

Functional and structural connectivity of reading networks in the adult brain

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I, Merina Su, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

A handwritten signature in black ink, appearing to read 'Merina Su', written over a horizontal line.

Abstract

Language processing draws upon many distributed regions in the brain. Reading in particular is a skill that emerges from the interaction between brain regions involved in phonological and orthographical processing. This project examined the reading network in adults (18-35 years old) with and without developmental dyslexia. Each participant was assessed on a comprehensive battery of standardised neuropsychological tests, which assessed IQ, reading accuracy and comprehension, spelling, phonological processing, working memory, grammatical understanding, motor coordination, and expressive and receptive language skills. In addition, each participant underwent a non-invasive MRI scan, during which structural and functional images were acquired. More specifically, T1-weighted and diffusion-weighted images were acquired to assess structural networks in the brain, whereas a simple reading task and resting-state fMRI were acquired to assess the functional networks involved in reading. Individuals with dyslexia were found to show reduced activation and reduced connectivity in regions typically associated with skilled reading. Moreover, results suggested that they rely on more effortful processing and attentional mechanisms instead to compensate for their reading difficulties. All in all, results indicated that individuals with developmental dyslexia had abnormal functional and structural brain networks related to reading performance, as well as other functions, such as working memory. These findings suggest that for successful reading remediation, it is important to focus on the integration of phonology with orthography, as well as with working memory. Literacy problems such as developmental dyslexia are thus better characterised as a complex disorder with multiple deficits rather than by a single phonological deficit.

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List of Abbreviations

AAL - automated anatomical labeling

(d)ACC - (dorsal) anterior cingulate cortex

AD - axial diffusivity

AD(H)D - attention deficit (hyperactivity) disorder

AF - arcuate fasciculus

AG - angular gyrus

ANCOVA - analysis of covariance

ASD - autism spectrum disorder

BOLD - blood oxygenation level-dependent

CELF-4 - Clinical Evaluation of Language Fundamentals 4

CSD - Constrained Spherical Deconvolution

CSF - cerebral spinal fluid

CTOPP - Comprehensive Test of Phonological Processing

DLPFC - dorsolateral prefrontal cortex

DMN - default mode network

dmRI - diffusion magnetic resonance imaging

DSI - diffusion spectrum imaging

DTI - diffusion tensor imaging

EPI - echo planar imaging

FA - fractional anisotropy

(RS)FC - (resting-state) functional connectivity

FDR - false discovery rate

FWE - family wise error

FFG - fusiform gyrus

FLASH - Fast Low-Angle Shot

(rs-)fMRI - (resting-state) functional magnetic resonance

FOD - fibre orientation function

FOV - field of view

FWHM - full width half maximum

GLM - General Linear Models

GT - Graph theory

HARDI - high angular resolution diffusion imaging

HRF - haemodynamic response function

ICA - independent component analysis

IFG - the left inferior frontal gyrus

IPL - inferior parietal lobe

IQ – intelligence quotient

ITG - inferior temporal gyrus

LFP - local field potentials

LGN - lateral geniculate nucleus

MEG - magnetoencephalography

MFG - middle frontal gyrus

MNI - Montreal Neurological Institute

MRI – magnetic resonance imaging

(p)MTG – (posterior) middle temporal gyrus

MUA - multi-unit activity

NBS - network based statistics

ODF - orientation distribution function

PA - phonological awareness

PET - positron emission tomography

PM - phonological memory

PT - planum temporale

QBI- Q-ball imaging

RAN - rapid automatized naming

RD - radial diffusivity

RF - radiofrequency

ROI - region of interest

RT - reaction time

SLF - superior longitudinal fasciculus

SLI - specific language impairment

SMA - supplementary motor area

SMG - supramarginal gyrus

SPM - Statistical Parametric Mapping

(p)STG - (posterior) superior temporal gyrus

SVC - small volume correction

TPJ - the left temporoparietal junction

TR - repetition time

TROG-2 - Test for the Reception of Grammar-2

UF - uncinate fasciculus

VBM - Voxel-based morphometry

VWFA - Visual Word Form Area

WASI-II - Wechsler Abbreviated Scale of Intelligence II

WIAT-II - Wechsler Individual Achievement Test II

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1. Developmental dyslexia

Reading is essential for daily life and academic success. Although exact prevalence studies are lacking, reports suggest that 5-17% of the population and about 15-17% of children have developmental dyslexia (Peterson & Pennington, 2012; Ramus et al., 2003, 2004).

Developmental dyslexia is a developmental learning disorder, characterized by a persistent difficulty in learning to read that is not explained by sensory deficits, cognitive deficits, lack of motivation, or lack of adequate reading instruction (Peterson & Pennington, 2012; Ramus, 2003; Shastry, 2007). Although it affects both girls and boys, it is more common in boys. People with dyslexia have difficulty in reading words accurately (decoding deficit), read very slowly (fluency deficit) and spell poorly. Although reading difficulties may improve over time in many children with dyslexia, fluency and spelling often remain poor (Nergård-Nilssen & Hulme, 2014; Peterson & Pennington, 2015).

The cause of the disorder is currently unknown, but there is some consensus in the literature, which acknowledges that the disorder has genetic risk factors, some of which may affect typical brain development. Since the first publications on developmental dyslexia in 1896 (Morgan, 1896), several theories have been proposed (e.g. Ramus, 2003, 2004; Shastry, 2007). This chapter outlines the five prominent theories of developmental dyslexia.

Theories of developmental dyslexia

Individuals with dyslexia display a wide range of impairments besides reading difficulties. This heterogeneity has led to the ongoing disputes on the cause of the disorder.

1.1. Phonological deficit of developmental dyslexia

Phonological processing refers to the linguistic skill where one uses the sounds of one's language (phonological information) in processing written and oral language. This section discusses the dominant theory in dyslexia, its nature and suggested causal role in learning to read, evidence to support this theory, and the limitations with this theory.

The relationship between phonology and reading

The writing system represents language at the phonological level. Printed symbols represent units of speech, and the unit of speech represented is the phoneme (Wagner and Torgesen, 1987). As such, the process of reading aloud requires an individual to decode (articulate) a string of visual symbols. In alphabetic languages like English, these symbols are letters. In logographic languages like Chinese, these symbols are characters. To correctly articulate words, one needs to convert visual symbols into speech sounds, according to linguistic rules specific to one's language. What is difficult in alphabetic languages is learning that printed symbols represent systematic phonemes. In other words, one must become aware of the grapheme-phoneme rules of one's language.

In addition, the sounds articulated based on a particular combination of visual symbols may or may not contain a meaning. For example, the English word 'banana' is articulated as /bə'nɑ:nə/ and refers to a long curved tropical fruit with a thick yellow skin and soft flesh. In contrast, 'banaka' could be pronounced as /bə'nɑ:kə/, but has no meaning in English. Therefore, reading real words like 'banana' and pseudowords like 'banaka' both rely on the integration of phonology (speech sounds) and orthography (visual letters). Developmental dyslexia is characterised by the failure to accurately decode written words and pseudowords. Thus, proponents of the phonological deficit hypothesis argue that dyslexia is caused by an underlying phonological deficit.

Wagner and Torgesen (1987) outlined in their original paper that phonological processing can be distinguished into three interdependent domains: i) phonological awareness, ii)

phonological recoding in lexical access (or rapid automatized naming), and iii) phonetic recoding to maintain information in working memory (phonological memory). The evidence in support of these assumptions will be discussed in each domain in turn.

Specifically, I will evaluate the core empirical assumptions of the phonological deficit hypothesis (PDH) in longitudinal and training studies:

1. Phonological ability is correlated with reading tasks
2. Early phonological ability predicts subsequent reading outcome
3. Training phonological ability improves reading

Phonological awareness

Phonological awareness (PA) refers to one's awareness and access to the phonology (i.e. speech sound structure) of one's language (Mattingly, 1972). Examples of experimental tasks tapping into PA include: tapping out the number of syllables in a word, reversing the order of sounds in a word, putting together sounds presented in isolation to form a word, and detecting rhyme and alliteration. These tasks share one critical feature of PA: the active segmentation or manipulation of the sound segments. Proponents of the view that PA is crucial to reading acquisition argue that learning to read new words involves segmenting the letter string into units that correspond to individual sounds (phonemes) and blending the individual sounds together to pronounce the word. As such, an awareness of phonemes is a prerequisite of the ability to segment letter strings into phoneme-based units and to blend the resulting phonemes into words (Catts, 1989; Wagner and Torgesen, 1987).

Indeed, dyslexia is often characterized by a lack of awareness or sensitivity to the speech sound structure of the language. Dyslexic children and adults are less skilled at identifying rhyme and alliteration than age-matched controls (e.g. Peterson and Pennington, 2012; Gabrieli, 2009). Dyslexic adults and children also perform less well than normal readers in

tasks involving the segmentation or manipulation of the sound segments (i.e., syllables, phonemes) in words (e.g. Wagner and Torgesen, 1987; Bruck, 1992). Furthermore, dyslexics have been shown to have difficulties in speech sound awareness, and these deficiencies are thought to be an important causal factor in their reading problems (Bradley and Bryant 1978; Catts, 1989).

Longitudinal studies investigating PA in children have consistently found significant correlations between early (and preliterate) PA skills and subsequent literacy outcome. For example, the earliest studies (Mann, 1984; Mann and Liberman, 1984; Bradley and Bryant, 1985; Lundberg, Olofsson and Wall, 1980) found that PA skills in kindergarten, such as syllable segmentation, phoneme reversal, and sound categorisation, significantly correlated (range from $r=.4$ to $r= .75$) with first-grade reading outcome. These correlations still hold after controlling for general ability (IQ) (Mann and Liberman, 1984) and uniquely predict variance in reading outcome (Bradley and Bryant, 1985; Lundberg, Olofsson and Wall, 1980). These findings were later replicated by several studies (e.g. Wagner et al., 1994; Elbro et al., 1998; Cardoso-Martins, 1995; Stuart, 1995). These findings in English have also been replicated in orthographically transparent languages (relative to English) such as Finnish (Lyytinen et al., 2001) and Dutch (De Jong and Van der Leij, 2002). Pennington and Lefly (2001) examined predictors of reading outcome in children with low- and high-risk for dyslexia, depending on the presence or absence of a parent with dyslexia, and found that PA was the main predictor of reading outcome in both groups.

However, the studies above did not exclude the possibility that reading acquisition may affect the subsequent development of PA. For example, Perfetti et al. (1987), in a longitudinal study following 82 English-speaking children from kindergarten to first grade, found that phoneme deletion appeared to be largely a product of reading ability rather than a predictor. Wagner and Torgesen (1987) reanalysed the data presented by Lundberg, Olofsson and Wall (1980) and found that the correlations between PA and reading outcome

dropped below significance after controlling for differences in reading ability at timepoint 1 of the study. One explanation is that learning to read provides explicit knowledge of the phonological structure of language that complements the largely implicit knowledge acquired from experience at listening and speaking as part of the natural course of language acquisition. Wagner and Torgesen (1987) provide an analogy with foreign language learning in their original paper putting forward the PDH: "Learning a foreign language typically requires considerable effort at mastering grammatical rules that a native speaker of the language takes for granted. Individuals sometimes report that learning the grammatical rules of a foreign language made them aware of grammatical rules of their own language, rules they previously were not aware of yet that guided their speech and writing nevertheless." (Wagner and Torgesen, 1987, p195). It therefore is important to note that (a proportion of) the difficulties dyslexics show in PA could be the result of their reading problems - a consequence rather than a cause. Reading experience with an alphabetic language substantially increases PA, particularly phoneme awareness (Liberman and Shankweiler. 1985). Therefore, dyslexics may have impaired PA because of their more limited reading experience.

On the other hand, some research does indicate that some aspects of PA (e.g., awareness of rhyme and syllables) may develop independent of reading experience and may have a significant effect on reading achievement (Mann and Liberman 1984). Thus, the relationship between phonological awareness and reading is best seen as reciprocal, adding to the complexity of distinguishing cause from consequence in reading disability.

Training studies may help disentangle cause and effect; however, the results are divided. Lundberg et al., (1988) found significant improvements in PA as well as transfer effects to reading and spelling after 8 months training in 235 Danish children at the beginning of literacy acquisition. Schneider et al. (1997) found the same effect in 371 German children after 6 months training. In a cross-linguistic study comparing American and German literacy

teaching methods, Mann and Wimmer (2002) reported that American kindergarteners, who were taught letters and sounds prior to schooling, performed better on PA tasks compared to German kindergartners who did not receive training prior to schooling. These findings provide support for the causal relationship of PA in learning to read.

In contrast, Olofsson and Lundberg (1985) did not find transfer effects on reading in 95 Swedish children after a 6-8 weeks training in PA, even though the performance on a PA test improved after training. Brennan and Ireson (1997) reported similar findings in 38 English-speaking children after explicit training in PA, which improved performance on subsequent phonemic tasks, but no transfer effects on reading or spelling. The lack of transfer effects could possibly be explained by the small samples sizes and the short duration of the intervention. Alternatively, the findings may be interpreted to suggest that training PA skills alone may not be sufficient to improve reading outcome.

Indeed, Bryant and Bradley (1985) compared children with poor PA skills randomly assigned to four training groups: 1) sound training only, 2) sound and letter training (sound-symbol correspondence), 3) semantic category training, and 4) no-treatment control, and found that sound training alone does not result in greater reading achievement, but when supplemented with letter training, it does. Fox and Routh (1984) comparing three training conditions: 1) segmenting only, 2) segmenting and blending, and 3) no-training, also found that only the group that received the combined treatment improved significantly. Similarly, Hatcher et al. (1994) reported that children who have received both reading instruction and PA training showed the most improvement in reading compared to children who have only received reading instruction alone. These results suggest that PA in combination with letter knowledge training offers the most effective intervention. However, these studies do not offer a direct comparison of the letter training alone. Thus, it is hard to deduce whether the letter training is the causal factor for improvement or the interaction or additive effect of PA and letter training.

Deficit in Phonological Representations?

Whereas the studies presented above investigated how difficulties in PA tasks may *directly* contribute to deficiencies in word recognition skills, another line of research argues that the relationship between PA deficits and reading disability is mediated by the accuracy of the underlying *phonological representations* of words in the mental lexicon (Swan and Goswami, 1997). As such, poor performance in PA tasks may not be due to a lack of phonological analysis skills per se, but may instead reflect inaccuracies in the phonological representations of the words asked to decode. One method of testing this phonological representations hypothesis is using picture naming data. In order to correctly identify a picture name, it may be assumed that an accurate phonetic code must be generated (Swan and Goswami, 1997a, 1997b).

Swan and Goswami (1997a) compared four groups of children (N=16 in each group): 1) dyslexic (DYS) poor readers, 2) non-dyslexic 'garden variety' (GV) poor readers (readers with low IQ<85), 3) reading-age (RA) matched controls, and 4) chronological age (CA) matched controls. The children completed a picture naming task, an object name recognition task, and a receptive vocabulary task. Two findings stood out. First, both the DYS and GV poor readers performed significantly worse than the CA and RA control groups on the naming task, suggesting that picture naming deficits may not be dyslexia specific. Second, the nature of the naming deficits differed between the two groups of poor readers. The GV readers performed significantly worse than other groups on the vocabulary task, suggesting that the GV readers performed poorly on the naming tasks due to impoverished vocabulary (i.e. they did not have the items in their vocabulary to retrieve). Dyslexic readers on the other hand, performed well on the object name recognition task and vocabulary scale, suggesting that they did have the items stored in their mental lexicons, but had difficulties *retrieving* the phonological codes during task. The authors proposed that poor

retrieval of phonological codes could be caused by poor representation of the phonological codes in the mental lexicon.

A subsequent study (Swan and Goswami, 1997b) with the same four groups of children, further examined the phonological representations hypothesis using phonological awareness tasks (syllable counting, onset-rhyme, phoneme counting) while adjusting for picture naming performance (used as a proxy measure of adequate representation). Prior to adjustment, the dyslexic children performed significantly worse than both CA and RA controls across all levels of phonological processing (syllable, onset-rhyme, and phoneme), in line with previous findings. However, after adjustment, the dyslexics performed comparably to both CA and RA controls on syllables, onsets and rhymes. This suggests that inadequate phonological representations in the mental lexicon could explain the dyslexics' failure on phonological awareness tasks on at least a few levels, supporting the phonological representations hypothesis. The deficits at phonemic level, however, remained. In other words, even adequate phonological representations do not appear to be sufficient to support a phonemic level of analysis. These latter findings do not directly support the phonological representation hypothesis, but do fit a more general phonological awareness deficit.

A severe limitation with the phonological representation hypothesis is the case of pseudowords – these by definition do not have representations in the mental lexicon. Proponents of the phonological representations hypothesis argue that the poor performance of dyslexic readers on pseudoword reading tasks can be explained as follows: if dyslexic readers have unstable representations for lexical items, they will also have greater difficulty in assembling new articulatory codes for nonlexical items. Evidence for this explanation has been taken from nonword repetition tasks, which provide a measure of dyslexics' ability to assemble articulatory instructions (Swan and Goswami, 1997a; Snowling, Chiat and Hulme, 1991). However, working memory contributions are not taken

into account in these explanations, which could possibly better explain the dyslexics' nonword repetition performance.

Phonological memory

Phonological memory plays a vital role for beginning readers. The task faced by the beginning reader is to: (a) decode a series of visually presented letters, (b) store the sounds of the letters in a temporary store, and (c) blend the contents of the temporary store to form words. Efficient phonetic coding for storing the sounds of the letters enables the beginning reader to devote the maximum amount of cognitive resources to the difficult task of blending the sounds to form words (Peterson and Pennington, 2012).

Working memory can be conceptualized as a collection of three interrelated subsystems (Baddeley and Logie, 1999): the central executive, a visuospatial sketch pad, and a phonological store or articulatory loop. The *central executive* is a limited capacity workspace that can be used to operate control processes (e.g., executive routines and decision making) or to briefly store information. The *visuospatial sketch pad* processes and stores visual or spatial information, whereas the phonological store or *articulatory loop* processes and stores verbal information. According to this working memory model, verbal information is recoded phonetically and stored in working memory in terms of its phonological features (Baddeley and Logie, 1999; Wagner and Torgesen, 1987). The means by which verbal information is registered in the phonological store depends on whether the information is heard or read. Verbal information that is heard is automatically registered in the phonological store. Verbal information that is read also may be registered in the phonological store, through an articulatory loop which will be activated when the reader subvocally articulates the information (Baddeley and Logie, 1999).

A number of studies argue that dyslexics have difficulties specifically using phonological codes in working memory (Swanson, Zheng and Jerman, 2009; Varvara et al., 2014). For

example, Swanson, Zheng and Jerman (2009) found that children with dyslexia performed significantly poorer compared to age-matched controls on tasks requiring sequence recall (e.g. digit span) and simultaneous processing of digits and words within sentences. These effects were not explained by age or IQ. These deficits in span tasks (e.g. digit span or repeating pseudowords) are now considered one of the major defining characteristics of developmental dyslexia (DD). Both verbal and visual-spatial components of working memory have been found impaired in children (e.g. Reiter et al., 2005; Poblano et al., 2000; Wolf et al., 2010; Menghini et al., 2011) and adults (Smith-Spark et al., 2003; Alloway and Gregory, 2013) with DD.

Although it has been argued that verbal short-term memory deficits are major problems of individuals with dyslexia (Swanson, Zheng and Jerman, 2009), this notion is not held true across all studies. Bree, Wijnen and Gerrits (2010) followed Dutch children with familial risk for dyslexia from age 4 to age 8 and found a positive correlation between nonword repetition at age 4 and literacy achievement at age 8, which was specific to the at-risk for dyslexia group and absent in age-matched controls and children with SLI. However, the study suffers from the limitation that no other measure of phonological skill was included (i.e. PA or RAN). Therefore, it cannot be ruled out that the association between nonword repetition and literacy could be mediated by a different measure of phonological processing. A number of recent studies have addressed this limitation and included other factors such as PA and rapid automatized naming (RAN) in their models.

Boets et al. (2010), in a longitudinal study following a cohort of 62 Dutch speaking children with familial risk of dyslexia, found that PM significantly predicted word reading accuracy only in first grade, whereas PA and RAN consistently predicted accuracy and speed. Dandache, Wouters and Ghesquiere (2014) further divided this sample into three diagnostic groups: dyslexic readers, high-risk normal readers, and low-risk normal readers. No significant differences were found in the developmental trajectories of PM in the

groups. In fact, all three groups performed at similar levels in sixth grade on the pseudoword repetition task, even though the three groups differed significantly on reading and spelling. Nation and Hulme (2011), using path analyses in 242 English children, found that that reading skills at time 1 (6 years old) predicted pseudoword repetition skills at age 7 ($r=0.23$), but pseudoword repetition at time 1 did not predict reading at time 2, suggesting that literacy acquisition positively affects pseudoword repetition. Furthermore, the strongest predictors were autoregressors: pseudoword repetition at time 1 predicted pseudoword repetition at time 2 ($r=0.72$), and reading skills at time 1 predicted reading at time 2 ($r=0.95$). These findings taken together suggest that the difficulties in PM observed in dyslexia may be a secondary (consequence of failure of reading acquisition) or concurrent deficit rather than a direct cause of the reading impairment. Therefore, current evidence from longitudinal studies does not support a causal factor for phonological memory in the PDH of dyslexia.

Training studies investigating PM specifically could provide further insights. However, the current literature does not report any validated training or intervention programme specifically designed to target phonological memory. The overwhelming majority of interventions target phonological awareness, explicit teaching of grapheme-phoneme correspondences, and increased exposure to reading texts. This is not surprising considering the large evidence base described earlier which found strong relationships between PA and literacy and the lack of evidence of such associations between PM and literacy. However, the finding that children and adults with dyslexia perform worse than peers on PM, together with the finding that literacy acquisition positively affects PM, does warrant future research in this area. Specifically, training studies are useful to test the following hypotheses:

1. If PM deficits are concurrent but unrelated to reading impairment, training studies targeting PM will not improve reading outcome.

2. If PM deficits are mediated by PA, training studies targeting PA should also improve PM but the improvement of PM should not correlate with literacy improvement/outcome.
3. If PM deficits are a consequence of reading failure, interventions targeting PA and/or reading should improve PM and the improvement in PA/reading should be correlated with improvements in PM.

An interesting, secondary finding of the longitudinal studies above (Boets et al., 2010; Dandache, Wouters and Ghesquiere, 2014; Nation and Hulme, 2011) with children with familial risk of dyslexia is the finding that at-risk children who do not meet diagnostic criteria for dyslexia in school do have impairments in PA, PM, reading and spelling (Snowling, Gallagher and Frith, 2003; Boets et al., 2010; Dandache, Wouters and Ghesquiere, 2014). These findings suggest that dyslexia is probably not an all-or-none condition, but should be seen on a continuum of reading abilities, where some children reach a threshold of impairments that is defined as dyslexia (Snowling, Gallagher and Frith, 2003).

Phonological recoding in lexical access/Rapid Naming

The last component of phonological processing is phonological recoding in lexical access, which refers to letter-sound recoding or retrieval of grapheme-phoneme conversions. Examples of tasks assessing this skill include the rapid naming of objects, colours, and other kinds of stimuli – tasks that rely on rapid automatized naming (RAN). Dyslexia is associated with problems in RAN (Wagner and Torgesen, 1987). Dyslexic children and adults also perform worse than controls recalling memorised/highly familiar lists such as the letters of the alphabet or the months of the year (Peterson and Pennington, 2012). Dyslexics are less accurate and/or slower in retrieving name codes or phonological codes from memory (Catts 1989; Wagner and Torgesen 1987).

RAN has been proposed to be a strong predictor in the later stages of reading, especially related to reading fluency. In a large longitudinal study in Finland, Puolakanaho et al. (2007) investigated the predictors of dyslexia in children measured at ages 3.5, 4.5 and 5.5 years. Logistic regression models showed that familial risk and letter-name knowledge measures before grade 1 predicted reading status in grade 2. PA and RAN were found to be additional predictors at ages 4.5 and 5.5. In a similar longitudinal study in English-speaking children, Thompson et al. (2015) found that phonology (PM and PA) and letter-knowledge are core predictors of dyslexia at all timepoints, but RAN becomes a stronger predictor at later stages (ages 6-8).

Van Bergen et al. (2012) investigated RAN in three groups of Dutch children: children with familial risk who went on to develop dyslexia, children with familial risk who did not meet diagnostic criteria, and typically developing controls. The authors found consistently impaired RAN from kindergarten to second grade. However, strikingly, the children with familial risk without dyslexia performed at similar levels to the controls. Another novel finding in this study was that the RAN abilities of the parents were strongly predictive of their children's reading status: 40% of children of parents with dyslexia and RAN deficits developed dyslexia, compared to 15% children of those without a RAN deficit. Based on these findings, the authors argue that RAN may indicate a protective factor as well as a risk factor. In other words, strong/intact RAN skills may protect children at risk for dyslexia from developing dyslexia, whereas poor RAN skills in these children should be seen as an increased risk (van Bergen et al., 2012, 2011).

It should be noted that the two large longitudinal studies mentioned previously (Puolakanaho et al., 2007 and Van Bergen et al., 2010, 2011) are conducted in relatively transparent orthographies (Finnish and Dutch). As such, reading disability status was determined based on reading fluency (number of accurately decoded words within a set time) rather than reading accuracy (number of accurately decoded words in an untimed

setting), which is the diagnostic criteria in English. The regularity/transparency of a language's orthographic system is determined in terms of spelling-sound correspondence (Share, 2008; Wimmer & Goswami, 1994). Languages with relatively inconsistent or opaque spelling-sound correspondence, like English, generally show a prolonged and more pronounced influence of PA on reading (e.g. Wagner et al., 1997; Share, 2008), whereas languages with relatively transparent grapheme-phoneme relations, such as Finnish, German, Italian, and Dutch found individual differences in RAN to be better predictors of reading outcome, over and above PA (Landerl & Wimmer, 2008; Verhagen, Aarnoutse and Van Leeuwe, 2008). This is due to the criteria used to determine successful reading acquisition: accuracy or fluency. Accuracy refers to the correct (untimed) decoding of written words (i.e. correctly saying a written word out loud), whereas fluency refers to the number of words correctly pronounced per defined period of time (e.g. seconds or minute).

Word reading accuracy in more transparent orthographies is found to be already at ceiling level after one year of formal reading instruction (e.g. Landerl & Wimmer, 2008; Verhagen et al., 2008). Therefore, dyslexic readers in more transparent languages generally experience fewer decoding problems than their English-speaking peers. Reading speed, however, remains a stumbling-block for the dyslexic readers in these more transparent orthographies (e.g. Landerl & Wimmer, 2008). Therefore, it is unsurprising that the diagnosis of dyslexia in transparent orthographies are characterised by reading speed or fluency rather than accuracy. This, however, could inflate the effects of RAN in such studies. Nevertheless, there is consistent evidence for a distinct contribution of RAN in English as well (e.g. Share, 2008; Wimmer & Goswami, 1994). Specifically, RAN and PA appear to be related to different aspects of reading (Elbro & Scarborough, 2003): RAN is associated with reading speed and orthographic pattern recognition, while PA is mainly related to reading accuracy and nonword reading. In addition, PA appears to be more important in the early stages of reading development (i.e. word-analytic decoding), whereas RAN has a larger

impact on the later stages of literacy development (e.g. reading fluency and word comprehension) (e.g. van den Bos, Zijlstra, & Spelberg, 2002).

Recent studies have also highlighted the importance of RAN in late emerging dyslexia. Little research has been conducted on the characteristics of resolving or late-emerging reading disability, although the proportion of late-emerging cases has been reported to be approximately 40% of all reading disability cases in English and Finnish (Catts et al. 2012; Leach et al. 2003; Lipka et al. 2006; Torppa et al., 2015) and 13.4% of all school-age children.

Only five studies have directly addressed the stability of dyslexia classification (Catts et al. 2012; Etmanskie et al. 2015; Leach et al. 2003; Lipka et al. 2006; Torppa et al., 2015), with varied diagnostic criteria and orthographic transparency. In studies with English-speaking children, Lipka et al. (2006) and Catts et al. (2012) identified dyslexia based on reading accuracy only, whereas Etmanskie et al. (2015) used a combined measure of reading accuracy and comprehension. In a retrospective study, Leach et al. (2003) used more comprehensive criteria based on reading accuracy, fluency and spelling. In the only study conducted in an orthographically transparent language (Finnish), Torppa et al. (2015) identified dyslexia based on multiple measures of reading speed.

Despite the differences in diagnostic criteria and orthographic consistency, the findings converge on the prevalence rate of late emerging dyslexia to account for 25-40% of all dyslexia cases reported at the latest point of follow-up. In addition, although these children display poor abilities in PA, vocabulary and letter-knowledge before school entry, these risk factors have poor predictive value to determine later reading status (Catts et al., 2012). This can in part be explained by the academic development and curriculum set-up in schools. Around grade 2-4, a shift in pedagogy occurs: learning to read changes into reading to learn. Children are expected to read more, increasing the demand for reading

speed/fluency. Because RAN is strongly correlated with reading speed and fluency (Torppa et al., 2015; Lervag and Hulme, 2009; Boets et al., 2010), any existing (minor) RAN deficits before school entry will exacerbate literacy impairments during this crucial stage. In other words, the skills of the late-emerging group seemed to be sufficient for the early grades, but not for reaching the typical level of fluency required in reading in later grades. This is also supported by Lervag and Hulme (2009), who found that reading experience has an reciprocal relationship with PA, but not with RAN.

Three training studies directly targeted letter naming speed (Fugate, 1997; De Jong and Vrieling, 2004; Conrad and Levy, 2011). Fugate (1997) examined the effects of letter naming training on 39 first-grade students' letter naming speed and reading skills. The participants were randomly assigned to either a letter-training (drill tasks in naming individual letters on flash cards) or comparison group (journal assignments and discussion with experimenter). Each training session was 12 to 15 minutes in length and training was provided over 12 school days. The authors report greater naming speed and reading fluency for the experimental group compared to the control group immediately after intervention. There were no significant differences at 7-week follow-up, suggesting that the effects of the intervention are short-lived.

Conrad and Levy (2011) investigated the effects of letter naming training in 44 poor readers in grade 1 and 2. Thirty-one of these students also had poor PA. The students were assigned to one of three groups: orthographic pattern training followed by letter naming training, letter naming training followed by orthographic training, or control (math instruction). Letter naming training involved the students rapidly naming randomly ordered letters presented in a matrix on a computer screen (three matrices per trial; five trials per day for six days). The authors found that letter naming speed improved only when it followed the orthographic training. The orthographic pattern training also significantly

improved reading speed. Therefore, they concluded that efficient letter naming skills may be linked or a consequence of orthographic training.

In contrast, De Jong and Vrielink (2004) trained Dutch first grade students in the rapid naming of letter sounds (ten 10-15 minute sessions over 2 weeks). The letter-sound training focused on eight sounds (four consonants, four vowels). The letter-sound trained group did not have faster letter-sound naming or improved word reading skills at post-test relative to a no-contact control group, or an addition-facts training group. Similar findings were reported by Hintikka, Aro, and Lyytinen (2005). They provided at-risk Finish grade 1 students (nonreaders) with a brief computerized training program (10 to 20 minutes, three times per week over six weeks) that taught relations between phonemes and their orthographic representations. The main difference is that this training did not involve serial naming. Instead, the students heard an auditory stimulus (e.g. a letter-sound) and then had to find the matching orthographic representation (e.g. a letter) as quickly as possible among distractors. The trained group did not make significant gains relative to a control group in naming speed or reading.

Other studies have assessed naming speed embedded in general literacy interventions. Nelson and colleagues (Nelson, Benner, & Gonzalez, 2005; Nelson, Stage, Epstein, & Pierce, 2005) reported a positive effect of an early literacy intervention program (25 lessons targeting letter knowledge, PA, understanding sentences, and RAN) on at-risk English-speaking kindergarten students' PA, letter naming speed, and word reading skills. Nelson, Benner and Gonzalez, (2005) found that the intervention program had a significant effect on PA, letter, object and color naming speed, and pseudoword reading fluency. In the second study, Nelson, Stage, et al., (2005) found that the intervention had a positive impact on PA, letter naming speed, and word and nonword reading, but there was no effect on the object and color naming speed. These results demonstrate that a broadly based intervention addressing emergent literacy skills (including naming speed training) can

improve letter naming speed and reading skills in young at-risk students. However, it is not possible to determine what was responsible specifically for the gains in naming speed, why the effect did not generalize to object and color naming in the second study, and whether the improvements in naming speed were responsible for the gains in reading.

It is also useful to examine whether training in other phonological processes such as PA would affect naming speed as such findings would support the argument that RAN is a component of phonology. Regtvoort and van der Leij (2007) found no effects of a home-based computerized training programme that targeted PA, letter-knowledge and decoding skills on RAN in Dutch kindergarteners at risk for dyslexia. Lovett et al. (2000) compared a phonological intervention with a metacognitive intervention and an active control. Although both interventions improved word decoding and phonological skills in poor readers, there were no significant effects on RAN. Thus, the students with naming deficits made gains in reading despite not receiving a programme that directly targeted naming speech processes and despite not improving in naming speed. In contrast, Vaughn et al. (2006) found significant improvements in PA, RAN, word decoding and comprehension in grade 2 children at-risk for dyslexia after an intervention that addressed PA, fluency, decoding, vocabulary and comprehension. However, it is again not clear if the improvements in naming speed were the cause of any of the improvements in reading.

Finally, Torgesen et al. (2010) found improved naming speed after intervention that targeted PA, decoding, and fluency in grade 1 children at risk for dyslexia. Importantly, the intervention group continued to outperform the control group at one-year follow-up post intervention. In fact, letter naming speed had the largest treatment effect size at follow-up, even though RAN was not directly addressed in the intervention. Thus, it remains unclear which components of the programs were responsible for the improvement in naming speed, and it was not shown that improvements in naming speed were associated with

improvements in reading. In summary, there is not a great deal of evidence to support that naming speed can be improved through instruction, and the evidence that exists is mixed.

Another limitation with RAN tasks is noted by Wagner and Torgesen (1987): “it may be impossible to devise a task that measures recoding in lexical access and little else” (Wagner and Torgesen, 1989: p 203). The authors argue that the “ideal task should measure the efficiency with which (a) the appropriate phonological codes are retrieved from memory, and (b) the lexicon is searched for a string of phonological codes that matches the search string of retrieved codes.” (Wagner and Torgesen, 1989: p 203). It is the latter that is problematic for the RAN tasks. For example, the rapid naming of letters does not involve making lexical access, as each letter is associated with a sound, but not with one specific meaning. In addition, this task cannot be used for young children who do not yet know the alphabet. Moreover, the performance on the task could heavily be influenced by differential knowledge of letter-sound correspondences. This can inflate the correlations between RAN of letters and literacy.

In other words, dyslexics perform worse than controls on the RAN of letter, not necessarily because of impaired phonological recoding of lexical access, but because of their poorer grapheme-phoneme knowledge. Nevertheless, longitudinal studies discussed above consistently find RAN as one of the strongest predictors of later literacy outcome as well as one of the core risk factors that predicts dyslexia, together with PA, letter-knowledge and familial risk. Indeed, there is an ongoing debate about whether RAN and phonological awareness are part of the same phonological deficit/skills set that underlies dyslexia or whether they should be seen as separate contributors to reading impairment, for example in the double-deficit hypothesis (Wolf and Bowers, 1999).

The double-deficit hypothesis (DDH): RAN as an independent predictor of reading disabilities?

The section above has grouped RAN as a component of the phonological system, arguably reflecting a measure of lexical retrieval/phonological access, but also highlighting the caveats with this assumption. An alternative account has been proposed by Wolf and Bowers (1999): the double-deficit hypothesis (DDH). The DDH argues that RAN is a specific and independent predictor of reading disability, largely independent from PA. According to this view, individuals with dyslexia can be classified into three groups: naming speed deficit, phonological deficit, and double-deficit (both deficits combined). It is assumed that the two independent factors have an additive effect and predict that the double-deficit group should suffer the most severe reading impairments.

Several results support the independent role of RAN as an independent predictor of dyslexia. Firstly, factor analyses show a modest association between RAN and PA with each measure loading onto separate factors (reviewed by Swanson et al., 2003). In addition, RAN and PA have been shown to have unique variance in reading ability in regression and structural equation models (e.g. Compton, DeFries, & Olson, 2001; Cutting & Denckla, 2001; Katzir et al., 2006; Powell et al., 2007). The majority of the studies listed above have found RAN and PA to be associated with separate aspects of reading skills: PA has been proven to have stronger associations with reading and spelling accuracy while RAN has primarily been associated with reading speed and fluency both in transparent orthographies like Finnish and Dutch (Boets et al., 2010; van Bergen et al., 2012) and in opaque orthographies like English (Compton et al., 2001; Cornwall, 1992; Pennington et al., 2001; Schatschneider, Carlson, Francis, Foorman, & Fletcher, 2002). Lastly, interventions based on phonological processing have failed to improve naming speed or word reading fluency (Regtvoort & van der Leij, 2007).

Not all studies, however, have found support for the DDH (e.g. Vukovic & Siegel, 2006). One of the reasons for this result is that studies differ in their diagnostic criteria of reading disability. As discussed above, many studies of English measured reading by accuracy, leaving the common variance of RAN and reading fluency unexplored and uncontrolled. In addition, the age when phonological awareness, RAN, and reading are evaluated may influence results. For example, Parrila, Kirby and McQuarrie (2004) found that the commonality between RAN and PA declined over time. In other words, each measure predicted reading in more unique/distinguishable ways in later school years than at the beginning of literacy acquisition. Therefore, it is possible that in studies investigating DDH in the early grades of schooling or in preliterate children, the unique role of RAN may be less prominent than in studies of older children or (young) adults. This could explain the pronounced role of RAN in late-emerging dyslexia, as these studies by nature are performed later in childhood/young adulthood.

Another criticism of the DDH is that RAN may rather reflect the speed of the process of integrating the associations between phonological and orthographic information, a process that is also represented in phonological awareness. This view is supported by findings where speeded measures of phonological awareness have accounted for part of the variance of RAN (Arnell et al., 2009) and reduced the shared variance between RAN and reading (Vaessen, Gerretsen and Blomert, 2009). However, even timed measures of phonological processing were not able to outperform RAN in explaining reading speed in these studies, a finding that continues to support the unique role of RAN in predicting reading speed.

Finally, if RAN is not a subcomponent of phonological processing, then in what way does it relate to reading? This question is still under investigation and many views have been explored. Some scholars explain the RAN-reading association as general processing speed. Support for this idea comes from studies in which children with dyslexia show deficits not

only in reading and naming speed, but also in other tasks requiring effective or fast processing (e.g. Catts et al., 2002). Indeed, Georgiou, Parrila, & Kirby (2009) show that processing speed explains a modest but significant part of the variance between RAN and reading fluency. However, the RAN-reading association cannot be fully explained by processing speed. If processing speed was a major factor behind the RAN-reading association, all kinds of RAN tasks would correlate with reading to a similar extent. However, alphanumeric stimuli (letters and numbers) show a stronger link with reading than non-alphanumeric stimuli like objects and colours (e.g., Benjamin and Gaab, 2012; Georgiou, Parrila, Kirby, & Stephenson, 2008; Georgiou, Parrila, & Papadopoulos, 2008), suggesting that alphanumeric RAN tasks reflect a more specific linguistic processing function that cannot be comprehensively accounted for by general processing speed.

A second explanation explains RAN-reading in terms of automatisisation (Nicolson & Fawcett, 1990; Nicolson, Fawcett, & Dean, 2001), suggesting that the automatisisation of skilled behaviour has been delayed or restricted in dyslexia due to a cerebellar deficit that causes impairment in implicit learning and automatisisation over a wide range of skills, including reading and naming. This explanation is supported in studies where individuals with dyslexia also show deficits in other skills requiring automatisisation, such as motor timing (Wolff, Michel, & Ovrut, 1990a, 1990b), balancing tasks (Nicolson & Fawcett, 1990; Yap & Van der Leij, 1994), and motor skills in general (Morris et al., 1998). However, not all individuals with dyslexia who have naming speed deficits have deficits in balancing performance or other skills related to skill automatisisation (e.g. Ramus et al., 2003). The cerebellar theory will be discussed further in a later section in this chapter.

Summary of the PDH

Section 1.1 discussed what has been for decades and still is currently, the dominant theory in dyslexia. The PDH proposes that reading difficulties arise from a deficit in processing the

speech sounds of words. Early manifestations include impairments in phonological memory, phonological awareness, and letter-name knowledge. Review of longitudinal and intervention studies in children and young adults suggest that there is strong evidence that phonological awareness is associated with dyslexia, especially in orthographically opaque languages such as English. There is also evidence to suggest that RAN is associated with dyslexia, more strongly in orthographically transparent languages, and is a strong predictor of late-emerging dyslexia. Whether a double-deficit model of dyslexia exists is still under debate. Limited evidence however, exists to support phonological memory as a significant independent predictor for dyslexia, even though there is evidence to suggest that it is a concurrent deficit.

1.2. (Rapid) Auditory Processing Deficit Hypothesis (APDH)

A vital part in the development of phonological representations is the awareness of how speech sounds correspond to a written symbol. This notion has led some researchers to propose the existence of an underlying deficit in low-level auditory temporal processing within the dyslexic population, which is thought to precede and cause the phonological deficits, ultimately resulting in reading disability (Tallal, 1980; Goswami et al., 2011). Specifically, it is hypothesised that deficits in rapid temporal auditory processing may adversely affect the process of learning to read by preventing the crucial formation of spelling-to-sound correspondences (Tallal, 1980). This is explained by the important role of rapid acoustic in formant transitions. Formant transitions carry phonetic information and bind phonetic segments together so that the temporal order of speech is preserved. Difficulties in analysing rapid temporal transitions may therefore lead to difficulties in analysing speech at the phonemic level. This theory has received a lot of attention in the research literature over the past few decades, because clinically, this hypothesis has important diagnostic value: “A robust sensory correlate of phonological difficulties enables

very early identification of risk for dyslexia and early targeted intervention to affect the trajectory of phonological development” (Goswami et al., 2011, p335).

Beginning with Tallal's (1980) study of temporal order judgment of children with dyslexia, research has explored the idea that the primary deficit of reading disability could be a result of deviant auditory processing skills of rapid acoustic signals. Early research related the interpretation of “temporal processing” to rapid succession of stimuli or short stimulus durations (Tallal, 1980). However, this theory has been criticised by Mody, Studdert-Kennedy and Brady (1997), who claimed that stimulus processing is temporal only when defining features of the stimuli are changing in time. As such, recent studies have demonstrated that the deficits observed in dyslexic readers are not merely limited to the processing of short, rapidly presented stimuli, but also to slow-rate dynamic acoustic stimuli such as frequency and amplitude modulations and sound rise time discrimination (e.g. Goswami et al., 2011). Therefore, this section will evaluate the auditory processing deficit hypothesis (APDH), not limited to rapid auditory stimuli.

One way to assess auditory processing is by using frequency modulation tasks. Frequency modulation (FM) detection assesses the individual's ability to detect frequency fluctuations in a carrier frequency at a certain modulation rate. Such FMs could be said to represent the fine structure found within the envelopes of the speech waveform (Rosen, 1992). Rise time measures the larger grain size of the speech waveform, which focuses specifically on the speech envelope (Rosen, 1992). Specifically, the rise time task assesses an individual's ability to detect subtle differences in the rate of change of an amplitude envelope. The perceptions of such cues are utilized in the segmentation of the speech signal into its base parts, such as syllables or onsets and rhymes, which is necessary for speech perception (Goswami et al., 2010). These aspects of auditory processing of (speech) sounds are important because identification of phonemes and syllables depends on changes in the amplitude that occur respectively around 50 ms (20 Hz) to 500 ms (2 Hz). Therefore, if an

individual were to be affected by poor auditory processing of slow-rate modulations (between 2 and 20 Hz), it would be expected that speech perception would be affected, which can constrain the segmentation of aspects of the speech signal into smaller elements, thus hampering the development of phonological representations and ultimately disrupting the creation of accurate grapheme-phoneme mapping (Poelmans et al., 2011; Van Ingelghem et al., 2005; Boets et al., 2007). These poor phoneme-grapheme representations will be expressed as poor coding and decoding abilities manifesting behaviourally as word reading and spelling disability.

Assumptions proposed by the APDH include:

1. As dyslexia is universal (as well as phonological deficit), auditory impairment should manifest similarly across languages even with different orthographic systems.
2. Auditory processing should predict phonological measures which in turn predict reading outcome.

Review of the evidence

Tallal (1980) was the first study to investigate auditory sensory deficits in children with dyslexia compared to controls. Specifically, Tallal hypothesised that dyslexia was related to impairments in the temporal patterns in sounds, regardless of whether the sounds encoded speech or not. Twenty children with developmental dyslexia (selected based on formal diagnosis) compared to 12 chronological-age matched controls on four tests of temporal auditory processing: association, discrimination, sequencing, and rate perception. Significant group differences were found for discrimination and rate perception, but only on stimuli with short interstimulus intervals (ISI). Errors on the rate perception test further correlated with nonword reading, spelling, word discrimination, word knowledge and composite reading. However, age and IQ were not explicitly controlled for in the same models, even though they do not appear to be significantly correlated to any literacy

measure in isolated correlation analyses. Tallal concluded on the basis of these findings that at least a subset of children with dyslexia suffer from impairments in processing fast auditory stimuli (regardless of whether these sounds are speech or non-speech).

Other studies have extended Tallal's findings and found that children with dyslexia are impaired in temporal order judgement (Farmer and Klein, 1995; Heath, Hogben and Clark, 1999), auditory choice reaction tasks (Nicolson and Fawcett, 1994a), and gap detection (Farmer and Klein, 1995). Murphy and Schochat (2009) provided direct evidence to support the rapid auditory processing deficit by examining the effects of temporal variables such as ISI, stimulus duration and type of task (discrimination or ordering) on children with and without dyslexia. They found that the dyslexic children performed worse than the controls across all variables, but more importantly, they found an interaction effect between group and duration of stimulus variables: the dyslexic group performed significantly poorer for short durations, whereas the controls performed at similar levels for both short and long stimulus durations.

After Mody, Studdert-Kennedy and Brady's (1997) critique on the rapid auditory processing deficit theory, a number of studies have extended investigations to include FM, amplitude modulation, and rise time detection. These reports were tallied in Hamalainen et al. (2013), who reported consistent impairments in dyslexic adults and children found in the literature for the perception of FM (reported in 76% of studies reviewed), formant modulation (92%), amplitude modulation (75%), rise time (92%), sound duration (75%), but only limited reports of significant group differences in intensity discrimination (13%) and gap detection (30%). Therefore, based on this qualitative overview of the findings, the majority of the experimental auditory studies published to date seem to support an auditory deficit in people with dyslexia. However, the limitations of these studies will be reviewed in more depth in the section (limitations) below.

More recently, a cross-linguistic study (Goswami et al., 2011) investigated auditory processing using psychoacoustic tasks in children in three languages, varying in orthographic complexity and syllable systems: Spanish (transparent alphabetic orthography, simple syllable structure), English (opaque alphabetic orthography, complex syllable structure), and Chinese (morphosyllabic orthography, simple syllabic structure). Appropriate tests of phonological awareness (PA) and reading were administered in each language: English children were tested on single word reading, rhyme awareness, and RAN; Spanish children were administered a spoonerism task, timed nonword decoding task, and RAN; Chinese children completed a tone awareness task, character recognition task, and RAN. In total, 229 children aged 7-13 years participated: 96 from England, 73 from Taiwan, and 60 from Spain. The groups were further divided into 1) dyslexic readers (DD), 2) chronological-age controls (CA), and 3) reading-age matched controls (RA). Psychoacoustic tasks assessed auditory thresholds for sound rise time, duration, frequency, and intensity.

As predicted, the dyslexic children performed significantly worse than CA group on all measures of phonological awareness and literacy, and at equivalent levels to the RA group. The DYS group also had significantly higher thresholds for rise time and duration compared to the CA group, with no differences compared to the RA group. These results were found in all three languages. Language specific results included: impaired frequency discrimination in Chinese, and impairment in both frequency and intensity discrimination in English. The authors concluded that these findings suggest a universal role of auditory processing and rise time discrimination in particular in literacy acquisition and dyslexia. Similarly, Talcott et al. (2003) and Van Ingelghem et al. (2005) have reported increased thresholds in FMs and gap detection in Norwegian and Dutch children with dyslexia, respectively.

Auditory processing → Phonology → Reading?

How does auditory processing lead to reading disability? The APDH postulates that auditory processing is the precursor to phonological development and subsequently, reading ability. Goswami and colleagues have published a series of studies which reported significant relationships between standardised measures of reading, and amplitude modulation (Goswami et al., 2002), rise time (Richardson et al., 2004; Thomson et al., 2006; Pasquini, Corriveau, and Goswami., 2007; Goswami et al., 2011), and duration (Thomson et al., 2006), even after controlling for age, non-verbal IQ and vocabulary. Similarly, Witton and colleagues (1998, 2002) found that amplitude and frequency modulation were significant predictors of phonological skills in both dyslexic adults and controls. In addition, Richardson et al., (2004) found that rise time perception accounted for up to 22% of the variance in measures of phonological processing, over and above age, IQ, and vocabulary in children. These results have been replicated in adults with dyslexia, where both rise time and temporal order judgement accounted for unique variance in phonological (spoonerisms and deletion) and reading tasks (nonword reading) and spelling (Pasquini, Corriveau, and Goswami, 2007). However, rise time no longer predicts unique variance in reading if phoneme deletion was controlled for. The authors argue that this suggests that the relations with literacy arise via phonological awareness, but it should be noted that the authors did not explore how much unique variance phonological awareness predicts in reading when rise time and temporal order judgment are controlled for.

Rosen (2003) re-analysed Goswami et al. (2002) data by looking at relationships between amplitude modulation and reading outcome in the three experimental groups (dyslexics, CA-, and RA-matched controls) separately, but found no correlation between amplitude modulation and nonword reading, a proxy measure of phonological awareness in the dyslexic groups alone. Instead, the correlation was only found in the two control groups (Rosen, 2003), even though there were significant correlations with word reading and

spelling (Richardson et al., 2004). This finding suggests a possibility that auditory processing may affect reading outcome via a tertiary variable that's not phonological awareness.

Using structural equation modelling, Watson and Miller (1993) found that speech perception, but not non-speech perception, was strongly related to phonological processing measures, which in turn were strongly related to reading in undergraduate students in higher education. However, there are two things to note about this study. Firstly, the fact that non-speech auditory processing was not related to phonological processing or reading actually contradicts the auditory processing deficit hypothesis. Tallal's original hypothesis explicitly alluded to this theory as a sensory, possibly cross-modal (i.e. visual as well as auditory), deficit theory. Instead, the finding reported by Watson and Miller (1993) suggest the impairments to be speech-, and thus language-specific. Secondly, the speech perception measure reported in their study consisted of discrimination of syllable sequences, syllable identification, speech repetition, and perception of degraded speech. It can be argued that the first three of these could better be classified as measures tapping into phonological awareness rather than sensory measures of auditory perception. These results can therefore be considered stronger support for the PDH and weak support for the auditory processing hypothesis.

Nevertheless, the relationship between rise time and literacy seems consistent across languages. Goswami et al. (2011) showed that rise time and intensity were consistent predictors of PA across three languages in children, over and beyond age and IQ. Frequency discrimination predicted PA in English and Chinese, and duration discrimination predicted PA in Spanish and Chinese. In terms of reading, only rise discrimination was a consistent predictor across languages (9% of unique variance for Spanish, 26% for English, and 14% for Chinese). Intensity and duration detection were further significant predictors of reading for Spanish, and intensity and frequency for English. For all languages, rapid naming affected reading development, and sensitivity to rise time still uniquely affected reading

development even when individual differences in rapid naming were controlled. The analyses for phonological awareness suggested that rise time affected reading development via its effect on phonological development for Chinese and Spanish, but not for English, where it had an independent effect on reading. It is difficult to extrapolate the cause of these differences as these languages differ significantly in orthographic depth and language system. Nevertheless, the study does converge on a universal contribution of rise time in literacy. These findings extend previous studies that have reported rise time to be related to PA in French, Hungarian, and Finnish, and Norwegian (Hämäläinen et al., 2009; Surányi et al., 2009; Muneaux et al., 2004). However, the fact that PA and RAN predict unique variance, after controlling for auditory processing, provides support for the PDH and contradicts the APDH.

In addition, Watson (1992) found that, although the reading-impaired group of college students performed relatively more poorly on temporal tasks, the majority of this group performed within the same range as the subjects in the control group. In fact, some skilled readers performed poorly on the temporal processing tasks. Therefore, it cannot be concluded that poor temporal processing is a sufficient cause by itself of reading disability.

Similarly, Van Ingelghem et al. (2005) found no correlations between FM-detection thresholds and measures of reading or phonology, despite a significant group difference in Dutch children with and without dyslexia. The authors suggest that the group differences may have resulted from a third unmeasured factor (e.g. attention).

Gibson, Hogben and Fletcher (2006) further found measures of auditory processing (frequency discrimination, frequency modulation detection and backward masking) to be significantly correlated with reading in the control group only. In the dyslexic group, frequency discrimination was found to be significantly, but weakly, correlated with non-

word reading only after accounting for irregular-word reading and age. The authors concluded that auditory processing deficits cannot be the core deficits of dyslexia.

Limitations of the theory

Therefore, despite the large volume of reports of reported auditory deficits in dyslexia, only a minority of the reported studies highlighted above have provided conclusive evidence to explain the mechanism through which a sensory auditory processing impairment will result in a reading disability. Moreover, the findings have been criticised for shortcomings in experimental design, poor validity of the auditory processing measures, and the heterogeneity of the dyslexic groups. These limitations with the auditory processing deficit theory will be discussed in more detail below.

Inconsistent findings in the literature

Despite the large number of studies converging on a deficit in auditory processing in children and adults with dyslexia (Hamalainen et al., 2013), there remain well-designed experimental studies where no differences between groups were found, which cannot be explained by the theory. For example, of the 12 papers examining FM perception in the review study by Hämäläinen et al. (2013), three of the studies were not able to replicate group differences (Halliday and Bishop, 2006; Stoodley et al., 2006; White et al., 2006). Of the eight separate studies that reported correlations between FM detection thresholds and reading and/or spelling skills, three studies were unable to replicate these results (Van Ingelghem et al., 2005; Heath et al., 2006; Dawes et al., 2009). In addition, significant group differences do not mean that the impairments are related to measures of reading or phonology (e.g. Watson, 1992; Gibson, Hogben and Fletcher, 2006; Van Ingelghem et al., 2005). To date, there is no argument that satisfactorily explains all these contradictory findings.

Heterogeneity of the dyslexia group

One possible explanation for the inconsistent findings in the literature is the heterogeneity of the dyslexic group, especially in terms of comorbidity. For example, Heath, Hogben and Clark (1999) and McArthur and Hogben (2001) found auditory deficits only in a comorbid reading- and language-impaired group. In fact, before their influential study in dyslexia, Tallal and Piercy (1973) developed the auditory temporal processing tests in a study with children with specific language impairments (SLI). Authors have also questioned whether SLI and dyslexia are in fact different manifestations of the same underlying deficit, even though it is now widely accepted that they are not (Bishop and Snowling, 2004).

Tallal (1980) further reported that the impairments were only observed in 45% (8/20) of the dyslexic sample of the study. Therefore, it cannot be concluded that the observed impairments are a universal causal factor of dyslexia, especially considering that contributions of auditory processing on other core deficits of dyslexia (e.g. PA, RAN) were not explored. Instead, the study raised questions about possible subgroups within the heterogeneous disorder: “to treat reading-impaired populations as homogeneous may result in incorrect interpretation of research data and may explain, at least in part, some of the many inconsistencies found in the literature” (Tallal, 1980, p195).

McArthur and Bishop (2001) also highlighted that not all dyslexics have auditory deficits. The group differences found seem to be due to a subgroup of dyslexics who perform poorly on the auditory tasks (e.g. Tallal, 1980; Witton et al., 1998; Wright et al., 1997). A number of studies have suggested that the subset of people with dyslexia or SLI who demonstrate poor rapid auditory processing may be characterized by concomitant reading and spoken language impairments (e.g. Heath et al., 1999; McArthur and Hogben, 2001). In a multiple case study of adults with dyslexia, Ramus (2003) estimated the incidence of auditory deficits to be about 40%. In another study, King et al. (2003) found approximately half of

their (rather small sample of 11) individuals with dyslexia showed clinically significant signs of auditory processing disorder.

Amitay, Ahissar and Nelken (2002) divided a group of adults with dyslexia into two groups: a group with poor auditory processing ability, and a group with good auditory processing ability. The rapid auditory temporal processing theory would predict that the group with poor auditory skills would also exhibit the poorest reading performance. However, the reading performance did not differ between the two groups. Moreover, the group with poor auditory skills showed no difficulty with brief intervals or amplitude modulation detection, whereas the other group showed some difficulties. These findings are puzzling and do not fit with the assumptions proposed by the APDH.

To date, not all studies exclude comorbid SLI or have considered the oral language abilities of their participants. This may have resulted in mixed samples with varying proportions of participants with both dyslexia and SLI, which may determine whether a particular research study finds evidence for or against the rapid auditory processing deficit hypothesis. This issue is addressed in this thesis by explicitly measuring oral language skills and excluding SLI.

Methodological limitations/task related effects

Other explanations to the inconsistent findings in the literature relate to experimental procedures and the validity of the measures used.

Firstly, and to some extent related to the heterogeneity of the dyslexia group, the performance variance is much larger in the dyslexia groups than in the controls. This could have a considerable effect on correlational analyses. The studies by Goswami and colleagues have employed correlation and regressions across the whole sample, i.e. both controls and dyslexics combined, and found consistent contributions of rise time on

measures of reading and phonological processing. On the other hand, studies that have studied relationships within group separately (e.g. Hamalainen et al., 2009; Rosen, 2003) have been conflicting. Whereas Hamalainen et al. (2009) found significant relationships with phonological processing in the dyslexic group only (despite no group differences in the measures). Rosen (2003), in a re-analysis of Goswami et al.'s (2002) data, found relationships with phonological processing, measured by nonword reading, in the control group only. Gibson, Hogben and Fletcher (2006) report a mismatch of variability between the dyslexic and control groups, with greater variability in the dyslexic group. Only a proportion of the dyslexic group performed poorly resulting in an extended tail in the distribution, which inflated the mean for the dyslexic group.

Secondly, group differences between dyslexics and controls in auditory processing tasks may reflect other non-sensory difficulties (e.g. attention, memory) not explicitly measured. Roach, Edwards and Hogben (2004) simulated the effect of errant trials, defined as “a trial on which any non-perceptual factor, such as momentary inattention, distraction, or confusion prevents the observer from responding as accurately as predicted from his or her psychometric function” (p. 819) on performance of psychophysical tasks. The simulation produced threshold distributions similar to the pattern of results frequently observed in dyslexic groups. These results suggest that the poor performance of dyslexic groups on psychophysical tasks could be equally well explained by general attention difficulties in these groups. However, if an underlying attention variable detrimentally affects the performance of the dyslexic group, one would expect to find poor performance of these individuals across the board in all tasks. In other words, if the dyslexics struggle with attention and/or distraction by not being able to complete tasks, this should be reflected on all tasks, rather than specific marked deficits in rapid auditory processing and/or reading alone. This is, however, not the case and studies consistently report marked difficulties in isolated domains instead.

Thirdly, the validity of auditory processing measures has been questioned (McArthur and Bishop, 2001). To address, this issue, Heath et al. (2006) studied 104 adults with a wide range of reading abilities and two comparison groups: 49 dyslexic adults and 41 skilled readers. Participants attended two sessions, either on the same day separated by a long meal break, or over two days up to two weeks apart. Results showed moderate-high test-retest reliability for most tasks. In contrast, construct validity was poor with no systematic covariation across tasks. Regression analyses controlling for IQ further showed weak unique predictive power for reading ability. The authors concluded that impairments on perceptual tasks including auditory processing measures commonly used (FM, rise time, frequency discrimination) may be an associated marker of dyslexia, but not a causal factor.

Lastly, the studies discussed so far are cross-sectional in nature. It is important to note that correlations do not prove a causal relationship between variables. Tallal's and Goswami's theories maintain that phonological deficits in dyslexia are a consequence of an impairment in auditory processing. There is currently a considerable lack of longitudinal and training studies testing the APDH.

Longitudinal studies

Heath and Hogben (2004) screened 227 preschoolers on phonological awareness, auditory temporal processing, phonological memory, vocabulary and listening comprehension. Reading outcome was measured two years later at the end of Year 2. The children were classified as at-risk for dyslexia if their performance on phonological awareness fell within the lowest quartile. Discriminant analyses found that this classification of risk based on measures of phonological awareness was the best classifier of future reading disability. Auditory temporal processing did not improve classification.

Similarly, Share et al. (2002) screened 543 children at school entry and followed them over three years, at which point they were classified as dyslexic (N=25), garden variety poor

readers (low-IQ)(N=14) or typical readers (N=414). Dyslexic children showed poor performance at school entry on phoneme segmentation, short-term memory, and RAN. On the auditory processing measures at school entry, the dyslexic readers performed significantly worse on the long-ISI trials but not the short-ISI trials – a direct contradiction to Tallal's (1980) findings. A further analysis comparing the dyslexic children with poor auditory processing and those with relatively good auditory processing skills did not find significant group differences in phonological processing or pseudoword reading. Further analyses with a selection of the sample matched on IQ and gender found that early auditory temporal deficit (of long ISI) did not predict later phonemic awareness nor was it related to any other phonological processing measure. The authors concluded that their findings are directly at odds with the APDH. Instead, auditory temporal processing deficits are found to be concurrent but not predictive/causal to reading impairment.

In addition, Boets et al. (2007) followed 62 Dutch speaking children from one year before onset of formal reading instruction to one year into reading instruction. Half of the children were at risk for dyslexia (i.e. had a family member with dyslexia), whereas the other half were not. Auditory processing was measured by gap-detection, FM, tone-in-noise detection, and speech-in-noise perception. Literacy measures were collected after a year of formal reading instruction, at which point the groups were further redistributed to three groups: high-risk dyslexic readers, high-risk normal readers, and low-risk normal readers. The high-risk dyslexic readers performed worse than the other groups on only the FM detection task and most of the phonological tasks. On the individual level, the authors could not find any consistent patterns of deficits across auditory, speech perception and phonological processing and only one third of the high-risk dyslexia group had auditory and speech perception impairments. The authors conclude that the core of literacy problems is found in the higher-level phonological domain and that it is unlikely that auditory perceptual problems would be at the base of these.

Lasly, Wright and Conlon (2009) tested 70 children and 52 controls nine-months apart on measures of visual and auditory (FM) processing skills. Similar to Boets et al. (2007), the authors reported sensory deficits in about 30% of the dyslexic children. Regression analyses, controlling for age, nonverbal ability, and trial performance, found weak unique predictive value of auditory processing on phonological processing (7.2%) at timepoint 2, but no predictive power for reading measures at either timepoint.

All in all, findings from longitudinal studies do not support the auditory processing deficit hypothesis.

Training studies

Training or intervention studies also provide an opportunity to test the causal relationships between rapid auditory processing and reading. If training in rapid or temporal auditory processing leads to subsequent improvements in a reading transfer task, over and above improvements over time (no-training passive control) or due to a non-auditory training method (active control group), then it can be assumed that auditory processing has a causal role in reading. Unfortunately, most studies training rapid auditory processing in individuals with dyslexia have trained these skills in conjunction with other linguistic skills. This makes it impossible to distinguish the specific effect of rapid auditory processing training on reading outcome.

Schaffler et al. (2004) found that 10 hours of discrimination training for intensity, frequency, silent gaps, and temporal order led to significant improvements in spelling in a group of 25 poor readers (7–22 years), in contrast to no training effects in smaller groups who did 10 hours of visual discrimination training (N = 11) or no training at all (N = 6). However, the children were receiving concurrent reading remediation throughout the study; the untrained test–retest control group lacked power (N = 6); and they only tested

the effect of auditory training on spelling and not reading. Therefore, the conclusions of the study are limited.

Strehlow et al. (2006) did find improved reading and spelling in 15 children with dyslexia after four weeks of training their reading and their ability to order frequency modulated tones. However, the active control group of 15 children with dyslexia, who received reading training alone, also improved in reading, suggesting that the improvements observed in the experimental group were due to the concurrent reading training.

McArthur et al. (2008) found improved performance on psychoacoustic measures in 20 children with dyslexia after training on a frequency discrimination task, rapid auditory processing task, vowel discrimination task, or consonant-vowel discrimination task. Further investigations, however, found that although the training group improved on repeating sentences and spelling of irregular words (but not on word reading), these effects could be completely explained by test-retest effects.

Taken together, the results of existing training studies suggest that although auditory processing deficits in children with dyslexia can be successfully treated, these training effects do not necessarily transfer to better reading outcome. Thus, the results of the existing training studies do not support a causal role for auditory processing deficits in reading.

Summary RAPDH

In summary, although there is some convergence in cross-sectional studies towards a deficit in auditory processing deficits in people with dyslexia, these findings are often limited to a proportion of the sample (approximately 40%). In addition, there is no evidence for a causal relationship based on existing reports of longitudinal and training studies.

1.3. The magnocellular theory (MCT) of developmental dyslexia

In the earliest reports of developmental dyslexia, the disorder was first hypothesised to be a result of visual-processing difficulties. Early accounts of dyslexia were called 'congenital word blindness' (Hinshelwood, 1900; Morgan, 1896) and were thought to be caused by a deficiency in the 'visual memory for words'. Hinshelwood (1900) described two boys, aged 10 and 11, who struggled with reading, despite being intelligent, and doing well in other subjects in school. In fact, one boy had a very good memory and could recall books/stories from memory, initially masking his inability to read in school. Morgan (1896) described a 14-year-old boy who was intelligent but who at 14, with seven years of schooling and tutoring could barely master the letters of the alphabet. Based on these observations, and before the phonological deficits in dyslexia were understood, researchers looked for an explanation for the reading difficulties in the visual domain. One visual processing theory that has spurred on a lot of investigations as well as controversy is the magnocellular theory (MCT).

The magnocellular and parvocellular systems

The magnocellular/parvocellular distinction of the visual system is based on the anatomical organization of the lateral geniculate nucleus (LGN). This nucleus is divided into six layers. The two ventral layers contain large neurons and are called the magnocellular layers. The four dorsal layers contain small neurons and are called the parvocellular layers. The magnocellular layers mediate the detection of movement and rapid temporal changes in stimulation while the parvocellular layers are specialized for detecting fine shape and for colour vision. Functions of the magnocellular and parvocellular systems have been measured using contrast sensitivity (Skottun, 2000), which is a measure of contrast detection. Specifically, the magnocellular cells are sensitive to contrasts at low spatial frequencies while the parvocellular system is sensitive to contrasts at high spatial frequencies.

The magnocellular theory of developmental dyslexia

The MCT of developmental dyslexia postulates that dyslexia is the result of reduced sensitivity in the magnocellular system. Originally postulated as the transient system deficit theory (Lovegrove, Garzia & Nicholson, 1990), the theory built on the notion that reading is characterised by a number of brief fixations separated by small saccades and postulated that the magnocellular system suppresses the parvocellular system during each saccade in successful reading. Without this suppression, the parvocellular representations from different fixations would become confused. Reports from dyslexic patients include 'letters moving on the page', and confusions of 'b' and 'd', as well as reading 'bad' as 'dab', providing some support to this notion. However, a number of studies (e.g. Bridgeman & Macknik, 1995; Uchikawa & Sato, 1995; Ross, Burr & Morrone, 1996) have since shown that it is not the parvocellular system but the magnocellular system that is suppressed during saccades. Therefore, the transient system deficit theory might not be able to provide the causal theory for dyslexia. Nevertheless, researchers have persisted that the magnocellular system still could play a causal role in dyslexia (Stein and Walsh, 1997, 2000) and put forward several alternative hypotheses.

Assumptions of the theory on potential functions of the magnocellular system in reading processes:

1. The magnocellular system helps control eye movements. Therefore, impaired magnocellular function might destabilize binocular fixation. As a consequence, letters might then appear to move around and cause visual confusion.
2. Anatomical connections from the magnocellular laminae of the LGN (mLGN) project to the posterior parietal cortex (PPC), which encompasses the somatosensory cortices (BA 5 and 7), the supramarginal gyrus (BA40) and the angular gyrus (BA39). Stein and Walsh (2000) argue that the PPC is important for normal eye-movement control, visuospatial attention and peripheral vision which are all important

components of reading, and that it is dominated by m-like properties: sensitivity to direction of movement, sensitivity to direction of gaze, and relative insensitivity to colour or visual form. It is also a region which, if damaged (in the right hemisphere), results in acquired reading disorders (Kinsbourne and Warrington, 1962).

Evidence to support the MCT

Lovegrove (1980) in an early report showed that developmental dyslexics have slightly reduced contrast sensitivity at the low spatial frequencies and low luminance levels, which is favoured by the magnocellular system, particularly during flicker, whereas at the higher spatial frequencies served by the parvocellular, sustained system their contrast sensitivity is normal if not superior to that of controls. Cornelissen et al. (1995) showed impaired visual motion sensitivity at high contrasts and illumination levels. Furthermore, Livingstone and Galaburda and colleagues (1991) demonstrated that the magnocellular layers of the lateral geniculate nucleus (LGN) in five dyslexic brains examined post mortem were more disorganized than in control brains, and that the magnocells themselves were over 20% smaller than in control brains. These findings suggest that many dyslexics may have a fundamental impairment of their visual processing. However, these studies have not included any correlations or regressions with reading outcome, so it is not exactly clear if and/or how these observed visual deficits are related to reading outcome.

Longitudinal studies in prereading children also found evidence for the MCT. Boets et al. (2007) found that children who are less sensitive to coherent motion in preschool subsequently went on to have poorer literacy skills in grade 1. Prereading children at risk for dyslexia have been reported to be significantly less sensitive to coherent motion and visual frequency doubling compared to a age-matched controls (Kevan and Pammer, 2008). A subsequent study (Kevan and Pammer, 2009) reported that contrast sensitivity in kindergarten predicted reading ability two years later. Similarly, Hood and Conlon (2004)

found that temporal order judgment in preschool children predicted their single word reading skill in Grade 1.

A small number of training studies have also been conducted. Fischer and Hertnegg (2000) trained children for three weeks on a saccadic control task. The dyslexic children's saccadic control seemed to have normalized after training, to a consistent level with the control group. However, there was no measure to indicate if the visual improvements translated into improved reading. Solan et al. (2004) trained poor readers on visuo-perceptual tasks. They demonstrated that children improved on reading comprehension and word attack measures after the intervention. However, the children were also "provided the opportunity to develop improved cognitive strategies" (p. 644), making it difficult to evaluate the impact of the visual training on reading independently of the increased exposure to words presented in a novel way.

