0.0004$, $R2= -0.87$). Additionally to pointing out an 'in cerebro' reading style as previously elaborated, these findings clearly stress the particular prominence of phonological-oriented reading style, that is, non-lexical reading, for reading skill. Also in line with this, in Chapter 3 all fourteen participants, including the two outliers, substantially relied on the non-lexical pathway. The only subject who relied more on lexical reading was the only one who did not fit our robust model during pseudoword reading ($p = 0.04$), but who perfectly did during word reading ($p = 1$). This suggests that the majority of proficient readers (here 14/15) efficiently rely on non-lexical (phonological) reading. These findings concur well with the vast behavioral evidence showing that phonological awareness, which is so necessary for phonological (non-lexical) reading, is the most critical component in learning to read, especially in the early phases of reading acquisition (Share, 1995; Sprenger-Charolles et al., 2003); it is even a prerequisite for learning of orthographic information (Share, 1995). Therefore it is not surprising that phonological skills highly correlate with reading skills, especially in the early phases of reading acquisition (Wagner and Torgesen, 1987). Most recently, the activation strength of the left occipito-temporal junction, correlated with phonological skills in (first-graders) children (Parviainen et al., 2006), further establishing the prominence of this area for reading skill and reading acquisition, already from an early age.

Likewise, these interesting observations are in agreement with the findings described in Chapter 3, relating to the central role that the LOT plays in mediating the non-lexical route. It also corroborates (i) the positive correlation between activation in this region and reading performance in adult skilled readers (Bruno et al., 2008); and (ii) the stronger modulatory effect on the feed-forward from this region to the left parietal observed in skilled vs. impaired (children) readers during an orthographic/phonological conflicting rhyming task (Cao et al., 2008); (iii) the positive correlation between gray matter volumes in this region and reading skills (Pernet et al., 2009); (iv) the positive correlation between activation in this region and the performance during the reading of unfamiliar but regular words (pseudowords) by dyslexic children (Shaywitz et al., 2002); and (v) the influence phonological training has on this region's activation in dyslexic children (Shaywitz et al., 2004). Furthermore, these converging papers highlight the existence of a non-lexical neuronal pathway (or even network) which plastically builds up and matures during early childhood to underlie reading; brain activations in the reading areas were markedly delayed in children compared to adults, indicating that the system is still under maturation (Parviainen et al., 2006). It therefore opens the possibility for prospective reading instruction methods to lean more on these converging data of neuronal pathway reliance. For instance, healthy or dyslexic children who are found to rely more on the non-lexical pathway, could receive a phonologically-based instruction, and vice versa (for more detail, see [Connor et al., 2007]).

A LOT of importance to reading

Combining the above information with data from Chapter 2 and Chapter 3, we obtain an even more tenable message regarding the prominent role of the left occipito-temporal (LOT) region during reading. As introduced in detail in Chapter 1, there has been quite a "notorious" debate on the existence of a so called "visual word form area" (VWFA), situated at the occipito-temporal junction in the left fusiform gyrus. The core of the controversy turns around its function: whether it supports the abstract representations of letters in the visual modality (Cohen et al., 2000, 2002), or not (Price and Devlin, 2003; Moore and Price, 1999), and rather reflects an operation common to the processing of words with regular (Kronbichler et al., 2007) or irregular (Bruno et al., 2008) orthographies, word sub-units (Binder et al., 2006), pictures (Starrfelt and Gerlach 2007), objects (Bar et al., 2001), or stored visual forms and structures in general (Joseph and Gathers, 2003). The work presented here suggests that to minimize conflicting reports, whenever referring to activation in the LOT it is of prime importance to index the y-axis position. This position noticeably determines the functionality of this patch of neurons, i.e. posterior patches mostly process letters and sub-lexical units, whereas anterior patches (such as the Visual Word Form Area, i.e. VWFA) tend to process lexical representations, that is, whole words. To the best of my knowledge, this view is compatible with the convergence from a large number of papers in recent years (Moore and Price 1999; Booth et al., 2002; Jobard et al., 2003; Mechelli et al., 2003, 2005; Dietz et al., 2005; Binder et al., 2005, 2006; James et al., 2005; Vigneau et al., 2006; Vinckier et al., 2007; Levy et al., 2008; Seghier et al., 2008).

To exemplify, LOT is usually more activated during pseudoword reading relative to word reading due to the excess of sub-word processing (Mechelli et al., 2003; Price et al., 2003; Levy et al., 2008); a closer scrutiny reveals that the effect is mainly observed in more posterior locations of the LOT. To explain the relation between pseudowords and the ampler recruitment (of the posterior patch for the analysis of letters and sub-word segments) that they obtain, one should examine more closely what actually occurs during pseudoword reading: it automatically triggers a process of recognition of familiar sub-word segments. Furthermore, sub-word units such as two or three consecutive letters (bigrams and trigrams) are very critical for word recognition (see [Jordan, 1990] for a review) and activate mnemonic representations much more than whole-words, especially when read fast (Abrams and Greenwald, 2000): The recognition of sub-words inevitably triggers a 'search' for their original real words, therefore rendering pseudoword reading slower than any other linguistic stimulus in lexical decision tasks (Ratcliff et al., 2004). These observations are notably pertinent here since such word units amply recruit the posterior LOT (Binder et al., 2006; Vinckier et al., 2007). As such, the posterior LOT is sensitive to 'low-level' linguistic stimuli (unfamiliar characters or infrequent letter-combinations), while activation becomes hierarchically more anterior as stimuli increasingly resemble words (frequent letters, bigrams, trigrams, quadrigrams), and the most anterior – for words (Vinckier et al., 2007).

