12-17-2012

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MEG Coherence Imaging in Dyslexia: Activation of Working Memory Pathways

by

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Dissertation

Submitted to the Department of Psychology

Eastern Michigan University

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Clinical Psychology

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December 17, 2012

Ypsilanti, Michigan

Abstract

The aims of this dissertation are to 1) review the genetic, neurodevelopmental, structural, and functional brain imaging studies that are the foundations of our understanding of dyslexia and 2) investigate the pattern of activation and functional connectivity of neuronal networks critical in working memory in dyslexics by means of magnetoenchephalographic (MEG) coherence imaging.

Dyslexics showed an early onset of activation in the precentral gyrus and the superior frontal gyrus, which differed from controls where activation was initiated in posterior cortical regions (supramarginal gyrus and superior temporal gyrus). Further, dyslexics showed lower normalized amplitudes of activation in the right superior temporal gyrus and right middle temporal gyrus than controls during a spatial working memory (SWM) task. In contrast, during a verbal working memory (VWM) task, dyslexics showed lower normalized amplitudes in the right insular cortex and right superior temporal gyrus and higher, likely compensatory, activation in the right fusiform gyrus, left parahippocampal gyrus, and left precentral gyrus.

Dyslexics performing a SWM task showed significantly reduced MEG coherence and lower 1) right frontal connectivity, 2) right fronto-temporal connectivity, 3) left and right frontal connectivity, 4) left temporal and right frontal connectivity, and 5) left occipital and right frontal connectivity. MEG coherence by frequency band showed lower mean coherences in dyslexics than in controls at each frequency range and when the bands were combined during the SWM task. In contrast, during the VWM task, dyslexics showed a higher coherence in the low frequency range (1-15 Hz) and lower coherence in the high gamma frequency range (30-45 Hz) than controls.

Logistic regression of the coherence by group membership was significant, with an overall predictive success of 84.4% (88.9% for controls and 77.8% for dyslexics). Coherence between the right lateral orbitofrontal gyrus and right middle orbitofrontal gyrus paired region substantially contributed to group membership. These findings deepen our understanding of the underlying pathophysiology of dyslexia, highlighting the importance of working memory circuits and prefrontal cortical dysregulation in this disorder. These results have far-reaching ramifications not only for prevention and early diagnosis, but also for the development of effective, evidence-based treatments and interventions.

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Introduction

An estimated 5% to 17% of school age children have significant difficulties learning to read despite an average or above average intelligence, adequate educational opportunities, and environmental support (Shaywitz et al., 1998; Vellutino, Fletcher, Snowling, & Scanlon, 2004). Thus defined, developmental dyslexia has far-reaching societal and economic consequences and often results in life-long emotional and psychological distress for the individuals suffering from this disorder and their families. While there is general agreement as to the physiological contribution to the development of dyslexia, there is little consensus as to the precise neurobiological mechanisms and brain circuits that may be involved. The introductory portion of this dissertation, therefore, reviews the psychopathology of dyslexia and the pathophysiological mechanisms that have been proposed. Data on heritability and the candidate genes thought to underlie dyslexia are presented, as well as the structural and functional imaging results to suggest that posterior cortical regions in concert with their frontal lobe connections are described. Several theoretical frameworks are offered to explain the deficits observed with dyslexia, as well as the evidence from diffusion tensor imaging (DTI) and coherence, functional Magnetic Resonance Imaging (fMRI), electroencephalographic (EEG) coherence, and magnetoencephalography (MEG) studies that support these theoretical positions. The introduction concludes with the unique role the frontal cortical pathways and visual working memory play in dyslexia and several hypotheses are offered and tested as part of these dissertation studies.

Psychopathology

Overview and Definition of Dyslexia

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR; American Psychiatric Association, 2000), of the American Psychiatric Association defines dyslexia as a reading disorder characterized by difficulties measured by individually administered standardized tests of reading accuracy or comprehension that are substantially below expectation given the person's chronological age, measured intelligence, and age-appropriate education. The reading disturbance significantly interferes with academic achievement or activities of daily living that require reading skills and, if a sensory deficit is present, the reading difficulties are in excess of those usually associated with it.

Suggested revisions of the diagnostic criteria of dyslexia in the DSM-V include difficulties in accuracy or fluency of reading that is not consistent with the person's chronological age, educational opportunities, or intellectual abilities. Multiple sources of information are to be used to assess reading, one of which must be an individually administered, culturally appropriate, and psychometrically sound standardized measure of reading and reading-related abilities. The disturbance in reading, without accommodations, significantly interferes with academic achievement or activities of daily living that require these reading skills.

While it is challenging to translate such broad, clinical criteria for dyslexia into its specific behavioral, neurobiological, and genetic components, such a deterministic and integrative approach is essential in advancing our understanding of the disorder and in designing effective diagnostic, preventive, and treatment strategies. Reading accuracy,

particularly when children are learning to read, is predominantly a decoding skill. The consensus view is that reading accuracy involves phonological awareness and processing or the ability to blend or parse out sounds (phonemes) and map them onto letters or syllables (graphemes) to form words. Individuals with dyslexia have trouble with such phonemic awareness and fail to translate a spoken word to its written form or perform the reverse function using grapheme to phoneme mapping principles. Reduced reading speed, or reading fluency, while dependent on the ability to phonologically process words, is a distinct construct and relates to the more automatic qualities of reading, involving the rapid recognition of a letter string as a word and accessing lexiconic and orthographic information the reader has previously learned.

Deficits in reading fluency, despite phonetic awareness remediation, are common and particularly problematic in older children, who are increasingly required to read more complex and lengthy texts as they progress with their education. As children with dyslexia enter adolescence and adulthood, they may be able to read words accurately, but their reading will not be fluent or automatic, characteristic of the kind of persistent deficits seen clinically (Lefly & Pennington, 1991).

Reading comprehension builds on the skills of phonological awareness and fluency, as well as incorporating other cognitive functions such as complex attention, visual and auditory working memory, executive function, and linguistic semantic abilities. As a first step in understanding the behavioral and biological processes that underlie reading comprehension, several investigators have examined semantic fluency or the ability to extract the meaning of words. Neural circuits that are distinct from those underlying phonological processing and awareness (Price & Mechelli, 2005), in fact,

mediate semantic fluency. For example, when performing a task such as deciding which two of three words are semantically related (e.g. tiger, circus, jungle), there is a differential functional activation in the left inferior frontal regions, as well as in the posterior temporal-parietal regions, compared to those regions activated during a phonological task such as deciding which two of three words sound the most alike (e.g. skill, hill, fill).

Single or Multiple Subtypes of Dyslexia

Benton (1975), in his landmark review of the literature of dyslexia, identified eight neuropsychological correlates of dyslexia, including deficits in visuo-perceptual and audio-perceptual functions, directional sense, right-left discrimination, finger recognition, and generalized language impairments. This led him to suggest that dyslexia may be due to a more generalized dysregulation of the cerebral hemispheres and that there may be greater heterogeneity of the disorder than had been previously appreciated. Controversy continues about whether all these deficits are central to a specific dyslexic phenotype or, rather, that there are multiple constellations of deficits, representing subtypes of the disorder (Skiba, Landi, Wagner, & Grigorenko, 2011).

As an extension of this idea, Wolf and Bowers (2000) have argued that there are three dyslexia subtypes: a phonological-deficit subtype, fluency or naming subtype, and a double-deficit subtype in which both phonological processing and fluency are affected. Review of the literature, however, does not support this hypothesis, since reading fluency does not appear to be an independent deficit in dyslexia and is concurrently expressed with phonological deficits (Vukovic & Siegel, 2006). More recently, some investigators have suggested that dyslexic subtypes may be defined by the degree to which they are

genetically based and resistant to intervention, with one subtype predominantly of genetic origin and the other having a more environmental etiology (Shaywitz, Lyon, & Shaywitz, 2006). With advanced neuroimaging methods and a richer understanding of the genetic basis of dyslexia, the question of subtypes of the disorder will undoubtedly be re-visited but, thus far, there is no consensus view.

Epidemiology

Developmental dyslexia is the most common form of learning disability, constituting 80% of all learning disorders (Galaburda, LoTurko, Ramus, Fitch, & Rosen, 2006). It affects an estimated 5% to 17% of school age children, with prevalence rates fluctuating depending on the severity criteria used in the assessment of reading (Shaywitz et al., 1998; Vellutino et al., 2004). Even by conservative estimates, this translates to 3.75 to 12.75 million children in the United States alone who have reading disabilities. Despite the prevalence of dyslexia, there is little consensus about the precise etiology, genetics, pathophysiology, and behavioral deficits that underlie this disorder and its differentiation from closely related disorders of language and social communication (Pennington & Bishop, 2009).

Epidemiological studies suggest that developmental dyslexia, while first recognized in childhood, persists into adulthood and has long-lasting social and economic consequences (Maughan et al., 2009; Shaywitz, Fletcher, & Shaywitz, 1995). Early diagnosis and intervention is, therefore, critical in addressing the clinical needs of this population.

In the United States, dyslexia is typically diagnosed when children are 7 to 8 years of age, when reading demands increase and difficulties are clearly measurable by

standardized psychometric instruments. There is broad agreement that dyslexia occurs with all studied Western languages (Johansson, 2006; Ziegler, Perry, Ma-Wyatt, Ladner, & Schulte-Körne, 2003) and shares a similar neurobiological origin (Paulesu et al., 2001; Ziegler, 2006). Males are at greater risk of developing dyslexia, with a 1.5 to 1 ratio to females, though the historical estimates have been as high as 3 to 4 males to females (Rutter et al., 2004). Rates of dyslexia are similar across racial and cultural groups, when socioeconomic and intellectual factors are controlled. There is compelling evidence for the genetic and neurobiological origins of dyslexia; however, environmental factors can modulate risk. In many children, if diagnosed early and intervention is started, dyslexia can be prevented (Alexander & Slinger Constant, 2004; Duff & Clarke, 2011; Gabrieli, 2009; Pennington, 2009; Snowling & Hulme, 2011).

Environmental risk factors. Similar to other developmental disorders that are largely genetically determined, the severity of the disorder is determined by a combination of factors. Clearly, environmental factors, as familial literacy and socioeconomic status, affect the development of dyslexia and the final expression of the disorder (Hayiou-Thomas, 2008; Noble & McCandliss, 2005; Olson, 2002). Family influences reading development by the value that is placed on these activities, the pressure to achieve, availability of reading materials, reading with and to children, and in creating opportunities for verbal interactions (Pennington et al., 2009). Bioecological G x E interactions have been suggested with dyslexia, such that genetic influences are expressed most strongly in enriched environments due to the lesser impact of environmental risk factors, while genetic influences account for less of the phenotypic variance in high-risk environments due to increased environmental variability (Harden,

Turkheimer, & Loehlin, 2007). Consistent with this conceptualization, heritability of dyslexia is higher in families with high parental education than families with low parental education (Friend, DeFries, & Olson, 2008).

Comorbid Disorders

The comorbidities of dyslexia and other psychiatric disorders are alarmingly high, with estimates of more than half of children with dyslexia having an additional psychiatric diagnosis (Carroll, Maughan, Goodman, & Meltzer, 2005; German, Gagliano, & Curatolo, 2010; Hinshaw, 1992; Taurines et al., 2010; Trzesniewski, Moffitt, Caspi, Taylor, & Maughan, 2006; Willcutt et al., 2010b). Individuals with dyslexia show elevated incidence of Attention-Deficit Hyperactivity Disorder (AHDH), oppositional defiant disorder, conduct disorder, anxiety disorder, and mood disorder. While externalizing behaviors and disorders are more strongly related to boys with dyslexia, those that have more internalizing characteristics are more strongly associated to girls with dyslexia (Mugnaini, Lassi, La Malfa, & Albertini, 2009).

Within attention disorders, dyslexia is more strongly associated with the inattentive, rather the hyperactive/impulsive or combined inattention/hyperactivity types of ADHD (Carroll et al., 2005; Katz, Brown, Roth, & Beers, 2011; Willcutt et al., 2010b), with comorbidity rates of 30%-40%. The relationship between ADHD and dyslexia is bi-directional, with each disorder reciprocally affecting the expression of the other. Similarly, a bi-directional relationship between dyslexia and anxiety disorders has been identified, with individuals with dyslexia most likely to express a generalized anxiety disorder or separation anxiety (Carroll et al., 2005).

Pathophysiology

Etiology

  Heritability. Dyslexia has a strong genetic component, occurring in 68% of identical twins and in 50% of individuals who have a parent or sibling with dyslexia (Pennington & Gilger, 1996). Heritability estimates have ranged widely from 29% and 82% (Fisher & DeFries, 2002; Gillis, Gilger, Pennington, & DeFries, 1992; Hawke, Wadsworth, & DeFries, 2006; Hohnen & Stevenson, 1999; Pennington & Gilger, 1996), suggestive that the risk for developing dyslexia is both complex and influenced by genetic and environmental factors.

  Chromosomes. To date, nine regions of the genome (loci DYX1 through DYX9) which comprise DYX1, 15q21; DYX2, 6p21;DYX3, 2p16–p15; DYX4, 6q13–q16; DYX5, 3p12–q12; DYX6, 18p11; DYX7, 11p15; DYX8, 1p34–p36; and DYX9, Xp27 have been identified to be associated with dyslexia (Francks, MacPhie, & Monaco, 2002; Gibson & Gruen, 2008; McGrath, Smith, & Pennington, 2006; Petryshen & Pauls, 2009; Poelmans, Buitelaar, Pauls, & Franke, 2011; Scerri & Schulte-Körne, 2010; Schumacher, Hoffmann, Schmal, Schulte-Körne, & Nothen, 2007; Williams & O'Donovan, 2006). From these molecular genetic studies, it is clear that multiple genes contribute to developmental dyslexia with strong evidence implicating five chromosomal regions: 1p, 2p, 6p, 15q, and 18p, and more modest evidence supporting 6q, 3p, 11p, and Xq.

  Candidate genes. The most intensely studied of the dyslexia gene candidates within these chromosomal regions are DCDC2 (Meng et al., 2005), FOXP2 (Pinel et al., 2012), KIAA0319 (Paracchini et al., 2006; Pinel et al., 2012), DYX1C1 (Wang et al.,

2006; Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012), and ROBO1 (Andrews et al., 2006), which, if their expression is knocked-out or knocked-down using molecular biological methods, results in an interference in neuronal development, migration, and axon path finding (Gabel, Gibson, Gruen, & LoTurco, 2010; Petryshen & Pauls, 2009; Scerri & Schulte-Körne, 2010; Schumacher et al., 2007; Watkins, 2011). Expression of such genetic clusters in individuals with dyslexia are likely to translate into abnormalities in neurogenesis, neuronal migration, cell differentiation, synaptogenesis, cell death, and pruning that will be reflected in neuronal number, size, and shape of cortical and subcortical regions, and the strength and organization of the neuronal circuits that can be visualized with structural and functional brain imaging methodologies (Bishop, 2009; Caylak, 2007, 2009; Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012; Pinel et al., 2012; Ramus, 2006; Fisher & Francks, 2006). Less clear is how these genetically mediated morphological and functional changes associated with dyslexia translate into specific behavioral deficits in phonological processing, fluency, and working memory. A further understanding of the precise genetic, neurobiological, and behavioral links that together underlie dyslexia continues to be imperative in the early and accurate diagnosis and treatment of the disorder.

Although more recent genetic linkage studies have focused on specific features of reading such as word recognition or phonological awareness, it is still not clear whether the genetic loci represent different subtypes of dyslexia or polygenic inheritance. Given the number of genetic loci and candidate genes associated with dyslexia and the diversity of cellular functions they mediate, it is likely that several etiological cascades contribute to dyslexia (Poelmans et al., 2011). Similarly, the genetic basis for dyslexia and its

relation to other psychiatric comorbidities (anxiety disorders and ADHD) remains an area of intensive investigation and likely mediated by multiple common genetic loci (Willcutt et al., 2010a, b) and gene (G) x environment (G X E) interactions (Pennington et al., 2009), particularly around overlapping susceptibility chromosomes 6p, 15q, and 18p.

Theories of Dyslexia

Several theoretical frameworks have been proposed to understand the mechanisms underlying dyslexia (for reviews: Pennington, 2006; Ramus, 2003; Vellutino et al., 2004).

(a) The phonological deficit framework argues that children with dyslexia have core problems with phonological processing which leads to difficulties in reading (Snowling, 2001; Stanovich, 1988; Torgesen & Wagner, 1998; Torgesen, Wagner, & Rashotte, 1994).

(b) The double-deficit framework proposes that developmental dyslexia is due to specific deficits in both phonological awareness and speed of visual naming (Bowers & Wolf, 1993; Wolf, 1991). The second deficit concerns deficiencies in rapidly accessing and retrieving of orthographic information such as letters, numbers, and words (Bowers & Swanson, 1991; Bowers & Wolf, 1993; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001).

(c) The magnocellular deficit framework argues for sensory-perceptual processing problems being central to dyslexia, with impairment in the magnocellular thalamic pathways for vision (Talcott, Hansen, Assoku, & Stein, 2000; Talcott et al., 2000) or audition (Tallal, Miller, & Fitch, 1993; Witton, Stein, Stoodley, Rosner, & Talcott, 2002; Witton et al., 1998). Consistent with this theory, dyslexic individuals have

a decreased sensitivity to low spatial and high temporal frequencies, visual-spatial attention difficulties, and decreased activation of motion areas (Schulte-Körne & Bruder, 2010; Zeffiro & Eden, 2000).

(d) From the perspective of the cerebellar deficit theoretical framework, dyslexia is more generally a procedural learning and memory problem that leads to difficulties in automatic behaviors mediated by the cerebellum (Ben Yehudah & Fiez, 2008; Nicholson & Fawcett, 2005; Nicolson, Fawcett, Brookes, & Needle, 2010; Nicholson, Fawcett, & Dean, 2001; Stoodley & Stein, 2011). Consistent with this conceptualization, individuals with dyslexia have difficulty with performing fast, fluent, over learned skills including reading or novel skills involving the blending of two actions.

(e) The disconnection deficit framework initially espoused by Norman Geschwind (1965) and more recently by others (Catani & ffytche, 2005; Demonet, Taylor, & Chaix, 2004; Epelbaum et al., 2008) argues that dyslexia is primarily a functional deficit that results from white matter (fiber pathway) lesions or impairment of association cortex.

(f) The neurodevelopment framework argues that dyslexia is predominantly genetic, resulting in abnormal neurogenesis, neuronal migration, cell differentiation, synaptogenesis, cell death, and pruning that will be reflected in neuronal number, size and shape of cortical and subcortical regions, and the strength and organization of the neuronal circuits (Ben-Ari, 2008).

These theoretical frameworks are by no means mutually exclusive and capture the range of deficits in phonological and orthographic processing (Habib, 2000; Pugh et al., 2001; Ramus, 2003; Ramus & Szenkovits, 2008; Shaywitz & Shaywitz, 2005; Torgesen

& Wagner, 1998; Torgesen et al., 1994; Willcutt et al., 2010a), spatial and non-spatial working memory (Barnes, Hinkley, Masters, & Boubert, 2007; Kibby, Kroese, Krebbs, Hill, & Hynd, 2009; Vidyasagar, 2005; Wolf et al., 2010), motor sequence learning (Orban, Lungu, & Doyon, 2008), oculomotor skills (Frith & Frith, 1996), visuo-spatial skills (Barton, 2011; Facoetti et al., 2010), and sensory processing (Bailey & Snowling, 2002; Wright & Conlon, 2009), as well as their neurobiological origins. Beyond the sensory and cognitive domains, some individuals with dyslexia are reported to also have difficulty with balance (Laycock & Crewther, 2008) or to have a poor sense of time (Stein, 2001), further reinforcing the view that multiple, dynamic, and interactive neurodevelopmental systems underlie the disorder.

Ramus (2003) and others (Shaywitz & Shaywitz, 2005), however, have argued that deficits in phonological awareness and processing are central to dyslexia, present in all individuals suffering from this disorder. Other areas of dysfunction, such as auditory and visual perception and cerebellar motor control, are only observed in some subjects and not universal. The National Reading Panel (2000) similarly concluded that while individuals with dyslexia may have multiple deficits that contribute to reading difficulties, the underlying core deficit is that of phonological processing and awareness. Secondary consequences may include reduced reading experience that can impede the growth of vocabulary, written expression, and overall knowledge.

Neurobiology of Dyslexia

Post-mortem studies. The earliest studies to suggest that the brains of individuals with dyslexia may be different from non-dyslexics were post-mortem studies. The landmark post-mortem studies by Geschwind and Levitsky (1968) demonstrated a

cerebral asymmetry in the planum temporale, being larger in the left hemisphere in neurotypicals, and hypothesized that this lateralization was due to an organization of language in the left hemisphere of the brain. In individuals without dyslexia, the left temporal-parietal lobe region (planum temporale) is larger in 65% of individuals, while in 11% of individuals the same region in the right hemisphere is larger than the left. Such cerebral asymmetries were subsequently identified in prenatal and newborn brains (Chi, Dooling, & Gilles, 1977; Witelson & Pallie, 1973) and likely the product of neuronal development.

In contrast, individuals with dyslexia fail to exhibit such morphological asymmetry seen in the general population for language. Post-mortem studies in individuals with dyslexia suggest a more symmetric organization of planum temporale on the left and right side of the brain (Galaburda, Sherman, Rosen, Aboitiz & Geschwind, 1985) that may be the result of reduced cell death during fetal development, leading to an excess of cells in the right hemisphere.

In addition to a reduced asymmetry, dyslexic brains had an increased number of neuronal ectopias or cytoarchitectonic anomalies in the left frontal and left temporal cortex that suggested abnormal neuronal development (Galaburda et al., 1985; Galaburda, 1994). These microscopic cortical ectopias are too small to be observed with conventional brain imaging studies, but animal studies suggest they are due to a disruption in neuroblast migration in fetal development (McBride & Kemper, 1982). Further support for aberrant neuronal migration as an etiological factor in dyslexia comes from studies demonstrating that inbred strains of mice with similar neocortical ectopias show impairments in working memory (Denenberg, Hoplight, Sherman, & Mobraaten,

2001; Hyde et al., 2001) and in the processing of rapid auditory stimuli as seen with humans with dyslexia (Frenkel, Sherman, Bashan, Galaburda, & LoTurco, 2000; Peiffer et al., 2001). Experimental interference with the dyslexia candidate genes (e.g. DYX1C1, KIAA0319, DCDC2, and ROBO1) leads to neuronal migration anomalies in the rodent cortex similar to the ectopias seen in human post-mortem studies performed on individuals with a history of dyslexia (Galaburda et al., 2006) as well as behavioral deficits in working memory and rapid auditory processing.