Similarly, Lorusso et al. (2006) used a technique in which the children were required to make a rapid attentional shift to a stimulus in either the right or left visual field. They demonstrated increases in reading accuracy and speed compared to a control group that was exposed to more traditional remediation methods. However, again the stimuli in the task were words that the children had to identify that "became increasingly difficult in terms of word length and complexity of spelling" (p. 201). Thus, it is difficult to fully distinguish the effects of visual processing deficits over and above any orthographic effects.

More recently, Chouake and colleagues (2012) trained individuals with dyslexia for five days using a motion detection task (magnocellular stimulation) or a parallel line detection task (parvocellular stimulation). Participants in both training groups improved their speed on a subsequent lexical decision test, but neither group improved their accuracy at recognizing words (in fact, a small decrease in accuracy for both groups was observed). However, only individuals in the magnocellular training group had final accuracy scores which correlated

positively with increased speed from the first to the final motion-detection training session. The authors interpreted this finding as evidence that magnocellular training can improve the ability to recognize words, even though no improvement from test 1 to test 2 was observed.

Another controversial treatment for dyslexia involves the use of coloured lenses or transparencies placed over pages of text. Ray, Fowler, and Stein (2005) argued that short wavelength (blue) cones inhibit magnocellular neurons; therefore, yellow transparencies should decrease this inhibition and improve reading performance. Additionally, coloured lenses and overlays are sometimes used to treat a subtype of dyslexia called “Irlen syndrome,” which has been described as oversensitivity to specific wavelengths of light (Kruk, Sumbler, & Willows, 2008).

In contrast to the above studies that have reported some (though limited) reading improvement from the use of treatments, others have failed to find any benefit. For example, children diagnosed with Irlen syndrome performed similarly on a test of reading (the Wilkins Rate of Reading Test (WRRT)) when i) using no coloured overlay, ii) an overlay made with their prescribed colour, or iii) an overlay made with the colour complimentary to their prescribed colour (Ritchie, Sala, & McIntosh, 2011). To control for placebo effects, the children were blind to what colour would supposedly assist their reading. However, the authors did not control for the knowledge of prescription, and the only children showing improved reading ability when reading through their prescribed colour of overlays were those familiar with what colour they had been prescribed, suggesting a placebo effect. In another study though, coloured overlays did produce faster reading on the WRRT in readers with and without dyslexia (Henderson, Tsogka, & Snowling, 2013). Therefore, there is currently conflicting evidence in the literature.

Controversies

It should be noted that the magnocellular impairments that have been found in dyslexics are very mild and are often demonstrated using very low contrasts, low light levels or unusual motion conditions that are not found during normal reading. Therefore it is still unclear how exactly such seemingly mild impairments under very specific conditions could lead to difficulties with reading. Indeed, the major criticisms of the MCT are briefly listed below. In fact, Stein, Talcott and Walsh (2000) admit: “At present, we can only speculate what precise effect these pathological changes [post-mortem dyslexic brains that neurones in the magnocellular layers of the lateral geniculate nucleus (LGN) were smaller and more disorganized than in control brains] would have on M-cell performance psychophysically” (p. 210).

Firstly, it is unclear how the MCT could explain the other deficits observed in dyslexia. Phonological deficits are the most consistently observed deficits in dyslexia, as well as deficits in auditory processing, and motor/cerebellar deficits in certain subsamples with dyslexia. These deficits are difficult to comprehend through a purely visual theory. Stein and Walsh (1997, 2000) outlined a few possible explanations:

1. Auditory processing: The auditory system does not have an anatomically distinct magnocellular pathway like the visual system, but there exists an auditory subsystem, characterised by large neurons which are involved in the processing of acoustic transients. As such, this auditory transient system is analogous to a visual magnocellular transient deficit. This is in line with Stein (1994) who suggested a multimodal temporal processing deficit as the basis of dyslexia. Early evidence that the deficits in the visual and auditory modalities may be related was reported by Galaburda, Menard, and Rosen (1994) who found abnormalities in the medial geniculate nucleus (projecting to the auditory system) as well as in the lateral

geniculate nucleus (projecting to the visual system). These magnocellular cells are thought to be responsible for processing temporal information in the visual and auditory domains respectively. Studies that have reported that visual and auditory deficits co-occur in some dyslexics provide behavioural evidence for a more general multimodal magnocellular deficit (e.g., Cestnick, 2001; Witton et al., 1998).

2. Cerebellar/motor deficits: The cerebellum receives many efferent connections from the magnocellular system, so it is proposed that cerebellar deficits are a result of primary impairment in the magnocellular system (via some form of cascading effect). However, there is no concrete evidence for this hypothesis, and cerebellar deficits in dyslexia are still poorly understood and inconsistent (see Cerebellar Deficit Hypothesis in the next section).
3. Phonological deficits: Phonological deficits in dyslexia are the most consistently observed and generally accepted as the core deficit. However, the cause of these deficits is still debated (see Phonological Deficit Hypothesis above). Talcott et al. (2000) found that visual motion sensitivity explained independent variance in orthographic skill, and that auditory sensitivity covaried with phonological but not orthographic skill. In a replication of Talcott et al. (2000), using a larger sample of unselected school children, Talcott et al. (2002) found smaller and less specific relationships between visual and auditory processing and component reading skills. A similar study by Gibson, Hogben, and Fletcher (2006) found that measures of visual processing were not specifically related to nonword or irregular-word reading. Instead, measures of auditory processing were found to be associated with phonological decoding skills. There is presently a lack of consistency in finding relationships between visual processing and reading skills.

A second major criticism of the MCT is that the visual deficits observed could be explained by a parvocellular as well as a magnocellular deficit (Skottun, 2000). In a comprehensive

review paper of contrast sensitivity studies in dyslexia, Skottun outlined that reduced contrast sensitivity to either low spatial frequency or high temporal frequency stimuli is by itself an imperfect indicator of a magnocellular deficit. Lesion studies in primates report that lesions restricted to magnocellular layers have relatively little effect on the overall contrast sensitivity (e.g. Merigan & Maunsell, 1993). Lesion studies in primates suggested that reductions in contrast sensitivity following such lesions are mainly apparent when contrast sensitivity is determined using stimuli having both low spatial and high temporal frequencies (Merigan et al., 1991a). Sensitivity to stimuli of either low spatial or high temporal frequencies by themselves can be (and may be even more severely) reduced following parvocellular lesions (e.g. Merigan et al., 1991b). Therefore, only studies that have investigated and reported deficits in contrast sensitivity to both high temporal and low spatial frequencies should be considered evidence for the specificity of the MCT (Skottun, 2000).

Lastly, some researchers have questioned if the poor performance of dyslexic individuals could be better explained by non-sensory, non-linguistic factors instead, such as attentional factors or problems with task completion (e.g. Gibson, Hogben and Fletcher, 2006; Vidyasagar and Pammer, 2010). For example, Amitay et al. (2002) found that, while a minor proportion of dyslexics (6/30) had deficits on visual and auditory magnocellular tasks, these individuals were also consistently impaired on a broad range of perceptual tasks that did not assess the magnocellular functioning. Therefore, these deficits cannot be explained by the MCT alone. Instead the authors reported that this subgroup of dyslexics may suffer from generally impaired perceptual skills.

Jones et al. (2008) used a novel design to tease apart the correlation with reading ability of motion perception (in a Ternus task) and attentional mechanisms (in a visual search task). The authors found that a significant visual deficit in the dyslexic group was found only when the task required visual search, but not when it involved motion perception alone. This

suggests that the visual processing deficit in dyslexia may be a deficit in visual attentional mechanisms, but not need be magnocellular specific. A recent longitudinal study (Franceschini et al., 2012) followed Italian-speaking prereading children over the course of 3 years and found that prereading attentional orienting, not magnocellular function, predicted future reading acquisition skills in grades 1 and 2 over and beyond age, nonverbal IQ, and speech-sound processing.

Summary MCT

In summary, there is conflicting evidence in the literature with regards to the MCT. Although there is some evidence in support of the MCT, these deficits are only reported to be very subtle and apparent under specific low-light, low contrast conditions. In addition, support is lacking for how the MCT could explain the other observed deficits in dyslexia.

1.4. Cerebellar deficit hypothesis (CDH)

The cerebellum has been termed a “neuronal learning machine” by Raymond, Lisberger and Mauk (1996) and can be divided into three lobes: anterior lobe (lobules I-V), posterior lobe (lobules VI-IX), and flocculonodular lobe (lobule X). It forms subcortical loops with the cerebral cortex via the thalamus and pons. Traditionally, the cerebellum has been associated with motor learning and control, and the coordination of smooth movements, balance and posture, and visually guided movements (Albus, 1971; Ito, 1972). However, the cerebellum has also been proposed to be involved in a myriad of cognitive skills, including language (Leiner, Leiner and Dow, 1993) and reading (Fulbright et al., 1999), although this remains controversial (e.g. Glickstein 2006, 2007).

For example, functional neuroimaging studies have found that the cerebellum activates during non-motor tasks (see Stoodley and Schmahmann, 2009 for review), although many studies do require a verbal or motor (button press) response, and eye movements could

not be excluded. In addition, patients with cerebellar damage experience cognitive deficits (Schmahmann and Sherman, 1998). Animal studies further found that lateral regions of the human cerebellum have expanded in conjunction with frontal cortical regions compared to those in primates (MacLeod et al., 2003) and that the largest proportion of white matter fibers to the human cerebellum come from prefrontal cortex (Ramnani, 2006). These studies suggest that the cerebellum is involved in cognitive functions beyond fine motor control. It is postulated that the regions in the cerebellum that receive inputs from cortical perisylvian language regions (ie Broca's area) will support language processing; regions that receive input from motor regions support motor control; and so on (Schmahmann, 1996; Stoodley and Schmahmann, 2009; Stoodley, 2009).

One of the main limitations of the casual deficit hypotheses discussed previously is that no one theory can explain the myriad of heterogeneous deficits observed in the dyslexia population. The phonological deficit hypothesis cannot explain the conjunct auditory or visual deficits observed in subgroups of dyslexic individuals. Equally, the findings of the magnocellular sensory hypotheses do not directly relate to the core phonological deficits. In an attempt to unify the disparate findings, and based on the theoretical foundations discussed in the previous paragraph, Nicolson, Fawcett and Dean (2001) proposed the cerebellar deficit hypothesis (CDH), which re-interpret the multifaceted deficits in dyslexia as a result of impaired skill automatization or implicit learning.

Assumptions postulated by the CDH (Nicolson, Fawcett and Dean, 2001):

1. The pattern of difficulties in cognitive, information processing and motor skills is predicted by the cerebellar deficit hypothesis.
2. The behavioural symptoms of dyslexia can be characterized as difficulties in skill automatization (the process by which, after long practice, skills become so fluent that they no longer need conscious control).

3. Cerebellar abnormality results in impaired implicit learning.
4. Dyslexic individuals showing the above behavioural manifestations of cerebellar impairment also show direct neurobiological evidence of cerebellar impairment.

Review of the evidence

Claim (1) "The pattern of difficulties in cognitive, information processing and motor skills is predicted by the cerebellar deficit hypothesis"

In a series of studies, leading to the proposal of the theory, Nicolson and colleagues demonstrated that dyslexic individuals showed impairments similar to those often observed in patients with cerebellar damage, such as impaired time-estimation (Nicolson et al., 1995), dystonia and dyscoordination (even when compared to younger reading-age matched controls) (Fawcett, Nicolson and Dean, 1996), balance (Nicolson and Fawcett, 1994b), and muscle tone (Fawcett et al., 1999). However, these early studies are limited by small samples sizes (approximately 10-15 in each group) and concurrent findings of poor phonological deficits in the dyslexic samples, which are expected but not further explained by the CDH in the papers. Most strikingly, though, is that many of these studies report subsets of data from the same cohort of participants (Nicolson and Fawcett, 1990), and either included new recruits over time (e.g. Nicolson and Fawcett, 1994b) or divided into different subgroups based on age (e.g. Nicolson, Fawcett and Dean, 1995; Fawcett, Nicolson and Dean, 1996). This means that the supporting evidence published may have come from a very specific sample which, for some unreported reason, may have cerebellar deficits.

Fawcett and Nicolson (1999) did replicate their previously reported impairments on cerebellar tasks and phoneme segmentation and non-word repetition in a sample of 59 dyslexic children, not included in their previous reports, and 67 controls, of which 19 had participated in a previous study (Fawcett, Nicolson and Dean, 1996). Furthermore, although

these studies report significant group findings, no relationships between cerebellar tasks and phonological or reading skills were further explored. All in all, these preliminary reports call for replication and investigations since these preliminary reports have reported mixed findings.

Fischer and Hartnegg (2000a,b) found that dyslexic individuals (N=262, age 7-17) made significantly more intrusive saccades when they were asked to look at a stationary fixation point compared to controls. Biscaldi, Fischer, and Hartnegg (2000) studied control of saccadic eye-movements in 506 individuals with dyslexia compared to 114 controls in the same age group (both groups age range 7-17) but found impaired performance in only half of the dyslexic group. Similar findings were reported by Ram-Tsu et al. (2006) and Bucci et al. (2008). In contrast, Huzler et al. (2006) found no significant differences between dyslexic and control groups.

In a (non-cognitive) intervention study, Stein, Richardson and Fowler (2000) reported that eye-patching in children with poor binocular stability, and who experience reading problems, led to a significant improvement in reading scores. However, Stein, Richardson and Fowler (2000) studied a very specific group of patients with reading difficulties who had concurrent unstable binocular control, which does not necessarily generalise to the wider dyslexic population. In fact, researchers argue that the poor eye-movement control observed in the dyslexic population is a result rather than a cause of their reading difficulties (discussed in Stein, Talcott and Wlsh, 2000). Moreover, oculomotor deficits in dyslexia can be interpreted as support for the rapid visual processing deficit hypothesis (e.g. Biscaldi et al., 2000), the magnocellular deficit hypothesis (e.g. Ram-Tsur et al., 2006; Huzler et al., 2006; Fischer and Hartnegg, 2000a,b) and/or the cerebellar deficit hypothesis (e.g. Bucci et al., 2008). In fact, the exact location of ocular motor learning is still unclear and “the cerebellum, but also cortical areas of the magnocellular stream such as the parietal cortex, could be the sites of ocular motor learning” (Bucci et al., 2008: p. 417).

Other studies on the 'classical' measures of cerebellar function have found that dyslexic participants have poor postural stability and balance compared to controls (Fawcett and Nicolson, 1999; Getchell et al., 2007; Moe-Nilssen et al., 2003; Nicolson and Fawcett, 1990; Stoodley et al., 2005; Yap and van der Leij, 1994). However, the findings suggest that dyslexic individuals are not impaired across all balancing tasks. Moe-Nilssen et al. (2003) and Stoodley et al. (2005) found children with dyslexia performed poorly only when asked to balance with eyes open compared to eyes closed. Getchell et al. (2007) found group differences on a composite balance score at a marginal level of significance ($p=0.05$). However, after correction for multiple comparisons, this effect fell below threshold.

In contrast, Wimmer, Mayringer, and Raberger (1999) did not find any differences on the same balancing tasks used by Nicolson and Fawcett (1990, 1999) in German children with dyslexia. After taking ADHD scores into account, the authors found that only those children with dyslexia who also had higher ADHD scores performed poorly on the balancing tasks. Indeed, in a subsequent study, Raberger and Wimmer (2003) investigated balancing impairments and rapid naming in children with dyslexia and/or ADHD. Their design was novel as they had four groups of ten children each: dyslexia only, dyslexia+ADHD, ADHD only, and control. This allowed them to investigate interaction effects of comorbidity. Indeed, they found that balancing impairments showed a main effect of ADHD, whereas RAN impairments showed a main effect of dyslexia. Therefore, it is possible that the balancing impairments reported in previous studies were a confound of comorbid ADHD, which was not explicitly measured or controlled for.

Another limitation is that it is hard to infer a causal role without data exploring any relationship between cerebellar measures and reading. Despite the reports of group differences, only a small number of studies have explored relationships with reading and/or phonology. Stoodley et al. (2005) found significant group differences on a balancing task and found a significant relationship between scores on the eyes-open balancing tasks and

reading and spelling in 16 dyslexic children and 19 controls. Specifically, the better readers were also better at the balancing task. This effect was still significant after controlling for age and within each group separately. However, it should be noted that only 50% of the dyslexic children fell within the 'impaired' range on the balancing task, and the best predictor within the control group was digit span.

In contrast, Stoodley et al. (2006) found no group differences in adults, but did report a marginal group difference ($p=0.045$) when accuracy and speed of a pointing task were combined. This combined score further explained unique variance in literacy scores; however IQ, phonological processing, and memory (digit span) were not controlled for, even though the groups differed significantly on the latter two.

Claim (2) “The behavioural symptoms of dyslexia can be characterized as difficulties in skill automatisaton”

Another claim of the CDH is that “the behavioural symptoms of dyslexia can be characterized as difficulties in skill automatisaton” (Nicolson, Fawcett and Dean, 2001: p 508), which could be investigated with measures of processing speed. A task that is highly automated should require little effort and a shorter amount of time to do. Studies investigating processing speed have indeed found that dyslexic adults and children are slower than controls (e.g. Stoodley and Stein, 2006; Velay et al., 2002; Catts et al., 2002). Stoodley and Stein (2006) further found that the scores from a peg-moving task significantly correlated with general processing speed and the reaction times on phonological and orthographic processing tasks in a combined group of dyslexic adults and age-matched controls. A longitudinal study following 279 children from second to fourth grade (Catts et al., 2002) also found significant group differences in processing speed between dyslexic and control children, which further explained unique variance in reading outcome even after taking IQ and phonological awareness into account.

However, Bonifacci and Snowling (2008) have criticised these studies as only low-IQ dyslexic readers show slower performance, and Shanahan et al. (2006) have criticised the inclusion of individuals with comorbid ADHD and dyslexia, which may have confounded results as children with ADHD show slower processing speeds than controls. The first criticism seems unlikely to be the case as almost all studies which reported significant differences have included participants with IQ>90, and therefore, who do not fulfil criteria for low-IQ. However, the latter criticism of comorbid ADHD requires further investigation.

Claim (3) "Cerebellar abnormality results in impaired implicit learning"

When asked to perform explicit and implicit learning tasks, dyslexic readers show poor performance compared to controls on implicit learning tasks only (e.g. Sperling et al., 2004; Stoodley, Harrison and Stein, 2006; Pavlidou and Williams, 2010). These implicit learning impairments have also been shown to be specific to dyslexic children, compared to skilled reading controls and low-IQ poor readers (Stoodley et al., 2008). Whereas skilled readers and low-IQ readers both showed learning on a motor sequence task, measured by significantly faster responses, the dyslexic readers did not.

On the other hand, Howard et al. (2006) found dyslexic college students not to be impaired across all implicit learning tasks, but only when the learning task required learning of sequences as compared to learning of spatial contexts. Learning scores of the sequence task further correlated positively with reading measures of word and non-word reading across groups combined. However, sequence learning scores did not correlate with phonological awareness, RAN or vocabulary. In contrast, spatial learning scores correlated negatively with word and non-word reading across groups combined. The authors also controlled for confounding effects of ADHD by excluding participants with ADHD, which did not change the results. Although both tasks require implicit learning, the authors propose that the two tasks are served by different brain systems.

Whereas sequence learning relies on fronto-striatal-cerebellar circuits (e.g. Prull et al., 2000), spatial learning relies on medial temporal lobe structures such as the hippocampus (e.g. Manns and Squire, 2001). However, the authors did not claim that the deficits were cerebellar specific: “The current study was not designed to test any of these theories [low-level sensory perception, lack of automaticity, articulatory fluency]” (Howard et al., 2006: p 1140) and “our data do not provide a clear picture or allow for a straightforward interpretation of the relationship between implicit sequence learning and phonological processing” (p1141).

Howards et al.’s (2006) findings of a possible dissociation between sequence and spatial learning could explain why Kelly, Griffiths and Frith (2002) did not find any group differences when testing dyslexic college students on a spatial sequence learning task, as implicit spatial learning could be unaffected in dyslexia. However, Russeler, Gerth and Munte (2006) found no group differences in either a motor sequence learning task or an artificial grammar learning task in dyslexic adults. These findings are directly at odds with the findings of Sperling et al. (2004), Stoodley, Harrison and Stein, (2006), Howards et al. (2006), who also used motor sequence learning tasks and those of Pavlidou and Williams (2010), who used an artificial grammar learning task.

To investigate unique contributions of general ability, reading ability and attention on implicit learning, Waber et al. (2003) investigated the performance of 422 children (7-11 years) with a wide range of general abilities and reading abilities. Regression analyses found that general ability was positively correlated with reading, whereas inattention symptoms were negatively correlated with reading, as expected from previous literature. When performance on the sequence learning task was entered as the dependent variable and general ability, reading competence and attention level were entered as predictors (with age, gender, trial as covariates), no specific effects on implicit learning was found for any of the three predictors. In other words, the implicit learning effect was equally strong across

ability levels. However, the predictors did have an effect on early task performance, where poorer ability generally indicated poorer performance. Nevertheless, with training/over time, the poor ability children did catch up and showed a learning effect. This could explain at least in part, the discrepancies in the literature. Waber et al. (2003) suggest that the implicit learning effects are similar regardless of ability after 5 to 6 trials, with variable performance especially in the first four trials. The studies reporting significant group differences between dyslexics and controls have often used fewer than 3 trials and could indeed have captured the early effects reported in Waber et al. (2003).

Claim (4) "Direct neurobiological evidence of cerebellar impairment"

The above studies have employed indirect (behavioural) tasks to test a biological (neurological) theory. Structural and functional imaging studies comparing dyslexic individuals and controls will offer a more direct test of differences at the neurological level, albeit at a macroscopic rather than microscopic level. MRI studies in dyslexia will be discussed in more depth in chapter 2 (Neurobiology of Dyslexia, tables 2.1 and 2.2). A subset of those studies is discussed here. To support the CDH, reports of cerebellar dysfunction in structural and functional imaging studies must be consistent.

Structural findings

Reviewing the 44 MRI structural studies of dyslexia published between 1990 and 2015, only 13 (29.5%) have reported findings in the cerebellum (table 2.1). In addition, the regional distributions of the findings within the cerebellum vary from study to study. For example, using voxel-based morphometry (VBM), Brambati et al. (2004) found significantly reduced grey matter volume in the cerebellar nuclei bilaterally in a small sample of 10 dyslexics (age 13-57), whereas Brown et al. (2001) showed reduced grey matter in right and left hemispheric regions of lobule VII in 16 adult dyslexic men. Eckert et al. (2003, 2005), Kronbichler et al. (2008), and Fernandez et al. (2013) replicated reduced cerebellar grey matter volume and density in bilateral anterior cerebellum in children with dyslexia.

Manual tracing studies further reported a reduction (Kibby et al., 2008) or absence (Rae et al., 2002) of a right-ward asymmetry of the cerebellum in dyslexia. Leonard et al. (2001) reported decreased leftward asymmetry of the posterior cerebellum in dyslexic adults. One recent intervention study (Krafnick et al., 2014) further found increased grey matter volume including the right anterior cerebellum after an eight-week intervention focusing on imaging/visualization of letters and syllables in 11 children with dyslexia.

In contrast to these studies that have reported reductions in the cerebellum, three studies have reported increases in the cerebellum in dyslexic individuals. Jednorog et al. (2014) investigated subtypes of dyslexia in Polish children and found that those with phonological deficits had increased grey matter volume in the left cerebellum compared to age-matched controls. Laycock et al. (2008) manually traced the vermis and white and grey matter of the cerebellum in adult dyslexics and found increased white matter volumes in the vermis and bilateral cerebellar hemispheres in 10 dyslexics compared to 11 controls. A Tract-based spatial statistics (TBSS) study (Richards et al., 2008) found increased FA in the middle cerebellar peduncle.

Relationships with reading have been reported in only four studies (Rae et al., 2002; Eckert et al., 2003; Kibby et al., 2008; Jednorog et al., 2014). Rae et al. (2002) and Kibby et al. (2008) reported negative correlations between the rightward asymmetry and reading errors and time in adults and children with dyslexia. In other words, the smaller asymmetry of the cerebellum, the worse the performance. Moreover, Eckert et al. (2003) and Jednorog et al. (2014) found that including the cerebellum improves classification accuracy.

Although these structural studies suggest that selective regions of the cerebellum may be affected in (a subsample of) dyslexics, these findings must be interpreted cautiously due to several methodological limitations, such as the small sample sizes, and lenient statistical thresholds (e.g. $p < 0.001$ uncorrected for VBM), selectivity of samples (e.g. male only or

male dominant), and inclusion of comorbidities (notably ADHD) – see limitations in table 2.1. It is also important to note that the regions where differences are found are not consistent across all studies and that the grand majority (>50%) of studies do not report differences in the cerebellum. Furthermore, there is still limited evidence of the relationships between the observed structural cerebellar deficits and reading performance.

Functional findings

A review of fMRI studies using literacy-related measures in dyslexia (Chapter 2, table 2.2) found only 9 out of 55 (16%) reported differences in the cerebellum. Brambati et al. (2006) found reduced activation in the right cerebellum in 13 Italian dyslexic participants compared to 11 controls during a reading task compared to false fonts. Similarly, Siok et al. (2008) found reduced activation in bilateral cerebellum in 16 Chinese dyslexic children compared to 16 age-matched controls during a rhyme judgement task. Hu et al. (2010) found reduced activation in the cerebellum in English and Chinese children with dyslexia compared to age-matched controls.

In contrast, Richlan et al. (2010) did not observe reduced activation in the cerebellum in 15 German dyslexic young adults compared to 18 age-matched controls. On the contrary, the authors reported increased activation in the cerebellum in the dyslexic adults compared to the controls during both word and pseudoword reading tasks. Rimrodt et al. (2009) further reported no differences in cerebellar activation between 14 English dyslexic children compared to 15 age-matched controls, but observed that the activation level in the cerebellum correlated negatively with reading comprehension and fluency scores across the full sample. Therefore, there seems to be equal reports of reduced as well as increased cerebellar activation in dyslexic individuals compared to controls.

Moreover, Baillieux et al. (2009) reported both reduced as well as increased activation in the cerebellum in 15 Dutch dyslexic children compared to seven age-matched controls

during a verb generation task. In addition, all fMRI studies discussed suffer from small sample sizes and liberal threshold of statistical analyses (whole-brain comparisons with $p < 0.001$ - 0.005 uncorrected thresholds).

However, cerebellar differences found using implicit learning paradigms do provide some support for the CDH. For example, Yang et al. (2013) reported abnormal activations in the left cerebellum (and left middle/medial temporal lobe and right thalamus) in 9 Chinese dyslexic children compared with 12 age-matched children during implicit motor learning. In a small PET study, Nicolson et al. (1999) asked matched groups of six dyslexic adult men and six control adult men to perform a prelearned as well as new motor sequence task. For both these conditions (compared to rest baseline), the dyslexic men showed reduced activation in the right cerebellum, which the authors report as direct evidence to support the CDH. However, what the authors do not discuss are the other regions of brain activation found between groups.

For example, the dyslexic men also showed reduced activation in the left cingulate gyrus in the prelearned vs rest condition. In addition, dyslexic men showed increased activation in bilateral angular gyri and left superior temporal gyrus during the new vs rest condition. Moreover, a better indication of learning is arguably the new vs prelearned condition, as the prelearned vs rest could also be interpreted as a memory recall exercise. In the direct new vs prelearned condition, the dyslexic men showed reduced activation in the left middle frontal gyrus and the left anterior cingulate gyrus, with no significant differences in the cerebellum. In contrast, the dyslexic men showed increased activation in the left insula and right medial prefrontal gyrus and right parahippocampal gyrus. Therefore, the findings only partially support an involvement of the cerebellum, but not fully.

In summary, although cerebellar differences have been reported in structural and functional MRI studies investigating dyslexia, these findings have been only reported in a

small subset of studies with contradicting directions of cerebellar differences (i.e. increase vs decrease). Furthermore, cerebellar dysfunction appear more apparent during implicit motor learning tasks than during reading tasks, putting into question its specific involvement in reading.

Limitations of CDH

One of the complications of these findings is that these tasks do not solely target cerebellar function; for example, procedural learning can also involve the basal ganglia, and many different cortical regions work together with the cerebellum during these tasks. Further, not all dyslexic participants show deficits on these tasks, and the majority of studies fail to find group differences. This could be due, in part, to differences in tasks and subject populations, including differences in diagnostic criteria and possible co-morbid disorders (especially ADHD). Longitudinal and training studies are also scarce.

Other major criticisms of the CDH include:

1. It is not causal, but an “innocent bystander” in dyslexia (Bishop, 2002; Zeffiro and Eden, 2001). The idea stems from the fact that sensorimotor deficits in dyslexia are associated, but not causal, aspects of the condition (e.g., Ramus, 2003, 2004). In addition, as evident from the review of existing research above, there is insufficient evidence from clinical cerebellar populations of reading difficulties, and cerebellar signs in dyslexic populations are not consistent.
2. It is not specific to dyslexia. This argument is based on findings that have reported similar cerebellar symptoms in dyslexia and comorbid disorders such as ADHD and developmental coordination disorder (DCD) (e.g. Raberger and Wimmer, 2003; Ramus et al., 2003; Wimmer, Mayringer, and Raberger, 1999). In addition, Leonard et al. (2008) found that a similar cerebellar structural “risk factor” was associated with the cognitive deficits in both dyslexia and schizophrenia. Other studies have

also reported alterations in cerebellar anatomy, including autism (e.g. Bauman et al., 2005) and attention deficit disorder (e.g. Bush, Valera, and Seidman, 2005). Future work is needed to differentiate the role of the cerebellum in different developmental disorders.

3. It does not explain all cases of dyslexia. Like all other theories of dyslexia, deficits vary between dyslexic groups and cerebellar deficits are only found in some but not all dyslexics (e.g. Ramus, 2003). However, given the heterogeneous group of individuals who are diagnosed under the umbrella of “dyslexia” (and the different methods of diagnosis and definitions of the disorder), it is not likely that any single neurobiological theory will explain all cases of dyslexia.
4. How does the theory explain the abnormalities observed in other areas of the dyslexic brain? Discussed in more detail in the next section, there are well-documented structural and functional differences found throughout the brains of dyslexic individuals. The causal explanation offered by the CDH cannot explain and does not make nor allow specific predictions regarding extra-cerebellar abnormalities to be made. Therefore, it is more likely that cerebellar dysfunction may be a correlate of dyslexia, as opposed to a direct cause.

1.5. Is dyslexia a disconnection syndrome?

The last theory of dyslexia relevant to this thesis is the disconnection hypothesis (DXH). Whereas the theories discussed above (Phonological, Auditory, Cerebellar, and Magnocellular) in varying parts were derived initially from behavioural symptoms, and have cited a large body of behavioural evidence (with some neuroanatomical and neurofunctional evidence for the cerebellar and magnocellular theories), the disconnection syndrome is largely and almost exclusively theorised at the neuroanatomical level.

The notion of disconnection syndromes started from the early work of Broca and Wernicke on the aphasias. However, it wasn't until Geschwind's seminal two-part volume on 'Disconnexion Syndromes in Animals and Man' (1965) that developmental dyslexia was proposed to be a disconnection syndrome. In this view, disconnection syndromes result from lesions of either grey matter regions or from lesions of white matter fibres that interconnected specialised regions.

In his work (1965), Geschwind specifically highlighted the inferior parietal lobule (roughly corresponding to BA 39 and 40) as the region that is developed in humans, but not recognised in primates. In addition, he pointed out that this region is one of the last regions in the brain to myelinate, maturing late in childhood, with a specific role in mediating cross-modal associations (for example visual-auditory): "... the parietal region is involved in the development of speech because of its importance in enhancing cross-modal associations" (p275). He derived this conclusion based on the speculation that connections to the auditory association/speech area (Wernicke's area) from other sensory modalities such as vision will be directed via the angular gyrus in the inferior parietal lobule.

Lesion studies describing alexia (or word-blindness) provide some support for the role of the angular gyrus as an association centre. Dejerine (1891, 1892) described two elderly patients who presented with right hemianopia and the inability to read and who had corresponding lesions in the left angular gyrus, left occipital lobe and the splenium of the corpus callosum. More notably, the second case (1892) had initially preserved spelling skills despite having lost the ability to read.

Post mortem examination revealed older lesions in the occipital lobe and the splenium, but relatively recent lesions in the left angular gyrus. Dejerine derived that the angular gyrus must encompass the centre for 'visual word memory'. His explanation can be summarised briefly as follows: spelling is learned only as part of learning to read and write. In order to

comprehend a word spelled out loud, the listener must transform it into written form and then "read" it. Conversely, to spell orally one must transform the spoken word into its written form and then "read" the letters one by one.

To preserve the ability to spell, the patient must still have the visual memory centre intact. The patient only lost his ability to spell later/closer to death and the lesions in the angular gyrus upon examination seemed more recent. Therefore, the lesion in the splenium, leading to a disconnection between right occipital areas and left angular gyrus, was responsible for the alexia, whereas the lesion in the angular gyrus was responsible for the agraphia. How then can this disconnection theory be applied to developmental dyslexia, a condition seemingly without apparent lesions in the brain?

Geschwind speculated that developmental dyslexia may be caused by delayed development of the angular gyrus region, due to its role as the area to store cross-modal associations between vision and hearing and the fact that it is one of the last regions in the human cortex to develop. As such, Geschwind hypothesised that children with developmental dyslexia would not have achieved adequate development of the angular gyrus by the time reading instruction usually starts in school. He goes on to present the hypotheses for this disconnection theory:

1. Due to the role of the angular gyrus in cross-modal integration, the deficits in dyslexia should extend to other modalities such as colour-naming and music-reading as these skills also require the integration of visual information to linguistic/motor output. Indeed, studies have converged on a consistent deficit in rapid automatized naming (of letters, numbers, and colours) in dyslexia (see phonological deficit theory for discussion).

2. Individuals with developmental dyslexia should present with 'disconnections' in the pathway between right occipital cortex and left angular gyrus. This would be analogous to the deficits observed in acquired dyslexia.

Unlike post-mortem studies of alexia or acquired dyslexia, it was mostly impossible to test for disconnections in the brain of children with developmental dyslexia until the emergence of in-vivo imaging techniques such as PET and (f)MRI. Indeed, it was a PET study by Paulescu et al. in 1996 that reawakened the interest in the disconnection theory of dyslexia. In this study, Paulescu et al. presented five adult dyslexic men and six controls with two tasks: a rhyming task and a short-term memory task.

PET imaging revealed that the dyslexic adults showed lower activation than the controls in a range of regions: the supplemental motor area (BA 6), left premotor cortex (BA 6), left superior temporal gyrus (BA21/22), left insula, left inferior frontal gyrus (BA6/44), left supramarginal gyrus (BA 40), left cerebellum, right striatum, right inferior frontal gyrus (BA 6/44) and right insula across the two tasks. In addition, the dyslexic participants did not activate these areas in sync like the controls did. These findings led the authors to propose that the phonological deficits observed may be the result of disconnections within the left language network. In other words, although the dyslexic participants could activate the language regions needed to perform the tasks, they did so in a less efficient (asynchronous) way. In addition, the dyslexics did not activate the insula region at all, suggesting a disconnection in the 'bridge area' between frontal (left inferior frontal gyrus) and posterior (left superior temporal gyrus) language regions.

It should be noted that even though both Geschwind and Paulescu described disconnection deficits in dyslexia, they differed in the localisation of such deficits. Geschwind hypothesised such disconnections to be localised in the splenium of the corpus callosum

and in association cortices such as the inferior parietal lobule (angular and supramarginal gyri), whereas Paulescu described the disconnection deficit in the insula.

Criticism of the Geschwind's theory

Geschwind's model has been criticised for its oversimplification of the association cortex, and specifically the inferior parietal cortex in the context of reading disorders, as a homogeneous relay station between primary sensory and motor areas (Catani and ffytche, 2005). Subsequent studies have suggested subdivisions within the inferior parietal lobule into five (Eidelberg and Galaburda, 1984) and seven (Caspers et al., 2006) regions based on (cyto)architectonics. These subdivisions further showed considerable interindividual variability (Caspers et al., 2006; 2008), for example with significant gender differences (i.e. larger volumes in males than females) in area PFcm in the rostral inferior parietal cortex (Caspers et al., 2008). More recently, two studies employed DWI tractography to segment right and left IPL (Mars et al., 2011; Wang et al., 2012). The right-hemispheric IPL was divided into five subregions (Mars et al., 2011), the left-hemispheric IPL into six subclusters (Wang et al., 2012). A resting-state functional connectivity study (Zhang and Li, 2014) applied clustering analysis on the functional connectivity maps of each voxel within a template of the inferior parietal lobule and found seven clusters/subdivisions.

A further criticism of Geschwind's theory was the predominantly feed forward, serial nature of his description: information passed from posterior sensory cortices, through the association cortices to limbic and anterior frontal (motor) cortices in a serial fashion. Little was said about feed-back and parallel pathways. Studies have since highlighted the importance of parallel, bidirectional processing for higher functions such as language (Mesulam, 1990; Matsumoto et al., 2004; Bitan et al., 2005; Catani et al., 2005).

Nevertheless, Geschwind's theory and subsequent renaissance of disconnection syndromes (Paulescu et al., 1996; Catani and ffytche, 2005) have brought forth a new model of the disconnectivity theory: higher cognitive function deficits arise from (a) the loss of specialized cortical function and/or (b) damage to connecting pathways. In the context of developmental dyslexia, one would hypothesise that such deficits would be found in (a) the inferior parietal lobule (angular gyrus) or the insula, and/or (b) in the splenium of the corpus callosum.

This theory is attractive for two reasons. Firstly, the hypotheses generated could be tested using in-vivo functional and structural connectivity techniques such as seed-based (resting-state) functional correlations and diffusion tensor imaging and white matter tractography, as well as network approaches like graph theory. Secondly, this theory does not preclude the other theories of dyslexia discussed above. Instead, a network/brain wide disconnection deficit may well explain the wide range of deficits observed in dyslexia. For example, the left inferior parietal cortex has been shown to be consistently impaired in patients with dyslexia in structural, functional, and connectivity studies (see review of imaging studies of dyslexia later in this chapter), with relationships to phonological processing (fitting the framework of the phonological deficit hypothesis). In addition, the inferior parietal cortex is part of the dorsal visual pathway and receives input from the magnocellular system (fitting in the framework of the magnocellular theory). Lastly, one study reported that the inferior parietal cortex in macaque monkeys is the target of output from the dentate nucleus of the cerebellum (Clower et al., 2001) (fitting the framework of the cerebellar deficit somewhat). However, the latter needs to be confirmed in the human brain, especially considering the expansion of the inferior parietal region in the human brain through evolution.

Connectivity studies in dyslexia

Thus far, the connectivity studies in dyslexia are relatively few with divergent findings. Connectivity studies will be discussed in more detail in chapters 2 and 8, and will be briefly summarised here.

Functional connectivity studies in dyslexia, which investigate interregional correlations or cooperation between different brain areas found reduced connectivity between the angular gyrus and several sites in the left hemisphere, including the posterior superior temporal gyrus, ventral occipitotemporal cortex, and early visual areas in dyslexics during phonological tasks (Horwitz, Rumsey, & Donohue, 1998; Pugh et al., 2000). Horwitz et al. (1998) also reported reduced left angular connectivity with the inferior frontal gyrus and cerebellum. These connectivity abnormalities have been observed in both children and adults (Cao, Bitan, & Booth, 2008; Richards & Berninger, 2008; Van der Mark et al., 2011; Vourkas et al., 2011; Koyama et al., 2011). Some (Cao, Bitan, & Booth, 2008) reported reduced connectivity between ventral visual cortex and the inferior parietal cortex, which would fit well within Geschwind's original hypotheses, while others (Richards & Berninger, 2008) reported abnormal connectivity between the left inferior frontal gyrus and multiple bilateral brain regions. Nevertheless, these studies illustrate the complex nature of the reading process and suggest that dyslexia may be associated with focal differences as well as disruptions of connections among regions.

Structural MRI studies using graph theory explored alterations in Chinese dyslexia and found both decreased (Qi et al., 2016) and increased (Liu et al., 2015) local clustering with constant global efficiency in dyslexic children compared with healthy controls. Structural networks of English-speaking children with familial risk of reading difficulties showed no significant difference in global topological properties compared with healthy controls, but with changes in local network properties (Hosseini et al., 2013).

Functional graph networks based on MEG data in dyslexia showed reduced global and local efficiency during both resting and task states compared with healthy controls (Vourkas et al., 2011; Dimitriadis et al., 2013). As to local network changes, abnormalities in both structural and functional networks were reported in the visual cortex, prefrontal areas for attention modulation, as well as the supramarginal gyrus, precentral gyrus, Heschl's gyrus, posterior cingulate, and hippocampus (Hosseini et al., 2013; Finn et al., 2014; Liu et al., 2015; Valk et al., 2015; Qi et al., 2016). The hubs (indication regions of higher importance in a network) in the structural networks of Chinese dyslexia were found to be more bilateral and anterior than those of healthy controls (Qi et al., 2016), which was consistent with the findings that in functional networks, skilled readers have stronger left lateralization for language than dyslexic readers, who rely on bilateral systems (Finn et al., 2014).

Multimodal brain imaging is proving to be a valuable tool for testing this theoretical framework. Using multivoxel pattern analysis of fMRI data in adult dyslexics, Boets and colleagues (2013) found intact phonetic representations in bilateral auditory cortices but disrupted functional and anatomical connections between these regions and the left inferior frontal gyrus, suggesting a problem of access.

Currently, there is a lack of replication and consistent findings in connectivity studies of dyslexia. However, the findings discussed so far have demonstrated that there is a possibility to bring together the divergent theories of dyslexia and explain the heterogeneous symptoms through a network model. Therefore, the main focus of this thesis will be using multimodal imaging methods to explore the connectivity deficit of dyslexia.

2. The neurobiology of dyslexia

Reading is an acquired skill that takes instruction and practice to master, which can take years. Unlike spoken language, people have only very recently in the history of our species started to rely on literacy. Therefore, it is unlikely that our brain has evolved to dedicate regions specifically to reading. Instead, reading most likely requires regions that have evolved for other purposes (e.g. vision, oral language, memory etc.). This section will review the brain imaging studies investigating the neuroanatomical and neurofunctional correlates of developmental dyslexia in the past two decades. Although an overview of the electrophysiological studies of dyslexia would provide insight into the any abnormalities in timecourses of reading events in dyslexia, this is beyond the scope of this PhD. Instead, this section will focus on MRI studies of dyslexia as that is the imaging method used in this PhD. Table 2.1 provides an overview of the structural MRI studies on dyslexia. Table 2.2 provides an overview of the functional MRI studies.

2.1. Anatomical differences in developmental dyslexia

Initial post-mortem structural studies have found reduced grey matter asymmetry in the planum temporale (PT) in dyslexia, relative to typical adults, showing symmetrical PT in five males with dyslexia (Galaburda & Kemper, 1979; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985), and three females with dyslexia (Humphreys, Kaufmann, & Galaburda, 1990). Similarly, Larsen et al. (1990) reported symmetry in the PT in 13 (out of 19) Norwegian adolescents with dyslexia and further reported that all participants who suffered phonological deficits had symmetrical PT.

However, these morphological results have not always been replicated in later studies. In fact, Leonard et al. (1993) found exaggerated leftward asymmetry of the PT in dyslexic readers. A number of studies have found no group differences at all with equal proportions

of left-ward asymmetry of the PT in dyslexics and controls (e.g. Rumsey et al., 1997; Robichon et al., 2000; Leonard et al., 2001; Eckert et al., 2003). These studies are limited by small sample sizes ($N < 18$) and included large age ranges (18-40) even though all were performed using adults.

Two recent studies (Bloom et al., 2013; Altarelli et al., 2014) revisited the investigation of the size and symmetry of the PT in samples of English (Bloom et al., 2013) and French children (Altarelli et al., 2014). Both studies reported reduced left-ward asymmetry in dyslexic children due to increased surface area in the right PT. Note should be taken that Bloom et al. (2013) included children with comorbid ADHD, and Altarelli et al. (2014) found this increased right PT in dyslexic boys only. The difference in findings between adult and paediatric studies is striking, but it is unclear whether these reflect developmental changes or are a result of methodological differences across studies.

Voxel-based morphometry (VBM) studies in children and adults showed morphological abnormalities in grey matter and white matter density and volume that are distributed across several regions of the left hemisphere (table 2.1). Reduced grey matter density and volume in dyslexia has been reported in superior temporal gyrus (5 out of 13 VBM studies), middle temporal gyrus (6/13), inferior parietal lobule (angular gyrus/supramarginal gyrus) (6/13), inferior frontal gyrus (4/13), cerebellum (5/13), and subcortical structures (e.g. caudate, putamen, thalamus). Few studies have reported increased grey matter in dyslexia compared to controls, such as LH middle temporal gyrus (Silani et al., 2005), bilateral precentral gyrus (Vinckenbosch et al., 2005), left inferior frontal gyrus (Pernet et al., 2009), cerebellum (Jednorog et al., 2014) and right putamen (Jednorog et al., 2014). VBM studies investigating whole-brain white matter differences in dyslexia have reported reductions in left and right inferior frontal gyrus (Silani et al., 2005; Eckert et al., 2005), left post-central gyrus (Silani et al., 2005), right cerebellum (Eckert et al., 2005).

Two meta-analyses of VBM studies (Linkersdörfer et al., 2012; Richlan, Kronbichler, & Wimmer, 2012) converged on bilateral posterior temporal gyrus/supramarginal gyrus as the most consistent region of difference between groups, even though Linkersdorfer and colleagues found additional reduced grey matter in the cerebellum bilaterally. Looking at the individual studies, it becomes apparent that many inconsistencies in the findings may be driven by research methodology and the nature of the participant groups (Altarelli et al., 2014 and Bishop, 2014).

A survey of the VBM findings in table 2.1 suggests that the most consistent findings are only reported by fewer than half of the studies. Moreover, the overwhelming majority of the studies reported findings at uncorrected level or using small volume correction. In addition, studies have included mostly male dyslexics (e.g. Brown et al., 2001; Eckert et al., 2005; Vinckenbosch et al., 2005; Kronbichler et al., 2008). These factors are not controlled for in meta-analyses and could lead to the importance of certain regions being inflated.

The three most recent VBM studies take some of these methodological issues into consideration and found that many anatomical differences were driven by gender (Evans et al., 2014), age (Evans et al., 2014; Krafnick et al., 2014), and subtype of dyslexia (Jednoróg et al., 2014). Evans et al. (2014) divided their participants into four groups: boys, girls, men, and women. The authors found different regions of reduced grey matter volume in each of these groups compared to their respective age-matched controls, with the previously reported reductions in left middle temporal gyrus and left inferior parietal lobule only found in men and boys respectively. However, the sample size for each group was small (N=13) and results were reported at an uncorrected level. Only two results survive family-wise error correction: left middle temporal gyrus reduction in men, and right precentral sulcus reduction in girls.

Jednorog et al. (2014) further investigated the effect of possible subtypes in dyslexia on grey matter volume. They found that all dyslexic subtypes showed reductions in the left inferior frontal gyrus, whereas the phonological dyslexics showed specific reductions in the right inferior frontal gyrus, with increased volumes in the left cerebellum and right putamen. Indeed, one recent study could not replicate any of the previous findings in a large sample of data from three different countries (Jednoróg et al., 2015). Reduced grey matter in left temporoparietal regions reported in the current literature may therefore be mainly driven by the selection bias for male, right-handed, adult participants.

2.2. White matter pathways in dyslexia

Earlier studies of dyslexia have suggested the corpus callosum (CC) (and splenium specifically) to be implicated in dyslexia (e.g. Geschwind, 1965). However, MRI findings of CC abnormality in dyslexia have been inconsistent. Hynd et al. (1995), for example, reported smaller genu in children with dyslexia compared to controls, with the size of the genu and splenium to be positively correlated with reading achievement. In contrast, Rumsey et al. (1997) reported larger isthmus and splenium in adults with dyslexia compared to controls. On the other hand, Robichon and Habib (1998) reported a larger total area of the corpus callosum in university students with dyslexia compared to controls, and the corpus callosum regions that did not have larger areas in the dyslexic readers were the genu and splenium.

Plessen et al. (2002) further suggested that it may not necessarily be the size but rather the shapes of the corpus callosum that distinguishes dyslexia. They found that despite no differences in area of the subdivisions of the corpus callosum, the shapes of these regions accounted for 78% classification accuracy. These studies have been based on manual delineation of the corpus callosum and subsequent measures of size, area and shape and

may be biased by inter-examiner ratings. It is also unclear how these differences are related to microstructural properties.

Diffusion-weighted MRI and diffusion tensor reconstruction allows for direct comparison of white matter metrics such as fractional anisotropy (FA), radial diffusivity (RD) and medial diffusivity (MD) (see chapter 3 for more in-depth explanation of these properties). Diffusion studies of the corpus callosum in dyslexia have reported no significant differences in the posterior corpus callosum or splenium in children (Hasan et al., 2012) or adults (Vandermosten et al., 2013). Instead, diffusion MRI studies have reported reduced FA in the left superior corona radiata (Niogi and McCandliss, 2006), which further correlated positively with reading (Odegard et al., 2009).

Voxel-based analyses of FA maps found reduced FA in the left superior longitudinal fasciculus, left middle frontal gyrus, left precuneus (Carter et al., 2009), as well as bilateral inferior frontal gyrus and left inferior parietal lobule (BA 40) (Rimrodt et al., 2010), which also correlated positively with reading (Beaulieu et al., 2005). It should be noted that these findings are all reported in children. Adult studies have found differences in regional FA in bilateral regions across the brain (Richards et al., 2008) as well as localised differences in the left arcuate fasciculus (Vandermosten et al., 2012; 2013).

A meta-analysis found reduced FA in a left temporoparietal area (close to the one identified in VBM meta-analyses) in dyslexic readers, but there is some uncertainty as to whether this implies a deficit in the arcuate fasciculus or the corona radiata as both of these pathways pass through this region (Vandermosten, Boets, Wouters, & Ghesquière, 2012).

2.3. Abnormal brain activation patterns during reading

In addition to the structural grey and white matter anomalies described above, dyslexic readers also show abnormal activation patterns during tasks. However, due to the

variability in the type of the task and the level of difficulty, studies have reported both under- and over-activation in the left-hemisphere network involved in skilled reading. The following discussion of differences in brain activation patterns in dyslexic readers is limited to fMRI studies that have used reading-related tasks as those are the most relevant for this thesis. A summary of these studies is provided in table 2.2.

A wealth of fMRI studies have investigated the neurobiological nature of dyslexia, most of which have used reading-related tasks to do so. These tasks can further be divided into those that have specifically studied sublexical processing (phoneme manipulation, rhyming), single word reading (word and pseudoword, covert and overt), lexical decision, semantic judgement, sentence reading, and categorical decision. Although all these skills come into play during natural reading processes at one point or another, the question remains whether these skills recruit the same brain system and how they exactly contribute to the process of reading.

Single word reading tasks most closely resemble the behavioural tasks used in the diagnosis of dyslexia. Therefore, one would expect to see the specific effect of reading impairment in the brain. Studies specifically using single word (real words and pseudoword) reading tasks have been conducted in English (Shaywitz et al., 2002; Olulade et al., 2013), German (Van der Mark et al., 2009; Wimmer et al., 2010; Richlan et al., 2010; Heim et al., 2013), Norwegian (Morken et al., 2014), Italian (Brambati et al., 2006), and French (Monzalvo et al., 2012), in both adults and children.

Shaywitz et al. (2002) studied a large sample of adults (70 dyslexic readers, and 74 age-matched controls) during pseudoword reading and found reduced activation in dyslexic readers compared to age-matched controls in the left IFG, left angular gyrus, bilateral middle temporal gyri, bilateral anterior middle occipital gyri. They also reported a positive correlation between the activation of a left occipito-temporal region and measures of

reading across the whole sample. No regions were reported that showed increased activation in the dyslexics compared to controls. These findings were only partly replicated in a smaller study in adults (Olulade et al., 2012), where reduced activation was also found in bilateral middle temporal gyri and bilateral inferior parietal lobules, including the supramarginal gyrus, in dyslexic adults compared to controls. Olulade et al. (2012) reported reduced activation in the left superior frontal gyrus, left insula, and left middle frontal gyrus during pseudoword reading compared to line judgment. Reduced activation in the left FFG was only reported for real word reading when compared to line judgement. In addition, the authors reported increased activation in the dyslexics compared to controls in right cuneus and right middle occipital gyrus for both word and pseudoword reading, as well as the left cingulate for word reading.

The above reports in English fMRI studies were replicated by studies in regular orthographies such as Italian, French, German and Norwegian. Brambati et al. (2006) in a small Italian study (age range 13-63) also found reduced activation in the left FFG during word and pseudoword reading, and reduced activation in bilateral middle temporal gyri, left IFG (triangularis) and the supplementary motor area (SMA) during pseudoword reading. German studies found reduced activation in the left inferior parietal lobule (supramarginal gyrus) during pseudoword reading in children (Van der Mark et al., 2009) and young adults (Wimmer et al., 2010), and the left FFG during word (Richlan et al., 2010) and pseudoword reading in adolescents and adults (Wimmer et al., 2010).

In addition, increased activation in dyslexic young adults during word (Richlan et al., 2010) and pseudoword reading (Wimmer et al., 2010) were reported in left pre-and postcentral gyrus, left IFG (opercularis), left anterior cingulate, and bilateral subcortical structures (caudate and putamen). Reduced activation in the left FFG was also reported in a French sample of children with dyslexia as compared to controls (Mozalvo et al., 2012).

Interestingly, the direct comparison of pseudoword > word reading showed reduced activation in the left posterior temporal gyrus and left inferior parietal lobule (angular gyrus) (Shaywitz et al., 1998; Heim et al., 2013) and left IFG (triangularis) (Brambati et al., 2006; Heim et al., 2013). This suggests that these regions are modulated by increasing phonological demands, as reading pseudowords relies solely on phonological decoding, whereas reading words may, in part, rely on orthographic and/or memory in addition to phonological decoding. Therefore, although these studies have identified areas of abnormal processing of words and pseudowords, it is unclear how these brain regions contribute to the different processes of reading. For example, do these regions indicate a phonological deficit or a more general sensorimotor deficit (e.g. magnocellular or cerebellar)? To this effect, many studies have investigated the neurofunctional correlates of sublexical (phonological) processing deficits in dyslexic children and adults.

Studies using rhyming tasks in alphabetic languages such as English (Temple et al., 2001; Hoefft et al., 2006, 2007; Cao et al., 2008, MacSweeney et al., 2009; Landi et al., 2010; Tanaka et al., 2011; Kovelman et al., 2012; McNorgan et al., 2013; Norton et al., 2014), German (Grunling et al., 2004), Dutch (Backes et al., 2002), French (Hernandez et al., 2013), and Italian (Pecini et al., 2011) converge on reduced activation in dyslexic children and adolescents compared to controls in the left middle occipital gyrus (Temple et al., 2001; Grunling et al., 2004), bilateral cingulate (Temple et al., 2001; Backes et al., 2002), left IFG (opercularis/triangularis) (Backes et al., 2002; Cao et al., 2008; Norton et al., 2014), bilateral superior temporal gyri (Backes et al., 2002), posterior parietal lobule (right-Backes et al., 2002; left- Pecini et al., 2011), superior frontal gyrus (right-Grunling, 2004; Hoefft et al., 2006; left-Pecini et al., 2011; Kovelman et al., 2012), middle temporal gyrus (left -Grunling, 2004; Cao et al., 2008; right -Hoefft et al., 2006; Landi et al., 2010), bilateral inferior parietal lobule (angular and supramarginal gyri) (Hoefft et al., 2006; Cao et al., 2008; Pecini et al., 2011; Tanaka et al., 2011; Norton et al., 2014), precentral gyrus (right - Landi et al., 2010,

left-Norton et al., 2014), and left FFG (Tanaka et al., 2011). These results in alphabetic languages were further replicated in a logographic language - Chinese (Siok et al., 2008). Interestingly, the two studies that have used rhyming tasks in adults did not find any reduced activation in dyslexic readers. Instead, they reported increased activation in left IFG (MacSweeney et al., 2009) and right cerebellum and bilateral precentral gyri (Hernandez et al., 2013). These results cannot be explained by performance and may instead reflect developmental changes possibly due to brain maturation and/or reading experience.

Of importance to note is that the majority of the studies have reported results at very low statistical thresholds ($p < 0.001$ uncorrected with a cluster-extent correction in the number of voxels) or have used specific ROI analyses. This suggests that either the differences in dyslexia are very subtle, or that reported differences represent type-I errors. In addition, questions remain about possible developmental effects and language-specific effects. Moreover, the majority of these studies have either targeted or interpreted the results in the light of the phonological deficit hypothesis. Other causal deficits theories are underrepresented in the literature. These questions have been addressed by three meta-analyses (Richlan, Kronbichler and Wimmer, 2011; Paulesu et al., 2014; Martin et al., 2016).

To harmonise the literature and provide a quantitative measure of convergence, several meta-analyses have been published over the last decade (Maisog et al., 2008; Richlan et al., 2009, 2011; Paulesu et al., 2014; Pollack, Luk, and Christodoulou, 2015; Martin et al., 2016). These meta-analyses differ in their selection criteria and methodology, and overlap in the studies they include, but do offer a quantitative convergence analysis in order to reduce the otherwise disparate findings across large numbers of the published studies. Three will be discussed here as they have addressed gaps in the literature.

Firstly, Richlan et al. (2011) distinguished abnormal activation patterns in reading-related tasks (PET and fMRI) that are specific to child and adult samples. These provided an insight into possible developmental mechanisms in mastering reading skills. In his meta-analysis, he matched nine studies with child samples of dyslexic readers and controls with nine adult studies. The studies resulted in a sample size of 336 children and 271 adults, with 36 foci of reduced activation in dyslexic children, 57 foci of reduced activation in dyslexic adults, 6 foci of increased activation in dyslexic children, and 38 foci of increased activation in dyslexic adults. Subsequent age and diagnostic group comparisons resulted in bilateral inferior parietal lobule (IPL) as a region of importance in children, and the left FFG and bilateral caudate as regions of importance in adults.

More specifically, bilateral IPL, which includes angular and supramarginal gyri, is found to have reduced activation during reading-related (phonological) tasks more often in children than in adults. Conversely, activation in the left FFG, including the so-called visual-word form area (VWFA), is found to be reduced in dyslexic readers in adult studies only, as compared to child studies. Bilateral caudate is found to be a region of increased activation in adult dyslexia studies compared to child studies. These findings fit the developmental hypothesis of reading (Sandak et al., 2004; Pugh et al., 2000) which postulates that beginning readers rely primarily on a left dorsal temporoparietal (TP) system (possibly embedded in the IPL) which is involved in phonology-based reading via phone-grapheme conversions.

Skilled readers, on the other hand, engage the left ventral occipitotemporal (OT) system (embedded in the FFG) for fast and efficient whole-word recognition. For example, Shaywitz et al. (2007) reported an age-related increase in activation during a nonword rhyme judgment task in the left OT cortex. Turkeltaub et al. (2003) reported engagement of left posterior STG regions during an implicit word reading task early in the course of reading acquisition, but they did not find an increase in left OT activation with increasing age.

Further support comes from a meta-analysis by Martin et al. (2015) using control samples only, which replicated the developmental contrasts of Richlan et al. (2011). Again, children recruit the posterior superior temporal gyrus/IPL area more than adults, whereas adults recruit the left middle occipital gyrus/FFG more than children.

A second question outstanding in the literature is how language-specific effects such as orthographic depth affect brain activation. Martin et al. (2016) addressed this question in a recent meta-analysis comparing the dyslexia studies in English (orthographically deep language) with dyslexia studies in orthographically shallow languages like German, Italian and Swedish. The analyses are currently limited to alphabetic languages due to the scarcity of functional dyslexia studies in non-orthographic languages, but such studies are emerging for the Chinese and Japanese languages.

Martin et al. (2016) compared 14 pairs of matched studies that included both children and adults in deep and shallow orthographies. This resulted in a sample size of 232 dyslexics and 203 controls in the deep orthography and 219 dyslexics and 253 controls in shallow orthographies, with 73 foci of reduced activation in dyslexics in both deep and shallow orthographies. In contrast, 22 foci of increased activation were included for dyslexics in deep orthography and 86 foci of increased activation of dyslexics in shallow orthographies. Subsequent analyses found two regions of overlapping reduced activation in dyslexics regardless of orthographic depth: (i) the left OT region (including, inferior temporal gyrus, FFG, middle temporal gyrus, and inferior occipital gyrus), and (ii) left dorsal TP region (largely supramarginal gyrus).

Larger convergence of reductions of dyslexic readers in deep compared to shallow orthographies were found in the bilateral intraparietal sulci, right superior temporal sulcus, left precuneus, left IFG (triangularis). Larger convergence of reductions of dyslexic readers in shallow compared to deep orthographies were found in left FFG, left IFG (orbitalis), left

TP cortex, left frontal operculum. Converse effects (larger convergence of increases in dyslexic readers in deep compared to shallow orthographies and vice versa) were found in left anterior insula and left precentral gyrus respectively. These results suggest that the neurobiological correlate of dyslexia in the left OT and left TP may be universal across alphabetic languages, despite the orthographic differences and the diagnostic differences of dyslexia due to these.

Orthography-specific reduced activations in dyslexia were found in the left IFG, where triangularis is associated with deep orthographies and orbitalis with shallow orthographies. Pars triangularis of the left IFG has been associated with both semantic and phonological processing (e.g., Vigneau et al., 2006), whereas pars orbitalis of the left IFG has been associated with semantic retrieval (Binder et al., 2009; Bokde et al., 2001). Furthermore, the left IFG is more generally linked to various linguistic processes including grapheme–phoneme conversion (e.g., Jobard et al., 2003), lexical access (e.g., Heim et al., 2013), phonological output computation and speech planning (Price, 2012), and semantics (Binder and Desai, 2011), as well as non-linguistic processes such as executive functions, working memory, reasoning, decision-making, inhibition, attention, and emotion (Laird et al., 2011; Price, 2012; Richlan et al., 2014). It is plausible that these distinctions in the IFG are related to the severity of dyslexia due to orthography (impaired decoding and fluency in deep orthography vs impaired fluency in shallow orthography), but it is currently unclear exactly what the underlying mechanism would be.

Lastly, how does the wealth of findings from fMRI studies sit with other causal theories of dyslexia? Is dyslexia a specific phonological deficit or a multisensory deficit? This question was addressed by the meta-analysis of Paulesu et al. (2014). The disconnection deficit hypothesis was explicitly left out of this meta-analysis as it cannot be tested by localisation fMRI studies. We will return to this theory in a later section and chapter 8.

Paulesu et al.'s (2014) meta-analysis differed from Richlan's (2011) and Martin's (2016) not only in the fact that it was not limited to reading-related tasks only, but also in the fact that it reported results that were derived from a conjunction of activation likelihood estimation (ALE), used by Richlan and Martin, and hierarchical clustering. Paulesu reports that "hierarchical clustering has the advantage of permitting posthoc statistical assessments of the functional or group assignments of individual clusters without the constraint of considering superhomogenous tasks at the stage of cluster identification, as when using ginger-ALE alone". This explains the matching of carefully selected pairs in Richlan and Martin. Paulesu included 53 (PET and fMRI) studies in the analyses, a total of 1402 foci associated with controls, and 958 with dyslexia.

The conjunction method identified 92 clusters, which were subjected to posthoc analyses, including tests for group-preferential assessment of clusters and interaction effects of age, group and task. These analyses of studies using reading-related tasks found nine clusters that were 'preferentially attached' to the control group. This means that these areas preferentially activate in the controls compared to the dyslexics. These regions include three peaks in the left inferior temporal gyrus/FFG. Tasks contributing to these clusters include an even distribution of reading-related tasks, including lexical decision. Peaks were also identified in the left middle temporal gyrus and supramarginal gyrus, associated with tasks involving active phonological manipulation and working memory. In addition, peaks were identified in the dorsal IPL (superior to supramarginal peak), SMA, superior parietal cortex, associated with phonological manipulation tasks as well as motoric and visuospatial attention tasks.

Conversely, five clusters were preferentially associated with dyslexia: left caudate and pallidum (reading-related tasks), right IPL, mid cingulum, and right precentral gyrus (non-reading related tasks). Interaction effects further found left middle temporal gyrus and lingual gyrus to be preferentially associated with reading-related tasks in adults, whereas

left middle frontal gyrus was preferentially associated with reading-related tasks in children. The former finding is in line with the developmental effect found in the OT region in Richlan's meta-analysis. However, Paulesu's findings suggest a developmental effect in the left middle temporal gyrus, whereas Richlan does not.

Interestingly, only the right IPL was associated with non-reading related tasks, especially by dyslexic readers, whereas controls use this region in reading-related tasks only. Further ROI analyses testing the magnocellular and cerebellar theory found no preferential group association in these regions. Instead, the cerebellum is activated by both controls and dyslexics and no cluster showed significant in area MT/V5. This study confirms previous reports that brain activation differences in the literature are related to reading-like tasks, supporting dyslexia as a reading or phonological deficit rather than a magnocellular or cerebellar deficit. However, the study also shows that there is significant overlap of brain systems activated for reading-related and non-reading related tasks in certain regions such as the left parietal lobe (superior and inferior parietal lobule) and dorsal frontal areas (SMA, precentral gyrus).

Another novel contribution of Paulesu's (2014) meta-analysis is its comparison to a previous fMRI study in typical adult readers, which identified regions of overlap as well as isolated regions specific to tasks testing different causal theories of dyslexia (Danelli et al., 2013). Twenty-eight right-handed Italian typical adult readers performed four conditions during fMRI: (1) silent word and pseudoword reading, (2) auditory rhyming task, (3) visual motion perception task, set out to test the magnocellular deficit theory, (4) motor sequence learning task, set out to test the cerebellar hypothesis.

The authors identified a rostro-caudal functional gradient in the left ITG/FFG, with an anterior region (posterior inferior temporal gyrus) that overlapped during reading and auditory rhyming tasks, and a posterior region (posterior FFG), which overlapped during

motion perception and word reading. In addition, the authors identified overlaps of reading, magnocellular and cerebellar tasks in the left precentral gyrus and bilateral cerebellum, suggesting these regions play a role in motor sequence learning and rehearsal and articulatory planning for reading. Overlap between reading, auditory rhyming, and cerebellar tasks were found in left IFG (opercularis) and left precentral gyrus, suggesting that they are involved in motor planning, speech and hand motor control. Interestingly, no conjunction region between all four tasks was found, suggesting that there is no universal region to explain all behavioural deficits manifested in dyslexia. Instead, these findings suggest that reading relies on disparate functional systems which may overlap to certain degree depending on the requirements of the component process of reading at hand.

A comparison of Paulesu's (2014) clusters with the conjunction regions of Danelli (2013) shows that the clusters preferentially attached in the control-group can be divided into those that correspond to a 'reading only system' (three clusters in ventral OT), a phonological manipulation and a working memory system (middle temporal and supramarginal gyrus), and a visual and motor learning system (dorsal IPL, superior parietal lobule and SMA).