At odds with the statement of posterior-anterior dissociation within the LOT, we notice that our findings in Chapter 2 illustrate that word reading activates a peak cluster at a posterior location (y = -72) of the LOT. We are not sure as for the exact reason for this exception; our main suspicion, however, directs us towards the transparent nature of the words that were used, i.e. they were 100% regular in terms of grapheme-phoneme conversion rules. This increases the chances of sub-lexical reading (posterior LOT) in comparison to irregular words which would directly access lexical reading (anterior LOT). On the other hand, to isolate the regions that are prominent for the orthographic analysis, that is, the processing of each letter, we performed a null conjunction of all the stimuli containing letters (single-letters, 3-consonnants, 5-consonnants, 3-letter syllable, 5-letter word, 5-letter pseudoword); this yielded activation in the LOT with a posterior activation peak (y = - 68). This confirms our above conjecture since this posterior patch should indeed underlie the processing of the most basic linguistic units, namely letters, and not that of more complex units, namely, syllables or sub-words. This is well instantiated by our ensuing conjunction on more complex stimuli (syllables, words and pseudowords), which did not reveal any activation peak in the LOT, but instead in more anterior areas (parieto-frontal) (Figure 2.2).

Furthermore, connectivity analyses performed in Chapter 3 strengthen this view: visual information routed towards the posterior LOT (y = - 68) significantly more during sub-lexical reading, namely, pseudoword and non-word reading, than during lexical reading, namely word reading (Figure 3.1). As previously implied, we presume that if we used irregular words, instead of 100 % regular words, we would find this difference to be even more ample. Likewise, the high regularity of words combined with the high degree of transparency in French, both imply that despite parallel visual information routing to both posterior LOT and LP, the latter dorsal branch, which is in charge of G-P conversion for regular/transparent words or pseudowords, was much more critical since solely it was able to predict reading skill (Figure 3.2). The results also agree with prior findings of connectivity: visual spelling task (match the spelling of two words from the first vowel onwards) which would probably involve similar processes to those during pseudoword reading, at least much more than during word reading, indeed yields stronger connectivity from the visual cortex to the posterior LOT (y = -72) than to the left parietal (Booth et al., 2008), a pathway which we found in Chapter 3 to be more implicated in lexical reading.

More recently, findings from the fMRI-adaptation study by Glezer et al (2009) are interesting to discuss in this regard: In the case of adaptation (decreasing activation) to repeatedly presented visual words, exchange of a single letter (e.g., coat instead of boat) led to the same increase of VWFA activation as the change of 4 letters (e.g., fish instead of boat). By contrast, when repeating the experiment but instead of words, this time using pseudowords, exchange of a single letter (e.g., soat instead of poat) led to a significantly smaller increase of activation than exchange of 4 letters (e.g., hime instead of poat). The authors interpreted their results as a straightforward demonstration that the VWFA is highly selective for individual real words, in compatibility with the notion of orthographic lexicon, but not selective to sub-lexical or letter representations. In relation to our introduction on global and local encoding, this finding may suggest that global reading is sub-served by anterior patches of the LOT, such as the VWFA. Several other reports support this notion; for instance, Kronbichler et al. (2004, 2007, 2009) whose reports on activation levels as a function of various parameters, also point to the existence of word-specific orthographic representations in the VWFA. Likewise, Mechelli et al. (2000) did not find any brain activation effect in the VWFA induced by word-length (3 to 9 letters). Instead, a monotonic positive effect on neural activity was found only in bilateral lingual and posterior fusiform gyri. As a corollary, it should be informative for future studies to localize the patches that encode local information (letters), thereby venturing to hypothesize the existence of a letter homolog to the VWFA, namely, the visual letter form/tuning area. As alluded to by the findings of Mechelli et al. (2000), we conjecture that neurons in posterior patches of the LOT may contribute to such encoding.

A Conscious Leap

The myriad of neuroimaging studies on language processes over the past two decades has substantially contributed to better understand the mapping between brain activation and linguistic functioning. However, the neuro-linguistic (and the neuro-cognitive) community begins to prevalently accept that mere activation of these locations does not allow intact language function. Different language operations are based on the dynamic mutual exchange of information between language relevant locations, and require different view of the neuronal processes involved such as for example, neuronal synchronization (for a review see [Bastiaansen and Hagoort, 2006]). This is particularly true when studying higher cognitive functions such as consciousness, whose emergence probably implies a diversity of brain events, and reentry among diverse brain areas; in this process synchronously active circuits across widely distributed brain areas are selectively favored (Edelman, 2003).