In addition to cerebral differences, post-mortem studies of individuals with dyslexia suggest subcortical anomalies, particularly in the lateral and medial geniculate nuclei of the thalamus, critical visual and auditory relay nuclei, respectively (Galaburda & Livingstone, 1993). The magnocellular cells in these thalamic nuclei are smaller and have an abnormal morphology compared to magnocellular cells found in normal brains. There are also fewer magnocellular cells in the left medial geniculate nucleus than in the right in individuals with dyslexia, which, in part, may underlie the phonemic processing deficits (Galaburda, 1994; Galaburda, Menard & Rosen, 1994).

Structural brain imaging.

Magnetic Resonance Imaging (MRI). MRI studies using voxel-based morphometric analyses have implicated a variety of brain regions and the cerebellum in dyslexia, suggesting there are differences in the volumes of gray and white matter of individuals with dyslexia compared controls (Eckert, 2004; Kronbichler et al., 2008; Leonard et al., 2001; Steinbrink et al., 2008). Confirming previous post-mortem analyses, MRI studies suggest that the planum temporale (perisylvian language area) is smaller in the left hemisphere than the right or that there is greater morphometric symmetry in the

left and right planum temporale in an individual with dyslexia than in controls (Foster, Hynd, Morgan, & Hugdahl, 2002; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Larson, Hoien, Lundberg, & Odegaard, 1990; Leonard et al., 1993; Rumsey et al., 1997). Phonological ability and degree of asymmetry in the planum temporale (Eckert, Lombardino, & Leonard, 2001) and the temporal-parietal region (Habib, Robichon, Lévrier, Khalil, & Salamon, 1995) positively correlate in individuals with dyslexia and non-dyslexics children even when IQ, socioeconomic status, and handedness are controlled, suggesting the degree of asymmetry in the planum temporale may be a general index of phonological ability.

In contrast, individuals with dyslexia who have compensated for their reading disorder show a greater left hemispheric asymmetry, suggestive that remedial strategies may produce structural as well as functional re-organization of these brain regions (Chiarello, Lombardino, Kacinik, Otto, & Leonard, 2006; Leonard & Eckert, 2008). Not all studies have been able to replicate these results, however, and some argue that dysfunction in the planum temporale is more related to primary language deficits rather than dyslexia (e.g. Heiervang et al., 2000; Kushch et al., 1993), as well as differences in age, sex, and overall brain size (Schultz et al., 1994).

A second brain region implicated in reading is the inferior frontal gyrus (IFG), which includes Broca's area. Using quantitative MRI, Brown and colleagues (2001) reported reduced grey matter volumes in the left IFG of dyslexics compared to controls and others have demonstrated an abnormal lateralization in individuals with dyslexia, with a morphologically larger IFG in the right hemisphere that correlated with psuedoword decoding performance (Brown et al., 2001; Eckert et al., 2003, 2005). These

results are consistent with functional imaging and lesion studies and suggest that the

inferior frontal gyrus is not only important in speech but in the phonological processing

associated with reading (Fiez, Tranel, Seager Frerichs, & Damasio 2006; Price et al.,

2003; Vigneau et al., 2006). In a meta-analysis combining 45 functional imaging studies,

activation peaks for tasks considered phonological including reading, rhyming,

discriminating, articulating, and repeating words and nonwords, extended in the frontal

region from the precentral gyrus to the inferior frontal gyrus and in the temporoparietal

region from supramarginal gyrus to the middle temporal gyrus (Vigneau et al., 2006).

Consistent with the IFG's role in phonological decoding, pseudoword reading and writing

is impaired in patients with selective lesions in the left inferior frontal gyrus (Fiez et al.,

2006).

Given the cerebellum's intimate connections to the inferior frontal gyrus, superior

temporal sulcus, and the posterior parietal cortical association areas, it has been an

intense target of investigation for its role in dyslexia and other developmental behavioral

disorders. Cerebellar morphometric symmetry is correlated with the severity of

phonological decoding deficits seen in individuals with dyslexia, with those who had the

greater cerebellar symmetry making more pseudoword decoding errors (Kibby, Fancher,

Markanen, & Hynd, 2008; Rae et al., 2002).

Anatomically, the right anterior lobes of the cerebellum and bilateral pars

triangularis have been reported to be smaller in individuals with dyslexia than in controls

and contribute significantly to the overall reduced brain volumes seen in individuals with

dyslexia (Eckert, 2004; Eckert et al., 2003). In these studies, structural MRI measures of

the right cerebellar anterior lobe and inferior frontal gyrus distinguished children with

dyslexia from controls with a high probability (72%). The frontal and cerebellar measures each contributed to classifying a subset of individuals with dyslexia by differentiating them as a group from controls and by predicted reading skill performance. Considering the high percentage of children with dyslexia in this sample with the double-deficit in rapid automatic naming and phonological awareness, this frontal-cerebellar network may be critical to the precise timing mechanism that Wolf and Bowers (2000) hypothesized to underlie the double-deficit theory.

Inconsistent MRI results have been reported in the size of the corpus callosum, the major fiber system connecting the left and right hemispheres (Paul, 2011). Some investigators have reported a decreased size of the corpus callosum in individuals with dyslexia compared to controls, particularly in the posterior mid-body/isthmus regions that contain inter-hemispheric fibers from primary and secondary auditory cortices (Fine, Semrud-Clikeman, Keith, Stapleton, & Hynd, 2007; Hasan et al., 2012; Robichon, Bouchard, Demonet, & Habib, 2000; von Plessen et al., 2002) and the genu of the corpus callosum that connects the frontal lobes (Hynd et al., 1995), while others have failed to replicate these results (Rumsey et al., 1996). As the mid-body of the corpus callosum contains larger, less densely packed axons than other regions, variations in the midbody of the corpus callosum likely reflect axon size, rather than number, consistent with reduced sensory integration of auditory and visual stimuli and impaired bimanual coordination observed in some individuals with dyslexia (Livingstone, Rosen, Drislane, & Galaburda, 1991; Moore, Brown, Markee, Theberge, & Zvi, 1995).

In contrast, the anterior splenium of the corpus callosum is larger in individuals with dyslexia, suggestive of a greater number of axons and stronger connectivity between

the left and right temporal lobes, which may account for the greater symmetry of activation with phonological processing seen with individuals with dyslexia (Rumsey et al., 1996).

Diffusion Tensor Imaging (DTI). Diffusion Tensor Imaging (DTI), a variant of MRI, provides an in vivo measure of the structural integrity of white matter pathways (anisotropy) and connectivity (coherence). Fractional anisotropy (FA) is a measure of directional diffusion of water molecules within a voxel of space and reflects the structural integrity of a white matter pathway. If water molecules are constrained in white matter fibers by the physical boundaries of the axon sheath, there is greater movement along the long axis of the fiber than across it; FA approaches unity and its numerical value nears 1. Water molecules in CSF, in contrast, that are not directionally constrained, have an FA value that nears 0. FA values increase throughout childhood and adolescence, stabilizing in the second and third decade of life, paralleling the increased myelination observed (Li & Noseworthy, 2002). Another measure that can be computed with DTI is intervoxel (i.e., between voxels) coherence, which is the degree to which diffusion in neighboring voxels has a common orientation (Pfefferbaum et al., 2000). This measure is similar to FA but views coherence on a larger spatial, voxel-to-voxel scale (in contrast with FA's intra-voxel scale).

Association and callosal projections. Using high-resolution DTI and 3D tract reconstruction, Wakana and colleagues identified 17 prominent white matter tracts in the human brain (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). Of the white matter pathways, five well-documented association tracts (intra-hemispheric), including the superior longitudinal fasciculus, inferior longitudinal fasciculus, superior fronto-

occipital fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus were identified (Figure 1). The superior longitudinal fasciculus projects to most lateral regions of the temporal lobe with a characteristic C-shaped trajectory. The inferior longitudinal and inferior fronto-occipital fasciculi share most of the projections at the posterior temporal and occipital lobes, while the uncinate and inferior fronto-occipital fasciculi share the projections at the frontal lobe. The superior fronto-occipital fasciculus is unique in that it is the only association fiber tract that projects medially to the thalamus and along the ventricle, forming a projection between the frontal and parietal lobes.

In contrast to the association fiber tracts, projections in the corpus callosum form the so-called callosal radiation, which connects the corresponding areas in the opposite hemisphere (inter-hemispheric). The projections from the genu of the corpus callosum form the forceps minor; those from the splenium form the forceps major. There are also strong projections from the splenium that sweep inferiorly along the lateral margin of the posterior horn of the lateral ventricle and project into the temporal lobes. In contrast to the association fibers that tend to occupy most lateral regions, the callosal fibers traverse to medial regions.

Association fibers travel along the anterior-posterior axis. Many association fibers (inferior fronto-occipital, uncinate, and superior longitudinal fasciculi) project through the external capsule, while the projection fibers (corticobulbar and thalamic fibers) penetrate the anterior limb of the internal capsule. In more anterior regions, the association fibers merge with the projection and thalamic fibers and further posteriorly with callosal fibers. The inferior fronto-occipital and uncinate fasciculi have prominent

projections to fronto-orbital cortical areas. At all anatomical levels, the inferior fronto-occipital fasciculus occupies the ventral area of the external capsule.

The superior longitudinal fasciculus has a prominent projection into the frontal cortex around the sylvian fissure, while the temporal lobe as a whole is dominated by the inferior longitudinal fasciculus projection. At more caudal levels, the inferior fronto-occipital and inferior longitudinal fasciculi start to merge and that projection and thalamic fibers join to form the retrolenticular part of the internal capsule and the posterior region of the corona radiate. The superior longitudinal fasciculus makes a sharp turn toward the temporal lobe, just lateral to the corona radiata. In the temporal lobe, lateral to the posterior horn of the lateral ventricle, there are three layers of tracts: the superior longitudinal fasciculus is the most lateral, with a superior-inferior orientation; the posterior region of the corona radiata (posterior thalamic radiation, corticobulbar tract, and inferior fronto-occipital and inferior longitudinal fasciculi), with an anterior-posterior orientation is in the middle; and the callosal projection to the temporal lobe is the most medial.

The activation of inferior frontal lobe and the posterior temporal-parietal and occipital-temporal language regions, critical to reading, are likely to involve frontal (uncinate and inferior fronto-occipital fasciculi), frontal-temporal (superior longitudinal fasciculus), temporal-occipital (inferior longitudinal and inferior fronto-occipital fasciculi), and frontal-parietal (superior fronto-occipital fasciculus) pathways, as well as commissural connections (e. g., callosal radiation), which connect the corresponding areas of the left and right hemispheres.

Diffusion Tensor Imaging studies in dyslexia. Several studies suggest that the brains of individuals with dyslexia have reduced FA and coherence bilaterally in the frontal-temporal pathway (superior longitudinal fasciculus) and in the left temporal-parietal white matter pathway (inferior longitudinal fasciculus) compared to controls, which correlated with speed of reading, spelling, and psuedoword decoding (Deutsch et al., 2005; Klingberg et al., 2000; Niogi & McCandliss, 2006; Rimrodt et al., 2009; Steinbrink et al., 2008; Thomason & Thompson, 2011). Concurrent to these intra-hemispheric fiber pathway differences, DTI studies suggest that the fiber orientation in the right superior longitudinal fasciculus differs in individuals with dyslexia, with an increased number of fibers in the superior-inferior orientation (in its temporal-parietal projection) compared to controls, whose fibers are oriented anterior-laterally (Carter et al., 2009). Such differences in fiber orientation in the superior longitudinal fasciculus, for example, may account for the differences in fiber connectivity between the anterior and posterior language areas in individuals with dyslexia and controls. Other investigators have suggested that FA differences that are located near the long suspected perisylvian language network are, in fact, within the callosal pathways between left and right hemispheres (Dougherty et al., 2007) or oriented along the superior to inferior axis within the internal capsule (Beaulieu et al., 2005).

A qualitative and quantitative review by Vandermosten and colleagues (Vandermosten, Boets, Wouters, & Ghesquiere, 2012) of the diffusion tensor imaging literature in dyslexia suggests that lower FA values in the left temporoparietal and frontal areas indicate poor reading ability and that most of these regions contain projections of the left arcuate fasciculus and corona radiata. Comparatively few studies have shown a

role for the posterior part of the corpus callosum or more ventral tracts as the inferior

longitudinal fasciculus to the inferior fronto-occipital fasciculus in differentiating

individuals with dyslexia from controls.

Six months post intense remedial reading instruction (100 hours), children with

dyslexia (8-10 years old) made substantial gains in their reading ability (phonological

decoding) that was associated with an increased FA in the anterior left centrum

semiovale, an area of reduced white matter connectivity, compared to non-dyslexics prior

to the intervention (Keller & Just, 2009). This increase in FA and, by inference, in inter-

cortical connectivity was associated with enhanced radial diffusivity, suggestive of an

increased axonal myelination due to the reading intervention.

Functional brain imaging. Functional imaging studies using diverse measures of

activation and visualization have been comparatively consistent in showing a differential

pattern of brain activation between individuals with dyslexia and proficient readers. In

non-dyslexic readers, functional activation was generally lateralized to the left

hemisphere, with activity centered in two posterior pathways for visual and orthographic

information (Pugh et al., 2000a, 2000b). The dorsal pathway that includes the angular and

supramarginal gyri of the parietal lobe, middle and superior gyri of the temporal lobe is

critical for cross-sensory integration and phonological processing (Rumsey, 1992;

Shaywitz et al., 1998). The function of the dorsal (temporal-parietal) reading system is to

map letters (graphemes) of a word onto phonemes or phonological bits of information.

This function is important in early phases of learning to read, and, in proficient readers, it

is involved in processing unfamiliar words. In individuals with dyslexia, there is an

underactivation of this dorsal system, which is interpreted as a phonological impairment in mapping graphemes onto phonemes.

The ventral pathway includes the basal occipital-temporal cortex and fusiform gyrus that is important in visual word recognition or orthographic coding (Damasio & Damasio, 1983; Geschwind, 1965). The function of the ventral system is for fast, automatic processing of familiar words or frequently used letter strings (Buchel, Price, & Friston, 1998; Cohen & Dehaene, 2004). The ventral reading system develops later in reading acquisition and has been referred to as the occipital-temporal "skill zone" (Sandak et al., 2004; Shaywitz, Gruen, & Shaywitz, 2007a; Shaywitz et al., 2007b). In individuals with dyslexia, an underactivation of the ventral system is interpreted as impairment in fast, effortless, automatic word or letter recognition.

An anterior region centered in the left inferior frontal gyrus connects to these posterior reading pathways, and functional activation of this region is associated with phonological fluency, word production, and working memory (McCandliss, Cohen, & Dehaene, 2003). Despite intense investigation, the precise role of the inferior frontal region in reading remains unclear. Some investigators have suggested that it plays a more primary role in phonological processing, particularly in the parsing and blending of words or when speech sounds need to be maintained in working memory, such as with in articulatory recoding or rehearsal (Barton, 2009; Hickok & Poeppel, 2004, 2007; Zeffiro & Eden, 2000). Others have suggested that the inferior frontal region, which is part of the fronto-temporal-occipital cortical and cerebellar system, is vital in reading fluency and automatic reading (Eckart et al., 2003; Nicolson & Fawcett, 2005). Price and Mechelli (2005) further postulate that activation of the anterior left inferior frontal region (pars

orbitalis and pars triangularis) is vital for semantic fluency, while phonological processing is mediated by the more dorsal and posterior left inferior frontal regions that include the pars opercularis and premotor cortex.

Functional Magnetic Resonance Imaging (fMRI). Overall, functional imaging studies have shown hypoactivation and a reduced lateralized activation in the left posterior temporal-parietal regions that comprises the dorsal system (middle and superior temporal gyri, inferior and superior parietal lobule, supramarginal gyrus), which is related to decreased phonological awareness and processing. The left occipital-temporal regions that comprise the ventral system (inferior temporal gyrus, fusiform gyrus, ventral occipital) have been associated with word recognition (Corina et al., 2001; Hoeft et al., 2007; McCandliss & Noble, 2003; Richlan, 2012; Shaywitz et al., 2004; Shaywitz et al., 1998; Temple, 2002).

Unlike in proficient readers, selective brain regions and networks fail to activate in individuals with dyslexia when performing phonological processing and word recognition tasks necessary for reading. For example, in individuals with dyslexia, the *right* inferior temporal-occipital region that is critical for cross-modal auditory and visual processing becomes more necessary and activated for rapid word recognition, as well as the rostral brain regions around the inferior frontal gyrus (Hoeft et al., 2011; Pugh et al., 2001; Shaywitz et al., 2002). Such greater lateralization to the right temporal cortex, increased activation in anterior frontal region, and the differential activation in the posterior (temporal-occipital) regions have led some investigators to postulate that these differences in brain activation may be compensatory, less efficient means to phonological processing and word decoding in individuals with dyslexia (Milne, Syngeniotis, Jackson,

& Corballis, 2002; Pugh et al., 2000a). For example, the overactivation in the left inferior frontal in individuals with dyslexia performing a word-reading task likely reflects covert articulation and an increased engagement of brain systems underlying attention during reading (Hoeft et al., 2011; Pugh et al., 2001; Shaywitz et al., 2002).

Similar inefficiencies or more widespread fMRI activation have been reported in the cerebellum of children with dyslexia when performing a noun-verb semantic association task compared to controls, whose cerebellar activation was bilateral, but well-defined and focused (Baillieux et al., 2009).

Not all studies, however, have reported a hyperactivation in the left inferior frontal cortex of individuals with dyslexia compared controls when performing a phonological reading task (Eden et al., 2004; Rumsey et al., 1994). Some studies have reported a hypoactivation in the left inferior frontal regions or hyperactivation in the right inferior frontal region, relative to controls (Georgiewa et al., 1999; Paulesu et al., 1996; Shaywitz et al., 2002). The differences in the functional activation observed in the inferior frontal regions might be due to differences in the research paradigms (e.g., duration and frequency of word presentation) and the degree to which the subjects engaged attention, working memory, premotor, and executive circuits. Subject selection is also a factor, with participants varying in severity of reading problems, reading proficiency, extent of compensation, and developmental age. Inconsistent functional activation in the cerebellum of individuals with dyslexia compared to controls has been observed (Nicolson et al., 2001).

To reconcile these differences in functional activation in the inferior frontal region and cerebellum, meta-analyses of the literature were performed (Maisog,

Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan, Kronbicher, & Wimmer, 2009).

A meta-analysis of 9 studies suggests that individuals with dyslexia concurrently

demonstrate a left hemispheric hypoactivation (precuneus, inferior parietal cortex,

superior temporal gyrus, thalamus, and inferior frontal gyrus) and right thalamus and

anterior insula hyperactivation compared to controls performing a phonological

processing task (Maisog et al., 2008). This meta-analysis did not support a left inferior

frontal differential activation in individuals with dyslexia or cerebellar dysfunction,

suggesting that functional activation in the inferior frontal region and cerebellum are

more varied in terms of their reproducibility and/or anatomical localization. Richlan and

colleagues (2009) performed a similar meta-analysis on 17 studies a year later and

reported underactivation maps that included clusters in the left dorsal inferior parietal to

the ventral occipital regions, left temporal and left inferior parietal. Overactivation maps

included right hemispheric regions—the medial frontal cortex, middle temporal gyrus,

and caudate—as well as left hemispheric regions in the anterior insula, primary motor

cortex, inferior frontal cortex, lingual gyrus, caudate, and thalamus (Richlan et al., 2009).

Dysfunctional activation in the cerebellum was similarly not supported in this meta-

analysis.

The differences in functional activation between individuals with dyslexia and

controls are unlikely due to primary sensory differences, since children with this disorder

process basic visuospatial information similarly to controls but rather reflect phonological

processing differences, as increasing phonologic processing demand in dyslexia does not

produce the systematic and associated increase in activity in the posterior dorsal and

ventral pathways in the temporal-parietal and occipital-temporal association cortex that is

seen in controls. Boys and adult males with dyslexia tend to activate the left inferior frontal gyrus more than non-dyslexic males, and females with dyslexia tend to activate right hemispheric areas to a greater extent.

Investigators have tried to differentiate functional brain activation that is specific to dyslexia versus an individual's current reading level, as the two variables are often confounded. Using a combination of structural and function MRI brain imaging and both age- and reading level-matched controls, Hoeft and colleagues (2007) demonstrated that of the regions of atypical activation observed in individuals with dyslexia, only hypoactivation in the left temporal-parietal region and fusiform gyrus was associated with reduced grey matter volume compared to reading level- and age-matched controls. Regions of hyperactivation, as the inferior frontal cortex, these investigators argue, were associated with current reading ability and independent of dyslexia (Hoeft et al., 2007).

As indicated previously, the hyperactivation in dyslexia extends beyond the frontal cortex and includes the caudate and thalamic nuclei, together comprising the fronto-striatal-thalamic system that is essential for working memory (Cropley, Fujita, Innis, & Nathan, 2006). The hyperactivation of the fronto-striatal-thalamic system, then, may reflect a greater recruitment of working memory neuronal resources to support phonological processing, fluency, and word retrieval required in reading (Crosson et al., 2003). Developmental studies suggest that with normal reading development there is a functional shift of activation from fronto-cortical-thalamic systems to temporal-parietal regions more specialized for reading and language (Gaillard, Balsamo, Ibrahim, Sachs, & Xu, 2003).

Similarly, in early development, language and word recognition are mediated bilaterally in the basal temporal gyrus, and in the vast majority of individuals, there is a lateralization or shift to the specialized basal temporal region in the left hemisphere (Booth et al., 2003; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). In contrast with dyslexia, these functional inter- and intra-hemispheric shifts in connectivity to regions of more specialized processing become arrested, resulting in differential, inefficient, and broader neuronal activation.

fMRI and reading remediation. Support for such neuroplastic changes that may underlie dyslexia comes from reading remediation studies. There is a convergence of evidence to suggest that effective reading intervention is associated with enduring increases in activation or a "normalization" in the left temporal-parietal and frontal regions that typically show a reduced or altered activation in dyslexia (Eden et al., 2004; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008; Shaywitz et al., 2003; Shaywitz et al., 2004; Temple et al., 2003). As part of this normalization of brain activity and development of reading skills, there is decreased right hemisphere activation and an increased left hemisphere engagement, which likely reflects a differential processing of letters and words not as visual stimuli, but rather as linguistic and phonological representations. Further, dependence on fronto-striatal-thalamic systems diminishes, suggestive of less reliance on working memory, sensory-perceptual, and motor integration with effective reading remediation.

The nature of the remedial reading intervention is critical, such that intensive, frequent, integrative phonological awareness and processing programs are the most effective in improving the reading of children and facilitating the re-organization of the

neural systems underlying these skills (Lovett, Lacerenza, & Borden, 2000; Shaywitz et al., 2004; Strong, Torgerson, Torgerson, & Hulme, 2011).

fMRI connectivity in dyslexia. Of particular relevance to this proposal is functional connectivity analysis using fMRI (McIntosh, Bookstein, Haxby, & Grady, 1996; McIntosh, Nyberg, Bookstein, & Tulving, 1997) which suggests that while non-dyslexic readers demonstrate connectivity between *left* posterior and *left* anterior frontal regions, individuals with persistent dyslexia demonstrate functional connectivity between *left* posterior regions (temporal-parietal and occipital-temporal) and *right* prefrontal regions associated with visual working memory (MacLeod, Buckner, Miezin, Petersen, & Raichle 1998). In other words, individuals with dyslexia use markedly different functional pathways when performing the same reading-related task as controls and tend to rely more on right hemispheric or bilateral as well as frontal lobe pathways.