Table 2.1 MRI Structural studies in dyslexia

Year	Authors	Sample	Mean age (SD) or range*	Language	Method	Structure of interest	Group differences	Correlations	Limitations
1990	Larsen et al.	19 DD 19 CA	15.1 (0.3)	Norwegian	manual	Size and symmetry of Planum Temporale	Symmetry of PT found for 70% of DD, in contrast to 30% of CA	All participants with phonological deficits had symmetrical PT	Bias in left handedness in dyslexic group
1993	Leonard et al.	9 DD 12 CA	14-52	English	manual	Size and symmetry of Planum Temporale	All DD had leftward asymmetries in temporal bank DD > CA in intrahemisphere RH asymmetry of parietal bank (planar tissue transferred from temporal to parietal bank)	N/A	Small sample size Large age range
1995	Hynd et al.	16 DD 16 CA	9.7	English	Manual	CC	Smaller genu in DD	Genu and splenium correlated with reading achievement	High comorbidity with ADHD
1996	Rumsey et al.	21 DD 19 CA	27 (6)	English	Manual	CC	Larger isthmus and splenium of CC in DD	N/A	Men only
1997	Rumsey et al.	16 DD 14 CA	18-40	English	ROI	Size and symmetry of Planum Temporale	No differences in asymmetries: leftward asymmetry reported in 70-80% of both groups	N/A	Inclusion of possible comorbidity (e.g. language disorder)
1998	Robichon and Habib	16 DD 12 CA	University students	French	Manual	CC	Larger total area in DD All regions except genu and splenium in DD had larger area	Interaction of handedness and total callosal area: larger in right-handed controls and left-handed DD	Men only
2000	Eliez et al.	16 DD 14 CA	18-40	English	Manual parcellation	GM volume	Decreased total brain volumes in DD Decreased volume in LH temporal lobe outside of STG	N/A	Right-handed men only
2000	Robichon et al.	16 DD 14 CA				Symmetry of Planum Temporale	No group differences	N/A	
2000	Klingberg et al.	6 DD 11 CA	31.5 (5.3)	English	VBA	FA	Reduced FA in LH temporoparietal region	FA in temporoparietal region correlated	Small sample size

								positively with word reading x = -36 to -26, y = -50 to -10, and z = 0 to 32	Control group significantly younger
2001	Brown et al.	16 DD 14 CA	24 (5)	English	VBM	GM volume	Reduced GM in: LH superior temporal gyrus/angular gyrus LH mesial temporal lobe (ITG, MTG, STG) RH occipital lobe/angular gyrus LH inferior frontal gyrus RH precentral gyrus LH & RH caudate LH & RH thalamus RH & LH cerebellum Frontal pole	N/A	Right-handed men only Same subjects as Eliez et al. (2000) P<0.05 cluster threshold
2001	Leonard et al.	15 DD 13 CA	Adult	English	Manual	Surface area: Cerebellum PT Heschl's gyrus	No group differences in PT asymmetry CA>DD on LH-asymmetry of posterior cerebellum	N/A	Findings did not survive correction for multiple comparisons
2002	Rae et al.	11 DD 9 CA	20-41	English	Manual	Cerebellum symmetry	Right-ward GM asymmetry absent in DD	GM symmetry ratios correlated positively with nonsense words reading time in DD only	Male only
2002	Plessen et al.	20 DD 20 CA	11.8	Norwegian	Manual	CC	No differences in total area, areas of seven subdivisions, or midsagittal brain areas	78% classification accuracy based on CC shapes	No group differences yet there was significant classification accuracy – unexplained
2003	Eckert et al.	18 DD 32 CA	11.5	English	Manual	Surface areas and volume of Cerebellum PT Pars Triangularis	CA>DD: RH anterior cerebellum RH pars triangularis No differences in PT	Using both volumes, 72% of DD and 88% of CA were correctly classified	Manual tracing of a priori regions
2004	Brambati et al.	10 DD 11 CA	13-57	Italian	VBM	GM volume	CA>DD: LH & RH PT LH & RH fusiform gyrus (BA 37) LH & RH middle temporal gyrus (BA21/20) LH superior temporal gyrus (BA	N/A	Wide age range Small sample P<0.05 small volume correction

							22) LH & RH cerebellum		
2005	Silani et al.	32 DD 32 CA	22-28 (4-6)	English, French, Italian	VBM	GM density	Reduced GM in LH middle temporal gyrus (BA21) (Tal: -56 - 51 2) Increased GM in LH mid posterior temporal gyrus (BA 37) (Tal: -60 - 60 5)	GM of LH inferior temporal gyrus (BA37) correlated positively with reading speed (i.e. More GM with longer reading time, which means worse performance)	Small volume correction (10mm spheres) centred on peaks identified by previous PET study as well as the cerebellum and MT/V5
						WM density	WM reductions in: LH inferior frontail gyrus (BA44) LH post-central gyrus (BA3)		
2005	Eckert et al.	13 DD 13 CA	10.1-12.7	English	VBM and manual	GM volume	Reduced GM volume in manual measures: RH anterior cerebellum RH pars triangularis	N/A	Male only
						WM volume	Reductions in VBM GM: LH & RH pars triangularis RH anterior cerebellum Reductions in WM in VBM: RH anterior cerebellum RH pars triangularis		P<0.001 uncorrected voxel-level
2005	Vinckenbosch et al.	10 DD 14 CA	17-30 (uni)	French	VBM	GM density	CA > DD: LH inferior and middle temporal gyrus DD > CA: LH & RH precentral gyrus	Correlations with auditory and visual rhyme judgement tasks: LH & RH middle frontal gyrus	Men only Mix of handedness
2005	Beaulieu et al.	32	11.1 (1.3)	English	VBA	FA		LH temporoparietal WM (-28 -14 24) correlated with reading in children	Mostly unimpaired readers (N=28)
2006	Niogi and McCandliss	11 DD 20 CA	7.8 (0.7)	English	DTI (deterministic)	FA	CA>DD: LH superior corona radiata LH centrum semiovale	In controls only: LH centrum semiovale correlated positively with word reading LH superior corona radiata correlated negatively with word reading	Very young, beginning readers Small sample

								Lateralisation of superior corona radiata correlated negatively with word reading	
2007	Hoefl et al.	23 DD 19 CA 12 RA	7-16	English	VBM	GM volume	CA>DD: Total GM volume LH & RH inferior parietal lobule (BA 40) LH & RH temporal gyri (BA22/41/42) LH & RH pre- and postcentral gyri (BA1/2/3/4) LH & RH insula (BA13/44)	N/A	No differences observed between RA and DD in VBM
2008	Kronbichler et al.	13 DD 15 CA	15.5 (0.6)	German	VBM	GM density	CA > DD: LH & RH fusiform gyrus LH & RH anterior cerebellum RH supramarginal gyrus	N/A	Boys only Small volume correction
2008	Steinbrink et al.	8 DD 8 CA	20.1 (3.9)	German	VBM	GM volume DTI FA and MD	CA > DD: LH medial temporal gyrus RH superior temporal gyrus CA > DD FA: LH & RH insula LH external capsule LH medial occipital gyrus CA > DD MD: LH inferior frontal gyrus LH medial temporal gyrus (-45 - 12 -6) RH insula	Negative correlation FA and reading time for pseudo-words Gray matter volume in the left superior temporal gyrus correlated with reading time for pseudowords in the control group only	Small sample size
2008	Wimmer et al.	13 DD 15 CA	14-16	German	VBM	GM volume	CA>DD: LH & RH anterior cerebellum LH fusiform gyrus RH supramarginal gyrus	Positive correlations with reading in these regions across all subjects	Small volume correction
2008	Laycock et al.	10 DD 11 CA	21.1 (2.1)	English	Manual tracing	Cerebellum volume	Larger total, vermis and WM volumes in bilateral cerebellar hemispheres in DD No differences in GM	PT asymmetry correlated negatively with Handedness	Small sample sizes PT associated with handedness, not phonological processing or VIQ
2008	Kibby et al.	20 DD	8-12	English	Manual	Cerebellum	Greater RH-asymmetry in CA	In CA:	Comorbidity with ADHD (11 DD, 11

		20 DD				volume		Positive correlations with phonological awareness and working memory In DD: LH cerebellum volume correlated negatively with RAN errors	CA), but no effects of ADHD observed in RM-ANCOVA
2008	Richards et al.	14 DD 7 CA	30-45	English	TBSS	FA	CA > DD: Bilateral regions across brain DD > CA: Middle cerebellar peduncle	N/A	Small sample No correlations with behaviour
2009	Pernet et al.	38 DD 39 CA	27.3 (7.9)	French	VBM	GM volume and connectivity (GM covariance)	No significant group differences in local GM volume or GM covariance	LI of the inferior frontal gyrus and the loan word reading performances GM volume correlated with pseudoword reading, phoneme deletion and spelling	Mix of handedness P<0.01 uncorrected: CA>DD in LH & RH temporal cortex DD>CA in LH frontal cortex
2009	Carter et al.	7 DD 6 CA	10-14	English	VBA, ROI	FA, DTI	CA > DD in FA: LH superior longitudinal fasciculus LH middle frontal gyrus (BA 8) LH precuneus (BA 7) DD > CA in fibre orientation: RH superior longitudinal fasciculus	N/A	Small sample
2009	Odegard et al.	10 DD 7 CA	10-14	English	TBSS	FA	N/A	Positive correlation of FA and reading in: LH superior corona radiata Negative correlation of FA in posterior CC and reading	Small sample DD children received form of remediation
2010	Elnakib et al.	16 DD 14 CA	18-40	English	ROI	CC	Automated divisions of the CC can classify DD and CA	N/A	Method developmental study
2010	Rimrod et	14 DD	7-16	English	VBA, DTI	FA	CA>DD:	FA correlated positively	P<0.001 uncorrected, k>5

	al.	17 CA			(probabilistic), Fibre orientation	Arcuate Fasciculus (direct segment)	LH & RH inferior frontal gyrus (BA 9) LH temporoparietal WM (BA 41/40/13) DD>CA: LH insula/inferior frontal gyrus (BA 13) RH fusiform gyrus (BA26) RH postcentral gyrus (BA 3) RH putamen RH middle occipital gyrus (BA 19) Orientation differences in DD: LH inferior frontal gyrus (BA44) LH thalamus LH superior temporal gyrus (BA22) RH anterior and posterior cingulate (BA 7/10) Mean FA of the arcuate: CA>DD in posterior superior temporal area	with TOWRE: LH & RH inferior frontal gyrus (BA 9/44/45/46) LH lingual gyrus (BA 18) LH superior parietal lobule (BA 7) LH fusiform gyrus (BA 20)	Comorbidity with ADHD (6 DD, 3 CA), although results were replicated excluding these Analysis for the area of lower FA in DD located in LH temporo-parietal region showed no overlap with the perisylvian language network Tractography conducted in normalised space
2011	Krafnick et al.	11 DD	9.1	English	VBM	GM volume	N/A	Reading intervention led to increased GM in LH middle temporal gyrus/fusiform gyrus (BA 20: -36 -11 -24), LH & RH precuneus (BA 7), RH anterior cerebellum, LH superior frontal gyrus (BA 10)	Small sample size No control group
2011	Raschle et al.	10 DD risk 10 CA	5.7	English	VBM	GM volume	CA>DD risk: LH occipitotemporal region LH & RH parietotemporal region LH fusiform gyrus RH lingual gyrus	Positive correlations for the LH temporoparietal and LH occipitotemporal ROI with RAN	Small sample size P<0.001 uncorrected at voxel-level P<0.01 cluster-level Correlations conducted using ROIs, not whole-brain
2012	Vander-	20 DD	22.1 (3.1)	Dutch	DTI	FA, RD, AD of:	CA > DD in FA:	FA of arcuate fasciculus	University students, selected

	mosten et al.	20 CA			(deterministic)	Three segments of the Arcuate Fasciculus bilateral FA of LH IFOF	LH Arcuate Fasciculus (direct)	(direct) correlated positively with and explained unique variance in phoneme awareness FA of arcuate fasciculus (posterior) correlated positively with speech perception FA of IFOF correlated positively with and explained unique variance in orthographic processing	poorest DD from larger sample, so severe DD (<3 rd percentile) p-value (p=0.03) not corrected for multiple comparisons and would not survive RH arcuate fasciculus successfully tracked in only 52% of participants
2012	Hasan et al.	24 DD 11 CA	13.4 (1.2)	English	ROI, DTI	FA, MD, RD of subdivisions of CC	DD>CA: area of splenium average FA posterior CC	MD of posterior middle sector of CC correlated positively with word decoding	Cut-off DD at <90 on word decoding Small control group
2013	Bloom et al.	26 DD 29 CA	10.5 (1.4)	English	Manual	Size and symmetry of Planum Temporale	Reduced leftward asymmetry in DD, driven by increased RH PT area	N/A	Inclusion of ADHD (N=10 in DD)
2013	Fernandez et al.	23 DD 16 CA	13.7	English	Manual tracing	Cerebellum volume	Reduced LH& RH anterior cerebellum lobe in DD No group differences in total cerebellar volume or asymmetry	N/A	Controls were significantly younger than DD
2013	Vandermosten et al.	20 DD 20 CA	22.1 (3.1)	Dutch	ROI, DTI (deterministic)	FA lateralisation of: LH posterior superior temporal gyrus Arcuate fasciculus Splenium of CC	Lack of left-lateralisation of posterior superior temporal gyrus in DD Reduced left-lateralisation of arcuate in DD No differences in splenium	In CA: Left-lateralisation of arcuate correlated with better processing of auditory modulations In DD: Opposite pattern to CA	Same sample as Vandermosten et al. (2012) p-value (p=0.03) not corrected for multiple comparisons and would not survive

2014	Evans et al.	59 DD 59 CA	9.6-10.1 (1.3-2.1) 34-42.9 (10.4- 11.6)	English	VBM	GM volume	CA>DD: DD men: LH Middle temporal gyrus (BA 21) (Tal -50 -30 -11) RH postcentral gyrus(BA 2)/Supramarginal gyrus (BA 40) DD women: RH precuneus (BA 7) RH medial frontal gyrus (BA 4/6) DD boys: LH supramarginal/angular gyri (BA39/40) DD girls: RH precentral sulcus (BA 4/6) LH cuneus (BA17) RH central sulcus (BA3/4)	N/A	Small sample sizes per group (~13) P<0.001 voxel, p<0.05 cluster Only two clusters survive FWE correction: DD men: LH Middle temporal gyrus (BA 21) (Tal -50 -30 -11) DD girls: RH precentral sulcus (BA 4/6)
2014	Jednorog et al.	46 DD 35 CA	10.3 (0.9)	Polish	VBM	GM volume	CA > all DD: LH inferior frontal gyrus Phonological Subtype of DD: Reduced RH inferior frontal gyrus Increased LH Cerebellum Increased RH putamen	Discriminating variables that provided 60-85.7% classification accuracy: LH parietal cortex LH cerebellum RH superior frontal gyrus RH putamen RH dorsal premotor cortex RH parietal cortex LH inferior frontal gyrus	P<0.001 voxel, p<0.05 cluster Small subtype groups (N=14-17)
2014	Clark et al. (pre- reading)	7 DD 10 CA	6-7	Norwegian	Freesurfer	Cortical thickness	CA>DD: LH Heschl's gyrus LH lingual gyrus LH medial frontal gyrus LH middle cingulate gyrus RH orbitofrontal cortex	Difference in lingual gyrus disappears over time Difference in LH Heschl's gyrus remains at time3 (reading diagnosis)	Small sample Age not included in analyses, difficult to attribute changes to age or reading instruction
2014	Clark et al. (post- reading)	11 DD 13 CA	11-12	Norwegian	Freesurfer	Cortical thickness	CA>DD: LH anterior middle temporal gyrus LH Orbitofrontal gyrus	All differences disappear over time/reading instruction	Small sample, even smaller looking at boys only (5 DD, 8 CA) Age not included in analyses,

							Boys only CA>DD: LH anterior middle temporal gyrus LH Orbitofrontal gyrus LH pars opercularis LH temporoparietal area LH fusiform gyrus		difficult to attribute changes to age or reading instruction
2014	Altarelli et al.	35 DD 46 CA	11 (1.4)	French	Manual	Heschl's gyri, PT	Greater rightward asymmetry of PT surface area in DD boys only	N/A	
2014	Fan et al.	19 DD 20 CA	8-17	English	DTI (probabilistic)	Thalamo-cortical tracts	DD>CA: thalamo-sensorimotor cortex thalamo-lateral prefrontal cortex	Thalamo-sensorimotor connectivity correlated negatively with reading scores.	Wide age range <25 th percentile on word decoding accuracy and fluency Correlations not controlled for group

*Age range is reported here when mean and standard deviations have not been reported in original paper.

Abbreviations: DD – developmental dyslexics, CA – chronological age-matched controls, RA – reading age-matched controls, GM – grey matter, WM – white matter, LH – left hemisphere, RH – right hemisphere, M – mean, SD – standard deviation, ROI – region of interest, PT – planum temporale, CC – corpus callosum, VBA – voxel-based analysis, FA – fractional anisotropy, MD – mean diffusivity, RD – radial diffusivity, IFOF – inferior fronto-occipital fasciculus, n.s. – not significant, N/A – not applicable (i.e. not explicitly studied in the original paper).

Table 2.2 Overview of functional MRI studies in dyslexia

Year	Authors	Sample	Mean Age (SD) or range*	Language	Contrast	Controls > DD	DD > controls	Correlations	Limitations
1998	Shaywitz et al.	29 DD 32 CA	16-54	English	Nonword > Word judgement	LH Posterior superior temporal gyrus LH Angular gyrus	LH inferior frontal gyrus	N/A	Wide age range ROI analyses only
1999	Georgiewa et al.	17 DD 17 CA	14	German	Non-word reading > letter strings Phonological transformation > letter strings	LH inferior frontal gyrus (BA 44) LH inferior frontal gyrus (BA 44) LH thalamus	n.s.	No correlations survived correction	IQ discrepancy diagnosis (>1SD below NVIQ)
2001	Temple et al.	24 DD 15 CA	10.7 (0.9)	English	Rhyming > matching	LH middle occipital lobe (BA 18) LH & RH cingulate (BA23/31/32)	LH lateral sulcus (BA 40/42)	N/A	P<0.001 uncorrected
2002	Backes et al.	8 DD 8 CA	11.6 (0.7)	Dutch	Nonword rhyming	LH inferior frontal gyrus (BA44/45) RH cingulate (BA 32) LH & RH superior temporal gyrus (BA 38/21/22) RH posterior parietal (BA 7/40)	LH occipital cortex (BA17/18/19)	N/A	Boys only Small sample P<0.05 corrected cluster-level
2002	Shaywitz et al.	70 DD 74 CA	10.9 (2.4)	English	Nonword reading and category judgement	LH inferior frontal gyrus LH angular gyrus LH & RH posterior middle temporal gyrus LH & RH anterior middle occipital gyrus	N/A	LH occipito-temporal region positively correlated with reading	DD significantly younger than CA P<0.05
2003	Ruff et al.	12 DD 14 CA	18-43	French	Categorical perception	LH angular gyrus RH inferior frontal gyrus (BA44/45) RH superior cingulate	n.s.	N/A	Men only P<0.005, k>50
2004	Grunling	17 DD	Adolescen	German	Pseudoword	RH superior frontal	LH & RH inferior and	n/a	P<0.01 uncorrected,

		21 CA	ts		rhyming>letter-strings matching	gyrus (BA 10) LH middle temporal gyrus (BA21) LH cuneus (BA 18)	middle frontal gyrus (BA45/47/6/9) LH & RH superior frontal gyrus and precentral gyrus (BA 4/10/11) LH & RH postcentral gyrus (BA 7) LH & RH middle temporal gyrus (BA 21) LH superior temporal gyrus (BA 42) RH fusiform gyrus (BA 20) LH & RH cingulate gyrus (BA 31/24) RH insula (BA 13)		k>10
2006	Kronbichler et al.	13 DD 15 CA	14-16	German	Sentence > false font	LH posterior middle temporal gyrus LH supramarginal gyrus	LH medial temporal gyrus LH motor cortex LH inferior frontal gyrus LH anterior insula RH lingual gyrus RH thalamus RH caudate	N/A	Male only Diagnosis based on fluency
2006	Hoefl et al.	10 DD 10 CA 10 RA	10.4 (1.3)	English	Rhyme > rest	CA > DD: LH middle frontal gyrus (BA 8) RH superior frontal gyrus (BA9) LH & RH inferior parietal lobule (BA39/40) RH middle temporal gyrus (BA 37)	n.s.	LH temporoparietal region correlated positively with word ID across all subjects	Small samples P<0.001 uncorrected, k>10 Group activation differences as ROIs for correlations Correlation reflect group difference as within-group correlations were not significant
2006	Cao et al.	14 DD 14 CA	11.6	English	Conflicting > null	LH inferior frontal gyrus (BA 45/47/46) LH precentral gyrus (BA	N/A	N/A	Small sample P<0.001 uncorrected

						6/9) RH middle frontal gyrus (BA 10) LH inferior temporal gyrus (BA 20/37)			voxel-level, k>15
2006	Brambati et al.	13 DD 11 CA	13-63	Italian	Reading > false fonts Word > false fonts Pseudowords > false fonts Pseudowords > words	LH inferior frontal gyrus (BA45) LH superior temporal gyrus (BA22) LH fusiform gyrus (BA37/19) RH middle frontal gyrus (BA 10) RH Cerebellum LH fusiform gyrus (BA37/19) LH inferior frontal gyrus (BA45) LH & RH middle temporal gyrus (BA21) Supplementary motor area LH superior temporal gyrus (BA22) LH fusiform gyrus (BA37/19) LH inferior frontal gyrus (BA45)	N/A	N/A	Small sample Probands from 5 families, large age-range P<0.005 uncorrected voxel-level, k>20
2007	Meyler et al.	41 DD 26 CA	8-11	English	Sentence comprehension task	N/A	N/A	Positive correlation with reading ability in: LH middle temporal gyrus (BA 22) LH postcentral gyrus (BA2) RH supramarginal gyrus (BA 40) Negative	P<0.0005 uncorrected, k>10

								<p>correlation with age: RH pars triangularis (BA 45) RH middle frontal gyrus (BA 9)</p> <p>Interaction age x reading: LH angular gyrus (BA 39) RH pars triangularis BA 45)</p>	
2007	Hoefl et al.	23 DD 19 CA 12 RA	7-16	English	Rhyme > rest	CA > DD: LH inferior parietal lobule (BA 40) LH & RH lingual gyri (BA 19/18)	DD > CA: LH insula (BA47/13) LH middle frontal gyrus (BA 9) RH thalamus LH cingulate (BA 23)	<p>Across all participants: LH inferior frontal gyrus was negatively correlated with rhyme performance</p> <p>LH inferior parietal lobule was positively correlated with rhyme performance</p>	<p>Wide age range and reading ability</p> <p>P<0.001 uncorrected, k>10</p> <p>Group activation differences as ROIs for correlations</p>
2007	Booth et al.	13 DD 11 CA	9-15	English	Word judgement > rest	LH inferior frontal gyrus (BA45) RH supramarginal gyrus (BA 40)	N/A	Negative correlation between L middle temporal gyrus (BA 21) and semantic association	<p>P<0.001 uncorrected, k>15</p> <p>Small sample</p>
2008	Siok et al.	16 DD 16 CA	11.0	Chinese	Rhyme > font size judgement	LH & RH middle frontal gyrus (BA 9/10/46) LH & RH inferior frontal gyrus (BA 44/45) LH precentral gyrus (BA 6) LH insula LH & RH cingulate (BA 32) LH cuneus (BA 17)	N/A	Positive correlation between activation and GM volume in middle frontal gyrus ROI	P = 0.005 uncorrected, k>10

						LH putamen and thalamus LH & RH cerebellum			
2008	Cao et al.	12 DD 12 DD	12.4	English	Rhyme > fixation	LH middle frontal gyrus (BA 11/47) LH inferior frontal gyrus (BA 46) LH precentral gyrus (BA 4) LH inferior parietal lobule (BA 40) LH middle temporal gyrus (BA 21)	RH posterior cingulate (BA29)	Correlations with level of activation not significant	DD significantly lower NVIQ and VIQ P<0.001 uncorrected, k>10
2008	Schulz et al.	16 DD 31 CA	11.5 (0.37)	German	Sentence reading > baseline Incongruent > congruent	LH middle frontal gyrus (BA 8/9/10) LH supramarginal gyrus (BA 40/39) LH precuneus (BA 31) LH supramarginal gyrus (BA 40/39) RH precuneus (BA 7)	N/A	N/A	Diagnosis on fluency P<0.05 FWE
2009	Schulz et al.	15 DD 15 CA 15 RA	8-12	German	Sentence reading > fixation	CA > DD: LH supramarginal gyrus (BA 40) LH medial frontal gyrus (BA 8/9) LH middle temporal gyrus (BA 21) LH fusiform gyrus (BA 37) RA > DD: LH & RH supramarginal gyrus (BA 40) LH & RH superior frontal gyrus (6) LH & RH medial frontal gyrus (BA 8/9/10) LH middle temporal gyrus (BA21/37) LH cingulate			Diagnosis <10%ile (<61.6) – severe dyslexics P<0.001 uncorrected, k>5

						(BA31/27/37) CA>DD and RA: LH supramarginal gyrus (BA 40)			
2009	Blau et al.	13 DD 13 CA	23.5 (3.7)	Dutch	Incongruent > congruent Multi-sensory integration of sounds and letters	Condition x group interaction in LH & RH superior temporal gyrus – CA>DD in incongruent trials	N/A	N/A	Small sample P<0.001 uncorrected
2009	Van der Mark et al.	18 DD 24 CA	11.3 (0.6)	German	Pseudohomophones > fixation Pseudoword > fixation Pseudohomophones > words	LH & RH insula (BA13) LH & RH middle frontal gyrus (BA47/46) LH inferior parietal lobule (BA 40) LH fusiform gyrus (BA 37) RH postcentral gyrus (BA 2) LH inferior parietal lobule (BA 40) LH inferior parietal lobule (BA 40) LH insula (BA13) LH superior temporal gyrus (BA 38)	N/A	N/A	P<0.001 uncorrected
2009	Beneventi et al.	11 DD 13 CA	13.5 (0.5)	Norwegian	Letter probe Sequence probe	LH precentral gyrus LH middle and superior frontal gyrus RH inferior frontal gyrus RH superior parietal lobe RH lingual gyrus RH parahippocampal gyrus	n.s.	N/A	P<0.001 uncorrected, k>10 Small sample
2009	MacSweeney et al.	7 DD 7 CA	32.1 (8.1)	English	Picture rhyme > same/different	n.s.	LH inferior frontal gyrus (BA44/45)	N/A	P<0.05 voxel-level, p<0.01 cluster-level

2009	Rimrodt et al.	14 DD 15 CA	9-14	English	Word recognition > Sentence comprehension	LH middle temporal gyrus LH superior temporal gyrus LH insula RH temporal RH inferior parietal lobe	n.s.	Cerebellum negatively correlated with reading comprehension and fluency	P<0.001 uncorrected, k>78
2009	Baillieux et al.	15 DD 7 CA	11-12	Dutch	Verb generation > rest	RH Cerebellum lobules V, VI LH cerebellum lobules VI and VIIa	RH Cerebellum Crus II, vermal lobules I, II, III and VII LH cerebellum Crus I, hemispheric lobule VI and vermal lobule V	N/A	Small sample Diagnosis on fluency <3%ile – severe dyslexia
2010	Wimmer et al.	20 DD 19 CA	15-34	German	Word > fixation Pseudohomophones > fixation Pseudowords > fixation Pseudohomophones > words Pseudowords > pseudohomophones	LH occipitotemporal area LH occipitotemporal area LH occipitotemporal area LH inferior parietal lobule LH pars opercularis LH occipitotemporal area LH lingual gyrus LH precentral gyrus LH pars triangularis	LH pre- and postcentral gyrus LH caudate LH pars opercularis LH anterior cingulate RH superior frontal gyrus LH pre- and postcentral gyrus LH pre- and postcentral gyrus LH & RH caudate and putamen LH & RH cingulum LH SMA LH putamen LH pallidum	N/A	Subsample of Kronbichler et al. (2007) Adolescents and adults P<0.001 uncorrected, k>10 Regions for contrasts of pseudohomophones and pseudowords > fixation survive p<0.05 FDR
2010	Richlan et al.	15 DD 18 CA	16-20	German	Word > fixation	RH inferior occipital LH VWFA	LH lingual gyrus LH SMA LH thalamus and putamen RH caudate RH cerebellum		P<0.005 uncorrected, k>20

					Pseudowords > fixation	RH inferior occipital LH VWFA LH lingual gyrus RH middle occipital gyrus LH cuneus LH angular and supramarginal gyrus LH middle temporal gyrus LH & RH inferior frontal gyrus RH insula RH anterior cingulate	LH precuneus RH SMA LH superior frontal gyrus LH precentral gyrus RH middle frontal LH thalamus RH putamen LH & RH caudate LH & RH cerebellum		
2010	Blau et al.	18 DD 16 CA	9.4 (0.4)	Dutch	Speech sounds Visual letters	LH & RH anterior superior temporal gyrus LH & RH fusiform gyrus	N/A	Interaction of multisensory integration in CA only in LH & RH superior temporal sulci Fusiform gyrus correlated positively with visual response LH PT, anterior STG, STS correlated positively with reading and letter-sound matching	P<0.01 uncorrected
2010	Bach et al.	14 DD 18 CA	8.3 (0.4)	(Swiss-) German	Letter substitution and lexical decision > control	LH inferior frontal gyrus LH middle frontal gyrus	N.S. in contrast, only significant in each condition separately	LH inferior frontal gyrus correlated positively with reading score	P<0.05 corrected cluster-level, p < 0.005 voxel-level Smoothing large (9mm ³)
2010	Hu et al.	11 DD 10 CA 8 DD	13.8 (12-16) 14.1 (13-	English Chinese	Semantic word matching	LH middle frontal gyrus LH middle temporal gyrus LH occipitotemporal	n.s.	N/A	P<0.001 uncorrected at whole-brain level, p<0.05 FWE small volume correction

		8 CA	15)			gyrus LH angular gyrus RH middle frontal gyrus Cerebellum			Cerebellar difference at $p < 0.001$ uncorrected Small sample size
2010	Landi et al.	13 DD 13 CA	13.2 (9-19)	English	Rhyme task > pseudoword baseline Rhyme task > word baseline	RH middle temporal gyrus RH precentral gyrus RH inferior temporal gyrus	n.s.	N/A	Large age range $p < 0.01$ FDR, $k > 20$ Small sample
2011	Pecini et al.	13 DD 13 DD	12-50	Italian	Rhyme generation > rest	LH precuneus (BA 7) LH middle frontal gyrus (BA 6) LH inferior parietal lobule (BA 40) LH superior temporal gyrus (BA 22)	n.s.	Positive correlation between reading speed and ROI LH superior temporal gyrus In DD group only: positive correlation between LH inferior frontal gyrus (BA47) and phonological memory	Included language delay – comorbid Language Disorder Mix of handedness Large age range $P < 0.05$ corrected
2011	Tanaka et al. (Stanford sample)	18 DD 36 CA 20 low-IQ poor readers	13.4 (2.5)	English	Rhyme judgment > rest	LH inferior parietal lobule LH FFG	N/A	Support vector machine classification show significant discrimination between DD and CA with accuracy of 79.7% (sensitivity = 76.3%, specificity = 83.3%; $p < .001$)	SVC $P < 0.05$ FDR (voxel-level)
2011	Tanaka et al. (Carnegie Mellon sample)	16 DD 26 CA 15 low-IQ poor readers	10.3 (1.1)	English	Rhyme judgment > rest	LH inferior parietal lobule LH FFG	N/A	Support vector machine classification show significant discrimination between DD and CA with accuracy of 78.9% (sensitivity = 83.9%, specificity =	SVC $P < 0.05$ FDR (voxel-level)

								73.1%; p < .001)	
2011	Grande et al.	20 DD 25 CA	9.7 (0.8)	German	Overt picture naming > rest – low vs high frequency Reading aloud single words > rest – low vs high frequency	n.s.	Interaction frequency (low>high) * group in READ condition only: DD>CA in LH IFG (BA44) and LH precentral gyrus (BA6) Interaction frequency (low>high)* group (DD>CA) * task (read>picture) in LH IFG (BA44)	N/A	More girls in CA group than DD group Sparse sampling P<0.001 unc, k>10 SVC for three-way interaction p<0.05
2011	Kast et al.	12 DD 13 CA	26.1 (6.3)	German	Lexical decision of words and pseudowords in unisensory or multisensory presentation > fixation	Main effect group (CA>DD): LH SMG (BA40) RH STS	Group * condition interaction: DD>CA in visual and AV conditions: RH insula Group * stimulus interaction (DD>CA) pseudoword reading: LH postcentral gyrus	Positive correlation between spelling performance and beta values in LH SMG in CA only during pseudoword processing	Controlled for no ADHD. Childhood diagnosis of DD P<0.001, k>30 Post-hoc ROI analyses centred around peak Correlations across all participants as well as separately
2012	Diaz et al.	14 DD 14 CA	23.5 (2.8)	German	Phonological > speaker task	RH medial geniculate body	n.s.	Positive correlation with reading comprehension in CA only Negative correlation with RAN in DD only	Small samples, but activation at p<0.05 FWE
2012	Steinbrink et al.	17 DD 16 CA	14 -24	German	Vowel length discrimination	n.s. At lower threshold: LH & RH anterior insula LH inferior frontal gyrus	n.s.	N/A	P<0.05 FWE
2012	Monzalvo et al.	38 DD 35 CA	9.8 (0.5)	French	Words > rest Faces > rest	LH fusiform gyrus RH fusiform gyrus	n.s.	LH & RH activation correlated positively with	Included children from low SES and bilingual children

								reading performance	P<0.001 uncorrected voxel-level, p<0.05 corrected cluster-level
2012	Peyrin et al.	12 DD 12 CA	10.3 (1)	French	categorical letter matching	n.s.	n.s.	N/A	Small sample No phoneme awareness disorder but visual attention span disorder – therefore not phonological dyslexics P < 0.001 uncorrected, k>15 Group differences only significant using ROI approach
2012	Kovelman et al.	12 DD 17 CA	9.0 (1.5) 5.9 (0.4)	English	Match > rest Rhyme > Match	n.s. LH DLPFC	RH temporoparietal cortex n.s.	N/A	Inclusion of left-handedness P<0.001 uncorrected voxel-level, p<0.05 cluster-level, k>25
2012	Olulade et al.	6 DD 9 CA	20.6 (1.3)	English	Word > Line judgment Nonword reading > line	LH fusiform gyrus (BA 37) LH superior frontal gyrus (BA 6) LH insula (BA 13) LH & RH middle temporal gyrus (BA 22/37/39) LH & RH inferior parietal lobule (BA 39/40) LH middle frontal gyrus (BA 46/9)	RH cuneus (BA 17) LH cingulate (BA 24) RH middle occipital gyrus (BA 18) RH cuneus (BA 17) RH middle occipital gyrus (BA 19)	N/A	Small sample p < .005 uncorrected, k >10

					Spatial rotation > line	RH precuneus (BA7/19) LH & RH middle frontal gyrus (BA 6/9) LH & RH middle occipital gyrus (BA 18)	LH paracentral lobule (BA 5) RH caudate		
					Spatial not rotated > line	LH pre- and paracentral (BA 4) LH& RH thalamus LH lingual gyrus (BA 18)	RH fusiform gyrus (BA 19) LH & RH middle temporal gyrus (BA37/39) RH superior frontal gyrus (BA 8)		
2013	Kita et al.	14 DD 43 controls	12.3 (2.0)	Japanese	Blending words	LH superior temporal gyrus	RH putamen	LH superior temporal gyrus activation correlated negatively with reaction time in scanner	Controls included 13 children and 30 adults P<0.001 uncorrected voxel-level, p<0.05 FWE cluster-level
2013	Kronshnel et al.	13 DD 22 CA	15.8 (0.6)	German	Three letter string conditions > rest	LH Fusiform gyrus LH Inferior/ middle frontal gyrus/ Rectus RH Sub-gyral	n.s.	Word and pseudoword reading correlated positively with LH ROI2 and RH ROI11 in the fusiform gyri of both hemispheres	Excluded ADHD P < 0.005, k>160
2013	Hernandez et al.	15 DD 16 CA	21.2 (2.4)	French	Word rhyming > font string matching	n.s.	RH cerebellum LH & RH precentral gyrus	Negative correlation between LI of pars opercularis and reaction times during rhyming task in DD Positive correlation between LI of pars opercularis and	Small sample Childhood diagnosis of DD and confirmed by speech therapist Significance at p<0.01 peak (uncorrected), cluster p<0.05 corrected

								reaction time of font-matching task in CA	
2013	Heim et al.	11 DD 25 CA 4 compensated DD	33.8-38.1	German	pseudoword > word low > high frequency words	LH IFG (BA 45) LH precentral gyrus (BA 6) LH angular gyrus (area PGa/BA 39) LH IFG (BA 45,44)	LH IFG (BA 44) SMA (BA 6) LH calcarine sulcus BA 17 LH superior parietal lobule (BA7, BA3) LH putamen LH calcarine sulcus (BA17) LH IFG (BA 44)	N/A	P<0.001 uncorrected Sparse scanning Supplementary analyses with small compensated group suggested that compensation builds upon increased recruitment of LH IFG BA 45 and LH pSTG, despite consistent/prolonged reduced activation of LH IPL/AG
2012	Reilhac et al.	12 DD 12 CA	24.9 (3.7)	French	Letter string matching > frame matching (whole-brain) ROI analyses	LH superior frontal gyrus (BA 10) LH& RH inferior occipital gyrus (BA18) LH superior parietal lobule (BA 7) LH & RH STG (BA 22) LH inferior temporal gyrus (BA 37) LH & RH IFG (BA 44) LH precentral gyrus (BA 4/6) LH middle frontal gyrus (BA 46/10) LH SPL (BA 7) LH FFG (BA 37) LH IFG (BA 44)	n.s. n.s.	N/A	All DD had comorbid visual attention span disorder GLM P<0.001 uncorrected Group comparisons in 6 ROIs: left SPL, BA 7; right SPL, BA7; left IPL; BA 40; right IPL, BA 40; left IFG, BA 44; left ITG,BA 37
2013a	Van Ermingen-Marbach et al.	32 DD (15 double deficit, 17	9-10	German	Initial phoneme deletion > rest	LH IFG (BA 44) RH (IFG (BA44,45)	LH IFG (BA44,45) RH IFG (BA44,45)	Positive correlation reading ability and bilateral BA 44	Sparse sampling ROI analysis: bilateral IFG (BA 44,45)

		RAN) 10 CA						Positive correlation inscanner performance and RH BA44	Unclear if p-values are corrected No whole-brain analyses
2013b	Van Ermingen-Marbach et al.	31 DD (17 phonological, 14 non-phonological) 13 CA	8-11	German	Phonological decision (contains the sound/a/) > sound direction judgment (left/right)	n.s.	RH cerebellum (Lobule VI)	N/A but: Phonological DD > non-phonological DD: LH SMA (BA6) LH & RH precentral gyrus (BA44) RH insula (BA13) non-phonological DD > phonological DD: LH SMG (BA 40) LH AG (BA 39)	P<0.001 unc, k>10
2013	McNorgan, Randazzo-Wagner, Booth	13 DD 13 CA	11.0 (8-13)	English	Cross-modal rhyming task > fixation	N/A	N/A	Positive correlation between elision and congruency effect in all ROIs for CA only, not DD	No LD or ADHD ROI analyses: PT, FG and pSTS
2014	Norton et al.	39 CA 27 Phon 10 RAN 14 Double	8-12	English	Word rhyme > fixation	CA > Phon > Double: LH IPL LH IFG LH precentral gyrus (BA6) (whole-brain) CA > RAN > Double: RH cerebellum (lobule VI) LH IPL (BA28,40) (whole-brain)	N/A	Only LH IPL showed positive correlation between parameter estimates and PA skills RH cerebellar lobule VI showed positive correlation between parameter estimates and RAN skills	ROI analyses for phonological deficit: LH IFG (BA44,45) and LH IPL ROI analyses for RAN deficit: LH IFG (BA44,45), RH cerebellum (lobule VI) SVC p=0.05 FWE Whole-brain analyses: p<0.001 unc, k=0

									FC seed-voxel analyses used ROI seeds: LH IFG, LH IPL, RH cerebellum (10mm diameter); p=0.01 peak, p=0.05 FWE cluster Correlations conducted with whole group
2012	Raschle, Zuk, Gaab	18 DD risk 18 CA	Pre-reading	English	Phonological decision task (do two words start with the same sound?) > voice-matching (same gender speaking?)	LH lingual gyrus LH & RH middle temporal/FFG LH STG LH MTG LH & RH cerebellum	n.s.	Positive correlation of nonword repetition with brain activation in left lingual gyrus and STG in CA In DDrisk, LG, MTG, and STG all showed positive correlation with nonword repetition, but DDrisk showed mainly negative parameter estimates in activation.	4 children ambidextrous P<0.005 unc, k>50 ROIs derived from task: lingual gyrus, STG, MTG
2014	Raschle et al.	14 DDrisk 14 CA	Pre-reading	English	Rapid auditory processing task > slow stimuli First sound matching > voice matching	LH superior frontal gyrus (BA9) LH middle frontal gyrus (BA9, 45, 46) LH cerebellum RH precentral gyrus (BA6) LH middle occipital gyrus/cuneus LH STG	n.s.	Task-based ROI analyses: LH prefrontal ROI of task correlated positively with CTOPP blending task Activation during RAP in LH BA9 positively correlated with activation during Phonological processing in LH BA22/41/42 and LH	4 children ambidextrous, 2 left-handed (left-handedness did not affect fMRI results) P<0.005 unc, k>50 A priori ROI analyses for activation-correlations: ROIs BA9 and 46; BA37, BA40, and a BA41/42/22

								BA37	
2014	Kronshnel et al.	13 DD 22 CA	16.1 (0.7)	(Swiss-) German	Audiovisual integration/congruency effects: interaction stimulus length x group Congruency x group interaction Stimulus length x congruency x group interaction	LH precentral gyrus LH postcentral gyrus LH cuneus RH calcarine sulcus LH & RH precentral gyrus RH superior frontal gyrus LH FFG LH & RH middle temporal gyrus LH & RH STG LH lingual gyrus RH cingulate gyrus LH middle frontal gyrus LH IPL LH postcentral gyrus LH superior parietal lobule LH middle temporal gyrus LH & RH STG	n.s. n.s. pons	N/A	Sparse sampling fMRI P<0.05 FEW first-level GLMs P<0.005 unc, k>160 second-level GLMs
2014	Morken et al.	11 DD 18 CA	11-12	Norwegian	Regular word reading Irregular word reading Sentence reading	Interaction in LH caudate Interaction in RH MFG No interaction	Interaction in R MFG No interaction Interaction in: RH SFG LH preSMA LH middle cingulate RH MFG RH SFG	N/A	DD children received computer-based literacy training. Part of Bergen Longitudinal Study All decoding tasks were based on semantic decisions P<0.001 unc, k>10 Brain differences despite no differences

									in performance in scanner
2014	Christodoulou et al.	12 DD 12 CA	23.3 (4.1)	English	Semantic decision of sentence > fixation Equated for in-scanner performance	LH middle frontal gyrus (BA9) LH STG (BA 22) RH cingulate gyrus (BA 32) Brainstem/cerebellum LH superior frontal gyrus (BA 6) LH IFG (BA45)	n.s. LH anterior cingulate gyrus (BA 24)	N/A	Task was semantic in nature (decide if sentence was semantically plausible) and presentation was sequentially of single words P<0.01 FDR cluster ROI analysis of VWFA
2015	Langer et al.	15 DD 15 CA	10.0 (1.42)	English	Sentence reading > letter reading	LH & RH FFG LH SMG LH middle temporal gyrus RH IFG LH lateral occipital cortex	n.s.	Positive correlation between ROI anterior FFG bilaterally and reading comprehension across whole sample	Severe dyslexia, as cases scored <2SD on standardised measures 3 word sentences ROI analyses on bilateral FFG Confusing reports of p-values. Table says p<0.001 corrected, figure says p<0.005 uncorrected
2015	Boros et al.	15 DD 18 CA	11.5	French	Target character detection task in strings Passive viewing of words (audiovisual), pseudowords, falsefonts	LH & RH middle occipital gyrus LH & RH VWFA LH middle occipital gyrus LH & RH VWFA RH IFG	LH insula LH SMG LH middle temporal gyrus RH IPL RH orbitofrontal region n.s.	N/A	DD if reading age <18 months on standardised test Excluded dyscalculia P<0.001 unc, k>40 ROI based analyses, ROI derived from the other fMRI task

*Age range is reported here when mean and standard deviations have not been reported in original paper.

Abbreviations: DD – developmental dyslexics, CA – chronological age-matched controls, RA – reading age-matched controls, LH – left hemisphere, RH – right hemisphere, M – mean, SD – standard deviation, ROI – region of interest, SMA – supplementary motor area, DLPFC – dorsolateral prefrontal cortex, VWFA – visual word form area, STG- superior temporal gyrus, MTG – middle temporal gyrus, IFG – inferior frontal gyrus, SMG – supramarginal gyrus, AG – angular gyrus, k – cluster extent, n.s. – not significant, N/A – not applicable (i.e. not explicitly investigated in the original paper).

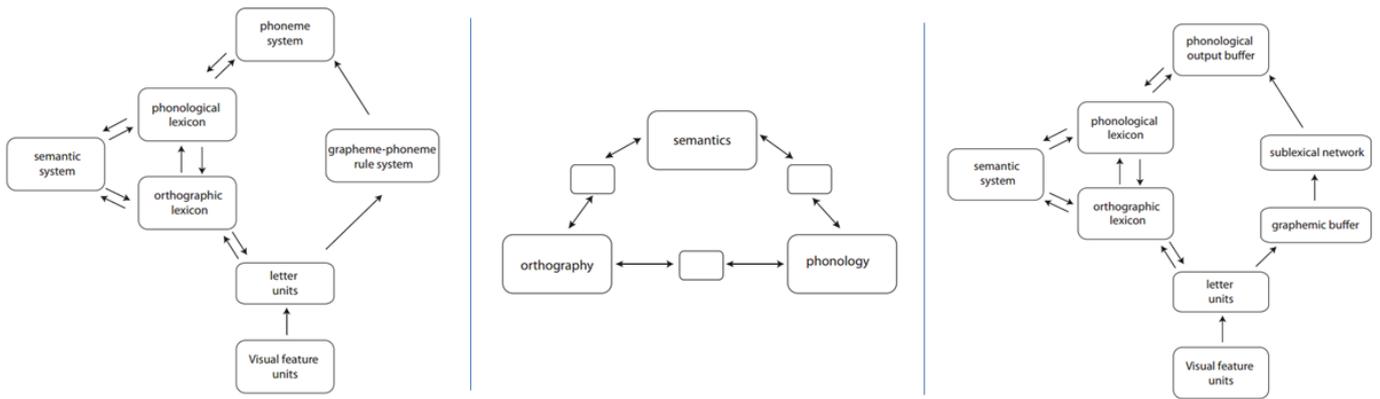
2.4. Integration of fMRI findings and cognitive models of reading

How do the above findings fit with existing cognitive models of reading, such as the dual-route cascaded (DRC) model (Coltheart et al. 2001), triangle model (Plaut et al., 1996), and the connectionist dual-process (CDP) model (Perry et al., 2010)?

The DRC postulates that there are two distinct and separate routes in the reading process of single words and pseudowords, a direct lexicosemantic route and an indirect graphophonological route (Coltheart et al. 2001). The direct/lexical route maps the orthographic form of whole words to their phonological form and is essential in reading irregular words via the semantic system. The indirect/nonlexical on the other hand is a rule-based system that transforms graphemes to phonemes, and is essential for reading pseudowords. Therefore, the DRC separates whole-word and subword reading strategies.

The triangle model, on the other hand, does not specifically distinguish whole-word and subword forms. Instead, it postulates reciprocal relationships between orthography, semantics and phonology. It learns the relationship between orthography and phonology by being presented with the orthographic form of a word, attempting a pronunciation, and receiving the correct pronunciation as feedback. This feedback then modifies the strength of the connections between units, thereby increasing the probability of generating correct pronunciations in future.

Lastly, the CDP model is similar to the DPC model as it postulates two pathways: an identical lexical/direct route, and an indirect/nonlexical route, the latter of which is further divided into a graphemic buffer and a sublexical network. Unlike the DPC where words and pseudowords are read by only one of the pathways, the CDP postulates that both pathways are activated in parallel during reading for all item types. However, the indirect/nonlexical route is more effortful, and is therefore slower than the direct/lexical route. Therefore, words which will activate both pathways will be preferentially decoded by the direct/lexical



Dual-route cascaded model

Triangle model

Connectionist dual-process model

Figure 2.1 Overview of the three cognitive models of reading.

route. Pseudoword can only be decoded by the indirect/nonlexical route as they do not have a representation in the orthographic lexicon. Any conflict is proposed to be resolved by the phonological output buffer.

These models have been tested using computational models using simulations of large corpus data (e.g. Harm and Seidenberg, 2004), but these do not make any assumptions on the neurobiological correlates of these models. Two meta-analyses of functional imaging literature have attempted to map the components of these models onto the different areas of the brain (Jobard et al., 2003; Taylor, Rastle and Davis, 2012). The fundamental assumption here is that “computational processes that are functionally separated in the two models can be mapped onto separate brain processes” (Taylor, Rastle and Davis, 2012, p. 3). Because all models make predictions about the preferred routes involved in pseudoword, word, and irregular word reading, these were the contrasts of interest in the meta-analyses. For example, the word > pseudoword contrast is associated with the direct/lexical route, whereas the pseudoword > word contrast is associated with the indirect/nonlexical route.

The first study (Jobard et al., 2003) evaluated the findings of 35 PET and fMRI (N=10) studies in the context of the DRC model only. The resulting functional structures that could

be associated with the direct route include the left posterior middle temporal gyrus, left inferior temporal gyrus, and left IFG (pars triangularis) (p.703). The indirect route, on the other hand, was mapped onto the left superior temporal gyrus (mid region), left middle temporal gyrus (mid region), left posterior superior temporal gyrus, left supramarginal gyrus, and left IFG (pars opercularis) (p.703). The left OT area, encompassing the VWFA, was found to be equally activated in words and pseudowords contrasts was interpreted as a pre-lexical processing region. It should be noted that the two regions in the IFG (triangularis and opercularis) also contained approximately equal number of activations for either side, but were interpreted as part of the respective streams based on other studies at the time. With regards to the specific components within the model, Jobard did not find regions specifically associated with the orthographic and phonological lexicons in the direct route, but instead interpreted the findings in terms of semantic access, based on studies that have found these regions to be associated with this (Pugh et al., 1996; McCrory et al., 2005; Bookheimer et al., 2002).

Taylor et al. (2012) extended Jobard's findings to include all three cognitive models. Instead of comparing the three models directly based on functional imaging findings, Taylor set out to find the areas of convergence among the models and their brain counterparts. Thirty-six PET and fMRI studies were included (8 PET) in the ALE meta-analysis. Like Jobard, Taylor included foci from words vs pseudoword contrasts. In addition, Taylor also included irregular vs regular word contrasts. Words > pseudoword contrasts converged on five regions in the left hemisphere: left anterior FFG, left angular gyrus, left posterior middle temporal gyrus, left middle frontal gyrus and precuneus. These clusters overlap with clusters of semantic processing identified by Binder et al. (2009) and therefore, like Jobard's interpretation, most likely reflect the semantic access in the DRC and CDP models and the semantics component of the triangle model.

Pseudoword > word contrasts converged on clusters in the left posterior FFG and OT cortex (VWFA), left IPL, left IFG (opercularis and triangularis), insula, precentral gyrus, and left middle temporal gyrus (mid region). These in part overlap with Jobard's findings (left middle temporal gyrus (mid region), left IFG (opercularis), left TP (IPL, posterior superior temporal gyrus/supramarginal gyrus). Whereas Jobard allocated the left IFG to grapheme-phoneme conversion with specific separation between pars opercularis and triangularis, Taylor proposed that the left IFG regions corresponds to the phoneme output system/phonological output buffer in the DRC/CDP models. This interpretation is based on imaging findings that found the left IFG to be phonological short-term memory (Owen et al., 2005) and conflict resolution (Novick et al., 2009). Binder et al. (2005) also found this region to correlate with reaction time when reading all word types, and Grande et al. (2011) found a strong word frequency effect in this region. These findings suggest that the left IFG is involved in more than grapheme-phoneme conversion, as initially proposed by Jobard.

Lastly, the irregular > regular words contrast converged on one cluster in the left IFG including orbitalis, triangularis, opercularis, and insula. This region overlapped fully with the frontal cluster identified by the pseudoword > word contrasts. Taylor interpreted this overlap to reflect increased effort in phonological output resolution. The triangle does not specify a specific phonological output buffer and therefore these regions would correspond to the phoneme component. It should be noted that despite the differences in methodology between Taylor and Jobard (cognitive models considered, hierarchical clustering vs ALE, and difference in PET/fMRI studies included), both reviews come to very similar conclusions.

Based on the evidence discussed above, one could derive the network of brain regions involved in typical reading and the processes they facilitate: (1) OT/FFG cortex – anterior region that facilitates semantic access during lexical processing, posterior region that

facilitates nonlexical orthographic processing, (2) TP region – angular gyrus/posterior middle temporal gyrus that facilitates semantic access and/or phonological lexicon, supramarginal gyrus/posterior superior temporal gyrus/ facilitating grapheme-to-phoneme conversion, (3) inferior frontal region – facilitating phonological output. This now allows one to put the differences in dyslexia into context. I will not reiterate the structural, white matter, and functional differences found in dyslexia discussed above. Instead, I would like to now synthesise the information so far into a coherent model. I will do so by updating the neurobiological model of dyslexia initially proposed by Pugh et al. (2001), below (fig 2.1). The text in black reflects original text by Pugh, with my additions in red.

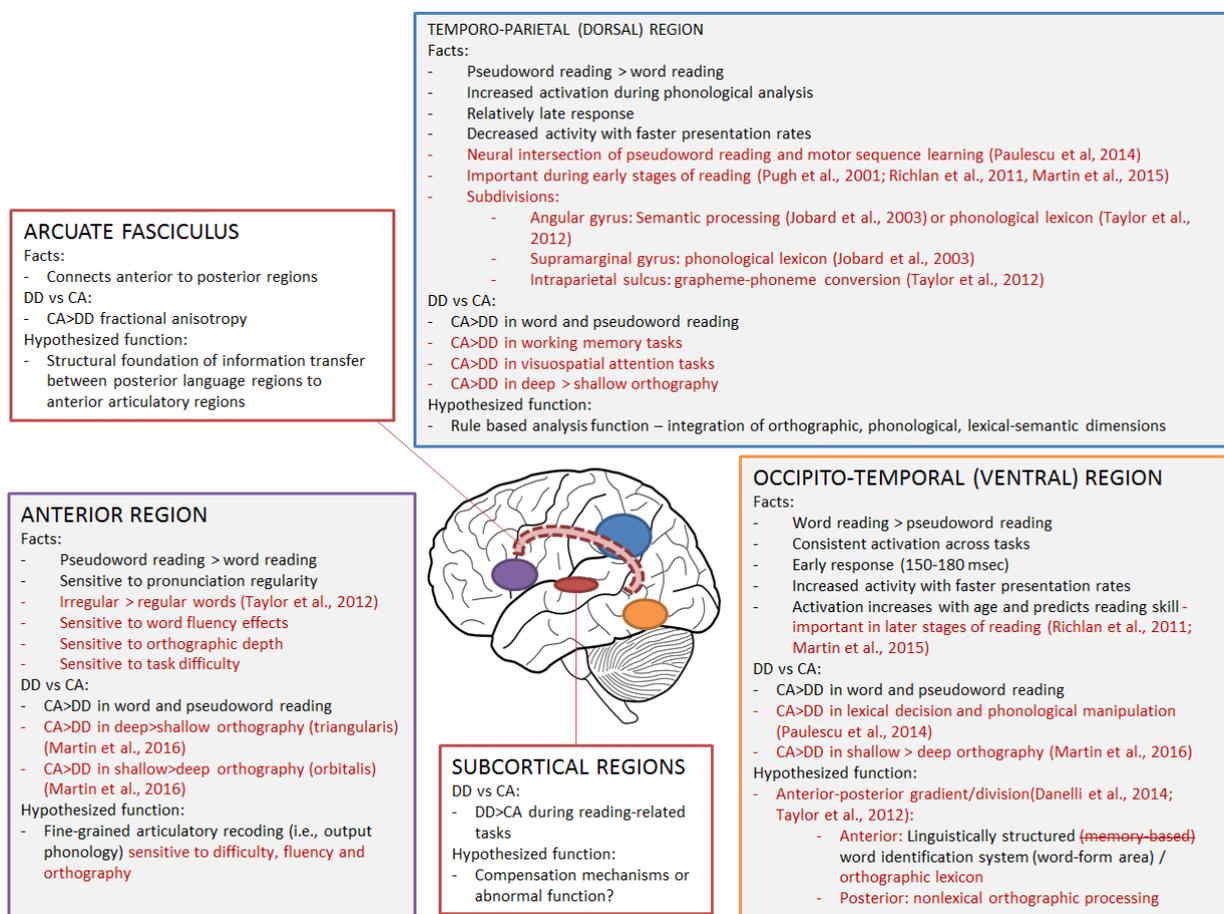


Figure 2.2 Updated model of the reading network in the brain. Adapted from Pugh et al., 2001. The text in black reflects original text by Pugh. Red text reflects updates.

The convergence between neuroimaging studies suggest that it is important to move away from purely localizationist views of reading, trying to pinpoint dyslexia to the dysfunction of

one particular region in the brain. Instead, it is important to study the interactions between the components in the reading network. Functional and structural connectivity studies provide further evidence to support the notion that dyslexia is associated with alterations in the connectivity between multiple brain regions.

2.5. Disrupted functional connectivity during task and rest

Analysing temporal correlations between blood oxygenation level-dependent (BOLD) signal time series provides a measure of coherent activation between distant brain regions that can be taken as a measure of functional connectivity (FC) between regions (see methods chapter for full description). A more in-depth review of studies of FC in developmental dyslexia is included in chapter 8, but a brief summary will be provided here.

Based on the neurobiological model of reading above (fig. 2.2), one would expect to find disrupted functional connectivity between the three regions of the network: left IFG, left TP cortex, and left OT/FFG. This can be tested using ROI-to-ROI functional connectivity analyses, which specifically investigate differences between temporal correlations of two ROIs of interest. This has been done while dyslexic participants were asked to perform reading-related task (Pugh et al., 2000), but not during rest.

In the first and only fMRI ROI-ROI functional connectivity study, Pugh et al. (2000) used regression analyses to predict the activation in bilateral angular gyrus using the activation levels of four predictor regions: primary visual cortex (BA17), lingual gyrus (BA 18/19), lateral extrastriate cortex (BA 18/19), and posterior superior temporal gyrus (BA 22) in a small sample of English adolescents and adults (age range 16-63) during phonological decision tasks. Typical readers exhibited robust FC in these regions in the left hemisphere whereas dyslexics did not. In the right hemisphere, both groups displayed robust FC between regions. However, no direct group comparison was conducted. In addition, FC between posterior regions and frontal regions were not examined.

Another form of ROI-to-ROI connectivity on a large scale is network analysis / graph theory. So far, only one study studied whole-brain FC and found divergent connectivity in dyslexic readers compared to controls in visual areas, VWFA, and right hemisphere regions (Finn et al., 2013). One limitation of ROI-to-ROI functional connectivity analysis is that it does not take the rest of the brain into account, neglecting, for example, additional areas that may be identified otherwise during fMRI tasks (i.e. regions of compensation or abnormal function). As such, researchers have used the seed-to-voxel functional connectivity method, where seed ROIs are defined a priori, but the fluctuations in BOLD response over time is correlated with every voxel in the brain.

In the first seed-voxel FC study, Shaywitz et al. (2003) compared functional connections associated with the left occipitotemporal (VWFA) region between persistently poor adult readers and typical readers during real word reading. In controls, FC was found between the seed region and left inferior frontal gyrus. In contrast, in the persistent poor readers, FC between seed region and right middle and inferior frontal gyri was found. These results suggest a divergent FC pattern from the same seed in dyslexic readers. However, no direct group comparison was performed.

In another FC study, Van der Mark et al. (2011) studied FC from five seed regions along the anterior-posterior axis of the FFG (centred on the VWFA – seed 3) in German children with and without dyslexia during a phonological lexical decision task. Group comparisons found reduced FC in dyslexic children only in the VWFA seed to left IPL, left precuneus, and left IFG. In contrast, increased FC in dyslexic children was found between the VWFA seed to left middle temporal and middle occipital gyri, and between an adjacent anterior seed to left superior temporal gyrus and left insula. Correlation analyses within each group separately found correlations between FC of the left VWFA – left IFG and left VWFA - left IPL to correlate with reading outcome in the controls only. These findings suggest that the FC abnormality in dyslexic children is specific to the VWFA area within the FFG. This was

replicated by Olulade et al. (2015) in English speaking children, suggesting this lack of this gradient of specificity in the FFG may represent a universal characteristic of dyslexia rather than one that is orthography specific, at least in alphabetic languages.

In addition, Olulade used a similar delineation of ROIs along a lateral-medial axis in the left IFG to investigate if such a gradient of specialisation was present in the frontal region of the reading network. Results indeed confirmed this, with the specialisation increasing from medial to lateral regions in controls only. Dyslexic children lack this gradient of specialisation in the left IFG. Moreover, the lateral IFG seed showed significant FC with the anterior FFG (VWFA seed) in controls, but not in the dyslexics. These findings taken together suggest a lack of specialisation of both the left FFG and the left IFG regions as well as a disconnection between these specialised regions in dyslexia.

However, the impaired FC between left FFG and left IFG was not found by Stanberry et al. (2006) and Richards and Berninger (2008) in adults and children, respectively. Instead, Stanberry et al. (2006) reported reduced FC from left IFG to right IFG, right middle and inferior occipital gyri and right cerebellum (lobule VI) in adult dyslexics compared to controls. Richards and Berninger (2008), on the other hand, reported reduced FC from left IFG seed to bilateral middle frontal gyri, bilateral SMA, left precentral gyrus, and right superior frontal gyrus.

The divergent results reported by Van der Mark (2011) and Olulade (2015) on the one hand and Stanberry (2006) and Richards and Berninger (2008) on the other may be explained by methodological differences. Whereas Van der Mark and Olulade investigated FC during a lexical decision task, Stanberry and Richards and Berninger investigated FC during a more phonologically demanding phoneme-mapping task. This highlights the importance of task selection in FC studies, which can significantly bias the results.

One complementary method to task-based FC is the so-called resting-state FC (RSFC). This type of spontaneous activity is thought to represent neural activity that is inherent to intrinsic network architecture and contributes to task-induced variability, while at the same time reducing biases introduced by explicit task demands (Fox et al., 2007; Vincent et al., 2008).

Schurz et al. (2014) examined the overlap in FC during silent reading and phonological lexical decision tasks and at rest in German adolescents with and without dyslexia. Six seeds were selected in the left hemisphere based on previous studies (Richlan et al., 2009, 2011): FFG, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, IPL, IFG (opercularis). The group difference (CA>DD) in FC was present for both tasks and rest for several seeds-target regions: left FFG–left IFG triangularis, left inferior temporal gyrus - bilateral IFG (triangularis, opercularis, and orbitalis), left STG – left IFG (triangularis), left IPL - frontal pole, IPL - IFG, left IPL - inferior temporal gyrus, left IPL – right cerebellum, left MTG - left IFG (opercularis), and left MTG - right frontal pole, left IFG – left MTG, IFG – left SMA.

In contrast, main effects of group in the opposite direction (DD>CA) were found between left IPL - right fusiform/hippocampus, left IPL- left middle frontal gyrus, left IPL - left precuneus, and left IPL - anterior cingulate gyrus for both tasks and rest. It is striking that the left IFG shows consistently reduced FC to left hemisphere seeds in left temporal, IPL, and FFG regions. These FC patterns also correlated with reading fluency and RAN. These findings support the disconnectivity between left IFG and left VWFA reported during task by Van der Mark et al. (2011) and Olulade et al. (2015). However, it should be noted that the sample in Schurz's study consisted of men only and the age range is very narrow (16-20 years old). It is important to see if these results generalise to females with dyslexia in younger and older samples.

2.6. Altered effective connectivity

Although FC provides evidence for dyslexia as a disconnection syndrome, FC itself does not provide any information of the types of interaction between regions. For example, is the disconnection between left IFG and left FFG caused by impaired bottom-up (FFG to IFG) or top-down (IFG to FFG) processing, or perhaps both? Insights into these interactions are important in understanding the development/maturation and specialisation of different components of the reading network. Effective connectivity (EC) is a type of FC that allows one to investigate the influence one brain region exerts over another. However, unlike FC which can assess networks of a large number of regions in a data-driven fashion, EC is limited to hypothesis-driven networks of only a few regions and rely on model of hypothesised interaction patterns (Friston, 1994).

The available effective connectivity studies to date have investigated the interaction between left inferior frontal gyrus, left middle temporal gyrus or left supramarginal gyrus, and left fusiform gyrus in children only (table 2.2) (Cao, Bitan, & Booth, 2008; Liu et al., 2010; Quaglino et al., 2008). All three studies conclude that children with dyslexia showed weaker bottom-up modulatory effects from left FFG to left IFG and/or left pSTG.

Interestingly, no top-down effects were found in these studies, possibly due to the participants being in the early stages of literacy development. These findings suggest that the observed reduced activation in frontal regions may be related to a decreased or a lack of expertise in reading, whereas reduced activation observed in posterior temporoparietal and occipitotemporal regions may be inherently different from an early age in dyslexia. Whether these effects persist into adulthood is currently unknown, as similar studies in adults are currently lacking.

2.7. Genetic contributions to developmental dyslexia

Currently, genetic linkage studies have identified six genes with putative risk variants in individuals with dyslexia: DCDC2, KIAA0319, DYX1C1, C2orf3/MRPL19, CYP19A1, and ROBO1 (Carrion-Castillo, Franke, & Fisher, 2013; Marino et al., 2014; Mascheretti et al., 2014; Newbury et al., 2010; Newbury, Monaco, & Paracchini, 2014). The exact contributions of these genes form an area of active research, but studies suggest that these genes are involved in neuronal migration (Currier, Etchegaray, Haight, Galaburda, & Rosen, 2011; Platt et al., 2013; Szalkowski et al., 2012; Tammimies et al., 2013) and cilia motility (Carrion-Castillo et al., 2013; Ivliev et al., 2012; Tarkar et al., 2013). Cilia are essential in the establishment of left/right axis determination in the first weeks of embryogenesis and mutations in genes controlling cilia function lead to a class of conditions often characterized by laterality defects (ciliopathies) (Newbury et al., 2014). DCDC2, DYX1C1 and KIAA0319 have been reported to play key roles in cilia function, which play a guiding role in neuronal migration during cortical development (Lee & Gleeson, 2011; Valente, Rosti, Gibbs, & Gleeson, 2014). In addition, ROBO1 is a neuronal axon guidance receptor that is also important for cortex development.

Brain imaging studies in typical young readers have found DYX1C1, DCDC2 and KIAA0319 to be associated with white matter volume in a temporo-parietal region (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012). DTI tractography through this region found the superior longitudinal fasciculus, connecting the middle temporal gyrus to the angular and supramarginal gyri, and the corpus callosum (Darki et al., 2012). A longitudinal follow-up study found DCDC2 mutations to be associated with cortical thickness (positive relationship) and white matter volume (negative relationship) in left temporoparietal regions, which predicted variation in reading comprehension scores (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2014).

Brain imaging studies of genetic risk in individuals with a diagnosis of dyslexia are rare. Existing studies in children with reading disabilities and/or SLI have found DCDC2 is specifically associated with reading disabilities and KIAA0319 with reading skills across abilities (Scerri et al., 2011). This finding was replicated by Cope et al. (2012), who also found associations with activation patterns during reading-related fMRI tasks (although not significant when corrected for multiple tests) in children with and without reading disability.

A recent study (Skeide et al., 2015) integrated resting-state fMRI, DTI, and genetic phenotyping in a sample of 34 right-handed German children (age 9-12), a subset of a larger longitudinal study. The children were separated into groups of carriers or non-carriers of dyslexia risk variant rs11100040 of gene SLC2A3 – a gene regulating neural glucose transport (e.g. Maher et al., 1994). Skeide et al. (2015) found children with risk allele rs11100040 to have significantly reduced RSFC between left IFG and left posterior superior temporal gyrus (pSTG) (using ROI-ROI FC analyses), as well as reduced FA in a cluster located in the left Arcuate Fasciculus. Moreover, the left IFG – left pSTG RSFC correlated positively with the FA of the Arcuate. The FA also correlated positively with performance on phonological awareness tasks, after controlling for effects of age, gender, IQ, speech therapy, musical instrument instruction, and attention deficit disorder. However, the relationship between FA and phonological awareness could be partly explained by RSFC. Unfortunately, it was not specified how many children had a diagnosis of dyslexia. This is needed in future research to establish links between genetic risk and diagnostic outcome. Furthermore, similar studies in adults are currently lacking in the literature.

Taken together, these studies support an interaction between biological pathways, which control the establishment of cortical asymmetries and neuronal migration, with genes

implicated in dyslexia. These studies further support the hypothesis that developmental dyslexia and reading deficits may be caused by dysfunctional connections in the brain.

2.8. Intervention studies

Lastly, a growing number of studies have investigated the effects of reading intervention on brain activity. These studies not only demonstrate the potential of reading remediation, but also highlight which areas in the brain are important contributors to reading gain in poor readers. Functional MRI studies of reading intervention indicate that before remediation, underactivation was present in bilateral IFG, left MTG and STG, left FFG in the dyslexic readers (adults and children) compared to controls, which is consistent with the reports above (Aylward et al., 2003; Eden et al., 2004; Temple et al., 2003).

After intervention, overactivation was observed in bilateral IFG, bilateral MTG and STG, right FFG, bilateral pre- and postcentral gyri, thalamus, and insula (Aylward et al., 2003; Barquero, Davis, & Cutting, 2014; Eden et al., 2004; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008; Richards et al., 2006; Shaywitz et al., 2004; Temple et al., 2003). A meta-analysis further found the effects of intervention to be most profound in the left thalamus, right insula/IFG, left IFG, right posterior cingulate cortex, and left middle occipital gyrus (Barquero et al., 2014). These findings suggest that although reading remediation can normalise the underactivation in the left hemisphere reading network, there is additional compensation from other systems to increase reading gain. Therefore, it is informative to characterise the connectivity and topology of these systems to identify compensatory mechanisms.

Besides changes in reading-related regions discussed above, reading intervention has also been shown to induce changes in visual- and cognitive-control brain networks in children (Horowitz-Kraus et al., 2014, 2015; Horowitz-Kraus and Holland, 2015). Whereas the post-intervention changes discussed above followed training in phonological, phonemic, or

letter-knowledge training, these latter studies employed training programmes based on executive function and attention training. This suggests that the nature of the training programme itself has an influence on which brain systems respond to training, even though the same improvements may be seen on a behavioural level. This in turn suggests that there may be several routes of compensation in the brain.

2.9. Conclusion

To summarise, despite the plethora of theories that aim to explain reading deficits and the heterogeneity among individuals with developmental dyslexia, there is some consensus in the brain imaging literature. Individuals with dyslexia show deviant brain structure, abnormal brain activation patterns during reading-related tasks, disrupted functional connectivity in the left hemisphere during task and rest, altered effective connectivity between left hemisphere language regions and bilateral frontal regions, and decreased fractional anisotropy in left hemisphere fronto-temporal and temporo-parietal white matter.

More recently, network studies have shown altered topological properties of brain networks in children with reading difficulties and children at familial risk for reading difficulties. These findings provide support for the disconnection deficit theory and demonstrate that reading is an emergent skill of an interconnected network of disparate regions in the brain. Therefore, it is warranted to move beyond localising the dysfunction within any particular region of the brain, and instead study the connectivity patterns and interactions between brain regions to understand the underlying brain substrate underpinning the behavioural differences that are apparent in dyslexia. This thesis sets out to investigate the disconnection deficit of theory using multimodal imaging techniques and network analyses.

3. Overview of thesis

The literature review thus far highlights the need to study the functional and structural connectivity in readers with dyslexia. However, few studies have used connectivity methods to study dyslexia, and existing studies show conflicting results. These conflicting results are most likely caused by sample selection (e.g. diagnostic criteria, child/adult, comorbidity) as well as methodological choices (e.g. a priori selection of regions, choice of task, task demands).

In addition, although the existing literature points to a disconnection deficit in the left hemisphere, there is little research into how disruptions in the reading networks may affect the brain networks as a whole. This is especially important as the reading network is embedded in the brain as a whole (Vogel et al., 2013) and regions, which contribute to reading, will also be linked to other subnetworks in one way or another. In other words, what are the topological properties of the whole-brain network and how do they relate to reading outcome?

The purpose of this thesis, therefore, was two-fold. Firstly, I aimed to characterize the reading networks in the brain of adults with and without developmental dyslexia, using both hypothesis-driven (i.e. defined task, a priori defined regions) and task-free approaches (i.e. resting-state, diffusion-weighted imaging, whole-brain parcellations). Secondly, I investigated how these network measures related to reading outcome in these adults, using novel analysis methods (graph theory and complex network analysis) and conventional brain imaging methods (structural MRI, tractography and functional MRI).

The first experimental chapters of this thesis, therefore, used a hypothesis-driven approach with a priori defined regions of interest, whereas the final experimental chapter used whole-brain and task-free methods. Specifically, chapter 5 explored the functional and structural topology of the language network using resting-state functional connectivity and

probabilistic tractography, seeding from a priori defined regions of interest in Broca's area in the left hemisphere in healthy adults with no history of reading impairments. Chapter 6 used Principal Component Factor analysis to characterize the cognitive profiles of the participants recruited during this PhD. Chapter 7 explored the reading network defined using a covert fMRI reading task and at rest, using a priori defined regions derived from a meta-analysis in adults with and without dyslexia. Chapter 8 extended beyond the conventional reading network to investigate changes at a whole-brain level, using network based statistics and graph theoretical analyses.

3.1. Research hypotheses

The purpose of this PhD was to describe the development of language networks in the brain of adults with dyslexia and typical readers, using novel analysis methods (graph theory and complex network analysis) and conventional brain imaging methods (structural MRI, tractography and functional MRI).