As a corollary, in Chapter 4 I took over from the findings in Chapter 2 and used the MEG approach. Having illustrated the piecemeal transition from lower to higher levels of linguistic processing which straightforwardly translates to an activation cascade with a posterior-to-anterior and bilateral-to-left gradient, we then selected the most prominent transition, which as discussed above, revealed a noticeable disentanglement between the posterior (occipito-temporo-parietal) and the anterior (parieto-frontal) sub-networks. We then sought to expand our scope of investigation by focusing on the access to consciousness underlying this automatic and unconscious transition. To this aim, we used magnetoencephalography and a stair-case paradigm, to pinpoint the boundary between consciousness access (CA) of lower and higher reading processes, namely, between perceptual and conceptual processes. The transition is reflected by localized neural oscillatory effects, which seem to be free of "contamination" by brain activations which are unspecific to CA, namely, report-ability, thereby introducing a possibly alternative solution to the almost impossible endeavor of disentangling report-ability and CA. This enterprise thus introduces an important contribution to the semi-controversial study of the neural correlates of consciousness. Additionally, the neuronal effects seem to mirror prominent regions for the transition towards higher linguistic processing, thereby possibly alleging against the reification of consciousness per se.

The neuronal oscillatory effect for the tested transition consisted in mainly alpha/beta suppression accompanied by milder frontal gamma enhancement. Similarly, Dalal et al. (2009) found that attentive reading enhances gamma, which was detected only using invasive recordings, and suppresses alpha and beta, detected in both the invasive and the non-invasive data. This supports our findings and together with many other reports (see Chapter 4) suggests that alpha and beta suppression may be coupled as a marker of word reading. Furthermore, it alludes to the possibility that gamma may not only mediate response related information, but may also sustain the CA of word reading processing as tested here. However, unless methodological improvements are made, the detection of such gamma response is probably bound to remain undetected by non-invasive recordings. Furthermore, in Chapter 3 we illustrated the differential reliance on specific neuronal pathways for non-lexical versus lexical reading, which was found to remarkably predict reading skill. The neuronal oscillations underlying the transition from lower to higher level of linguistic processing, as illustrated in Chapter 4, could perhaps also predict reading skill. In the future, it would be extremely interesting to converge these two disparate sub-fields, namely, prediction of reading skill and CA of linguistic processing.

Note bene that I consider the above statements (observed effects underlying "accessing processes" rather than consciousness itself) valid only with respect to local brain synchrony during CA of reading processes, that is, the synchronization within a node of a functional network. However, it may be that probing long-range synchrony, that is, the synchronization between different nodes of a network (also called neuronal coherence), may modulate brain activation independently from language processing. This proposition draws support from various lines of research. For instance: (i) conscious perception is related to coordinated dynamical states of the cortical network, rather than to the activation of specific brain regions (Fries et al., 1997, 2002; Engel and Singer, 2001; Thompson and Varela, 2001; Lamme, 2006); (ii) theoretical frameworks postulating that CA is underlain by long-distance synchronized/connected activity (Tononi and Edelman, 1998; Dehaene and Naccache 2001; Edelman, 2003; Dehaene and Changeux, 2005); (iii) the firm proposition that only coherently oscillating neuronal groups can interact effectively (Fries, 2005); and most recently, the report of coherent oscillations as markers for CA (Melloni et al., 2007; Gaillard et al., 2009). Nevertheless, a review of the language literature does not suggest convincingly different findings compared to those from the literature on local synchrony (see [Bastiaansen and Hagoort, 2006] for a review): more precisely, coherence in frequencies higher than 10 Hz seem predominantly to reflect higher level cognitive-linguistic differences related to word type, whereas coherence under 10 Hz tends to reflect non-specific components of word processing such as sensory, attentional, mnemonic and basic semantic parts of the task (see [Weiss and Mueller, 2003] for a review). This could indicate that even long-range oscillations may sub-tend the CA of certain cognitive processes rather than "pure consciousness" by itself. Despite the strong evidence mentioned above, as further discussed in Chapter 4, none of it could guarantee that effects reflected consciousness per se; instead, they seem to be causal to cognitive processes accessing consciousness.