Similarly, using exception words/psuedoword paradigm and measuring fMRI connectivity, Horwitz, Rumsey, and Donohue (1998) demonstrated that in non-dyslexics, the left angular gyrus activity in the parietal cortex was strongly correlated with activity in the left posterior superior temporal gyrus, left inferior frontal gyrus, and extrastriate occipital-temporal cortex of the left hemisphere. Activation of the angular gyrus was also correlated with areas in the ipsilateral lingual and fusiform gyri. In individuals with dyslexia, however, there were no significant positive correlations between activation in the angular gyrus and superior temporal gyrus, inferior frontal gyrus, or the lingual and fusiform gyri.

Thus, not only is the pattern of brain regions activated differently in individuals with dyslexia compared to controls, but the neural connectivity or pathways used and

cognitive domains recruited also differ when compared to neurotypically developing controls. In dyslexia, there is a greater dependence on neural networks and functional connectivity in the right hemisphere, as well as frontal cortical and subcortical systems to mediate the phonological processing and orthographic demands of reading as compared to controls.

Positron Emission Tomography (PET) imaging. While PET imaging has not been as broadly used as fMRI in visualizing the brain regions activated in phonological processing, PET studies confirm the differential activation in individuals with dyslexia compared to non-dyslexic controls (Dufor, Serniclaes, Sprenger-Charolles, & Démonet, 2007). PET imaging studies suggest that the left temporal-parietal cortex and the left insula, which extends between the frontal and temporal lobes, fail to be activated in individuals with dyslexia performing a rhyme detection task (Paulesu et al., 1996; Rumsey, 1992; Rumsey et al., 1994, 1997), suggesting a possible functional disconnection between the anterior and posterior language and reading regions. PET has detected diminished functional connections within the left hemisphere between the angular gyrus and parietal and temporal areas that typically mediate the grapheme to phoneme conversion necessary in reading (Horwitz et al., 1998). As seen with fMRI, regions of PET activation in the right frontal cortex are morphologically larger than controls (Dufor et al., 2007). Thus, PET, as well as other brain imaging methods, suggest that the brain activation pattern across brain regions, functional connectivity between brain regions, and the specific pathways activated in individuals with dyslexia differ from controls and likely reflect inefficient, effortful phonological processing, reduced fluency, and diminished automatic reading.

Electroencephalographic (EEG) Studies.

Coherence. When performing a complex cognitive function such as reading, the brain needs to integrate and process information from multiple sources and synchronizes the activity of a widely distributed set of neuronal regions and networks to result in accurate and fluent responses. Such large-scale neuronal synchronization of neuronal activity during cognitive information processing can be studied with electroencephalographic (EEG) and magnetoencephalographic (MEG) techniques and the computation of *coherence* (Weiss & Rappelsberger, 2000). In general, brain regions activated during a cognitive operation show an increased coherence or a neuronal cooperation and synchronization within specific frequency bands (delta: 0-4Hz, theta; 5-8Hz, alpha: 9-13Hz, beta: 14-30Hz, and gamma; 31-100Hz). Strength of coherence, as measured by the correlational probabilities of the in-phase, frequency-dependent synchronous activation, will depend on the nature and difficulty of the task and the neuronal networks and pathways activated (Weiss & Mueller, 2003). Coherence values will range from 0 to 1, where 0 indicates that the frequency component of the corresponding signals are not correlated; 1 indicates that the frequency component of the signals are 100% correlated with constant phase shifts, although they may show differences in amplitude. High coherence between signals is interpreted as high connectivity and synchronization between underlying brain regions within a certain frequency band.

The interpretation of the EEG and MEG coherence results depends on the frequency band investigated, as different components of a cognitive task are processed via different frequencies (Basar, 1998; Klimesch, 1999; Weiss & Rappelsberger, 2000).

During linguistic information processing, for example, several studies point to the different roles of high and low frequency-synchronization (e.g., Weiss and Rappelsberger, 2000). The theta frequency band (around 3–7 Hz; originates as a result of cortico-hippocampal interactions) correlates with language-related mnemonic processes, and theta coherence increases if task demands increase and more efficient working memory is required. The alpha frequency band (8–12 Hz; generated mainly but not exclusively by reverberating propagation of nerve impulses via cortico-thalamic connections) is important for sensory and, in the higher range, is important for semantic processing. The beta (14–30 Hz) and gamma (>30 Hz) coherence frequency bands (both presumably generated inside the cortex) are correlated with more complex linguistic, multi-modal, sub-processes such as syntax or semantics. Despite these broad distinctions, complex and integrative brain functions, such as reading and language, elicits modulation of multiple oscillations in all frequency ranges and is characterized by a superposition and participation of different frequencies (Basar, 1998).

Quantitative EEG studies. Duffy and colleagues (Duffy, Denckla, Bartels, & Sandini, 1980) were among the first to demonstrate statistical differences in the electrophysiological activity in the brains of "pure dyslexics" (those individuals with reading deficits that did not have other co-morbidities) and controls performing a reading task. During reading, the quantitative EEG of individuals with dyslexia suggested a dysregulation in a complex and widely distributed neural systems including the medial frontal cortex, Broca's area (frontal cortex), Wernicke's area (temporal-parietal cortex), and primary and associative visual cortical areas (occipital cortex). More recently, studies have confirmed a dysregulation in multiple neuronal networks subserving phonological

processing, word fluency, and working memory, with a further clarification of the specific EEG frequency bands that may be involved in dyslexia. Compared with controls, children with dyslexia show a delay in their behavioral response, which is associated with a sustained theta EEG peak activity, indicative of greater engagement of working memory circuits (Klimesch et al., 2001). In addition, non-dyslexics typically show a greater theta and beta activation in the left frontal cortical areas specifically during a phonological (psuedoword) task, while the pattern of theta and beta activation in dyslexia is lateralized to right frontal regions in response to orthographic (rapid naming) and phonological tasks. At more posterior regions (basal temporal-occipital), individuals with dyslexia in contrast to controls, show greater activation during both phonological and orthographic tasks, which some investigators have interpreted as a difficulty in phonological transcoding during the verbal and visual working memory phases of word processing (Spironelli, Penolazzi, & Angrilli, 2008). These results point to a deficit in dyslexia in the recruitment of left hemisphere structures for encoding and integrating the phonological components of words, and suggest that the fundamental hierarchy within the linguistic networks may be disrupted, with greater right frontal theta and beta activation and a reduced specialized processing of phonological and orthographic information.

Developmentally, the EEG frequency bands utilized by children with dyslexia differ from the adult patterns (Penolazzi, Spironelli, & Angrilli, 2008). In the study by Penolazzi and colleagues (2008), delta amplitude was computed as an index of cortical inhibition in four different phases of word processing. In anterior sites, controls showed left activation (reduced delta) during the phonological task and bilateral activation in

semantic and orthographic tasks. Conversely, children with dyslexia showed greater overall delta amplitude, indicating a cerebral maturation delay and an altered language laterality pattern. During a phonological task, individuals with dyslexia had larger left anterior delta (inhibition of left frontal linguistic locations) and smaller left posterior delta amplitude: activation of left posterior sites was silent in control subjects (Penolazzi et al., 2008).

EEG coherence. Coherence analysis was first applied to EEG, measuring pairwise correlations of spectral energy in various frequency bands at distinct sensor sites (Srinivasan, Winter, Ding, & Nunez, 2007; Weiss & Mueller, 2003, for reviews), but these recordings were not imaged into the source space and therefore lacked the ability to identify the specific neuronal areas and pathways activated. For example, using a dominant frequency EEG coherence analysis, Dhar and colleagues (Dhar, Been, Minderaa, & Althaus, 2010) demonstrated that there was a reduced and more diffuse inter-hemispheric coherence of alpha activity in the central-parietal cortex of dyslexic male adults, suggesting aberrant functional connections between the two sides of the brain in processing visual-spatial information. Similar reductions in inter-hemispheric coherence were observed with dyslexic children in the parietal-occipital cortex during the performance of a visual sustained attention task (Leisman, 2002). The results may vary with experimental state and frequency band as Marosi and colleagues (1995) reported frequency-dependent EEG coherence differences between proficient readers and individuals with dyslexia, with the children with dyslexia showing lower coherence in the delta, theta, and beta bands but higher coherence in the alpha band during resting state.

Within language related regions, children with dyslexia show an increased slow EEG activity (delta and theta) in the frontal and temporal regions compared to non-dyslexic controls (Arns, Peters, Breteler, & Verhoeven, 2007). There is a symmetric increase in coherence for the lower frequency bands (delta and theta) in frontal and temporal regions and a specific right-temporocentral increase in coherence for the higher frequency bands (alpha and beta). Significant correlations were observed between subtests such as rapid naming of letters, articulation, spelling and phoneme deletion, and the EEG coherence profiles. These results were interpreted as supporting the double-deficit theory of dyslexia, in that there was a symmetric increase in low frequency EEG coherence in both the frontal (fluency) and temporal (phonological awareness) regions in individuals with dyslexia compared to controls. Further, the differences seen between the dyslexia and control groups, particularly in the increased high frequency coherence of the right-temporocentral region, suggest compensatory right hemispheric functional connectivity.

Word perception elicits various patterns of coherence changes within both low and high frequencies of the EEG (Weiss & Mueller, 2003). Lower frequencies (1–10 Hz) tend to reflect non-specific components of word processing such as sensory, attentional, mnemonic and basic semantic parts of the task, whereas higher frequencies (11–31 Hz and possibly higher) reflect specific coherence patterns, which differ depending on the word class/category investigated. However, no specific single higher frequency band seems to be exclusively responsible for "word type differences." In general, there are specific coherence patterns within different frequencies (> 11 Hz), and these patterns differ with word types such as concrete and abstract nouns, high-imagery and low-

imagery verbs, common nouns and proper names, with high coherence associated with the increasingly multimodal features of the specific word types.

Magnetoencephalographic (MEG) studies. The great advantage of MEG imaging (Lounasmaa, Hämäläinen, Hari, & Salmelin, 1996) is that it combines the spatial resolution of hemodynamic and metabolic based functional imaging methods such as PET and fMRI in identifying specific brain areas activated and the temporal resolution and time-locked properties of EEG to more precisely correlate neural activity and the specific cognitive processes associated with reading (Rutten, Ramsey, van Rijen, Noordmans, & van Veelen, 2002; Salmelin & Kujala, 2006). In other words, MEG imaging provides the spatial and temporal resolution to sequence the activation of specific brain areas and networks and tightly links them to concurrent behavioral elements involved in reading.

Early MEG studies demonstrated that the integration of letters and speech sounds activates a network of brain areas including the heteromodal superior temporal sulcus and superior temporal gyrus, extending posteriorly from the Heschl's gyrus into the superior temporal plane (Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin 1999; Raij, Uutela, & Hari, 2000; Salmelin, 2007; Salmelin, Service, Kiesilä, Uutela, & Salonen, 1996; Simos et al., 2000). Initially, speech sounds and letters activate primary auditory and visual processing in cortical and subcortical brain areas. The acoustic-phonetic features of speech modulate activity in non-primary auditory cortex (e.g., superior temporal sulcus, superior temporal gyrus), which occurs 50-100 milliseconds (N100m response) from the onset of stimulus presentation (Obleser, Lahiri, & Eulitz, 2004).

In non-dyslexics, the strength of the N100m response in the left hemispheric superior temporal sulcus and superior temporal gyrus are sensitive to stimulus content, with stronger activation to speech sounds and far weaker to simple non-speech sounds, such as tones. Both left and right superior temporal cortex are involved in processing all sounds, but there is a left hemispheric shift in activity for speech sounds in non-dyslexics after 100 milliseconds, when phonological information is processed. In non-dyslexics, the letter specific activation, then, appears to be the gateway from visual to linguistic (phonological) analysis and a fast route for automatic, fluent reading (Simos et al., 2000).

In contrast, in dyslexic individuals the left superior temporal and parietal activation is weaker, delayed, and less sensitive to the orthographic and phonemic content of the stimulus compared to controls (Helenius et al., 1999; Laine, Salmelin, Helenius, & Marttila, 2000; Simos, Breier, Zouridakis, & Papanicolaou, 1998). Individuals with dyslexia, in contrast, also show a late (approximately 400 millisecond) activation in the left inferior frontal area in response to letters and words that is absent in non-dyslexics, suggestive of recruitment of additional, possibly compensatory, neuronal systems.

Indefrey and Levelt (2004) integrated the results of several functional brain mapping studies and modalities and suggested that there are specific time intervals and subprocesses that take place in reading. Visual object recognition and conceptualization occur at 0-175 milliseconds post stimulus presentation and involve occipital and ventrotemporal regions. First, there is basic visual feature analysis around the occipital midline at approximately 100 milliseconds. In non-dyslexics, about 50 milliseconds later, the activation becomes lateralized to the left occipital-temporal cortex if letters or words are involved (word recognition). The selection of the semantic-syntactic representation

occurs at 175-250 milliseconds and is associated with activation of the left middle and superior temporal gyri. Phonological processing (word decoding) occurs at 250-330 milliseconds and involves the activation of left middle and superior temporal gyri and the parietal cortical regions (supramarginal gyrus, angular gyrus). Oral output or the articulation of a word or speech sound occurs after 330 milliseconds and results in activation of Broca's area in the left inferior frontal gyrus and bilateral sensorimotor areas.

Functional deficits in semantic fluency and written language are associated with the left occipital-temporal activation, which is selectively diminished in individuals with dyslexia for words but not for faces (Tarkiainen, Helenius, & Salmelin, 2003). Similar differences have been observed in word reading versus picture-naming tasks between individuals with dyslexia and non-dyslexics, suggesting the deficits may be more specific for reading (Trauzettel-Klosinski, Dürrwächter, Klosinski, & Braun, 2006). Thus, MEG imaging provides both information regarding the specific brain regions that are activated and the time windows of activity to begin to tease out the neural networks involved at each stage of word or letter processing.

During a word recognition task using MEG imaging, children with dyslexia show an initial activation in the *left* basal temporal regions (fusiform gyrus) followed by activation of the *right* temporal-parietal regions (including the angular, superior temporal and supramarginal gyri). Neurotypical controls, in contrast, show an initial activation in the *left* basal temporal regions followed by activation of the *left* temporal-parietal regions (Simos et al., 2000). These results suggest an anomalous functional connectivity between the left basal temporal and the left temporal-parietal regions in dyslexics during word

recognition. Instead of relying on specialized left hemispheric brain systems for reading as did controls, individual with dyslexia activate homotopic, less efficient regions in the right hemisphere for word recognition.

MEG spatiotemporal brain activation patterns or signatures associated with a psuedoword rhyme-matching task similarly show a reduced or slowed left temporal-parietal (posterior part of superior temporal, angular and supramarginal gyri) activation and increased activity in the homotopic region on the right hemisphere of dyslexic individuals (Papanicolaou et al., 2003). To better assess the phonological basis of this difference in brain activation in individuals with dyslexia, investigators used an auditory discrimination task (Wehner, Ahlfors, & Mody, 2007) and demonstrated that the reduced MEG left hemispheric activation in individuals with dyslexia correlated with the phonological difficulty of the task. Further, the individuals with dyslexia did not benefit from the degree of phonological contrast compared to the control group. Taken together, these results suggest that the phonological and orthographic deficits of dyslexia are due to the aberrant functional connections of the brain areas that mediate reading, as opposed to the dysfunction of a specific brain region.

MEG and reading remediation. Reading remediation studies further demonstrate a dysregulation of neuronal connections with dyslexia, and there is a functional re-organization of neuronal pathways with intervention. Eighty hours of intensive remedial reading instruction over a two-month period improved reading skills and resulted in increased left superior temporal gyrus activation in dyslexics performing a psuedoword reading task (Simos et al., 2002; Simos et al., 2006). Similar benefits of reading remediation have been demonstrated with MEG on a word-reading task, in which they

observed a reduced aberrant right temporal-parietal activation and lateralized activation to the left hemisphere following treatment (Sarkari et al., 2002).

Further, the changes in the temporal characteristics of the MEG activation profiles were striking in dyslexic children following reading intervention, with decreased latency and prolonged engagement of brain areas mediating these processes. Thus, the data from MEG imaging studies suggest that effective reading remediation results in a functional re-organization of connections to more closely resemble the pattern activation seen in the average non-dyslexic reader.

MEG coherence. Coherence analysis of MEG data provides a functional map of the brain areas activated in any millisecond time segment and the correlational probability (certainty) of forming such functional connections. As with EEG, MEG coherence analysis has routinely been applied to the sensor space, analyzing which channels having similar frequency content. MEG coherence imaged in the source space has been applied to the study of motor control (Belardinelli et al., 2007) and recently to the lateralization of temporal lobe epilepsy (Elisevich et al., 2011), but thus far has not been widely applied to other clinical population such as dyslexia, where a better understanding of the functional neuronal networks and the neuroplastic changes that underlie this disorder can be detected. Nagarajan and colleagues (1999) examined evoked MEG coherence responses in the sensor space of the auditory cortex of adults with poor and good reading abilities. Adults with poor reading abilities showed lower average beta and gamma (20–60 Hz) coherence than controls. While this study is important in examining MEG coherence in dyslexia, it is limited in that it was not imaged in source space and, therefore, anatomical networks could not be explored.

In healthy controls, Kujala and colleagues (2007) identified a left-hemisphere neural network sensitive to reading performance using MEG coherence analysis and imaged source space. Regardless of the stimulus rate, communication within the long-range neural network occurred at a frequency of 8–13 Hz (alpha). Using a rapid visual presentation task that simulates reading without the need of performing saccades, coherence-based detection of interconnected nodes reproduced several brain regions previously reported to be active in reading. The face motor cortex and the cerebellum, typically associated with speech production, and the orbitofrontal cortex, linked to visual recognition and working memory, additionally emerged as densely connected components of the network. The left inferior occipitotemporal cortex, involved in early letter-string or word-specific processing, and the cerebellum turned out to be the main forward driving nodes of the network. Interestingly, synchronization within a subset of nodes formed by the left occipitotemporal, the left superior temporal, and orbitofrontal cortex were increased with the subjects' effort to comprehend the text.

Role of Working Memory in Dyslexia

Although there is an abundance of evidence supporting the role of phonological processing and awareness in dyslexia, these constructs are insufficient to account for the range of deficits observed in dyslexia (Bailey & Snowling, 2002; Benton, 1975; Kibby et al., 2009; Nicolson et al., 2010; Talcott et al., 2000; Zeffiro & Eden, 2000). Visual attention and working memory affect reading performance and contribute to the processing of phonological information in such a way that deficits in these cognitive domains translate into poor reading performance (Berninger, Raskind, Richards, Abbott, & Stock, 2008; Eden, VanMeter, Rumsey, & Zeffiro, 1996; Facoetti et al., 2010; Pammer, Hansen, Holliday, & Cornelissen, 2006; Swanson, Howard, & Saez, 2006; Valdois, Bosse, & Tainturier, 2004).

Reading proficiency is not only dependent on phonological awareness and on processing, but it also requires the ability to attend, organize, manipulate, and monitor in verbal and visual working memory multiple sequences of sounds and letters (Baddeley, 2007; Bishop & Snowling, 2004; Conway et al., 2008; Stuss, 2011; Stuss & Alexander, 2007). Lesions in the left frontal operculum produce selective phonological (pseudoword) processing deficits, suggesting that in addition to the posterior language/reading areas, the left frontal region makes a critical contribution to the phonological processing of words in reading (Fiez et al., 2006). Some investigators, in fact, have suggested the use of the term *phonological short-term memory* to emphasize frontal lobe involvement, rather than *phonological awareness*, as a phenotypic marker for dyslexia for gene linkage studies given its prevalence in this population and clinical validity (Newbury, Bishop, & Monaco, 2005).

In addition to a hypoactivation of left hemispheric posterior regions associated with reading and language, some investigators have demonstrated that individuals with dyslexia show a hyperactivation in the prefrontal gyrus, as well as the caudate and thalamic nuclei, together comprising the fronto-striatal-thalamic system that is essential for working memory (Cropley et al., 2006). This hyperactivation of the fronto-striatal-thalamic system may reflect a greater recruitment of working memory resources to support phonological processing, fluency, and word retrieval required in reading (Crosson, 1999; Crosson et al., 2003).

As indicated earlier, with normal reading development there is a functional shift of activation from fronto-cortical-thalamic systems to temporal-parietal region specialized for language processing needed for reading (Gaillard et al., 2003). Despite such a relative shift to temporal-parietal regions mediating reading, the functional connection between the inferior parietal cortex and prefrontal cortex remain critical for reading. Using a transcranial magnetic stimulation to disrupt the temporal-parietal regions mediating reading, Dong and colleagues (2005) demonstrated that reversible disruption of the left inferior parietal lobule and prefrontal cortex resulted in impaired reading. Dong and colleagues suggested (2005) that attentional (working memory) systems in the prefrontal cortex alert the dorsal language/reading system (inferior parietal lobule, angular gyrus, supramarginal) during the presence of word-like stimuli, which results in top-down activation of the prefrontal cortex and a further amplification of attention of the material being read.

Using a verbal working memory paradigm and independent component analysis of fMRI data, investigators have identified functional pathways that are dysregulated with

dyslexia (Wolf et al., 2010). Individuals with dyslexia showed an increased functional connectivity within the "phonological" left prefrontal cortex and inferior parietal region and a decreased functional connectivity between the dorsolateral prefrontal cortex and the posterior parietal regions. The latter is a stream that has consistently been implicated in working memory. The development of functional connectivity between the left and right inferior frontal lobes may, in fact, facilitate treatment response and represent a form of compensatory neuroplastic change in individuals with dyslexia (Farris et al., 2011).

Taken together, the evidence suggests that the spatial and verbal working memory systems are intimately involved in the phonological and orthographic processing that underlies reading and dysregulated in dyslexia.

Dissertation Proposal

Despite advances in structural and functional brain imaging, the precise functional neuronal networks that differentiate dyslexics from neurotypical controls are poorly understood. Several attempts have been made to investigate the functional connectivity in the brains of individuals with dyslexia utilizing fMRI and PET; however, these methods lack the temporal resolution to precisely time lock the behavioral elements associated with reading to the hemodynamic or metabolic events measured by these methods. Further, while DTI provides indices (FA and coherence) of axonal integrity, this imaging technique primarily provides measures of structural rather than functional connectivity.