The hypotheses tested in this PhD were:

H1: Developmental dyslexia is a specific reading disability, which persists into adulthood, despite compensation status. (Chapter 6)

H2: Connectivity differences exist in language/reading specific regions between typical readers and dyslexic readers. (Chapter 7)

H3: Adults with dyslexia have abnormal topological properties in functional and structural whole-brain networks. (Chapter 8)

H4: Measures of functional and structural connectivity correlate with measures of reading. (Chapters 7 and 8)

4. Methods

The work conducted in this thesis concerns the analysis of brain imaging data that has been acquired using magnetic resonance imaging (MRI). This chapter provides brief background information about MRI physics, and consequently, provides a general overview of the specific methods employed in my research. As all the experiments presented in this thesis were acquired as one large data set, the procedures for which are described in this chapter. The subsequent chapters contain brief methods sections describing only the methodological components specific to the experiment being presented.

4.1. Brief introduction to the principles of MRI

Nuclear Magnetic Resonance and image formation

MRI uses the magnetic properties of protons in the hydrogen atoms within water molecules to map the structure and function of the brain in a non-invasive manner, based on the principles of nuclear magnetic resonance (Bloch, 1946) (figure 4.1). Protons in the hydrogen nuclei in the brain spin around their axis, generating a magnetic field (magnetic moment). Under normal circumstances, these atoms spin in random orientations. When placed in an external strong magnetic field (e.g. a MRI scanner), the spins will align (precession) to the direction of that field (B_0). Precessing protons can take on two states: spin up or spin down. There will be more atoms in the more stable spin up state, as this requires less energy than the spin down state. However, atoms can go into the spin up state by releasing energy in the form of electromagnetic radiation. Equally, atoms can fall into the spin down state by absorbing electromagnetic radiation. Transitions between the two energy states can occur when a radiofrequency (RF) field is applied at the resonant frequency of the protons, according to the Larmor equation (McRobbie, Moore, Graves, & Prince, 2006).

In the MRI scanner, the RF coils emit electromagnetic radiation in the radiofrequency range to cause protons to jump into high-energy spin down states. When the RF pulse is turned off, protons in the spin down state will relax and release the radiofrequency energy to revert back to their low-energy state. The RF receiver coil measures this energy that constitutes the measured signal in MRI. In the classical description of MRI, longitudinal magnetisation is established when the object is placed in the magnetic field. The RF pulse then tips the rotating magnetisation into the transverse plane. If the so-called 'rotating frame of reference' is used the transverse magnetisation vector is static. Different tissue types (grey matter, white matter, cerebral spinal fluid) are characterised by their different longitudinal relaxation time (e.g. between states, T_1) and the transverse relaxation time (e.g. loss of coherence or phase between spins, T_2). The longitudinal relaxation time depends on the time for the longitudinal magnetisation to return to equilibrium. The transverse relaxation time depends on the time taken for the transverse magnetisation to decay due to de-phasing. Lastly, transverse relaxation can also result from local field inhomogeneities in the magnetic field, which can be characterised as T_2^* and is essentially what is measured in fMRI. In order to construct the 3D MR images, magnetic gradients are applied alongside the RF pulses to localise the location of hydrogen atoms in 3D volume elements (voxels).

All the images in this research have been acquired using echo planar imaging (EPI) sequences (DeLaPaz, 1994), which allow the rapid acquisition of whole brain images by collecting slices by using a rapidly oscillating readout gradient following a spin echo or gradient echo sequence.

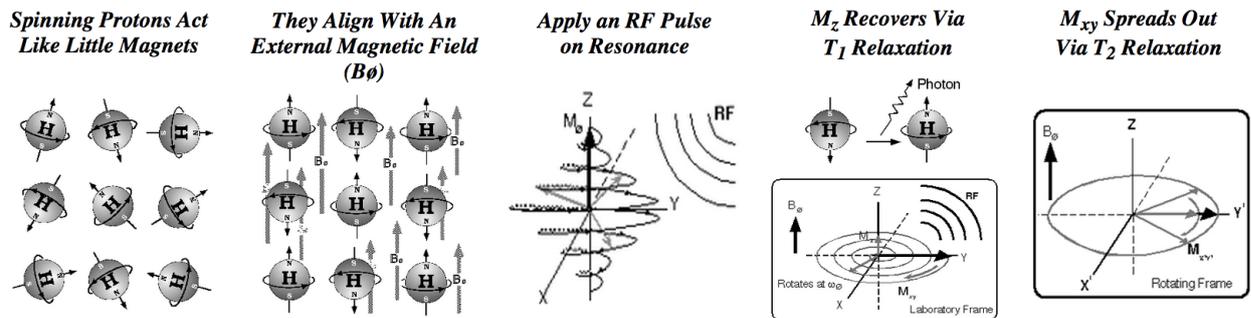


Figure 4.1 Basics of MRI. Hydrogen atoms spin around their own axes. When a uniform magnetic field is applied (B_0), all hydrogen atoms align their axes. Radiofrequency pulses cause atoms to precess about the Z-axis and dephase about the xy axis. Images adapted from www.simplyphysics.com.

4.2. BOLD fMRI

Functional MRI provides an indirect measure of neural activity by detecting changes in the oxygenated state of blood that in turn is related to regional blood flow. More specifically, the MRI signal is sensitive to the level of oxygenated haemoglobin in reaction to regional neural activity. Deoxygenated haemoglobin is paramagnetic and induces local magnetic field inhomogeneities, which influence the T_2^* decay time. Hence, this BOLD contrast provides an indirect measure for the metabolic state (e.g. changes in bloodflow in response to neural activity) for each voxel.

The haemodynamic response function (HRF) characterises the relationship between the BOLD response and the underlying neural activity within a region (fig 4.2). First there is an increase in metabolic demand due to the increase in neural activity. This leads to an initial dip in the BOLD response, as oxygen is used up faster than it can be replaced (Buxton, Wong, & Frank, 1998). Subsequently, the BOLD signal increases as the supply of oxygenated blood to the region increases, peaking around six seconds after the onset of activity. Lastly, there is an undershoot after the BOLD peak has subsided, which lasts for several seconds.

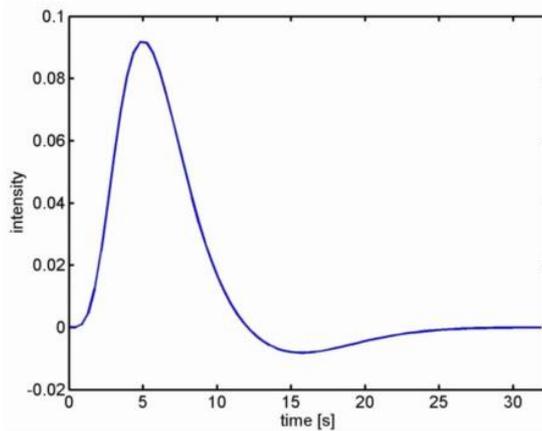


Figure 4.2. Canonical haemodynamic response function.

The neuronal basis of the BOLD signal is currently still unknown. However, there is evidence to suggest that the excitatory neurotransmitter glutamate allows for vasodilation to increase blood to the activated region (Stefanovich et al., 2007; Takano et al., 2006). In addition, the BOLD signal has been found to be correlated with electrophysiological measures such as multi-unit activity (MUA) and local field potentials (LFP) (Goense & Logothetis, 2008; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Logothetis, 2002, 2008). Initial studies suggested that the BOLD signal correlates most strongly with the input of and processing in a given cortical area rather than its spiking output (Logothetis et al., 2001). However, subsequent studies reported it to reflect oscillatory activity, particularly within the gamma band (Goense & Logothetis, 2008; Logothetis, 2002, 2008; Magri, Schridde, Murayama, Panzeri, & Logothetis, 2012), which have been proposed as an important mechanism for temporal coding of cognitive processing (Magri et al., 2012).

The task-based fMRI data acquired in this thesis used blocked designs, where stimuli were presented sequentially within each condition, with alternating conditions. In the covert (silent) reading task, four conditions were presented in randomised order: words, pseudowords, fixation cross, symbols (fig 4.3). More details of these tasks are listed below (4.6 Procedures used in this thesis).

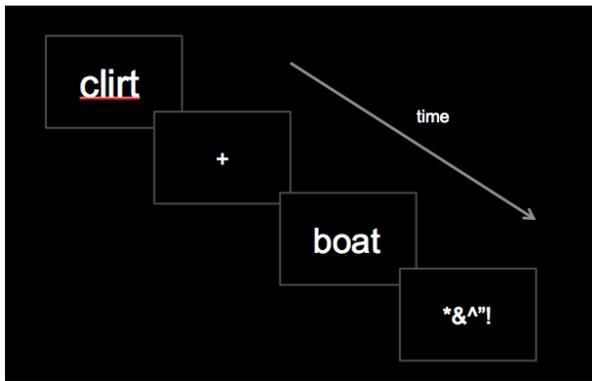


Figure 4.3 Covert reading task. The participant is presented with four types of stimuli in randomized blocks. He/She was instructed to covertly read the words and pseudowords, but not the fixation crosses and symbols.

BOLD preprocessing in SPM

All task-based fMRI data acquired in this thesis were analysed using the Statistical Parametric Mapping (SPM) software, in particular SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>), developed at the Wellcome Department of Imaging Neuroscience. In short, SPM8 consists of a set of MATLAB routines to preprocess and analyse fMRI data. I will provide a brief overview of the preprocessing steps carried out in this thesis.

- 1) *Discard dummy scans.* Firstly, the initial volumes acquired in each scanning session (dummy volumes) were discarded to allow for T1-equilibrium effects (Kiebel & Holmes, 2003). For the task-based sequences, this was always the first five volumes. For the resting-state sequences, this was the first ten volumes.
- 2) *Realign and reslice.* Following step 1, the remaining volumes were spatially realigned to the first volume using rigid-body transformation in order to correct for head movements during the duration of the scan. This was done using the *realign* and *reslice* function in SPM8, which estimated six movement parameters (three

translation, three rotation). This procedure minimises the difference between volumes to allow for better anatomical alignment.

- 3) *Coregister: estimate.* After realignment of the functional volumes, the individual data were coregistered to each participant's anatomical T1 image.
- 4) *Normalise: write.* Spatial normalisation was applied to the functional volumes to allow for statistical inferences across groups of participants as each individual's data is transformed into the same space (in this case, the Montreal Neurological Institute – MNI - standard).
- 5) *Smooth.* The normalised images were then smoothed with a three-dimensional isotropic Gaussian kernel of 6mm FWHM. This step is necessary to fit the assumptions of the Gaussian random field model (Brett, Penny, & Kiebel, 2003) used in the statistical inferences. Smoothing also compensates for any residual small anatomical variations between subjects.
- 6) *General linear model.* SPM uses General Linear Models (GLM) and Gaussian Random Field Theory to make statistical inferences. For each voxel, the GLM explains the variations in the BOLD signal time series (Y) in terms of a linear number of experimental variables (x) plus an error term/noise (e), all expressed in a matrix formulation (Kiebel & Holmes, 2003): $Y = X\beta + e$. Within this equation, β is a vector containing the parameters to be estimated and reflect the independent contribution of each independent explanatory variable to the dependent variable. The regressors (X) are convolved with the HRF. The movement parameters from step 2 are included in the first-level design matrices as covariates of no interest to control for non-linear movement related effects (Friston et al., 1996). GLMs are applied at the individual level (first-level) to estimate the contrast images for each

participant, which are then inputted into second-level GLMs for group comparisons.

Gaussian Random Field Theory is implemented in SPM to deal with the issue of multiple comparisons. The commonly used Bonferroni correction method, which divides the statistical threshold ($p < 0.05$) by the total number of independent tests conducted, is not suitable for fMRI data, as there are tens of thousands of tests (individual voxels). Gaussian Random Field Theory instead corrects the statistical threshold based on the number of spatial clusters as well as individual voxels.

In addition, if there is a strong hypothesis about the location of activation, a more restricted multiple comparisons correction can be used: small volume correction (SVC). This is applied by specifying a specific anatomical region, in which the Gaussian Random Field Theory corrections are applied.

7) *Statistics.* T-tests in first-level GLMs were used on the parameter estimates to test for experimental effects. In the verb generation task, the noise conditions were subtracted from the word conditions. In the covert reading task, the fixation and symbol conditions were subtracted from the word and pseudoword conditions. Independent sample t-tests in second-level GLMs were used to investigate group effects.

4.3. Functional connectivity and resting-state fMRI

The previous section has discussed fMRI and the BOLD response in relation to stimulus-induced activation of a particular brain area. This will be referred to as task-based fMRI from now on. One limitation of studying cognitive networks using task-based fMRI is the challenge of finding the 'ideal task' to probe the network of interest. These tasks often

come with age-constraints: tasks are often not suited for very young children and infants, or a challenging task for children might be too simple for adults.

One possible solution is offered by task-free fMRI, such as resting-state (rs-fMRI). Rs-fMRI allows the investigation of the functional architecture of the brain without task constraints (Biswal et al., 1995). Participants are instructed to relax in the MRI scanner and not think of anything in particular for the duration of the scan. These experiments have been argued to measure “spontaneous” brain activity (Biswal, Yetkin, Haughton, & Hyde, 1995; Kelly, Biswal, Craddock, Castellanos, & Milham, 2012; Smith et al., 2013; van den Heuvel & Hulshoff Pol, 2010; Zhang et al., 2010).

Biswal and colleagues (1995) were the first to show that during rest, the motor cortex in the left and right hemisphere showed ongoing information processing by ongoing synchronised activity. The Biswal study, as well as that of Lowe et al. (2000), have shown the feasibility of examining functional connectivity between brain regions as the level of co-activation of functional MRI time-series measured during rest (Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000).

Functional connectivity can be defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions (Deco, Jirsa, & McIntosh, 2011; Smith et al., 2013; van den Heuvel & Hulshoff Pol, 2010). A wealth of subsequent studies have replicated Biswal’s initial finding and prove that the brain is not idle during rest, but shows highly correlated activity between multiple regions, forming functional networks which resemble the well-studied networks derived from task-based fMRI (fig 4.4) (Smith et al., 2009).

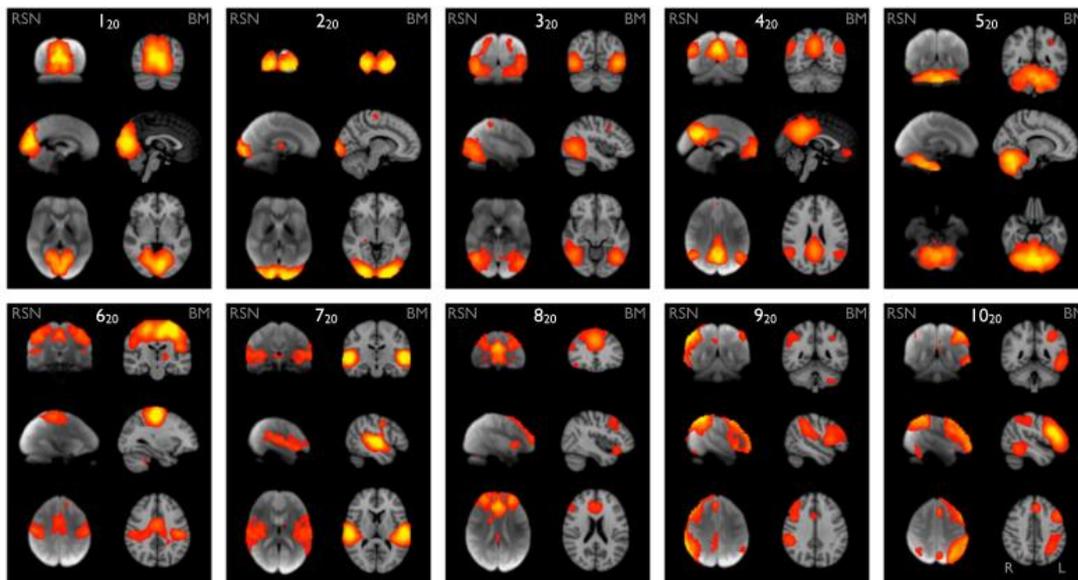


Figure 4.4 Functional networks in the brain. Correspondence between resting-state networks (RSN) and activation profiles from the BrainMap database (BM). Figure adapted from Smith et al. (2009).

Although functional networks are consistently found in rs-fMRI studies, the underlying neuronal basis of rs-fMRI is not yet understood. There is an ongoing debate as to whether the functional synchronisation observed results from physiological processes, such as respiratory and cardiac oscillations (Birn, Diamond, Smith, & Bandettini, 2006; Chang & Glover, 2009, 2010), or whether they originate from neuronal co-activation of these regions (Buckner, Krienen, & Yeo, 2013; Damoiseaux et al., 2006; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Zeng et al., 2014).

To minimise aliasing effects from high frequency respiratory and cardiac oscillations, research has focused on low frequency oscillations of $\sim 0.01-0.1$ Hz in rs-fMRI time series (Cole, Smith, & Beckmann, 2010; Deco et al., 2011; Smith et al., 2013; van den Heuvel & Hulshoff Pol, 2010a; Wig, Schlaggar, & Petersen, 2011). Such low frequency resting-state functional connectivity (RSFC) patterns have been found to represent intrinsically organized functional networks in the brain. Cordes and colleagues (2001) have further found that cardiac and respiratory oscillations have higher frequency patterns (>3 Hz), which

contribute minimally to low frequency dominated spontaneous BOLD signals. Moreover, studies have found a strong association between spontaneous BOLD signal fluctuations and electrophysiological recordings of neuronal firing (Niessing et al., 2005; Shmuel, Augath, Oeltermann, & Logothetis, 2006; Wang, Saalmann, Pinsk, Arcaro, & Kastner, 2012). Together these findings support a neuronal basis of the rs-fMRI signal.

Noise correction and global signal regression

Due to the uncontrolled nature of resting-state studies, there is a concern that the observed fluctuations in 'spontaneous' time series are caused or contaminated by artefacts, such as scanner instabilities or physiological noise (heart rate and respiration). The relative contributions of such artefacts have been documented in the literature (Bianciardi et al., 2009): up to 49.9% of fluctuations at rest can be attributed to artefacts, including scanner instabilities (34.7%), respiration (8.6%), and cardiac pulsation (6.6%). However, this study was done at 7T, so may differ from measurements taken at 1.5T. Fortunately, there are ways to filter such nuisance variables out of the signal. Thermal noise caused by the scanner environment, for instance, cancels out when signal is averaged over multiple voxels. Physiological noise mainly relates to frequencies above 0.1 Hz. Therefore, bandpass filtering the data around 0.01 Hz – 0.1 Hz should remove most of these artefacts.

Recently, the removal of the global signal has been heavily debated. Most early studies of resting-state fluctuations have regressed out the BOLD fluctuations common to the whole brain (Fox et al., 2006; Fox, Zhang, Snyder, & Raichle, 2009). The rationale underlying global signal regression is the assumption that common BOLD fluctuations are caused by physiological factors. However, recent studies have shown that global signal regression leads to spurious negative correlations (Chai et al., 2012; Murphy et al., 2009). The concern is that some observed anticorrelations are in fact false positives (artefacts) caused by global signal regression. This issue is still unresolved. Therefore, the resting-state analyses done in this thesis did not incorporate global signal regression. Instead, the CompCor method

(Behzadi, Restom, Liau, & Liu, 2007) was used, in which principal components from noise regions of interest (white matter and cerebral spinal fluid) were removed. This method has demonstrated valid anticorrelations at rest (Chai et al., 2012).

Extracting resting-state networks

There are several ways to extract functional networks from resting-state data. The appropriate method for a study depends on the experimental question. The most common methods are independent component analysis (ICA) and seed-voxel or seed-seed approaches.

ICA uses a fully automated algorithm to decompose the BOLD time series into a number of components, which are maximally statistically independent from each other (Allen, Erhardt, Wei, Eichele, & Calhoun, 2011; Damoiseaux et al., 2006; Dobromyslin et al., 2012; Smith et al., 2013). These components are reflected in spatial maps, which show how much of the data in each voxel can be explained by that particular component. However, the interpretation of these maps is not always straightforward. Whereas some maps reflect functional networks, others reflect noise components. Which functional networks these components correspond to can also be a potential source of bias. Moreover, the maps are highly dependent on the set number of components.

Seed-based approaches extract the time series from a voxel or a region of multiple voxels, and determine the temporal correlation between the extracted signal and the signal of another region (seed-seed approach) or every other voxel in the brain (seed-voxel approach). Although simplistic in nature, this approach has been widely used in the literature and has demonstrated robust identification of functional networks at rest (Biswal et al., 1995; Fox et al., 2006; Kelly et al., 2009; Zhang et al., 2010). This is the approach used in this thesis, because we can use existing task-based literature to inform our choice of seed regions. However, this method is limited by the a priori choice of the seed region(s).

Therefore, I have also included whole-brain FC approaches such as network based statistics (NBS) and graph theory (chapter 8) in this thesis.

4.4. Diffusion weighted imaging and tractography

Diffusion weighted MRI offers a non-invasive and in vivo approach to study the microstructure of brain white matter tissue (Bihan & Johansen-Berg, 2012; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005). This is done by indirectly measuring the properties of the diffusion process of water molecules in the brain. When water molecules are equally likely to move in any direction – as in cerebrospinal fluid and grey matter – the diffusion can be considered isotropic. In white matter, on the other hand, the diffusion of water is restricted by myelinated axons running parallel to each other. Therefore, the diffusion will be anisotropic, meaning it will be larger parallel to the tract than perpendicular to it (Kochunov et al., 2011; Nagy, Westerberg, & Klingberg, 2006; Qiu, Tan, Zhou, & Khong, 2008).

Large magnetic field gradients are applied in different directions to visualise variations in diffusion (Hajnal et al., 1991) and a tensor model can be fitted for anisotropic diffusion, which is then converted into three eigenvalues (λ_1 , λ_2 , λ_3) to represent the magnitude of the diffusion in the direction of the corresponding eigenvectors (v_1 , v_2 , v_3) (Bihan & Johansen-Berg, 2012). Thus, in tissues organized in parallel bundles, the largest eigenvalue (λ_1) would correspond to the diffusivity along the direction of the fibers, while λ_2 and λ_3 would correspond to the diffusivity perpendicular to the fiber (fig 4.5 A).

From the tensor model, one can extract the fractional anisotropy (FA) index, which ranges from 0-1, to quantify the amount of anisotropy in each voxel, which is also often used as a proxy measure for white matter integrity (fig 4.5 B) (Bihan & Johansen-Berg, 2012; Parker et al., 2005; Vandermosten et al., 2012). The micro- and macroscopic factors underlying FA is still debated. Such factors include myelination, number of axons, axon density, axon

caliber, and coherence of the axons within a voxel (parallel versus crossing fibers) (Bihan & Johansen-Berg, 2012; Huang et al., 2006; Vandermosten et al., 2012). To help interpret FA values, two other indices were recently proposed: radial diffusivity (RD) and axial diffusivity (AD). RD quantifies the diffusivity in directions perpendicular to the principal axis of diffusion (λ_2 and λ_3), whereas AD is the diffusivity along the principal axis (λ_1). Studies using longitudinal designs in animals indicated that the different time course of myelin degradation correlates with RD, and axon degradation correlates with AD (Budde, Xie, Cross, & Song, 2009; Harsan et al., 2007; Song et al., 2002, 2005), although it remains unclear exactly to what extent these parameters are specific to these microstructural components.

One application of diffusion-weighted images is the visualisation of structural connectivity in the brain in terms of white matter connections using fibre-tracking algorithms (Bihan & Johansen-Berg, 2012; Jeurissen, Leemans, Jones, Tournier, & Sijbers, 2011), all of which rely on a fibre orientation model. However, issues exist about the reliability of such fibre-tracking techniques, especially due to a lack of gold standard in-vivo validation techniques. Several models exist to relate diffusion signal to direction/orientation of fibres (fig 4.6): diffusion tensor model and deterministic tractography, and high angular resolution diffusion imaging (HARDI) and probabilistic tractography.

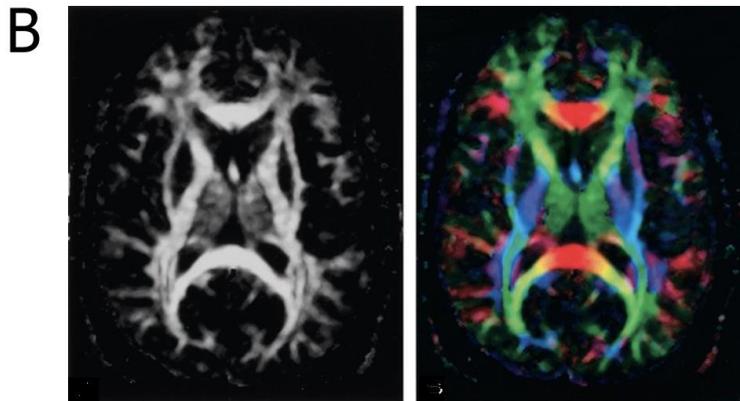
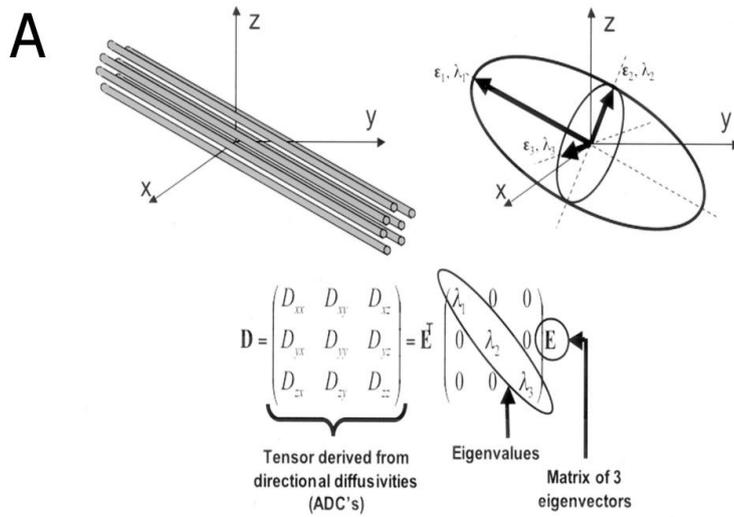


Figure 4.5 Diffusion tensor imaging. (A) The diffusion ellipsoid and tensor metrics. (B) Left – FA map. Right – combined FA and directional map. Colour indicate direction: green: anterior-posterior, red: left-right, blue: superior-inferior. Images adapted from Jellison et al. (2004).

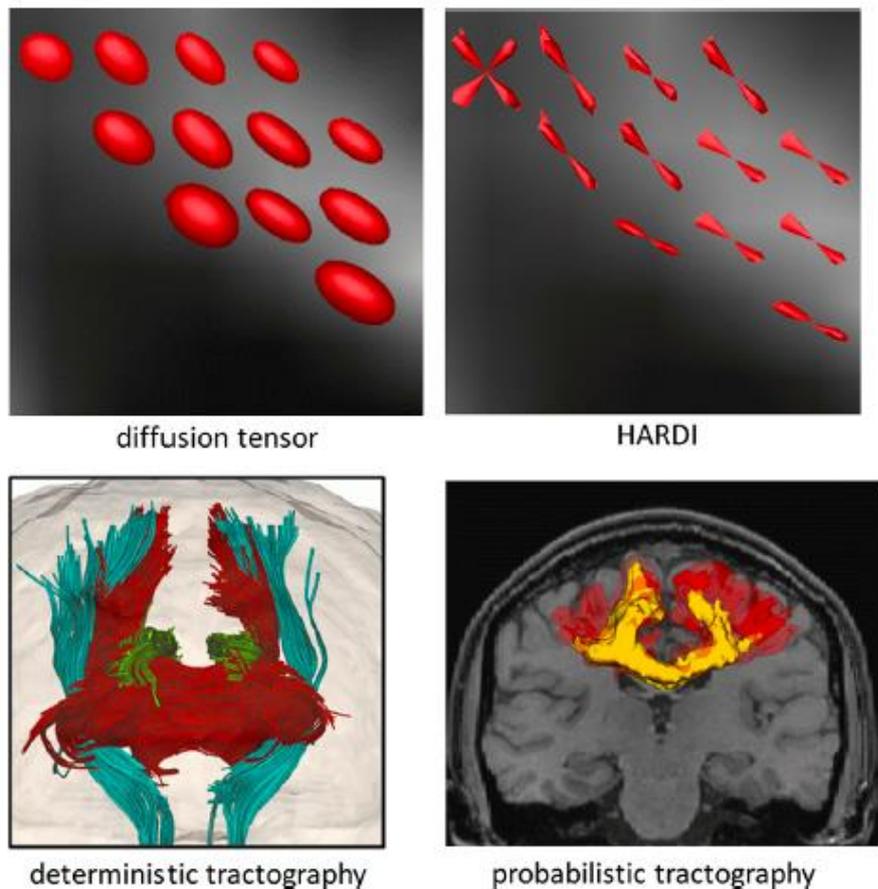


Figure 4.6 Fiber tractography. Diffusion tensor model (top left) only reconstructs one fibre direction per voxel, whereas HARDI can resolve multiple directions (top right). Deterministic tractography (bottom left) shown as streamlines and probabilistic tractography (bottom right) shown as isosurfaces to reflect maps of confidence in connections. Adapted from Jellison et al., 2004

Diffusion tensor model and deterministic tractography

Tractography using the diffusion tensor (DT) model produces streamlines that follow the principal axis of diffusion (λ_1), which were hypothesized to correspond to the trajectories of underlying fiber pathways (Bihan & Johansen-Berg, 2012; Catani & Jones, 2005; Glasser & Rilling, 2008). This method is referred to as deterministic tractography. However, this method is severely limited in voxels containing multiple fibre orientations due to partial volume effects between adjacent tracts or due to kissing or crossing fibres (Binney, Parker, & Lambon Ralph, 2012; Jeurissen et al., 2011; Parker et al., 2005; Tournier, Yeh, Calamante, & Cho, 2008), which can be found in a large proportion of white matter voxels in the brain

(Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013). In these voxels, DT tractography will fail to identify real connections (false negatives) or infer connections that do not exist (false positives) or simply terminate.

Probabilistic methods

A group of probabilistic models of diffusion have been proposed as alternatives to the DT model. These include Q-ball (Tuch, 2004), diffusion spectrum imaging (DSI) (Wedeen et al., 2008), and constrained spherical deconvolution (CSD) (Tournier, Calamante, & Connelly, 2007; Tournier, Calamante, Gadian, & Connelly, 2004; Tournier et al., 2008). These methods take the uncertainty in estimating the principal diffusion direction into account and represent these explicitly and probabilistic tractography methods allow white matter pathways to be traced into their grey matter targets. Q-ball imaging (QBI), DSI and CSD all directly estimate the orientation distribution function (ODF) to resolve multiple fibre orientations within a voxel. The ODF can be reconstructed within each voxel and used to perform tractography (fig 4.7).

To reliably calculate the ODF, these methods rely on the acquisition of HARDI data (Tournier et al., 2004, 2007). However, QBI and DSI require large b-values (4000s/mm² and up) and with wide ranges, which come with practical limitations, especially in terms of long scan times. CSD on the other hand has been found to provide accurate ODF estimates and resolve crossing fibres at relatively low b-values (1000s/mm²) (Tournier et al., 2008), which can be obtained on clinical scanners. One recent study compared the performance of six dMRI analysis methods using simulated data and found CSD to yield the least orientation error, while recovering the greatest number of fibers and largest fraction of correct tractography for complex fiber-crossing regions (Wilkins, Lee, Gajawelli, Law, & Leporé, 2014). Therefore, CSD was used in this thesis for white matter tractography.

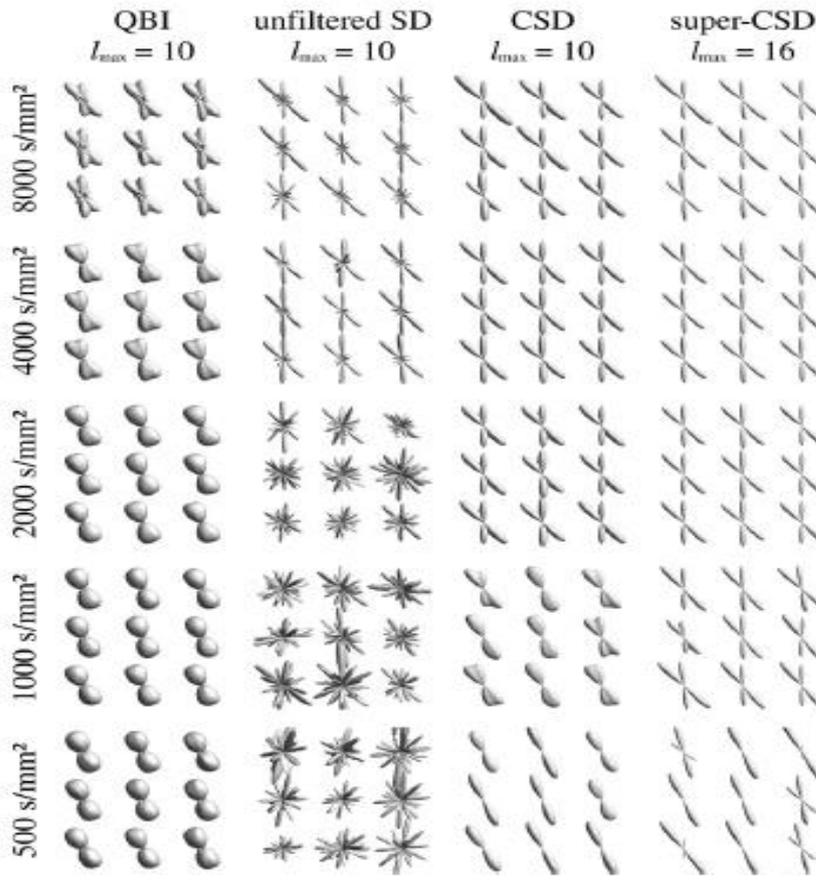


Figure 4.7 Reconstruction of fiber orientation. Reconstruction of the fiber orientation distribution across different b-values and different probabilistic methods. Image adapted from Tournier et al. (2008).

Constrained Spherical Deconvolution

Spherical deconvolution (SD) relies on the assumption that the diffusion weighted signal originating from the various fibre populations present in the voxel add up linearly (Tournier et al., 2004). The diffusion signal profile for a typical fibre population is represented in a response function. Performing spherical deconvolution on the response function allows for the desired fibre orientation function (FOD) to be estimated (Tournier et al., 2004). However, this method is susceptible to noise. To reduce noise sensitivity, Tournier and colleagues (2007) constrained the model to eliminate negative values in the FOD, which are physically impossible, producing the CSD implemented in the MRtrix software.

Regions of interest for tractography

Fibre tractography allows for the visualisation of structural connectivity in the human brain. These studies are important to complement functional MRI data to establish networks underlying cognitive processes. To obtain tracts of interest, the tractography algorithm (deterministic or probabilistic) must be guided or restricted using seed and target ROIs. There are two approaches to do this. The first approach is to delineate a seed ROI, based on either functional localization or anatomical landmarks, in which the tractography algorithm starts to propagate. Target or way point ROIs, in addition, restrict the algorithm to include additional regions. The second approach uses the whole brain white matter mask as the seed ROI, resulting in a collection of fibres across all of the brain white matter. From this collection, the tracts of interest can be filtered using target or waypoint ROIs. Although both approaches may use the same ROIs for tractography, the results may differ slightly in the number of streamlines retained, volume of the tract, and therefore the measured FA.

Mrtrix is one such tractography algorithm that allows the user to manually set the maximum number of streamlines retained and the maximum number of streamlines generated. By default, the algorithm terminates when either the maximum number of streamlines retained has been reached (regardless of the number of streamlines generated), or when the maximum number of streamlines generated is 100x the maximum number of streamlines retained (regardless of whether that target is reached). The values of these variables depend on user input, which depends on the question of interest. I performed whole brain tractography in all participants, and subsequently used regions of interest to filter specific tracks of interest. In order to compare volumetric measures of the tracks (ie voxel count) across groups, the first method (script terminates when maximum number of streamlines retained has been reached) was used in this thesis.

4.5. Network analysis and graph theory

The methods above have described using functional connectivity in the brain using rs-fMRI and diffusion-weighted imaging and tractography to study structural connectivity in the brain. Although these methods provide measures of connectivity within a network, they rely on a priori defined regions of interest (seed ROIs). Such hypothesis-driven approaches can be limited by the selection of regions and can miss crucial regions beyond the a priori defined network. To deal with this ‘missing regions’ dilemma, the final chapter of this thesis employs hypothesis-free, whole-brain methods. Chapter 8 uses network-based statistics to investigate differences in functional networks between adults with and without dyslexia, and employs graph theory as a framework to investigate both whole-brain functional and structural networks in developmental dyslexia.

Graph theory

Graph theory (GT) studies the mathematical structure of relationships between elements in a collection, e.g. a network (Bullmore & Sporns, 2009). It is the exact mathematical study of networks, which can be formally represented as graphs. This mathematical framework allows exact descriptions of various network topologies and offers methods of studying adaptive network dynamics through mathematical modelling. Since the publication of Watts & Strogatz (1998) and Barabási & Albert (1999), many researchers have applied network analyses to various fields of study, including the study of the human brain.

This approach describes the brain as a large network consisting of many nodes (parcellated brain regions) and edges (type of connections, e.g. structural or functional) between the nodes. Instead of emphasizing the characteristics of the individual nodes, GT places the focus on the study of the relationships between the nodes. Important characteristics are degree (amount) of connections, clustering, path length, and efficiency (fig 4.8). I will briefly describe these properties qualitatively with their mathematical notations. For a

comprehensive mathematical description, please see Boccaletti, Latora, Moreno, Chavez, & Hwang, (2006).

A *graph* (G) is made up of a *number of nodes* (N). The *degree of a node* (k) is the number of direct connections of that node to other nodes. Often the *degree distribution* $P(k)$ is described. This refers to the probability that a node chosen at random has a certain degree.

The communication or transfer of information within a network depends on the connections between the nodes: the *edges*. How information travels through the network depends on the paths taken between nodes. For efficient communication, information travels over the shortest paths between two nodes. This *shortest path length* between two nodes is the smallest number of edges that have to be traveled to get from one node to the other. The *average shortest path length* (L) is defined as the mean of shortest lengths over all couples of nodes.

Clusters (C) of nodes occur when neighboring nodes are connected to each other in triangular forms. Highly connected nodes with many paths crossing that node are said to

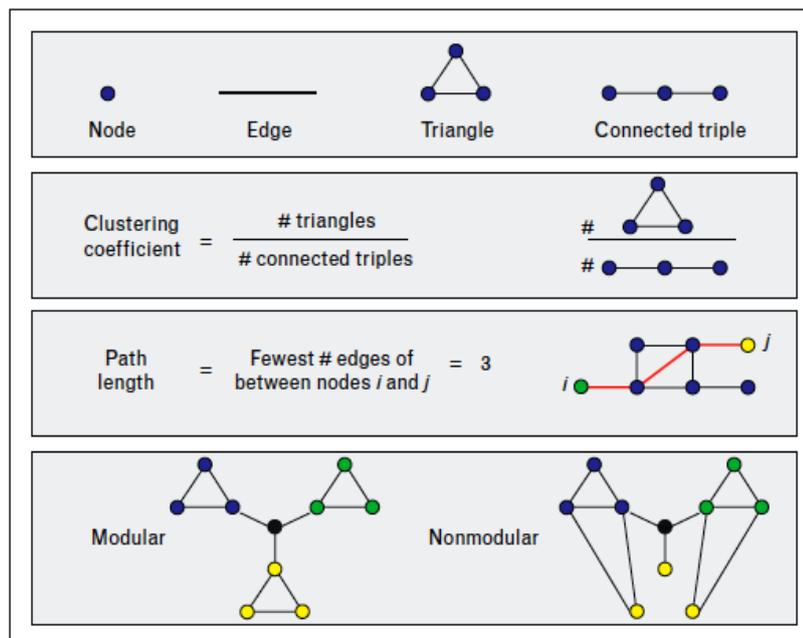


Figure 4.8 Description of basic network concepts. Definitions of a node, an edge, a triangle, clustering coefficient C , the average path length, L , and modularity. Figure adapted from Bassett and Bullmore (2009).

have high *centrality*, which reflects a measure of importance for that node to the network as a whole. Table 4.1 provides a comprehensive qualitative overview of graph theoretical metrics (table 4.1 adapted from Guye et al., 2010).

Based on these characteristics, various network topologies have been identified in complex systems, of which the small world networks (Watts & Strogatz, 1998) and scale-free (Barabási & Albert, 1999) networks are the two most prominent.

Whereas traditional graph theory focuses on regular graphs and completely random graphs, graph theoretical studies of the brain have found a network that differ radically from these standard models: the so called small-world networks (fig 4.9) (Bullmore & Sporns, 2009; Watts & Strogatz, 1998). Graphs with a regular, lattice-like structure consist of only short-range connections, with no long-range connections. This organization allows efficient local interactions but costly distributed processes involving distant nodes. Random graphs, on the other hand, allow for efficient long-range information transfer but are poor at local information processing. Systems are defined as complex when they exhibit properties that are radically different from the traditional regular lattices and totally random graphs; in other words - a mixture of regularity and randomness (fig 4.9).

Table 4.1 Definition of basic graph theory metrics (Guye et al., 2010)

Clustering coefficient (C)	Measure the number of connections of a node with its nearest nodes (neighbors) proportionally to the maximum of possible connections in the network
Characteristic path length (L)	Measure the average number of minimum connections that should be passed to join any two nodes in the network
Global efficiency	Measure how efficiently is the network to exchange the information at the global level
Local efficiency	Measure how efficiently is the network to exchange the information at the clustering level
Degree	Measure the number of connections of a node
Degree distribution	Measure the probability that a randomly selected node has n connections in the network
Modularity	Measure how the network is organized into modules or communities with high level of local clustering
Hierarchy	Measure how hubs are sparsely connected rather than provincially clustered
Centrality or betweenness centrality	Measure the number of shortest paths between any two nodes that pass through this node and identify hubs
Small-worldness	Measure how the network is from a random network with the same number of nodes

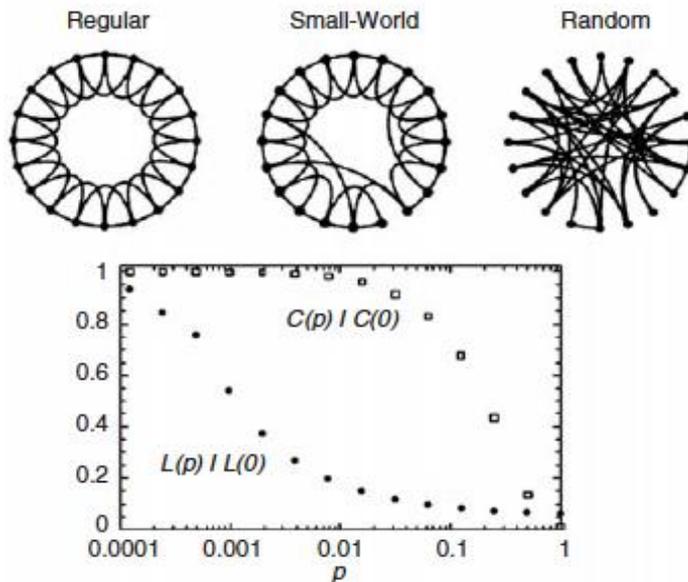


Figure 4.9 Small world diagram (Watts & Strogatz, 1998)

Connecting nodes with their nearest neighbours produces a regular graph. The network is random, when it has a short average path length and clustering coefficient. A small world network has some dense local clustering, characteristic of regular networks, and some long-range connections, characteristic of random networks.

Deriving graphs from MRI data

Based on graph theory, the complex networks analysis of the brain focuses on the organization of the brain in networks, both structural and functional. Figure 4.10 illustrates the overview of constructing structural and functional networks. First, the brain is parcellated into regions (nodes), which can be done using an existing atlas such as the automated anatomical labeling (AAL) atlas, or using arbitrary parcels. For structural networks, whole-brain tractography yields white matter connections (e.g. streamlines) as edges. Streamlines are generated within the whole-brain white matter. Edges (connections) are counted for those streamlines that pass into each parcellated region (node). Functional networks, on the other hand, are constructed using the correlation coefficients or Fisher transformed z-scores between nodes as edges. The values of edges are subsequently entered into $N \times N$ connectivity matrices (N being the number of nodes), which are used in graph theoretical analyses.

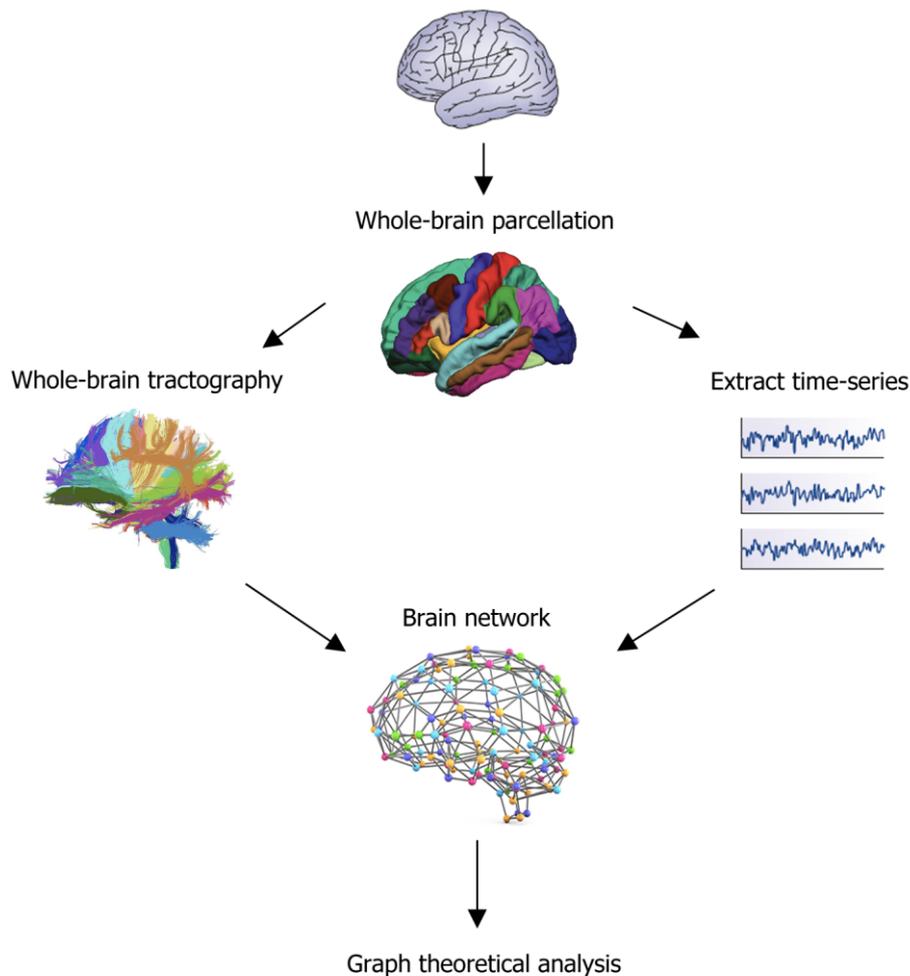


Figure 4.10. Overview of brain network construction using MRI data. Structural graphs are constructed using diffusion-weighted tractography. Functional networks are constructed using resting-state functional connectivity.

Graph theoretical studies of the brain have identified small-world and scale-free network properties (Bullmore & Sporns, 2009), which are hypothesized to reflect the optimal efficacy of the brain's functioning. Rapid synchronization and information transfer as well as minimal wiring costs allow for an optimal balance between local processing (functional segregation) and global integration.

4.6. Experimental procedures used in this thesis

Two separate experiments in different groups of participants were conducted as part of this thesis. The data presented in chapter 5 were acquired as part of a study to investigate the

feasibility of deriving the language network from resting-state fMRI data in healthy volunteers. The data presented in chapters 6-8 were acquired as one large study to investigate developmental dyslexia. Therefore, the experimental procedures of testing and data acquisition are described here rather than repeated in each chapter. However, the methods of data processing and analyses were specific to each chapter, and are described in the methods sections of the subsequent chapters instead.

4.6.1 Feasibility study

Participants

Twenty-one healthy, right-handed adults (10 males, 11 females, mean age=26 yr, SD=4.9 yr), all monolingual speakers of English, participated in this study. All participants were recruited via social media and newsletters within University College London. Participants were included if they were monolingual English speakers, right-handed, and between the ages of 18 – 35 years old. Participants were excluded if they were on long-term medication, had a diagnosis of neurological or psychiatric disorders, or had any contraindications for MRI. Participants signed informed consent after the experimental procedures were explained and received monetary compensation in the form of a gift voucher after completion of the experiment. The study was approved by the Research Ethics Committee of University College London (London, UK).

MRI data acquisition

Images were acquired on a 1.5T Siemens Avanto scanner (Siemens Healthcare, Erlangen, Germany) with 40mT/m gradients and a 32-channel receive head coil. Whole brain T1-weighted (3D Fast Low-Angle Shot (FLASH), 176 contiguous sagittal slices, FOV=256x224mm, voxel size=1x1x1mm, flip angle=15, TE=4.94ms,TR=11ms) and diffusion-weighted MRI (60 directions; b=1000s/mm², 3 b=0s/mm², FOV=240x240mm, voxel size=2.5x2.5x2.5mm, TE=81ms, TR=7300ms) were conducted, as well as a 5 minute resting-

state fMRI acquisition (rs-fMRI) (TE=50ms, TR=3320ms, voxel size=3x3x3mm, 125 volumes, slice thickness 2mm with 1mm gap, interleaved acquisition). During the resting-state, subjects were asked to relax with eyes open.

4.6.2. Reading study

Participants

A total of 48 participants were recruited for the study, who responded to advertisements sent out via UCL emails and posts on various social media platforms such as Facebook, Twitter, Gumtree, the ICN subject database, the UCL Psychology SONA system, and various online dyslexia forums. After excluding participants outside of the stated age range (18-30 years), and those who could not complete the full experiment, a remaining 44 volunteers were included in the analyses: 21 adults with dyslexia and 23 age, gender and IQ matched adult controls. All participants had English as first and only language to exclude any confounding effects of having acquired additional languages. Participants with dyslexia had been formally diagnosed by an educational psychologist prior to testing. All participants had two testing sessions: a behavioural assessment and a brain MRI scan. These were done either on the same day or on separate days depending on the volunteer's preference, but no longer than a week apart.

Due to time and technological limitations, a subset of these participants completed the full testing battery of neuropsychological assessments and MRI scan. The exclusion criteria for each analysis will be further expanded in the respective chapters.

Neuropsychological assessment

This involved the administration of standardised tests of intelligence, language, reading and spelling (table 4.2). The Wechsler Abbreviated Scale of Intelligence II (WASI-II) (Wechsler, 1999) was administered to obtain a verbal and non-verbal IQ score for each participant as

well as a combined full-scale IQ. Reading skills were assessed using the reading comprehension, single word and pseudoword reading subtest from the Wechsler Individual Achievement Test-II (WIAT-II) (Wechsler, 2001). The spelling subtest from the WIAT-II was also administered. General language skills were assessed using the repeating sentences and formulating sentences subtests from the Clinical Evaluation of Language Fundamentals 4 (CELF-4) (Semel, Wiig, and Secord, 2003). In addition, we also administered the Test for the Reception of Grammar-2 (TROG-2) (Bishop, 2003) to account for comorbidity with Specific Language Impairment (Bishop & Snowling, 2004); and the Comprehensive Test of Phonological Processing (CTOPP) (Wagner, Torgesen, and Rashotte, 1999) to assess phonological processing as phonological deficits are central in developmental dyslexia. These tests allowed for a full profile of strengths and difficulties in the reading and language domain for each participant.

Table 4.2. Summary of standardised neuropsychological measures

(sub)test	Measure
Wechsler Abbreviated Scale of Intelligence II (WASI-II)	Intelligence Quotient (IQ)
Wechsler Individual Achievement Test-II (WIAT-II): <ul style="list-style-type: none"> • single word reading • pseudoword reading • reading comprehension • spelling 	Reading accuracy, reading comprehension and spelling
Clinical Evaluation of Language Fundamentals 4 (CELF-4): <ul style="list-style-type: none"> • Repeating sentences • Formulated sentences • Forward and backward digit span • Rapid Automatic Naming 	General language production and working memory
Test for the Reception of Grammar-2 (TROGG-2)	Receptive language skills: grammatical understanding (screen for Specific Language Impairment)
Comprehensive Test of Phonological Processing (CTOPP)	Phonological awareness, phonological memory and rapid naming

Language task in the scanner

fMRI TASK – Covert reading

Linguistic and non-linguistic stimuli were presented on a screen (fig 4.11). Linguistic stimuli were single words and made-up/pseudo words. Non-linguistic stimuli were fixation crosses and strings of random symbols. A stimulus was presented every 2 seconds in a blocked design. The participant also received a button to press. The participant was asked to read the linguistic stimuli covertly and press a button after he/she had read it, and look at the non-linguistic stimuli and press a button as soon as he/she had seen it. This task was repeated once so that together, two runs lasted for about 10 minutes, during which 50 linguistic stimuli and 50 non-linguistic stimuli were presented. A previous study has shown that this task reliably activates the reading network in children (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). Therefore, we expected this task to reliably activate the reading network in adults and children.

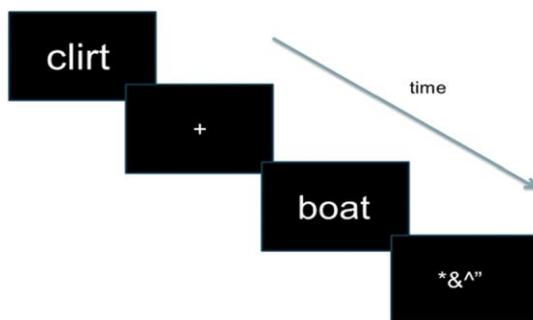


Figure 4.11 Schematic overview of the reading task in the MRI scanner

MRI data acquisition

Participants were scanned on a 1.5T Siemens Avanto MRI scanner at Great Ormond Street Hospital with 40mT/m gradients and a 32-channel receive head coil. All scans were performed by a qualified radiographer.

The blood oxygen level dependent (BOLD) functional images were acquired using the echo planar imaging (EPI) method (time of echo (TE) = 50 ms, flip angle = 85°, matrix size = 64 x 64, field of view = 24 cm, slice thickness = 2.5 mm, 1mm gap, number of slices = 33; time of repetition (TR) = 2376 ms). Structural T1-weighted 3D images were also acquired (flip angle = 15°; TR = 11 ms; TE = 4.94 ms; voxel size = 1mm isotropic; slices = 176), as well as diffusion-weighted MRI (60 directions; b=1000s/mm², 3 b=0s/mm², FOV=240x240mm, voxel size=2.5x2.5x2.5mm, TE=81ms, TR=7300ms).

MRI preprocessing and analyses are described in the subsequent chapters in this thesis.

5. Integrating RSFC and white matter tractography to characterize the intrinsic language network: a feasibility study

5.1. Introduction

Language functions are represented in disparate regions in the brain. The classical Broca's area in the inferior frontal gyrus and Wernicke's area in the superior temporal gyrus are the most studied brain regions involved in language processing. Recent neuroimaging studies have also suggested a role for the inferior parietal lobule, known as Geschwind's territory (Catani, Jones, & Ffytche, 2005). Summaries of activation studies suggest the majority of the left hemisphere to be employed by language processes (Price, 2012). Therefore, language processing can be characterised as a skill, which emerges from the interactions of a network of brain regions.

One limitation of studying cognitive networks using task-based fMRI is the challenge of finding the 'ideal task' to probe the network of interest. A possible solution is offered by resting-state (rs-fMRI). Rs-fMRI allows the investigation of the functional architecture of the brain without task constraints (van den Heuvel & Hulshoff Pol, 2010). During rest, functionally related regions in the brain exhibit synchronized fluctuations in low-frequency (<0.1 Hz) blood oxygen level-dependent (BOLD) signal. Such resting-state functional connectivity (RSFC) patterns represent cognitive networks and have been found to overlap with networks observed during performance of cognitive tasks (Smith et al., 2009; Power et al., 2011). It has been hypothesised that such interregional coupling patterns often partly reflect anatomical connectivity (O'Reilly et al., 2013). One of the aims of this thesis is to test the disconnection hypothesis of dyslexia by integrating structural and functional connectivity methods. However, this relies on the critical assumptions that (1) cognitive networks can be characterized during rest as well as task, and (2) there is some level of

correspondence between functional and structural connectivity. Although the first assumption has accrued a large base of support in the literature, the second assumption remains unclear. This chapter therefore serves as a feasibility study to test these assumptions in a healthy adult sample to establish the validity and limitations of combining these measures for the subsequent chapters of this thesis.

Identifying the language network using Broca's area

One consistent method to identify the default language network is by using Broca's area as a seed region (Tomasi and Volkow, 2012). Tomasi and Volkow (2012) demonstrated good reproducibility of RSFC across 970 healthy participants from 22 research sites (with a range of field-strengths and scan parameters) using a seed centred on the left pars triangularis (BA 45) within IFG and seed-voxel FC method. The resulting RSFC map included left inferior parietal lobule (supramarginal and angular gyri – BA 40,39), bilateral IFG (BA44, 45, 47), left middle frontal gyrus (BA46), bilateral inferior temporal gyri (BA20,21), left superior frontal gyrus (BA8), bilateral caudate, left putamen and thalamus, and right cerebellum (crus). In addition, an anti-correlated network of regions was found, including right striate and extrastriate cortex (BA17,18), right superior parietal lobule (BA5, 7), bilateral superior temporal gyrus (BA42), and the cingulate cortex (BA 24).

A subsequent study (Zhu et al., 2014), using the same seed and seed-voxel FC method as Tamasi and Volkow (2012) on the rs-fMRI data of 35 healthy adults, found that the resulting RSFC network showed good test-retest reliability over short and long-term follow-up. Regions with high reliability were located at the bilateral frontal cortices, middle temporal gyrus (MTG) and inferior parietal lobule (IPL), left middle occipital gyrus (MOG), precuneus, and posterior cingulate gyrus. Further analyses showed that the RSFC network as a whole showed leftward lateralisation. These findings confirm previous findings based on

functional activation during task and DTI tractography that the left IFG plays a central role in a left-lateralised network.

The above findings were further replicated by a RSFC study (Muller and Meyer, 2014) using two seeds in the left IFG (pars triangularis and pars opercularis), defined based on previous fMRI activation during comprehension and syntactic processing (Lohmann et al., 2010; Friederici et al., 2011; Friederici et al., 2006). Again, the RSFC to left IFG was found to include bilateral IFG (BA 44, 45), left supramarginal gyrus (BA40), right angular gyrus (BA39), left SMA (BA6), bilateral cerebellum (crus), and right middle and inferior temporal gyrus (BA21,20). In addition, the authors showed, using graph theoretical analysis, that the left supramarginal gyrus and the right cerebellum were 'hub' regions within this network. In other words, they have the highest number of connections to other regions, which facilitates fast information transfer.

However, it should be noted that Tamasi and Volkow (2012) and Zhu et al. (2014) used seed ROIs defined using an automated anatomical framework, whereas Muller and Meyer (2014) used seed ROIs defined by task. Furthermore, these studies have not considered further subdivisions within the left IFG, for example pars opercularis (BA44), pars triangularis (BA45), and pars orbitalis (BA47) (Amunts, Schleicher, Ditterich, & Zilles, 2003; Amunts & Zilles, 2012; Friederici, 2011; Keller, Crow, Foundas, Amunts, & Roberts, 2009). These subregions have been found to serve different functional aspects of language processing (Friederici, 2011; Price, 2012; Xiang, Fonteijn, Norris, & Hagoort, 2010). For example, Hagoort proposed that BA44 is involved in phonological processing; BA44 and BA45 contribute to syntactic processing; BA47 and BA45 have a role in semantic processing (Hagoort, 2005).

In terms of structure, the subregions of Broca's area have been found to have distinct anatomical connections (Amunts et al., 2003; Amunts & Zilles, 2012). Using dMRI and

probabilistic tractography, Parker and colleagues (2005) initially identified two pathways to connect anterior language regions in the inferior frontal gyrus (IFG) to posterior language regions in the superior temporal gyrus (STG): a dorsal pathway that includes the arcuate fasciculus (AF) and superior longitudinal fasciculus (SLF), and a ventral pathway that runs via the external capsule/uncinate fasciculus (UF). The dorsal pathway has been subsequently segmented into three parts: a direct segment connecting IFG with posterior STG, and two indirect segments: the anterior one connects IFG with inferior parietal lobule, and the posterior one connects inferior parietal lobule with STG (Catani et al., 2005). A recent review (Friederici, 2009) further discusses four major pathways of language: dorsal pathway I connects the STG to the premotor cortex via the AF and SLF; dorsal pathway II connects Pars Opercularis (BA44) to STG via AF and SLF; ventral pathway I connects Pars Triangularis (BA45) and the temporal cortex via the extreme capsule; and finally ventral pathway II connects frontal operculum and anterior temporal cortex via the UF.

These functional and structural studies provide evidence not only that the language system in the human brain extends beyond the classical Broca's and Wernicke's regions, but that the system consists of functional and structural subnetworks, which fulfil different roles in language processing. For example, Hagoort (2005) proposed a memory, unification, and control (MUC) model, which postulates that language processing consists of three core components: memory, unification and control. Within this model, Broca's area is hypothesised to contribute to unification processes by retrieving lexical information stored in temporal brain regions, and unifying these into phonological output (Hagoort, 2005). In addition, the model proposes an anterior ventral to posterior dorsal gradient of functional processing in the left IFG. Specifically, BA 44 and parts of BA 6 are hypothesised to play a role in phonological processing; BA 44 and BA 45 to syntactic processing; and BA 47 and BA 45 to semantic processing.

The topological layout of the human perisylvian language network at rest

Xiang et al. (2010) tested the memory, unification, and control (MUC) model suggested by Hagoort (2005) using RSFC in a small sample of 12 healthy adults. The authors delineated three ROIs in bilateral areas BA 44, 45, and 47 based on the automated anatomical labeling template, and used seed-voxel FC analyses to create topological maps of the resulting RSFC patterns. Lastly, post-hoc tests directly compared mean FC in the left middle frontal, parietal, and temporal lobes. The results include a structured gradient FC of the three left seeds in left middle frontal gyrus (MFG), left temporal lobe, and left parietal lobe. In the MFG, the gradient followed an inferior-to-superior direction (FC to BA47-45-44). The parietal lobe showed the opposite dorsal anterior-to-posterior gradient (BA44-45-47). The posterior temporal lobe showed an anterior-to-posterior gradient for BA 47-45-44. RSFC targets specific to each seed (ie stronger in one compared to other two seeds) include the posterior superior temporal gyrus (STG) (BA44 seed), and posterior inferior temporal gyrus (BA 47 seed). These findings confirm the existence of functional parcellations within the left IFG, and additionally show that these parcellations follow a graded pattern of connectivity within temporal region (corresponding to classical Wernicke's areas) and parietal areas (corresponding to Geschwind's territory). These findings replicate and expand upon a previous study (Margulies and Petrides, 2013), which found left BA 44 to be connected with the supramarginal gyrus, and BA 45 to be connected with the angular gyrus, supporting a gradient of RSFC to subregions of the IFG within the parietal cortex.

Correspondence between human and macaque

Based on the observation of homologues of ventral inferior frontal regions in macaques (Petrides and Pandya, 2009) and their anatomical connections to other regions in the temporal and parietal cortex, Kelly et al. (2010) set out to test the correspondence between human RSFC patterns of the IFG and the anatomical connections in macaques, using

automated delineation of the subregions in the IFG (BA6, 44, 45) and seed-voxel and hierarchical clustering FC methods. The authors found overlap as well as distinct regions within the temporal and parietal cortex corresponding to individual seed ROIs. For example, area BA 6 was distinctly connected to the anterior supramarginal gyrus (SMG), areas BA 44 and 45 were connected to the posterior SMG and angular gyrus. Furthermore, areas BA 44 and 45 had strong correlations with the cortex in the superior temporal sulcus and the middle temporal gyrus, whereas BA 6 did not. These functional findings correspond to the anatomical connections observed from the homologues of these areas in the macaque to regions in the parietal and temporal homologues (Petrides & Pandya, 2009). However, correspondence between human and macaque was not directly tested.

Neubert et al. (2014) did directly compare functional and structural connectivity in man and monkey using probabilistic tractography and RSFC. The authors first parcellated the ventral inferior cortex (including areas BA6, 44, 45, 47, frontal pole, frontal operculum) into subregions (areas 6d, 6v, 44d, 44v, inferior frontal sulcus, 45, 46, 47, operculum, frontal pole) based on probabilistic structural connectivity. These subregions were entered as seed ROIs in ROI-ROI RSFC analyses. The resulting RSFC patterns were compared between human and monkey. Although including a larger region in the ventral inferior frontal region than Kelly et al. (2010), Neubert et al. (2014) also found similarities between human and monkey, as well as striking differences in mirror neuron regions (macaques), auditory association areas (humans), and frontal pole (human).

The findings of these two studies taken together suggest that human and macaque inferior frontal regions are similar in their interactions with specific regions in temporal, parietal, premotor and cingulate cortex, while differing in their interaction with the superior temporal auditory association areas. These findings also suggest a role of the IFG including BA 44 and 45 in functions other than language.

Correspondence between function and structure

Morgan et al. (2009) investigated the correspondence between functional and structural connectivity at rest between left IFG (BA44/45), SMA (BA6/8), and left STG (BA22), in a small sample of 12 healthy adults. The ROIs were identified based on group maps of activation during verb generation tasks. Functional connectivity was measured by the ROI-ROI FC method (see methods chapter), and structural connectivity was measured by deterministic DTI tractography between the ROIs and the extracted mean FA and mean radius of the resulting fibre pathways. The authors found one white matter fibre pathway connecting left IFG with left SMA, and two fibre pathways connecting left STG and left IFG: a dorsal and a ventral pathway. Interestingly, the ventral pathways could only be identified in four participants, whereas the dorsal pathway was identified in all participants.

Although the authors did not explicitly map the found white matter structures to existing anatomical maps, upon visual inspection of the published figures, the dorsal and ventral pathways resemble, respectively, the superior longitudinal fasciculus/arcuate fasciculus and the extreme capsule fibre system, reported by Friederici and Gierhan (2013). The novel contribution of the study is its effort to directly relate DTI tractography measurements with RSFC. Only one linear relationship was found: between the RSFC and mean radius of the connection between left IFG and left SMA. No linear relationships were observed in the ventral or dorsal pathways. These findings suggest no direct relationship between FA and RSFC between two well-characterised regions in the language network, and are inconsistent with previous studies using similar methods which reported increased mean FA with increased FC in sensorimotor networks (e.g. Lowe et al., 2008).

Methodological differences/limitations

Several methodological differences within the literature must be noted. Firstly, the definition of seed ROIs in RSFC is fairly trivial and can be either driven by anatomical

structure or task activation. In addition, there is some debate how many subdivisions exist within the left IFG/Broca's area (e.g. Amunts & Zilles, 2012). For example, whereas Xiang and colleagues defined Broca's region to consist of BA 44, 45, and 47, Kelly and colleagues studied the connectivity of BA 44, 45 and 6. Secondly, some studies used global signal regression, which later work have shown to introduce artificial negative correlations in RSFC (Chai, Castañón, Ongür, & Whitfield-Gabrieli, 2012; Fox, Zhang, Snyder, & Raichle, 2009; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). This could have had two consequences: 1) studies refrained from reporting negative correlation patterns to avoid false interpretations, and 2) these studies may have discarded some true connections as false negatives. Negative correlations within the resting-state time course have been shown to provide valuable information and should be reported where possible (Chai et al., 2012).

Research aims

Therefore, the aims of this chapter are three-fold:

1. To replicate the intrinsic language network at rest as well as its subnetworks based on the connectivity patterns of three subregions with the left IFG: BA 44, 45, and 47.
2. Address previous methodological issues by including negative correlations in RSFC, without regressing out the global mean. In addition, this study directly links the RSFC patterns with the underlying white matter connectivity derived from white matter tractography.
3. Investigate the anatomical pathways underlying RSFC using probabilistic tractography.

5.2. Materials and methods

Participants

Twenty-one healthy, right-handed adults (10 males, 11 females, mean age=26 yr, SD=4.9 yr), all monolingual speakers of English, participated in this study. All volunteers were free of neurological or psychiatric disorders. Participants signed informed consent after the experimental procedures were explained and received monetary compensation in the form of a gift voucher after completion of the experiment. The study was approved by the Research Ethics Committee of University College London (London, UK).

MRI data acquisition

Images were acquired on a 1.5T Siemens Avanto scanner (Siemens Healthcare, Erlangen, Germany) with 40mT/m gradients and a 32-channel receive head coil. Whole brain T1-weighted (3D Fast Low-Angle Shot (FLASH), 176 contiguous sagittal slices, FOV=256x224mm, voxel size=1x1x1mm, flip angle=15, TE=4.94ms, TR=11ms) and diffusion-weighted MRI (60 directions; $b=1000\text{s/mm}^2$, 3 $b=0\text{s/mm}^2$, FOV=240x240mm, voxel size=2.5x2.5x2.5mm, TE=81ms, TR=7300ms) were conducted, as well as a 5 minute resting-state fMRI acquisition (rs-fMRI) (TE=50ms, TR=3320ms, voxel size=3x3x3mm, 125 volumes, slice thickness 2mm with 1mm gap, interleaved acquisition). During the resting-state, subjects were asked to relax with eyes open and think of nothing in particular and to let their minds wander.

Functional data preprocessing

The fMRI data from each subject were first preprocessed in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>). Using the algorithms implemented in SPM8, each participant's images were realigned to correct for motion, co-registered with the individual T1-weighted MRI, and normalised to $2\text{x}2\text{x}2\text{mm}^3$ resolution using the DARTEL method (Ashburner, 2007), and smoothed with a kernel of 6mm FWHM.

Anatomical division of Broca's region

Broca's region was divided into 3 subregions (fig. 5.1): pars opercularis (BA44), pars triangularis (BA45) and pars orbitalis (BA47). Initially, ROIs were created using the AAL atlas of the MarsBar toolbox (Brett et al., 2002) for SPM for Broca's region. This provided rather large ROIs. The influence of ROI size and selection procedure is currently debated in the literature (Cole, Smith, & Beckmann, 2010; Marrelec & Fransson, 2011; Van Dijk et al., 2010). Therefore, to control for effects of ROI size, we also created ROIs by drawing a sphere (6mm radius, henceforth "spherical ROIs") around the following MNI coordinates: pars opercularis (x=-51, y=10, z=15); pars triangularis (x=-51, y=27, z=18); pars orbitalis (x=-45, y=33, z=-9). These MNI coordinates were derived as an approximate centre of mass of the AAL template regions. Both methods resulted in similar network maps, thus results reported subsequently are for the AAL ROIs.