Reflections on the Evolution of the Neural Reading Network

As raised in the general introduction of the thesis, it is of particular interest to understand how a process which has appeared so late in human history has become so much specialized in such a short period of time. After all, 6000 years is an insufficient time period for selective evolutionary pressures to engineer a specialized network for reading. To better comprehend how this happened, I suggest observing our ancestors, the primates, who of course do not read and write, but their vocal and gestural communication is very rich. Gesture in human communication is highly related to verbal language (for a review see [Willems and Hagoort, 2007]), thereby implying that specialization for gesture may have preceded specialization for language (Rizzolatti and Arbib, 1998), in congruence with observations of (a) non-human primates, whose gestural communication is more at ease than facial expressions and vocalizations (Pollick and Waal, 2007); and (b) in human infants, the earlier appearance of gestural communication than speech (Petitto and Marentette, 1991). Moreover, the same neural networks for gesture may have taken on itself the endeavor to accommodate written communication, as late as the latter appeared in human history. This presumption draws support from the recent autoradiographic study (Petrides and Pandya, 2009) showing the existence of the ventral and dorsal pathways in the primate brain with a remarkable similarity to those in the human brain. In the primate brain however, these pathways retrieve information from posterior cortical regions, and translate it into action (e.g. gestural communication). Indeed, gestural communication is subtended by both the non-human and the human primate left-hemisphere in general (Hopkins and Leavens, 1998), and by the ape homologue of Broca's area in particular (Cantalupo and Hopkins, 2001). Considering the tight relationship between language and action in humans (for a review see [Willems and Hagoort, 2007]), the preexisting network subtending action control probably accommodated written language as late as the later appeared in the history of humans.

I suggest that this postulate regarding the accommodation of verbal language function by the already preexisting network for action-control can be further paralleled to the specialization of reading. The infero-temporal cortex is well known for its role in invariant visual object recognition, a function long time existing in the history of living organisms, and largely observed in the animal realm. Thus, it is no coincidence that a parcel of this cortex (LOT) became responsive to letter forms that were extensively learned and practiced. This is of course not the sole fate of reading, but other visual stimuli undergoing extensive practice by the visual system also induce cortical adaptation in specific areas of the perceptual visual system (e.g. Tarr and Gauthier, 2000). This is why the VWFA, lying in the LOT, is not exclusive for linguistic material, but instead to stored visual forms and structures in general (e.g. Joseph and Gathers, 2003). Consequently, it is not surprising that activation in the LOT is positively correlated to increasingly familiar (thus stored) letter combinations (Binder et al., 2006). Furthermore, the ability of the visual system to adapt to letter forms is so efficient and fast that novel alphabets are learned so quickly, that in short time new learners attain the same proficiency in letter identification as fluent readers (Pelli et al., 2006). In terms of plasticity, the network is malleated for adaptation to reading in the early years of school, when the brain is still plastic (Parviainen et al., 2006); however, late reading practice (university) improves skill but does not re-shape or alter the network (see Chapter 3). To summarize, reading was not preprogrammed long time ago in the evolution of the species. Instead, reading instruction and practice trigger an anatomical-functional specialization of the preexisting pathway for visual object recognition.

Another line of evidence supporting specialization along the visual object recognition system comes from studies on how letters are visually recognized. Just as recognizing words is so much dependent on the recognition of letter sequences (for a review see [Jordan, 1990]), increasing evidence points out that letter features are highly diagnostic for letter recognition (Grainger et al., 2008). Recent findings suggest that the identification of a letter is mediated by the detection of circa seven visual features. The efficiency of letter recognition is inversely proportional to perimetric complexity (perimeter squared over "ink" area), that is its number of visual features, and nearly independent of everything else. To be more specific, it is independent of age and years of reading, of presentation duration, overall contrast, and eccentricity, and only weakly dependent on size, suggesting that letters are identified by a similar computation across this wide range of viewing conditions (Pelli et al., 2006). Most recently, the psychophysical work of Fiset and colleagues further revealed that only about a quarter of the printed area of letters, mainly letter terminations, is used for the visual recognition of letters (Fiset et al., 2008). Altogether, recognition of letters via its features further favors the idea that learned and practiced visual patterns are stored in memory to be subsequently recognized during reading.

Finally, reading does not only rely on the “lower” level processes, i.e. the visual recognition of letters and its sub-features, but also on “higher” processes, such as for instance, the attribution of sounds to letters. This process, labeled phonology, except from facilitating the storage of language representation in memory, is extremely useful as it allows us to translate reading into the vocalized form of human communication, speech. This goes far back in the history as our ancestors were probably speaking a million years ago, but with a slower delivery, a smaller vocabulary and above all, a simpler grammar than we are accustomed to today. Likewise, such mental representations of letter and sound assemblies have a certain meaning, which is also stored in memory. This ability to formulate a notion and to store it in memory is intrinsic to the human brain, and dates far back in human history. It therefore appears that just like the visual system can accommodate the novel cultural invention of reading as a result of adaptation to the tasks to which we put it to, the networks underlying sound and meaning also derived from preexisting networks with more general attributes. Understanding how such higher linguistic processes endured progressive specialization is a subject for future work.