Reading requires the integration and processing of information from multiple sources and the synchronization of activity from a widely distributed set of brain regions and networks. EEG and MEG coherence methods provide the necessary temporal resolution to investigate the functional and dynamic connectivity that is fundamental to reading. While coherence analysis was first applied to EEG, measuring pairwise correlations of spectral energy in various frequency bands at distinct source sites, these recordings lack the spatial resolution to identify the specific underlying neuronal areas and networks that are activated. MEG coherence imaging, however, provides the only high-resolution temporal and spatial method to simultaneously measure the frequency-dependent, time-locked activity associated with reading and the specific anatomical loci and neural networks comprising these dynamic functional connections.

The following study, therefore, investigates the regional brain activation patterns and functional connectivities that differentiate individuals with dyslexia from controls using MEG coherence imaging during orthographic (e.g., letters of the alphabet) and non-

orthographic (e.g., shapes) visual working memory tasks. The far-reaching goal of this research is to deepen our understanding of the pathophysiology of dyslexia and translate these discoveries into improved prevention, diagnosis, and treatment of individuals suffering from this disorder. The following are the hypotheses and predictions proposed.

Hypotheses and Predictions

(a). It is hypothesized that the MEG activation patterns, as defined by the averaged normalized amplitudes and/or latencies of activation, will differ between individuals with dyslexia and age, gender and IQ matched-controls in a visual working memory paradigm and these results will depend on the stimulus presentation (orthographic versus non-orthographic) and temporal course (early versus late activation). Individuals with dyslexia are likely to activate earlier (0-350ms), particularly in the inferior frontal region and basal temporal lobe, demonstrate more bilateral or right hemisphere activation, and process orthographic and non-orthographic information in a similar manner, indicative of a reliance on less specialized language circuits. Conversely, controls will likely activate later (>350ms), demonstrate lateralized activation in the inferior frontal and temporal-parietal lobe regions dependent on stimulus presentation, with a greater activation of the left hemisphere with orthographic stimuli and the right hemisphere activation with non-orthographic stimuli.

(b). It is hypothesized that the MEG coherence will differ between individuals with dyslexia and matched-controls during the performance of orthographic and non-orthographic visual working memory tasks. The pattern and strength of MEG coherence will depend on the following factors.

i) Frequency band. Lower frequency band (delta, theta and alpha) coherence

tends to reflect sensory, attentional, mnemonic components of word processing, whereas higher frequency band (beta and gamma) coherence typically reflects multimodal, higher order cognitive processing. In contrast to controls, individuals with dyslexia are expected to show greater coherence in these lower frequency (1-15Hz) ranges and reduced coherence in the higher frequency beta and low gamma (15-30Hz and 30-45 Hz) ranges, and this pattern is likely to be dependent on stimulus presentation (orthographic versus non-orthographic).

ii) Neuronal connectivity pathway. As indicated earlier, there are five well-documented association tracts (intra-hemispheric), including the superior longitudinal fasciculus, inferior longitudinal fasciculus, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus as identified in Figure 1. The superior longitudinal fasciculus projects to most lateral regions of the temporal lobe with a characteristic C-shaped trajectory. The inferior longitudinal and inferior fronto-occipital fasciculi share most of the projections at the posterior temporal and occipital lobes, while the uncinate and inferior fronto-occipital fasciculi share the projections at the frontal lobe. The superior fronto-occipital fasciculus is unique in that it is the only association fiber tract that projects medially to the thalamus and along the ventricle, forming a projection between the frontal and parietal lobes. In addition to these intra-hemispheric tracts, there are commissural pathways that provide inter-hemispheric connections to homotopic regions. Individuals with dyslexia are likely to show reduced coherence in left intra-hemispheric frontal-temporal (superior longitudinal and superior fronto-occipital fasciculi) and temporal-parietal (inferior longitudinal fasciculus) pathways compared to controls, as well as posterior commissural pathways in the temporal and parietal lobes. In

contrast, within the restricted frontal association tracts of the uncinate fasciculus or in the right hemisphere, individuals with dyslexia, who have a greater reliance on fronto-cortical working memory and right hemispheric functioning, may demonstrate an increased coherence compared to controls.

iii) Stimulus presentation. In dyslexia, the functional inter- and intra-hemispheric connectivities to regions of more specialized processing for orthographic or phonological stimuli are arrested, resulting in a dysfunctional, inefficient, and broader neuronal activation compared to controls. As a result, individuals with dyslexia process letters and words just like any other visual stimuli, rather than having specific linguistic and phonological significance. In contrast to controls, MEG coherence patterns in individuals with dyslexia are, therefore, unlikely to vary with the orthographic nature of stimulus.

c). It is hypothesized that MEG coherence frequency bands and connectivity of the intra- and inter-hemispheric pathways will vary with external measures of phonological awareness and processing. This hypothesis would be supported if logistic regression of MEG coherence values in a brain region pair(s) predicted group membership (dyslexics versus controls) and/or there was a statistically significant correlation between the MEG coherence values in a brain region pair or pathway and phonological awareness and processing.

Methods

Participants

This study is a secondary analysis of an existing MEG imaging dataset of dyslexics and age-, gender-, and IQ-matched neurotypical controls evaluated in the Neuromagnetism Laboratory at Henry Ford Hospital, Detroit, MI (Bowyer et al., 2010). A group of men and women with dyslexia (N=7, Males=5, Mean Age=24, Mean FSIQ=112) and an age-, gender-, and IQ-matched neurotypical control group (N=9, Males =8, Mean Age= 26, Mean FSIQ=115) were recruited from the Michigan Dyslexia Institute and the surrounding metropolitan Detroit Michigan area. Subjects were excluded if they had a comorbid psychiatric illness or if they were taking or prescribed psychotropic medications within the last three months. The dyslexia group consisted of individuals whose performance on word reading and phonological decoding (Wilkinson & Robertson, 2006, Woodcock, McGrew, & Mather, 2001) was a minimum of one standard deviation below their scores on standard intelligence testing (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999) and/or was in the lower 25th percentile for reading. Eastern Michigan University master's or doctoral students who were blind to the specific hypotheses of the study performed the neuropsychological testing.

Study Design

All participants provided written informed consent prior to entry into the study, and the Institutional Review Boards of Henry Ford Hospital and Eastern Michigan University approved the research protocol prior to initiation of the study and the post-hoc analyses. The participants changed into a hospital gown and removed all metal articles

from their bodies. During MEG imaging, participants were monitored continuously by intercom and video camera. A commercial videotape eraser was used to demagnetize dental work as needed. Three small electrode coils used to locate the subjects' head position with respect to the neuromagnetometer probe were taped to the forehead with two-sided tape. Two additional localization electrodes were taped in front of the subjects' ears on the cheek (just in front of the pre auricular). The subjects then entered a magnetically shielded room to lie comfortably on a bed in the supine position. Each subject's head shape was digitized; the locations of fiducial landmarks and the head position electrode coils with respect to the neuromagnetometer detector coils were registered (Fastrack, 4D Neuroimaging, San Diego, CA, USA). The neuromagnetometer helmet containing the detector array was placed around the subject's head in close proximity to the skull surface, and the subject was asked to avoid excessive eye blinks and body movements during data collection. Data collection runs lasted 10-15 minutes.

Orthographic (verbal) and non-orthographic (spatial) working memory paradigms. Subjects' MEG field responses were measured following the visual presentation of a series of upper case letters (verbal or orthographic stimuli) or squares (spatial, non-orthographic stimuli). Non-orthographic or spatial working memory (SWM) was studied by measuring the subjects' MEG field responses to the visual presentation of a series of white squares presented for 2 seconds every 3 seconds in one of 12 different locations around an imaginary circle (D'Esposito et al., 1998). During each presentation (N=40), the subjects were asked to mentally determine whether each square was in the same position as the square presented two prior images ago (n-2 back task: Gevins & Cutillo, 1993). Subjects were instructed to respond only to displays in which this was the

case by pushing a keypad with their right forefinger. This test consisted of two trials

lasting approximately 7 minutes each. Orthographic or **v**erbal working memory (VWM)

was studied by measuring the subjects' MEG field responses to visual presentations of a

series of upper case letters for 2 seconds presented every 3 seconds (D'Esposito et al.,

1998). During each presentation (N=40), the subjects were asked to mentally determine

whether the letter being presented was the same as the letter presented two images ago

(n-2 back task). Subjects were instructed to respond only to correct targets by pushing a

keypad with their right forefinger. This test consisted of two trials lasting approximately

7 minutes each.

The visual stimuli were generated by a Promax Desktop Projector (Model 5950,

1250 Lumens) onto a large mirror tilted 45 degrees to reflect the image upward to another

mirror also tilted 45 degrees toward a white screen. The test images on the white screen

were viewed from a mirror placed above the subject (the center of the mirror was 14

inches above the face) and tilted 45 degrees to the white screen.

MEG Imaging

The study was performed using a 148-channel neuromagnetometer (4D

Neuroimaging WH2500), a helmet-shaped device covering the entire adult head, except

the face. The individual sensors in the device have SQUID (superconducting quantum

interference device) magnetometers, and all measurements were taken inside a

magnetically shielded room located in the Neuromagnetism Laboratory at Henry Ford

Hospital. During acquisition, the data were band-pass filtered 0.1 to 100 Hz and digitally

sampled and continuously recorded for later analysis. The timing of stimuli was recorded

as pulse codes (representing the type of stimulus) on a trigger channel simultaneously

collected with the MEG data. In post-processing, noise artifacts due to heart and body movement were eliminated using an independent component analysis (ICA) of the data. Next, the location of events on the trigger and response channels were used to select 2-second epochs of MEG data. These activation epochs were signal averaged and forward and backward band-pass filtered 1.0 to 50 Hz. All epochs had a baseline of 500ms before stimuli onset (which is necessary for calculating significance values) and 1500 ms of data after stimulus onset.

     MRI/MEG co-registration. MEG localizations were computed in reference to the Cartesian coordinate system defined by a set of three anatomical landmarks (fiducial points): the right and left external meatus or pre aurical and the nasion. Prior to the MEG scan, the head surface was digitized using a Polhemus (Fasttrack, 4D Neuroimaging, San Diego, CA, USA). The nose and circles around the eyes were also recorded. Head digitization points were used to ensure a precise registration, when the points lay on the scalp surface of the MRI scan. STA/R software (4D Neuroimaging, San Diego CA) was used to co-register the MRI row, column, and slice coordinates to the subject's MEG x, y, z co-ordinate system established during data acquisition. The techniques for co-registration of MEG and MRI are well established in this laboratory (Bowyer et al., 2004) and allow precise correspondence between anatomical structures and MEG areas of cortical activation with errors less than 5mm. If the subject's MRI was not available, we used a standard MRI and rescaled to fit the patient's digitized head shape collected during the MEG scan. The standard head and brain model was constructed from the magnetic resonance imaging (MRI) scan of a normal subject, consisting of 124 ($256{\times}256$) sagittal T1 images, which includes the entire skin surface of the head.

MEG data analyses. Source localization of the MEG data was imaged using the MR-FOCUSS (Moran, Bowyer, & Tepley, 2005) imaging technique in MEG-TOOLS, a MatLab based software program (Moran, 2008). A model of the subject's cortical brain was created for the MR-FOCUSS imaging technique. MRI images for each subject were then segmented, and the cortical continuum represented by a cortical model with x, y, and z oriented dipoles at approximately 4000 cortical sites were approximated. Cortical sensor sites were distributed such that each represented the same volume of cortical gray matter (~1mm^3). For all MEG techniques, forward model calculations for dipoles utilized a spherical volume conductor model fit to the local curvature of the skull at six locations. The six regions (Frontal, Parietal, Occipital in both right and left hemispheres) of the skull were fit separately.

The analyses were performed on the averaged MEG evoked epochs from the point of stimulus presentation to 650 ms after the stimulus onset. Latencies of activation, locations, size of activation regions, and normalized amplitudes were determined for cortical sites activated during the subject's performance of the orthographic and non-orthographic working memory tasks. Based on MNI coordinates, average normalized amplitude per active sources in 54 brain regions was calculated. The left and right hemisphere regions of interest (ROIs) were averaged based on total active sources for that ROI to generate normalized mean amplitudes for the ROI over the activation epochs to compare groups. The amplitude normalization procedure allows us to compare across brains by collapsing 4134 brain sources into 54 anatomical areas of interest (Table 1) defined by MNI/Talairach coordinates.

MR-FOCUSS

Multi Resolution –FOCal Underdetermined System Solver (MR-FOCUSS; Moran et al., 2005) is a current distribution imaging technique that can image simultaneously active regional sources involved in cognitive processing. MR-FOCUSS incorporates the recursive solution approach of FOCUSS as well as control of the L_P norm of the solution (focal imaging properties). Thus, MR-FOCUSS is able to image both focal and extended sources of brain electric activity. Control of focal imaging properties of the solution and noise suppression is accomplished by the use of an innovative multi-resolution model of source activity. For our cognitive processing studies, MR-FOCUSS solutions were created by averaging a set of 20 solutions at each millisecond. This ensures that the brain activity common to all 20 solutions is in the final image for that millisecond. This technique minimizes initialization bias and allows lower amplitude sources to be more readily imaged. This technique produces a time sequence of whole brain images including both focal and extended source structures for the underlying cortical tissue. Regions with significant activation are determined by a method similar to that used by Sekihara, Nagarajan, Poeppel, Marantz, and Miyasshita (2001), where the baseline of MEG-imaged brain activity before the stimulus is presented is used to establish a threshold scale of statistical significance for each brain imaging response post stimulus presentation. Image activations were compared between the orthographic (verbal) and non-orthographic (spatial) working memory paradigms for both the dyslexic and control groups.

Coherence Analysis

For the current coherence analysis, the continuous digitally filtered MEG data (band pass 3–50 Hz) for both the dyslexic and control groups were reloaded into the

MEG Tools software (Moran, 2008). For each of the data segments, signals from neuronal sources were isolated using an ICA spatiotemporal decomposition technique designed to extract signals from distinct compact sources that exhibit burst behavior and minimal temporal overlap with other active sources. These ICA signal components have MEG spatial magnetic field patterns corresponding to one or a few spatially distinct compact sources that are much easier to image accurately using the MR-FOCUSS source imaging technique (Moran et al., 2005). Separate from the imaging algorithm, the cross-spectrum between ICA signals was calculated. In these cross-spectrum calculations, a sequence of FFT spectra was calculated using 0.5 s windows and 25% overlap with FFT amplitudes for 24 frequency bins of 2-Hz width between 1 and 50 Hz. The imaging results and the signal cross-spectrum were used to calculate the coherence between all pairings of active cortical locations within each of the 24 frequency bins. Finally, for each active source, the average coherence across frequencies and sources was calculated. MEG coherence data from the 24 frequency bins were analyzed as 3 separate frequency ranges (1-15Hz, 15-30Hz, and 30-45Hz) approximating the delta/theta/alpha, beta, and gamma bands and combined to provide an estimate of overall coherence (1-45Hz).

In the coherence imaging results, the localization of imaged brain activity is strongly dependent on the frequency bands with greatest power. A detailed coherence calculation is presented below. Intra-hemispheric coherence was determined by calculating the mean coherence values for each individual hemisphere. Similar connectivity estimates for inter-hemispheric, intra-cortical, and cortical-subcortical pathways were determined by calculating mean coherence values between homotopic regions, within a cortical region, and between cortical and subcortical regions,

respectively. The coherence value of each source in a hemisphere or brain area was summed and divided by the number of sources.

Coherence calculation. To calculate coherence, the temporal sequence of source activation, $Q = Q_{ICA}T_{ICA}$, is converted to a temporal sequence of cortical source FFT spectra, Q_{FFT}. This is accomplished by generating FFT spectra for a sequence of short data segments, with 256 time points in each, created by segmenting each ICA time series component of T_{ICA}. This creates the matrix, F_{ICA}, consisting of a sequence of FFT spectra for the ICA time series components in T_{ICA}. The FFT matrix of neuronal sources is, $Q_{FFT} = Q_{ICA}F_{ICA}$. Corresponding to each FFT frequency there is a sub-matrix, f_{ICA}, in F_{ICA}. A row in f_{ICA} corresponds to an ICA component with the column corresponding to the time sequence of complex FFT amplitudes specifying amplitude and phase. For each frequency, the cross-spectral matrix between ICA components is $S_f = f_{ICA}f_{ICA}^{\#}$, where the superscript # is the vector-matrix complex conjugate transpose operator. Finally, for each frequency, the cross-spectral matrix of the brain source activation, $S_{Qf} = Q_{ICA}S_fQ_{ICA}^{T}$, is calculated, where the superscript T is the vector-matrix transpose operator. While this matrix is very large, the auto-spectral components on the diagonal can be efficiently calculated and ranked by amplitude. Most of the 4000 sources in the brain model have insignificant auto-spectral amplitudes. In the MEG coherence imaging technique, 1000 sources with the greatest auto-spectrum amplitude are retained in S_{Qf} to insure all significant network activation contributes to the imaging results. The coherence between all network structures, $C_{Qf} = NS_{Qf}N$, is calculated by applying a normalization transformation, where the normalization matrix, N, has diagonal elements that are the inverse of the square root of the diagonal elements of SQ. Thus, the diagonal elements of

the coherency matrix, C_{Qf}, are equal to 1 and the magnitudes of the complex off-diagonal components quantify the coherence between cortical sites. Next, for each active cortical site, the average coherence with all other sources is calculated for each frequency. Finally, coherence is averaged for all frequencies, 1–45 Hz. As presently implemented in MEG Tools (Moran 2008), coherence for individual frequencies or averaged across frequencies can be visualized as MRI overlays.

Statistical Analysis

Statistical analysis methods used to evaluate the latencies of activation, normalized MEG amplitudes, and coherence data included standard descriptive techniques for continuous variables. To calculate the latencies of MEG activation, pre-determined brain regions were selected based on a manualized region of interest procedure to facilitate analysis of onset of activation and compared using an independent samples *t*-test. An average normalized amplitude per active sources of 54 brain regions (Table 1) was calculated and group differences (dyslexics versus controls) by brain region was determined using an independent samples *t*-test. For both the average normalized amplitude and latency data, statistical significance was set at the *p*<.05 level.

MEG coherence in the cortical sources was calculated for each pair of the 54 brain regions (N = 1431) within the theta/alpha (1-15 Hz), beta (15-30 Hz), and low gamma (30-45 Hz) frequency bands, as well as by combining all three frequency bands within a working memory paradigm to gain an estimate of overall coherence across all frequencies. Coherence values were compared with independent sample *t*-tests using the Benjamini-Hochberg algorithm to control the False Discovery Rate at 0.10 (Benjamini & Hochberg, 1995). The False Discovery Rate (FDR) is the proportion of tests declared

significant that are actually different only due to chance (or the proportion of significant tests that are false positives). The FDR is a widely accepted approach to adjusting for multiple testing in large-scale problems such as the coherence analysis presented here. Such an analysis allows the identification of the anatomical pairs or pathways whose coherence differs between dyslexics and controls that are actually different only due to chance (i.e. false positives).

From each t-test, a z-score was computed according to the method of Efron (2010) to summarize the difference in coherence values between dyslexics and controls in each of the frequency ranges (1-15Hz, 15-30Hz, and 30-45Hz) and their combination (1-45Hz). Positive z-scores indicate higher coherence in the dyslexic group. If the null hypothesis is true and there is no difference in coherence between groups, then z-scores will follow a Normal (0, 1) distribution. If the distribution of z-scores varies from a Normal distribution, the null hypothesis would not be supported.

Logistic regression analysis was used to evaluate how well MEG coherence within specific brain region pairs predicted dyslexic versus control group membership. Statistical significance (Chi-square) was set at the $p < .05$ level. Linear correlational analysis was used to evaluate the relationship between phonological decoding (as measured by Word Attack standard scores of the Woodcock-Johnson III and MEG coherence within specific brain region pairs, with a statistical significance set at the $p < .05$ level.

Results

Mean latencies of brain activation and averaged normalized amplitudes of activation detected by MEG in the evoked data analysis trials were significantly different between groups and across stimuli. MEG coherence also significantly differed between individuals with dyslexia and matched-controls when performing a working memory paradigm and these results depended on the stimulus presentation (orthographic versus non-orthographic).

Latency of MEG Activation

In contrast to controls, individuals with dyslexia activated frontal cortical regions earlier than controls. The frontal cortical region activation depended on the working memory paradigm.

Spatial working memory (SWM)--non-orthographic. Individuals with dyslexia showed an early mean latency of activation when performing the SWM task in the precentral gyrus (mean latency = 167 ms, t (8) = -3.502, p = .008) compared to controls (mean latency = 343 ms; Table 2). In control subjects, MEG activation was initiated in more posterior cortical regions such as the supramarginal gyrus (mean latency =236 ms) and superior temporal gyrus (mean latency = 233 ms) during the performance of a SWM task.

Verbal working memory (VWM)--orthographic. Individuals with dyslexia showed a significantly early activation in the superior frontal gyrus (mean latency = 209 ms, t (12) = -2.021, p = .056) during the verbal working memory (VWM) task when compared to controls (mean latency = 325 ms; Table 2). In contrast, control subjects showed an earlier activation in the posterior cortical regions (supramarginal gyrus mean

activation latency = 227 ms; superior temporal gyrus mean activation latency = 290 ms) prior to engaging fronto-cortical area during the performance of the VMW task.

MEG Normalized Amplitudes of Activation

The pattern and strength of MEG activation differed in individuals with dyslexia and controls, which varied with working memory paradigm and the presentation of orthographic versus non-orthographic stimuli.

Spatial working memory (SWM)--non-orthographic. Of the 54 brain regions examined (Table 1), two regions showed significant differences in MEG activation between dyslexics and controls performing a SWM task. Individuals with dyslexia showed a significantly reduced average normalized amplitude of activation in the right superior temporal gyrus (mean normalized amps = 1.156 nAm, t (13) = 2.847, p = .014) and right middle temporal gyrus (mean normalized amps = 1.022 nAmp, t (13) = 2.653, p = .020) compared to controls (Table 3). In contrast, control subjects showed a greater mean MEG activation in the right superior temporal gyrus (mean normalized amps = 1.528 nAm) and right middle temporal gyrus (mean normalized amps = 1.501 nAm). Figures 2 and 3 compare the MEG normalized amplitudes in the right middle temporal gyrus (Figure 2) and right superior temporal gyrus (Figure 3) in dyslexics and controls.

Verbal working memory (VWM)--orthographic. Within the right hemisphere, individuals with dyslexia showed reduced normalized mean amplitudes in the right insular cortex (mean normalized amps = .569 nAm, t (13) = 2.225, p = .044) and right superior temporal gyrus (mean normalized amps = 1.116 nAm, t (13) = 3.341, p = .005) when performing the VWM compared to controls (Table 3; Figure 4). In contrast to these declines in mean activation, individuals with dyslexia showed an increased mean

activation in the right fusiform gyrus during the VWM task compared to controls (mean

normalized amps = 1.352 nAm, t (13) = -2.660, p = .020). In the left hemisphere,

individuals with dyslexia showed greater mean activation than controls in the left

parahippocampal gyrus (mean normalized amps = .859 nAm, t (13) = -2.181, p = 0.048)

and left precentral gyrus (mean normalized amps = 1.085 nAm, t (13) = -2.448, p =

.029) during a VWM task (Figure 5). Such increases in the right fusiform cortex, left

parahippocampal gyrus, and left precentral gyrus in individuals with dyslexia compared

to controls seen during the VMW task may represent neuroplastic compensatory

changes associated with the disorder.