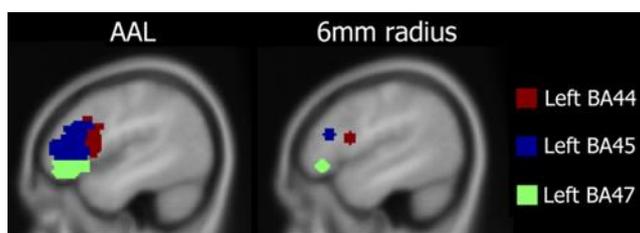


Figure 5.1 Broca's region parcellated into 3 subregions: Pars Opercularis (red), Pars Triangularis (blue), and Pars Orbitalis (green). Left: ROIs derived from the AAL atlas. Right: 6mm radius spheres around approximate centre of mass ("spherical ROIs")

Resting-state functional connectivity (RSFC) analyses

Seed-to-voxel connectivity analyses were carried out in the CONN toolbox implemented in MatLab (Whitfield-Gabrieli & Nieto-Castanon, 2012). The signal fluctuations over time were averaged over all the voxels in each ROI and extracted for subsequent correlation analyses. Effects of motion were regressed out as well as signal from white matter and CSF using the CompCor method implemented in the toolbox (Behzadi et al., 2007). Lastly, a low pass filter of 0.01-0.1 Hz was applied to discard cardiovascular and respiratory noise (Chai et al.,

2012). The averaged signal from each ROI was then correlated with the signal of every voxel masked in the gray matter in the brain. A threshold of $r=0.5$ was then applied, based on previous literature (Chai et al., 2012; Whitfield-Gabrieli & Nieto-Castanon, 2012). Lastly, the correlation coefficients were normalised using Fisher's r -to- z transforms. The results of these analyses are statistical parametric maps (SPMs) of the brain that show regions of significant correlation (thus connectivity) to the seed-ROI. Group-level maps of RSFC for each ROI were computed using one-sample t -tests (cluster significance $p<0.05$ FWE corrected, peak-level $p<0.001$, $k>10$ uncorrected). Direct comparisons between maps were computed using independent t -tests and corrected for multiple comparisons using Random Field Theory (cluster significance $p<0.05$ FWE corrected, peak-level $p<0.001$, $k>10$ uncorrected).

Diffusion data preprocessing and tractography

The dMRI data were preprocessed in MRtrix using constrained spherical deconvolution (CSD) (Tournier et al., 2007; Tournier et al., 2012). The fiber orientation distribution (FOD) is estimated by spherical deconvolution of the diffusion-weighted signal assuming that the signal measured from any fiber bundle is adequately described by a single response function. This method has shown to provide FOD estimates that are robust to noise while preserving angular resolution and allowing tracking of crossing fibers. CSD was performed with the maximum harmonic order set to 8 (as recommended in Tournier et al. (2012), and set as default in MRtrix). Probabilistic tractography was performed based on the fibre orientations estimated via CSD (Tournier et al., 2007), combined with a probabilistic streamlines algorithm as implemented in MRtrix (Tournier et al., 2012). The maximum number of sample tracks generated was set to 50000 using the 'maxnumber' parameter in MRtrix to ensure no bias was introduced across subjects, as we did not expect any structural connection between regions to contain more than 500 streamlines.

Masks for tractography

Tractography requires seed and target masks in order to estimate the connectivity between two brain regions. Seed masks used were the same AAL ROIs (of Broca's region) as in the RSFC analyses (figure 5.1). Target masks were derived from the clusters of the RSFC maps (figures 5.2 and 5.3). These seeds and target regions were coregistered onto each individual subject's diffusion images using the inverse normalisation and coregistration functions in SPM8. Tractography was done in each individual's diffusion space.

5.3. Results

Gradient of RSFC

RSFC from both the AAL atlas derived ROIs and the 6mm radius spherical ROIs revealed similar regions, with larger clusters in the maps of the AAL ROIs. Therefore, we report regions that were observed for both the AAL and 6mm spherical ROI analyses (table 5.1). Figures used were taken from the AAL ROI analyses.

The language network as a whole was identified at rest. Most notably, the topography of the RSFC for the subregions showed a gradient of connectivity (see figure 5.2). In the frontal regions, there was an anterior to posterior topology with area 47 connecting to anterior prefrontal cortex (BA 8, 10), area 44 connecting to superior frontal cortex (SMA), and area 45 in between with connections to the dorsolateral prefrontal cortex (BA46) and preSMA. The connectivity to the parietal regions showed an anterior dorsal to posterior ventral gradient of regions connecting to respectively, area 44, 45 and 47. Area 44 connected to anterior parietal cortex (postcentral gyrus and supramarginal gyrus), area 47 connected to posterior parietal cortex extending into occipital cortex (angular gyrus and extrastriate cortex), with area 45 again connected to the regions in between (supramarginal gyrus, angular gyrus).

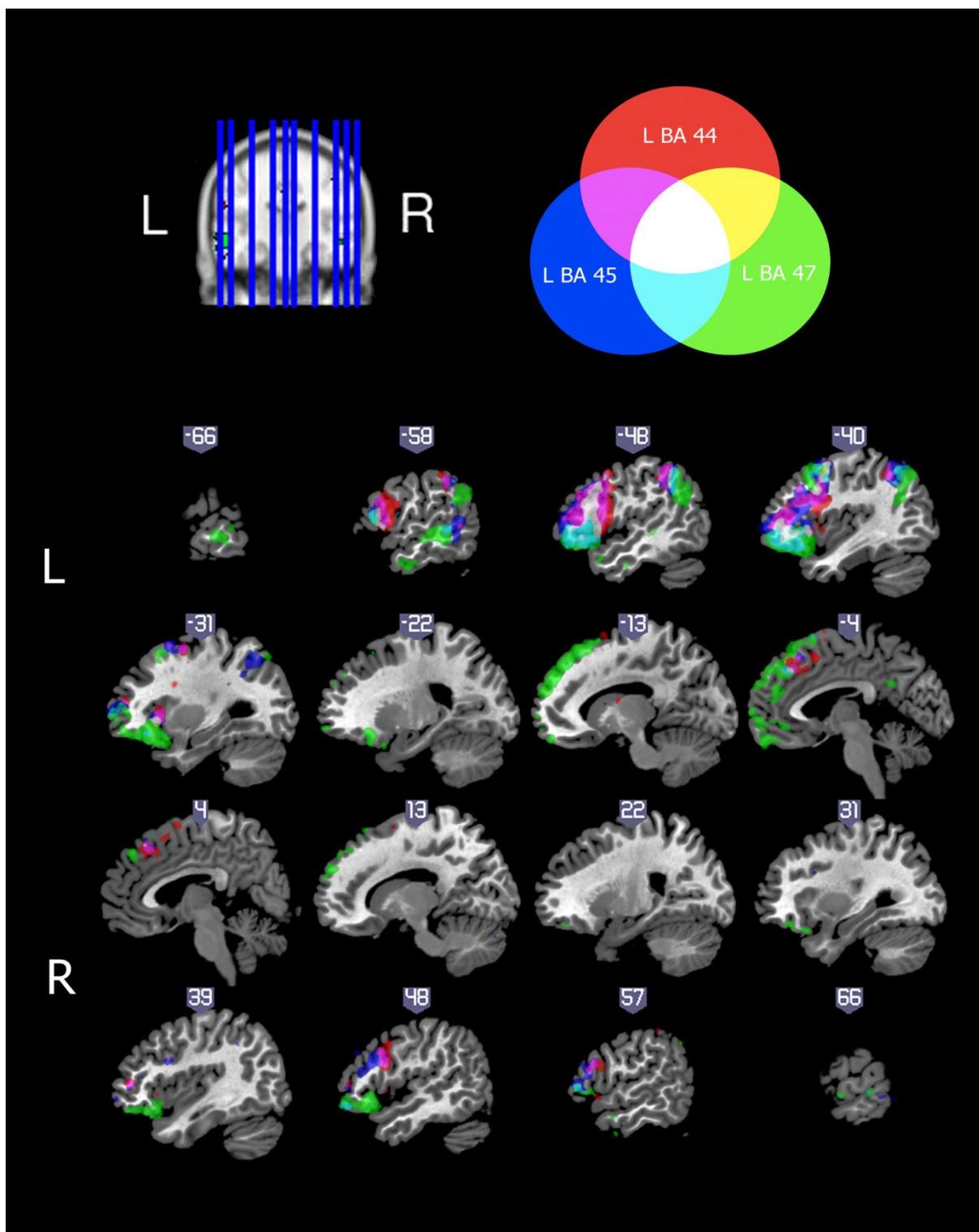


Figure 5.2 Gradient of RSFC in the brain displayed on sagittal slices. Brain regions in red connect to left BA 44. Brain regions in blue connect to left BA 45. Brain regions in green connect to left BA 47. Lighter colours show regions of overlap in connectivity: overlap between L BA44 and L BA45 in magenta, overlap between L BA 44 and L BA 47 in yellow, overlap between L BA 45 and L BA 47 in cyan. Overlap between all regions is in white. Slice location is indicated by x-coordinate above each slice

Resting state functional connectivity of Broca's subregions

Left Broca's region (as a whole) showed connectivity to superior parietal regions, superior and middle temporal regions, anterior temporal lobe, premotor regions in the left hemisphere as well as inferior frontal regions, superior parietal regions and cerebellum in the right hemisphere. These regions are well documented in the literature as involved in language processing (Friederici, 2011; Price, 2012). More specifically, the RSFC for each subregion is detailed below.

Left BA 44

Area 44 (Pars Opercularis) (left column in figure 3) in the left hemisphere showed positive RSFC with bilateral ventrolateral and dorsal frontal regions (including areas 45 (pars triangularis), insula, premotor cortex), bilateral anterior superior parietal cortex (supramarginal gyrus, postcentral gyrus), left posterior temporal cortex, and right cerebellum. In addition, left area 44 showed negative RSFC with bilateral dorsal posterior cingulate cortex and orbitofrontal areas.

Left BA 45

Area 45 (Pars Triangularis) (middle column in figure 3) in the left hemisphere showed positive RSFC with bilateral anterior frontal cortex (area 47, dorsolateral prefrontal cortex, anterior prefrontal cortex, pre-SMA), bilateral posterior superior parietal cortex (supramarginal gyrus, angular gyrus, somatosensory association area BA7), bilateral mid temporal cortex (middle part of middle and inferior temporal gyri), and bilateral cerebellum. Negative RSFC were found with bilateral dorsal posterior cingulate cortex, but only with the larger AAL atlas ROIs. No significant negative RSFC were found with the 6mm radius spherical ROIs.

Left BA47

Left area 47 (Pars Orbitalis) (right column in figure 3) showed positive RSFC with bilateral inferior frontal cortex (orbitofrontal and anterior prefrontal cortex), bilateral ventral posterior parietal cortex (angular gyrus, associative visual area BA19), bilateral mid to anterior temporal cortex (middle and inferior temporal gyri, temporal pole), bilateral cerebellum, and bilateral posterior cingulated cortex.

Similar to areas 44 and 45, negative RSFC were found with dorsal posterior cingulate, however only in the right hemisphere. In addition, negative correlations were observed with right postcentral gyrus and right superior parietal regions.

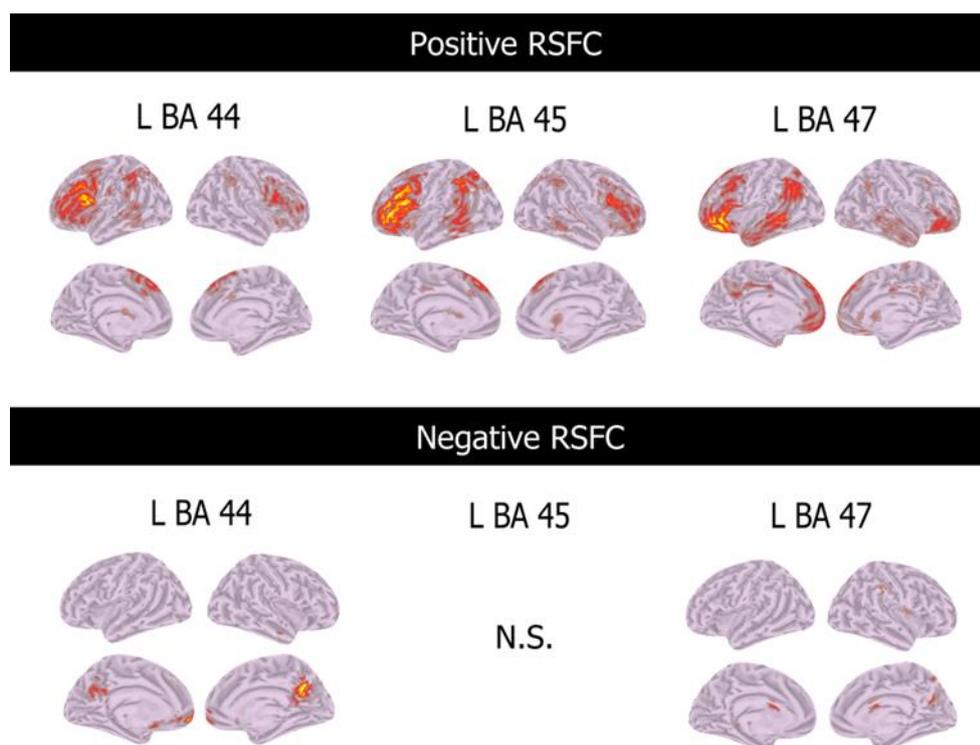


Figure 5.3 Resting-state functional connectivity (RSFC) maps from left subregions of Broca's area. Top row show positive RSFC, bottom row show negative RSFC maps. L = left hemisphere, R = right hemisphere, BA = Brodmann area

Table 5.1 Resting-state functional connectivity table of coordinates of subregions of Broca's area in the left hemisphere. L = left hemisphere, BA = Brodmann area

Left BA44		
Region	MNI (x y z)	
	AAL atlas	6 mm sphere
Positive correlations		
Left inferior frontal gyrus	-48 12 10	-50 10 10
Right inferior frontal gyrus	46 14 30	54 18 22
Left supramarginal gyrus	-44 -44 48	-42 -46 46
Right supramarginal gyrus	60 -38 50	52 -38 50
Left angular gyrus	-60 -20 26	-60 -20 26
Right cerebellum	34 -64 -32	
Right cerebellum	16 -78 -28	
Left insula	-12 -02 12	
Left supplementary motor area		-6 14 46
Negative correlations		
Dorsal posterior cingulate	10 -60 24	4 -62 30
Orbitofrontal cortex	0 60 -04	0 54 -6
Right anterior prefrontal gyrus	8 62 38	8 62 36
Left dorsal anterior cingulate	-10 8 -10 -16 42 -10	-10 26 -10
Right middle temporal gyrus		64 -2 -18
Left BA45		
Region	MNI (x y z)	
	AAL atlas	6 mm sphere
Positive correlations		
Left inferior frontal gyrus	-46 34 10	-52 28 14 -16 60 20
Left parietotemporal cortex	-52 -42 42	-42 -52 46 (parietal) -60 -46 -6 (temporal)
Right frontal cortex	46 14 26	54 26 32 52 42 -12 4 34 54
Right posterior superior temporal gyrus	68 -32 0	68 -34 -14
Right supramarginal gyrus	42 -46 40	44 -44 40
Right cerebellum	16 -82 -28	12 -86 -34
Caudate	10 12 02	
Left cerebellum	-14 -84 -32	-40 -70 -32
Left dorsal posterior cingulate	-6 -34 38	
Negative correlations		
Right superior parietal cortex (BA5, BA7)	24 -42 68	
Dorsal posterior cingulate cortex	10 -58 26	
Left subgenual cortex	-10 10 -10	
Left medial posterior temporal gyrus	-32 -48 2	
Left BA 47		

Region	MNI (x y z)	
	AAL atlas	6 mm sphere
Positive correlations		
Left middle frontal gyrus	-36 34 -16	-40 36 -14
Right cerebellum	46 -62 -34	16 -82 -28
Left posterior cingulate	-6 -48 28	-2 -20 38 -4 -54 26 -2 -68 38
Right supramarginal gyrus	58 -56 40	58 -54 26
Right dorsolateral prefrontal cortex	42 16 46	40 14 50
Left anterior inferior temporal gyrus	-18 -8 -40	
Premotor area	6 -26 56	4 -26 60
Insula	8 14 8	
Left cerebellum	-14 -78 -30	
Negative correlations		
Right medial superior parietal lobule	10 -72 50	12 -72 48
Right dorsal posterior cingulate cortex	18 -60 24	14 -58 22
Right primary somatosensory cortex	54 -24 40	54 -26 40
Right insula	42 0 14	
Left postcentral gyrus		-58 -26 26

Direct comparisons between RSFC

Figure 5.4 illustrates RSFC differences between networks. Coordinate tables for corresponding regions can be found in table 5.2.

Left BA 44 and left BA 45

Direct comparisons between areas 44 and 45 revealed area 44 to have stronger positive RSFC with left posterior ventral frontal regions (area 44, insula), left SMA, and left supramarginal gyrus. Area 45 showed stronger positive correlations with left anterior prefrontal cortex, bilateral posterior parietal cortex, bilateral mid ventral temporal cortex (middle and inferior temporal cortex, fusiform gyrus), left pre-SMA, and bilateral dorsal posterior cingulate cortex.

Left BA 45 and left BA 47

Direct comparisons between areas 45 and 47 showed increased connectivity of area 45 with bilateral dorsolateral prefrontal regions, bilateral supramarginal gyri, left premotor

cortex, and left posterior temporal cortex. In contrast, area 47 showed stronger connectivity with bilateral orbitofrontal regions, bilateral anterior temporal cortex, and bilateral angular gyri.

Left BA 44 and left BA 47

Lastly, comparisons between areas 44 and 47 revealed stronger connectivity of area 44 with posterior regions in the frontal cortex (area 44, insula) in both hemispheres, bilateral postcentral gyri and supramarginal gyri, and bilateral premotor areas and precentral gyri. Area 47 showed stronger connectivity with bilateral orbitofrontal areas, bilateral posterior parietal areas, bilateral anterior temporal regions, as well as bilateral dorsal posterior cingulate.

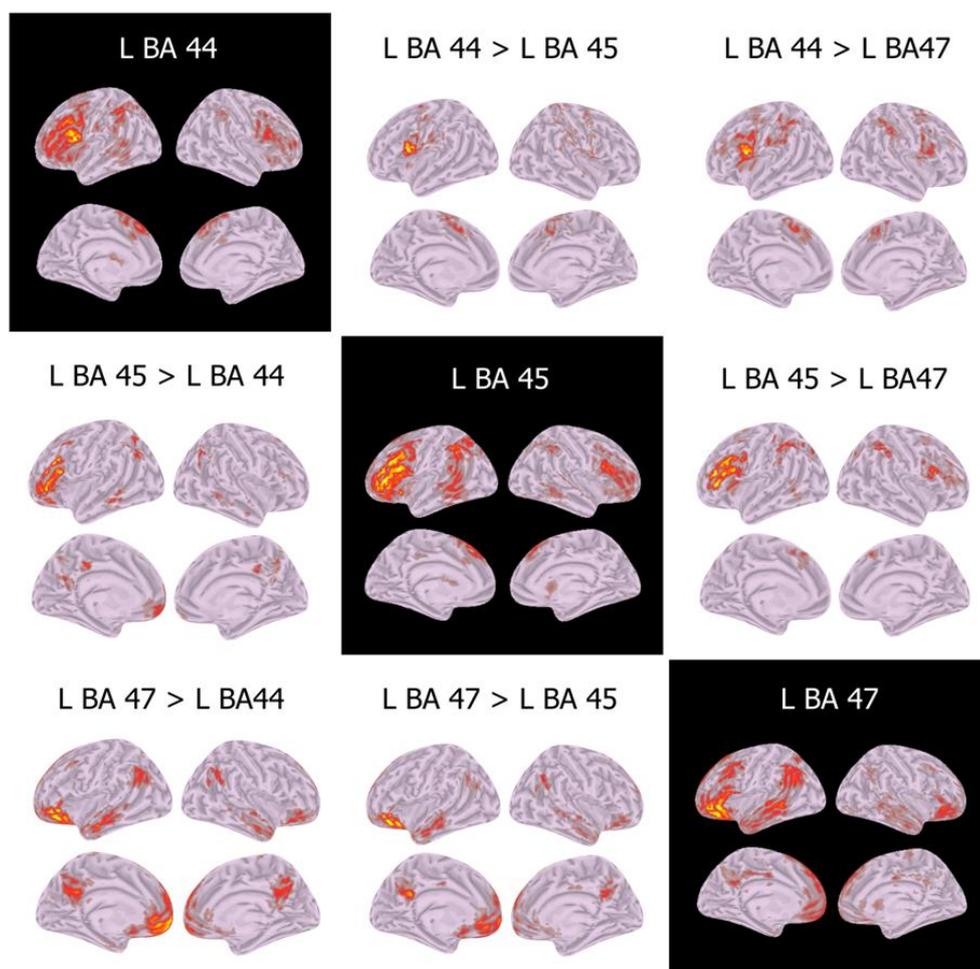


Figure 5.4 Direct comparisons between resting-state functional connectivity maps of the subregions of Broca's area in the left hemisphere. L = left hemisphere, BA = Brodmann area

Table 5.2 Direct comparisons between resting-state functional connectivity maps of the subregions of Broca's area in the left hemisphere. L = left hemisphere, BA = Brodmann area

L BA44 > LBA45		
Region	MNI (x y z)	
	AAL atlas	6 mm spheres
Left BA 44, premotor cortex (BA6) Left supramarginal gyrus	-56 12 18	-48 10 12
Bilateral premotor cortex (BA6)	-2 6 48	14 6 64
Right BA44, premotor cortex	44 4 10	
Right inferior anterior parietal cortex, supramarginal gyrus (BA40)	64 -20 34 36 -36 46	
Right somatosensory association cortex (BA5, BA7)	14 -48 66	
Right premotor cortex (BA6)	28 -8 56	
L BA45 > L BA44		
Region	MNI (x y z)	
	AAL atlas	6 mm spheres
Left anterior, prefrontal cortex	-48 22 26	-48 26 18 (DLPFC, BA45) 0 56 -14 (orbitofrontal cortex) -12 64 20 (anterior PFC, BA10) -36 30 -12 (BA47)
Left posterior superior parietal cortex (BA7, BA39, BA19)	-38 -68 48	-28 -76 50
Left dorsal premotor cortex (BA6), dorsal frontal cortex (BA8)	-34 14 54	-30 18 60
Bilateral dorsal posterior cingulate cortex	-2 -34 34	14 -48 26
Right angular gyrus (BA39)	46 -70 42	42 -68 40
Right posterior middle temporal cortex (BA21, 22, 20, 37)	70 -34 -4	68 -34 -14
Left posterior temporal cortex (BA 21, 20, 37)	-58 -36 -12	
Left ventral dorsal posterior cingulate cortex (BA23, 31)	-2 -58 16	
Right premotor cortex (BA 6, 8)	22 28 54	28 28 54
Right dorsolateral prefrontal cortex (BA9, 46)	54 26 32	
Right middle temporal gyrus	62 -6 -20	
Right somatosensory association cortex (BA7)	46 -56 52	
L BA 44 > L BA 47		
Region	MNI (x y z)	
	AAL atlas	6 mm spheres
Left dorsolateral prefrontal cortex, insula, premotor cortex, pars opercularis (BA9, BA13, BA6, BA44)	-56 10 16	-50 6 14
Left primary somatosensory cortex, supramarginal gyrus (BA2, BA40)	-48 -40 50	-46 -40 52 -10 -62 54
Right dorsolateral prefrontal cortex, pars opercularis, insula (BA9, BA44, BA13)	48 10 30	52 8 16 32 14 8
Right supramarginal gyrus, primary somatosensory	56 -30 46	52 -34 50

cortex (BA40, BA2)		
Bilateral premotor cortex (BA6), dorsal anterior cingulate (BA32)	-2 8 50	-4 4 50
Left premotor and primary motor cortex (BA6, BA4)	-30 -4 46	-42 -10 48
Left dorsolateral prefrontal cortex and anterior prefrontal cortex (BA 46, BA10)	-42 40 24	-44 40 24
Right premotor cortex (BA 6), dorsal anterior cingulate (BA32)	26 4 60	24 2 60
Right posterior somatosensory association cortex (BA7)	12 -70 56	
Right dorsolateral prefrontal cortex (BA9)	38 38 30	
L BA47 > L BA44		
Region	MNI (x y z)	
	AAL atlas	6 mm spheres
Left anterior prefrontal cortex (BA 10, 11)	-8 56 -16	-10 36 50
Left inferior prefrontal cortex (BA 47, 11)	-42 38 -12	-46 36 -14
Bilateral dorsal posterior cingulate (BA 31)	-6 -50 28	4 -54 34
Left anterior middle temporal cortex (BA21,20)	-60 -6 -22	-64 -16 -14
Left posterior ventral parietal cortex – angular gyrus (BA39), supramarginal gyrus (BA40), SSA (BA7), Associative visual cortex (BA19)	-56 -60 38	-54 -58 28
Right posterior ventral parietal cortex – angular gyrus (BA39), supramarginal gyrus (BA40), SSA (BA7), Associative visual cortex (BA19)	48 -68 40	50 -56 30
Left dorsal frontal cortex (BA8, 6)	-36 14 54	-34 18 52
Left parahippocampal cortex (BA36)	-18 -8 -30	
Right premotor cortex (BA6)	2 -28 70	10 30 58
Right inferior prefrontal cortex (BA47)		48 36 -12
Right anterior temporal cortex (BA21,20)		60 -8 -14
L BA45 > L BA47		
Region	Peak MNI (x y z)	
	AAL atlas	6 mm spheres
Left dorsolateral prefrontal cortex (BA 46, BA9)	-46 42 8	-50 28 18 -48 12 30
Left supramarginal gyrus (BA40), SSA (BA7), associative visual cortex (BA19)	-48 -40 50	-32 -50 36 -28 -68 42
Right dorsolateral prefrontal cortex (BA 46, BA9)	44 16 28	48 30 16
Right supramarginal gyrus (BA40), SSA (BA7)	54 -32 46	46 -42 46
Right dorsal frontal cortex, premotor cortex (BA8, 6)	8 18 48	
Left premotor cortex (BA6)	-26 6 56	-28 6 54
Right premotor cortex (BA6)	30 6 58	
Left posterior middle temporal cortex (BA37, 21)	-56 -52 -2	-56 -54 -6
Right SSA (BA7), associative visual cortex (BA19)	32 -68 36	28 -66 36
Right inferior temporal gyrus, fusiform gyrus (BA20, 37)		54 -42 -12
L BA47 > L BA45		
Region	MNI (x y z)	
	AAL atlas	6 mm spheres
Left inferior prefrontal cortex (BA47, 11, 10)	-34 24 -16	-44 32 -8 -20 60 -8
Right inferior prefrontal cortex (BA47, 11, 10)	42 32 -20	54 24 -8

Bilateral dorsolateral prefrontal cortex (BA9)	8 60 28	12 60 36
Left anterior temporal cortex (BA21, 20, 38)	-58 -6 -28	-56 -8 -30 -60 -24 -14
Bilateral dorsal posterior cingulate cortex (BA31)	-6 -48 26	
Right anterior temporal cortex (BA21, 20)	62 -2 -16	58 -2 -36
Right angular gyrus, supramarginal gyrus (BA39, 40)	46 -60 34	46 -52 30
Left angular gyrus, supramarginal gyrus (BA39, 40)	-58 -60 36	-58 -58 36
Left dorsal frontal cortex, premotor cortex (BA8, 6)	-14 36 52	-12 34 50
Right posterior middle temporal cortex (BA21)		54 -32 -4

White matter tractography results

When seeding from subregions in Broca's area in the left hemisphere using target masks in parietal and temporal regions derived from the RSFC maps, tractography showed both the dorsal (Arcuate Fasciculus) and the ventral (Extreme capsule/Uncinate Fasciculus) pathways associated with language (fig. 5.5). Area 44 had connections mainly through the dorsal route to both parietal and temporal regions (anterior and direct segment of the arcuate fasciculus). Area 45 had connections via the dorsal as well as the ventral route. Lastly, area 47 mainly had connections through the ventral route.

Tractography using the other RSFC target regions did not produce sufficient streamlines. This was due to two factors. Firstly, probability of tractography decreased with distance, as was the case in for example left IFG to right cerebellum. Secondly, no direct white matter tracts (as can be identified using tractography) exist between non-homologous hemispheric regions, for example left IFG to right superior parietal cortex).

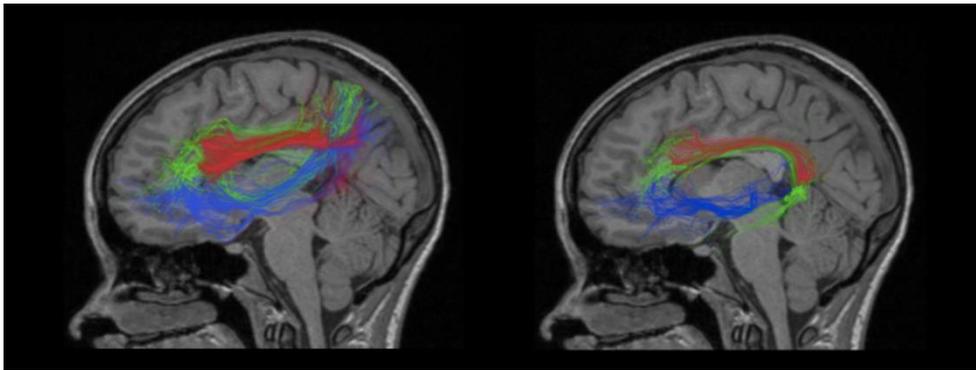


Figure 5.5 White matter fibers connecting inferior frontal regions to superior parietal (left image) and temporal regions (right image) in the left hemisphere for a single representative subject. Only parietal and temporal RSFC regions produced reliable white matter tractography results, and are shown here. The same sagittal slice is used in both images. Red fibers show connections from area 44. Green fibers show connections of area 45. Blue fibers show connections for area 47.

5.4. Discussion

The present study revealed that the topology of the language network at rest is organised in gradients of functional connectivity, representing subnetworks within the larger default language network. More specifically, subregions in Broca's area connect to distinct and adjacent regions in frontal, temporal and parietal cortices, which have been previously documented to assist language processing in explicit task-based fMRI paradigms (Price, 2012; Vigneau et al., 2006). White matter tractography, in addition, showed that each subnetwork has its distinct set of white matter pathways.

Gradients of functional connectivity

The topology of connectivity in the parietal regions show an anterior dorsal to posterior ventral gradient of regions connected to respectively, area 44, 45 and 47 (figure 2). In the temporal cortex, this gradient shows a reverse posterior to anterior gradient of connectivity to respectively area 44, 45, and 47 (see fig. 2). These findings replicate the topology observed previously by Xiang and colleagues (2010). Whereas Xiang and colleagues observed a superior to inferior gradient in the posterior temporal cortex only, this study found an anterior to posterior gradient across the whole of the temporal cortex. More

specifically, we observed area 44 to connect to posterior temporal cortex, area 45 to connect to mid temporal cortex and area 47 to connect to anterior temporal cortex. This connectivity pattern is more in line with the findings of a review of the localisation of language function across the temporal cortex, with semantics located more anteriorly and syntax and phonology more posteriorly (Price, 2012).

Gradations in cortical architecture have been discussed before by Amunts and Zilles (2012), more specifically referring to Sanides' gradations. These gradations can be observed in all lobes in the brain and are hypothesized to reflect architectonic similarities between neighbouring cortical areas, which change in a step-wise manner (Sanides, 1964 in Amunts and Zilles, 2012). Although fMRI data currently cannot image such fine level details found in architectonics, we hypothesize that the gradients observed in the RSFC maps may reflect Sanides' gradations.

Negative correlations with posterior cingulate cortex

Negative correlations were found with bilateral posterior cingulate cortex for bilateral areas 44 and left area 47 (figure 3). The posterior cingulate is part of the default mode network (DMN) (Smith et al., 2009), which is also known as the task negative network. The function of the DMN is still unknown, but tasks that require mentalising, internal planning of future behaviour, autobiographical memory, theory of mind, or self-referential decision making (Buckner et al., 2008; Andrews-Hanna et al., 2010) are known to activate DMN nodes. The DMN also shows increased activation during wakeful rest, but is decreased during active tasks (Dosenbach et al., 2007; Fox et al., 2009). The relationship and mediation between task positive and task negative networks are still unclear (Chai et al., 2012; Fox et al., 2009). Nevertheless, the negative correlations observed between the language network and the DMN at rest is in line with previous literature that suggests a decoupling of task-active (language in this case) and task-negative (DMN) networks (e.g. Tomasi and Volkow, 2012; Zhu et al., 2014).

Relevance for theories for language processing and production

The replication of the gradient of RSFC from left IFG to left parietal and temporal cortices provide support for the MUC model of language (Hagoort, 2005). The model proposes an anterior ventral to posterior dorsal gradient of functional processing in the left IFG, which serve distinct cognitive functions. Specifically, BA 44 and parts of BA 6 are hypothesised to play a role in phonological processing; BA 44 and BA 45 to syntactic processing; and BA 47 and BA 45 to semantic processing. Area BA6 was not included in the present analysis, but the RSFC gradients observed for areas BA 44, 45 and 47 are in line with these predictions.

The RSFC network found for left BA44 included bilateral postcentral gyri, bilateral STG, left MTG and left IFG. These target regions strongly resemble the regions of activation found during phonological tasks such as phoneme manipulation and auditory-motor integration tasks (Friederici, 2011; Peschke, Ziegler, Eisenberger, & Baumgaertner, 2012; Vigneau et al., 2006). Moreover, the posterior STG/STS, which includes the planum temporale (PT) has been found to differentiate speech from non-speech and noise (Meyer et al., 2005). Area 45 connected to caudal superior parietal regions, mid temporal regions and the preSMA. Functional studies investigating modulations in syntactic processing consistently find activations in the left IFG, and area 45 in particular (Price, 2012; Vigneau et al., 2006).

The RSFC network derived from area 47 strongly overlaps with brain regions engaged in semantic judgement tasks (Vigneau et al., 2006). This network includes the posterior parietal cortex, anterior temporal cortex and prefrontal cortex. Anterior temporal cortex is found to activate as a function of intelligibility (Friederici, 2011) suggesting a crucial role in speech comprehension. This is further supported by patient studies, where lesions in anterior temporal regions led to speech comprehension deficits (Hodges, Patterson, Oxbury, & Funnell, 1992). However, there is evidence that suggests that this network might only support semantic processing in syntactic structures, and should be taken as a confined semantic processing network rather than a general semantic one (Friederici, 2011).

Intraoperative stimulation has provided direct evidence for the function of this pathway by demonstrating that direct electrostimulation results in errors in word meaning (Duffau et al., 2005).

In addition, the white matter connections observed here agrees with previous DTI studies of the white matter connectivity between these regions (e.g. Saur et al., 2008; Makris & Pandya, 2009). These findings are in agreement with theoretical views that suggest a dual stream model for auditory language processing (e.g. Hickok & Poeppel, 2004; Warren et al., 2005). According to the dual stream model, initial auditory processing in the STG proceeds via a dorsal stream to the inferior parietal lobule and then to the IFG for auditory-motor integration, which is necessary for articulatory output. This dorsal stream has since been proposed to be the arcuate fasciculus/superior longitudinal fasciculus (e.g. Friederici, 2011; Friederici and Gierhan, 2013). The arcuate fasciculus (AF) is a critical pathway of language and supports auditory-motor integration, including phonological processing (Friederici, 2011). Evidence comes from lesion studies showing that damage to the AF leads to difficulties repeating words, as well as electrocortical stimulation studies, where people substitute incorrect sounds when the AF direct segment was stimulated intraoperatively (Duffau, 2008).

At the same time, a ventral stream is hypothesized to map sounds to meaning in lateral temporal areas. Saur et al. (2008) combined fMRI during two prototypical tasks tapping dorsal (speech repetition) and ventral (language comprehension) streams with diffusion tensor imaging. The authors showed that fibers of the arcuate fasciculus and the superior longitudinal fasciculus are indeed linked to speech repetition and those of the extreme capsule to language comprehension.

Probabilistic tractography results here showed that the RSFC network of area BA 44 is connected primarily via the dorsal pathway, more specifically, the anterior segment of the

arcuate fasciculus to parietal regions, and via the direct segment to posterior temporal regions, also previously observed by Catani and colleagues (2005). On the other hand, tractography results of area 45 found this network to be connected via two pathways: one dorsal (AF/SLF) and one ventral (extreme capsule system). White matter tractography seeding from area 47 showed only ventral connections to anterior temporal and posterior parietal regions.

Thus, the combination of using both DTI and RSFC suggest that the network of area 44 supports phonological processing in the dorsal route, area 45 supports syntactical and semantic processing via dual routes, and area 47 supports semantic processing via the ventral route. This contributes to the understanding of how different zones of language-related cortex are linked together, highlighting neural circuits underlying various aspects of linguistic processing.

Link to animal studies

Previous studies have investigated the correspondence between human RSFC patterns of the left IFG and those of the macaques (Kelly et al., 2010; Neubert et al., 2014). This was not a primary question of interest in the present thesis, thus will be discussed here only briefly.

Tract tracing studies in the macaque have shown that areas 44 and 45 are strongly connected with more posterior inferior parietal lobule areas, which in the monkey are referred to as areas PFG and PG (Petrides, 2006; Petrides & Pandya, 2009), and which correspond to the human posterior supramarginal gyrus and human angular gyrus respectively (cf Petrides and Pandya, unpublished observations, in Kelly et al., (2010). The same studies have also shown in the macaque, area 45 has stronger connections than area 44 with area PG (corresponding to the human angular gyrus) and stronger connections than area 44 with the temporal cortex that lies within and below the superior temporal sulcus

(which corresponds to the middle temporal gyrus of the human brain). This correspond to the gradients observed in the RSFC in this study as well as in the direct comparisons between areas 44 and 45.

A direct comparison (Neubert et al., 2014) between areas 45 and 47 in human and macaques found no differences between species in their RSFC pattern, but found a main difference between 45 and 47 instead: the latter was more closely linked to anterior parts of the temporal cortex (i.e. temporal pole) in both species. This pattern was also observed in the present study as part of the gradient and the direct comparison between areas 45 and 47. The present results therefore replicate previous results observed in both humans and monkeys.

Limitations

A few limitations of the present study should be noted. Firstly, the a priori anatomical definition of the subregions within Broca's area was based on a normalised automated atlas of a single subject (AAL atlas). Previous studies show that there is large individual variability in the exact localisation of the subregions (Amunts & Zilles, 2012; Anwender et al., 2007; Friederici, 2011). This individual variability is not taken into account on the MNI map. However, each individual's functional images were normalised to MNI space using non-linear registration methods, therefore minimizing the impact such individual variability may have on the RSFC maps.

Secondly, one may be concerned that the gradients observed may be a confound of the nature and size of the a priori defined ROIs. For example, the gradient overlaps may be an artefact of the smoothing of the large ROIs, creating blurred boundaries and a mixture of signals. This was controlled for in two ways. Firstly, the seed-signal was an average of the seed-cluster as a whole. If there had been confounding signals from possible blurred boundaries, these would most likely be averaged out by the larger cluster. Secondly, the

same analyses were done with ROIs defined as 6mm spheres. It was ensured that there was no overlap between regions (thus signal) between these smaller ROIs. The resulting maps were not significantly different from the maps derived from the larger ROIs. This gave better assurance that the gradients observed were not an artefact of seed selection.

Lastly, future work is needed to address possible further subdivisions of Broca's area, as proposed by the work of Amunts and Zilles (2003, 2012). These studies suggest that Broca's area can be parcellated into more than a dozen areas based on cytoarchitectonics and neurochemical receptors. However, such level of detail will require far higher spatial resolutions than is currently possible with existing fMRI protocols.

5.5. Conclusion

In summary, the present RSFC revealed that the human language network can be subdivided into meaningful subnetworks, with their own distinct anatomical connections. This is the first study to demonstrate that white matter language pathways can also be found using resting-state connectivity maps as seed regions in tractography analyses. These white matter connections have previously only been found using task-based fMRI (Saur & Kreher, 2008) or using anatomical or manually delineated ROIs. All in all, these findings suggest that it is feasible to investigate meaningful networks at rest using combined RSFC and DTI tractography. This forms the foundation for the connectivity methods used in the subsequent chapters.

6. The cognitive profiles of high achieving adult readers with dyslexia

6.1. Introduction

This chapter explores the cognitive profiles of the adult dyslexic readers in further detail.

Despite the heterogeneity of dyslexia, it has been well established in the literature that the core deficit of developmental dyslexia is a deficit in phonological processing (e.g. Snowling, 2000). Most of the studies carried out have focused on children in the stages of acquiring and establishing their reading skills, when their difficulties become apparent, to inform early and effective intervention design. Some studies have started to investigate adult dyslexics as well. Adult populations with dyslexia differ from children with dyslexia in many ways due to neurodevelopmental changes, compensation strategies, reading experience, and academic achievements.

Adult dyslexics are an interesting group for investigation for two reasons. Firstly, characterising the deficits in adults with dyslexia provides insight into the primary core deficits in dyslexia, since the most persistent features of a disorder can be considered the 'core' or primary features (e.g. Everatt, 1997; Felton, Naylor, & Wood, 1990; Gottardo, Siegel, & Stanovich, 1997; Hatcher, Snowling, & Griffiths, 2002; Kinsbourne, Palmer, & Berliner, 1991; Nergård-Nilssen & Hulme, 2014). Secondly, adults with a history of childhood dyslexia may or may not have compensated for their reading difficulties, which provides insight into possible compensatory mechanisms. Adult dyslexic populations can thus be divided into two groups: a group of 'compensated' dyslexics whose reading achievements are good enough for them to continue on to academic education as opposed to the group of 'non-compensated' dyslexics whose reading achievements remain very low, and who thus find formal study difficult (Deacon, Parrila, & Kirby, 2006; Felton et al., 1990; Hatcher et al., 2002; Lefly & Pennington, 1991; Nergård-Nilssen & Hulme, 2014; Reid, Szczerbinski, Iskierka-Kasperek, & Hansen, 2007).

Questions surrounding 'compensation'

Studies investigating adults with a history of childhood dyslexia estimated that 22-25% of childhood dyslexics have 'compensated' (performance scores fall within the 'average' range but often below those of age-matched controls) for their reading impairments (e.g. Felton et al., 1990; Lefly & Pennington, 1991). Although these studies bring optimistic news that up to a quarter of children with dyslexia may eventually compensate for their reading difficulties, there are some puzzling questions remaining.

Firstly, what does 'compensated' actually mean? Compensation in these early studies was defined using a composite score made up of single word reading accuracy and reading comprehension of short texts in an algorithm designed by Finucci et al. (1984). These scores were entered into empirically derived regression equations that predicted expected composite scores. Deviation scores were determined by subtracting observed scores from expected scores and dividing by standard errors of prediction. Negative deviation scores of more than 2.0 defined persistent dyslexia (Felton et al., 1990; Finucci, Whitehouse, Isaacs, & Childs, 1984; Kinsbourne et al., 1991). One study (Parrila, Georgiou, & Corkett, 2007) estimated about 27% (8 out of 29) of adults readers with childhood history of dyslexia to have partially compensated based on reading comprehension as outcome measure. However, when other measures such as word reading, decoding, spelling, and phonological processing were considered as outcome measures, only 7% (2 out of 29) were considered compensated. Therefore, the early studies may have overestimated numbers of compensated individuals by using reading comprehension as the main outcome measure.

Secondly, being 'compensated' does not mean 'free of impairments or difficulties'. Despite improvement in academic skills of compensated dyslexics, a large number of studies have found persistent difficulties in rapid automatized naming (RAN), pseudoword reading, phonological awareness (Felton, Naylor and Wood, 1990; Kinsbourne et al., 1991; Gross-Glen et al., 1990; Pennington et al., 1990), as well as spelling (Kinsbourne et al., 1991;

Bruck, 1990; Hanley, 1997; Everatt, 1997; Miller-Shaul, 2005; Law et al., 2014; Ramus et al., 2003; Reid et al., 2007; Snowling et al., 1997; Nergard-Nilssen and Hulme, 2014) and reading comprehension, under timed conditions only, in contrast to untimed comprehension (Kemp, Parrila and Kirby, 2009; Parrila, Georgiou and Kirby, 2007). These studies clearly indicate persistent and possibly life-long impairments (Lefly and Pennington, 1991).

Lastly, the mechanisms of compensation are currently unknown. Why are some people able to compensate for dyslexia while others are not? Studies comparing compensated dyslexic readers with severe (non-compensated) dyslexics and controls suggest that compensated dyslexics may have, at least in part, achieved reading success through contextual cues (Bruck, 1990), semantic knowledge (Bruck, 1990, 1993; Everatt, 1997; Hatcher et al., 2002), orthographic knowledge (Bruck, 1990, 1993; Lefly & Pennington, 1991), morphological knowledge (Law, Vandermosten, Ghesquiere, & Wouters, 2014; Miller-Shaul, 2005), more reading exposure (Kinsbourne et al., 1991), or vocabulary (Deacon et al., 2006). The evidence in this field is currently scarce and is derived from the fact that severe dyslexic readers are more impaired in these domains than compensated dyslexics, even though both groups of dyslexic readers perform significantly worse compared to controls. In fact, these compensatory factors may merely “minimise the expression of [reading] difficulties” rather than fully ameliorate them (Law et al., 2015).

Profile of adult dyslexics

Recent studies have attempted to determine how best to define dyslexia in the adult years in the hope of finding the best diagnostic instruments for use in the assessment of adults with dyslexia. Research studies examining the ‘compensated’ group indicate a number of findings for which this group continued to show impaired performance. In the majority of the studies, these adult dyslexics continue to have difficulty with phonological ability. Their accuracy on different phonological tasks such as spoonerisms (exchanging the first sounds

of two words, e.g. 'shoving leopard' instead of 'loving shepherd'), Pig Latin task (initial sound of word is moved to the end and 'ay' is added, e.g. 'pig' becomes 'igpay'), phoneme deletion (e.g. 'sling' → 'sing'), and rhyme judgement continues to be low (Bruck, 1992; Felton et al., 1990; Gross-Glenn, Jallad, Novoa, Helgren-Lempesis, & Lubs, 1990; Hatcher et al., 2002; Miller-Shaul, 2005; Nergård-Nilssen & Hulme, 2014; Parrila et al., 2007; Pennington, Van Orden, Smith, Green, & Haith, 1990; Ramus, 2003; Snowling, Nation, Moxham, Gallagher, & Frith, 1997). They were also found to be slower and less accurate than both reading-age and chronological-age matched controls during decoding of familiar and unfamiliar, single and multi-syllabic words, and during pseudoword reading (Bruck, 1990, 1992). They are also insensitive to omissions at the beginning and end of the word (Bruck, 1992). Studies with dyslexic university students, who arguably should be the most compensated to achieve academic success, found them to be significantly worse than controls in all measures of literacy (reading speed and accuracy, spelling, pseudoword reading accuracy and time) as well as phonological tests (RAN, spoonerisms)(Ramus, 2003; Reid et al., 2007; Snowling et al., 1997).

Few studies have directly compared compensated and non-compensated dyslexic readers. Beside phonological deficits, non-compensated dyslexics also struggle with orthographic processing (Bruck, 1990, 1993) and short-term memory (STM) (Pennington et al., 1990). Instead of using whole word orthographic strategies like skilled readers, these readers continue to rely on phonological decoding of even familiar words, even though it is inefficient. The group of compensated dyslexics, however, do show some evidence of using the orthographic system which is hypothesized to compensate for the deficient phonological system, but not to the same automatic extent as typical readers (e.g. Bruck, 1990, 1992). They also use compensation strategies within the phonological system to circumvent their phonological difficulty, such as separating the word into syllables (e.g. Bruck, 1990).

Kinsbourne et al. (1991) studied 23 severe dyslexics and 11 compensated dyslexics with 21 controls and found both dyslexic groups to be impaired on all measures of literacy. Severe dyslexic readers were significantly worse than the compensated dyslexics in word decoding, comprehension, spelling and RAN. Similarly, Gross-Glen et al. (1990) found 23 severe dyslexic readers to perform worse than 27 compensated readers, who in turn performed worse than the controls on a nonsense passage-reading task, where participants were asked to read out a text with occasional pseudowords embedded into the passage. A study by Parrila, Georgiou and Kirby (2007) found 10 adults with a diagnosis of dyslexia and 18 adults with a self-reported history of reading difficulties to perform at similar levels on most measures of literacy (decoding, spelling, comprehension) and phonological decoding (pseudoword decoding, phoneme discrimination), except on the phoneme elision, pseudoword repetition, and RAN digits test, which tap into phonological awareness, phonological memory and retrieval respectively. The consistent finding in these studies is that the only factor that sets compensated and non-compensated dyslexics apart is the severity: the compensated readers perform within the 'average' range on standardised scores, whereas the non-compensated readers perform below average (<1-2 SD from population mean). Yet both perform well below chronological-age matched controls. These findings support the claim that dyslexia should not be considered an all-or-none condition, but should be seen on a continuum of reading abilities (Snowling, Gallagher and Frith, 2003).

The above findings raise important clinical questions. Should these 'compensated' readers still be considered impaired and therefore be eligible to receive intervention and special educational needs such as extra time? What are the best diagnostic measures to identify dyslexia in the adult years? What should be the diagnostic cut-off score to accurately diagnose dyslexia in adulthood? For example, Snowling and colleagues (Snowling et al. 1997; Hatcher et al., 2002) found pseudoword reading, spelling, short-term memory and

writing speed to be enough to correctly classify dyslexic readers from controls, whereas Kinsbourne et al. (1991) found RAN to be the best predictor (79% accuracy). In contrast, Gross-Glen et al. (1990) found performance on tests of nonsense passage reading to be the most sensitive measure of residual deficits regardless of compensation status. Both non-compensated and compensated dyslexics made significantly more errors and took longer to read a nonsense passage. These findings together with those of Kirby and colleagues (Parrila, Georgiou and Kirby, 2007; Kemp, Parrila and Kirby, 2009), who found differences in timed measures of reading comprehension in contrast to untimed measures, suggest that accuracy, fluency, as well as memory are the key features that are impaired in adults with dyslexia, regardless of compensation status, and that 'compensated' dyslexics should indeed be seen as impaired and in need of targeted intervention.

Double-deficit hypothesis

Another issue of current debate is whether there exist different subtypes of developmental dyslexia; the double-deficit hypothesis (DDH) (see chapter 1). Therefore, a secondary aim of this chapter was to explore the double-deficit hypothesis in the present dataset. The double deficit theory has important theoretical and practical implications.

On a theoretical level, the DDH implicates naming speed as a second, independent, core deficit of dyslexia (Wolf & Bowers, 1999). Naming speed refers to how quickly one can retrieve the names (or phonological representations) of a set of familiar stimuli, and is measured using RAN tests of letters, numbers, colours or objects. Subtyping based on the DDH places dyslexic readers into 3 groups: 1) phonological-deficit only (characterised by poor phonological awareness with intact RAN), 2) naming speed-deficit only (intact phonological awareness with poor RAN), or 3) double-deficit group (poor phonological awareness and RAN). Therefore, this form of subtyping is informative for understanding the independent cognitive processes contributing to reading acquisition.

Clinically, the DDH also offers a powerful diagnostic tool for effective diagnosis and intervention. For example, children with only RAN difficulties (and intact phonological decoding) should not receive ineffective phonemic-based interventions (e.g. Cronin, 2011; Kirby, Georgiou, Martinussen, & Parrila, 2010; Vukovic & Siegel, 2006; Wolf & Bowers, 1999).

Consistent RAN deficits have been found in adult dyslexic readers, regardless of compensation status (Kinsbourne et al., 1991; Parrila, Georgiou and Kirby, 2007; Felton, Naylor and Wood, 1990; Gross-Glen et al., 1990; Pennington et al., 1990; Ramus et al., 2003). Earlier studies and proponents of the phonological deficit theory have interpreted these naming speed deficits as part of the phonological system as “retrieval of phonological codes from a long-term store” (Wagner, Torgesen, & Rashotte, 1994) or phonological recoding in lexical access (Wagner & Torgesen, 1987). In contrast, Wolf and Bowers (1999) proposed an alternative view in their seminal paper outlining the DDH with the following, testable assumptions:

1. There are strong relationships between RAN and word- and text-reading fluency and between PA and pseudoword decoding. When RAN and PA both contribute to one reading skill, each variable contributes uniquely to that skill and has some variance in common.
2. Dyslexic individuals with a double deficit are more severely impaired than those with a single deficit. In addition, those with a phonological-deficit only should display more pronounced difficulties with decoding, whereas those with RAN-deficits should display more pronounced difficulties with fluency.

Empirical evidence to support the DDH, however, has been inconsistent. Few studies have directly investigated the DDH (for reviews see Vukovic and Siegel, 2006 and Kirby et al., 2010). Vukovic and Siegel (2006) only identified 9 papers which have directly investigated

the DDH. From these 9 studies, four studies have found RAN to be independent from PA (Compton, DeFries, & Olson, 2001; Sunseth & Bowers, 2002) with contributions to reading (Manis, Doi, & Bhadha, 2000; Wolf et al., 2002) whereas two have not found these relationships (Badian, 1997; Lovett, Steinbach, & Frijters, 2000), and three studies provided mixed evidence, for example when the RAN relationship with reading was found for the dyslexic group only (McBride-Chang & Manis, 1996; Pennington, Cardoso-Martins, Green, & Lefly, 2001), or was based on individual case studies (Deeney, Wolf, & Goldberg O'Rourke, 2001).

Subsequent studies have also found mixed evidence only partially supporting the DDH. Escribano (2007), in a study with Spanish dyslexic students, found that the double-deficit group and the phonological-deficit group differed from the no-deficit group in pseudoword reading accuracy. However, no significant differences in literacy measures were detected between the phonological-deficit and the double-deficit groups. In a longitudinal study with Greek-speaking children, Papadopoulos, Georgiou, & Kendeou (2009) showed that the double-deficit group performed significantly worse than the other groups on real word and pseudoword reading accuracy in grade 1. The single deficit groups also performed worse than the no-deficit group on both reading accuracy tasks in grade 1. However, by grade 2, the differences within the single-deficit groups disappeared, and only the differences between the double-deficit and the no-deficit groups remained significant, providing some evidence that the most severe deficits (double-deficit) persist. Heikkila et al. (2015), in a sample of Finnish children, found the prevalence and severity of reading disability were greatest in the double-deficit group, but the means of reading measures in the single-deficit groups were similar to those of the no-deficit group, despite the greater prevalence of reading disabilities in single-deficit groups compared to the no-deficit group. These findings support assumption (2), suggesting that double deficits in PA and RAN are more severe

than single deficits and persist over time. However, little evidence for assumption (1) has been found.

Double-deficits in adults with dyslexia

To date, only three studies have investigated the DDH in adults. In an indirect investigation of the DDH, Chiappe et al. (2002), compared 30 adults with severe dyslexia (word reading below 25th percentile) with 32 chronological age- and 31 reading-matched controls, and found weak independent contribution of RAN to word reading (6.3%) with 9.0% variance shared with phonological processing. In addition, Vukovic, Wilson, & Nash (2004) found reading rate to be a better predictor of reading comprehension than either naming speed or phonological processing in 25 university students with reading disability (reading comprehension <27th percentile). Lastly, Nelson (2015), in a study of 149 young adults (16-24 years) with dyslexia (reading and spelling <85), found RAN to be independent from phonological awareness using a confirmatory factor analysis. Although RAN had predictive value beyond phonological awareness and verbal IQ, examination of subtypes did not support the assumption that the double-deficit group performed significantly worse than both single-deficit groups. In addition, Nelson found lower prevalence of the double-deficit subtype in this large-sample study compared with those found in previous smaller-sample studies. For example, Lovett (1995) and Goldberg et al. (1998) estimated the prevalence rates of each subtype to be approximately 14-22% for phonological-deficit only, 24-29% for RAN deficit only, 49-54% for double-deficit and 8% non-impaired/unclassified. In contrast, Nelson (2015) found 23% prevalence of phonological-deficit, 24% RAN-deficit, and only 34% double deficit. More research into the DDH in adult samples of dyslexia is warranted, especially in compensated dyslexics. This is the first study to examine the DDH in compensated readers.

Questions and hypotheses

Therefore, this chapter addresses two questions:

1. What are the cognitive characteristics of the sample recruited in the current project?
2. Is there evidence to support the double-deficit theory in the present sample?

To address the first question, I have investigated group differences across all measures. In addition, I have conducted a principal component analysis (PCA) to capture the factors that explain the majority of variance within the sample, which will be used in the regression analyses in subsequent chapters of this thesis. Due to the fact that the majority of the current sample consisted of university students or those who have completed a university degree, I hypothesized that this sample would have profiles similar to the 'compensated' dyslexic readers in the previous studies.

The second question is addressed in a preliminary fashion by investigating the number of participants who could be classified as 'phonological deficit', 'RAN deficit', or 'double deficit' based on their performance on the phonological processing subdomains. Also the relationship between RAN, phonological awareness and word reading, spelling, pseudoword reading, reading comprehension and reading fluency will be explored. To support the DDH, RAN should contribute independently to measures of reading, particularly measures of fluency. Moreover, if the PCA finds two independent factors representing phonological awareness and rapid naming, this would provide additional evidence in support of this theory. Studying a high achieving population maximizes chances of finding pure cases of the different possible subtypes while minimizing the chances of studying individuals with another comorbid developmental disorder, such as specific language impairment (SLI) (Ramus et al., 2003). The DDH postulates that readers with double-deficits should be most severely impaired in decoding and fluency. Hence, these individuals are

likely to be the ones with the least potential to compensate for their difficulties and achieve academic success. Therefore, I expected to find most of the compensated readers in the current sample to be characterised by single deficits.

6.2. Methods

Participants

The participants and testing protocol are detailed in chapter 4.6.2. To summarise, 44 participants were included in these analyses: 21 adults with a current diagnosis of developmental dyslexia (mean age 23.4, age range 18-32, 10 females), and 23 skilled adult readers (mean age 23.6, age range 18-32, 12 females). All participants were monolingual speakers of English to exclude any possible confounding effects of having acquired additional languages. Participants with developmental dyslexia had been formally assessed by an educational psychologist within 5 years of testing date. All participants completed two testing sessions as part of the study: a neuropsychological assessment and a brain MRI scan. These were done either on the same day or on separate days no more than five days apart, depending on the participant's preference. All participants gave informed written consent to participate in this study. The majority of the participants were university students at or graduates from the University of London. The fact that the adults with dyslexia were selected from a university population, means that a higher level of reading achievement can be expected than in a general sample of individuals of the same age, due to the selectivity of universities. This is reflected in the dyslexic student's reading and spelling scores as seen in Table 6.1, which fall within the 'typical' range.

Neuropsychological assessment

All participants completed an extensive battery of standardised neuropsychological tests, which lasted between 2-3 hours per individual. All tests were completed on the same day. Because the majority of the current sample consisted of university students and graduates,

it was important to capture a full cognitive profile for each individual. This was especially important in the dyslexic sample, to determine whether they are indeed a high achieving population as reported by previous studies, and whether indeed they should still be classified as dyslexic.

General ability

The Wechsler Abbreviated Scale of Intelligence II (WASI-II) (Wechsler, 1999) was administered to obtain a verbal and non-verbal IQ score for each participant as well as a combined full-scale IQ. The verbal IQ consisted of the performance on two tests: vocabulary and similarities. Participants were asked to explain the meaning of words, and to explain how two words were alike. The non-verbal IQ consisted of performance on the block-design task and the matrix reasoning. The full IQ score is a composite score of both verbal and non-verbal IQ.

Literacy

Literacy skills were assessed using the untimed reading comprehension, single word, pseudoword reading, and spelling subtest from the Wechsler Individual Achievement Test-II (WIAT-II) (Wechsler, 2001). During the reading comprehension task, participants could choose to read passages of text out loud or silently. All participants except one (control) read these passages silently. Although this task was untimed, the reading time for each participant was recorded.

Core language and working memory

The Clinical Evaluation of Language Fundamentals 4 (CELF-4) (Semel, Wiig, and Secord, 2003) was administered to assess general language skills and working memory. The core language score consisted of the repeating sentences and formulating sentences subtests. Working memory consisted of a composite score of digit span forward and backward, as well as familiar sequences, a test which required participants to name familiar sequences as

quickly as they can. As such, both working memory tasks rely heavily on verbal working memory and verbal retrieval.

Phonological processing

Phonological skills were assessed using the Comprehensive Test of Phonological Processing (CTOPP) (Wagner, Torgesen, and Rashotte, 1999). Phonological processing skills are made up of three core components (Snowling, 2000): phonological awareness, phonological memory, and rapid automatized naming (RAN). The CTOPP offered a comprehensive test to assess all three components. Phonological awareness was tested using phoneme deletion and blending words. Participants were asked to repeat words with certain sounds deleted, and to form the words from a sequence of sounds respectively. Phonological memory consisted of repeating pseudowords and digit span forward. RAN consisted of naming digits and letters presented on paper.

Grammatical comprehension

Lastly, I also administered the Test for the Reception of Grammar-2 (TROG-2) (Bishop, 2003) to account for possible comorbidity with Specific Language Impairment (Bishop & Snowling, 2004). Scores below 85 (<1 SD and <16th percentile) were classified as impaired and warrant diagnosis of SLI.

Analyses

All analyses were conducted in SPSS (v21). As all participants performed above diagnostic threshold on the TROG, this was not included in any further analyses. A multiple analysis of covariance (MANCOVA), with age and gender as covariates, was conducted on the remaining measures of IQ, language, working memory, and phonological processing to determine group differences.

In order to avoid the possibility of making a false positive conclusion in group comparisons, all reported p-values for posthoc tests were adjusted using a Bonferroni correction.

Data reduction

To reduce the data and resolve issues of colinearity in the regression analyses conducted in the subsequent chapters in this thesis, a principal component analysis (PCA) was conducted to find independent composite scores. These components could also provide additional insight into which tests are the most sensitive to use in a high achieving population to determine reading impairment. In other words, how are high achieving dyslexic readers best characterised? Age, gender, and IQ scores were used as descriptive measures to characterise the current sample and were therefore omitted from the PCA. Measures included in the PCA were: working memory, phonological awareness, phonological memory, RAN, word reading, pseudoword reading, spelling, reading comprehension, and core language score.

Double deficit analyses

Additional correlation analyses were conducted to investigate the relationships between phonological awareness and RAN on literacy (word reading, pseudoword reading, spelling) and reading comprehension. The double-deficit hypothesis states that RAN is an independent contributor to reading (Wolf and Bowers, 1999). This relationship was first explored across all subjects, as the original hypothesis by Wolf and Bowers (1999) argued for the mechanisms as fundamental to reading development. In addition, the analyses were repeated for each group separately. The double-deficit hypothesis was further investigated by classifying each individual dyslexic reader's impairments in the phonological domain as 'phonological only', 'RAN only' or 'double deficit'. Using the criterion discussed in Wolf and Bowers (1999), participants were impaired if their standard score was 1 SD below the control group mean.

6.3. Results

This chapter reports the results of the behavioural session of the reading study. Results of the MRI session are reported in subsequent chapters.

Group comparisons

The groups did not differ on measures of IQ and reading comprehension ($p > 0.5$). As expected, the group with developmental dyslexia performed significantly worse on measures of word and pseudoword reading, spelling, working memory, RAN and phonological processing compared to their peers ($p < 0.001$) (table 6.1). Measures of working memory, phonological memory, word and pseudoword reading and spelling were within the 'average' range with regards to their age, but RAN score is below average and phonological awareness score is borderline average. Therefore, this sample of dyslexic readers can be considered as 'compensated' dyslexic readers. However, the dyslexic readers performed significantly worse on these measures compared to their peers, and well below the level expected based on their IQ scores.

Principal component analysis

A principal component analysis (PCA) was conducted on the 9 subtests with orthogonal rotation (varimax). The Kaiser-Meyer-Olkin measure verified the sampling adequacy for the analysis (KMO = 0.769), and the KMO values for individual subtests ranged from 0.530-0.836, above the acceptable limit of 0.5 (Field, 2009). Bartlett's test of sphericity $\chi^2(36) = 158.579$, $p < 0.001$, indicated that correlations between subtests were sufficiently large for PCA.

Table 6.1 Sample characteristics and group comparisons reported in mean scores (standard deviations). Demographic variables as well as standard scores (SS) on neuropsychological assessments for adults with and without dyslexia, including significant group differences highlighted in bold.

	Dyslexic readers (N=21)	Skilled readers (N=23)	P-value	T
	Mean (SD)	Mean (SD)		
Descriptive statistics				
Age (years)	23.4 (±4.2)	23.6 (±4.0)	0.84	0.052
Sex (males/females)	11/10	11/12	0.771	
Full scale IQ (SS)	115.4 (±9.8)	114.8 (±9.3)	0.86	0.183
Verbal IQ (SS)	111.6 (±12.5)	115.9 (±10.7)	0.24	1.703
Non-verbal IQ (SS)	114.71 (±9.8)	112.0 (±13.2)	0.48	1.258
Neuropsychological performance				
Working memory (SS)	95.1 (±12.0)	112.7 (±8.9)	<0.001	27.388
Phonological awareness (SS)	87.3 (±12.0)	104.6 (±10.8)	<0.001	20.766
Phonological memory (SS)	96.4 (±10.0)	107.3 (±10.8)	0.001	10.677
Rapid automatised naming (SS)	79.86 (±17.1)	102.4 (±10.4)	<0.001	26.695
Word reading (SS)	106.6 (±5.6)	112.7 (±3.6)	<0.001	18.770
Pseudoword reading (SS)	92.1 (±9.9)	109.7 (±7.2)	<0.001	41.163
Reading comprehension (SS)	109.7 (±8.2)	111.3 (±7.7)	0.53	0.208
Spelling (SS)	97.8 (±10.3)	118.0 (±4.6)	<0.001	63.196
CELF-4 core language (T-score) ²	10.7 (±1.8)	11.2 (±1.2)	0.35	0.356

¹Chi-square

²T-scores were used instead of standard scores, because only 2 subtests were used. T-scores are standardised around mean of 10

An initial analysis was run to obtain eigenvalues for each component in the data. Four components had eigenvalues over Jolliffe's criterion of 0.7 and in combination explained 81.19% of the variance. Table 6.2 shows the factor loadings after rotation. The component matrix loadings suggested that spelling, pseudoword reading, word reading, and phonological awareness loaded on component 1. These are the core literacy skills reported in the literature to be impaired in dyslexia. Therefore, component 1 composite score

represents a literacy composite score. Phonological memory, working memory and RAN loaded on component 2. All three tasks require the retrieval and manipulation of verbal information in short-term memory. Hence component 2 composite score represents a working memory composite. Core language and phonological awareness loaded on component 3, which represented a language composite score. Lastly, reading comprehension loaded on component 4, which formed a comprehension composite score.

The literacy and working memory components both had high reliabilities (Cronbach's alpha >0.7 for cognitive ability tests), but the core language component had relatively low reliability (Cronbach's alpha = 0.16) and Cronbach's alpha cannot be computed for a factor consisting of a single variable.

Table 6.2 Rotated (varimax) Component Matrix from the Principal Component Analysis with factor loadings (>0.4).

	Component			
	1. Literacy	2. Working memory	3. Language	4. Comprehension
Spelling	.851			
Pseudoword reading	.822			
Word reading	.812			
Phonological memory		.861		
Working memory		.790		
RAN		.636		
Core language			.853	
Phonological awareness	.498		.680	
Reading comprehension				.868
Eigenvalues	2.597	2.063	1.407	1.241
Variance explained (%)	28.85	22.92	15.63	13.78
Cronbach's α	0.82	0.74	0.16	-

Further independent t-tests comparing groups on the four composite scores, controlling for multiple comparisons ($0.05/4 = p < 0.0125$), found significant differences between groups on two composite scores: literacy ($p < 0.001$) and working memory ($p = 0.002$), with the controls being significantly better on these measures than the dyslexic readers. No significant differences between groups were found for language ($p = 0.22$) or reading comprehension ($p = 0.53$) composite scores. A boxplot of the composite scores are represented in figure 6.1. The results from the PCA analyses are largely in line with the initial group comparisons across each test separately.

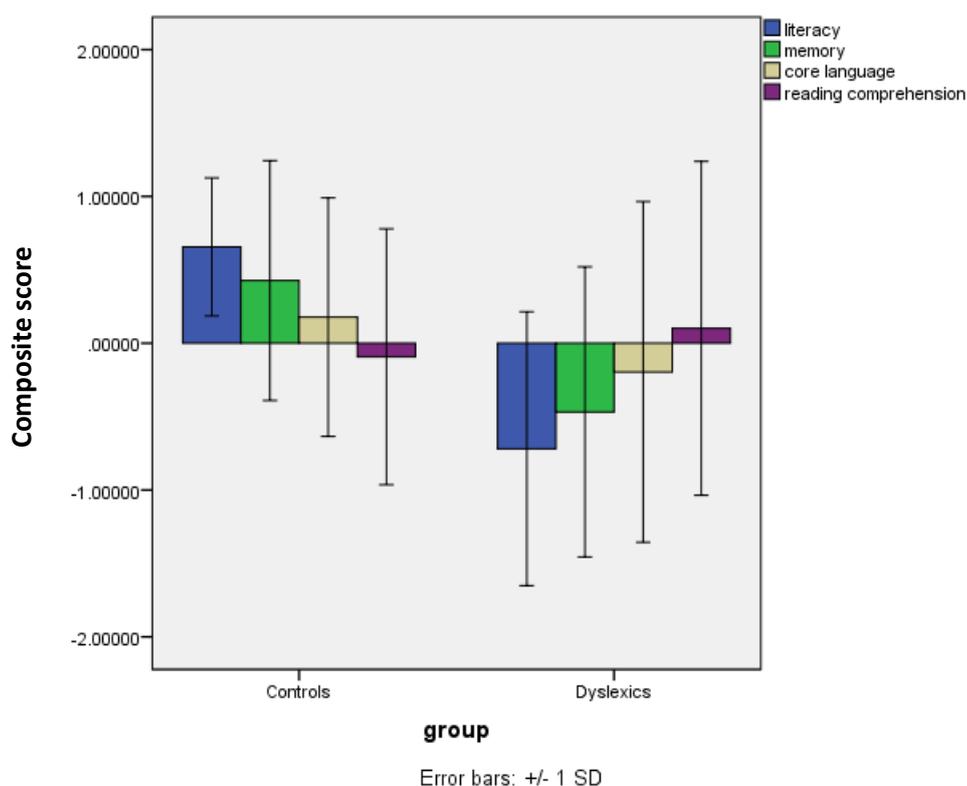


Figure 6.1. Boxplot of composite scores of the PCA within each group.

Double-deficit theory

Correlation analyses across the whole sample (table 5.3) showed a significant positive correlation between phonological awareness and RAN. Phonological awareness further correlated with word reading, pseudoword reading, and spelling. RAN correlated with

pseudoword reading and spelling. All correlations remained significant even after controlling for effects of age, gender and full scale IQ.