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Summary

While you are now reading this text, you are unaware of a complex series of extremely rapid processes which is taking place: Within less than 250 ms of viewing a written word, the visual system extracts the information needed to identify its linguistic significance, and this, despite wide variations in print, script, font, size and retinal position. This complex endeavor is orchestrated by a network of specialized brain regions constantly communicating and trafficking information to and from each other, by discharging electrical pulses at various frequencies. On the surface, since those processes are highly automated, they operate underneath our level of consciousness. The aim of the present dissertation is to shed light on the complex brain dynamics underlying those unconscious processes, and thereby better comprehending the automated and efficient mechanism that we know as reading. To this aim, we used a variety of measurement-tools including fMRI, magnetoencelography, neuronal connectivity and behavioral measures.

Chapter 1 of the thesis provides an outlook of the thesis, and introduces the reader to some important information regarding automatic brain processes during reading. In Chapter 2, we illustrate the cerebral distribution and information trafficking of these processes. Over the past two decades there has been an extensive number of neuroimaging studies interested in unraveling the brain organization that sustains reading (reviewed by: Price, 2000; Jobard et al., 2003; Demonet et al., 2005; Salmelin, 2007), altogether conveying an image of bilateral posterior activations which are induced by linguistically elementary stimuli, and of more left hemispheric anterior activations induced by stimuli, higher in terms of linguistic processing. Despite this converging unequivocal notion of a gradient of left anteriority for linguistic processing, it is intriguing that a proper investigation was never conducted to empirically prove a notion which is so internalized, even outside of the scientific community. In Chapter 2, we undertook the enterprise of demonstrating the above converging view in a single experiment. This was done by contrasting a large repertoire of eight categories of stimuli ranging from simple orthographic-like characters to words and pseudowords. BOLD ("Blood-Oxygen-Level Dependent") activation patterns and connectivity measurements confirmed our prediction, namely, the existence of a bilateral-to-left and posterior-to-anterior recruitment of reading related areas, straightforwardly resulting from the increase in linguistic processing. This work

demonstrates the spatio-functional recruitment of reading areas and as a corollary, separates lower and higher reading processes.

In Chapter 3, we expanded our scope of study to explore neural pathways during reading; we were originally intrigued to comprehend if and how such 'in cerebro' dynamics predict reading skill. The chapter presents distinct anatomical pathways corresponding to the two routes for the processing of written language. It compares effective connectivity data during reading with out-of-scanner reading tests. Reliance on these neural pathways predicts reading skill. The findings of this Chapter could be summed up as follows: (i) they confirm prior neuropsychological data by providing a remarkably good neural account of the early processing (visuo-orthographic) of the two routes in the dual-route cascade model (Coltheart et al., 2001), (ii) extend the knowledge about the non-lexical route by unraveling that the latter is substantially mediated via the posterior LOT, (iii) demonstrate that incongruent or congruent reliance on these pathways predicts poor or skilled reading. Most importantly, the data (iv) raises the novel idea of efficient 'in cerebro' reading style depending on the stimulus to be read (known word vs. unknown word) and argue that individually unique reading styles may translate to either skilled or deficient reading ability. Finally, the findings reveal that (v) late (university) education, but not gender nor age, predicts reading performance. Nevertheless, these factors could not be explained by cerebral information trafficking, thereby reinforcing our view that late education can improve reading performance, but cannot significantly remodel the cerebral reading network.

In Chapter 4 I took over from the findings in Chapter 2 and attempted to understand how the abovementioned processes access consciousness. Neuroimaging studies have investigated the temporal and spatial dissociation between the different linguistic processes underlying word reading. In parallel, in recent years, there has been a surge of studies probing the neural correlates of consciousness (NCCs). Notwithstanding the progress in this field, it seems, unfortunately, as if the consciousness community has reached an impasse. To bridge between the opposing views, we raise here an alternative approach: to compare between levels of consciousness access, instead of between consciousness and non-consciousness, as done so far. To this end, we investigated the neural mechanisms enabling the leap from partial to full access to consciousness, or more precisely, from lower to higher level of linguistic processing. We used magnetoencephalography and focused on neuronal oscillations because they often correlate with conscious perception. We devised a (stair-case) paradigm while purposely fluctuating masking luminance in the aim of maintaining a constant bottom-up and top-down stimulation for every participant while each viewed masked words.

Linguistic perception was successfully brought to the subtle boundary between partial (letters) and full (words) consciousness access (CA). This transition was mirrored as a left hemispheric occipito-parietal decrease in oscillatory activity in the alpha band (9-13 Hz) and in the beta band (17-20 Hz) starting at 650 ms post stimulus onset, and followed by a pre-response increase in gamma power (65-85 Hz) over left centro-frontal sensors. The results seem to reflect the transition from partial to full linguistic CA, while implications on the study of the NCCs are discussed. This endeavor thus introduces an important contribution to the semi-controversial field of consciousness study, and additionally links it to the domain of language. Finally, in Chapter 5 I outline the main findings described in this thesis, their implication to the domain of reading and consciousness, and reflect on interesting future follow-up studies or applications. As concluding remark, it is interesting to note that, in human evolutionary terms, the findings presented in this thesis allege that reading is not preprogrammed in the human DNA, and that instead, reading instruction and practice trigger an anatomical-functional specialization of the preexisting pathway for visual object recognition.