MEG Coherence

MEG coherence analysis of the cortical sources for each pair of the 54 brain

regions (N = 1431) within the theta/alpha (1-15 Hz), beta (15-30 Hz), and low gamma

(30-45 Hz) frequency bands as well as their combination revealed differences between

individuals with dyslexia compared to controls that depended on the working memory

paradigm and coherence frequency. An example of the MEG gamma coherence imaging

differences during the SWM, for individuals with dyslexia compared to controls, is

displayed in Figure 6.

Spatial working memory (SWM)--non-orthographic. The z-distribution plots

of the MEG coherence differences in dyslexic and controls during SWM are presented in

Figures 7-10, with the corresponding summary statistics provided in Table 4. Individuals

with dyslexia demonstrated lower connectivity when all three frequency ranges were

combined (mean z value = -0.85, t-stat = -27.30, p = 0.000) as well as at the individual

low frequency (mean z value = -0.63, t-stat = -21.32, p = 0.000), beta (mean z value = -

0.09, t-stat = -4.61, p = 0.00), and gamma (mean z value = -0.99, t-stat = -40.39, p = 0.000) frequency bands when performing a spatial working memory task (Table 4; Figure 8-10). While there was statistically lower MEG coherence at all three frequency ranges, the largest differences were seen at the low and gamma frequency bands.

False Discovery Analysis revealed that of the possible 1431 brain region pairs that were analyzed, 69 region pairs or coherence paths differentiated individuals with dyslexia from controls when the frequency ranges were combined (Table 5). Individuals with dyslexia during SWM showed lower 1) right frontal connectivity, 2) right fronto-temporal connectivity, 3) left and right frontal connectivity, 4) left temporal and right frontal connectivity, and 5) left occipital and right frontal connectivity (Table 6). In contrast, differences in short range connectivity (gamma) in posterior brain regions within the parietal and occipital cortices failed to differentiate the dyslexic and control groups.

Of the 69 brain region pairs that differentiated dyslexics from controls in the SWM task, 41 included the right middle orbitofrontal (23) or the right lateral orbitofrontal (18) as one of the brain region pairs. Of the remaining 28 brain region pairs, 11 included other right frontal regions as one of the pairs: right superior gyrus (4), right inferior gyrus (4), right gyrus rectus (2), and right precentral gyrus (1). Taken together, the MEG coherence results suggested an overall reduced coherence in the right frontal cortex in dyslexics performing a SWM task, with a convergence of aberrantly lower connectivity particularly in the right middle orbitofrontal gyrus and the right lateral orbitofrontal gyrus for their intra- and inter-hemispheric connections (Figure 6).

Logistic regression of the coherence values of the 69 brain region pairs by membership group of dyslexics versus controls was significant (Chi square=19.036, p <.000, df=1). Nagelkerke's R^2 of .466 indicated a moderately strong relationship between MEG coherence and the prediction of group membership. Overall, predictive success was 84.4%: 88.9% for controls and 77.8% for dyslexics. Coherence or connectivity in the right lateral orbitofrontal gyrus and right middle orbitofrontal gyrus region pair substantially contributed to group membership (Wald=13.169, p<.000) such that the forward addition of other pathways failed to significantly add to the predictive value of the model.

Further, there was a significant positive linear correlation between the coherence of the right lateral and right middle orbitofrontal gyri and phonological decoding when all three frequency ranges were assessed (r=.600, p<.008, df=17). This was also true when just the gamma coherence (30-45Hz) frequency in this anatomical pathway was correlated with phonological decoding abilities (r=.796, p<.032, df=6).

Verbal working memory (VWM)--orthographic. The z-distribution plots of the MEG coherence differences in dyslexic and controls during VWM are presented in Figures 7-10, with the corresponding summary statistics provided in Table 4. Individuals with dyslexia demonstrated an overall modestly greater MEG coherence when all three coherence frequency ranges were combined (mean z value = 0.10, t-stat = 3.38, p = 0.00) while performing a verbal memory task (Table 4; Figure 7). Analysis of the MEG coherences in individual frequency ranges revealed that individuals with dyslexia showed a higher coherence at the low (mean z value = 0.77, t-stat = 35.71, p = 0.000) and beta (mean z value = 0.08, t-stat = 2.92, p = 0.00) frequency bands but a lower coherence at

the gamma frequency band (mean z value = -0.99, t-stat = -40.39, $p = 0.000$) when performing a verbal working memory task (Table 4; Figure 8-10). While there was statistically higher MEG coherence in both the low and beta frequency ranges, the largest differences were seen at the low frequency band, with only a modestly higher coherence in the beta (15-30Hz) frequency range.

False Discovery Analysis failed to identify which of the 1431 brain region pairs differentiated dyslexics and controls when performing a verbal working memory task when all three frequencies were combined (1-45Hz). This was in part due to the opposing differences in coherence seen in the low (1-15Hz) and gamma (30-45Hz) frequency ranges. When the False Discovery Analysis was applied separately for each of the three frequency ranges, there was insufficient statistical power to reliably identify specific brain region pairs or paths that reliably differentiated dyslexics from controls during VWM.

Discussion

The findings of this study provide the first comprehensive view of the brain regions and functional neural circuits that are differentially active in individuals with dyslexia and controls during the performance of orthographic and non-orthographic visual working memory tasks, significantly advancing our understanding of the pathophysiology of this disorder. Not only did individuals with dyslexia process orthographic information, as letters, differently than controls, but the two groups also differed in their processing of spatial information in the context of working memory, further highlighting the importance of visual working memory in the etiology of this disorder. In fact, MEG coherence in the right middle and right lateral orbitofrontal gyri during the performance of the spatial working memory task was sufficiently robust to predict group membership (dyslexics versus controls) at an overall rate of 84.4% and was positively correlated to phonological ability.

In the present study, MEG neuroimaging during the performance of orthographic and non-orthographic visual working memory task suggests fronto-temporal inefficiencies/impairments in individuals with dyslexia as evidenced by the early onset and reliance on prefrontal cortical areas, the differential activation of fronto-temporal brain systems, and an altered pattern of functional connectivity in the fronto-temporal pathways mediating these behaviors. The following is a discussion of the hypotheses addressed in the study, evidence for fronto-temporal inefficiencies/impairments in dyslexia, and the diagnostic and clinical implications of these findings.

Hypothesis 1: MEG Signatures (Latency and Pattern of Activation) Will Vary Between Dyslexics and Controls

      Latency. In contrast to controls, individuals with dyslexia tended to recruit prefrontal cortical regions earlier over more posterior temporal or parietal cortical gyri as the superior temporal gyrus and the supramarginal gyrus, regardless of whether they were processing orthographic or non-orthographic information. Specifically, individuals with dyslexia showed an early activation in the superior frontal gyrus (209 ms), whereas control subjects showed an earlier activation in the language-related posterior cortical regions (supramarginal gyrus = 227 ms; superior temporal gyrus = 290 ms), prior to engaging superior frontal gyrus (325 ms) during the performance of the verbal working memory task. Similarly, during the spatial working task, individuals with dyslexia showed an early latency of activation in the precentral gyrus (167 ms) compared to controls (343 ms), who initiated in more posterior cortical regions of the supramarginal gyrus (236 ms) and superior temporal gyrus (233 ms) during the SWM task.

      These findings in dyslexics performing verbal and spatial working memory tasks are consistent with a general reduced reliance or dysregulation on temporo-parietal circuits in favor of fronto-cortical pathways or from more specialized regions mediating functions such as language (Corina et al., 2001; Hoeft et al., 2007; McCandliss & Noble, 2003; Richlan, 2012; Shaywitz et al., 2004; Shaywitz et al., 1998; Temple, 2002) and multi-modal attention and phonological awareness, compared to those mediating goal-directed, executive, attentional, monitoring, and manipulative functions. Activation of the left superior temporal and parietal cortex in individuals with dyslexia is typically weaker, delayed, and less sensitive to the orthographic and phonemic content of the stimulus than

controls (Helenius et al., 1999; Laine et al., 2000; Simos et al., 1998) with a suggestive, though inconsistent, compensatory recruitment of the left inferior frontal, right inferior frontal, or bilateral fronto-cortical areas in response to letters and words (Richlan et al., 2009). In the present study, individuals with dyslexia demonstrated a comparatively early activation and reliance on the precentral gyrus and the superior frontal gyrus during the SWM and VWM paradigms, respectively. These fronto-cortical regions are involved in higher levels of working memory processing (monitoring and manipulation) that remain oriented to spatial and verbal input (Boisgueheneuc et al., 2006; Machizawa, Kanai, Rees, & Driver, 2010), and the early activation in these brain areas in individuals with dyslexia suggest a differential processing of orthographic and non-orthographic information, using working memory circuits compared to controls.

MEG activation patterns. The pattern of MEG activation differed in individuals with dyslexia and controls, which varied with the working memory paradigm and the presentation of orthographic versus non-orthographic stimuli. Of 54 brain regions examined in the left and right hemisphere, individuals with dyslexia demonstrated a reduced MEG activation in the right superior and right middle temporal gyri compared to neurotypical controls during the spatial working memory task. Reduced activation in the right superior gyrus may reflect a primary deficit in dyslexia, as the rostral part of the superior temporal gyrus acts as an interface between the dorsal and ventral streams of visual input processing to allow the exploration of both object-related and space-related information (Karnath, 2001), which is likely to be integral in reading.

The activational pattern and differences between individuals with dyslexia and controls are more complex with the presentation of orthographic stimuli (i.e. letters) and

may reflect a combination of primary deficits and compensatory changes. As seen with the spatial working memory task, individuals with dyslexia showed a reduced activation in the right superior temporal gyrus, suggestive of an orthographic-independent processing deficit in the dorsal (space-related) and ventral (object-related) streams. During the orthographic working memory task, individuals also showed a reduction in mean activation in the right insular cortex compared to controls, suggestive of a deficiency in switching between brain networks and stimulus modalities that has been associated with this brain region (Sridharan, Levitin, & Menon, 2008).

In contrast to these declines in mean MEG activation, individuals with dyslexia showed increases in activation in the right fusiform gyrus, left parahippocampal gyrus, and left precentral gyrus during the VWM task, which may represent neuroplastic compensatory changes associated with the disorder. In general, during the VWM task, dyslexics showed a greater reliance on and activation of the right hemisphere, particularly the object-related fusiform gyrus, and left hemispheric non-specialized language-related regions of the parahippocampal and precentral gyri, which are implicated in memory formation and higher level working memory processing, respectively. Concurrent with these presumed compensatory increases in activation were reductions in right hemispheric regions, critical for the integration of object- and space-related processing streams (right superior temporal gyrus) and in switching between brain networks and stimulus modalities (right insular cortex).

Hypothesis 2: MEG Coherence and Functional Connectivity Will Vary Between Dyslexics and Controls

MEG coherence frequency ranges. MEG coherence analysis of the 54 brain region pairs within each of the three frequency bands, as well as their combination, revealed marked differences between individuals with dyslexia and controls that depended on the working memory paradigm and coherence frequency band. During a SWM paradigm, individuals with dyslexia demonstrated an overall lower MEG coherence when all three coherence frequency ranges were combined and when frequency was analyzed separately, with the largest differences seen at the theta/alpha and gamma frequency bands. In contrast, during the VWM paradigm, individuals with dyslexia demonstrated an overall modestly greater MEG coherence when all three coherence frequency ranges were combined. Analysis of the MEG coherences at separate frequency ranges during VWM revealed that individuals with dyslexia showed a higher coherence at the theta/alpha and beta frequency bands but a lower coherence at the gamma frequency band. While there was statistically higher MEG coherence in the two lower frequency ranges, the largest differences were in the low 1-15Hz frequency range. Unlike the coherence results seen during the spatial working memory task that demonstrated a consistent decline in MEG coherence at all the frequency ranges, during the verbal working memory task dyslexics showed an increased MEG coherence at the low frequency range, suggestive of a compensatory change in connectivity, and a concomitant decline at the high frequency range. As low EEG coherence frequencies (e.g., 1–10 Hz) reflect non-language specific components of word processing such as the sensory, attentional, and mnemonic parts of the task and higher gamma frequencies

reflect higher-order orthographic cognitive processing (Weiss & Mueller, 2003), the increased MEG coherence observed here in the low frequency range suggests that in dyslexics there is a shift or greater reliance on attentional fronto-cortical systems from those left parietal-temporal and occipito-temporal higher-order orthographic cognitive processing systems.

Support for this hypothesis comes from an EEG coherence study (Arns et al., 2007) that reported a symmetric increase in coherence for the lower frequency bands (delta and theta) in frontal and left temporal regions and a specific right-temporocentral increase in coherence for the higher frequency bands (alpha and beta). Significant correlations were observed between subtests such as Rapid Naming Letters, Articulation, Spelling and Phoneme Deletion, and the EEG coherence profiles.

MEG connectivity pathways and neuroanatomical tracts. The reduced overall MEG coherence observed in the present study in individuals with dyslexia performing a spatial working memory task reflected a lower 1) right frontal connectivity, 2) right fronto-temporal connectivity, 3) left and right frontal connectivity, 4) left temporal and right frontal connectivity, and 5) left occipital and right frontal connectivity. In contrast, differences in short range connectivity in posterior brain regions within the parietal and occipital cortices failed to differentiate the dyslexic and control groups. Similarly, homotopic commissural connectivity that differentiated individuals with dyslexia from neurotypical controls was limited to fronto-temporal projections (medial orbitofrontal, lateral orbitofrontal, and superior temporal gyrus).

Analysis of the functional pathways that demonstrate a significantly reduced MEG coherence in dyslexics when performing a spatial working memory task suggests a

dysregulation and diminished connectivity in both intra- and inter-hemispheric pathways, with the crossed inter-hemispheric pathways being predominant. Such reduced inter-hemispheric connectivity in individuals with dyslexia is likely related to morphological differences seen in the callosal fibers of dyslexic readers in the mid-body/isthmus regions that contains inter-hemispheric fibers from primary and secondary auditory cortices (Fine et al., 2007; Hasan et al., 2012; Robichon et al, 2000; von Plessen et al., 2002) and the genu of the corpus callosum that connects the frontal lobes (Hynd et al., 1995). As the mid-body of the corpus callosum contains larger, less densely packed axons than other regions, variations likely reflect axon size, rather than number, consistent with reduced sensory integration of auditory and visual stimuli and impaired bimanual coordination observed in some individuals with dyslexia (Livingstone et al., 1991; Moore et al., 1995).

Intra-hemispherically, there is reduced connectivity in local cortical areas, particularly in the right and left frontal cortex, as well as in long bilateral connections that extend from the temporal to frontal cortex and, to a limited extent, from the occipital to frontal cortex. Consistent with these differences in functional connectivity, DTI studies suggest that the brains of individuals with dyslexia have reduced FA and coherence bilaterally in the frontal-temporal pathway (superior longitudinal fasciculus) and in the left temporal-parietal white matter pathway (inferior longitudinal fasciculus) compared to controls, which were correlated with speed of reading, spelling, and pseudoword decoding (Deutsch et al., 2005; Klingberg et al., 2000; Niogi & McCandliss, 2006; Rimrodt et al., 2009; Steinbrink et al., 2008; Thomason & Thompson, 2011). Concurrent to these intra-hemispheric fiber pathway differences, DTI studies suggest that the fiber orientation in the right superior longitudinal fasciculus differs in individuals with

dyslexia, with an increased number in the superior-inferior orientation in its temporal-parietal projection as compared to controls, whose fibers are oriented anterior-laterally (Carter et al., 2009). Such differences in fiber orientation in the superior longitudinal fasciculus, for example, may account for the differences in fiber connectivity between the frontal and temporal cortices.

The intra-hemispheric MEG coherence differences and functional connectivity in the right and left frontal lobe are likely to be mediated short frontal lobe connections in the fronto-orbitopolar tract that connect the posterior orbitofrontal cortex with the anterior polar region and the frontal superior longitudinal fasciculus (Catani et al., 2012). In addition, there is a more complex system of U-shaped fibers in the regions of the central, precentral, perinsular, and fronto-marginal sulcus (Catani et al., 2012).

A qualitative and quantitative review by Vandermosten and colleagues (2012) of the diffusion tensor imaging literature in dyslexia suggest that lower FA values in the left temporoparietal and frontal areas are indicative of poorer reading ability and that most of these regions coincide with the left arcuate fasciculus (superior longitudinal fasciculus) and corona radiata, with comparatively few studies showing a role for the posterior part of the corpus callosum or more ventral tracts as the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus. The conclusions of Vandermosten and colleagues (2012) are entirely consistent with those of the present study and provide a neuroanatomical framework for our intra-hemispheric MEG coherence and functional connectivity results.

Role of the right orbitofrontal cortex and other frontal cortical areas in dyslexia. Of the 69 MEG coherence brain region pairs that differentiated dyslexics from

controls in the SWM task, 41 included the right middle orbitofrontal (23) or the right lateral orbitofrontal (18) as one of the brain region pairs. Of the remaining 28 brain region pairs, 11 included other right frontal regions as one of the pairs: right superior gyrus (4), right inferior gyrus (4), right gyrus rectus (2), and right precentral gyrus (1). Taken together, the results suggested an overall reduced coherence in the right frontal cortex in dyslexics performing a spatial working memory task, with a convergence of evidence suggesting a lower connectivity specifically in the right middle orbitofrontal gyrus and the right lateral orbitofrontal gyrus and their intra-hemispheric local pathways (fronto-orbitopolar, fronto-marginal, frontal longitudinal, and uncinate), long pathways (superior longitudinal fasciculus, inferior fronto-occipital fasciculus), and inter-hemispheric frontal and temporal lobe connections (e.g. anterior and midbody callosal radiations).

Orbitofrontal cortical projections, anatomy, and functions. The orbitofrontal cortex , the part of prefrontal cortex that receives projections from the magnocellular cells of the mediodorsal thalamus, has extensive projections with other association cortices, primary sensory and association cortices, limbic system (insular cortex, parahippocampus, hippocampus, amygdala, hypothalamus), and other subcortical areas (striatum, mesolimbic dopamine reward system), ideally positioning it for the integration of sensory information, monitoring ongoing behavior, and interpretation of the motivational, reward/risk, emotional, and social aspects of a behavior to be able to make an adaptive decision (Stuss, 2011; Stuss & Alexander, 2007). Corticocortical connections include extensive local projections to and from other prefrontal regions, as well as with motor, limbic, and sensory cortices. Areas projecting to motor cortices are densely

interconnected with other prefrontal cortical regions, reflecting integration for executive motor control (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000).

Functionally distinct pathways for auditory processing in the orbitofrontal cortex include a rostral stream associated with phonetic processing and a more caudal stream terminating just posterior to the orbitofrontal cortex in the periarcuate prefrontal cortex associated with auditory-spatial processing. Both ventral and dorsal visual streams share connections with orbitofrontal cortical areas, including rich projections to and from the superior temporal gyrus, important for integration of spatial and object processing (Cavada et al., 2000) and the only region in the present study to demonstrate a reduced amplitude of activation in individuals with dyslexia during both verbal and spatial working memory paradigms. Meta-analysis of functional imaging studies and selective lesions suggests that it's the medial orbitofrontal cortex that is related to the initial evaluation of the affective or motivational significance of stimuli, monitoring, learning, and memory of the reward value of reinforcers, whereas the lateral orbitofrontal is related to the evaluation of punishers, the reappraisal of emotional significance of stimuli, and response suppression, which may lead to a change in ongoing behavior (Stuss & Levine, 2002; Happaney, Zelazo, & Stuss, 2004; Kringelbach & Rolls, 2004).

Hypothesis 3: MEG Coherence in Specific Pathways Will Vary with External Measures of Phonological Awareness and Processing

Diagnostic marker. Of particular clinical importance is the potential use of evoked MEG coherence and connectivity in the right medial and lateral orbitofrontal gyri as a diagnostic marker for dyslexia. Logistic regression of the coherence values by group membership was significant, with an overall predictive success of 84.4% (88.9% for

controls and 77.8% for dyslexics). MEG coherence or connectivity in the right lateral orbitofrontal gyrus and right middle orbitofrontal gyrus region pair substantially contributed to group membership such that the forward addition of other pathways failed to significantly add to the predictive value of the model. Further, there was a significant positive linear correlation between the coherence of the right lateral and right middle orbitofrontal gyri and phonological decoding when all three frequency ranges were assessed and when just the gamma coherence frequency in this functional pathway was correlated with phonological decoding abilities.

Diagnostic Implications

Comorbidity. Dysregulation and a reduced functional connectivity in the right medial and right lateral orbitofrontal gyri and their intra-hemispheric, inter-hemispheric, and subcortical connections likely contribute to the high comorbidity of dyslexia with other psychiatric disorders such as Attention Deficit and Hyperactivity Disorder (ADHD), anxiety disorders, and mood disorders (Carroll et al., 2005; German et al., 2010; Hinshaw, 1992; Taurines et al., 2010; Trzesniewski et al., 2006; Willcutt et al., 2010b) that have been hypothesized to involve the dysregulation of neural reward circuits mediating motivation and impulsivity that include the orbitofrontal cortex (Katz et al., 2011; Kerestes et al., 2012; Toplak, Jain, & Tannock, 2005). In addition to such shared neuroanatomical dysregulation, multiple common genetic loci (Willcutt et al., 2010a, b) and gene (G) x environment (G X E) interactions (Pennington et al., 2009), particularly around susceptibility chromosomes 6p, 15q, and 18p, are common to both dyslexia and ADHD.

Importance of early diagnosis. Randomized control studies have consistently shown that reading instruction needs to be intensive (e.g., 120 minutes per day for 8 weeks), occur in small groups of 1 or 2 students per teacher, and include explicit and systematic instruction in phonological awareness and decoding strategies to be effective in improving reading accuracy and fluency (Alexander & Slinger-Constant, 2004; Keller & Just, 2009; Snowling & Hulme, 2010; Strong et al., 2011). Even with such intensive, evidence-based instruction, there are children who fail to benefit from reading remediation. Typically, the gains achieved from such reading programs are maintained for one to two years in approximately half of the children who return to their school's standard curriculum. Such improvements are much more likely to occur in children who are beginning to read (ages 6 to 8) than in older children and are much more difficult to achieve for reading fluency than for accuracy. Thus, these resource-demanding interventions are effective for many children, but there are still challenges in developing early diagnostic methods, strategies for prevention, and treatments that are effective in a broader range of children and adolescents.