No significant correlations were found for either phonological awareness or RAN with reading comprehension. Reading speed was also explored as previous studies suggested RAN to influence fluency rather than accuracy (Wolf and Bowers, 1999), but no significant correlations were found. Correlations remained non-significant after controlling for group, age, and gender.

Table 6.3 Partial correlations between Phonological awareness and RAN with literacy measures.
Significant correlations highlighted in bold.

		PA	RAN
1. Word reading	r	.356	.295
	p	.023	.062
2. Pseudoword reading	r	.565	.549
	p	<.001	<.001
3. Reading comprehension	r	.089	-.01
	p	.581	.918
4. Spelling	r	.526	.473
	p	<.001	.002
5. RAN	r	.481	
	p	.001	

Investigating the relationships in each group separately yielded some surprising results. No relationships between phonological awareness and any literacy measures were found in either group separately. However, in the controls only, RAN correlated significantly with pseudoword reading ($r=0.556$, $p=0.006$) and spelling ($r=0.580$, $p=0.004$). After controlling for age, gender and IQ, these correlations do not survive correction for multiple comparisons ($p<0.0125$): pseudoword reading ($r=0.472$, $p=0.036$) and spelling ($r=0.529$, $p=0.017$).

Each individual dyslexic reader's performance on phonological tests was further classified into one of three categories: 'phonological deficit', 'naming deficit', or 'double deficit'. The classification was based on the standard score of the phonological awareness and RAN subtests of the CTOPP. Scores below 1 SD from the mean of the controls were classified as impaired (Wolf and Bowers, 1999). Using these criteria, the dyslexic group can be divided into 2 phonologically impaired (10%), 7 RAN impaired (33%), 8 double deficit (38%), and 4 non-classifiable (with deficits in word and pseudoword reading instead) (19%). The subgroups of each subtype are too small to infer valid statistical comparisons.

6.4. Discussion

This chapter explored the cognitive profiles of the adult dyslexic readers in this study. Specifically, two questions were examined. Firstly, are the adult dyslexic readers in this thesis considered compensated or non-compensated readers? Secondly, is there evidence to support the double-deficit model of dyslexia?

Are the adult dyslexic readers in this thesis considered compensated or non-compensated readers?

Although the dyslexic students did not differ in age, gender and overall cognitive ability from the comparison group, they were unable to read or spell as well as them. The dyslexic readers' literacy problems were coupled with deficits in phonological decoding, phonological processing, RAN and short-term memory. The controls achieved standard scores that were on average one standard deviation above the mean, while the dyslexic students performed only at the 'typical' level for their age, which was significantly poorer than to be expected given their IQ. Their performance was also one standard deviation below the mean of the controls. Given that the participants in this study were students in higher education, these high mean scores for the controls and the 'typical' mean scores for the dyslexics are not unexpected. These findings are in line with the findings of Pennington, Orden, Smith, Green, & Haith, (1990), Felton, Naylor, and Wood (1990), Ramus et al.

(2003), Nergard-Nilssen and Hulme (2014); Kinsbourne et al. (1992), Bruck, (1992), Kemp et al. (2009), Parrila et al. (2007), Miller-Shaul (2005), Hatcher et al. (2002), Reid et al. (2007), Law et al. (2014). In addition, the persistent low average performances on phonological awareness and RAN suggest that their core cognitive deficits of dyslexia carry on well into adulthood regardless of compensation. Therefore, I argue that that these readers should indeed be classified as ‘compensated dyslexics’. This, however, does not mean that they are not impaired.

Unlike Gottardo et al. (1997) and Kinsbourne et al. (1991), no differences were observed in reading comprehension between the dyslexics and controls, a finding also reported in Reid et al. (2007) and Ramus et al. (2003), who studied university students with dyslexia. These differences could be explained by methodological differences. Pennington and Lefly (1991) found non-compensated DYS to perform significantly worse than compensated dyslexics who performed similar to controls on a reading comprehension test. Kinsbourne et al. (1991) also found compensated readers to perform better than non-compensated readers, even though the compensated readers still performed worse than the controls. The current sample of compensated readers are more compensated than the Kinsbourne et al. sample and more similar to the Pennington and Lefly (1991), Reid et al. (2007) and Ramus et al. (2003) samples, most crucially reflected in the level of education: the latter samples, like the current sample of university students and graduates, had higher education levels than the Kinsbourne et al. (1991) sample.

A second explanatory factor is the difficulty of the reading comprehension test administered. Gottardo et al. (1997) administered a comprehension test consisting of passages drawn from high school and college textbooks. Kinsbourne et al. (1991) used both a reading aloud and a silent reading test. Both of these tests are arguably harder than the silent reading of simple passages in the WIAT-II designed for readers of 16 years and above

used in this study. Parrila et al. (2007) and Kemp et al. (2009) further found that compensated dyslexics performed worse than controls on timed reading but not untimed reading. These results suggest that compensated readers can comprehend text as well as controls if given extra time to do so.

Core impairments in compensated dyslexics

The principal component analysis further determined that the profiles of readers can be best captured in 4 independent factors, which together explained 81.18% of the variance. Variables that loaded strongly onto component 1 are word reading, pseudoword reading, spelling and phonological awareness. These are the typical literacy impairments associated with dyslexia. Moreover, these skills rely on accurate phonological awareness and decoding skills (Snowling, 2000). Variables that loaded onto component 2 are working memory, phonological memory and RAN. All three measures are based on the fast (automated) retrieval and manipulation of verbal material, which have been implicated as independent impairments above phonological ability (Paulesu et al., 1996; Trecy, Steve, & Martine, 2013), and as strong predictors of fluency (Kinsbourne et al., 1991; Ransby & Swanson, 2003).

An interesting finding here is that phonological awareness loaded strongly onto both factor 1 and 3. The importance of phonological awareness in literacy acquisition in childhood is well documented (see chapter 1), which explains the loading of PA on factor 1. The relationships between phonological awareness and the two subtests of core language in factor 3 may be somewhat less straight forward. The first subtest is the sentence recall test from the CELF, where participants are asked to recall a sentence as accurately as possible. Although the test is a primarily expressive memory recall test, participants can use semantic and syntactical cues to help them encode and recall the sentence. On the second subtest, participants are asked to form a sentence using a specific word to describe a

visually presented picture. Again, the participants can use semantic and episodic skills to help them complete this task. How are these then related to the phonological awareness tests? Although the two phonological subtests require accurate and intact phonological representations, they can also be aided by the use of orthographic or lexical information. For example, many participants used an orthographic strategy to solve the phoneme deletion test by mentally visualising the word and then deleting the letter to form the new word. Equally, participants can make educated guesses on the blending words test by guessing the closest semantically sensible word with certain sounds. Therefore, I hypothesize that component 3 reflects the shared linguistic factors in these tests. Lastly, reading comprehension is an independent factor in itself.

Group comparisons of the composite factor scores indicated that the controls and dyslexics differed significantly in factor 1 (accuracy) and factor 2 (fluency). In other words, these two composites contain the most sensitive measures to distinguish compensated dyslexics from skilled readers. These measures corroborate Hatcher et al.'s (2002) findings that pseudoword reading, spelling, short-term memory and writing speed were sensitive enough to correctly classify dyslexic readers in higher education settings. Therefore, the present findings suggest that these may be the core deficits in developmental dyslexia, which persist well into adulthood regardless of compensation status.

Is there evidence to support the double-deficit model of dyslexia?

The second aim of this chapter was to examine the DDH in a sample of compensated dyslexic adults. To date, the three papers that have examined the DDH in adult samples with severe dyslexic adults (standard performance below 85) found limited evidence to support the DDH (Chiappe et al., 2002; Vukovic, Wilson, & Nash 2004; Nelson, 2015). This is the first study to examine the DDH in compensated readers.

According to the DDH, RAN should contribute independently to measures of reading, particularly measures of fluency. Correlation analyses (table 5.4) showed a significant, strong positive correlation between phonological awareness (PA) and RAN ($r=0.482$) and both phonological awareness and RAN correlated equally strongly with pseudoword reading and spelling. Correlations with the only measure of fluency in the present data (reading speed) are not significant. Therefore, the present results contradict Wolf and Bowers (1999), who argued that correlations between PA and RAN should be weak and should contribute independently to measures of reading.

Somewhat surprising results were found when looking at correlations in each group separately. Two previous studies in children have found relationships between RAN and word reading in dyslexic readers only, not in controls (McBride-Chang et al., 1996; Pennington et al., 2001). Nelson (2015) found similar evidence in adult dyslexics; however, it is unknown whether the same relationship can be found in adult controls as Nelson did not include a control group. The group-specific results in the present work contradict all three previous studies as the only significant relationships found between RAN and pseudoword and spelling was in the controls only, which do not survive Bonferoni correction for multiple comparisons. No such relationships were present in the dyslexic group.

In addition, limited evidence for the DDH is provided by the first two independent components containing PA and RAN respectively in the PCA analysis. The fact that the two groups differed on only these two components further suggests that both play a role in reading impairment. In a sample of Dutch children with poor decoding skills, Van den Bos (1998) also found PA and RAN to load onto different factors. Nelson (2015) also found PA and RAN to load onto independent factors using confirmatory factor analysis. However, in the present study, RAN loaded onto the same factor as working memory, suggesting a

shared cognitive mechanism. This directly contradicts the original proposal by Wolf and Bowers (1999), which suggested that RAN has a direct relationship to reading and is not mediated by IQ or memory.

Lastly, a more qualitative approach was used to examine the DDH by classifying the present compensated readers into the three subtypes: 'phonological deficit', 'naming deficit', or 'double deficit'. DDH postulates that readers with double-deficits are likely to be the most severely impaired in decoding and fluency. Hence, these individuals should be the ones with the least potential to compensate for their difficulties. Therefore, I expected to find most of the compensated readers in the current sample to be characterised by single deficits. Using an impairment criteria of 1 SD below the control mean (Wolf and Bowers, 1999), the dyslexic group can be divided into 10% phonologically impaired, 33% RAN impaired, 38% double deficit, and 19% unclassified (with deficits in word and pseudoword reading instead). Hence, the present sample of compensated dyslexics contains a surprisingly large proportion of double-deficit dyslexics, which should arguably be least likely to compensate. Instead, the prevalence found in the present study is in line with those found previously in severely dyslexic children and adults: 14-24% for phonological-deficit only, 24-29% for RAN deficit only, 34-54% for double-deficit and 8-19% non-impaired/unclassified. The present results do not support the severity hypothesis of the DDH.

6.5. Conclusion

In conclusion, this chapter found that the dyslexic adults recruited for the study presented in this thesis showed persistent difficulties in decoding, phonological processes, working memory, and RAN, despite performing in the 'typical' range. Therefore, the dyslexic adults can be considered 'compensated' dyslexic readers with persistent difficulties. PCA has identified two out of four independent components which differ significantly between the

groups. The relationship between the composite scores on these two factors and MRI measures will be explored in regression analyses in the subsequent chapters. Lastly, limited evidence was found for the double-deficit hypothesis in the present sample.

7. Functional and structural connectivity in compensated adults with dyslexia

7.1. Introduction

As discussed in chapter 2, reading draws upon many distributed regions in the brain (e.g. Turkeltaub et al., 2003; Vigneau et al., 2006, Schlaggar & McCandliss, 2007; Price, 2012), and developmental dyslexia has been hypothesized to be a disconnection syndrome (e.g. Paulesu et al., 1996; Horwitz, Rumsey, & Donohue, 1998; Shaywitz et al., 2002; van der Mark et al., 2011; Boets et al., 2013; Hosseini et al., 2013) – i.e. it is characterised by abnormal connectivity patterns in the brain. Few studies have investigated how functional connectivity patterns and structural connectivity relate to reading outcome. This study examines the relationship between reading performance and functional and structural connectivity patterns within the reading network in adult skilled readers and compensated dyslexic readers, using task-based fMRI, resting-state fMRI and diffusion MRI and tractography.

Developmental dyslexia is characterised by persistent difficulties with reading which cannot be attributed to low IQ, poor reading instruction or any sensory deficits (Peterson & Pennington, 2012; Ramus, 2004). As learning to read relies upon learning and correctly applying phoneme-grapheme correspondence rules, dyslexia can be characterised as a core phonological deficit (Snowling, 1998). The phonological processing deficit theory of dyslexia has been tested in the majority of existing neuroimaging studies of reading and dyslexia. However, more recent neuroimaging studies present evidence to suggest that reading deficits arise from abnormal activation and connectivity patterns within a network of regions in the left hemisphere (see chapter 2), thus characterising dyslexia as a disconnection syndrome.

Neuroimaging studies of adults and children with developmental dyslexia show marked differences within a left hemisphere reading network of the left inferior frontal gyrus, the left temporo-parietal junction, and the left ventral occipito-temporal junction (the putative Visual Word Form Area in the left fusiform gyrus (Cohen et al., 2000)) (e.g. Richlan, Kronbichler, & Wimmer, 2009, 2011). Dyslexic readers have been found to show reduced activation in these areas (e.g. Richlan et al., 2009, 2011), as well as reduced white matter properties underlying these regions, most consistently in the left arcuate fasciculus (e.g. Ben-Shachar et al., 2007; Vandermosten et al., 2012; Boets et al., 2013). These findings suggest that the development of skilled reading relies on interactions between brain regions integrating information from different modalities into coherent percept (Schlaggar & McCandliss, 2007; Blomert, 2011; Richlan, 2014). Brain regions that are partially active at the onset of reading acquisition become more strongly connected over time with reading experience and print exposure, relying on the strengthening of audiovisual integration regions (Blomert, 2011). This integration deficit of dyslexia was first suggested by Blomert and colleagues in a series of studies investigating the integration of letters and sounds in successful and failing reading development, but has received little further investigation (Atteveldt et al., 2004; Atteveldt et al., 2009; Blau et al., 2009; Blomert, 2011).

Furthermore, often overlooked is the fact that to date, the overwhelming majority of brain imaging studies have included adults and children with severe dyslexia. The characteristics of compensated dyslexic readers have been discussed in the previous chapter. In short, compensated dyslexic adults may perform within the 'typical' range of standardised tests of reading accuracy, but struggle with persistent difficulties in speeded reading tasks and phonological processing tasks such as phonological awareness, RAN and verbal memory. There is no single measure of the severity of impairment in dyslexia, although individuals who achieve a standard score below 85 on measures of single word reading or pseudoword reading would generally be considered severe, whereas individuals who achieve a standard

score of 90 or above could be considered 'compensated' even if they score significantly below age- and/or education-matched controls.

Few brain imaging studies have studied compensated adult dyslexics. However, the available imaging studies agree with the message found in the neuropsychology literature (and the conclusion from the previous chapter of this thesis): even though they are called 'compensated', adult compensated dyslexics show persistent impairments in literacy, and persistent abnormalities in the brain. For example, Ilingworth and Bishop (2009) found reduced left lateralisation of functional activation in compensated dyslexic adults compared to controls using transcranial Doppler ultrasound during a word generation task cued by the visual presentation of a letter (i.e. 'think of as many words as you can that start with the letter *k*'). This reduced lateralisation could not be attributed to the dyslexics' poorer performance on the task or the larger number of right-lateralised individuals in the dyslexic group. This finding was partly replicated by Hernandez et al. (2013) who found a lack of left lateralisation of functional activation in the left FFG (BA37), left superior occipital gyrus (BA17), left IFG (Opercularis, BA44), left angular gyrus (BA39) in 15 male adult compensated dyslexics compared to controls during a fMRI rhyme judgement task. However, functional left lateralisation in the dyslexics was found in left precentral gyrus (BA6) and left IFG (Triangularis, BA 45).

Paulescu et al. (1996) used PET during an English rhyme judgement task and found a lack of activation in the left insula in five male adult compensated dyslexics compared to controls during a rhyming task, hypothesizing that dyslexia is a disconnection syndrome caused by inactivity of the left insula. Ingvar et al. (2002) also using PET but during covert and overt reading of Swedish real words and pseudowords, found increased activation in right medial prefrontal cortex (BA10), the right globus pallidus, and the right perisylvian cortex (BA 47, 40, and 22) during reading aloud real words in nine male compensated dyslexics, which were not found to be activated in the nine male controls. In addition, dyslexics showed

reduced activation of the right globus pallidus during pseudoword reading compared to real word reading as well as reduced activation of the left insula, left dorsolateral prefrontal cortex (BA46) and left middle occipital gyrus (BA19) during real word reading compared to pseudoword reading. Of particular interest to the current study are the differences found in the silent word reading condition compared to rest, reported by Ingvar et al. (2002), as the current study also employed a covert (silent) single word reading paradigm. During silent word reading compared to rest, the dyslexics showed reduced activation in right orbitofrontal cortex (BA10) and right angular gyrus (BA39) as well as increased activation of the right FFG (BA37) and left insula.

Although the two PET studies reported similar sample characteristics (all male, right-handed, sample size 5-9), the results of the two studies seem at odds with one another, with Paulescu et al. (1996) reporting a lack of activation in the left insula, while Ingvar et al. (2002) reported an increase in activation in the same region. One explanation for the difference could be the difference in task used: Paulescu studied activation during a rhyme judgement task, a more demanding task with regards to verbal working memory, whereas Ingvar used a covert and overt single word reading task with little demands on verbal working memory. Another difference between the studies is the language used. English (Paulescu et al., 1996) is a more orthographically opaque language than Swedish (Ingvar et al., 2002).

Using fMRI, Brambati et al. (2006) studied 13 familial dyslexics (age 13-63) and found reduced activation in left IFG (BA45), left posterior STG (BA22), left FFG (BA37), right middle frontal gyrus (BA10), and right cerebellum in the group of mixed compensated and severe dyslexics compared to controls. The main limitation of this study is that both compensated and severe dyslexics were pooled together and spanned a large age range, including potential confounds of age and compensation. This issue was partly resolved by Shaywitz et al. (2003), who studied three groups of readers: 1) persistently poor readers, who had

impairments in both accuracy and fluency (PPR); 2) accuracy improved (compensated) readers, who were accurate but dysfluent readers (AIR); and 3) nonimpaired readers (controls) (NI). During a nonword rhyming task, both AIR and PPR demonstrated reduced activation in the left posterior STG/STS compared to NI. Compared to PPR, AIR had increased activation in left anterior cingulate and right superior frontal gyrus and right MTG. During a semantic category judgement task, AIR demonstrated reduced activation in the left STG and left MTG compared to NI, whereas PPR demonstrated increased activation in the bilateral middle occipital gyrus and left inferior occipital gyrus compared to NI. Compared to AIR, PPR had increased activation in left MTG, left middle occipital gyrus and left inferior occipital gyrus. Further seed-voxel functional connectivity analyses found that NI readers demonstrated connectivity between the left occipitotemporal seed region in the left posterior middle temporal gyrus (BA 21) and the left inferior frontal gyrus. In contrast, PPR participants demonstrated functional connectivity between the same seed region and right middle and inferior frontal gyri. AIR showed FC between the same seed region and right lingual gyrus and left superior frontal gyrus, a region that is often associated with working memory and memory retrieval suggesting that in the persistently poor readers the occipitotemporal area functions as a component of a memory network. These results suggested persistent impairments in left posterior STG/MTG in dyslexia, with left anterior cingulate and right superior frontal gyrus and right middle temporal gyrus as possible regions used in compensation. Unfortunately, the authors failed to provide coordinates of local activation maxima, making it hard to compare the anatomical locations to other studies.

To study mechanisms of compensation more directly, Eden et al. (2004) used fMRI to investigate a phonological intervention in 19 adults with persistent severe dyslexia. Before intervention, the dyslexic group displayed reduced activation in left SMG/AG (BA40/39) and left SPL (BA7) during a sublexical sound deletion task compared to controls. Nine dyslexics

then received 112 hours of structured phonological intervention, and subsequently showed increased activation in left FFG (BA37), right IFG (45/46), and right SPL (BA7) as well as decreased activation in left middle occipital gyrus (BA19) compared to the ten dyslexics who did not receive such intervention. These findings suggest improvement through compensation (recruitment of right hemisphere regions) rather than normalisation (e.g. by increasing activation levels in regions found before intervention).

More recently, Schurz et al. (2014) analysed seed-voxel connectivity in task-based and resting-state fMRI in a small sample of 15 male compensated (accurate but dysfluent) German dyslexic adolescents and young adults (16-20) and 14 age-matched controls. Their study found FC differences which were consistently present in both task-based as well as resting-state. More specifically, they found reduced FC between left posterior areas (fusiform (BA37), inferior temporal (BA20), superior temporal (BA22)) and the left IFG (opercularis, BA 44) in the dyslexics compared to controls, and increased FC between the posterior areas and precuneus (BA31) and between the left IFG (opercularis, BA 44) and bilateral angular gyrus (BA39) in the dyslexics compared to controls.

Although the existing literature differed in methodology and results, there seems to be some consensus in very broad lines: dyslexic adults, regardless of compensation status, show impairments (reduced activation and reduced FC) in left IFG and FFG, with some evidence of possible compensation mechanisms in the right hemisphere (right FFG, right IFG, right AG, precuneus, right SPL). In addition, the previous chapter highlighted persistent deficits in compensated dyslexics particularly in phonological processing, working memory and pseudoword reading.

The current chapter combines task-based fMRI, resting-state fMRI, and probabilistic tractography to study functional and structural differences in the reading network of adult compensated readers with dyslexia. These techniques provide complementary information

to study the functional and structural networks involved in reading disability. Task-based fMRI provides functional topological maps of the reading network by highlighting the regions activated by the demands of the task, whereas resting-state fMRI provides information about the synchrony of regions within the network at rest, also referred to as intrinsic functional connectivity. White matter tractography further investigates the underlying white matter pathways between functional regions. No such study has been reported previously in the literature of compensated dyslexia. Therefore, the present study is the first to provide a holistic overview of the functional and structural abnormalities associated with adult compensated readers with dyslexia.

I hypothesized that, relative to matched peers, compensated individuals with dyslexia would show:

- (i) reduced activation in the reading network, especially during pseudoword reading,
- (ii) reduced functional coupling within the reading network, particularly between left FFG and left IFG,
- (iii) decreased FA in the white matter pathway underlying the functional deficits,
- and (iv) that these differences would reflect their levels of reading performance.

7.2. Materials and methods

Participants, neuropsychological testing, MRI acquisition

We included 44 subjects in the task-based fMRI and dMRI analyses: 21 adults with a current diagnosis of developmental dyslexia (18-35 years old, 10 females), and 23 age-, and IQ-matched controls (18-35 years old, 12 females). Four participants (2 controls, 2 dyslexics) did not have complete rs-fMRI acquisition and were excluded from the RSFC analyses (see below). Further details of the recruitment procedures, MRI acquisition parameters can be

found in chapter 4 (Methods). Details of the neuropsychological assessment can be found in the previous chapter.

Functional task data preprocessing

The same preprocessing procedure was used for the task-based and resting-state fMRI data in SPM 8 (Statistical Parametric Mapping) (<http://www.fil.ion.ucl.ac.uk/spm>). Details of this procedure were as follows. The first five volumes of each run were discarded to allow for equilibrium effects. Images were spatially realigned to the first volume to correct for head movements. No individual runs had more than 3 mm maximum displacement in either X, Y, or Z translation. Each participant's images were then co-registered with the individual T1-weighted MRI and normalised to MNI space (2x2x2 mm resolution) using the unified normalisation method (Ashburner & Friston, 2005). Lastly, smoothing was applied with an 6mm isotropic FWHM Gaussian kernel.

For the task-based fMRI, first-level statistical analyses were calculated using a block design. A high-pass filter with a cutoff period of 128 sec was applied. Trials were modelled using a canonical hemodynamic response function (HRF). Individual activations between conditions were modelled as follows: words > fixation; words > symbols; pseudowords > fixation; pseudowords > symbols. The beta-values from these contrasts were then taken into second-level analyses to compare group differences across the different conditions. Direct group comparisons were conducted using two-sample t-tests. All areas of activation were reported using $p < 0.001$ uncorrected with a cluster size greater than 10 voxels ($k > 10$). Group differences were reported as significant if $p < 0.05$ family wise error (FWE) corrected at both cluster- and peak-level.

Regression analyses with cognitive components

As phonological processing is a core deficit of developmental dyslexia (Snowling, 1998), regression analyses were conducted to explore the relationship between phonological

processing and activation during the reading conditions in the scanner. Since the fMRI task has two conditions that qualify as phonologically demanding (pseudoword > fixation; pseudoword > symbols), both conditions were used in the regression analyses. A 2 (group) by 2 (PCA components) ANOVA assessed the relationships between fMRI activation and PCA 1 - literacy and PCA 2 - working memory with group. A similar ANOVA was run to assess the relationship between RSFC and the two PCA components.

Regions of interest for functional connectivity analyses

Functional connectivity was assessed between a priori defined regions and the rest of the brain (seed-voxel approach). Seeds were taken from the meta-analysis by Richlan et al. (2011) which found these regions to be consistently reported to activate during reading tasks. This study was specifically chosen as it is the most recent meta-analysis to assess activation differences between dyslexic and skilled adult readers. Spherical ROIs (8mm radius) were created around the peak coordinates reported by Richlan et al. (2011) where dyslexics showed consistent reduced activation compared to controls (fig. 7.1 and table 7.1): left inferior frontal gyrus (IFG – more specifically BA44/pars opercularis), left fusiform gyrus (FFG), and left posterior temporal gyrus (pSTG). As Richlan et al. reported Talairach coordinates, peak coordinates were first transformed into MNI space using Brett's tal2mni.m script (<http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m>).

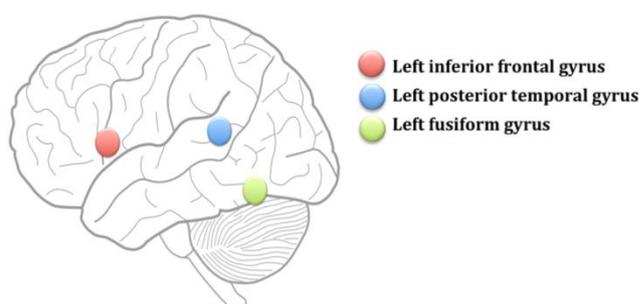


Figure 7.1 A priori defined regions of interest for seed-to-voxel resting-state functional connectivity analyses

Table 7.1 MNI coordinates for the a priori defined regions of interest for seed-to-voxel resting-state functional connectivity analyses

Region of interest	MNI of peak (x y z)
Left inferior frontal gyrus (BA44)	-52 16 16
Left posterior superior temporal gyrus (BA21)	-50 -35 5
Left fusiform gyrus (BA37)	-48 -52 -14

Resting-state functional connectivity preprocessing

Four participants' (2 dyslexic and 2 skilled readers) rs-fMRI data were excluded from resting-state functional connectivity (RSFC) analyses due to incomplete acquisition. Therefore, 38 participants were included in the RSFC analyses: 19 participants with dyslexia, 21 age-, and IQ-matched skilled readers.

The fMRI data from each subject were first preprocessed in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) as follows. Each participant's images were corrected for motion, co-registered with the individual T1-weighted MRI, and normalised to 2 mm³ resolution using unified normalization (Ashburner & Friston, 2005). Group comparison of mean movement displacement parameters show no significant differences in motion between groups ($t = 0.28693$, $df = 34.92$, $p = 0.78$).

Seed based functional connectivity analyses

Seed-to-voxel connectivity analyses were carried out in the CONN toolbox implemented in MatLab (Whitfield-Gabrieli & Nieto-Castanon, 2012). The signal fluctuations over time were averaged over all the voxels in each ROI and extracted for subsequent correlation analyses. In addition, the Artifact Detection Tools (ART) toolbox (www.nitrc.org/projects/artifact_detect) was used to assess additional motion and noise artifacts in the data, which were added into subsequent analyses as additional regressors to correct for motion artefacts (CompCor method) (Behzadi et al., 2007; Chai et al., 2012).

Lastly, a low pass filter of 0.01-0.1 Hz was applied to discard cardiovascular and respiratory noise (Chai et al., 2012). The averaged signal from each ROI was then correlated with the signal of every voxel masked in the grey matter in the brain. A threshold of $r=0.5$ was then applied, based on previous literature (Chai et al., 2012; Whitfield-Gabrieli & Nieto-Castanon, 2012). Lastly, the correlation coefficients were normalised using Fisher's r-to-z transforms. The results of these analyses are statistical parametric maps of the brain that show regions of significant correlation (thus connectivity) to the seed-ROI.

Whole-brain and small volume analyses of functional connectivity

Group-level maps of RSFC for each ROI were computed using one-sample t-tests (cluster significance $p<0.05$ uncorrected, peak-level $p<0.001$, $k>10$ uncorrected). Direct comparisons between maps were computed using independent t-tests and corrected for multiple comparisons using Gaussian Random Field Theory (cluster significance $p<0.05$ uncorrected, peak-level $p<0.001$, $k>10$ uncorrected). Furthermore, independent regression analyses were performed to assess the relations of RSFC to reading and phonological performance across both groups (cluster significance $p<0.05$ uncorrected, peak-level $p<0.001$, $k>10$ uncorrected).

In addition, small volume corrections were performed within a radius of 8 mm of the left middle temporal gyrus region found in the functional reading task. This was to assess whether functional differences found during the task could be found at rest. Significant results are reported as $p<0.05$ FWE SVC.

Diffusion data preprocessing and tractography

The dMRI data were preprocessed in MRtrix using constrained spherical deconvolution (CSD) (Tournier et al., 2007; Tournier et al., 2012). The fiber orientation distribution (FOD) is estimated by spherical deconvolution of the diffusion-weighted signal assuming that the signal measured from any fiber bundle is adequately described by a single response

function. This method has shown to provide FOD estimates that are robust to noise while preserving angular resolution and allowing tracking of crossing fibers. CSD was performed with the maximum harmonic order set to 8 (as recommended in Tournier et al. (2012), and set as default in MRtrix). Probabilistic tractography was performed based on the fibre orientations estimated via CSD (Tournier et al., 2007), combined with a probabilistic streamlines algorithm as implemented in MRtrix (Tournier et al., 2012).

Masks for tractography

Based on the functional findings, probabilistic tractography was used to explore the white matter structure underlying the left inferior frontal gyrus ROI and the left middle temporal gyrus ROI. Masks were created by drawing a sphere with 15 mm radius around the MNI coordinates of the peak. The radius of these spheres were chosen to be large on purpose to encompass grey-white matter boundaries as the functional ROIs were found in deep grey matter. Small spheres would only encompass grey matter, making tractography inaccurate. These masks were coregistered onto each individual subject's diffusion images using the inverse normalisation and coregistration functions in SPM8. Tractography was done in each individual's diffusion space.

Whole-brain tractography was run using each subject's white matter mask as seed and the whole brain as target. The maximum number of sample tracks retained was set to 100,000 using the 'maxnumber' parameter in MRtrix to ensure no bias was introduced across subjects. The generated whole-brain tractography maps were then filtered using ROI masks of the left IFG and left MTG.

7.3. Results

In-scanner task performance

The reaction times (RT) of the button presses for each condition were averaged across both runs. A 2 (groups) by 4 (conditions) mixed ANOVA revealed that there were significant

effects between conditions. Main effect of condition showed that participants were slowest reading pseudowords, words, symbols and fixation crosses, respectively ($F(3,37)=54.440$, $p<0.001$) (fig. 4.2). Although there were no main effect of group averaged across conditions ($p>0.05$), there was a significant interaction effect ($F(3,37)=3.145$, $p=0.026$). Post-hoc simple effects analyses revealed that the skilled readers read the words and pseudowords as quickly as the symbols, but all three slower than the fixation, whereas the dyslexic readers read the fixation and symbols much faster than the words and pseudowords, with no difference between the fixation and symbols. Further post-hoc independent sample t-tests revealed a trend in pseudoword reading between groups ($p=0.060$), i.e. the dyslexic groups were marginally slower at reading pseudowords.

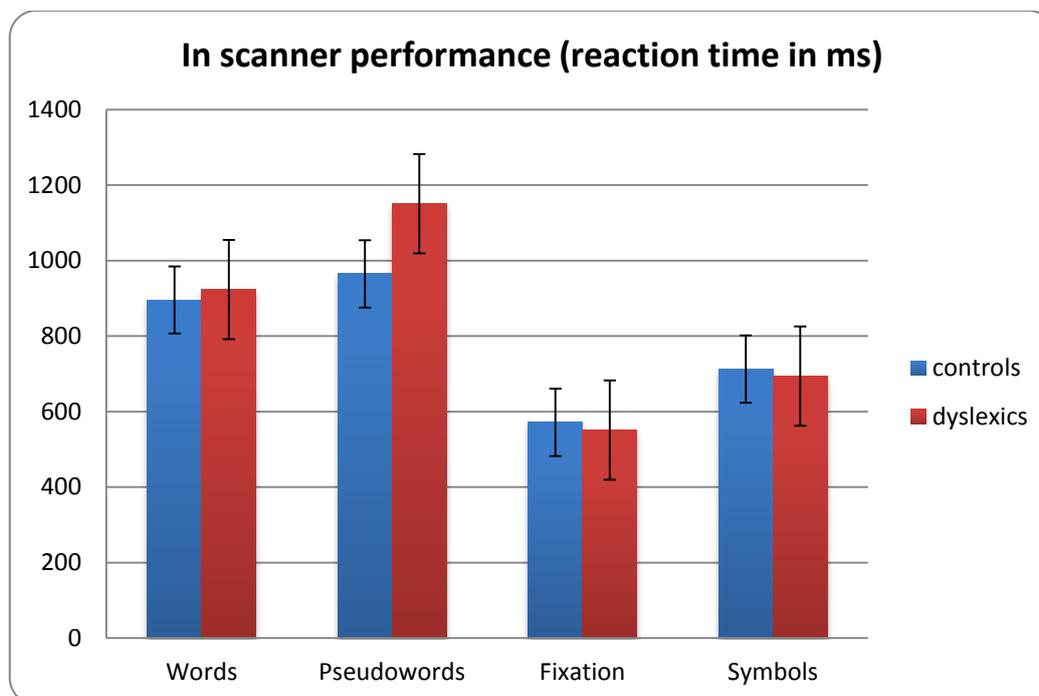


Figure 7.2 In-scanner performance on the reading task. Reaction times in ms. Error bars indicate standard error.

Reading activations

Task-based fMRI in both groups revealed a network of posterior brain regions for semantic reading conditions (words>symbols; words>fixation) and additional frontal regions for the

phonological reading conditions (pseudowords>fixation; pseudowords>symbols), which are in line with previous literature (Richlan et al., 2009, 2011). Group specific activation maps and peak coordinates can be found in figure 7.3 and table 7.2.

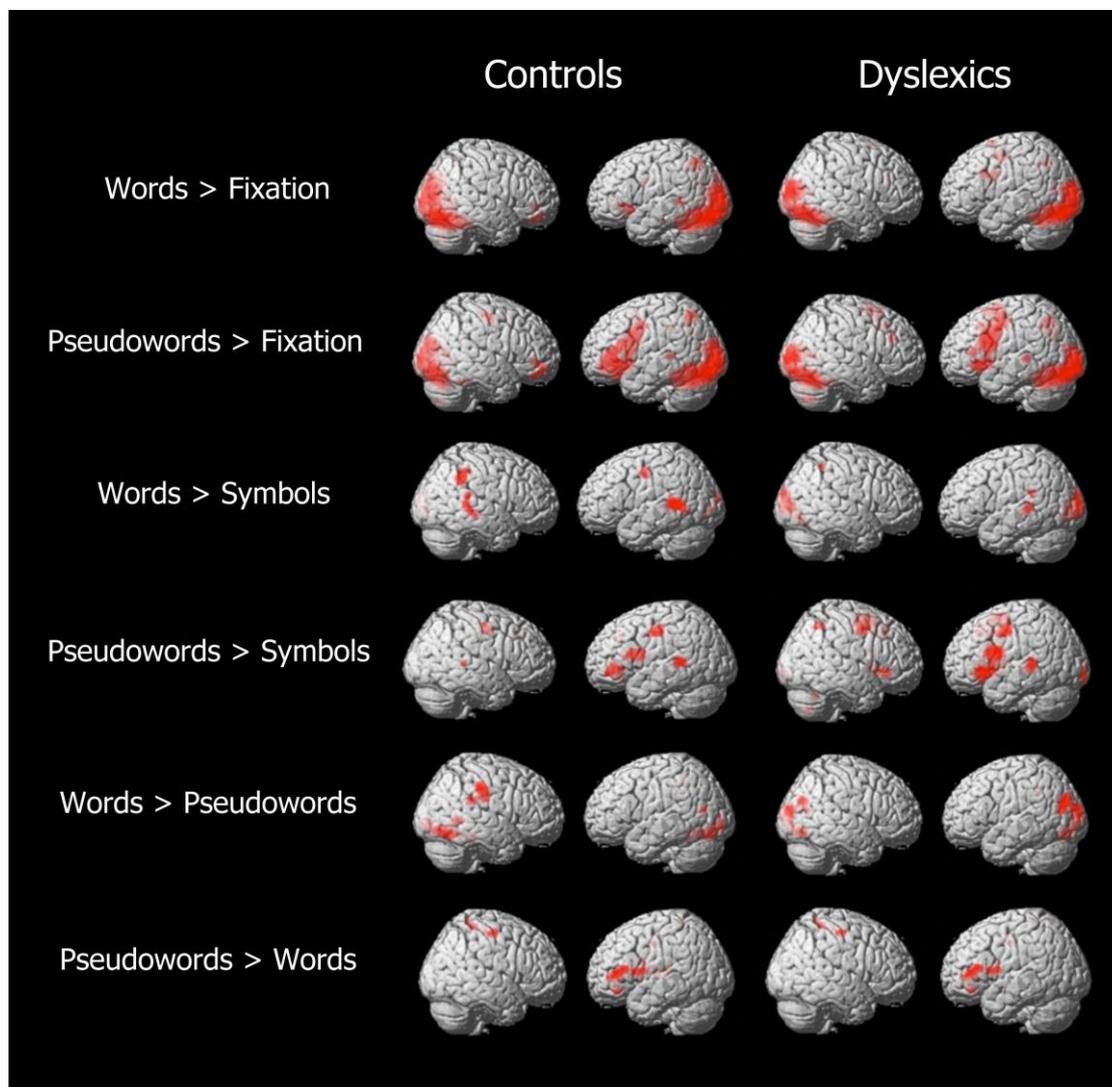


Figure 7.3 Activation maps for each group during the reading task ($p < 0.001$ uncorrected, $k > 10$)

Table 7.2 Summary of activated regions in each group during the reading task ($p < 0.001$ uncorrected, $k > 10$).

	Skilled readers		Dyslexic readers	
	Region	Peak MNI (x y z)	Region	Peak MNI (x y z)
Words > Fixation	Left visual association are (BA18)	-15 -91 -8	Left visual association are (BA18)	-15 -88 -11
	Right inferior occipital gyrus (BA19)	33 -76 -14	Right primary visual cortex (BA17)	12 -91 -5
			Left superior parietal	-21 -61 43

			cortex (BA 7) Left precentral gyrus (BA6)	-42 5 31
Pseudowords > Fixation	Left visual association are (BA18) Right primary visual cortex (BA17) Left inferior frontal gyrus (BA47) Right fusiform gyrus (BA37) Left superior parietal cortex (BA7)	-18 -85 -8 12 -94 -5 -42 35 -2 36 -43 -26 -30 -64 55	Left visual association are (BA18) Right visual association are (BA18) Left precentral gyrus (BA6) Left superior parietal cortex (BA7) Supplementary motor area (SMA) Left posterior middle temporal gyrus (BA21)	-15 -91 -11 15 -91 -11 -42 5 28 -24 -61 46 -6 2 61 -60 -34 4
Words > Symbols	Left visual association are (BA18) Left posterior fusiform gyrus (BA37) Right posterior middle temporal gyrus (BA21)	-12 -91 1 -63 -52 1 54 -34 -2	Left visual association are (BA18) Left posterior middle temporal gyrus (BA21) Right posterior middle temporal gyrus	-12 -94 1 -60 -37 7 66 -43 7
Pseudowords > Symbols	Left inferior frontal gyrus (BA47) Right primary motor cortex (BA4) Left postcentral gyrus (BA1) Left supplementary motor area (SMA) Left posterior middle temporal gyrus (BA21) Right posterior superior temporal gyrus (BA22)	-39 32-2 51 -13 52 -54 -16 43 -6 14 58 -54 -40 7 60 -37 7	Left inferior frontal gyrus (BA44) Right precentral gyrus (BA6) Left precentral gyrus (BA6) Left supplementary motor area (SMA) Left posterior middle temporal gyrus (BA21) Right cerebellum Right insula (BA13)	-54 5 22 48 5 52 -57 2 40 -3 2 61 -60 -34 7 27 -58 -29 36 26 -2
Words > Pseudowords	Left visual association are (BA18) Right visual association are (BA19) Right supramarginal gyrus (BA40)	-12 -91 -5 27 -73 -8 60 -40 25	Left visual association are (BA18) Left posterior cingulate cortex (BA 31)	-18 -91 19 -9 -52 43
Pseudowords > Words	Left inferior frontal gyrus (BA45) Right postcentral gyrus (BA1) Right insula (BA13) Left insula (BA13)	-45 32 10 27 -28 58 39 -16 22 -33 -16 4	Left supplementary motor area (SMA) Left inferior frontal gyrus (BA44) Left putamen (BA49)	-6 5 61 -48 5 19 -24 14 4

Reduced activation in the dyslexic readers compared to controls during pseudoword reading was found for two regions: left middle temporal gyrus (MTG, BA 21) (MNI: -60 -13 -

11, $p < 0.05$ FWE corrected) and the right precentral gyrus (BA 4) (MNI: 20 -28 60, $p < 0.05$ FWE corrected) (fig. 7.4. left).

Relation of activation to behavioural components

The first two components from the PCA analysis in the previous chapter were used to explore relationships between behaviour and brain activation. No significant main effects were found for group or component. No interaction effects were found at the whole-brain level, but small volume correction using the activation maps found an interaction effect at $p < 0.05$ FWE corrected at cluster-level in left MTG (MNI: -60 -13 -11, $k=12$, $Z=3.89$) for PCA1-literacy. This interaction was driven by a stronger positive correlation of the first component in the controls compared to the dyslexics (fig 7.4. right).

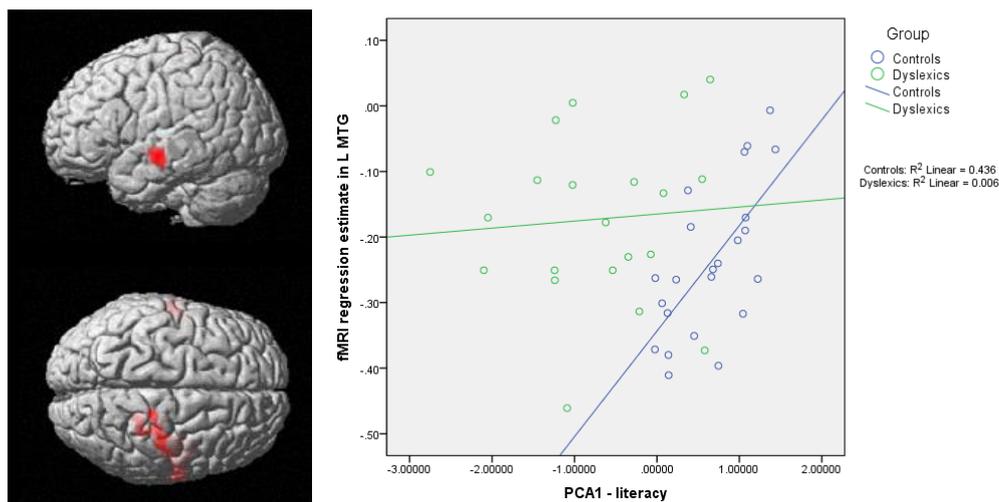


Figure 7.4 Group differences in fMRI reading task. Left) Decreased activation in the compensated dyslexics compared to controls in the left middle temporal gyrus and the right precentral gyrus during pseudoword reading compared to fixation cross. Right) Interaction effect of group and PCA-1 literacy in the left MTG (fMRI regression estimate in arbitrary units in SPM).

Functional connectivity in adult readers

Direct comparisons in RSFC (summarised in table 7.3) further indicated a difference between the adult dyslexics and controls in the left MTG (BA21) ($p < 0.05$ FWE corrected, small volume correction). Left IFG was found to have reduced functional coupling to the left MTG in the dyslexic readers compared to the controls. In addition, the left FFG seed

showed reduced RSFC to the left IFG (MNI: -54 32 -4, $p < 0.05$ FWE cluster level) in dyslexic readers than in controls. In contrast, dyslexic readers showed increased connectivity between left FFG and right somatosensory association cortex (MNI: 22 -46 60, $p < 0.001$ FWE corrected at cluster level).

The relationship of functional connectivity to PCA

A 2 (group) by 2 (PCA) ANOVA assessed the relationships between RSFC and PCA 1 - literacy and PCA 2 - working memory with group across the three seed ROIs. Main effects were found for PCA1: PCA1 was found to correlate positively with the FC between left IFG and left angular gyrus (BA 39), whereas a negative correlation was found with the FC between left FFG and left superior parietal cortex (BA7) (table 7.4). No significant relationships were found for PCA 2. No relationships were found for the left STG seed. No significant interaction effects were observed.

Table 7.3 Summary of direct comparisons of resting-state functional connectivity between skilled adult readers and adults with dyslexia for the three regions of interest: IFG - inferior frontal gyrus, FFG - fusiform gyrus, pSTG - posterior superior temporal gyrus. No regions were found for the left pSTG seed. FWE – family wise error correction, SVC – small volume correction, n.s. – not significant.

Controls > Dyslexics				Dyslexics > Controls		
	Region	Peak MNI coordinates	P	Region	Peak MNI coordinates	P
Left IFG seed	Left middle temporal gyrus (BA 21)	-60 -18 -10	$p < 0.05$ FWE SVC	-	-	n.s.
Left FFG seed	Left inferior frontal gyrus (BA 45)	-54 30 -2	$P < 0.05$ FWE	Right superior parietal cortex (BA 7)	22 -46 60	$P < 0.001$ FWE
Left pSTG seed	-	-	n.s.	-	-	n.s.

Table 7.4 Positive and negative correlations of resting-state functional connectivity measures and PCA across both groups. FWE – family wise error rate correction, n.s. – not significant.

Left inferior frontal gyrus seed				Left fusiform gyrus seed		
	Region	MNI	P	Region	MNI	P
Positive correlations						
PCA 1	Left angular gyrus (BA 39)	-60 -62 14	<0.001 FWE	-	-	n.s.
PCA 2	-	-	n.s.	-	-	n.s.
Negative correlations						
PCA 1	-	-	n.s.	Left superior parietal cortex (BA 7)	-14 -58 72	<0.05 FWE
PCA 2	-	-	n.s.	-	-	n.s.

White matter tractography results

Probabilistic tractography found the left arcuate fasciculus (AF) as the main white matter pathway between left inferior frontal gyrus and left middle temporal gyrus. The AF was found for all subjects, except for two (one control, one dyslexic reader) (fig. 7.5), where the tractography algorithm failed to find more than 50 streamlines (a priori defined cut-off). No group differences were found for number of streamlines, voxel count, or FA between groups.

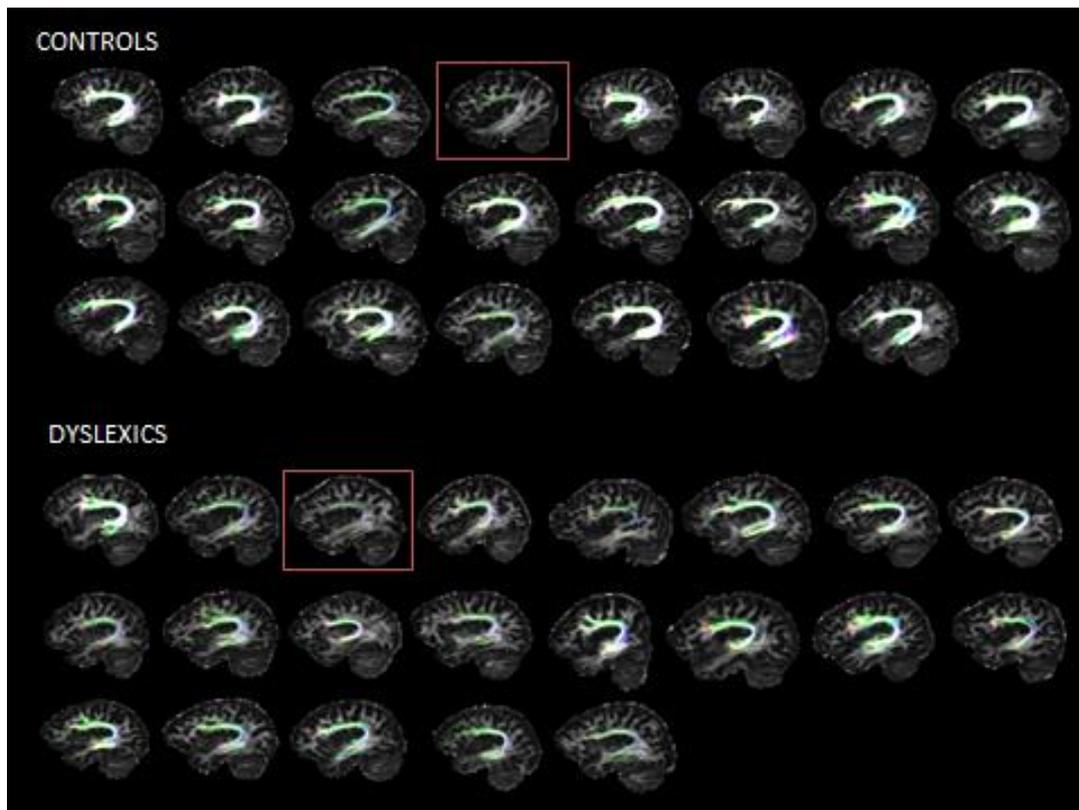


Figure 7.5 Arcuate fasciculi(AF) in all participants. The AF with red outlines represent the participants for which less than 50 streamlines were found in the AF.

Partial correlation analyses found significant negative correlations between FA in the AF and working memory (PCA2) ($r=-0.413$, $p=0.009$), and a positive trend with literacy (PCA1) ($r=0.287$, $p=0.077$) after controlling for age, IQ and group (fig 7.6). No significant correlations were found with number of streamlines or voxel count.

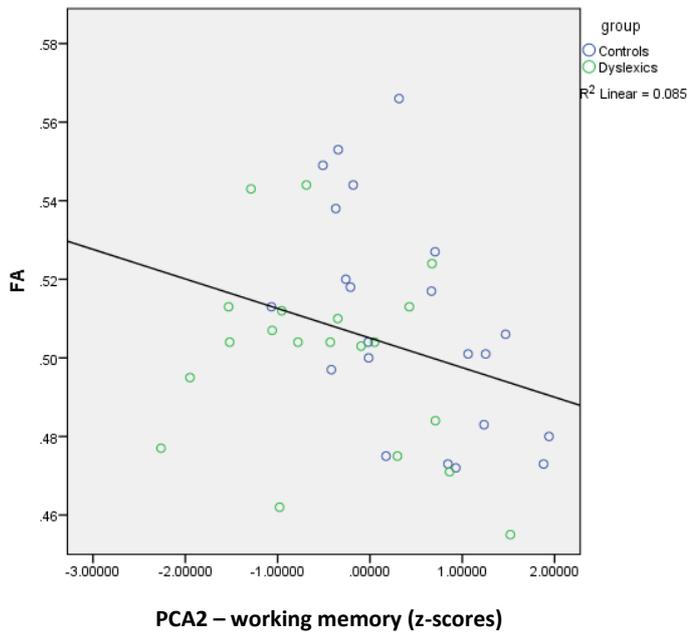
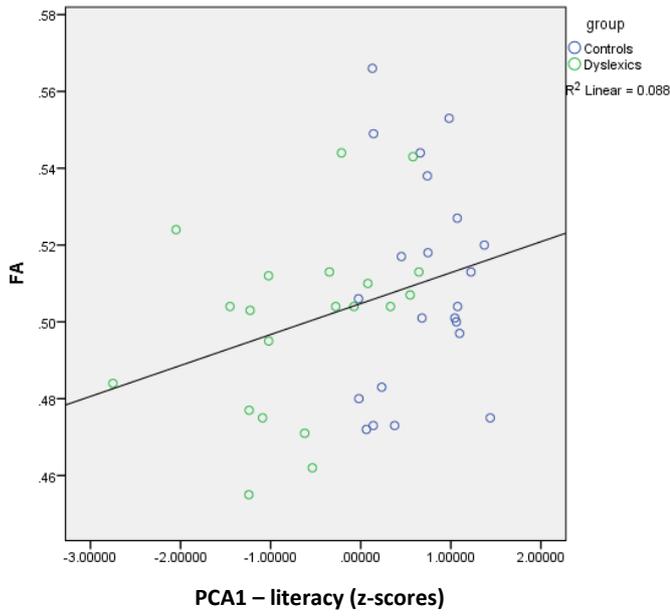


Figure 7.6 Fractional anisotropy (FA) showed a positive trend with literacy (top) and a significant negative correlation with working memory (bottom) after controlling for age, IQ, and group.

7.4. Discussion

Combining task-based activation, functional connectivity at rest and probabilistic tractography, this study provides converging evidence for the characterisation of developmental dyslexia as a connectivity deficit in the brain. Although the same network of regions is implicated during reading in both skilled and dyslexic readers, dyslexic readers showed specific differences in functional activation and connectivity.

Main finding: reduced functional activation and connectivity to left MTG

As expected, the compensated dyslexic readers showed subtle persistent difficulties, specifically with pseudoword reading as evidenced by the trend of longer RT during the pseudoword conditions of the fMRI reading task ($p=0.06$).

In addition, the compensated dyslexics showed significantly reduced activation in the left middle temporal gyrus (MTG) compared to the controls during pseudoword reading in the scanner. Direct comparisons in RSFC in a priori defined reading-related regions between adults with and without dyslexia further showed a difference in the left MTG. Specifically, the left MTG was less strongly connected to the left IFG seed in the dyslexic readers compared to the skilled readers. The left IFG has been consistently demonstrated to support phonological and hierarchical syntactical processing (Friederici, 2011; Price, 2012) and is part of the dorsal graphophonological route of reading (Jobard et al., 2003).

Lastly, probabilistic tractography found the left MTG to be connected to left IFG via the arcuate fasciculus, which constitutes the dorsal phonological route of reading. These findings from multiple modalities suggest that compensated dyslexic readers have persistent brain abnormalities, specifically in the dorsal route of reading, despite compensation status.

The left MTG has been found to support phonological aspects of speech processing (Friederici, 2011; Hickok & Poeppel, 2004) and activation during implicit word and

pseudoword reading in this region has been found to correlate with the development of reading ability in children (Turkeltaub et al., 2003, MNI -51 -12 -11). Previous functional and structural studies (Binney et al., 2012; Blau et al., 2009; Blomert, 2011; Boets et al., 2013; Turken & Dronkers, 2011) reported the left MTG as a multimodal 'integration centre' of unimodal sensory information (e.g. visual and auditory). Blomert and colleagues found the left temporal cortex (specifically superior temporal sulcus) to be the centre of orthographic-phonological binding in both skilled and poor readers (Atteveldt et al., 2004, 2009; Blau et al., 2009; Blomert, 2011). Diffusion-weighted tractography (deterministic in Turken and Dronkers (2011), probabilistic in Binney et al. (2012)) showed that the left MTG has direct anatomical connections to the left frontal regions (BA44/Pars Opercularis and BA46/9/dorsolateral prefrontal cortex) via the arcuate fasciculus (also found in the present study) and extreme capsule tracts; to parietal language regions (BA39/angular gyrus and BA40/supramarginal gyrus) via the middle longitudinal fasciculus and posterior segment of the arcuate fasciculus; as well as to posterior occipital regions via the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. A recent neuroimaging meta-analysis found that phonological processing of speech (phonemes and words) is located in mid and anterior STG (pseudoword stimuli: MNI -59 -8 -1; word stimuli: MNI -62 -10 -7) (DeWitt and Rauschecker 2012).

The left MTG found in the present study shows large overlaps with the left MTG outlined in the functional and structural studies outlined above. The reduced activation and reduced connectivity found in the present functional analyses suggest reduced or inefficient information transfer between frontal phonological regions and temporal integration regions. These findings provide support for the disconnection hypothesis of dyslexia, that the reading deficit in the dyslexic readers might reflect an integration/connectivity deficit within the dorsal route of reading. Inefficient integration of auditory and visual stimuli can lead to impoverished phonological representations and impoverished grapheme-phoneme

correspondences, which lead to the core phonological deficits observed in developmental dyslexia (Blau et al., 2009; Blomert, 2011; Boets et al., 2013). As such, the phonological deficit and integration deficit hypothesis do not have to be mutually exclusive. On the contrary, the two theories are complementary as they provide a cognitive (phonological theory) as well as a neurobiological (integration deficit/connectivity theory) explanation. In line with this hypothesis, Boets et al. (2013) found that phonetic representations of speech sounds were intact in adult dyslexic readers, and were stored in primary and secondary auditory cortices. Similar to the present study, the authors found reduced functional and structural connectivity with the left IFG in the dyslexic adults, suggestive of impaired access to retrieve stored phonetic codes rather than impaired phonological representations *per se*.

However, in a fMRI intervention study, Heim et al. (2014) found the left MTG (-48 -16 -2) to be more strongly activated during single word overt reading in dyslexic children who have received attention intervention compared to dyslexic children who have either received phonology-based or reading-based intervention. The authors proposed that the increase might reflect a 'right ear advantage': better sound discrimination in the right ear due to stronger functional lateralisation of language in the left hemisphere (Heim et al., 2014), which may be linked to attention via the influence of top-down processes such as orienting of attention. However, the authors cautioned that this is a tentative hypothesis and requires further investigation. Moreover, the majority of the participants who received the attention training (5 out of 7) received such training in the context of systematic scanning of word fragments. As such, any secondary/spill-over effects from the additional word exposure cannot be excluded.

Secondary findings: Divergent RSFC of L FFG in controls and dyslexics

Reduced L FFG – L IFG FC in dyslexia

The RSFC between the left FFG and left IFG (Pars Triangularis) was reduced in the compensated dyslexics compared to controls. This region in the left FFG (MNI -48 -52 -14), close to the putative Visual Word Form Area (MNI -42 -57 -15, Cohen et al., 2000), is implicated in visual word form recognition and processing (McCandliss et al., 2003). These findings are consistent with previous studies. Koyama et al. (2011) found significant positive correlation between the L FFG - L IFG FC with reading competence in healthy adults, but not in children. This suggests that stronger L FFG – L IFG FC is beneficial for reading in adults. FC studies during task (Shaywitz et al. 2003; van der Mark et al. 2011) have found reduced FC between the left occipito-temporal areas and the left IFG in dyslexic individuals. Finn et al., 2013 using an unbiased whole-brain parcellation method, further found reduced connectivity between the left FFG and the left IFG. More recently, Schurz et al. (2014) found consistent reduced FC between left FFG and left IFG in dyslexic young adults compared to controls across two tasks and at rest, suggesting a permanent nature of the disconnectivity. Schurz et al. (2014) further found that FC between the left FFG and the left IFG showed correlations with reading fluency as well as RAN. McCrory et al. (2005) found that dyslexic readers exhibited reduced local brain activation in the occipito-temporal cortex not only for word reading but also for picture naming. These findings suggest an impairment of a more general function of the left occipito-temporal cortex, such as the integration between visual and verbal information (Price and Devlin, 2011).

Increased FC L FFG – R SPL in dyslexia

Although task-based fMRI did not indicate regions of increased activation in dyslexic adults compared to controls, RSFC indicated increased functional coupling between left FFG and somatosensory area BA 7 in the right superior parietal cortex. This could reflect a compensatory mechanism in the compensated dyslexic readers.

The superior parietal cortex has been implicated in sequential (letter-by-letter) reading (Braet & Humphreys, 2006; Vidyasagar, 2013), visual attention (Behrmann, Geng, & Shomstein, 2004; Han et al., 2004), and working memory (Wager, Jonides, & Reading, 2004). Although the exact nature of the over-connectivity remains unclear, the dyslexic readers may have relied more strongly on visual attention, working memory and sequential letter-by-letter reading strategies, reflecting more effortful processing during the more challenging pseudoword conditions. This hypothesis is especially attractive considering the high levels of reading in the present dyslexic sample. It is likely that this high performing group would have developed compensatory mechanisms to help them read for academic attainment.

In line with the hypothesis of compensation mechanisms, one previous intervention study in adults with persistent severe dyslexia (Eden et al., 2004) found increased activation in right SPL (BA7) in dyslexic adults who have received 112 hours of phonological intervention compared to the dyslexic adults who did not receive such intervention. Similarly, an intervention study in children (Heim et al., 2014) found increased activation in bilateral SPL (BA 5/7) for children with dyslexia who have received phonological and general literacy training compared to dyslexic children who have received attention training. The authors suggested that the increased activation might reflect improved processing of graphemes and phonemes in word strings.

Other findings:

Relationships with reading performance

Positive trends were observed between activation in left MTG and the FA of the arcuate fasciculus with literacy (PCA 1), suggesting that both regions may serve an important role during skilful reading. The roles of both structures have been discussed above.

A significant positive correlation was also observed between literacy and the left IFG – left AG RSFC (MNI: -60 -62 14). In a previous RSFC study, Koyama et al. (2011) have found that the RSFC between left IFG (opercularis) and left STG/AG (MNI: -64 -50 8) was significantly positively correlated with word reading competence in both healthy adults and children. In contrast, Schurz et al. (2015) found significant negative correlations with reading fluency, RAN and verbal IQ and the RSFC between left IFG (opercularis) and left AG (MNI: -50 -54 50). However, these associations fell below significance after controlling for the group factor, which suggests that the negative associations were driven by the increased RSFC between left IFG and left AG in the compensated adult dyslexics compared to the controls in their study. The positive association found in the current study remained significant even after controlling for group, suggesting that stronger RSFC between left IFG and left AG have beneficial effects on reading performance, in line with Koyama's findings.

Two negative correlations were observed in this study. Firstly, working memory (PCA 2) was found to be significantly negatively correlated with the FA of the arcuate fasciculus, even with age, IQ and group membership as covariates. Secondly, a negative association was found for literacy (PCA 1) and the RSFC between left FFG and left superior parietal cortex (BA 7). Each is briefly discussed below.

The arcuate fasciculus is recognised to be an important structure in language (for review, see Friederici (2011), and has been found to be abnormal in developmental dyslexia (for review see Vandermosten et al. (2013). Lesions in the AF result in conduction aphasia, characterised by phonological, word repetition, and verbal short-term memory impairments (Damasio and Damasio, 1980; Baldo, Klostermann, & Dronkers, 2008). These skills are encompassed in the composite working memory (PCA-2) composite score in this study. In line with the current results, a recent study found a significant negative relationship between word learning (using an auditory learning task with heavy demands on working memory) and the radial diffusivity of the long segment of the left AF in healthy

right-handed adults (Lopez-Barroso et al., 2013). No significant relationships were found with FA. This relationship was specific to the left hemisphere and specific to the long segment, as no such relationships were found either with the anterior or the posterior segments nor in the three segments in the right hemisphere. Yeatman et al. (2011) found a significant negative correlation between phonological awareness and the FA of the AF in healthy children, with no significant relationships observed with phonological memory or reading. However, further analyses found that the correlation was found to be strongly driven by the 'blending phonemes' task, which has a large working memory component: participants need to hold strings of sounds with increasing lengths in working memory to make a meaningful word.

These results are in contrast to the 18 DTI studies reviewed by Vandermosten et al. (2012), six of which have included an investigation of working memory or RAN. The findings of these studies are mixed. Klingberg et al. (2000) found lower FA in the superior corona radiata in compensated adults with a childhood history of dyslexia compared to controls. A positive correlation was found with FA in this region and reading performance as well as non-verbal intelligence, raising questions about specificity of the relationship between FA of this region and reading skill per se. However, multiple regression analyses demonstrated that FA in this region accounted for at least some unique variance in reading skill beyond the variance shared with IQ. Similarly, Deutsch et al. (2005) found a significant positive correlation with reading ability, spelling and RAN and FA in the left superior corona radiata in seven children with dyslexia and seven age-matched controls. Niogi and McCandliss (2006) found verbal short-term memory (measured by digit recall) to correlate positively with bilateral anterior corona radiata in children with dyslexia and controls. In contrast, Carter et al. (2009) found a range of reading measures, including RAN, to correlate positively with left AF/SLF in a small sample of children with dyslexia (N=7) and controls (N=6). Lastly, Frye et al. (2008) found phonological awareness and RAN to be positively

correlated in the splenium of the corpus callosum in controls only, not in adults with dyslexia. However, this study specifically investigated the sections of the corpus callosum and did not include any other white matter structures such as the AF. It is clear that no systematic study has been conducted to date which has specifically investigated the relationships of verbal working memory and white matter microstructures in dyslexia. In addition, Schmahmann and Pandya (2006) challenge the notion that the AF is language specific. Using data from the anatomy of the macaque, the authors argue that the AF serves sound localization “but is not related to language per se” (page 408). Further research is needed on this matter.

A negative correlation was further observed for literacy (PCA 1) and the RSFC between left FFG and left superior parietal cortex (BA 7). As discussed above, possible contributions of the superior parietal cortex to reading include sequential (letter-by-letter) reading (Braet & Humphreys, 2006; Vidyasagar, 2013), visual attention (Behrmann, Geng, & Shomstein, 2004; Han et al., 2004), and working memory (Wager, Jonides, & Reading, 2004). Furthermore, one intervention study (Heim et al., 2014) in German dyslexic children found increased activation in bilateral SPL after receiving phonological and literacy training. Interestingly, this region in the left superior parietal cortex (MNI -14 -58 72) is contralateral to the right hemisphere region (MNI 22 -46 60), which was found to show increased RSFC with the left FFG in the compensated dyslexic adults, discussed earlier. Therefore, it is possible that the negative association observed in the left hemisphere may be a factor for the increased RSFC in the right hemisphere. I hypothesise the following interpretation:

In controls, the RSFC between left FFG – left SPL is not important for literacy as they can rely on the dorsal and central routes for skilled reading (Jobard et al., 2003). However, compensated dyslexics may need to rely more on measures of sequential letter processing to overcome phonological deficits, which calls upon the functional link between left FFG and left superior parietal cortex. However, if for any reason, this left lateralised link is

impaired, compensated dyslexics may be forced to capitalise on the contralateral right hemisphere instead, as found in this study and supported by the findings of one previous intervention study in adults with persistent severe dyslexia (Eden et al., 2004). Theoretically, this would be a probable hypothesis, but requires further empirical testing.

Increased activation in right motor cortex during pseudoword reading

In addition to the left MTG, skilled readers also activated right precentral gyrus (BA 4) significantly more than the compensated dyslexic adults during pseudoword reading. It is unclear what the involvement of this region in the primary motor cortex is in pseudoword reading. Hauk, Johnsrude and Pulvermuller (2004) have demonstrated with a fMRI study that reading action words provokes activation in the primary motor and premotor cortices corresponding to the 'motoric semantic' representation of the word. For example, reading the verb 'kick' elicited activation in bilateral motor regions, with overlap with regions activated when the participant moved his/her feet. These findings demonstrate an associative model of word processing in the brain, where distributed neuronal regions represent words, actions and perceptions which frequently co-occur. However, in the present study, this increased activation in right primary motor cortex was observed during pseudoword reading, which should not have elicited any semantic representations. Therefore, it is unclear what the increased activation in this region means in the current study. Future studies could examine possible semantic associations and motoric representations of pseudowords to clarify this issue.

Limitations

It should be noted that the present sample of dyslexic adults were compensated, i.e. performed within the 'typical' range on a standardised test of reading. Therefore, the present results may not be generalisable to severe dyslexic readers whose reading levels fall well below 2 SD from the mean, or to those who may have more complex profiles including the co-occurrence of other developmental disorders (e.g. SLI, attention deficit

disorder (ADD) and/or motor-coordination disorder). The protocol used in this PhD screened for comorbidities (SLI with TROG-II, AD(H)D with self-report), and found none present at the time of testing.

7.5. Conclusion

In summary, this study is the first multimodal imaging study to examine reading performance in compensated adults with dyslexia, incorporating task-based fMRI, resting-state fMRI and dMRI tractography. The results showed dysfunction specifically in the left MTG in the compensated dyslexic adults in both task-based fMRI and RSFC. Literacy was positively correlated with the activation in the left MTG during pseudoword reading, the RSFC between L IFG- L AG, and the FA in the AF. In contrast, working memory was negatively correlated with the FA in the AF and with the RSFC between left FFG and left SPL. Increased connectivity was observed in dyslexic readers to the right superior parietal cortex, which could reflect possible compensatory mechanisms. Together, these findings provide converging evidence in support of a connectivity deficit in the brains of adult dyslexics.

8. Whole-brain functional networks in dyslexia

8.1 Introduction

One limitation of defining the reading network is the dependence on a good ‘localiser’ task or ROI based on meta-analyses of tasks. Chapters 5 and 7 have shown that these a priori defined ROIs do form meaningful networks in rs-fMRI, which overlap with task-based networks. However, the increased RSFC found in dyslexic readers suggests that there may be additional regions outside the ‘conventional’ three-region reading network involved in impaired reading, especially in compensated readers. Although the RSFC in the previous chapter has identified a disconnection within regions of the reading network, the findings are biased to a certain extent due to the selection of the seed-regions which have been consistently associated with reading. It is therefore unclear whether the deficits observed in this sample are isolated (and specific) to the reading network, or whether there are more widespread disconnections in the brain as a whole.

In addition, there is controversy around the implications of sensory, visual and motor deficits observed in individuals with dyslexia. Do these deficits play a causal role in reading disability (as proposed by the auditory processing, visual magnocellular, and cerebellar deficit hypotheses) or are they merely concurrent/comorbid with dyslexia (e.g. Ramus et al., 2003, 2004)? A review of behavioural and neuroimaging findings is provided in chapter 1 and 2 and will not be repeated here. Although the literature converges on a clear phonological deficit behaviourally and neurobiologically in the left temporoparietal cortex, it should be noted that these hypotheses have been tested through specifically designed paradigms to test each hypothesis separately. In addition, if reading disability is caused by primary sensory deficits, it is plausible that these primary deficits may have cascading detrimental effects on other cognitive systems in the brain beyond the domain of reading.

This assumption is difficult to test using conventional task-based paradigms. Network based methods that are data-driven and hypothesis-free can provide additional insight.

In addition, genetic studies have identified a number of genetic loci and candidate genes related to the disorder (see chapter 2). *DCDC2*, *ROBO1*, *DYX1C1* and *KIAA0319* are among the genes identified and have been linked to processes involved in neuronal migration and establishment of cortical asymmetries early during cortical development. Therefore, it is plausible that these early genetic risk factors have manifested in deviant connectivity patterns across the whole brain. These developmental difficulties should be reflected in global dysfunctional connections that persist into adulthood.