Nederlandse Samenvatting

Terwijl u deze tekst leest, bent u zich niet bewust van een complexe serie extreem snelle processen die zich in uw hersenen voltrekken. Binnen 250 ms na het lezen van een woord haalt het visuele systeem er de informatie uit die het nodig heeft om de taalkundige betekenis te identificeren. Het doet dit ondanks grote variaties in het lettertype, de grootte van de letters, de afdruk en de positie van het netvlies. Deze complexe onderneming wordt geregisseerd door een netwerk van gespecialiseerde hersengebieden. Deze zijn continue bezig met elkaar te communiceren en informatie uit te wisselen door elektrische signalen met verschillende golflengten uit te zenden. Aan de oppervlakte onttrekken deze processen zich aan ons bewustzijn, aangezien zij in sterke mate geautomatiseerd zijn. Het doel van deze dissertatie is om licht te werpen op de complexe hersendynamiek die aan deze onbewuste processen ten grondslag ligt. Daardoor wordt het mogelijk het automatische en efficiënte mechanisme te begrijpen dat wij kennen als lezen. Met dit doel in ons achterhoofd hebben we verschillende meetmethoden ingezet waaronder fMRI, magnetische encefalografie, neuroconnectiviteit en gedragsmaten. We hebben ons eerst gericht op de belangrijkste automatische verwerkingsstappen die voor het lezen noodzakelijk zijn. Vervolgens hebben we hun spreiding en informatie-routing in de hersenen bekeken. We ontdekten dat hun ruimtelijk-functionele rekrutering een gradiënt volgt bilateraal naar links en van achter naar voren. Ten tweede hebben we onderzocht of deze processen de leesvaardigheid konden voorspellen. De uitkomsten laten specifieke anatomische paden zien, die corresponderen met twee overbekende routes voor het verwerken van geschreven taal. Zoals we ontdekten, kan het gebruik van deze neuronale paden leesvaardigheid voorspellen. Het werk brengt het nieuwe idee van efficiënte “in cerebro' leesstijlen naar voren, afhankelijk van de vingerafdruk van het woord. Een uitkomst die in potentie in de toekomst gebruikt zou kunnen worden voor de vroege identificatie van ontwikkelingsdyslexie. Ten derde hebben we geprobeerd te begrijpen op welke manier deze processen toegang krijgen tot het bewustzijn. Het is ons gelukt de vinger te leggen op de perceptiegrens tussen toegang tot het bewustzijn van hogere en lagere leesprocessen. De resultaten suggereren dat gelokaliseerde neuronale oscillaties het 'opwaarderen' van het bewustzijn naar een hoger linguïstisch verwerkingniveau weerspiegelen. Al met al levert deze onderneming een belangrijke bijdrage aan het domein van het lezen met mogelijke preventieve toepassingen. Bovendien legt het een link met het semi-controversiële onderzoeksgebied van de neurale correlaten van het bewustzijn.

Résumé en Français

Pendant que vous lisez ce texte, vous n'êtes pas au courant d'une série de processus extrêmement rapides ayant lieu: en moins de 250 ms de visualisation d'un mot écrit, le système visuel extrait toute l'information nécessaire pour son identification, tout ce, malgré de grandes variations de script, police, taille et position rétinienne (McCandliss, Cohen et Dehaene, 2003). Ceci est orchestré par un réseau de régions cérébrales spécialisées, échangeant des informations par des décharges électriques à des fréquences variables. Superficiellement, ces processus sont tellement automatisés qu'ils opèrent en dessous de notre niveau de conscience. Nonobstant le caractère avantageux d'un tel mécanisme aussi simple, automatisé et efficace, nous profiterions davantage de comprendre les dynamiques neuronales sous-tendant ce mécanisme. L'objectif de la thèse présentée ici est d'éclairer, au moins en partie, ces processus inconscients, pour lever l'ambiguïté de certaines notions débattues, et de proposer de nouvelles perspectives pour de futures recherches.

Au Chapitre 1, nous avons donné un aperçu de la thèse ; nous avons également introduit le lecteur aux principales connaissances actuelles concernant les processus cérébraux automatiques lors de la lecture. Au Chapitre 2, nous avons illustré la distribution et le trafic d'information cérébral de ces processus. Pendant les 2 dernières décennies, il ya eu un nombre important d'études de neuro-imagerie intéressées dans le décryptage de l'organisation cérébral soutenant la lecture (revues par: Price, 2000; Jobard et al., 2003; Démonet et al., 2005; Salmelin, 2007). Ces études proposent que des activations bilatérales et postérieures sont induites par des stimuli linguistiquement élémentaires, et que des activations latéralisées gauche et antérieures sont induites par des stimuli plus élevés, en termes du traitement linguistique qu'ils comportent intrinsèquement. En dépit de cette convergente notion équivoque d'un gradient d'antériorité gauche résultant de l'accroissement en traitement linguistique, il est curieux qu'une recherche appropriée n'a jamais été menée pour empiriquement démontrer une notion qui est si intériorisée, même en dehors de la communauté scientifique. Au Chapitre 2, nous avons entrepris l'initiative de démontrer cette convergente notion en une seule expérimentation. Cela a été fait en opposant un large répertoire de huit catégories de stimuli allant de simples caractères de nature pseudo-orthographique, tels que les pseudo-lettres, jusque aux stimuli linguistiquement complexes, tels que les mots et les pseudo-mots. Les activations BOLD (pour dénommer « Blood-Oxygen-Level Dependent ») mesurées en IRMf (Imagerie par Résonance