Applications of the current evoked MEG coherence findings in the right orbitofrontal cortex in dyslexia could serve as the basis for an early diagnostic strategy that could be implemented prior to the development of reading. As a prospectively defined demonstration study, children with a familial risk for developing dyslexia would be screened using MEG imaging during the performance of an age-appropriate spatial working memory task. Instead of employing an n-2 back task used in the present study, an n-1 back spatial task could be substituted in the behavioral-imaging screen. In conjunction with MEG imaging, those children that demonstrating a reduced connectivity

in the right orbitofrontal cortex would be predicted to be at a heightened risk of developing dyslexia.

Prevention

Hoeft and colleagues (2007) examined the utility of behavioral (standardized tests) and functional and structural neuroimaging measures taken with children (8-12 years of age) at the beginning of a school year for predicting their decoding ability at the end of that school year. Specific patterns of brain activation during phonological processing and morphology, revealed by voxel-based morphometry (VBM) of gray and white matter densities, predicted later decoding ability. Standardized behavioral measures of reading and language yielded a behavioral model that accounted for 65% of the variance in end of the year performance on a measure of phonological decoding (Woodcock-Johnson Word Attack subtest). Brain imaging measures consisting of both fMRI and DTI yielded a neuroimaging model that accounted for 57% of the end-of-the-year variance in phonological decoding. However, it was the combined model of behavioral and neuroimaging measures that was the most predictive of decoding skills, explaining 81% of the variance. These findings suggest that neuroimaging methods may be useful in enhancing the early identification of children at risk for poor decoding and reading skills.

Similarly, a spatial working memory task in conjunction with MEG imaging of the right orbitofrontal cortex could be used not only to predict children who were at risk of developing dyslexia but also to signal the initiation of a visual working memory intervention to prevent the development of the disorder, targeting children who are vulnerable at the time when treatment is likely to be the most efficacious. Such a strategy

holds the potential of reducing the alarming rates of dyslexia and the years of emotional and psychological distress that is associated with the disorder.

Implication for Treatment and Interventions

Traditional reading remediation or intervention programs for individuals with dyslexia have exclusively focused on phonological awareness and decoding strategies (Alexander & Slinger-Constant, 2004; Keller & Just, 2009; Snowling & Hulme, 2010; Strong et al., 2011). Rarely do these programs address the subprocesses and functions that underlie these behaviors and, more broadly, reading. The present MEG coherence study in dyslexia, as well as numerous others (i.e. Eden et al., 2004; Eden et al., 1996; Galaburda & Livingstone, 1993), has clearly implicated the fundamental importance of spatial working memory in reading. Individuals with dyslexia refractory to remediation or intervention may have fundamental deficits in complex attention and visual working memory, which may not be directly addressed in reading programs. Bacon, Parmentier, and Barr (2012), in fact, recently demonstrated that a consistent visual spatial deficit in adult dyslexics, in performing a Corse block task backwards, could be ameliorated by visual strategy instruction.

Limitations

A number of limitations need to be considered in the interpretation of these results. The study included a comparative small number of subjects: a total of nine neurotypical controls and seven individuals with dyslexia. While the results were sufficiently robust to demonstrate significant statistical differences between individuals with dyslexia and controls, the generalizability of these findings may be limited, as they may not apply to a larger population. The subjects were largely male, and the mean ages

of the dyslexic and control groups were 24 and 26 years of age, respectively. While the participants in the study were matched for age, gender, and IQ, the results may be particularly applicable to an adolescent-adult male population. The subjects in this study had an above-average IQ (Dyslexics=112 FSIQ, Controls=115 FSIQ), which may reflect a bias in the selection process.

To be included in the study, individuals suspected of dyslexia underwent a neuropsychological evaluation were diagnosed with a reading disorder if their performance on a standardized reading measure was in the lower 25th percentile or their performance on a standardized reading measure was at least one standard deviation below their standard IQ score. Both of these entry criteria indicate clinical difficulties with reading and are consistent with the DSM-IV diagnostic criteria of dyslexia but may have added to the variability of the results. The present study is insufficiently powered to identify differences that may exist between such differentially defined subsets of individuals with dyslexia and to determine whether the results reflect primary reading deficiencies or a combination of such deficiencies and levels of compensation.

Neuroimaging studies comparing a clinical population to controls are inherently limited, as they are correlational. The present MEG coherence study is no exception and should not be misinterpreted as implying a causative link between brain activation and connectivity and the etiology of dyslexia. To address this and the other limitations delineated above, future studies will need to be prospectively defined and use a double-dissociative design, such as assigning individuals to the dyslexia or control groups a priori based on their MEG coherence in the right medial and lateral orbitofrontal gyri during a spatial working memory task. If the functional connectivity in the right

orbitofrontal cortex is a determinant of dyslexia, those with MEG coherence within this region would be predicted to have a reading disorder on standardized measures, while those individuals whose MEG coherence within the right orbitofrontal gyri was within normal limits when performing this spatial working memory task would be unlikely to have a reading disorder. The study will also need to be sufficiently powered to dissociate contributing factors (e.g., age, gender, IQ, current reading abilities, etc.) to facilitate the generalizability of the results.

Finally, the present study focused on the lower end (30-45Hz) of the gamma frequency range that extends from 30-100Hz. While the findings may vary at the higher end of the gamma frequency band (above 45Hz), gamma activation is generally most robust at 40Hz during the performance of high-order language tasks (Weiss & Mueller, 2003), with frequencies of 60Hz and higher often introducing recording artifacts.

Conclusion

The results of these studies are consistent with and extend our understanding of the pathophysiological and psychobiological bases of dyslexia. MEG neuroimaging during the performance of orthographic and non-orthographic visual working memory tasks suggests fronto-temporal inefficiencies/impairments in individuals with dyslexia as evidenced by the early onset and reliance on prefrontal cortical areas, the differential activation of fronto-temporal brain systems, and the pattern of functional connectivity of the fronto-temporal pathways mediating these behaviors. MEG coherence analysis in individuals with dyslexia suggested a dysregulation and a lower connectivity in functional circuits of the 1) right frontal, 2) right fronto-temporal, 3) left and right frontal, 4) left temporal and right frontal, and 5) left occipital and right frontal, consistent with deficits in both intra- and inter-hemispheric integration and communication. These functional connectivity findings in dyslexia complement the neuroanatomical findings that report a reduced DTI coherence in the intra-hemispheric (fronto-orbitopolar, superior longitudinal fasciculus, and inferior fronto-occipital fasciculus) and inter-hemispheric (corona radiata, corpus callosal fibers in the genu and mid-body/isthmus regions) tracts. The present studies highlight the importance of visual working memory and the functional connectivity of right orbitofrontal cortex and its frontal and temporal lobe projections in dyslexia, with ramifications for prevention, early diagnosis, and the development of effective, evidence-based treatments and interventions.

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Tables

Table 1

Left and Right Hemispheric Brain Regions Analyzed

Angular gyrus
Caudate
Cingulate gyrus
Cuneus
Fusiform gyrus
Gyrus rectus
Hippocampus
Inferior frontal gyrus
Inferior occipital gyrus
Inferior temporal gyrus
Insular cortex
Lateral orbitofrontal gyrus
Lingual gyrus
Middle frontal gyrus
Middle occipital gyrus
Middle orbitofrontal gyrus
Middle temporal gyrus
Parahippocampal gyrus
Postcentral gyrus
Precentral gyrus
Precuneus
Putamen
Superior frontal gyrus
Superior occipital gyrus
Superior parietal gyrus
Superior temporal gyrus
Supramarginal gyrus

Note: Twenty-seven brain regions in the left and right hemisphere to result in the 54 brain regions that were analyzed.

Table 2

Latency of Activation in Dyslexics Performing SWM and VWM Tasks

<u>*Spatial Working Memory (SWM)-Non-Orthographic*</u>

Brain Region	Mean (ms)	STD	*t*-stat	*df*	*p*-value
Precentral gyrus					
Control	343.9	109.11	-3.502	8	.008*
Dyslexics	167.9	50.57			

<u>*Verbal Working Memory (VWM)-Orthographic*</u>

Brain Region	Mean (ms)	STD	*t*-stat	*df*	*p*-value
Superior frontal gyrus					
Control	325.3	149.65	-2.021	12	.056*
Dyslexics	209.7	130.81			

Table 3

Normalized MEG Amplitudes in Dyslexics Performing SWM and VWM Tasks

Brain Region	Mean (nAm)	STD	*t*-stat	*df*	*p*-value
Spatial Working Memory (SWM)-Non-Orthographic					
R. middle temporal gyrus					
Control	1.5018	.36742	2.653	13	.020*
Dyslexics	1.0221	.30007			
R. superior temporal gyrus					
Control	1.5286	.28093	2.847	13	.014*
Dyslexics	1.1562	.18395			
Verbal Working Memory (VWM)-Orthographic					
L. parahippocampal gyrus					
Controls	.3402	.20956	-2.181	13	.048*
Dyslexics	.8591	.63788			
L. precentral gyrus					
Controls	.8101	.21209	-2.448	13	.029*
Dyslexics	1.0850	.22264			
R. fusiform gyrus					
Controls	.6171	.38086	-2.660	13	.020*
Dyslexics	1.3522	.66973			
R. insular cortex					
Controls	.8770	.27822	2.225	13	.044*
Dyslexics	.5692	.25396			
R. superior temporal gyrus					
Controls	1.4695	.16265	3.341	13	.005*
Dyslexics	1.1161	.24416			

Table 4

Differences in MEG Coherence Distributions in Dyslexics versus Controls by Frequency

Coherence Frequencies	Mean	Lower CI	Upper CI	*t*-stat	*p*-value
Spatial WM (1-15Hz)	-0.63	-0.69	-0.57	-21.32	0.00
Spatial WM (15-30Hz)	-0.09	-0.13	-0.05	-4.61	0.00
Spatial WM (30-45Hz)	-0.99	-1.03	-0.94	-40.39	0.00
Spatial WM (overall)	-0.85	-0.91	-0.79	-27.30	0.00
Verbal WM (1-15Hz)	0.77	0.73	0.81	35.71	0.00
Verbal WM (15-30Hz)	0.08	0.03	0.14	2.92	0.00
Verbal WM (30-45Hz)	-0.99	-1.03	-0.94	-40.39	0.00
Verbal WM (overall)	0.10	0.04	0.15	3.38	0.00

Note: WM indicates working memory and overall frequency is a combination of the 1-15Hz, 15-30Hz, and 30-45Hz frequency bands. CI refers to confidence interval.

Table 5

Differential Coherences in Dyslexics Performing a Spatial Working Memory Task

Coherence Pathways	*z*-value	*p*-value
R. lateral orbitofrontal gyrus - R. middle orbitofrontal gyrus	-4.33	0.0000
L. superior temporal gyrus - R. middle orbitofrontal gyrus	-4.22	0.0000
R. middle orbitofrontal gyrus - R. middle temporal gyrus	-4.15	0.0000
L. superior temporal gyrus - R. lateral orbitofrontal gyrus	-4.20	0.0000
L. middle temporal gyrus - R. middle orbitofrontal gyrus	-4.15	0.0000
R. lateral orbitofrontal gyrus - R. superior frontal gyrus	-4.12	0.0000
L. inferior occipital gyrus - R. middle orbitofrontal gyrus	-4.04	0.0001
L. middle temporal gyrus - R. lateral orbitofrontal gyrus	-4.14	0.0001
R. middle orbitofrontal gyrus - R. superior temporal gyrus	-3.96	0.0001
L. gyrus rectus - R. lateral orbitofrontal gyrus	-3.91	0.0001
R. lateral orbitofrontal gyrus - R. superior temporal gyrus	-3.96	0.0002
R. middle orbitofrontal gyrus - R. superior frontal gyrus	-3.78	0.0002
L. lateral orbitofrontal gyrus - R. middle orbitofrontal gyrus	-3.80	0.0002
L. superior frontal gyrus - R. lateral orbitofrontal gyrus	-3.84	0.0002
R. gyrus rectus - R. lateral orbitofrontal gyrus	-3.67	0.0002
L. gyrus rectus - R. middle orbitofrontal gyrus	-3.68	0.0002
L. gyrus rectus - L. middle orbitofrontal gyrus	-3.62	0.0003
L. middle orbitofrontal gyrus - R. middle orbitofrontal gyrus	-3.67	0.0003
L. middle orbitofrontal gyrus - R. lateral orbitofrontal gyrus	-3.68	0.0003
L. superior frontal gyrus - R. middle orbitofrontal gyrus	-3.58	0.0004
L. inferior temporal gyrus - R. middle orbitofrontal gyrus	-3.53	0.0004
L. middle occipital gyrus - R. lateral orbitofrontal gyrus	-3.55	0.0005
R. lateral orbitofrontal gyrus - R. middle temporal gyrus	-3.58	0.0005
L. gyrus rectus - R. inferior frontal gyrus	-3.46	0.0005
L. inferior occipital gyrus - R. lateral orbitofrontal gyrus	-3.44	0.0007
R. inferior temporal gyrus - R. lateral orbitofrontal gyrus	-3.48	0.0007
L. fusiform gyrus - R. lateral orbitofrontal gyrus	-3.42	0.0007
R. inferior temporal gyrus - R. middle orbitofrontal gyrus	-3.42	0.0007

L. inferior temporal gyrus - R. lateral orbitofrontal gyrus	-3.45	0.0007
L. superior temporal gyrus - R. superior temporal gyrus	-3.37	0.0009
L. middle occipital gyrus - R. middle orbitofrontal gyrus	-3.32	0.0009
L. fusiform gyrus - R. middle orbitofrontal gyrus	-3.34	0.0010
L. gyrus rectus - R. superior temporal gyrus	-3.30	0.0010
R. inferior frontal gyrus - R. middle orbitofrontal gyrus	-3.37	0.0011
R. gyrus rectus - R. middle orbitofrontal gyrus	-3.26	0.0011
L. gyrus rectus - L. superior temporal gyrus	-3.25	0.0012
R. fusiform gyrus - R. lateral orbitofrontal gyrus	-3.24	0.0013
R. gyrus rectus - R. inferior frontal gyrus	-3.22	0.0013
L. gyrus rectus - R. middle temporal gyrus	-3.21	0.0014
L. gyrus rectus - R. inferior temporal gyrus	-3.15	0.0017
R. inferior frontal gyrus -R. lateral orbitofrontal gyrus	-3.30	0.0018
L. precentral gyrus -R. middle orbitofrontal gyrus	-3.15	0.0018
L. gyrus rectus -L. lateral orbitofrontal gyrus	-3.11	0.0019
L. gyrus rectus -R. fusiform gyrus	-3.15	0.0019
L. middle occipital gyrus -R. superior frontal gyrus	-3.09	0.0020
L. gyrus rectus - R. superior frontal gyrus	-3.07	0.0021
R. fusiform gyrus - R. middle orbitofrontal gyrus	-3.08	0.0023
L. gyrus rectus - L. middle frontal gyrus	-3.05	0.0023
L. middle temporal gyrus - R. superior temporal gyrus	-3.07	0.0027
L. superior temporal gyrus - R. superior frontal gyrus	-3.02	0.0028
L. gyrus rectus - L. superior frontal gyrus	-2.98	0.0029
L. middle temporal gyrus - R. superior frontal gyrus	-3.01	0.0029
L. parahippocampal gyrus - R. middle orbitofrontal gyrus	-3.01	0.0030
R. inferior occipital gyrus - R. middle orbitofrontal gyrus	-2.98	0.0030
L. gyrus rectus - R. precentral gyrus	-2.95	0.0032
L. fusiform gyrus - L. gyrus rectus	-2.95	0.0032
L. middle orbitofrontal gyrus - L. superior temporal gyrus	-2.95	0.0035
L. middle occipital gyrus - L. middle temporal gyrus	-2.95	0.0035
R. gyrus rectus - R. superior temporal gyrus	-2.92	0.0036
L. middle temporal gyrus - R. inferior frontal gyrus	-3.01	0.0036
L.gyrus rectus - L. middle temporal gyrus	-2.92	0.0036
R. middle orbitofrontal gyrus - R. precentral gyrus	-2.95	0.0038
L. middle occipital gyrus - R. superior temporal gyrus	-2.91	0.0039

L. middle frontal gyrus - R. lateral orbitofrontal gyrus	-2.93	0.0039
L. middle occipital gyrus - L. superior temporal gyrus	-2.90	0.0040
L. superior temporal gyrus - R. inferior frontal gyrus	-2.96	0.0041
L. middle orbitofrontal gyrus - L. middle temporal gyrus	-2.87	0.0046
L. middle orbitofrontal gyrus - R. gyrus rectus	-2.84	0.0046

Note: Differential coherences between brain region pairs that distinguish dyslexics from controls performing a spatial working memory task presented in descending order of significance (*p*-values). L. signifies left hemispheric structures and R. signifies right hemispheric structures.

Table 6

Differential Coherence Pathways During Spatial Working Memory in Dyslexics

Intra-Hemispheric (associational)

Frontal-Frontal (right)
  R.lateral orbitofrontal gyrus-R.middle orbitofrontal gyrus
  R.lateral orbitofrontal gyrus-R.superior frontal gyrus
  R.middle orbitofrontal gyrus-R.superior frontal gyrus
  R.gyrus rectus-R.lateral orbitofrontal gyrus
  R.inferior frontal gyrus-R.middle orbitofrontal gyrus
  R.gyrus rectus-R.middle orbitofrontal gyrus
  R.gyrus rectus-R.inferior frontal gyrus
  R.inferior frontal gyrus-R.lateral orbitofrontal gyrus
  R.middle orbitofrontal gyrus-R.precentral gyrus

Frontal-Frontal (left)
  L.gyrus rectus-L.middle orbitofrontal gyrus
  L.gyrus rectus-L.lateral orbitofrontal gyrus
  L.gyrus rectus-L.middle frontal gyrus
  L.gyrus rectus-L.superior frontal gyrus

Frontal-Temporal (right)
  R.middle orbitofrontal gyrus-R.middle temporal gyrus
  R.middle orbitofrontal gyrus-R.superior temporal gyrus
  R.lateral orbitofrontal gyrus-R.superior temporal gyrus
  R.lateral orbitofrontal gyrus-R.middle temporal gyrus
  R.inferior temporal gyrus-R.lateral orbitofrontal gyrus
  R.inferior temporal gyrus-R.middle orbitofrontal gyrus
  R.fusiform gyrus-R.lateral orbitofrontal gyrus
  R.fusiform gyrus-R.middle orbitofrontal gyrus
  R.gyrus rectus-R.superior temporal gyrus

Frontal-Temporal (left)
  L.gyrus rectus-L.superior temporal gyrus
  L.fusiform gyrus-L.gyrus rectus
  L.middle orbitofrontal gyrus-L.superior temporal gyrus
  L.gyrus rectus-L.middle temporal gyrus
  L.middle orbitofrontal gyrus-L.middle temporal gyrus

Occipital-Frontal (right)
  R.inferior occipital gyrus-R.middle orbitofrontal gyrus

Posterior Local (right)
  None

Posterior Local (left)
  L.middle occipital gyrus-L.middle temporal gyrus
  L.middle occipital gyrus-L.superior temporal gyrus

Inter (Cross)- Hemispheric
  Frontal-Frontal
        L.gyrus rectus-R.lateral orbitofrontal gyrus
        L.lateral orbitofrontal gyrus-R.middle orbitofrontal gyrus
        L.superior frontal gyrus-R.lateral orbitofrontal gyrus
        L.gyrus rectus-R.middle orbitofrontal gyrus
        L.middle orbitofrontal gyrus-R.lateral orbitofrontal gyrus
        L.superior frontal gyrus-R.middle orbitofrontal gyrus
        L.gyrus rectus-R.inferior frontal gyrus
        L.precentral gyrus-R.middle orbitofrontal gyrus
        L.middle frontal gyrus-R.lateral orbitofrontal gyrus
        L.middle orbitofrontal gyrus-R.gyrus rectus
        L.gyrus rectus-R.superior frontal gyrus
        L.middle orbitofrontal gyrus-R.middle orbitofrontal gyrus
        L.lateral orbitofrontal gyrus-R.lateral orbitofrontal gyrus

  Temporal-Frontal
        L.superior temporal gyrus-R.middle orbitofrontal gyrus
        L.superior temporal gyrus-R.lateral orbitofrontal gyrus
        L.middle temporal gyrus-R.middle orbitofrontal gyrus
        L.middle temporal gyrus-R.lateral orbitofrontal gyrus
        L.inferior temporal gyrus-R.middle orbitofrontal gyrus
        L.fusiform gyrus-R.lateral orbitofrontal gyrus
        L.inferior temporal gyrus-R.lateral orbitofrontal gyrus
        L.fusiform gyrus-R.middle orbitofrontal gyrus
        L.superior temporal gyrus-R.superior frontal gyrus
        L.middle temporal gyrus-R.superior frontal gyrus
        L.parahippocampal gyrus-R.middle orbitofrontal gyrus
        L.middle temporal gyrus-R.inferior frontal gyrus
        L.superior temporal gyrus-R.inferior frontal gyrus
        L.gyrus rectus-R.middle temporal gyrus
        L.gyrus rectus-R.inferior temporal gyrus
        L.gyrus rectus-R.fusiform gyrus

  Occipital-Frontal
        L.middle occipital gyrus-R.lateral orbitofrontal gyrus
        L.inferior occipital gyrus-R.lateral orbitofrontal gyrus
        L.middle occipital gyrus-R.middle orbitofrontal gyrus
        L.middle occipital gyrus-R.superior frontal gyrus

  Temporal-Temporal
        L.middle temporal gyrus-R.superior temporal gyrus
        L.superior temporal gyrus-R.superior temporal gyrus

  Occipital-Temporal
        L.middle occipital gyrus-R.superior temporal gyrus

Note: Differential coherences between brain region pairs that distinguish individuals with dyslexics from controls performing a spatial working memory task. L. signifies left hemispheric structures and R. signifies right hemispheric structures.

Figure Legends

Figure 1. Four viewing angles of 3D depictions of association fibers. A, Anterior view; B, left lateral view; C, superior view; D, oblique view from right anterior angle. Reconstructed fibers are superior longitudinal fasciculus (slf, yellow), inferior longitudinal fasciculus (ilf, brown), superior fronto-occipital fasciculus (sfo, beige), inferior frontooccipital fasciculus (ifo, orange), and uncinate fasciculus (unc, red). E, F, Left lateral views without superior longitudinal fasciculus (E) and inferior longitudinal fasciculus (F) (Wanaka et al., 2004).

Figure 2. MEG amplitudes in the right middle temporal gyrus during SWM. Coronal, sagittal, and axial planes of MEG normalized amplitudes at the right middle temporal gyrus of dyslexics (A-C) and controls (D-F) while performing a spatial working memory (SWM) task.

Figure 3. MEG amplitudes in the right superior temporal gyrus during SWM. Coronal, sagittal, and axial planes of MEG normalized amplitudes at the right superior temporal gyrus of dyslexics (A-C) and controls (D-F) while performing a spatial working memory (SWM) task.