The aim of this chapter is to study dyslexia from a hypothesis-free perspective, using whole-brain network methods. This method breaks free from the bias of using a priori seed regions specifically chosen to identify reading-related impairments. Instead, the brain is examined as a whole. For example, if deficits in dyslexia are language specific, these should be reflected in isolated deficits within language- and/or reading-specific nodes embedded in the whole-brain network. However, if dyslexia affects the brain as a whole (possibly due to cascading effects of primary sensory deficits to higher order cognitive systems or global neuronal migration deficits), these deficits should be reflected in impairments on a global level. In other words, is dyslexia a local disconnection disorder of the reading network or a global disconnection syndrome? This research question is examined in this chapter within the resting-state, whole-brain network using network based statistics and graph theory, to investigate group differences at the global and local network level. Relationships between network components and reading ability are also explored. Network based statistics (NBS) allows for identification of deviant network topology (Zalesky et al., 2010). Graph theoretical measures further quantify and compare the overall efficiency of information transfer within the whole-brain networks in non-impaired and compensated dyslexic adult readers.

Background review of FC studies

There is consistent evidence to support dyslexia as a disconnection syndrome from functional connectivity (FC) using hypothesis-driven a priori defined regions. Previous studies of FC have found consistent reduced FC in reading-related regions in participants with dyslexia (see table 8.1) and are reviewed in more detail below.

The first study published by Horwitz et al. (1998) reported disrupted FC between the left angular gyrus (AG) and posterior occipital and temporal regions in a small sample of dyslexic male adult dyslexic readers (N=17) compared to controls (N=14) during a pseudoword reading task using PET. These findings have since been replicated by Pugh et al. (2000) using fMRI during word and pseudoword reading. However, this earlier study was based on visual comparisons of group connectivity maps and did not apply direct statistical group comparisons.

Stanberry et al. (2006) and Richards and Berninger (2008) used cluster analysis during phoneme mapping to investigate the extent of FC of bilateral IFG and bilateral cerebellum in dyslexic adults (Stanberry et al., 2006) and children (Richards and Berninger, 2008). Whereas Stanberry et al. (2006) found smaller extent of both IFG and cerebellum FC maps in the dyslexic adults compared to controls, Richards and Berninger (2008) found greater FC between left IFG seen and bilateral middle frontal regions in dyslexic children compared to controls. Moreover, this increased FC was found to be normalised (i.e. reduced to similar levels of controls) after reading intervention. These contradicting results using the same procedures (the same analysis during the same task) could be caused by developmental effects, considering that one study was conducted in adults and the other in children, but the exact cause remains unknown.

Another region of interest for FC studies in dyslexia has been the so-called visual word form area (VWFA) in the left fusiform gyrus (FFG). Studies have consistently found strong FC

between the left FFG and left inferior frontal gyrus (IFG) in children and adult controls, which was either absent in dyslexic readers (Shaywitz et al., 2003; Olulade et al., 2015) or reduced in strength (Van der Mark et al., 2011; Schurz et al., 2015). Shaywitz et al. (2003) studied the FC between the left occipitotemporal area (OT) and the rest of the brain in 24 non-compensated, 19 compensated, and 27 non-impaired adult readers during a fMRI category judgement task. The authors found the left OT to be most connected to the left IFG in controls, in contrast to the right prefrontal cortex in non-compensated dyslexics, and the right lingual gyrus and superior frontal gyrus in compensated dyslexics. They concluded that the dyslexic readers rely on memory strategies to achieve reading as the right superior frontal and prefrontal regions are involved in working memory (Shaywitz et al. 2003). However, no direct group comparisons and no correlations with performance data were conducted. Furthermore, the non-compensated dyslexics had a significantly lower IQ than the other two groups which was not controlled for in the analyses.

Van der Mark et al. (2011) studied the FC of five non-overlapping seed regions within the FFG along an anterior-posterior axis during a phonological lexical decision task in children with and without dyslexia. The authors found reduced FC from the VWFA to classical left hemisphere language regions in the dyslexic children compared to controls, and increased FC between a posterior ROI in the FFG and left middle temporal, left superior temporal, left middle occipital gyrus and left insula in the dyslexic children. The decreased FC in the dyslexic children were related to performance effects in the scanner, and differences disappeared when in-scanner performance was taken into account. More recently, both Schurz et al. (2015) and Olulade et al. (2015) reported decreased FC from the left FFG to the left IFG in adults and children respectively. In addition, Horowitz-Kraus and Holland (2015) found increased FC between the left FFG and the left IFG during a lexical decision task after a 4-week reading intervention program in control children but not dyslexic children, suggesting a critical role of the connection during reading development.

In contrast, dyslexic readers have been found to show increased FC between regions in the left hemisphere reading network (left inferior parietal lobule, left IFG, left FFG) to right middle occipital gyrus (Koyama et al., 2013), right medial prefrontal gyrus (Koyama et al., 2013; Richards and Berninger, 2008; Shaywitz et al., 2003, Finn et al., 2013), left middle frontal gyrus (Zhou et al., 2015; Van der Mark et al., 2011, Richards and Berninger, 2008), and regions in the default mode network (Schurz et al., 2014; Horowitz-Kraus and Holland, 2015). These increased FC are seen over a variety of reading tasks and at rest and suggest possible compensatory mechanisms, such as increased reliance on error-monitoring (Horowitz-Kraus and Holland, 2015; Horowitz-Kraus et al., 2015). For instance, after a 4-week reading intervention programme designed to train executive functions, attention redirection and error-monitoring, Horowitz-Kraus and Holland (2015) found increased FC between left FFG (BA37) and right anterior cingulate (BA33) in dyslexic children, whereas the FC between left FFG and left IFG (pars triangularis) increased in control children after the same intervention. The increased FC in dyslexic children further correlated positively with word reading and visual attention scores.

A different analysis of the same data, using independent component analysis (ICA) (Horowitz-Kraus et al., 2015), found increased FC between the visual processing component and the language component in the dyslexic children. Correlation analyses further found a positive relationship between the gain in reading ability and the increased FC between the visual processing component and the executive function component. These findings suggests that in typical readers, increased reading training further strengthens existing connections within the language and reading network, whereas dyslexic children rely on error-monitoring mechanisms to achieve better reading outcome.

Another candidate region for compensation (in a visually-driven fashion) is the right middle occipital gyrus (BA19) (Finn et al., 2013; Koyama et al., 2013). In the only whole brain parcellation FC study in adults and children, Finn et al. (2013) found disruption of the

whole-brain connectivity within the middle occipital gyrus (BA19) in dyslexic adults and children compared to controls after regressing out task effects. Koyama et al. (2013) found increased FC at rest from left FFG to right middle occipital gyrus (BA19) in compensated children with dyslexia compared to non-compensated children with dyslexia and typically developing controls. These results suggest that the FC between left FFG and right middle occipital gyrus form an important pathway during reading development and may form the basis of a compensation mechanism through visual strategies as they are both part of the ventral visual processing stream.

However, these studies have limitations. Firstly, the majority of the studies conducted are with children, with only six studies investigating an adult sample (Horwitz et al., 1998; Pugh et al., 2000; Shaywitz et al., 2003; Stanberry et al., 2005; Finn et al., 2014; Schurz et al., 2015). Moreover, these studies in adults have included samples with severe dyslexia. Secondly, to date, only one study used a whole-brain parcellation method (Finn et al., 2013), but the authors did not examine any relationships with reading performance. Thirdly, the majority of the literature examined FC extracted from task-based paradigms, which may confound results. Time-series during tasks have been suggested to be dominated by fluctuations coupled to the processing of the task. Although regressing out task effects may control for linear confounding effects, non-linear effects may still be present in the overall brain state during task performance and may subtly affect fluctuations (Finn et al., 2013). For example, Schurz et al. (2015) found similar patterns of connectivity at rest and during two reading tasks, but note should be taken that the resting-state session was conducted after the reading tasks and that there may be some spill-over effects. Therefore, the primary aim of the present chapter is to investigate RSFC in compensated adult dyslexic readers using a whole brain parcellation method. This is done through two complementary network analysis methods: network based statistics (NBS) and graph theoretical (GT) analysis.

GT provides a unique framework to directly test differences in topological properties of brain networks. A large number of studies using GT have found alterations in topological properties of brain networks in Alzheimer's disease, schizophrenia, and epilepsy (e.g. Guye, Bettus, Bartolomei, & Cozzone, 2010; Lo, He, & Lin, 2011). For example, Supekar et al. (2008) found characteristic small-world organization in healthy adult controls using rs-fMRI, characterized by a high clustering coefficient and a low average path length. In contrast, functional brain networks in patients with Alzheimer's disease showed loss of small-world properties, characterized by a significantly lower clustering coefficient indicative of disrupted local connectivity, specifically in the left and right hippocampi compared to the control group. Using a support vector machine, the authors further showed that the clustering coefficient distinguished AD participants from the controls with a sensitivity of 72% and specificity of 78%.

In addition, Lynall et al. (2010), using rs-fMRI, found reduced clustering and reduced global small-worldness in patients with schizophrenia compared to controls, and decreased nodal degree in medial parietal, premotor and cingulate, and right orbitofrontal cortical nodes. Lastly, Ponten, Bartolomei and Stam (2007) found changes in topological properties before, during and after epileptic discharges in patients with epilepsy measured by intracerebral EEG. More specifically, the network changed from a small-world graph to a more orderly/regular graph during and after seizures with an increase of clustering and path length most prominent in the alpha, theta and delta frequency bands. These findings highlight changes in topological properties associated with distinct disease states.

GT studies on reading and dyslexia are scarce. This is surprising, especially considering the evidence from activation studies, functional connectivity studies, and effective connectivity studies that dyslexia can be characterized as a disconnection deficit.

Background review of GT studies

To date, only six studies have used GT to investigate topological differences in dyslexia, all testing children (see table 8.2). The first two studies constructed graphs using the phase lag index (Stam et al., 2007) in MEG across a range of frequencies (Dimitriadis et al., 2013; Vourkas et al., 2011). Although one study derived networks during a phoneme task (Vourkas et al., 2011) and the other during rest (Dimitriadis et al., 2013), both studies found reduced global and local efficiency across frequency bands in children with reading disabilities. Moreover, Dimitriadis and colleagues (2013) found the global efficiency in alpha and beta bands at rest to relate to the children's performance on the Woodcock Johnson word attack (Dimitriadis et al., 2013).

A study by Hosseini and colleagues (2013) investigated structural networks derived from cortical thickness and surface area measures in children with and without familial history of dyslexia, who were just starting reading instruction. In contrast to the MEG studies, no group differences were observed between groups for global network measures such as small worldness, global efficiency and local efficiency. However, when studying these measures at the nodal level (e.g. the global efficiency, degree, betweenness centrality etc for each node), children with familial history of dyslexia showed reduced topological properties in left posterior cingulate, hippocampus, and left precentral gyrus (Hosseini et al., 2013).

Two recent studies investigated global and local network properties of structural grey matter covariance networks (of grey matter volume) in Chinese children with and without dyslexia (Liu et al., 2015; Qi et al., 2015). Contrary to previous studies, Liu et al. found increased local efficiency in the grey matter volume at the global level in the dyslexic children compared to controls, as well as increased nodal properties in left precentral gyrus, but decreased nodal properties in right Heschl's gyrus. Qi et al. (2015) reported

decreased local clustering in the dyslexic network based on cortical thickness and surface area, as well as more interhemispheric connections and more frontal hubs compared to age-matched controls. It should be noted, however, that Chinese is a logographic language, and it is currently unclear whether dyslexia in non-alphabetic language have the same neurobiological underpinnings as dyslexia in alphabetic languages.

The most recent study used rs-fMRI and found increased global efficiency of the cingulo-opercular attention network in dyslexic children after a 4-week reading intervention, specifically targeted to train executive function and visual attention to improve reading (Horowitz-Kraus, Toro-Serey & DiFrancesco, 2015).

These findings highlight the importance of studying both global and regional network measures. Differences in global network properties will highlight impairments or gains across the brain, whereas regional measures will specify exactly which nodes show deviant connectivity patterns. The discrepancies in current findings may be due to sample selection (children with diagnosis or pre-reading), orthography (English or Chinese), modality (structural or functional), and node selection (channels or anatomically defined regions).

No GT studies have been published on adult samples to date. The current chapter is, therefore, a preliminary study to investigate topological differences using GT in resting-state fMRI networks and structural diffusion networks in adults with and without dyslexia. Both global and regional measures will be examined between groups, as well as relationships between both modalities and relationships with behavioural performance.

Table 8.1 Summary of existing literature investigating functional connectivity in developmental dyslexia

Year	Study	CON/DYS	Age (yr)	Seeds (MNI)	Method	Main finding(s)	Limitations
1998	Horwitz et al.	17/14 (all male)	18-40 DYS mean = 27, SD = 8 CON mean = 25, SD = 5	Bilateral angular gyri	PET data – interregional correlations during pseudoword and exception word reading	Disconnection of AG to left occipital and temporal regions in dyslexic men	<ol style="list-style-type: none"> 1. Small sample 2. All men 3. Limited to one region 4. No correlations with performance 5. No direct group comparison
2000	Pugh et al.	29/32	DYS: 16-54; CON 18-63 Mean and SD not reported	BA17 (primary visual cortex) BA18/19 medial (occipital gyrus) BA18/19 lateral (medial occipital gyrus) BA22 (posterior STG) BA39 (Angular Gyrus)	fMRI: regression analyses during pseudoword reading, semantic category, letter case judgement, and single-letter rhyming tasks	In the left hemisphere, on tasks that demand substantial phonological assembly, CON displayed robust functional connectivity, but DYS readers did not. This finding is consistent with that of Horwitz et al. (1998), who also examined word and nonword reading.	<ol style="list-style-type: none"> 1. Used regression analyses rather than simple correlations 2. No direct group comparisons, but all within group
2003	Shaywitz et al.	24 non-compensated, 19 compensated dyslexics, 27 controls	18.5 – 22.5	Left occipitotemporal area (Tal -55 -36 -5)	fMRI: pseudoword rhyming and category judgment task. FC only examined during category judgment task.	<ol style="list-style-type: none"> 1. In controls: L OT – L IFG 2. In non-compensated dyslexics: L OT – R PFC (memory network) 3. In compensated dyslexics: L OT – R lingual gyrus and L SFG 4. Conclusion: PPR rely on memory strategies for reading, rather than phonological strategies 	<ol style="list-style-type: none"> 1. Non-compensated had significantly lower IQ than both compensated dyslexics and controls as early as first grade 2. No direct group comparisons 3. No negative correlations 4. No correlations with performance
2005	Stanberry et al.	10/13 (all male)	30-45, means not reported	Right inferior frontal gyrus Left inferior frontal gyrus Bilateral cerebellum	fMRI: Cluster analysis during phoneme mapping task	Extent of FC in all seeds smaller in dyslexic adults compared to controls.	<ol style="list-style-type: none"> 1. Small sample 2. Men only 3. Only studied reduced FC in dyslexia not increased FC 4. Task specific 5. No correlation with

							performance
2008	Richards and Berninger	18/21	Children, age range not provided	Right inferior frontal gyrus Left inferior frontal gyrus Bilateral cerebellum	fMRI: Cluster analysis during phoneme mapping task	Dyslexic children showed greater FC between L IFG seed and bilateral middle frontal regions before treatment but not after treatment.	<ol style="list-style-type: none"> 1. No correlations with performance 2. Opposite pattern from Stanberry although using same task and ROIs 3. Task specific
2011	Van der Mark et al.	24/18 (mixed genders)	DYS: mean=11.4, SD=0.7 CON: mean=11.3, SD=0.4 Range not reported	five non-overlapping seeds in left VWFA (MNI cords): ROI1 (-42, -80, -14), ROI2 (-42, -68, -16), ROI3 (VWFA; -42, -54, -17), ROI4 (-42, -42, -18), ROI5 (-42, -30, -20)	fMRI: seed-to-voxel correlations during phonological lexical decision task	<ol style="list-style-type: none"> 1. Reduced FC from VWFA to classical left hemisphere language regions in dyslexia. 2. Greater FC in dyslexic children to left middle temporal, left superior temporal, left middle occipital gyrus and insula. 3. CON>DYS differences in ROI3 disappeared when performance was covaried out -> performance effect, but DYS>CON in ROI4 remained sign. 4. In controls but not dyslexics, FC between L VWFA and L IFG and L IPL correlated positively with in- and out- of scanner performance 	<ol style="list-style-type: none"> 1. Task-specific 2. Region (VWFA) specific 4. Performance related effects rather than inherent effects?
2013	Koyama et al.	11/33 (remediation subgroups of 11 each) (mixed genders)	7.7-15.7, mean = 12.2	Inferior occipital gyrus (-25 - 87 -10) Left FFG (-48 -57 -20) Left STG (-53 -31 9) Temporoparietal junction (-59 -45 15) Inferior parietal lobule (-40 -48 42) Intraparietal sulcus (-30 -58 48)	fMRI: seed-to-voxel at rest	<ol style="list-style-type: none"> 1. Weaker FC between left inferior parietal lobule to left middle frontal gyrus in all dyslexia groups. 2. Compensatory (increased) FC observed for left fusiform seed to right middle occipital gyrus (BA 19) and compensatory (decreased) right medial prefrontal gyrus (BA 33) 3. Compensation relying on more visual reading strategies 4. Stronger dissociation between 	Small sample size of each group (11)

				Precentral gyrus (-48 -12 45) Supplementary motor area (-4 10 58) Left pars opercularis (-51 10 10) Left pars triangularis (-48 32 6) Left middle frontal gyrus (-44 10 30) Left thalamus (-10 -14 8)		reading network and default mode network (strong negative FC L FFG – R MPFC/BA 33) is characteristic of typical adult readers at rest (Koyama et al. 2010)	
2013	Finn et al.	Children: 43/32 Adults: 64/40 (mixed genders)	Children: mean = 8.9 Adults: mean = 20.8	Whole brain automated parcellation method: 205 nodes in children, 207 nodes in adults	fMRI: ROI to ROI correlations after regression of task	Disruption of visual and attention areas and increased right hemisphere FC in dyslexia	1. No correlations with behaviour 2. Different number of nodes in children and adult groups
2014	Schurz et al.	11/14 (all male)	16-20, mean = 18	Left FFG (-46 -50 -16) Left ITG (-52 -62 -8) Left MTG (-60 -56 2) Left STG (-52 -44 20) Left IPL (-52 -46 44) Left IFGOp (-46 16 6)	fMRI: seed-to-voxel at rest and during two tasks	1. Reduced FC between left posterior temporal regions and left IFG in dyslexic readers 2. Increased FC between reading regions and precuneus in DMN in dyslexic readers	1. Only male dyslexics were included 2. Small sample size 3. Young adult sample 4. No investigations with reading ability
2015	Zhou et al.	26/21 (mixed genders)	Mean = 12.0	Left intraparietal sulcus (-24 -67 40) (BA 7) Left VWFA (-48 -51 -12) (BA 37)	fMRI: seed-to-voxel at rest	1. Increased RSFC in dyslexics than controls in L IPS-L MFG (-36 6 39, BA9) 2. Decreased RSFC in dyslexics in LVWFA-L MFG (-39 54 9, BA10 and -48 6 45, BA9) 3. Partial correlation L IPS-L MFG and L VWFA-L MFG with reading fluency, not lexical decision 4. Supplementary analysis found correlation between lexical decision	1. Conflicting finding of both increased and decreased RSFC in dyslexics in L MFG 2. Reading task has not been standardised

						with L VWFA-L AG	
2015	Olulade et al.	12/16 (mixed genders)	Mean = 10	Left occipitotemporal cortex (-39 -44 -24) Left IFG (-56 12 -6)	fMRI: ROI to ROI during implicit reading task	Significant FC between left VWFA and left IFG in controls, but not in dyslexic children	<ol style="list-style-type: none"> 1. Small sample size 2. Task specific connectivity 3. Results reported at $p < 0.001$ uncorrected level
2015	Horowitz-Kraus and Holland	18/18 (mixed genders)	8-12 DYS mean = 9.9, SD=1.27 CON mean = 9.68, SD=1.63	Seed: L FFG (BA37) Target ROIs: <ul style="list-style-type: none"> - anterior cingulate cortex (BA 33) - pars opercularis (BA 44) - pars triangularis (BA 45) - dorsolateral prefrontal cortex (BA 46) - inferior frontal gyrus (BA 47) - dorsal frontal cortex (BA 8) - anterior prefrontal cortex (BA 10) - ventral anterior cingulate cortex (BA 24) - dorsal anterior cingulate cortex (BA 32) 	fMRI: seed to target ROI during lexical decision task	<ol style="list-style-type: none"> 1. After intervention, FC between L FFG and R ACC (BA33) increased in dyslexic readers, suggesting better error-monitoring 2. After intervention, FC between L FFG and L pars triangularis increased in controls, suggesting increased strengthening of language/reading network 3. Greater FC correlated positively with word reading and visual attention scores 	<ol style="list-style-type: none"> 1. fMRI results reported at $p < 0.001$ uncorrected 2. Task specific 3. Very short paradigm, with only 50 data-points
2015	Horowitz et al.	18/18 (mixed genders)	8-12 DYS mean = 9.9, SD=1.27 CON mean = 9.68,	ICA components (seed): <ul style="list-style-type: none"> - Visual processing (IC1) ICA components (targets): <ul style="list-style-type: none"> - Executive function (IC2) - Attention (IC3) 	RS-fMRI (fixation cross): functional correlation between IC1 and ICs 2-8.	<ol style="list-style-type: none"> 1. Before intervention: decreased FC of IC1-IC2 (executive function) and IC1-IC3 (attention), and increased FC of IC1-IC4 (sensory-motor) in dyslexics compared to controls. 2. After intervention: increased FC of IC1-IC5 (language) in dyslexics. 	Same data set as Horowitz-Krause and Holland (2015)

			SD=1.63	<ul style="list-style-type: none"> - Sensory-motor (IC4) - Language (IC5) - Occipito-temporal (IC6) - Dorsal attention (IC7) - Memory (IC8) 		<ol style="list-style-type: none"> 3. Within-subject test reveal increased FC of IC1 to IC2 (executive function), IC6 (occipito-temporal), IC7 (dorsal attention), and IC8 (memory) in dyslexics. 4. Greater gain in reading ability correlated with increased FC of IC1 to IC2 (executive function) components. 	
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Table 8.2 Summary of graph theoretical studies of dyslexia to date

Year	Study	CON/DYS	Age	ROIs	Graph metrics	Results
2010	Vourkas et al.	15/12	Mean age 10 (range not reported)	MEG channels during phoneme task	Degree Global efficiency Local efficiency	Reduced global and local efficiency for children with reading disability in theta, alpha and gamma band
2013	Dimitriadis et al.	27/23	7-14 (mean age 11.78)	MEG channels during rest	Global efficiency Local efficiency	Decreased global efficiency across all bands in dyslexia. Global efficiency in alpha and beta bands relate to word attack performance
2013	Hosseini et al.	20 without family history of dyslexia, 22 with family history	Mean age 5.59 (range not reported)	Freesurfer parcellation of surface area and cortical thickness	Smallworldness Degree Betweenness centrality Hubs	No group differences for global network measures. Regional measures showed reduced betweenness centrality and/or degree in children with family history of dyslexia
2015	Liu et al.	25/25	7.58–10.83 (mean age 8.65)	Gray matter volume using SPM and AAL atlas	Path length Global and local efficiency at global level Betweenness centrality and degree at local level (hubs)	Increased local efficiency in Chinese dyslexic children Increased betweenness centrality in left precentral gyrus in children with dyslexia Decreased degree and betweenness centrality in right Heschl's gyrus
2015	Qiu et al.	17/17	10.25-13.08	Cortical surface area and cortical thickness and AAL atlas	Smallworld-ness Path length Clustering coefficient Degree Between-ness centrality Hubs	Lower small-worldness in the thickness network in Chinese dyslexic children More anterior and bilateral connectivity in Chinese dyslexic children Hubs in dyslexic children more in frontal lobe compared to parietal lobe in controls
2015	Horowitz-Kraus, Toro-Serey & DiFrancesco	17/15	DYS M=10.27 (1.48); CON M=9.77 (1.44)	Rs-fMRI: 9 ROIs in cingulo-opercular network and 9 ROIs in fronto-parietal network	Global efficiency	Increased global efficiency of cingulo-opercular network after training regardless of group (no group or interaction effects), driven by DYS group. No main or interaction effects in fronto-parietal network. Combined gain in Eglob across both EF networks was correlated positively with reading in DYS only.

8.2. Materials and methods

Resting-state functional connectivity

The preprocessing steps for the rs-fMRI data are the same as described in chapter 4. However, instead of seed-voxel correlations, ROI-to-ROI analyses were conducted. The ROI regions in this analysis were 84 Brodmann areas covering the whole brain (excluding the cerebellum), provided within the CONN toolbox. Subsequent ROI-to-ROI analyses were performed, where the mean time-series within each ROI region was extracted and then correlated with the mean-signal of every other ROI. These results are summarized in 84 x 84 connectivity matrices for each individual subject. The r-values were normalized to z scores using the Fischer's transformation. Second-level analyses directly compared these matrices between groups using independent sample t-tests and permutation tests, controlling for age, IQ and gender.

Network based statistics

The group-comparisons of functional connectivity matrices were done using network-based statistics (NBS) (Zalesky et al., 2010). Network-based statistics is a validated method for performing statistical analysis on large networks (Zalesky et al., 2010). The method is used to independently test the same hypothesis at each and every connection. This is a nonparametric statistical method to deal with the multiple comparisons problem on a graph and controls for the family-wise error rate (FWER) when performing mass univariate hypothesis testing on all graph edges. The set of all edges constitutes the family.

General linear models (GLM) were used to test between-group and within-subject effects. The software generated a visualization of the specific connections and networks for which the null hypothesis can be rejected. NBS takes a set of connectivity matrices as input into a

GLM model. Significance testing is done using permutation testing with the GLM (Freedman & Lane, 1983). The output is a set of connections comprising any network (i.e. graph component) that is found to show a significant effect with the corresponding p-value for each such network.

NBS methodology

The steps conducted in NBS are briefly discussed here, but a complete description is provided in Zalesky et al. (2010).

Once the connectivity matrices are defined for each participant, NBS will firstly independently test the hypothesis of interest at every connection in the network (mass univariate testing). Each connection will be endowed with a single test statistic value quantifying the evidence in favour of the null hypothesis.

Secondly, a test statistic threshold (primary threshold) is chosen (set to $p=0.05$ in this study). The connections with a test statistic exceeding this threshold are admitted to a set of supra-threshold connections. This set of connections represent candidates for which the null hypothesis, that the value of connectivity between the two populations comes from distributions with equal means, can be rejected, although statistical significance cannot yet be established at this stage.

Thirdly, topological clusters among the set of suprathresholded connections are identified. These clusters are defined in topological space, i.e. where a path can be identified between any two nodes. The critical assumption underlying NBS is that the connections for which the null hypothesis can be rejected are arranged in an interconnected configuration rather than being confined to a single connection or distributed over several connections that are in isolation of each other (which could be provided by false discovery rate - FDR).

Lastly, a FWER-corrected p-value is calculated for each graph component using permutation testing. For designs with nuisance regressors, the residuals are permuted instead of the raw data. During this step, the above three steps are repeated 5000 times. Each permutation repeats the first three steps on the permuted data. The size of the largest component is recorded for each permutation, thereby yielding an empirical null distribution for the size of the largest component size. This yields an empirical estimate of the null distribution of maximal component size. A corrected p-value for each observed component is then calculated using this null distribution. The one-sided FWE p-value for a component of a given size is then estimated as a proportion of permutations for which the largest component was of the same size or bigger. The size of a component is measured by the total number of connections, and this is referred to as component extent. Alternatively, the size can be measured as the sum of the test statistic values across all connections comprising the component, and is referred to as intensity. The extent is more sensitive to weak effects, which may be distributed over many connections, whereas intensity detects strong focal and distributed effects.

NBS and FDR

The main alternative to NBS is false discovery rate (FDR; Genovese et al., 2002), which is more sensitive to focal effects involving single, isolated connections, whereas NBS improves power to detect distributed networks spanning multiple connections. However, NBS provides the option to use intensity rather than extent to measure the size of an effect. The intensity option provides NBS with greater sensitivity to focal effects.

Whereas NBS rejects the null hypothesis at the network level while controlling for FWER, the FDR enables rejection of the null hypothesis at the level of individual connections while controlling for false discovery rate. NBS and FDR are complementary and should be seen as,

respectively, the equivalent of cluster-level and peak-level correction in task-based analyses in SPM.

Structural networks using diffusion tractography

The diffusion-weighted images (60 directions, $b=1000\text{s/mm}^2$) were pre-processed and analysed using TractoR's pipeline for creating connectivity graphs (Clayden et al., 2011). Firstly, the anatomical T1-weighted images were parcellated using the same AAL mask as in the CONN toolbox, to keep both analyses coherent. Using TractoR's `xtrack` command, probabilistic streamlines were generated, which pass through each target region of interest. The `graph-build` command was then used to construct a binary connectivity matrix, in which an edge exists between each pair of regions if there is at least one streamline connecting the pair. This binary graph was then re-weighted using the '`graph-reweight nStreamlines`' command to only keep edges where there were at least 20 streamlines between a pair of regions. This weighting was given to decrease the density of the graph and to minimise false positive edges due to low number of streamlines.

Graph analyses

The organization of the functional and structural networks was examined using graph theory (Bullmore & Bassett, 2011; Rubinov & Sporns, 2010). I was specifically interested in two aspects of the network: centrality and efficiency. Centrality allows for the investigation of possible specific core brain regions underlying dyslexia, whereas efficiency reflects the global functioning of the brain.

Centrality or the importance of a node

The relative importance of a node within the network is reflected in two measures: degree and betweenness centrality. The *degree* for a node is defined as the number of connected neighbours. *Betweenness centrality* assesses the importance of a node as a connector hub,

connecting different modules (subcomponents) within the network (Rubinov and Sporns, 2010).

Efficiency

The average shortest pathlength reflects the level of global integration in the network, i.e. the smallest number of edges to cross to get from one node to another. Global efficiency is the inverse of the average shortest path and used here as a measure of efficiency.

Statistical analyses

The graph measures of the structural matrices were calculated in TractoR using the graph-props command and extracted for group analyses in SPSS (v21). The graph measures of the functional matrices were calculated in CONN, where the group analyses were conducted using a built-in graph analysis and visualisation tool. However, to explore relationships between structure and function, the graph measures from CONN were exported into SPSS. Global NBS results are reported for $p < 0.05$ corrected, whereas local topological results are reported for $p < 0.05$ uncorrected for multiple comparisons.

Using NBS components as constraints for GT

A limitation of NBS is that a large number of nodes may be found within a single component. This makes the interpretation of components complicated and does not allow for a straight-forward way to test for false-positive nodes within the component. A more informative way to solve this problem is to use the NBS not as a standalone method but as a constraining factor in subsequent GT analyses. In a way, this approach parallels the small volume or masking approach used in SPM. In other words, only the nodes identified by NBS will be examined using GT. The discussion in this chapter will therefore focus on the results obtained using this constrained approach.

Relationships with reading ability

Separate regression analyses were carried out within each group to investigate relationships between the first two components of the PCA (see chapter 6) with NBS (z-values) and GT global efficiency.

8.3. Results

8.3.1. Functional NBS results

Group differences

Two functional network components were found to be less connected in the dyslexic readers compared to the skilled readers ($p < 0.05$ NBS) (fig 8.1 (red lines), table 8.3). In addition, two network components were found to be more connected in the dyslexic readers compared to the controls (fig 8.1 (blue lines), table 8.3).

Compared to skilled readers, dyslexic readers showed reduced FC in one large component, which encompassed language regions (superior and middle temporal gyri, angular gyrus, pars triangularis), default mode network regions (bilateral anterior cingulate cortex), and executive control region (dorsolateral prefrontal cortex). One smaller component was reduced in the dyslexic readers, connecting right primary somatosensory area (BA1) and right associative visual cortex (BA19).

In contrast, dyslexic readers showed increased FC in two components compared to the skilled readers. The first included left anterior cingulate cortex (BA33) and right primary motor cortex (BA4). The second encompassed right homologues of left hemisphere language regions (insula, pars opercularis, pars orbitalis and right anterior prefrontal cortex).

Table 8.3 Group differences in network components identified using network based statistics

	Controls>dyslexics (p<0.05 NBS)	Dyslexics>controls (p<0.05 NBS)
Component 1	Right BA 1 (primary somatosensory) Right BA 19 (associative visual)	Left BA 33 (anterior cingulate cortex) Right BA 4 (primary motor cortex)
Component 2	Right BA 46 (dorsolateral prefrontal cortex) Bilateral BA 21 (MTG) Right BA 27 (piriform cortex) Bilateral BA 39 (angular gyrus), Bilateral BA 32 (dorsal anterior cingulate cortex) Right BA 35 (perirhinal cortex) Left BA 45 (pars triangularis) Right BA 22 (STG)	Right BA 13 (insula) Right BA 10 (anterior prefrontal cortex) Right BA 44 (pars opercularis) Right BA 47 (pars orbitalis)

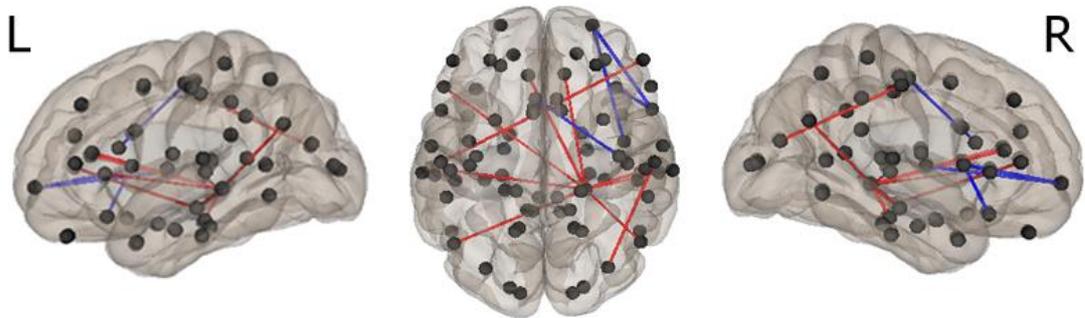
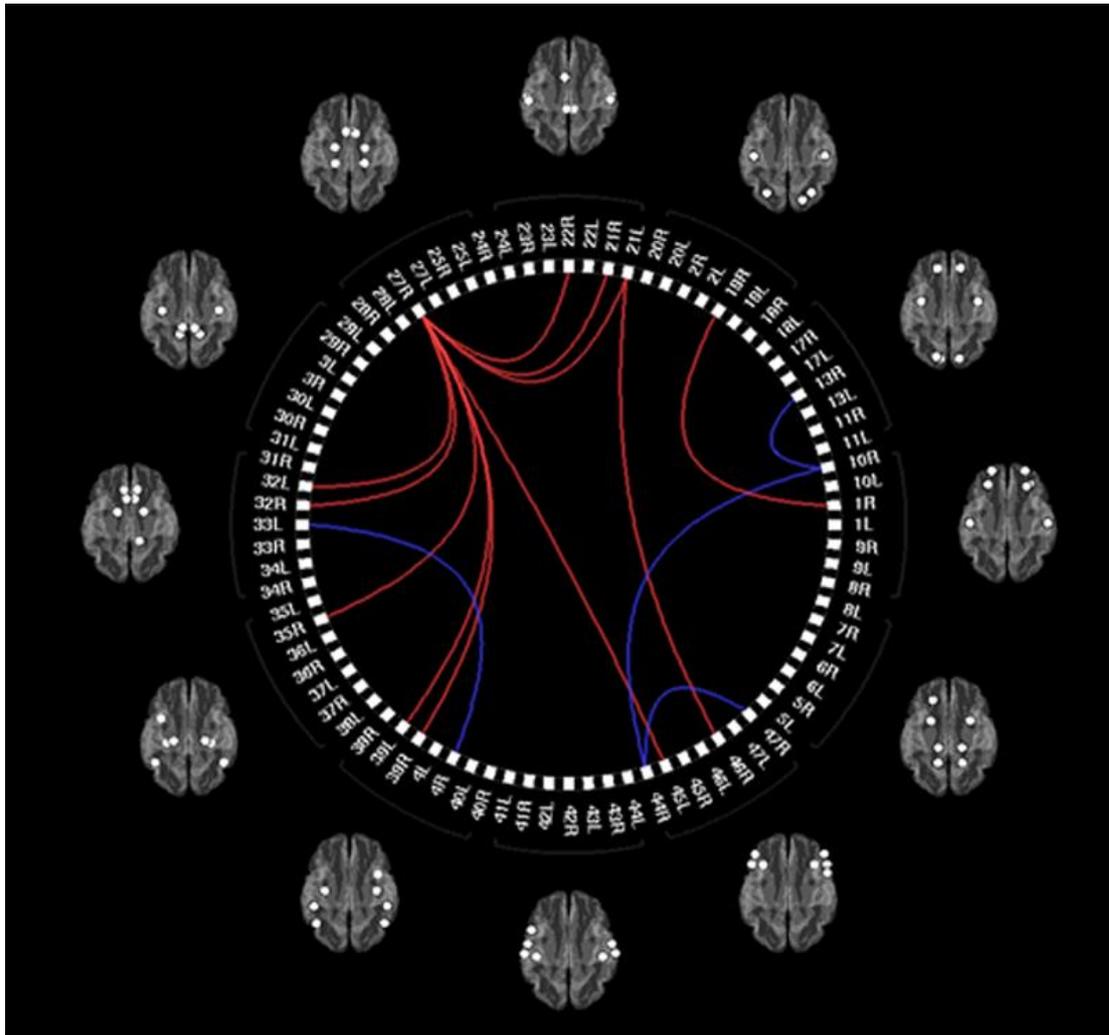


Figure 8.1 NBS components that differ between groups. Red lines indicate connections that are reduced in dyslexic readers, blue lines indicate connections that are increased in dyslexic readers compared to controls.

8.3.2. Topological differences (GT)

Functional networks

Group differences

No group differences were found for the global graph properties between groups.

Regional differences were constrained using the nodes identified in the NBS analyses (table 8.3). Specifically, a controls > dyslexics contrast was tested for the local properties of nodes: right BA 1 (primary somatosensory), right BA 19 (associative visual), right BA 46 (dorsolateral prefrontal cortex), bilateral BA 21 (MTG), right BA 27 (piriform cortex), bilateral BA 39 (angular gyrus), bilateral BA 32 (dorsal anterior cingulate cortex), right BA 35 (perirhinal cortex), Left BA 45 (pars triangularis), right BA 22 (STG). In addition, left associative visual cortex (BA 19) was also tested as it was found to be an important node by Finn et al. (2014).

In contrast, again using the nodes identified in the NBS analyses (table 8.3) as constraints, a dyslexics > controls contrast was tested for nodes: left BA 33 (anterior cingulate cortex), right BA 4 (primary motor cortex), right BA 13 (insula), right BA 10 (anterior prefrontal cortex), right BA 44 (pars opercularis), right BA 47 (pars orbitalis).

Controls > dyslexics

Decreased degree and global efficiency was reduced only in node left MTG (BA21) in the dyslexic readers compared to the controls (table 8.4). Not only is the left MTG connected to more regions in controls (ie regions reflected in NBS component 2), but the information transfer via the left MTG is slower (has to cross more edges) in the dyslexics compared to the controls.

Dyslexics > controls

Increased degree and global efficiency in the dyslexics compared to controls were found for the right insula (BA 13) and left anterior cingulate cortex (BA 33) (table 8.4). These regions were also found to have higher betweenness centrality in the dyslexics than the controls, suggesting they are important hub regions in the dyslexics.

Relationships with reading ability

No significant relationships were found between PCA components and GT measures ($p > 0.05$).

Table 8.4 Group differences in local topological properties

	Controls > dyslexics	Dyslexics > controls
Degree	Left BA 21 (middle temporal gyrus)	R BA13 (insula) L BA 33 (anterior cingulate cortex)
Global efficiency	Left BA 21 (middle temporal gyrus)	R BA13 (insula) L BA 33 (anterior cingulate cortex)
Betweenness centrality	Right BA 19 (associative visual cortex)	L BA33 (anterior cingulate cortex) R BA13 (insula)

Structural networks

Group differences

Like the functional graphs, no group differences were found for the structural graphs globally. Due to the software being in its developmental stages, no further analyses were performed for each node at this stage. However, this would be an interesting area for future research and development, for example specifically investigating the local nodal properties of the left MTG node to mirror the functional GT analysis above.

Relationships with reading ability

Similar to the functional results, no significant relationships were found with PCA components and GT measures ($p > 0.05$).

8.4. Discussion

The analyses in this chapter allowed for a hypothesis-free whole-brain network comparison between the adult skilled and dyslexic readers using topological properties of functional and structural networks.

Left middle temporal gyrus - a core node disrupted in dyslexia

A primary finding in this chapter is decreased degree and global efficiency in the left MTG in dyslexic readers, which suggest that this region is less well connected and integrated within the rest of the brain in these impaired readers compared to the controls. Chapter 7 described reduced activation and reduced RSFC in the left MTG. These findings complement each other and converge on the left MTG as a core node of dysfunctional connectivity in adult compensated readers with dyslexia. These functional connectivity findings are consistent with evidence for the left MTG as a multimodal 'integration centre' of unimodal sensory information, hypothesized by activation-based studies in typical

reading and dyslexia (Atteveldt et al., 2004, 2009; Blau et al., 2009; Blomert, 2011) and white matter tractography studies in typical readers (Turken & Dronkers, 2011; Binney et al., 2012) (see chapter 9 discussion).

No evidence for global network disruption in adults with dyslexia

Contrary to previous MEG studies, the results from both functional and structural networks in the present chapter found no significant differences between skilled and dyslexic readers in global network properties of global efficiency, mean average pathlength, and clustering coefficient. This lack of difference in global network properties has also been reported in cortical thickness and surface area networks of dyslexia (Hosseini et al., 2013). The current MRI findings suggest that overall brain topology and the global network segregation and integration seems as efficient in individuals with dyslexia as in typical readers. These findings corroborate the notion that dyslexia is a reading specific deficit reflected in disruptions of regional rather than global properties (e.g. Hosseini et al., 2013). In other words, the dyslexic readers in the present sample have efficiently wired brain networks, however, they use network components (left MTG in particular) in different and evidently less effective ways for reading.

Disrupted visual pathways in dyslexia

A secondary finding in this chapter was decreased betweenness centrality in the right associative visual area BA 19 in the dyslexics compared to the controls. Betweenness centrality is a measure of importance of a node within the network. More specifically, it describes the nodes that form critical bridges between different subnetworks or modules within the network (Bullmore and Sporns, 2008). Disrupted connectivity in the visual pathways in dyslexia has been previously reported in the literature and forms the basis of the visual deficit hypothesis of dyslexia and Geschwind's disconnection deficit hypothesis (see chapter 1). Using FC and NBS, Finn et al. (2013) also reported divergent connectivity

within the visual pathways in adults and children with dyslexia. More specifically, the authors found reduced FC between visual association areas and prefrontal attention areas, suggesting that the disconnection of these regions is detrimental to reading ability. Interestingly, Koyama et al. (2013) found increased FC between L FFG - R MOG (BA 19) in compensated dyslexic children using RSFC, which correlated with reading and spelling. These findings contradict those of Finn et al. (2013), but keeping in mind that the compensated dyslexic children in Koyama et al. (2013) significantly improved their reading performance after intervention, it is possible that this improvement was related to the increased RSFC of the right visual association cortex.

Increased network properties in high-functioning adults with dyslexia

In this study, dyslexic readers are considered high-functioning or compensated dyslexic readers (see chapter 6). The present results showed increased network properties (degree and efficiency) in a component which includes right insula (BA 13) and left anterior cingulate (BA 33) in these dyslexics compared to controls. Although the exact nature of these increased network properties in the dyslexic readers in the present study remains unclear, one hypothesis is that the compensated dyslexic readers might have developed alternative reading strategies to reach adequate reading levels for academic attainment. For example, they may rely more on attention and error-monitoring systems when reading (Horowitz-Kraus et al., 2015). Recent studies by Horowitz-Kraus and colleagues (Horowitz-Kraus et al., 2015; Horowitz-Kraus and Holland, 2015; Horowitz-Kraus & Breznitz, 2010; Horowitz-Kraus & Breznitz, 2013;) have found increased FC between left FFG (BA37) and right anterior cingulate (BA33) in dyslexic children after a 4-week reading intervention programme designed to train executive functions, attention redirection and error-monitoring (Horowitz-Kraus and Holland, 2015). The anterior cingulate cortex is historically considered part of the cingulo-opercular network thought to be responsible for cognitive control and set maintenance (Dosenbach et al., 2008). One study further discussed the

functionally lateralisation of the anterior cingulate cortex (Lutcke & Frahm, 2008). Using a higher spatial-resolution scanning technique during a Go/No-Go task, the authors suggested that adult participants show greater bilateral activation for error monitoring and right lateralized activation for conflict monitoring. It has been suggested that this network is part of language-learning processes, including feedback processing, errors, ambiguity/conflict and reaction times (Dosenbach et al., 2008; Neta, Schlaggar, & Peterson, 2014). Therefore, the present results suggest that the compensated dyslexic adults in the present sample rely more heavily on error monitoring and conflict monitoring systems when reading, when they cannot rely on a phonological reading strategy.

8.5. Conclusion

This study investigated topological differences in functional and structural networks in skilled and dyslexic adult readers using graph theoretical analyses. Although no differences were found in global topological properties, dyslexic readers showed decreased local properties in left middle temporal gyrus, corroborating the findings of chapter 7. In addition, increased topological properties were found in the left anterior cingulate and right insula of the dyslexic readers compared to the controls, which suggest compensatory mechanisms through cognitive control. This chapter complement the findings of the previous chapter to provide some convergent evidence to support dyslexia as a disconnection syndrome, and provides support for dyslexia as a reading-specific disorder, reflected in disrupted local network properties, rather than a global disconnection syndrome

9. Discussion and future directions

9.1 Overview of findings

Developmental dyslexia has been hypothesized to be a disconnection disorder as reading requires the interaction of various brain regions. This thesis has explored the nature of this disconnection deficit using various methodologies in adult readers with and without dyslexia.

Characterising the intrinsic language network

In chapter 5, I demonstrated that the language network is inherently connected in twenty typical right-handed monolingual adult readers, in the absence of a language task. This chapter replicated the intrinsic language network at rest as well as its subnetworks based on the connectivity patterns of three subregions with the left IFG: BA 44, 45, and 47. Results demonstrated a topological gradient of RSFC in the parietal and temporal lobes, replicating and extending previous findings by Xiang et al. (2010). In addition, the findings suggest an anti-correlation with the cingulate cortex in the default mode network. Probabilistic tractography further found the dorsal and ventral pathways implicated in language processing (e.g. Friederici, 2011), supporting the dual stream model of language processing (e.g. Saur et al., 2008; Hickok and Poeppel, 2004). This study corroborates existing studies to demonstrate that resting-state functional connectivity (RSFC) is a valid measurement for detecting meaningful functional networks (Tomasi and Volkow, 2012; Zhu et al., 2014, Muller and Meyer, 2014).

Cognitive profiles of compensated dyslexics in adulthood

Chapter 6 provided an in-depth characterisation of the cognitive profiles of the adults with dyslexia recruited in this PhD project. Although the dyslexic adults did not differ in age, gender and cognitive ability from the age-matched control group, they were unable to read and spell as well as them. The performance of the dyslexic readers on word and

pseudoword reading were at the 'typical' level for their age, and thus could be considered 'compensated' dyslexics. However, their performance was one standard deviation below the average of the controls and significantly poorer than to be expected given their IQ. Therefore, they are still classified as impaired and remain diagnosed as dyslexic.

Principal component analysis (PCA) further determined that the profiles of readers can be best captured in 4 independent factors which together explained 81.18% of the variance: 1) literacy component, 2) working memory component, 3) language component, 4) comprehension component. The compensated dyslexics were significantly impaired on the literacy and working memory component compared to the controls.

A secondary analysis explored the prevalence of the so-called double-deficit hypothesis (DDH), the first investigation in a sample of compensated dyslexics. DDH implicates naming speed as a second, independent, core deficit of dyslexia (Wolf & Bowers, 1999). The theory predicts weak correlation between phonological awareness and RAN, with both contributing independent variance to reading skill. In addition, the theory predicts that individuals with only a single deficit should present with relatively mild impairments and the best prospect of compensation.

The findings in chapter 6 do not support the DDH as phonological awareness and RAN both correlated significantly with each other and with literacy measures. PCA analysis further found RAN and working memory to be loaded onto the same factor, suggesting a shared cognitive mechanism. Lastly, a qualitative classification of the dyslexic sample into the three groups predicted by the DDH found 38% to present a double deficit in both phonological awareness and RAN. This is a surprisingly high proportion for a 'compensated' sample.

Dysfunctional connectivity in left middle temporal gyrus

In chapter 7, I combined RSFC, task-based fMRI, and probabilistic tractography to study the left-hemisphere reading network in adults with and without dyslexia to investigate activation and connectivity differences and their relationships with reading outcome. A consistent deficit in the left middle temporal gyrus was observed in the dyslexic readers, which showed reduced activation during task and reduced RSFC to left inferior frontal gyrus region associated with skilled reading. The level of activation and the RSFC were both related to reading outcome, in particular pseudoword reading. Due to this marked functional deficit in the connectivity between the left inferior frontal and left middle temporal region, I further investigated the structural connectivity between these regions using probabilistic tractography. These results found decreased white matter properties in the arcuate fasciculus in the dyslexic readers, supporting the disconnection deficit of dyslexia. The implication of this region for existing models of reading is discussed below.

Local, not global, topological deficits

As chapter 7 used hypothesis-driven a priori defined regions of interest, it is possible that more wide-spread changes in the brain are neglected. Chapter 8 tackled this issue by using a whole-brain parcellation scheme based on the automatic anatomical labeling (AAL) atlas to investigate deficits in both functional connectivity (using network based statistics) and brain topology (using graph theory). A deficit in the left MTG, which I observed in chapter 7, was found again using both NBS and graph theory. Graph theoretical analysis, constrained by the functional components identified by NBS, further quantifies the topological properties of the whole brain networks and showed a deficit in local properties in dyslexic readers. Specifically, dyslexic readers showed decreased degree and efficiency in left MTG, but increased degree and efficiency in the left anterior cingulate and right insula. The anterior cingulate is thought to be involved in cognitive control and error monitoring. It is possible that the high-functioning dyslexics in this thesis rely strongly on error-monitoring

to compensate for their phonological impairments. This requires additional research. In addition, this chapter provides support for dyslexia as a reading-specific disorder, reflected in disrupted local network properties, rather than a global disconnection syndrome.

Compensatory mechanisms

A secondary finding in chapters 7 and 8 is the increased connectivity to right hemisphere regions in adult with dyslexia. Increased right hemisphere activations in dyslexic readers have been observed previously in task-based studies, and have been considered to reflect compensatory mechanisms. Considering the high levels of reading achievement in this sample of dyslexic readers, the presence of the increase of right-hemispheric connections in the dyslexic readers provides further evidence for a compensatory mechanism. Further longitudinal studies following reading intervention are needed to confirm this relationship.

Specifically, two possible compensatory mechanisms have been reported in chapters 7 and 8 respectively. Chapter 7 reported increased RSFC between left FFG seed and right superior parietal lobule (BA7). Previous studies have identified bilateral superior parietal lobules as the neural correlates of visual attention span (e.g. Peyrin et al., 2011; Peyrin et al., 2012). For instance, Peyrin et al. (2011) found a lack of activation in the superior parietal lobules in children with visual attention span disorder during a flanked letter categorisation task compared to typical controls. In addition, Lobier et al. (2012) showed higher activation of bilateral superior parietal lobule during multiple element processing compared to single element during visual categorisation tasks of alphanumeric characters (Lobier et al., 2012). These findings suggest a specific role of the superior parietal regions in multi-character processing and visual attention span. Increased RSFC between the left FFG to the right SPL may indicate increased integration of orthographic processing (in left FFG) and visual attention demands for multi-character strings (in the right SPL) in the compensated dyslexic readers.

Secondly, chapter 8 found increased network properties (degree and efficiency) in the dyslexic readers in right insula (BA 13) and left anterior cingulate (BA 33). Previous qualitative papers have assumed that increased activation in right IFG and insula reflected compensatory reliance on effortful pronunciations in word recognition (e.g. Sandak et al. 2004; Démonet, Taylor and Chaix, 2004). These two regions have previously been reported by Shaywitz et al. (2003) in a task-based fMRI study, comparing compensated adult readers (AIR), persistent poor readers (PPR) and non-impaired readers (NI). Compared to PPR, AIR showed increased activation in the left anterior cingulate gyrus, suggesting that AIR readers, who perform better than do PPR on all reading tasks, have come to rely on the cingulate to compensate. In addition, both AIR and PPR activated the right posterior IFG/insula more than the NI readers. These findings suggest that the left anterior cingulate may indeed be involved in compensatory strategies, whereas the right IFG/insula may be a locus of abnormal activation and connectivity possibly contributing to the etiology of dyslexia.

Horowitz-Kraus and colleagues (Horowitz-Kraus et al., 2015; Horowitz-Kraus and Holland, 2015; Horowitz-Kraus & Breznitz, 2010; Horowitz-Kraus & Breznitz, 2013) have found increased FC to the right anterior cingulate (BA33) in dyslexic children after an intervention programme designed to train executive functions, attention redirection and error-monitoring (Horowitz-Kraus and Holland, 2015). It has also been suggested that the anterior cingulate is involved in language-learning processes, including feedback processing, errors, ambiguity/ conflict and reaction times (Dosenbach et al., 2008; Neta, Schlaggar, & Peterson, 2014). Therefore, the present results suggest that the compensated dyslexic adults may rely more heavily on error monitoring and conflict monitoring systems when reading, when they cannot rely on a phonological reading strategy.

Further work is needed to address possible compensatory mechanisms found in this thesis. Nevertheless, the current studies have demonstrated the existence of such connections.

Understanding compensatory mechanisms and interaction/moderating effects from or to other cognitive systems will help inform future reading instruction and/or intervention and better management of comorbid difficulties experienced by individuals with dyslexia.

9.2 Implications of this research

Reframing the disconnection deficit hypothesis

The work presented in this thesis support the phonological and disconnection deficit theories of dyslexia. No evidence was found for the auditory processing deficit, cerebellar deficit or magnocellular deficit theories. The experiments presented here show that connectivity deficits are present in mature readers, despite compensation status, and that the connectivity deficits directly relate to persistent phonological processing deficits. However, the findings do not fit the classical model of disconnection theory. Instead, the findings are consistent with other recent reports of disconnections in dyslexia, providing an update to the classical predictions of the theory.

In the earliest work on disconnection syndromes, Geschwind speculated that developmental dyslexia may be caused by delayed development of the angular gyrus region and predicted that individuals with developmental dyslexia should present with 'disconnections' in the pathway between right occipital cortex and left angular gyrus. Disconnection was indeed observed with the right occipital cortex in chapter 8. In this chapter, network analyses found decreased betweenness centrality in the right associative visual area BA 19 in the dyslexics compared to the controls. Betweenness centrality is a measure of importance of a node within the network. More specifically, it describes the nodes that form critical bridges between different subnetworks or modules within the network (Bullmore and Sporns, 2008). Reduced betweenness centrality in the dyslexic readers suggest a reduced importance of the right visual associative cortex for information transfer between cognitive networks. This provides partial support to Geschwind's theory.

However, no group differences were observed in the left angular gyrus between groups during reading task, resting-state fMRI, or network analyses. This is somewhat surprising considering the consistent deactivation observed in the task-based fMRI literature in this region (see chapter 2). This difference can be partly explained by the sample characteristics. The sample in the present thesis consists of compensated adult dyslexic readers, in contrast to severe dyslexic readers in other studies. In addition, developmental studies have suggested that the left dorsal temporoparietal system (including the angular gyrus) plays a prominent role during the early stages of reading acquisition. As reading proficiency increases, the involvement of the left dorsal temporoparietal system decreases, and the involvement of the left ventral occipitotemporal system increases (e.g. Shaywitz et al., 2007; Richlan et al., 2011; Martin et al., 2015). The reduced RSFC from the left FFG seed in the current adult sample supports this developmental hypothesis.

Lastly, Geschwind hypothesised the cause of the disconnections to be localised in the splenium of the corpus callosum. Instead, the present findings suggest structural disconnection in the arcuate fasciculus, a finding consistent with recent white matter tractography studies (e.g. Vandermosten et al., 2014). Therefore, the present results do not support Geschwind's original theory.

In an update to Geschwind's disconnection theory, Paulesu et al. (1996) proposed that the disconnection deficit in adults with dyslexia is located in the insula, which was hypothesised to function as a 'bridge' between inferior frontal regions and posterior superior temporal regions. The present findings did find a deviant network pattern in the right insula, but in the opposite direction as predicted by Paulesu et al. (1996). Whereas Paulescu hypothesised the lack or reduced connectivity through the insula, the findings of this PhD included increased network properties (degree and efficiency) in the dyslexic readers compared to controls. It is currently unclear whether this increased importance of the right insula within the whole brain network reflects etiology or compensation in this sample.

However, based on the previous finding by Shaywitz et al. (2003), who reported increased activation in the right insula for both compensated and non-compensated adult dyslexics, it is likely that the abnormality observed in this region reflects a deficit rather than compensation.

Lastly, recent connectivity studies have reported abnormal connectivity patterns between left IFG and left FFG to multiple bilateral regions in dyslexia (e.g. Richards & Berninger, 2008; Horwitz, Rumsey, & Donohue, 1998; Pugh et al., 2000; Van der Mark et al., 2011; Vourkas et al., 2011; Koyama et al., 2011). For example, Boets et al. (2013) postulated that adults with dyslexia had intact phonological representations but impaired phonological retrieval, reflected by reduced functional and structural connectivity between left IFG and left auditory cortices in the superior temporal gyrus/sulcus. The findings reported in this thesis are consistent with these reports of disrupted connectivity between left FFG and left IFG (reported in chapter 7) and left IFG and left temporal gyrus (MTG, reported in chapters 7 and 8).

These findings taken together suggest that the disconnection deficit is present in dyslexia, but not in the way predicted by the classical model proposed by Geschwind. Instead, the disconnection hypothesis should be reframed as follows: Skilled reading is an emergent property from the efficient transfer of information between many brain regions, which include the classical language regions as well as executive and attention regions in both hemispheres. Disconnections within this interconnected network will lead to behavioural impairments. The nature of the impairments will depend on the nature of the disconnection (location and severity). This perspective fits with the heterogeneity of behavioural symptoms observed in dyslexia and supports the multi-componential models of dyslexia, which suggest that it is very unlikely that a single underlying causal factor drives the heterogeneous patterns of reading difficulties across individuals with dyslexia (Pennington et al., 2012).

It is by studying the brain network as a whole and looking at the global and local properties of this network that we can fully understand a complex disorder such as dyslexia. The graph theoretical analyses reveal that the overall brain topology and the global network segregation and integration are, in fact, intact in individuals with dyslexia. Instead, these findings emphasize the notion that the reading deficit is reflected in disruptions of regional properties, which have wide-spread effects across the whole network. In other words, dyslexic readers have efficiently wired brains; however, they use network components in different and less effective ways for reading.

Contributions to cognitive models of reading

This thesis also contributes to existing cognitive models of reading. The three prominent cognitive models of reading are: the dual-route cascaded (DRC) model (Coltheart et al. 2001), triangle model (Plaut et al., 1996), and the connectionist dual-process (CDP) model (Perry et al., 2007) (see chapter 2). Two meta-analyses have evaluated PET and fMRI findings within these cognitive models (Jobard et al., 2003; Taylor et al., 2012) and found that the existing findings in the literature could be interpreted within any of the three models.

The left MTG was the main and highly consistent finding in this thesis. However, this MTG region was not originally included in the three-region model of the reading network proposed by Pugh et al. (2001) (chapter 2). Interestingly, this region was found by both Jobard et al. (2003) and Taylor et al. (2012) in their meta-analyses, suggesting that it is a region consistently reported in the literature contrasting word and pseudoword reading in dyslexia – tasks similar to those used in this thesis. Both Jobard and Taylor found this region to be consistently reported in the literature for the pseudoword > word reading contrast, suggesting that it is part of the dorsal or nonlexical route in reading. This is also consistent with previous reports that the left MTG supports phonological processing (Friederici, 2011;

Hickok & Poeppel, 2004), correlates with reading ability (Turkeltaub et al., 2003), functions as a multimodal 'integration centre' of unimodal sensory information (Blau et al., 2009; Blomert, 2011; Boets et al., 2013), and structurally connects to the left IFG and to left temporoparietal regions (BA39/angular gyrus and BA40/supramarginal gyrus) (Binney et al., 2012; Turken and Dronkers, 2011).

However, it is unclear which component of the three models would correspond to this region. For example, both Jobard and Taylor hypothesised that the grapheme-phoneme conversion system resides in the left inferior parietal lobule (although in Jobard's model this is the angular gyrus, whereas in Taylor's model this is the supramarginal gyrus). The left MTG in the present study also overlaps with region T1a identified by Vigneau et al. (2006) in a meta-analysis of 129 reports encompassing phonological, semantic and sentence processing in adults and children. Although area T1a (MTG) was found consistently for all three processes, there was a clear overlap in this region for phonology and semantics. Vigneau proposed that this area serves as a transitional zone between "the perception and semantic integration of language stimuli" (p.1424). An integrative role between semantics and phonology would fit best within the triangle model (see fig 9.1).

The contribution of semantics to phonology is less straightforward in the DRC and CDP. Semantics within the DRC and CDP has been explicitly assigned to the lexical/direct route, to help the retrieval of the phonological representation of words stored in the phonological lexicon. It is possible that the MTG fulfils this integration/retrieval role between phonological and orthographic lexicons. However, this seems incompatible with the finding that this region consistently activates more strongly for pseudowords than words. Pseudowords do not have a meaning and therefore should be read via the indirect/nonlexical route via grapheme-phoneme conversion according to the DRC and CDP models. However, this assumes that the reader employs either a whole word reading strategy (via lexical route) or a letter-by-letter decoding strategy (via indirect route). It does

not take into account alternate reading strategies. Considering that the present sample consists of skilled typical readers and compensated dyslexic readers, it is unlikely that both groups would employ a letter-by-letter reading strategy as this would increase reaction time. Instead, it is plausible that readers employed a strategy relying on semantic similarity or breakdown of pseudowords into meaningful syllables or other semantic/morphological parcels (for example 'bloom' → 'b' + 'loom'). This is purely speculative at this stage and requires empirical tests in the future.

Therefore, as it currently stands, it is more likely that the MTG observed in this thesis supports the triangle model than the DRC or CDP. As such, the model proposed by Taylor et al. (2012) can be updated as follows in fig 9.1.

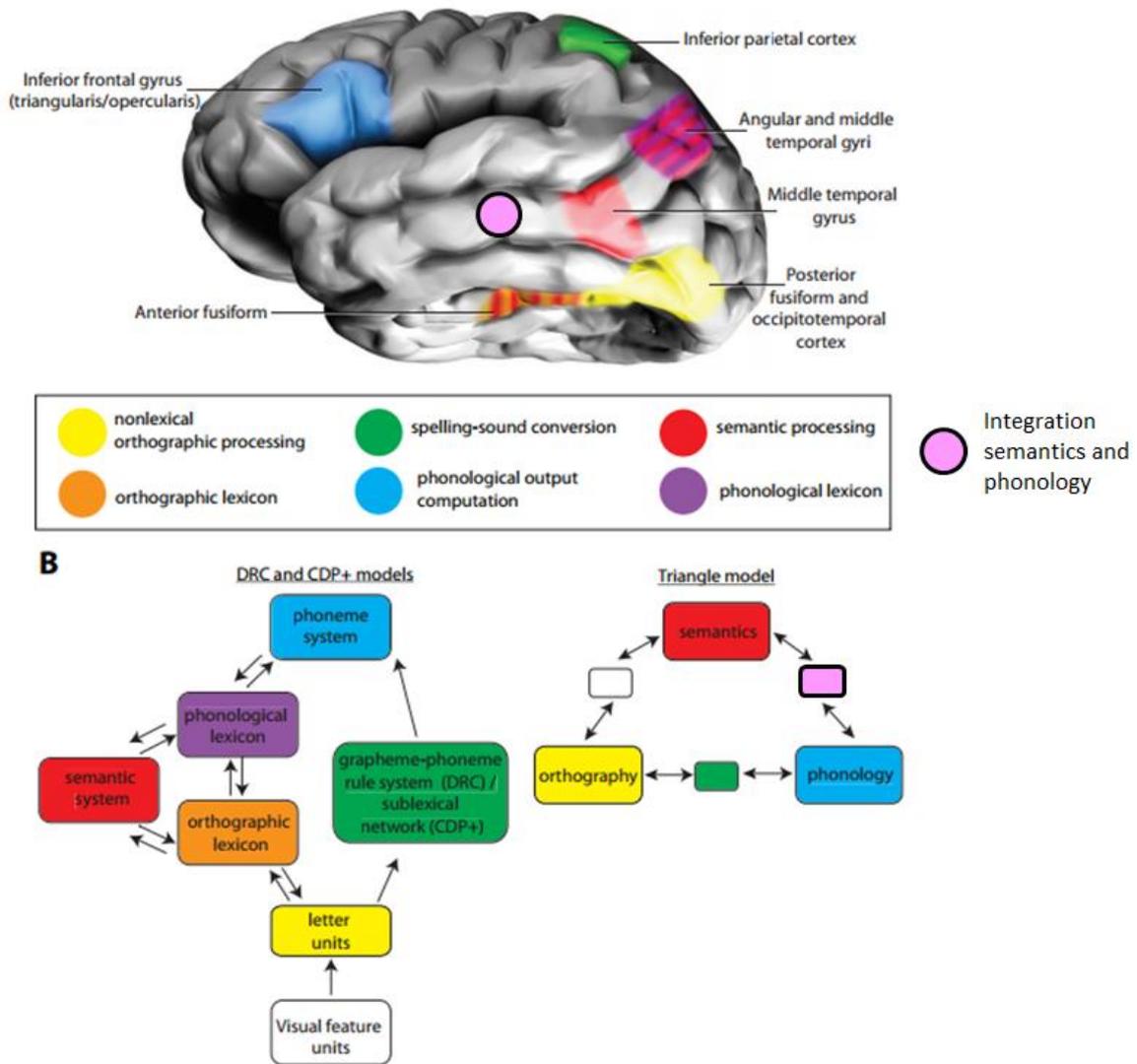


Figure 9.1. Illustration of the relationship between processes involved in word and pseudoword reading, cognitive model components, and brain structures. Adapted from Taylor, Rastle and Davis (2012). The pink region shows updates to the model to include the left middle temporal gyrus region found in this thesis.

9.3 Experimental limitations

Some limitations and outstanding issues will need to be addressed in future studies. Firstly, the task-based activations for all conditions across groups were below a statistical level of significance when corrected for multiple (voxel-level) comparisons, even though regions of activations found at uncorrected levels were in line with previous literature. This is most likely due to the relatively easy nature of the reading task for the adult readers. I designed

the task with a level of difficulty in mind that would be suitable for both adults and children, to allow for such age-group comparisons. Therefore, the level of difficulty of the task is challenging for children, but very easy for highly educated adult readers. Nevertheless, this study was successful at identifying the regions previously identified in the literature (Richlan et al., 2009; 2011), employed by adult readers with and without dyslexia.

Secondly, due to the compensated nature of the dyslexic readers in this sample, the present results may not generalise to severe dyslexic readers whose reading levels fall well below 1.5 standard deviations from the mean, or to those who may have more complex profiles including the co-occurrence of other developmental disorders (e.g. SLI, attention deficit disorder (ADD) and/or motor-coordination disorder). My protocol screened for comorbidities (SLI with TROG-II, AD(H)D with self-report), and found none present at the time of testing. However, the existence of subtypes in developmental dyslexia is currently still a matter of debate and it remains to be seen whether these subtypes have the same or different underlying etiology (Ramus, 2003; Pernet et al., 2009; Peterson et al., 2013).

Lastly, the question remains whether the changes observed in this thesis are a cause or consequence of dyslexia, which cannot be inferred from this project alone. Longitudinal studies, which follow a large cohort of children with and without familial histories of dyslexia from pre-reading age to adulthood would be the ideal experimental setting to directly test this question and are required for future investigations. However, dyslexia, as any developmental disorder, is caused by a complex interaction between genes, environment and experience and the network differences observed in the current work are a reflection of these complex interactions. Although the current work investigated adult readers, previous studies in pre-reading children with familial history of dyslexia have found structural differences (Raschle, Chang, & Gaab, 2011), functional activation differences (Hoeft et al., 2007, 2011), and topological differences (Hosseini et al., 2013). These studies

are not confounded by any experience or remediation effects, and suggest that before reading-onset, the dyslexic brain is organized differently, which limits successful reading acquisition. The work presented here further illustrates that although word reading may be ameliorated over the years due to maturation, intervention, or compensation, the dysfunctional connections in the brain persist.

9.4 Future directions

The need for longitudinal studies in preliterate children

This thesis has focused on adults with dyslexia, and in particular adults who show behavioural compensation for reading difficulties. Much of our current understanding of the aetiology and the brain basis of dyslexia is derived from studies of adults or school-aged children, who have started acquiring literacy. This is understandable as group assignment depends on clinical diagnosis, which in turn depends on the emergent failure of successful literacy acquisition. Hence, this can only be established once children have received adequate reading instruction. However, one could argue that the brain differences observed may reflect reduced reading experience rather than the true cause of dyslexia (e.g. Hoeft et al., 2007; Cunningham and Stanovich, 1998). For example, studies of non-literate adults showed learning-induced plasticity in the brain as a result of learning to read (Dehaene et al., 2015). In addition, a MRI study comparing dyslexic children with both chronological age-matched and reading age-matched controls suggested that some of the brain differences observed in dyslexia could be explained by differences in the amount and quality of reading experience (Hoeft et al., 2007).

This chicken-or-egg debate requires empirical evidence from carefully designed longitudinal studies that follow children before they start learning to read into adulthood. Such studies allow the identification of risk factors and protective factors, as well as providing insight into the stability of dyslexia diagnosis across the life span. In addition, these studies may

shed light on the characteristics of late-emerging dyslexia and resolving or compensated dyslexia. Cross sectional studies with preliterate children have started to emerge, but these are few in number and require longitudinal follow-up.