Magnétique fonctionnelle), ainsi que les mesures de connectivité, ont confirmé notre prédiction, à savoir, l'existence d'un recrutement bilatéral-à-gauche et arrière-en-avant des aires impliquées dans la lecture, résultant sans détour de l'accroissement en traitement linguistique. Ce travail démontre le recrutement de type spatio-fonctionnel des aires cérébrales de la lecture, et par corollaire, sépare les processus de lecture inférieurs des supérieurs.

Au Chapitre 3, j'ai agrandi l'étendue de l'étude en dévoilant comment les dynamiques neuronales sous-tendant ces processus automatiques peuvent prédire la performance de lecture. Nous avons étudié les voies anatomiques correspondant aux deux routes traitant le langage écrit, comme proposé par le modèle en cascade à double voie (Coltheart et al., 2001). Le chapitre compare des données de connectivité effective lors de la lecture avec des tests de lecture mesurés en dehors du scanner (IRMf). Les résultats du chapitre peuvent se résumer comme suit: (i) ils confirment les données neuropsychologiques connues jusqu'à présent, en fournissant une explication remarquable du traitement précoce (visuo-orthographique) des deux routes dans le modèle en cascade à double voie ; (ii) ils étendent les connaissances actuelles sur la route non lexicale en révélant que la dernière se fait par l'intermédiaire de la partie postérieure du LOT (pour dénommer le cortex occipito-temporal gauche) ; (iii) ils démontrent qu'un recours de façon non-congruente ou congruente à ces voies, est respectivement prédictif de mauvaises ou de bonnes performances de lecture ; et peut être le plus important, les données (iv) soulèvent l'idée originale d'un style de lecture efficace « in cérébro » en fonction de l'empreinte digitale du mot, et font valoir que, des styles de lecture individuellement uniques se traduisent par une lecture qualifiée ou déficiente ; finalement, les données (v) démontrent que le niveau d'enseignement universitaire, mais non pas le sexe ou l'âge du participant, pourrait expliquer sa compétence en lecture. Toutefois, ces facteurs ne pouvaient expliquer le recours aux voies cérébrales, raffermissant ainsi la conjecture originale qu'un entrainement tardif (enseignement universitaire) peut améliorer les performances de lecture, mais non pas remodeler le réseau neuronal soutenant la lecture chez l'adulte.

Au chapitre 4, j'ai cherché à comprendre comment ces mécanismes automatiques accèdent à la conscience. Dans ce but, nous avons utilisé la magnéto- encéphalographie ainsi qu'un paradigme « stair-case », pour repérer la frontière perceptuelle entre l'accès à la conscience des processus de lecture inférieurs et supérieurs. Comme élaboré aux chapitres précédents, les études de neuroimagerie ont beaucoup enquêté sur la dissociation temporelle et spatiale entre les différents processus linguistiques sous-tendant la lecture. En parallèle, ces dernières années, il y a eu une vague d'études explorant les corrélats neuronaux de la conscience. Malgré le progrès dans ce domaine, il semble, malheureusement qu'il ait mené à un cul-de-sac en raisons des points de vues opposés et infranchissables. Pour atténuer la différence entre les vues opposées, nous proposons ici une approche alternative: faire la comparaison entre deux niveaux d'accès à la conscience, au lieu de celle qui compare un niveau de conscience à un niveau d'absence de conscience, telle qu'elle est pratiquée jusqu'à présent. À cette fin, nous avons étudié les mécanismes neuronaux permettant le saut d'accès d'un niveau de conscience partielle à un niveau de conscience complet, ou plus précisément, d'un traitement linguistique bas à un traitement de plus haut niveau. Les effets neuronaux oscillatoires semblent refléter une telle transition. Cette entreprise se dote ainsi d'une contribution importante à l'étude semi-controversée de la conscience, et en plus la lie au domaine du langage.