Figure 4. MEG amplitudes in the right superior temporal gyrus during VWM. Coronal, sagittal, and axial planes of MEG normalized amplitudes at the right superior temporal gyrus of dyslexics (A-C) and controls (D-F) while performing a verbal working memory (VWM) task.

Figure 5. MEG amplitudes in the left precentral gyrus during VWM. Coronal, sagittal, and axial planes of MEG normalized amplitudes in the left precentral gyrus of dyslexics (A-C) and controls (D-F) while performing a verbal working memory (VWM) task.

Figure 6. MEG coherence in the right middle and lateral orbitofrontal gyrus during SWM. Coronal, sagittal, and axial planes of MEG coherence (30-45Hz) at the right middle and lateral orbitofrontal gyrus of dyslexics (A-C) and controls (D-F) while performing a spatial working memory (SWM) task.

Figure 7. Z score differences in coherence at combined frequencies. Z value distributions summarizing the differences in coherence between dyslexics and controls at the combined frequency ranges (1-15Hz, 15-30Hz, and 30-45Hz) while performing a spatial working memory (A) or verbal working memory (B) task. Negative z-scores indicate lower coherence by the dyslexic group during SWM. The null or Normal distribution is plotted (in blue) along with the empirically observed distribution (in red).

Figure 8. Z score differences in coherence at low frequency range. Z value distributions summarizing the differences in coherence between dyslexics and controls at the low frequency range (1-15Hz) while performing a spatial working memory (A) or verbal working memory (B) task. Z-score distribution differences indicate lower coherence by the dyslexic group during SWM at the 1-15Hz frequency range and a higher coherence at

this frequency range during VWM. The null or Normal distribution is plotted (in blue) along with the empirically observed distribution (in red).

Figure 9. Z score differences in coherence at middle frequency range. Z value distributions summarizing the differences in coherence between dyslexics and controls at the beta frequency range (15-30Hz) while performing a spatial working memory (A) or verbal working memory (B) task. Z-score distribution differences indicate lower coherence by the dyslexic group during SWM at the 15-30Hz frequency range. The null or Normal distribution is plotted (in blue) along with the empirically observed distribution (in red).

Figure 10. Z score differences in coherence at low gamma frequency range. Z value distributions summarizing the differences in coherence between dyslexics and controls at the gamma frequency range (30-45Hz) while performing a spatial working memory (A) or verbal working memory (B) task. Z-score distribution differences indicate lower gamma coherence for the dyslexic group when performing a SWM and VWM task. The null or Normal distribution is plotted (in blue) along with the empirically observed distribution (in red).
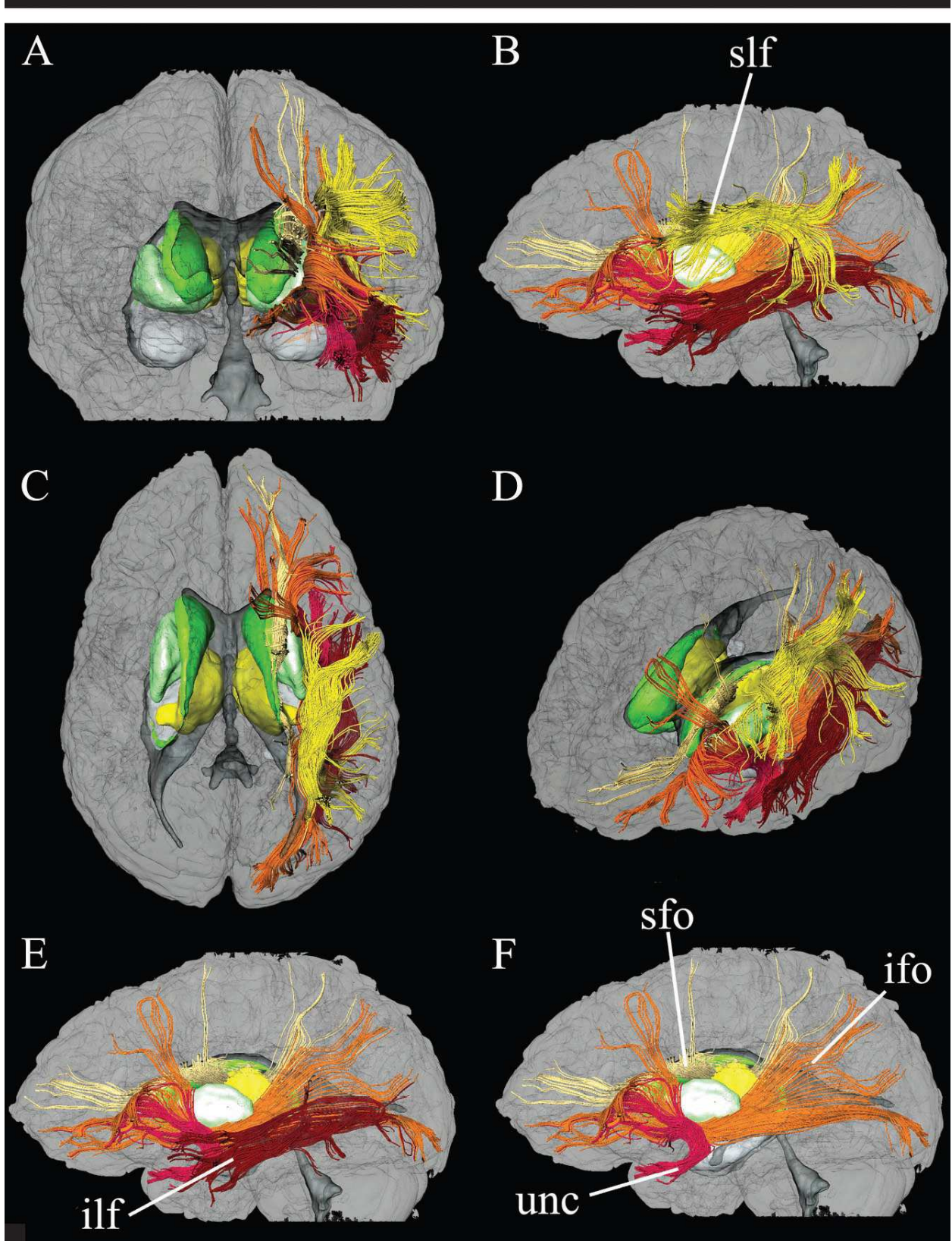
Figure 1. Four viewing angles of 3D depictions of association fibers.
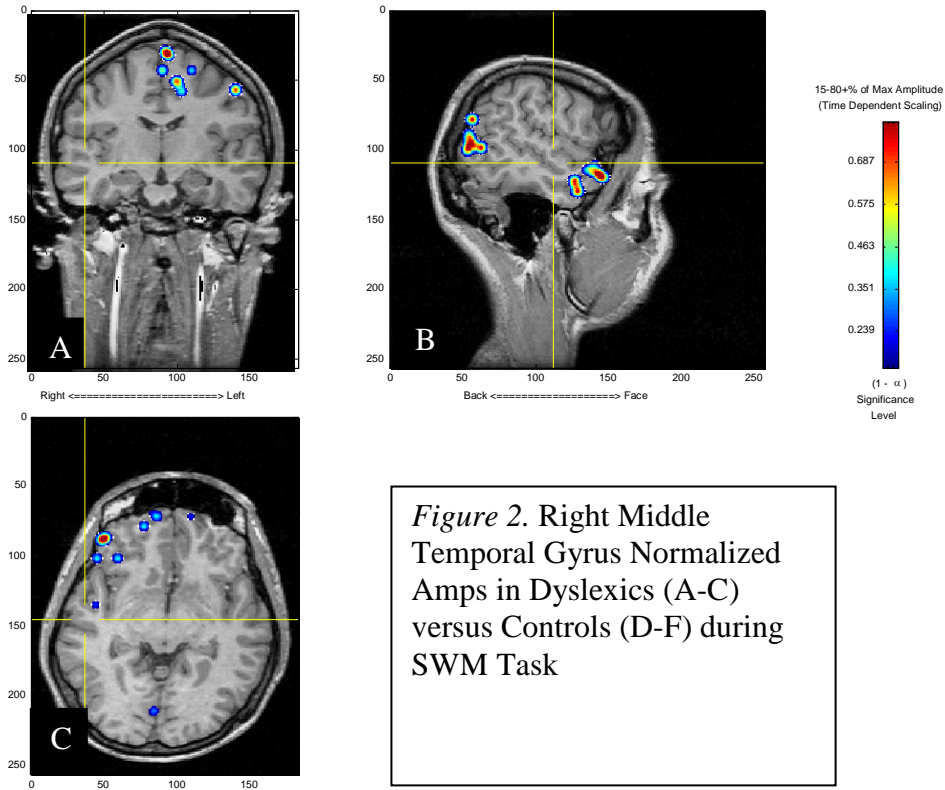
Figure 2. Right Middle Temporal Gyrus Normalized Amps in Dyslexics (A-C) versus Controls (D-F) during SWM Task
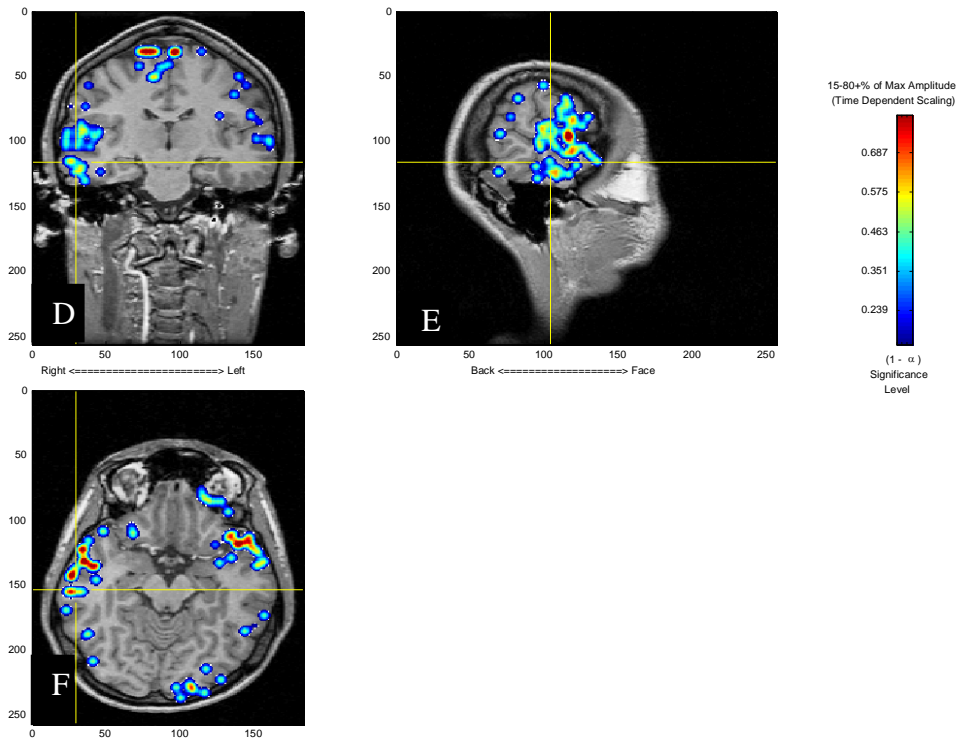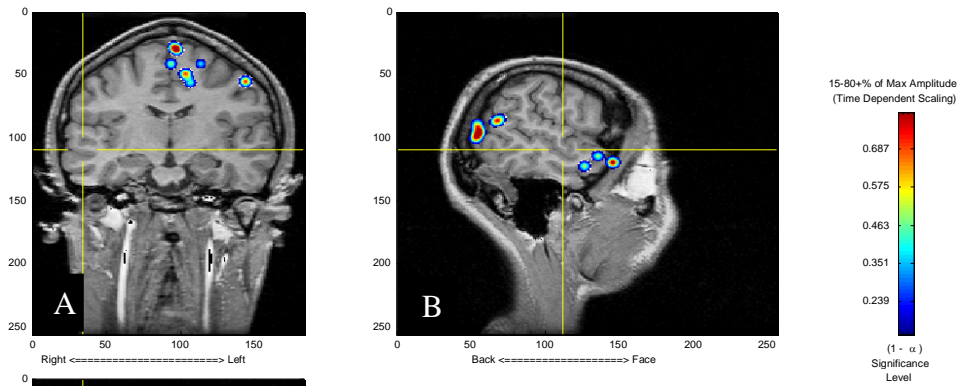
Figure 3. Right Superior Temporal Gyrus Normalized Amps in Dyslexics (A-C) and Controls (D-F) during SWM Task
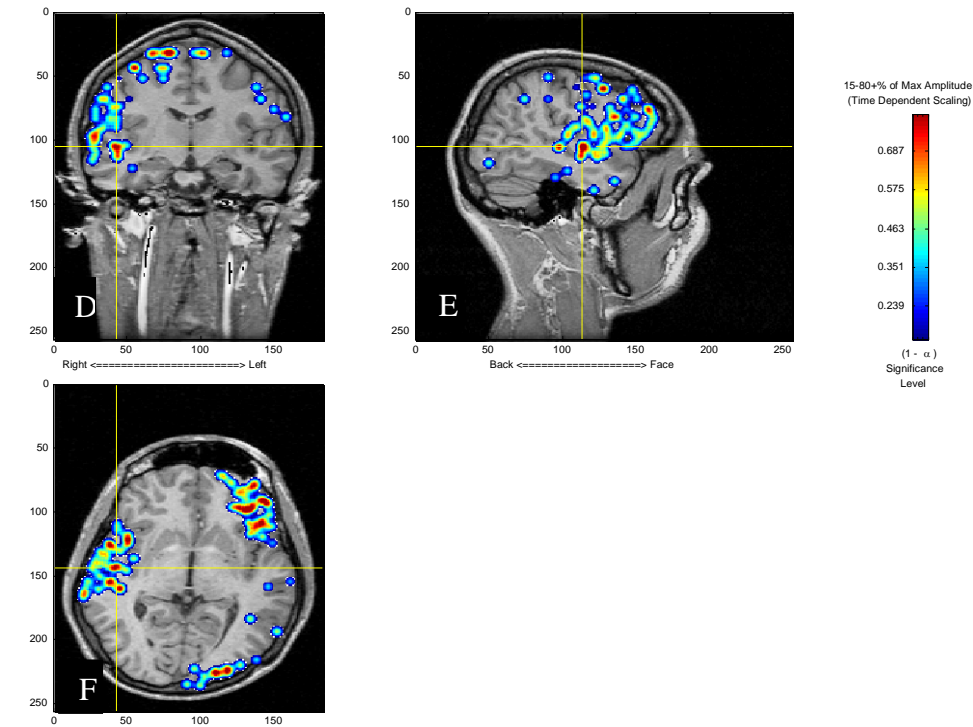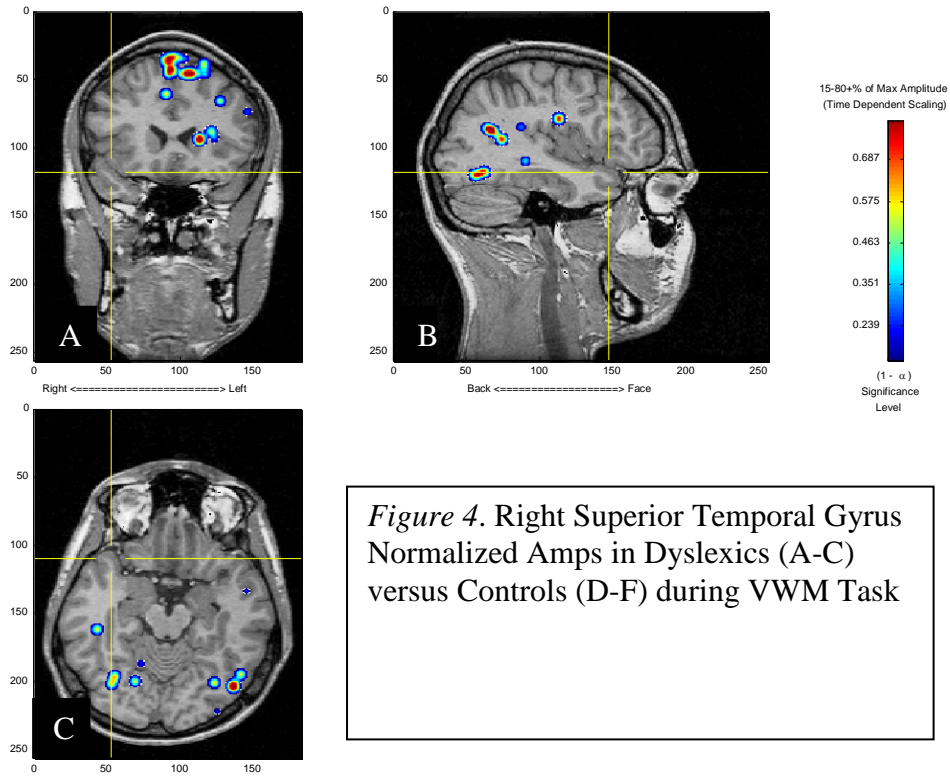
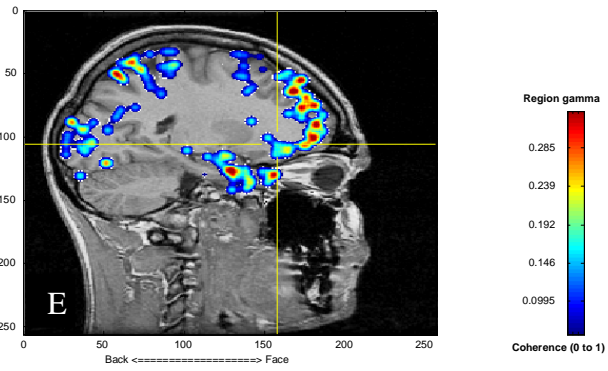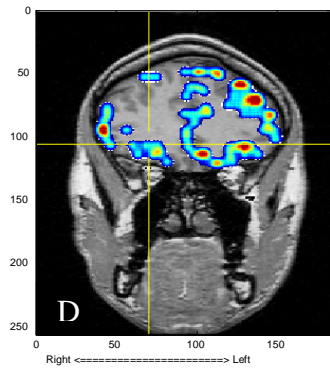*Figure 4.* Right Superior Temporal Gyrus Normalized Amps in Dyslexics (A-C) versus Controls (D-F) during VWM Task