Ainsi, au chapitre 5, je présente les principaux résultats décrits dans cette thèse, leur implication dans le domaine de la lecture et la conscience, et pense à des études prospectives qu'il serait intéressant de suivre ou d'appliquer. En inspectant les résultats des chapitres 2 et 3, une image intéressante émerge vis-à-vis du réseau de lecture que nous avons isolé: ceci pourrait être divisé en deux sous-réseaux : le premier, (i) comprenant des zones intermédiaires-postérieurs (occipito-temporo-pariétale) ayant un rôle présumable dans la prédiction de compétence de lecture, conséquemment confirmant les résultats des études préalables, l'ayant testé indirectement ; et le second, (ii) comprenant des zones antérieures (pariéto-frontal), représentant une mesure de corrélation positive et linéaire entre leur degré de recrutement et l'accroissement en traitement linguistique. Comme abordé en détail au Chapitre 2, le deuxième réseau a été jugé d'une importance primordiale pour l'accroissement en traitement linguistique, mais non pas le premier réseau (postérieur). Toutefois, le premier, contrairement au second, s'est révélé être impliqué dans l'analyse visuo-orthographique, et non pas dans les processus supérieurs tels que la phono-lexico-sémantique. Au Chapitre 3, nous avons en outre révélé l'important rôle de ce réseau dans la prédiction de compétence de lecture. De plus, au Chapitre 4, même si nous n'étions pas encore en mesure d'enquêter sur la localisation précise du réseau neuronal qui sous-tend l'accès à la conscience des traitements linguistiques supérieurs, cet effet semble se concentrer principalement au-dessus du cortex pariétal gauche, mais également au-dessus des régions frontales gauches. En supposant une cartographie entre ces données et la fonctionnalité corticale, les résultats mettent en lumière le rôle dominant du sous-réseau pariéto-frontal gauche dans la transition du traitement linguistique de bas en haut. Je soutiens que cette dissociation fonctionnelle entre les réseaux postérieur et antérieur est une constatation intéressante, sortant de nos différentes lignes de travail, et devraient être gardés à l'esprit pour des perspectives à envisager.

Finalement, le travail réfléchit sur l'évolution de la spécialisation du réseau neuronal de lecture. Le cortex inféro-temporal est bien connu pour son rôle dans la reconnaissance visuelle et invariante des objets, une fonction très ancienne dans l'histoire des organismes vivants, et largement observée dans le règne animal. Ainsi, il n'est pas un hasard si une parcelle de ce cortex (LOT) soit devenue sensible à la forme des lettres au cours de l'apprentissage et la pratique de lecture. Cette notion est renforcée par ce travail de thèse, qui a réaffirmé le rôle très important du LOT pour des divers traitements des mots écrits. En plus, cela corrèle bien avec des constatations récentes suggérant que la capacité du système visuel de s'adapter à la forme visuelle des lettres est tellement efficace et rapide, que des nouveaux alphabets sont appris tellement vite : des lecteurs novices atteignent le même niveau de compétence en matière d'identification de lettres que des lecteurs habiles de longue durée (Pelli et al., 2006) ! En termes de plasticité, le réseau neuronal est modelé pour se spécialiser à la lecture pendant les premières années de l'école, quand le cerveau est encore plastique (Parviainen et al., 2006) ; cependant, une pratique tardive de lecture (enseignement universitaire) améliore les compétences de lecture, mais ne remodèle pas le réseau (voir Chapitre 3). Pour résumer, les travaux présentés dans cette thèse, soutiennent l'idée que la lecture n'a pas été préprogrammée dans l'ADN humain, mais l'apprentissage et la pratique de la lecture déclenchent un processus efficace de spécialisation fonctionno-anatomique de la voie, déjà préexistante, et responsable de la reconnaissance visuelle d'objets.

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Publications

Levy J, Pernet C, Treserras S, Boulanouar K, Berry I, Aubry F, Démonet JF and P Celsis (2008) Piecemeal recruitment of left-lateralized brain areas during reading: a spatio-functional account. Neuroimage 43: 581–591.

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Curriculum Vitae

Jonathan Levy was born on July 26th of 1979 in Tel-Hashomer, Israel. In 2000 he began his undergraduate studies at the Université Joseph Fourier (Grenoble, France) majoring in Life Sciences. In 2003, after obtaining his bachelor degree, he moved to complete his Master's degree in Molecular Biology at the Australian National University's Research School of Biological Sciences (Canberra, Australia). His Master's thesis was entitled "Transcriptional profiling of putative circadian genes in the Honeybee (Apis mellifera)" and was obtained under the academic supervision of both Ryszard Maleszka and Yves Markowicz. In 2005, he moved to Toulouse, where he started a Master's degree in Neuropsychology at the Université Paul Sabatier (Toulouse, France) under the co-supervision of Pierre Celsis and Jean-François Démonet. After completing his degree with excellence, he was admitted to a joint PhD project between the Université Paul Sabatier Toulouse1 and Radboud University Nijmegen under the supervision of Jean-François Démonet and Pascal Fries. He started the project in October 2006 in Toulouse, where he focused on fMRI analysis, and in October 2007 he moved to the F.C. Donders Centre where he began his MEG project. The work done during his stay in Toulouse and in Nijmegen is manifested in the formation of this dissertation. Currently, he lives in Nijmegen and works at the Donders Centre for Cognitive Neuroimaging on a post-doctoral position on the oscillatory correlates of linguistic morphological unification, in collaboration with Jean-François Démonet, Peter Hagoort and Pascal Fries.

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