Figure 5. Left Precentral Gyrus Normalized Amps in Dyslexics (A-C) versus Controls (D-F) during VWM Task
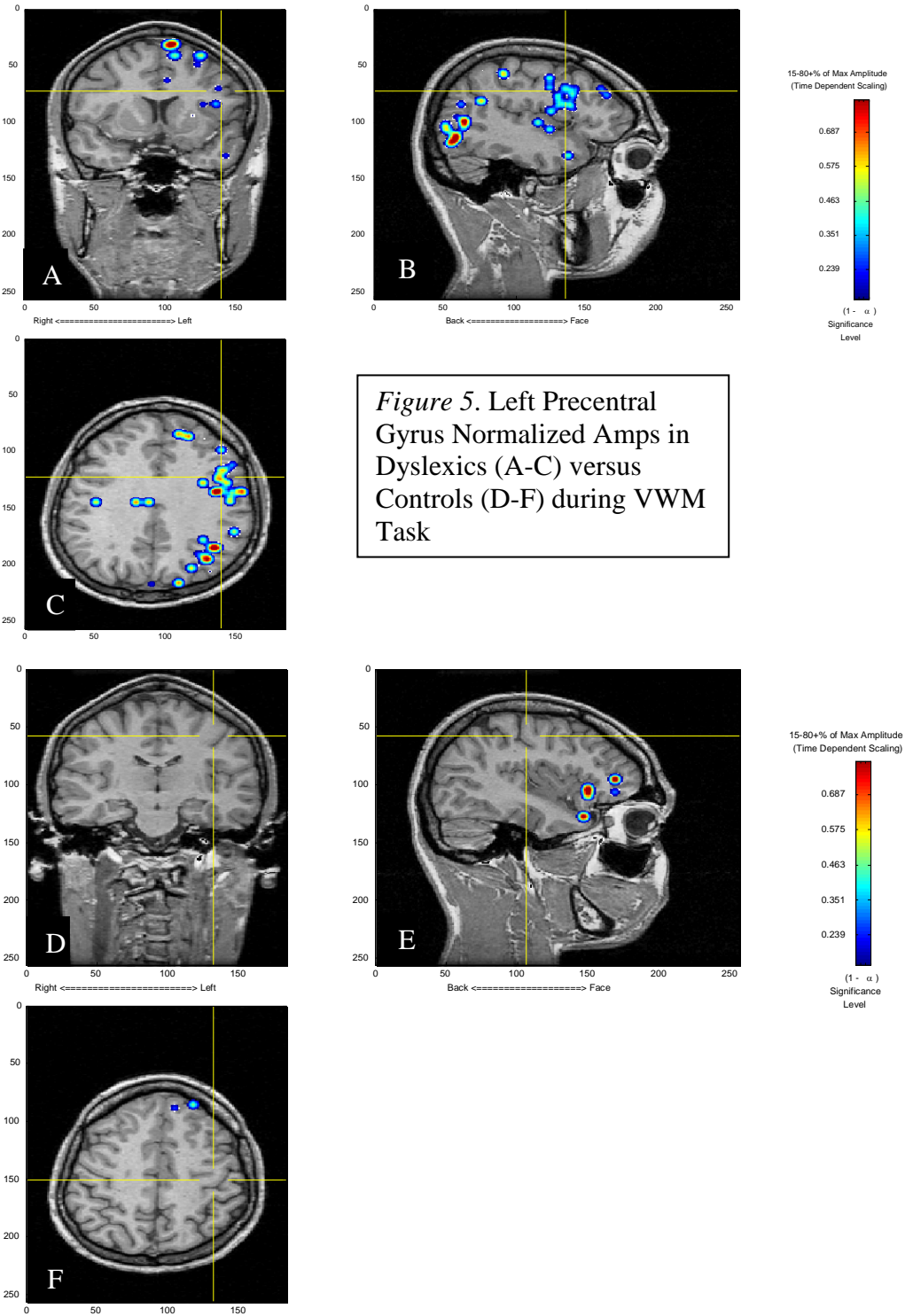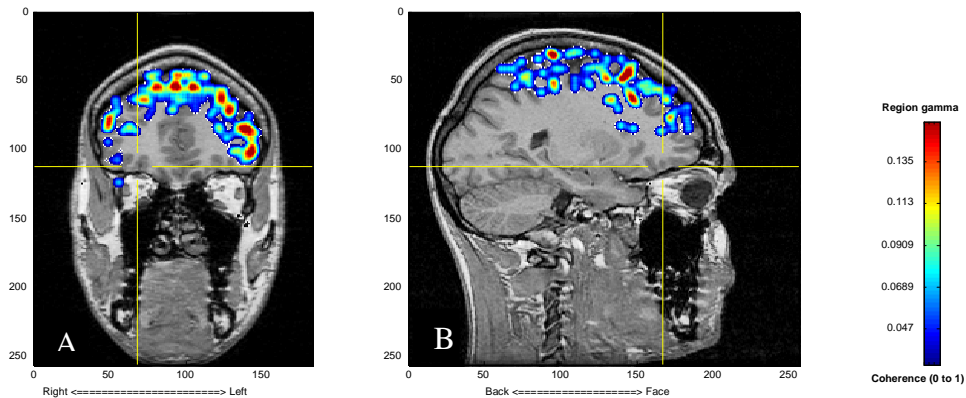
Figure 6. MEG Coherence in Right Middle Orbitofrontal Gyrus in Dyslexics (A-C) versus Controls (D-F) during SWM
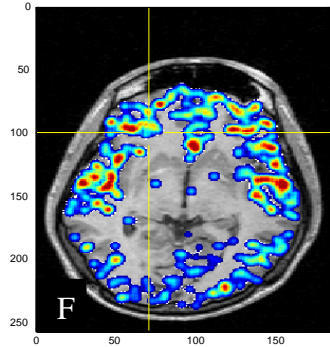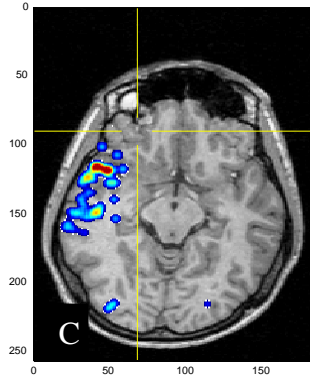
A. Spatial Working Memory
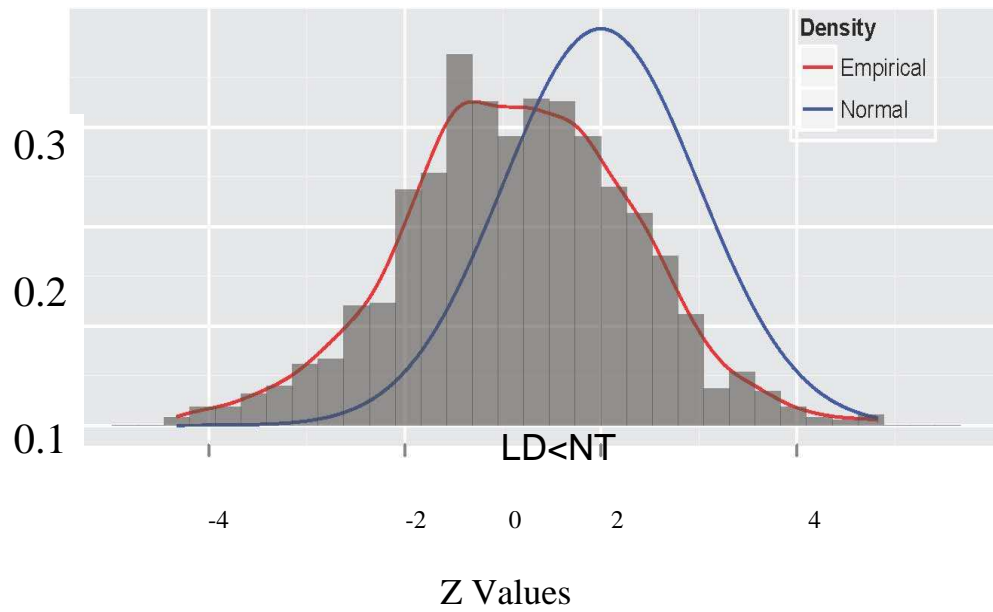
B. Verbal Working Memory
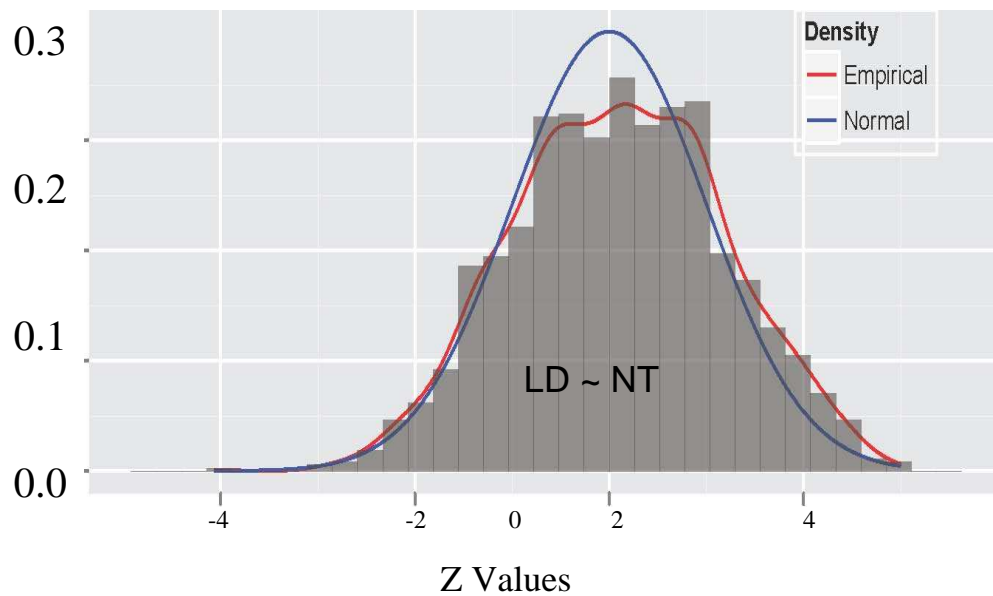
Figure 7. Differences in Overall MEG Coherence in Dyslexics and Controls

A. Spatial Working Memory (1-15 Hz)
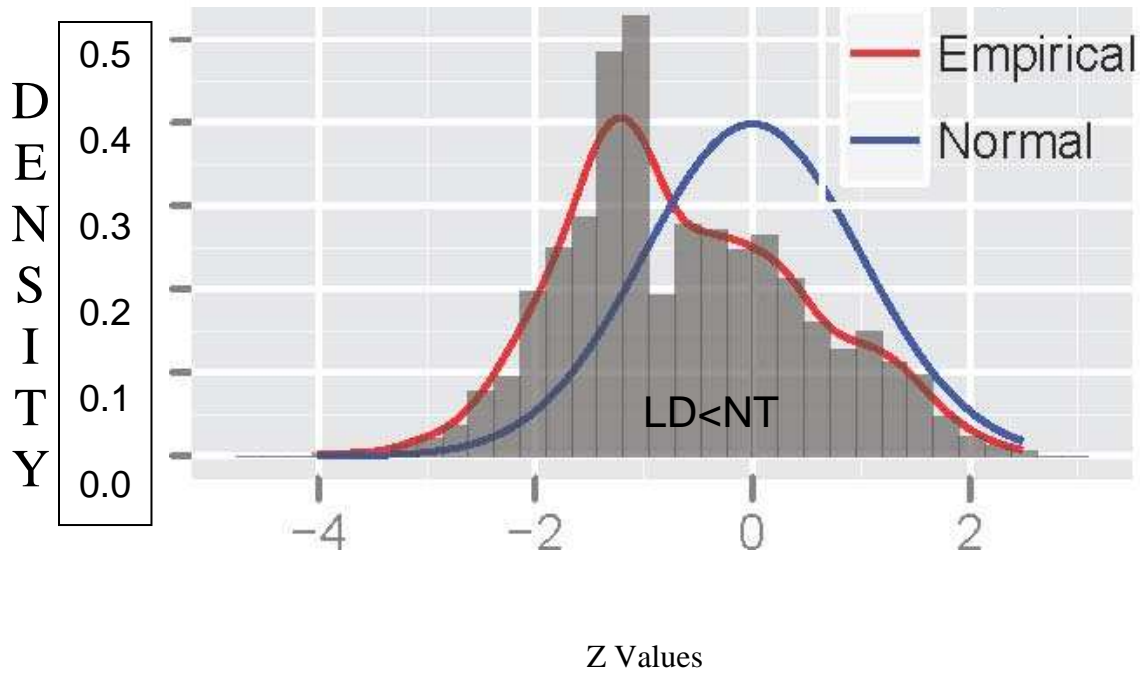
B. Verbal Working Memory (1-15 Hz)
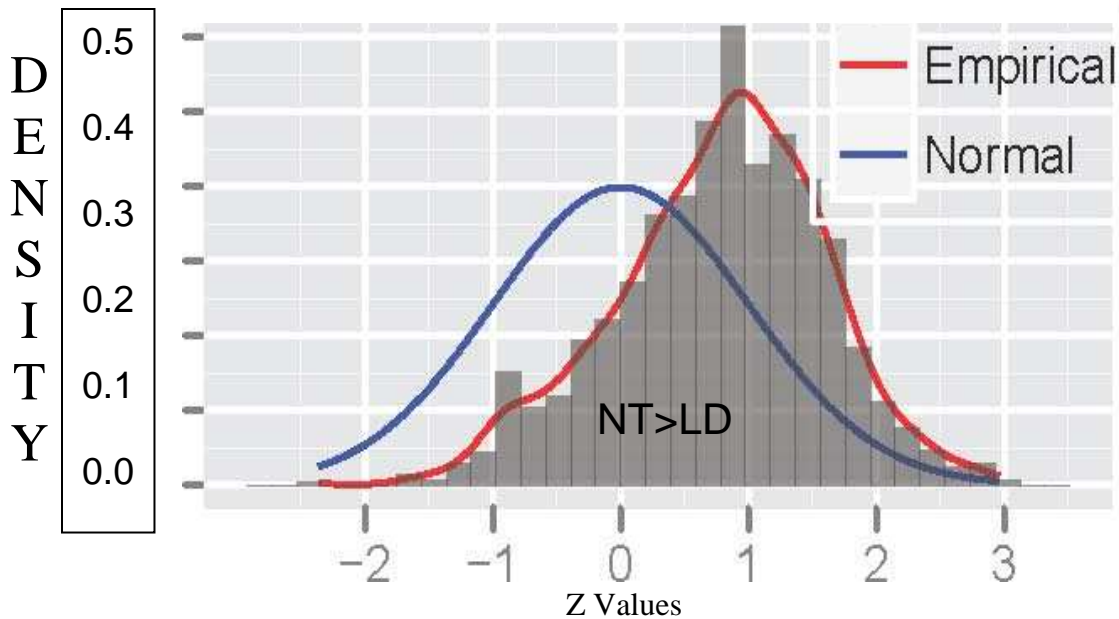
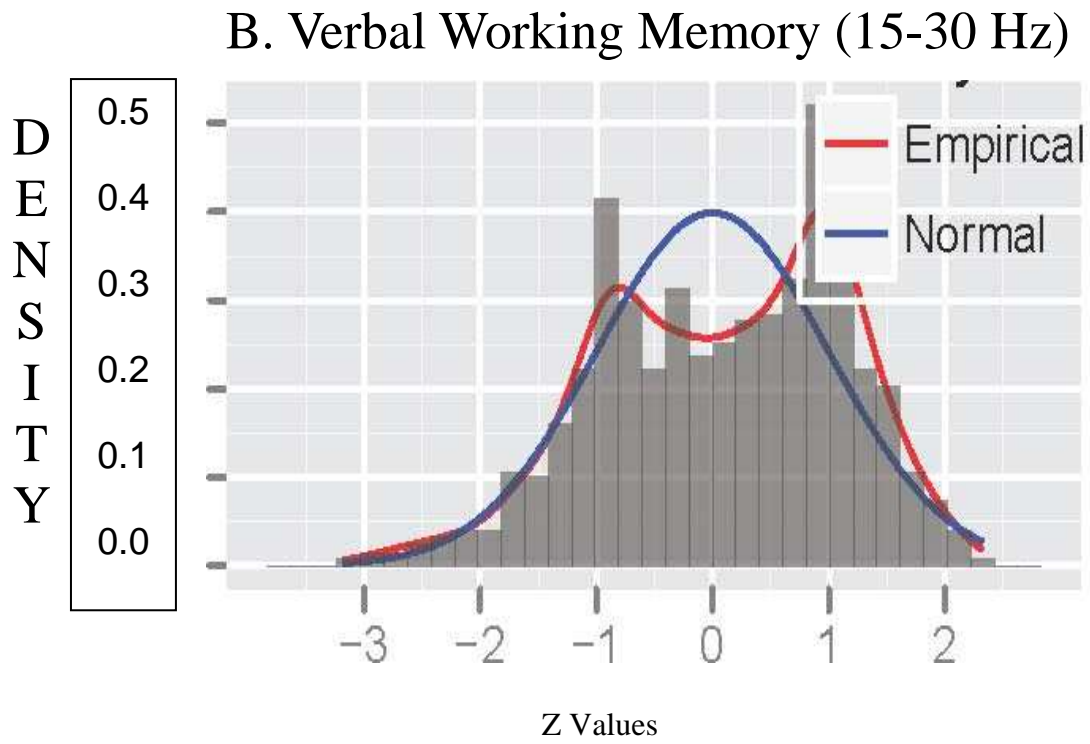*Figure 8*. Differences in Alpha/Theta MEG Coherence in Dyslexics and Controls
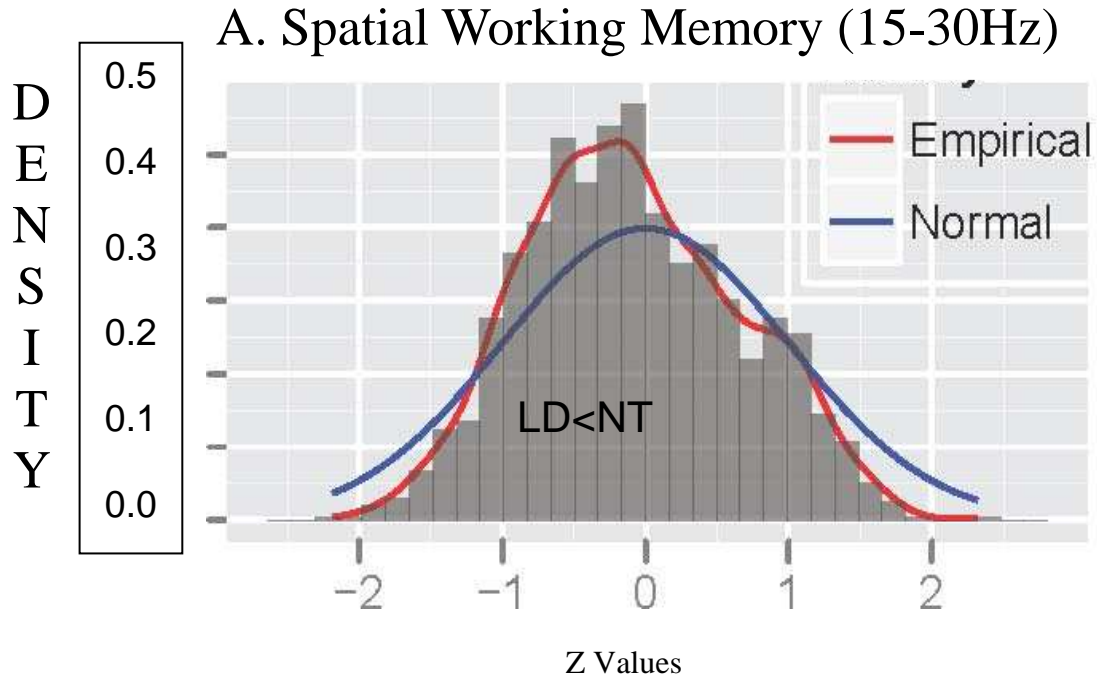
A. Spatial Working Memory (15-30Hz)

B. Verbal Working Memory (15-30 Hz)

Figure 9. Differences in Beta MEG Coherence in Dyslexics and Controls

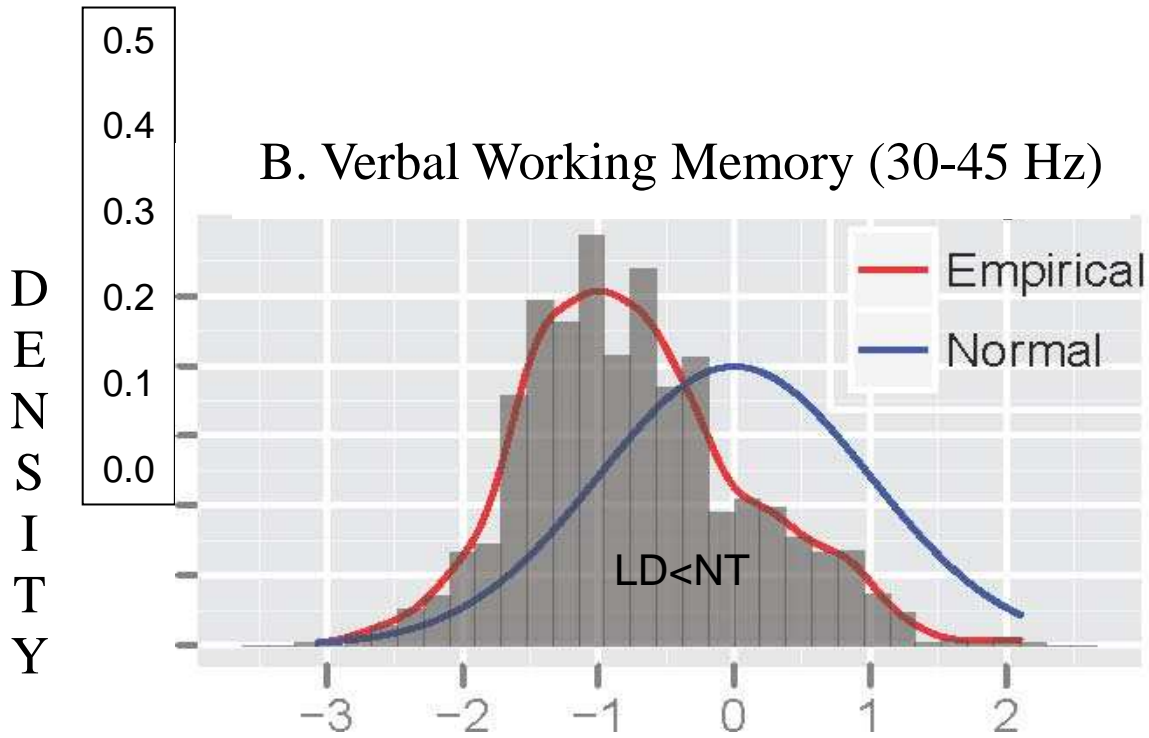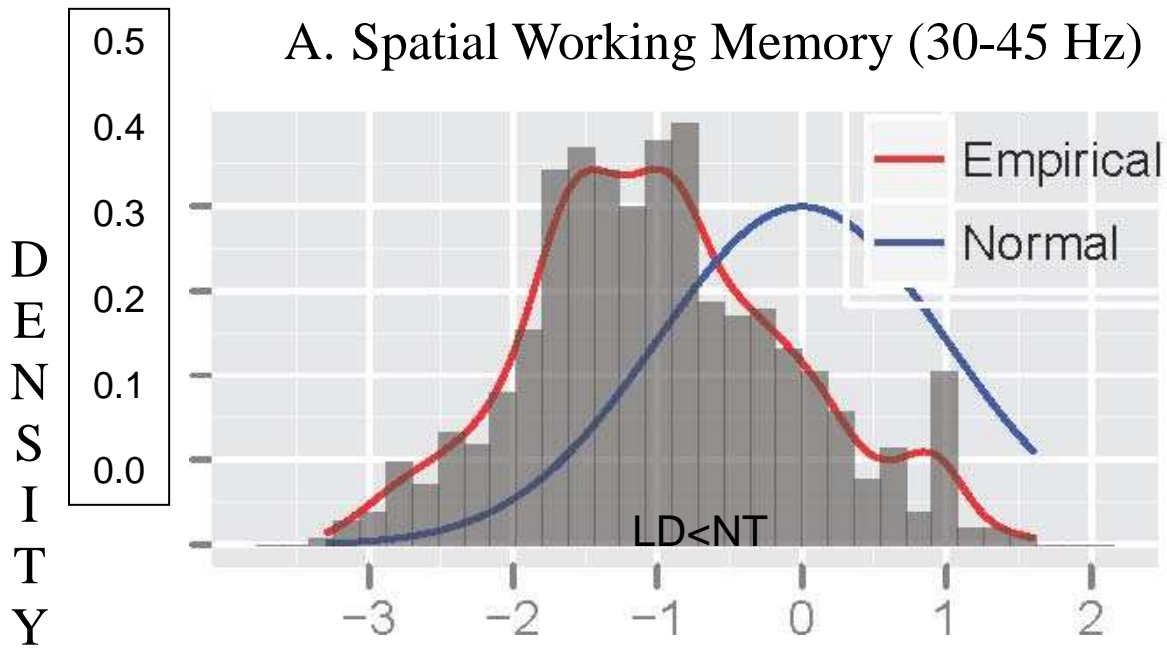*Figure 10.* Differences in Gamma MEG Coherence in Dyslexics and Controls

Appendix

January 30, 2012
Application Determination

EXEMPT APPROVAL

To: Dr. Alfred Mansour
     Department of Psychology

Re: **UHSRC** #120117c   Category: EXEMPT # 4
     Approval Date: **January 29,2012**

Title: MEG Coherence Neuroimaging in Dyslexia: Activation of Working Memory Pathways

The Eastern Michigan University Human Subjects Review Committee (UHSRC) has completed their review of your project. I am pleased to advise you that **your research has been deemed as exempt** in accordance with federal regulations.

The UHSRC has found that your research project meets the criteria for exempt status and the criteria for the protection of human subjects in exempt research. **Under our exempt policy the Principal Investigator assumes the responsibility for the protection of human subjects** in this project as outlined in the assurance letter and exempt educational material.

Renewals: Exempt protocols do not need to be renewed. If the project is completed, please submit the **Human Subjects Study Completion Form** (found on the UHSRC website).

Revisions: Exempt protocols do not require revisions. However, if changes are made to a protocol that may no longer meet the exempt criteria, a **Human Subjects Minor Modification Form** or new **Human Subjects Approval Request Form** (if major changes) will be required (see UHSRC website for forms).

Problems: If issues should arise during the conduct of the research, such as unanticipated problems, adverse events, or any problem that may increase the risk to human subjects and change the category of review, notify the UHSRC office within 24 hours. Any complaints from participants regarding the risk and benefits of the project must be reported to the UHSRC.

Follow-up: If your exempt project is not completed and closed after three years, the UHSRC office will contact you regarding the status of the project and to verify that no changes have occurred that may affect exempt status.

Please use the UHSRC number listed above on any forms submitted that relate to this project, or on any correspondence with the UHSRC office.

Good luck in your research. If we can be of further assistance, please contact us at 734-487-0042 or via e-mail at human.subjects@emich.edu. Thank you for your cooperation.

Sincerely,

Deb de Laski-Smith, Ph.D.
Interim Dean
Graduate School
Administrative Co-Chair
University Human Subjects Review Committee