Studies to date have compared children who have at least one parent with dyslexia, and thus are at risk of developing dyslexia themselves later in life, to those who do not have a family history of dyslexia (e.g. Hosseini et al., 2013; Black et al., 2012; Raschle, Zuk and Gaab, 2012; Rachle, Chang and Gaab, 2011; Raschle et al., 2014; Vandermosten et al., 2015; Specht et al., 2009; Yamada et al., 2015). Differences associated with familial risk of dyslexia are found across studies in three main brain regions, which show consistency with the existing literature in school-age children and adults: left temporoparietal cortex, left occipitotemporal cortex, and cerebellum. These findings suggest that the neurobiological differences observed in adults and children with dyslexia are not purely reading experience-driven, but are more likely related to causal factors. Whether these factors are genetic or environmental remains to be fully understood, but it is most likely a complex interaction of both. Longitudinal studies are needed to fully identify what these factors are and clarify the exact contributions of each factor across development into adulthood.

Effective connectivity and classification

The connectivity differences reported in this thesis were derived from correlational analyses between timeseries of brain regions. Although these correlations provide a proxy measure for the functional coupling and interaction between brain regions, these measures do not provide information about the directionality of such interactions. Effective connectivity analyses such as dynamic causal modeling (Friston, Li, Daunizeau, & Stephan, 2011; Kiebel, Klöppel, Weiskopf, & Friston, 2007) will provide better estimates of the directionality of interactions. This is especially important to investigate the theory proposed by Boets et al. (2014) that dyslexia is marked by impaired access from left frontal regions to phonological representations stored in left temporal regions. In addition,

modeling the interaction of both the left hemisphere reading network and the right hemisphere visual attention regions can provide insight into the role of the right hemisphere as a compensatory system in dyslexic readers.

The outcomes of such DCM studies in turn can be used in subsequent classification analyses (Brodersen et al., 2011). This is particularly interesting in the light of the heterogeneous nature of dyslexia. If different subtypes of dyslexia exist, can we identify them based on brain patterns? Can we identify surface and phonological dyslexics from their brain connectivity patterns? These issues are not easily answered with conventional cross-sectional group studies. Looking at the variability in connectivity patterns and using generative models is a start to address these important questions.

Interhemispheric connectivity

Lastly, further structural and functional investigations into interhemispheric connectivity are needed to further elucidate the contribution of the right hemisphere to the predominantly left hemisphere reading network. Currently, increased right hemisphere activations are inconsistently found in the literature, which reflect possible compensatory mechanisms, but direct evidence for this is limited. Literature on structural lateralization is limited, although Vandermosten et al. (2008) did not find any differences in lateralization indices of major language tracts in typical and dyslexic readers, studies of the corpus callosum have found increased FA in the splenium of dyslexic readers compared to controls (Dougherty et al., 2007; Frye et al., 2008) and an inverse relationship with reading (Westerhausen et al., 2006).

9.5 Conclusion

In conclusion, I have explored the connectivity deficit of dyslexia in this thesis. Using a range of complementary MRI methods and analyses, I have provided converging evidence to demonstrate that dyslexia is marked by connectivity deficits in the brain, which extend

beyond the activation and connectivity deficits currently reported within the conventional left hemisphere reading network. I have demonstrated that these connectivity deficits are a reflection of both reading impairments as well as possible compensatory mechanisms.

This work suggests that dyslexia cannot be caused by a single deficit and has advanced our understanding of dyslexia as a reading specific disorder embedded within the larger system of the brain with interactions with other systems (attention, executive control, visual, auditory). Rather than a disconnection deficit, characterized by missing connections between regions, dyslexia should be seen as characterized by altered connectivity within existing brain systems, leading to less efficient processing for reading.

There are many questions, which remain to be answered, including the developmental trajectory, the directionality of the interactions observed, and the role of the right hemisphere connections observed. The work in this thesis contributes towards addressing the complex network that is the brain and the importance of efficient information transfer between regions. More practically, I hope that the work in this thesis highlights the potential to use network measures as biomarkers for complex disorders and the importance of studying compensatory mechanisms from a networks perspective.

10. Bibliography

- Albus, J. S. (1971). A theory of cerebellar function. *Mathematical Biosciences*, *10*(1), 25-61.
- Alegria, J., Pignot, E., & Morales, J. (1982). Phonetic analysis of speech and memory codes in beginning readers. *Memory & Cognition*, *10*, 451-456.
- Allen, E. A., Erhardt, E. B., Wei, Y., Eichele, T., & Calhoun, V. D. (2011). Capturing inter-subject variability with group independent component analysis of fMRI data: A simulation study. *NeuroImage*, *59*(4), 4141-4159.
- Alloway, T. P., & Gregory, D. (2013). The predictive ability of IQ and working memory scores in literacy in an adult population. *International Journal of Educational Research*, *57*, 51-56.
- Altarelli, I., Leroy, F., Monzalvo, K., Fluss, J., Billard, C., Dehaene-Lambertz, G., ... & Ramus, F. (2014). Planum temporale asymmetry in developmental dyslexia: revisiting an old question. *Human brain mapping*, *35*(12), 5717-5735.
- Amitay, S., Ahissar, M., & Nelken, I. (2002). Auditory processing deficits in reading disabled adults. *Journal of the Association for Research in Otolaryngology*, *3*, 302-320.
- Amitay, S., Ben-Yehudah, G., Banai, K., & Ahissar, M. (2002). Disabled readers suffer from visual and auditory impairments but not from a specific magnocellular deficit. *Brain*, *125*: 2272-2285.
- Amunts, K., Schleicher, A., Ditterich, A., & Zilles, K. (2003). Broca's region: cytoarchitectonic asymmetry and developmental changes. *The Journal of Comparative Neurology*, *465*(1), 72-89.
- Amunts, K., & Zilles, K. (2012). Architecture and organizational principles of Broca's region. *Trends in Cognitive Sciences*, *16*(8), 418-26.
- Andrews-Hanna, J. R., Reidler, J. S., Huang, C., & Buckner, R. L. (2010). Evidence for the default network's role in spontaneous cognition. *Journal of neurophysiology*, *104*(1), 322-335.
- Anwander, a, Tittgemeyer, M., von Cramon, D. Y., Friederici, a D., & Knösche, T. R. (2007). Connectivity-Based Parcellation of Broca's Area. *Cerebral Cortex (New York, N.Y. : 1991)*, *17*(4), 816-25.
- Arnell, K. M., Joanisse, M. F., Klein, R. M., Busseri, M. A., & Tannock, R. (2009). Decomposing the relation between Rapid Automatized Naming (RAN) and reading ability. *Canadian Journal of Experimental Psychology/Revue canadienne de psychologie expérimentale*, *63*(3), 173.
- Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839-51.

- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, 38(1), 95–113.
- Atteveldt, N. Van, Formisano, E., Goebel, R., & Blomert, L. (2004). Integration of letters and speech sounds in the human brain. *Neuron*, 43, 271–282.
- Atteveldt, N. Van, Roebroek, A., & Goebel, R. (2009). Interaction of speech and script in human auditory cortex: insights from neuro-imaging and effective connectivity. *Hearing Research*, 258(1-2), 152–164.
- Backes, W., Vuurman, E., Wennekes, R., Spronk, P., Wuisman, M., van Engelshoven, J., & Jolles, J. (2002). Atypical brain activation of reading processes in children with developmental dyslexia. *Journal of Child Neurology*, 17(12), 867-871.
- Baddeley, A. D., and Logie, R. H. (1999). “Working memory: the multiple component model,” in *Models of Working Memory: Mechanisms of Active Maintenance and Executive Control*, eds A. Miyake and P. Shah (New York, NY: Cambridge University Press), 28–61.
- Badian, N. A. (1997). Dyslexia and the double deficit hypothesis. *Annals of Dyslexia*, 47(1), 69–87.
- Badian, N. A. (1998). A validation of the role of preschool phonological and orthographic skills in the prediction of reading. *Journal of Learning Disabilities*, 31, 472–482.
- Baillieux, H., Vandervliet, E. J., Manto, M., Parizel, P. M., De Deyn, P. P., & Mariën, P. (2009). Developmental dyslexia and widespread activation across the cerebellar hemispheres. *Brain and language*, 108(2), 122-132.
- Barabási, A. (1999). Emergence of Scaling in Random Networks. *Science*, 286(5439), 509–512.
- Barquero LA, Davis N, Cutting LE. (2014) Neuroimaging of reading intervention: a systematic review and activation likelihood estimate meta-analysis. *PLoS One* 9(1):e83668.
- Bauman, M. L., & Kemper, T. L. (2005). Neuroanatomic observations of the brain in autism: a review and future directions. *International journal of developmental neuroscience*, 23(2), 183-187.
- Beaulieu, C., Plewes, C., Paulson, L. A., Roy, D., Snook, L., Concha, L., & Phillips, L. (2005). Imaging brain connectivity in children with diverse reading ability. *Neuroimage*, 25(4), 1266-1271.
- Behrens, T. E. J., Berg, H. J., Jbabdi, S., Rushworth, M. F. S., & Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage*, 34(1), 144–55.
- Behrmann, M., Geng, J. J., & Shomstein, S. (2004). Parietal cortex and attention. *Current Opinion in Neurobiology*, 14(2), 212–7.

- Behzadi, Y., Restom, K., Liu, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, 37(1), 90–101.
- Benjamin, C. F., & Gaab, N. (2012). What's the story? The tale of reading fluency told at speed. *Human brain mapping*, 33(11), 2572-2585.
- Ben-Shachar, M., Dougherty, R. F., Deutsch, G. K., & Wandell, B. A. (2007). Contrast responsivity in MT+ correlates with phonological awareness and reading measures in children. *Neuroimage*, 37(4), 1396-1406.
- Ben-Shachar, M., Dougherty, R. F., & Wandell, B. A. (2007). White matter pathways in reading. *Current Opinion in Neurobiology*, 17(2), 258–70.
- Bihan, D. Le, & Johansen-Berg, H. (2012). Diffusion MRI at 25: exploring brain tissue structure and function. *Neuroimage*, 61(2), 324–341.
- Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, 19(12), 2767-2796.
- Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. *Trends in cognitive sciences*, 15(11), 527-536.
- Binney, R. J., Parker, G. J. M., & Lambon Ralph, M. A. (2012). Convergent connectivity and graded specialization in the rostral human temporal lobe as revealed by diffusion-weighted imaging probabilistic tractography. *Journal of Cognitive Neuroscience*, 24(10), 1998–2014.
- Birn, R. M., Diamond, J. B., Smith, M. A., & Bandettini, P. A. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *NeuroImage*, 31(4), 1536–48.
- Biscaldi M, Fischer B, and Hartnegg K. (2000) Voluntary saccadic control in dyslexia. *Perception*, 29, 509–521.
- Bishop, D. V. (2002). Cerebellar abnormalities in developmental dyslexia: Cause, correlate or consequence?. *Cortex*, 38(4), 491-498.
- Bishop D.V.M. and Snowling M.J. (2004) Developmental dyslexia and specific language impairment: Same or different? *Psychological Bulletin*, 130, 858–886.
- Bishop, D. V. M. (2014). The interface between genetics and psychology: lessons from developmental dyslexia. In *Proc. R. Soc. B* (Vol. 282, No. 1806, p. 20143139). The Royal Society.
- Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 34(4), 537–41.

- Bitan T, Booth JR, Choy J, Burman DD, Gitelman DR, Mesulam MM. (2005) Shifts of effective connectivity within a language network during rhyming and spelling. *J Neurosci* ; 25: 5397–403.
- Blachman, B. A., Schatschneider, C., Fletcher, J. M., Murray, M. S., Munger, K. A., & Vaughn, M. G. (2014). Intensive reading remediation in grade 2 or 3: Are there effects a decade later? *Journal of Educational Psychology*, 106, 46–57.
- Black, J. M., Tanaka, H., Stanley, L., Nagamine, M., Zakerani, N., Thurston, A., ... & Serrone, C. (2012). Maternal history of reading difficulty is associated with reduced language-related gray matter in beginning readers. *NeuroImage*, 59(3), 3021-3032.
- Blau, V., Atteveldt, N. Van, & Ekkebus, M. (2009). Reduced Neural Integration of Letters and Speech Sounds Links Phonological and Reading Deficits in Adult Dyslexia. *Current Biology*, 19(6), 503–508.
- Bloch, F. (1946). Nuclear Induction. *Physical Review*, 70(7-8), 460–474.
- Blomert, L. (2011). The neural signature of orthographic-phonological binding in successful and failing reading development. *NeuroImage*, 57(3), 695–703.
- Bloom, J. S., Garcia-Barrera, M. A., Miller, C. J., Miller, S. R., & Hynd, G. W. (2013). Planum temporale morphology in children with developmental dyslexia. *Neuropsychologia*, 51(9), 1684-1692.
- Boccaletti, S., Latora, V., Moreno, Y., Chavez, M., & Hwang, D. (2006). Complex networks: Structure and dynamics. *Physics Reports*, 424(4-5), 175–308.
- Boets B., Wouters J., van Wieringen A., Ghesquiere P. (2007). Auditory processing, speech perception and phonological ability in pre-school children at high-risk for dyslexia: a longitudinal study of the auditory temporal processing theory. *Neuropsychologia* 45, 1608–1620.
- Boets, B., De, S. B., Cleuren, L., Vandewalle, E., Wouters, J., & Ghesquiere, P. (2010). Towards a further characterization of phonological and literacy problems in Dutch-speaking children with dyslexia. *British Journal of Developmental Psychology*, 28, 5–31.
- Boets, B., de Beeck, H. P. O., Vandermosten, M., Scott, S. K., Gillebert, C. R., Mantini, D., ... & Ghesquière, P. (2013). Intact but less accessible phonetic representations in adults with dyslexia. *Science*, 342(6163), 1251-1254.
- Bokde, A. L., Tagamets, M. A., Friedman, R. B., & Horwitz, B. (2001). Functional interactions of the inferior frontal cortex during the processing of words and word-like stimuli. *Neuron*, 30(2), 609-617.
- Bonifacci, P., & Snowling, M. J. (2008). Speed of processing and reading disability: a cross-linguistic investigation of dyslexia and borderline intellectual functioning. *Cognition*, 107(3), 999-1017.

- Bookheimer, S. (2002). Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annual review of neuroscience*, 25(1), 151-188.
- Boros M, Anton JL, Pech-Georgel C, Grainger J, Szwed M, Ziegler JC. (2016) Orthographic processing deficits in developmental dyslexia: Beyond the ventral visual stream. *Neuroimage* 128: 316-27.
- Bradley, L., and Bryant, P. 1978. Difficulties in auditory organization as a possible cause of reading backwardness. *Nature* 271:746-747.
- Bradley, L., & Bryant, P. (1983). Categorizing sounds and learning to read – a causal connection. *Nature*, 301, 419–421.
- Bradley, L., & Bryant, P. (1985). Rhyme and reason in reading and spelling. Ann Arbor, MI: University of Michigan Press.
- Brady, S., Fowler, A., Stone, B., & Winbury, N. (1994). Training phonological awareness: a study with inner-city kindergarten children. *Annals of Dyslexia*, 44, 26–59.
- Braet, W., & Humphreys, G. W. (2006). Case mixing and the right parietal cortex: evidence from rTMS. *Experimental Brain Research*, 168(1-2), 265–71.
- Brambati, S. M., Termine, C., Ruffino, M., Stella, G., Fazio, F., Cappa, S. F., & Perani, D. (2004). Regional reductions of gray matter volume in familial dyslexia. *Neurology*, 63(4), 742-745.
- Brambati, S. M., Termine, C., Ruffino, M., Danna, M., Lanzi, G., Stella, G., ... & Perani, D. (2006). Neuropsychological deficits and neural dysfunction in familial dyslexia. *Brain research*, 1113(1), 174-185.
- Brennan, F., & Ireson, J. (1997). Training phonological awareness: a study to evaluate the effects of a program of metalinguistic games in kindergarten. *Reading and Writing*, 9, 241–263.
- Brett, M., Penny, W., & Kiebel, S. (2003). An Introduction to Random Field Theory. In *Human Brain Function*, 1–23.
- Bridgeman, B., & Macknik, S. L. (1995). Saccadic suppression relies on luminance information. *Psychological research*, 58(3), 163-168.
- Brodersen, K. H., Schofield, T. M., Leff, A. P., Ong, C. S., Lomakina, E. I., Buhmann, J. M., & Stephan, K. E. (2011). Generative embedding for model-based classification of fMRI data. *PLoS Computational Biology*, 7(6), e1002079.
- Brown, W. E., Eliez, S., Menon, V., Rumsey, J. M., White, C. D., & Reiss, A. L. (2001). Preliminary evidence of widespread morphological variations of the brain in dyslexia. *Neurology*, 56(6), 781-783.
- Bruck, M. (1990). Word-recognition skills of adults with childhood diagnoses of dyslexia. *Developmental Psychology*, 26(3), 439–454.

- Bruck, M. (1992). Persistence of dyslexics' phonological awareness deficits. *Developmental psychology*, 28(5), 874.
- Bruck, M. (1993). Word recognition and component phonological processing skills of adults with childhood diagnosis of dyslexia. *Developmental Review. Special Phonological Processes and Learning Disability*, 13(3), 258–268.
- Bucci MP, Bremond-Gignac D, and Kapoula Z. (2008) Poor binocular coordination of saccades in dyslexic children. *Graefes Archives of Clinical and Experimental Ophthalmology*, 246: 417–428.
- Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network. *Annals of the New York Academy of Sciences*, 1124(1), 1-38.
- Buckner, R. L., Krienen, F. M., & Yeo, B. T. T. (2013). Opportunities and limitations of intrinsic functional connectivity MRI. *Nature Neuroscience*, 16(7), 832–7.
- Budde, M. D., Xie, M., Cross, A. H., & Song, S.-K. (2009). Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: a quantitative pixelwise analysis. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 29(9), 2805–13.
- Bullmore, E. T., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience*, 10(3), 186–98.
- Burns, MK , Senesac, BV. and Symington, T. (2003) The effectiveness of the hosts program in improving the reading achievement of children at-risk for reading failure, *Reading Research and Instruction*, 43:2, 87-103.
- Bush, G., Valera, E. M., & Seidman, L. J. (2005). Functional neuroimaging of attention-deficit/hyperactivity disorder: a review and suggested future directions. *Biological psychiatry*, 57(11), 1273-1284.
- Buxton, R. B., Wong, E. C., & Frank, L. R. (1998). Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. *Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 39(6), 855–64.
- Carter, J.C., Lanham, D.C., Cutting, L.E., Clements-Stephens, A.M., Chen, X.J., Hadzipasic, M., Kim, J., Denckla, M.B., Kaufmann, W.E. (2009) A dual DTI approach to analyzing white matter in children with dyslexia. *Psychiatric Research-Neuroimaging*, 172, 215–219.
- Catani, M., & Jones, D. K. (2005). Perisylvian language networks of the human brain. *Annals of Neurology*, 57(1), 8–16.
- Catani, M., Jones, D. K., & Ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology*, 57(1), 8–16.
- Cao, F., Bitan, T., & Booth, J. R. (2008). Effective brain connectivity in children with reading difficulties during phonological processing. *Brain and language*, 107(2), 91-101.

- Cardoso-Martins, C. (1995). Sensitivity to rhymes, syllables and phonemes in literacy acquisition in Portuguese. *Reading Research Quarterly*, 30, 808–828.
- Carrion-Castillo, A., Franke, B., & Fisher, S. E. (2013). Molecular genetics of dyslexia: an overview. *Dyslexia*, 19(4), 214–40.
- Carter, J. C., Lanham, D. C., Cutting, L. E., Clements-Stephens, A. M., Chen, X., Hadzipasic, M., ... & Kaufmann, W. E. (2009). A dual DTI approach to analyzing white matter in children with dyslexia. *Psychiatry Research: Neuroimaging*, 172(3), 215–219.
- Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., & Zilles, K. (2006). The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. *Neuroimage*, 33(2), 430–448.
- Castro-Caldas A, Peterson KM, Reis A, Stone-Elander S and Ingvar M. (1998) The illiterate brain: Learning to read and write during childhood influences the functional organization of the adult brain. *Brain*, 121: 1053-1063.
- Catani, M. (2005). The rises and falls of disconnection syndromes. *Brain*, 128(10), 2224–2239.
- Catani M, Jones DK, ffytche DH. (2005) Perisylvian language networks of the human brain. *Ann Neurol*; 57: 8–16.
- Catts (1989). Defining dyslexia as a developmental language disorder. *Annals of Dyslexia* 39 (1): 50 – 65.
- Catts, H. W., Gillispie, M., Leonard, L. B., Kail, R. V., & Miller, C. A. (2002). The role of speed of processing, rapid naming, and phonological awareness in reading achievement. *Journal of learning disabilities*, 35(6), 510–525.
- Catts, H. W., Compton, D., Tomblin, J. B., & Bridges, M. S. (2012). Prevalence and nature of late-emerging poor readers. *Journal of educational psychology*, 104(1), 166.
- Cestnick L. (2001). Cross-modality temporal processing deficits in developmental phonological dyslexics. *Brain Cogn.* 46, 319–325.
- Chai, X. J., Castañón, A. N., Ongür, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *NeuroImage*, 59(2), 1420–8.
- Chang, C., & Glover, G. H. (2009). Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *NeuroImage*, 47(4), 1448–59.
- Chang, C., & Glover, G. H. (2010). Time-frequency dynamics of resting-state brain connectivity measured with fMRI. *NeuroImage*, 50(1), 81–98.
- Chiappe, P., Stringer, R., Siegel, L. S., & Stanovich, K. E. (2002). Why the timing deficit hypothesis does not explain reading disability in adults. *Reading and Writing*, 15(1), 73–107.

- Chouake, T., Levy, T., Javitt, D. C., & Lavidor, M. (2012). Magnocellular training improves visual word recognition. *Frontiers in human neuroscience*, *6*, 14.
- Christodoulou JA, Del Tufo SN, Lymberis J, Saxler PK, Ghosh SS, Triantafyllou C, Whitfield-Gabrieli S, Gabrieli JD. (2014) Brain bases of reading fluency in typical reading and impaired fluency in dyslexia. *PLoS One* *9*(7):e100552.
- Clayden, J. D., Maniega, S. M., Storkey, A. J., King, M. D., Bastin, M. E., & Clark, C. A. (2011). TractoR: Magnetic resonance imaging and tractography with R. *Journal of Statistical Software*, *44*(8), 1-18.
- Clower, D. M., West, R. A., Lynch, J. C., & Strick, P. L. (2001). The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *The Journal of Neuroscience*, *21*(16), 6283-6291.
- Cohen, L., Dehaene, S., Naccache, L., Lehéricy, S., Dehaene-Lambertz, G., Hénaff, M. a, & Michel, F. (2000). The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. *Brain : A Journal of Neurology*, *123* (2), 291–307.
- Cole, D. M., Smith, S. M., & Beckmann, C. F. (2010). Advances and pitfalls in the analysis and interpretation of resting-state fMRI data. *Frontiers in Systems Neuroscience*, *4*(April), 8.
- Coltheart, M., Rastle, K., Perry, C., Langdon, R., & Ziegler, J. (2001). DRC: a dual route cascaded model of visual word recognition and reading aloud. *Psychological review*, *108*(1), 204.
- Compton, D. L., DeFries, J. C., & Olson, R. K. (2001). Are RAN-and phonological awareness-deficits additive in children with reading disabilities? *Dyslexia*, *7*(3), 125-149.
- Conrad, N. J., & Levy, B. A. (2011). Training letter and orthographic pattern recognition in children with slow naming speed. *Reading and Writing*, *24*(1), 91-115.
- Cope, N., Eicher, J. D., Meng, H., Gibson, C. J., Hager, K., Lacadie, C., ... & Gruen, J. R. (2012). Variants in the DYX2 locus are associated with altered brain activation in reading-related brain regions in subjects with reading disability. *Neuroimage*, *63*(1), 148-156.
- Cordes, D., Haughton, V. M., Arfanakis, K., Carew, J. D., Turski, P. A., Moritz, C. H., ... Meyerand, M. E. (2001). Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. *AJNR. American Journal of Neuroradiology*, *22*(7), 1326–33.
- Cornwall, A. (1992). The relationship of phonological awareness, rapid naming, and verbal memory to severe reading and spelling disability. *Journal of Learning Disabilities*, *25*(8), 532-538.
- Cornelissen, P., Richardson, A., Mason, A., Fowler, S., & Stein, J. (1995). Contrast sensitivity and coherent motion detection measured at photopic luminance levels in dyslexics and controls. *Vision research*, *35*(10), 1483-1494.

- Cronin, V. S. (2013). RAN and double-deficit theory. *Journal of Learning Disabilities, 46*(2), 182-190.
- Crowder, R. G. (1982). *The psychology of reading*. New York: Cambridge University Press.
- Cunningham, A. E., & Stanovich, K. E. (1998). The impact of print exposure on word recognition.
- Currier, T. A., Etchegaray, M. A., Haight, J. L., Galaburda, A. M., & Rosen, G. D. (2011). The effects of embryonic knockdown of the candidate dyslexia susceptibility gene homologue *Dyx1c1* on the distribution of GABAergic neurons in the cerebral cortex. *Neuroscience, 172*, 535–46.
- Cutting, L. E., & Denckla, M. B. (2001). The relationship of rapid serial naming and word reading in normally developing readers: An exploratory model. *Reading and Writing, 14*(7-8), 673-705.
- Damasio H, Damasio AR (1980) The anatomical basis of conduction aphasia. *Brain 103*(2), 337–350.
- Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America, 103*(37), 13848–53.
- Dandache, S., Wouters, J., & Ghesquière, P. (2014). Development of reading and phonological skills of children at family risk for dyslexia: A longitudinal analysis from kindergarten to sixth grade. *Dyslexia, 20*(4), 305-329.
- Danelli, L., Berlingeri, M., Bottini, G., Ferri, F., Vacchi, L., Sberna, M., & Paulesu, E. (2013). Neural intersections of the phonological, visual magnocellular and motor/cerebellar systems in normal readers: implications for imaging studies on dyslexia. *Human brain mapping, 34*(10), 2669-2687.
- Darki, F., Peyrard-Janvid, M., Matsson, H., Kere, J., & Klingberg, T. (2012). Three dyslexia susceptibility genes, *DYX1C1*, *DCDC2*, and *KIAA0319*, affect temporo-parietal white matter structure. *Biological Psychiatry, 72*(8), 671–6.
- Darki, F., Peyrard-Janvid, M., Matsson, H., Kere, J., & Klingberg, T. (2014). *DCDC2* Polymorphism Is Associated with Left Temporoparietal Gray and White Matter Structures during Development. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(43), 14455–62.
- Dawes, P., Sirimanna, T., Burton, M., Vanniasegaram, I., Tweedy, F., & Bishop, D. V. M. (2009). Temporal auditory and visual motion processing of children diagnosed with auditory processing disorder and dyslexia. *Ear & Hearing, 30*, 675–686.
- Deacon, S. H., Parrila, R., & Kirby, J. R. (2006). Processing of derived forms in high-functioning dyslexics. *Annals of Dyslexia, 56*(1), 103–128.

- De Bree, E., Wijnen, F., & Gerrits, E. (2010). Non-word repetition and literacy in Dutch children at-risk of dyslexia and children with SLI: results of the follow-up study. *Dyslexia*, 16(1), 36-44.
- De Jong, P. F., & Van der Leij, A. (2002). Effects of phonological abilities and linguistic comprehension on the development of reading. *Scientific Studies of Reading*, 6, 51–77.
- De Jong, P. F., & Vrieling, L. O. (2004). Rapid automatic naming: Easy to measure, hard to improve (quickly). *Annals of dyslexia*, 54(1), 65-88.
- Deco, G., Jirsa, V. K., & McIntosh, A. R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nature Reviews. Neuroscience*, 12(1), 43–56.
- Deeney, T., Wolf, M., & Goldberg O'Rourke, a. (2001). "I like to take my own sweet time": Case Study of a Child with Naming-Speed Deficits and Reading Disabilities. *The Journal of Special Education*, 35(3), 145–155.
- Dehaene, S., Cohen, L., Morais, J., & Kolinsky, R. (2015). Illiterate to literate: behavioural and cerebral changes induced by reading acquisition. *Nature Reviews Neuroscience*, 16(4), 234-244.
- Déjérine J. Sur un cas de cécité verbale avec agraphie suivi d'autopsie. *Mém Soc Biol* 1891; 3: 197–201.
- Déjérine J. Contribution a l'étude anatomo-pathologique et clinique des différentes variétés de cécité-verbale. *Mém Soc Biol* 1892; 4: 61–90.
- DeLaPaz, R. L. (1994). Echo-planar imaging. *Radiographics : A Review Publication of the Radiological Society of North America, Inc*, 14(5), 1045–58.
- Démonet, J. F., Taylor, M. J., & Chaix, Y. (2004). Developmental dyslexia. *The Lancet*, 363(9419), 1451-1460.
- Deutsch, G.K., Dougherty, R.F., Bammer, R., Siok, W.T., Gabrieli, J.D., Wandell, E. B. (2005) Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. *Cortex*, 41, 354–363.
- Dewitt, I., & Rauschecker, J. P. (2012). Phoneme and word recognition in the auditory ventral stream. *Proceedings of the National Academy of Sciences of the United States of America*, 109(8), E505–14.
- Díaz B, Hintz F, Kiebel SJ, von Kriegstein K. (2012) Dysfunction of the auditory thalamus in developmental dyslexia. *Proc Natl Acad Sci* 109(34):13841-6.
- Dimitriadis, S. I., Laskaris, N. A., Simos, P. G., Micheloyannis, S., Fletcher, J. M., Rezaie, R., & Papanicolaou, A. C. (2013). Altered temporal correlations in resting-state connectivity fluctuations in children with reading difficulties detected via MEG. *Neuroimage*, 83, 307-317.

- Dobromyslin, V. I., Salat, D. H., Fortier, C. B., Leritz, E. C., Beckmann, C. F., Milberg, W. P., & McGlinchey, R. E. (2012). Distinct functional networks within the cerebellum and their relation to cortical systems assessed with independent component analysis. *NeuroImage*, *60*(4), 2085–2073.
- Dosenbach, N. U. F., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A. T., ... Petersen, S. E. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(26), 11073–8.
- Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in cognitive sciences*, *12*(3), 99-105.
- Dougherty, R. F., Ben-Shachar, M., Deutsch, G. K., Hernandez, A., Fox, G. R., & Wandell, B. a. (2007). Temporal-callosal pathway diffusivity predicts phonological skills in children. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(20), 8556–61.
- Eckert, M. A., Leonard, C. M., Richards, T. L., Aylward, E. H., Thomson, J., & Berninger, V. W. (2003). Anatomical correlates of dyslexia: frontal and cerebellar findings. *Brain*, *126*(2), 482-494.
- Eckert, M. A., Leonard, C. M., Wilke, M., Eckert, M., Richards, T., Richards, A., & Berninger, V. (2005). Anatomical signatures of dyslexia in children: unique information from manual and voxel based morphometry brain measures. *Cortex*, *41*(3), 304-315.
- Eden, G. F., Jones, K. M., Cappell, K., Gareau, L., Wood, F. B., Zeffiro, T. A., ... Flowers, D. L. (2004). Neural changes following remediation in adult developmental dyslexia. *Neuron*, *44*(3), 411–22.
- Ehri, L. C. (1979). Linguistic insight: Threshold of reading acquisition. In T. Waller & G. Mackinnon (Eds.), *Reading research: Advances in theory and practice* (pp. 63-114). New York: Academic Press.
- Eidelberg, D., & Galaburda, A. M. (1984). Inferior parietal lobule: divergent architectonic asymmetries in the human brain. *Archives of neurology*, *41*(8), 843-852.
- Elbro, C., Borstrom, I., & Peterson, D. K. (1998). Predicting dyslexia from kindergarten: the importance of distinctness of phonological representations of lexical items. *Reading Research Quarterly*, *33*, 36–60.
- Elbro, C., & Scarborough, H. S. (2003). *International handbook of children's reading*.
- Escribano, C. L. (2007). Evaluation of the double-deficit hypothesis subtype classification of readers in Spanish. *Journal of Learning Disabilities*, *40*(4), 319–330.
- Etmanskie, J. M., Partanen, M., & Siegel, L. (2015). A longitudinal examination of the persistence of late emerging reading disabilities. *Journal of Learning Disabilities*.

- Evans, T. M., Flowers, D. L., Napoliello, E. M., & Eden, G. F. (2014). Sex-specific gray matter volume differences in females with developmental dyslexia. *Brain Structure and Function*, 219(3), 1041-1054.
- Everatt, J. (1997). The Abilities and Disabilities Associated with Adult Developmental Dyslexia. *Journal of Research in Reading*, 20(1), 13–21.
- Farmer M. E., Klein R. M. (1995). The evidence for a temporal processing deficit linked to dyslexia: a review. *Psychon. Bull. Rev.* 2, 460–493.
- Fawcett, A. J., & Nicolson, R. I. (1994). Naming speed in children with dyslexia. *Journal of Learning Disabilities*, 27(10), 641-646.
- Fawcett, A. J., Nicolson, R. I., & Dean, P. (1996). Impaired performance of children with dyslexia on a range of cerebellar tasks. *Annals of Dyslexia*, 46(1), 259-283.
- Fawcett, A.J. and Nicolson, R.I. (1999) Performance of dyslexic children on cerebellar and cognitive tests. *J. Mot. Behav.* 31, 68–78.
- Felton, R. H., Naylor, C. E., & Wood, F. B. (1990). Neuropsychological profile of adult dyslexics. *Brain and Language*, 39(4), 485–497.
- Fernandez, V. G., Stuebing, K., Juranek, J., & Fletcher, J. M. (2013). Volumetric analysis of regional variability in the cerebellum of children with dyslexia. *The Cerebellum*, 12(6), 906-915.
- Field, A. (2009). *Discovering statistics using SPSS*. Sage publications.
- Finn, E. S., Shen, X., Holahan, J. M., Scheinost, D., Lacadie, C., Papademetris, X., ... & Constable, R. T. (2013). Disruption of functional networks in dyslexia: a whole-brain, data-driven analysis of connectivity. *Biological psychiatry*, 76(5), 397-404.
- Finucci, J. M., Whitehouse, C. C., Isaacs, S. D., & Childs, B. (1984). Derivation and validation of a quantitative definition of specific reading disability for adults. *Developmental Medicine and Child Neurology*, 26(2), 143–153.
- Fischer, B. and Hartnegg, K. (2000a) Effects of visual training on saccade control in dyslexia. *Perception* 29, 531–542
- Fischer B and Hartnegg K. (2000b) Stability of gaze control in dyslexia. *Strabismus*, 8: 119–122.
- Fox, B., & Routh, D. K. (1974). Analyzing spoken language into words, syllables and phonemes: a developmental study. *Journal of Psycholinguistic Research*, 4, 331–342.
- Fox, B., and Routh, D. 1980. Phonemic analysis and severe reading disability. *Journal of Psycholinguistic Research* 9:115-119.
- Fox, B., & Routh, D. K. (1984). Phonemic analysis and synthesis as word attack skills: revisited. *Journal of Educational Psychology*, 76, 1059–1064.

- Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, 8(9), 700-711.
- Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences of the United States of America*, 103(26), 10046-51.
- Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The Global Signal and Observed Anticorrelated Resting State Brain Networks, 1, 3270-3283.
- Franceschini, S., Gori, S., Ruffino, M., Pedrolli, K., & Facoetti, A. (2012). A causal link between visual spatial attention and reading acquisition. *Current Biology*, 22(9), 814-819.
- Freedman, D., & Lane, D. (1983). A nonstochastic interpretation of reported significance levels. *Journal of Business & Economic Statistics*, 1(4), 292-298.
- Friederici, A. D., Bahlman, J., Heim, S., Schubotz, R., and Anwander, A. (2006). The brain differentiates human and non-human grammars: functional localization and structural connectivity. *Proc. Natl. Acad. Sci. U.S.A.* 103, 2458-2463.
- Friederici, A. D. (2009). Pathways to language: fiber tracts in the human brain. *Trends in Cognitive Sciences*, 13(4), 175-81.
- Friederici, A. D. (2011). The brain basis of language processing: from structure to function. *Physiological Reviews*, 91(4), 1357-92.
- Friederici, A. D., Brauer, J., and Lohmann, G. (2011). Maturation of the language network: From inter to intrahemispheric connectivities. *PLoS ONE* 6:e20726.
- Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. P., Frith, C. D., & Frackowiak, R. S. (1994). Statistical parametric maps in functional imaging: a general linear approach. *Human brain mapping*, 2(4), 189-210.
- Friston, K. J., Li, B., Daunizeau, J., & Stephan, K. E. (2011). Network discovery with DCM. *NeuroImage*, 56(3), 1202-1221.
- Frye, R.E., Hasan, K., Xue, L., Strickland, D., Malmberg, B., Liederman, J., Papanicolaou, A. (2008) Splenium microstructure is related to two dimensions of reading skill. *Neuroreport*, 19, 1627-1631.
- Fugate, M. H. (1997). Letter training and its effect on the development of beginning reading skills. *School Psychology Quarterly*, 12(2), 170.
- Fulbright, R. K., Jenner, A. R., Mencl, W. E., Pugh, K. R., Shaywitz, B. A., Shaywitz, S. E., ... & Marchione, K. E. (1999). The cerebellum's role in reading: a functional MR imaging study. *American Journal of Neuroradiology*, 20(10), 1925-1930.
- Gabrieli, J. D. (2009). Dyslexia: a new synergy between education and cognitive neuroscience. *science*, 325(5938), 280-283.

- Galaburda, A. M., & Kemper, T. L. (1979). Cytoarchitectonic abnormalities in developmental dyslexia: a case study. *Annals of neurology*, *6*(2), 94-100.
- Galaburda, A. M., Sherman, G. F., Rosen, G. D., Aboitiz, F., & Geschwind, N. (1985). Developmental dyslexia: four consecutive patients with cortical anomalies. *Annals of neurology*, *18*(2), 222-233.
- Galaburda, A. M., Menard, M. T., & Rosen, G. D. (1994). Evidence for aberrant auditory anatomy in developmental dyslexia. *Proceedings of the National Academy of Sciences*, *91*(17), 8010-8013.
- Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*, *15*(4), 870-878.
- Georgiou, G. K., Parrila, R., Kirby, J. R., & Stephenson, K. (2008). Rapid naming components and their relationship with phonological awareness, orthographic knowledge, speed of processing, and different reading outcomes. *Scientific Studies of Reading*, *12*(4), 325-350.
- Georgiou, G. K., Parrila, R., & Papadopoulos, T. C. (2008). Predictors of word decoding and reading fluency across languages varying in orthographic consistency. *Journal of Educational Psychology*, *100*(3), 566.
- Geschwind, N. (1965). Disconnexion syndromes in animals and man. *Brain*, *88*(3), 585-585.
- Getchell N, Pabreja P, Neeld K, and Carrio V. (2007) Comparing children with and without dyslexia on the Movement Assessment Battery for Children and the Test of Gross Motor Development. *Perceptual and Motor Skills*, *105*: 207–214.
- Gibson, L. Y., Hogben, J. H., & Fletcher, J. (2006). Visual and auditory processing and component reading skills in developmental dyslexia. *Cognitive Neuropsychology*, *23*, 621–642.
- Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex (New York, N.Y. : 1991)*, *18*(11), 2471–82.
- Glickstein, M. (2006). Thinking about the cerebellum. *Brain*, *129*(2), 288-290.
- Glickstein, M. (2007). What does the cerebellum really do?. *Current Biology*, *17*(19), R824-R827.
- Goense, J. B. M., & Logothetis, N. K. (2008). Neurophysiology of the BOLD fMRI signal in awake monkeys. *Current Biology : CB*, *18*(9), 631–40.
- Goldstein, D. M. (1976). Cognitive-linguistic functioning and learning to read in preschoolers. *Journal of Educational Psychology*, *68*, 680–688.
- Goswami, U., Thomson, J., Richardson, U., Stainthorp, R., Hughes, D., Rosen, S., & Scott, S. K. (2002). Amplitude envelope onsets and developmental dyslexia: A new hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *99*, 10911–10916.

- Goswami U., Gerson D., Astruc L. (2010). Amplitude envelope perception, phonology and prosodic sensitivity in children with developmental dyslexia. *Reading and Writing*, 23, 995–1019.
- Goswami, U., Wang, H.-L. S., Cruz, A., Fosker, T., Mead, N., & Huss, M. (2011). Language-universal sensory deficits in developmental dyslexia: English, Spanish, and Chinese. *Journal of Cognitive Neuroscience*, 23, 325–337.
- Gottardo, A., Siegel, L. S., & Stanovich, K. E. (1997). The assessment of adults with reading disabilities: what can we learn from experimental tasks? *Journal of Research in Reading*, 20(1), 42–54.
- Grande, M., Meffert, E., Huber, W., Amunts, K., & Heim, S. (2011). Word frequency effects in the left IFG in dyslexic and normally reading children during picture naming and reading. *Neuroimage*, 57(3), 1212-1220.
- Gross-Glenn, K., Jallad, B., Novoa, L., Helgren-Lempesis, V., & Lubs, H. a. (1990). Nonsense passage reading as a diagnostic aid in the study of adult familial dyslexia. *Reading and Writing*, 2(2), 161–173.
- Grünling, C., Ligges, M., Huonker, R., Klingert, M., Mentzel, H. J., Rzanny, R., ... & Blanz, B. (2004). Dyslexia: The possible benefit of multimodal integration of fMRI-and EEG-data. *Journal of Neural Transmission*, 111(7), 951-969.
- Guye, M., Bettus, G., Bartolomei, F., & Cozzone, P. J. (2010). Graph theoretical analysis of structural and functional connectivity MRI in normal and pathological brain networks. *Magnetic Resonance Materials in Physics, Biology and Medicine*, 23(5-6), 409-421.
- Hagoort P. (2005) On Broca, brain, and binding: a new framework. *Trends Cogn Sci* 9: 416-423.
- Hajnal, J. V, Doran, M., Hall, A. S., Collins, A. G., Oatridge, A., Pennock, J. M., ... Bydder, G. M. (1991). MR imaging of anisotropically restricted diffusion of water in the nervous system: technical, anatomic, and pathologic considerations. *Journal of Computer Assisted Tomography*, 15(1), 1–18.
- Halliday, L. F., & Bishop, D. V. M. (2006). Auditory frequency discrimination in children with dyslexia. *Journal of Research in Reading*, 29, 213–228.
- Hämäläinen, J., Leppänen, P. H. T., Torppa, M., Muller, K., & Lyytinen, H. (2005). Detection of sound rise time by adults with dyslexia. *Brain and Language*, 94, 32–42.
- Hämäläinen, J., Leppänen, P. H. T., Eklund, K., Thomson, J., Richardson, U., Guttorm, T. K., et al. (2009). Common variance in amplitude envelope perception tasks and their impact on phoneme duration perception and reading and spelling in Finnish children with reading disabilities. *Applied Psycholinguistics*, 30, 511–530.

- Hämäläinen J. A., Salminen H. K., Leppanen P. (2013). Basic auditory processing deficits in dyslexia: systematic review of the behavioral and event-related potential/field evidence. *J. Learn. Disabil.* 46, 413–427.
- Han, S., Jiang, Y., Gu, H., Rao, H., Mao, L., Cui, Y., & Zhai, R. (2004). The role of human parietal cortex in attention networks. *Brain : A Journal of Neurology*, 127(Pt 3), 650–9.
- Harsan, L. A., Poulet, P., Guignard, B., Parizel, N., Skoff, R. P., & Ghandour, M. S. (2007). Astrocytic hypertrophy in dysmyelination influences the diffusion anisotropy of white matter. *Journal of Neuroscience Research*, 85(5), 935–44.
- Hasan KM, Molfese DL, Walimuni IS, Stuebing KK, Papanicolaou AC, Narayana PA. Diffusion tensor quantification and cognitive correlates of the macrostructure and microstructure of the corpus callosum in typically developing and dyslexic children. *NMR in Biomedicine*. 2012;25:1263–1270.
- Hatcher, J., Hulme, C., & Ellis, A. W. (1994). Ameliorating early reading failure by integrating the teaching of reading and phonological skills: the phonological linkage hypothesis. *Child Development*, 65, 41–57.
- Hatcher, J., Snowling, M. J., & Griffiths, Y. M. (2002). Cognitive assessment of dyslexic students in higher education. *The British Journal of Educational Psychology*, 72(Pt 1), 119–133.
- Hauk, O., Johnsrude, I., & Pulvermüller, F. (2004). Somatotopic Representation of Action Words in Human Motor and Premotor Cortex. *Neuron*, 41(2), 301–307.
- Heath S.M., Hogben J.H., Clark C.D. (1999) Auditory temporal processing in disabled readers with and without oral language delay. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 40, 637–647.
- Heath SM, Hogben JH (2004) The reliability and validity of tasks measuring perception of rapid sequences in children with dyslexia. *J Child Psychol Psychiatry* 45,1275–1287.
- Heath S. M., Bishop D. V. M., Hogben J. H., Roach N. W. (2006). Psychophysical indices of perceptual functioning in dyslexia: a psychometric analysis. *Cogn. Neuropsychol.* 23, 905–929.
- Heikkilä, R., Torppa, M., Aro, M., Närhi, V., & Ahonen, T. (2015). Double-deficit hypothesis in a clinical sample extension beyond reading. *Journal of learning disabilities*, 0022219415572895.
- Heim, S., Wehnelt, A., Grande, M., Huber, W., & Amunts, K. (2013). Effects of lexicality and word frequency on brain activation in dyslexic readers. *Brain and language*, 125(2), 194–202.
- Heim, S., Pape-Neumann, J., van Ermingen-Marbach, M., Brinkhaus, M., & Grande, M. (2014). Shared vs. specific brain activation changes in dyslexia after training of phonology, attention, or reading. *Brain Structure and Function*, 2191–2207.

- Henderson, L.-M., Tsogka, N., & Snowling, M. (2013). Questioning the benefits the coloured overlays can have for reading in students with and without dyslexia. *Journal of Research in Special Educational Needs*, 13(1), 57-65.
- Hernandez N, Andersson F, Edjlali M, Hommet C, Cottier JP, Destrieux C, Bonnet-Brilhault F. Cerebral functional asymmetry and phonological performance in dyslexic adults. *Psychophysiology* 50(12):1226-38.
- Hickok, G. & Poeppel, D. (2004) Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. *Cognition*, 92, 67–99.
- Hinshelwood, J. (1900). CONGENITAL WORD-BLINDNESS. *The Lancet*, 155(4004), 1506-1508.
- Hintikka, S., Aro, M., & Lyytinen, H. (2005). Computerized training of the correspondences between phonological and orthographic units. *Written Language & Literacy*, 8(2), 79-102.
- Hodges, J., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain*, 1783–1806.
- Hoefl, F., Hernandez, A., McMillon, G., Taylor-Hill, H., Martindale, J. L., Meyler, A., ... & Whitfield-Gabrieli, S. (2006). Neural basis of dyslexia: a comparison between dyslexic and nondyslexic children equated for reading ability. *The Journal of Neuroscience*, 26(42), 10700-10708.
- Hoefl, F., Meyler, A., Hernandez, A., Juel, C., Taylor-Hill, H., Martindale, J. L., ... & Deutsch, G. K. (2007). Functional and morphometric brain dissociation between dyslexia and reading ability. *Proceedings of the National Academy of Sciences*, 104(10), 4234-4239.
- Hood, M. and Conlon, E. (2004) Visual and auditory temporal processing and early reading development. *Dyslexia* 10, 234–252.
- Horwitz, B., Rumsey, J. M., & Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences*, 95(15), 8939-8944.
- Horowitz-Kraus T, Vannest JJ, Kadis D, Cicchino N, Wang YY, Holland SK. (2014) Reading acceleration training changes brain circuitry in children with reading difficulties. *Brain Behav.* 4(6):886-902.
- Horowitz-Kraus T, Holland SK. (2015) Greater functional connectivity between reading and error-detection regions following training with the reading acceleration program in children with reading difficulties. *Ann Dyslexia*. 65(1):1-23
- Horowitz-Kraus T, DiFrancesco M, Kay B, Wang Y, Holland SK. (2015) Increased resting-state functional connectivity of visual- and cognitive-control brain networks after training in children with reading difficulties. *Neuroimage Clin.* 8:619-30.

- Horowitz-Kraus, T., Toro-Serey, C., & DiFrancesco, M. (2015). Increased resting-state functional connectivity in the cingulo-opercular cognitive-control network after intervention in children with reading difficulties. *PLoS one*, *10*(7), e0133762.
- Hosseini, S. H., Black, J. M., Soriano, T., Bugescu, N., Martinez, R., Raman, M. M., ... & Hoefl, F. (2013). Topological properties of large-scale structural brain networks in children with familial risk for reading difficulties. *Neuroimage*, *71*, 260-274.
- Howard Jr JH, Howard DV, Japikse KC, and Eden GF. Dyslexics are impaired on implicit higher-order sequence learning, but not on implicit spatial context learning. *Neuropsychologia*, *44*: 1131–1144.
- Hu, W., Lee, H. L., Zhang, Q., Liu, T., Geng, L. B., Seghier, M. L., ... & Price, C. J. (2010). Developmental dyslexia in Chinese and English populations: dissociating the effect of dyslexia from language differences. *Brain*, *133*(6), 1694-1706.
- Huang, H., Zhang, J., Wakana, S., Zhang, W., Ren, T., Richards, L. J., ... Mori, S. (2006). White and gray matter development in human fetal, newborn and pediatric brains. *NeuroImage*, *33*(1), 27–38.
- Humphreys, P., Kaufmann, W. E., & Galaburda, A. M. (1990). Developmental dyslexia in women: neuropathological findings in three patients. *Annals of neurology*, *28*(6), 727-738.
- Hutzler F, Kronbichler M, Jacobs AM, and Wimmer H. (2006) Perhaps correlational but not causal: No effect of dyslexic readers' magnocellular system on their eye movements during reading. *Neuropsychologia*, *44*: 637–648.
- Hynd, G. W., Hall, J., Novey, E. S., Eliopoulos, D., Black, K., Gonzalez, J. J., ... & Cohen, M. (1995). Dyslexia and corpus callosum morphology. *Archives of Neurology*, *52*(1), 32-38.
- Ito, M. (1972). Neural design of the cerebellar motor control system. *Brain research*, *40*(1), 81-84.
- Illingworth, S., & Bishop, D. V. M. (2009). Atypical cerebral lateralisation in adults with compensated developmental dyslexia demonstrated using functional transcranial Doppler ultrasound. *Brain and Language*, *111*(1), 61–65.
- Ingvar, M., Af Trampe, P., Greitz, T., Eriksson, L., Stone-Elander, S., & Von Euler, C. (2002). Residual differences in language processing in compensated dyslexics revealed in simple word reading tasks. *Brain and Language*, *83*(2), 249–267.
- Ivliev, A. E., 't Hoen, P. a C., van Roon-Mom, W. M. C., Peters, D. J. M., & Sergeeva, M. G. (2012). Exploring the transcriptome of ciliated cells using in silico dissection of human tissues. *PLoS One*, *7*(4), e35618.
- Jednoróg, K., Gawron, N., Marchewka, A., Heim, S., & Grabowska, A. (2014). Cognitive subtypes of dyslexia are characterized by distinct patterns of grey matter volume. *Brain Structure and Function*, *219*(5), 1697-1707.

- Jednorog, K., Marchewka, A., Altarelli, I., Monzalvo Lopez, A. K., van Ermingen-Marbach, M., Grande, M., ... & Ramus, F. (2015). How reliable are gray matter disruptions in specific reading disability across multiple countries and languages? insights from a large-scale voxel-based morphometry study. *Human brain mapping, 36*(5), 1741-1754.
- Jeurissen, B., Leemans, A., Jones, D. K., Tournier, J.-D., & Sijbers, J. (2011). Probabilistic fiber tracking using the residual bootstrap with constrained spherical deconvolution. *Human Brain Mapping, 32*(3), 461–79.
- Jeurissen, B., Leemans, A., Tournier, J.-D., Jones, D. K., & Sijbers, J. (2013). Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. *Human Brain Mapping, 34*(11), 2747–66.
- Jobard, G., Crivello, F., & Tzourio-Mazoyer, N. (2003). Evaluation of the dual route theory of reading: a metaanalysis of 35 neuroimaging studies. *Neuroimage, 20*(2), 693-712.
- Jones, M.W. et al. (2008) Visual deficits in developmental dyslexia: relationships between non-linguistic visual tasks and their contribution to components of reading. *Dyslexia 14*: 95–115.
- Kast M, Bezzola L, Jäncke L, Meyer M. (2011) Multi- and unisensory decoding of words and nonwords result in differential brain responses in dyslexic and nondyslexic adults. *Brain Lang. 119*(3):136-48.
- Katzir, T., Kim, Y., Wolf, M., O'Brien, B., Kennedy, B., Lovett, M., & Morris, R. (2006). Reading fluency: The whole is more than the parts. *Annals of dyslexia, 56*(1), 51-82.
- Keller, S. S., Crow, T., Foundas, A., Amunts, K., & Roberts, N. (2009). Broca's area: nomenclature, anatomy, typology and asymmetry. *Brain and Language, 109*(1), 29–48.
- Kelly S, Griffiths S, and Frith U. (2002) Evidence for implicit sequence learning in dyslexia. *Dyslexia, 8*: 43–52.
- Kelly, A. M. C., Di Martino, A., Uddin, L. Q., Shehzad, Z., Gee, D. G., Reiss, P. T., ... Milham, M. P. (2009). Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cerebral Cortex 19*(3), 640–57.
- Kelly, C., Uddin, L. Q., Shehzad, Z., Margulies, D. S., Castellanos, F. X., Milham, M. P. and Petrides, M. (2010), Broca's region: linking human brain functional connectivity data and non-human primate tracing anatomy studies. *European Journal of Neuroscience, 32*: 383–398.
- Kelly, C., Biswal, B. B., Craddock, R. C., Castellanos, F. X., & Milham, M. P. (2012). Characterizing variation in the functional connectome: promise and pitfalls. *Trends in Cognitive Sciences, 1*–8.
- Kevan, A., & Pammer, K. (2008). Visual deficits in pre-readers at familial risk for dyslexia. *Vision research, 48*(28), 2835-2839.

- Kevan, A., & Pammer, K. (2009). Predicting early reading skills from pre-reading measures of dorsal stream functioning. *Neuropsychologia*, 47(14), 3174-3181.
- Kibby, M. Y., Fancher, J. B., Markanen, R., & Hynd, G. W. (2008). A quantitative magnetic resonance imaging analysis of the cerebellar deficit hypothesis of dyslexia. *Journal of child neurology*, 23(4), 368-380.
- Kiebel, S., & Holmes, A. (2003). The general linear model. In R. S. Frackowiak, K. J. Friston, J. Ashburner, & W. Penny (Eds.), *Human brain function* (2nd ed.). Retrieved from [http://ftp.mpg.de/pub/kyb/chaimow/For Me/Func_Imag/GLM.pdf](http://ftp.mpg.de/pub/kyb/chaimow/For%20Me/Func_Imag/GLM.pdf)
- Kiebel, S. J., Klöppel, S., Weiskopf, N., & Friston, K. J. (2007). Dynamic causal modeling: a generative model of slice timing in fMRI. *NeuroImage*, 34(4), 1487-96.
- King, W. M., Lombardino, L. J., Crandell, C. C., & Leonard, C. M. (2003). Comorbid auditory processing disorder in developmental dyslexia. *Ear & Hearing*, 24, 448-456.
- Kinsbourne, M., & Warrington, E. K. (1962). A variety of reading disability associated with right hemisphere lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, 25(4), 339-344.
- Kinsbourne, M., Palmer, R. L., & Berliner, A. K. (1991). Neuropsychological Deficits in Adults With Dyslexia. *Developmental Medicine & Child Neurology*, 763-775.
- Kirby, J. R., Georgiou, G. K., Martinussen, R., & Parrila, R. (2010). Review of Research: Naming Speed and Reading: From Prediction to Instruction. *Reading Research Quarterly*, 45(3), 341-362.
- Klingberg, T., Hedehus, M., Temple, E., & Salz, T. (2000). Microstructure of Temporo-Parietal White Matter as a Basis for Reading Ability: Evidence from Diffusion Tensor Magnetic Resonance Imaging. *Neuron*, 25(2), 493-500.
- Kochunov, P., Glahn, D. C., Lancaster, J., Thompson, P. M., Kochunov, V., Rogers, B., ... Williamson, D. E. (2011). Fractional anisotropy of cerebral white matter and thickness of cortical gray matter across the lifespan. *NeuroImage*, 58(1), 41-49.
- Kovelman, I., Norton, E. S., Christodoulou, J. A., Gaab, N., Lieberman, D. A., Triantafyllou, C., ... & Gabrieli, J. D. (2012). Brain basis of phonological awareness for spoken language in children and its disruption in dyslexia. *Cerebral Cortex*, 22(4), 754-764.
- Koyama, M. S., Di Martino, A., Zuo, X. N., Kelly, C., Mennes, M., Jutagir, D. R., ... & Milham, M. P. (2011). Resting-state functional connectivity indexes reading competence in children and adults. *The Journal of Neuroscience*, 31(23), 8617-8624.
- Koyama, M. S., Di Martino, A., Kelly, C., Jutagir, D. R., Sunshine, J., Schwartz, S. J., ... & Milham, M. P. (2013). Cortical signatures of dyslexia and remediation: an intrinsic functional connectivity approach. *PloS one*, 8(2), e55454.

- Krafnick, A. J., Flowers, D. L., Luetje, M. M., Napoliello, E. M., & Eden, G. F. (2014). An investigation into the origin of anatomical differences in dyslexia. *The Journal of Neuroscience*, *34*(3), 901-908.
- Kronbichler, M., Wimmer, H., Staffen, W., Hutzler, F., Mair, A., & Ladurner, G. (2008). Developmental dyslexia: gray matter abnormalities in the occipitotemporal cortex. *Human brain mapping*, *29*(5), 613-625.
- Kronschnabel J, Schmid R, Maurer U, Brandeis D. (2013) Visual print tuning deficits in dyslexic adolescents under minimized phonological demands. *Neuroimage*. *74*: 58-69.
- Kronschnabel J, Brem S, Maurer U, Brandeis D. (2014) The level of audiovisual print-speech integration deficits in dyslexia. *Neuropsychologia* *62*:245-61.
- Kruk, R., Sumbler, K., & Willows, D. (2008). Visual processing characteristics of children with Meares-Irlen syndrome. *Ophthalmic and Physiological Optics*, *28*(1), 35-46.
- Laird, A. R., Fox, P. M., Eickhoff, S. B., Turner, J. A., Ray, K. L., McKay, D. R., ... & Fox, P. T. (2011). Behavioral interpretations of intrinsic connectivity networks. *Journal of cognitive neuroscience*, *23*(12), 4022-4037.
- Landerl, K., & Wimmer, H. (2008). Development of word reading fluency and spelling in a consistent orthography: An 8-year follow-up. *Journal of Educational Psychology*, *100*(1), 150.
- Landi, N. (2010). An examination of the relationship between reading comprehension, higher-level and lower-level reading sub-skills in adults. *Reading and Writing*, *23*(6), 701-717.
- Langer N, Benjamin C, Minas J, Gaab N. (2015) The neural correlates of reading fluency deficits in children. *Front Psychol*. *6*: 191.
- Larsen, J. P., Høien, T., Lundberg, I., & Ødegaard, H. (1990). MRI evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia. *Brain and language*, *39*(2), 289-301.
- Law, J. M., Vandermosten, M., Ghesquiere, P., & Wouters, J. (2014). The relationship of phonological ability, speech perception, and auditory perception in adults with dyslexia. *Frontiers in Human Neuroscience*, *8*, 1-12.
- Laycock, S. K., Wilkinson, I. D., Wallis, L. I., Darwent, G., Wonders, S. H., Fawcett, A. J., ... & Nicolson, R. I. (2008). Cerebellar volume and cerebellar metabolic characteristics in adults with dyslexia. *Annals of the New York Academy of Sciences*, *1145*(1), 222-236.
- Leach, J. M., Scarborough, H. S., & Rescorla, L. (2003). Late-emerging reading disabilities. *Journal of Educational Psychology*, *95*, 211-224.
- Lee, J. E., & Gleeson, J. G. (2011). Cilia in the nervous system: linking cilia function and neurodevelopmental disorders. *Current Opinion in Neurology*, *24*(2), 98-105.

- Lefly, D. L., & Pennington, B. F. (1991). Spelling errors and reading fluency in compensated adult dyslexics. *Annals of Dyslexia*, 41(1), 141–162.
- Leiner, H. C., Leiner, A. L., & Dow, R. S. (1993). Cognitive and language functions of the human cerebellum. *Trends in neurosciences*, 16(11), 444-447.
- Leonard, C. M., Voeller, K. K., Lombardino, L. J., Morris, M. K., Hynd, G. W., Alexander, A. W., ... & Agee, O. F. (1993). Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. *Archives of neurology*, 50(5), 461-469.
- Leonard, C. M., Eckert, M. A., Lombardino, L. J., Oakland, T., Kranzler, J., Mohr, C. M., ... & Freeman, A. (2001). Anatomical risk factors for phonological dyslexia. *Cerebral Cortex*, 11(2), 148-157.
- Leonard, C. M., Kuldau, J. M., Maron, L., Ricciuti, N., Mahoney, B., Bengtson, M., & DeBose, C. (2008). Identical neural risk factors predict cognitive deficit in dyslexia and schizophrenia. *Neuropsychology*, 22(2), 147.
- Lervåg, A., & Hulme, C. (2009). Rapid automatized naming (RAN) taps a mechanism that places constraints on the development of early reading fluency. *Psychological Science*, 20(8), 1040-1048.
- Lesgold, A., & Resnick, L. (1982). How reading difficulties develop: Perspectives from a longitudinal study. In J. Das, R. Mulcahey, & A. Wall (Eds.), *Theory and research in learning disabilities* (pp. 155-187). New York: Plenum Press.
- Liberman, I. Y. (1973). Segmentation of the spoken word and reading acquisition. *Bulletin of the Orion Society*, 23, 65-77.
- Liberman, I., and Shankweiler, D. 1985. Phonology and the problems of learning to read and write. *Remedial and Special Education* 6:8-17.
- Linkersdörfer, J., Lonnemann, J., Lindberg, S., Hasselhorn, M., & Fiebach, C. J. (2012). Grey matter alterations co-localize with functional abnormalities in developmental dyslexia: an ALE meta-analysis. *PloS one*, 7(8), e43122.
- Lipka, O., Lesaux, N., & Siegel, L. (2006). Retrospective analyses of the reading development of Grade 4 students with reading disabilities: risk status and profiles over 5 years. *Journal of Learning Disabilities*, 39, 364–378.
- Liu, L., Vira, A., Friedman, E., Minas, J., Bolger, D. J., Bitan, T., & Booth, J. R. (2010). Children with reading disability show brain differences in effective connectivity for visual, but not auditory word comprehension. *PloS One*, 5(10), e13492.
- Liu, K., Shi, L., Chen, F., Wayne, M. M., Lim, C. K., Cheng, P. W., ... & Wang, D. (2015). Altered topological organization of brain structural network in Chinese children with developmental dyslexia. *Neuroscience letters*, 589, 169-175.

- Livingstone, M. S., Rosen, G. D., Drislane, F. W., & Galaburda, A. M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. *Proceedings of the National Academy of Sciences*, *88*(18), 7943-7947.
- Lo, C. Y. Z., He, Y., & Lin, C. P. (2011). Graph theoretical analysis of human brain structural networks. *Reviews in the neurosciences*, *22*(5), 551-563.
- Lobier, M., Peyrin, C., Le Bas, J. F., & Valdois, S. (2012). Pre-orthographic character string processing and parietal cortex: a role for visual attention in reading?. *Neuropsychologia*, *50*(9), 2195-2204.
- Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *357*(1424), 1003–37.
- Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869–78.
- Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150–7.
- Lohmann, G., Hoehl, S., Brauer, J., Danielmeier, C., Bornkessel-Schlesewsky, I., Bahlmann, J., et al. (2010). Setting the frame: the human brain activates a basic low-frequency network for language processing. *Cereb. Cortex* *20*, 1286–1292.
- López-Barroso, D., Catani, M., Ripollés, P., Dell'Acqua, F., Rodríguez-Fornells, A., & de Diego-Balaguer, R. (2013). Word learning is mediated by the left arcuate fasciculus. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(32), 13168–73.
- Lorusso, M.L. et al. (2006) Effects of visual hemisphere-specific stimulation versus reading-focused training in dyslexic children. *Neuropsychol. Rehabil.* *16*, 194–212.
- Lovegrove, W. J., Bowling, A., Badcock, D., & Blackwood, M. (1980). Specific reading disability: differences in contrast sensitivity as a function of spatial frequency. *Science*, *210*(4468), 439-440.
- Lovegrove, W. J., Garzia, R. P., & Nicholson, S. B. (1990). Experimental evidence for a transient system deficit in specific reading disability. *Journal of the American Optometric Association*.
- Lovett, M. W., Lacerenza, L., Borden, S. L., Frijters, J. C., Steinbach, K. A., & De Palma, M. (2000). Components of effective remediation for developmental reading disabilities: Combining phonological and strategy-based instruction to improve outcomes. *Journal of educational psychology*, *92*(2), 263.
- Lovett, M. W., Steinbach, K. a, & Frijters, J. C. (2000). Remediating the core deficits of developmental reading disability: a double-deficit perspective. *Journal of Learning Disabilities*, *33*(4), 334–358.

- Lowe, M. J., Dzemidzic, M., Lurito, J. T., Mathews, V. P., & Phillips, M. D. (2000). Correlations in low-frequency BOLD fluctuations reflect cortico-cortical connections. *NeuroImage*, *12*(5), 582–7.
- Lukatela, K., Carello, C., Shankweiler, D., & Liberman, I. (1995). Phonological awareness in illiterates: observations from Serbo-Croatian. *Applied Psycholinguistics*, *16*, 463–487.
- Lundberg, I., Olofsson, A., & Wall, S. (1980). Reading and spelling skills in the first school years predicted from phonemic awareness skills in kindergarten. *Scandinavian Journal of Psychology*, *21*, 159–173.
- Lundberg, I., Frost, J., & Petersen, O. (1988). Effects of an extensive program for stimulating phonological awareness in preschool children. *Reading Research Quarterly*, *23*, 263–284.
- Lütcke, H., & Frahm, J. (2008). Lateralized anterior cingulate function during error processing and conflict monitoring as revealed by high-resolution fMRI. *Cerebral Cortex*, *18*(3), 508-515.
- Lynall, M. E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., & Bullmore, E. (2010). Functional connectivity and brain networks in schizophrenia. *The Journal of Neuroscience*, *30*(28), 9477-9487.
- Lyytinen, H. et al. (2006) Trajectories of reading development; a follow-up from birth to school age of children with and without risk for dyslexia. *Merrill-Palmer Quarterly* *52*, 514–546.
- MacLeod, C. E., Zilles, K., Schleicher, A., Rilling, J. K., & Gibson, K. R. (2003). Expansion of the neocerebellum in Hominoidea. *Journal of Human Evolution*, *44*(4), 401-429.
- MacSweeney, M., Brammer, M. J., Waters, D., & Goswami, U. (2009). Enhanced activation of the left inferior frontal gyrus in deaf and dyslexic adults during rhyming. *Brain*, *132*(7), 1928-1940.
- Magri, C., Schridde, U., Murayama, Y., Panzeri, S., & Logothetis, N. K. (2012). The amplitude and timing of the BOLD signal reflects the relationship between local field potential power at different frequencies. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *32*(4), 1395–407.
- Maher, F., Vannucci, S.J., Simpson, I.A. (1994) Glucose transporter proteins in brain. *FASEB J.*, *8*, 1003-1011.
- Makris, N. & Pandya, D.N. (2009) The extreme capsule in humans and rethinking of the language circuitry. *Brain Struct. Funct.*, *213*, 343–358.
- Manis, F. R., Doi, L. M., & Bhadha, B. (2000). Naming speed, phonological awareness, and orthographic knowledge in second graders. *Journal of Learning Disabilities*, *33*(4), 325–333, 374.

- Mann, V. A. (1984). Longitudinal prediction and prevention of early reading difficulty. *Annals of Dyslexia*, 34, 117–136.
- Mann, V. A., & Liberman, I. Y. (1984). Phonological awareness and verbal short-term memory. *Journal of Learning Disabilities*, 17, 592–599.
- Mann, V. A., & Wimmer, H. (2002). Phoneme awareness and pathways to literacy: a comparison of German and American children. *Reading and Writing*, 15, 653–682.
- Manns, J. R., & Squire, L. R. (2001). Perceptual learning, awareness, and the hippocampus. *Hippocampus*, 11(6), 776–782.
- Margulies, D. S., & Petrides, M. (2013). Distinct parietal and temporal connectivity profiles of ventrolateral frontal areas involved in language production. *The Journal of Neuroscience*, 33(42), 16846–16852.
- Marino, C., Scifo, P., Della Rosa, P. a, Mascheretti, S., Facoetti, A., Lorusso, M. L., ... Perani, D. (2014). The DCDC2/intron 2 deletion and white matter disorganization: focus on developmental dyslexia. *Cortex* 57, pp. 227–43.
- Marrelec, G., & Fransson, P. (2011). Assessing the influence of different ROI selection strategies on functional connectivity analyses of fMRI data acquired during steady-state conditions. *PLoS One*, 6(4), e14788.
- Mars RB., Jbabdi S., Sallet J., O'Reilly JX., Croxson PL., Olivier E., Noonan MP., Bergmann C., Mitchell AS., Baxter MG., Behrens TE., Johansen-Berg H., Tomassini V., Miller KL., Rushworth MF. (2011) Diffusion-weighted imaging tractography-based parcellation of the human parietal cortex and comparison with human and macaque resting-state functional connectivity. *J Neurosci* 31:4087–4100.
- Martin A, Schurz M, Kronbichler M, Richlan F (2015): Reading in the brain of children and adults: A meta-analysis of 40 functional magnetic resonance imaging studies. *Hum Brain Mapp* 36:1963–1981.
- Martin, A., Kronbichler, M. and Richlan, F. (2016), Dyslexic brain activation abnormalities in deep and shallow orthographies: A meta-analysis of 28 functional neuroimaging studies. *Hum. Brain Mapp.*, 37: 2676–2699. doi:10.1002/hbm.23202
- Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibusaki H, et al. (2004) Functional connectivity in the human language system: a cortico-cortical evoked potential study. *Brain*, 127: 2316–30.
- Mattingly, I. G. (1972). Reading, the linguistic process, and linguistic awareness.
- McArthur, G. M., & Bishop, D. V. (2001). Auditory perceptual processing in people with reading and oral language impairments: Current issues and recommendations. *Dyslexia: The Journal of the British Dyslexia Association*, 7, 150–170.

- McArthur G.M., Hogben J.H. (2001) Auditory backward recognition masking in children with a specific language impairment and children with a specific reading disability. *Journal of the Acoustical Society of America*, 109, 1092–1100.
- McArthur G.M., Ellis, D., Atkinson, C.M., Coltheart, M. (2008) Auditory processing deficits in children with reading and language impairments: Can they (and should they) be treated? *Cognition* 107(3), 946-977.
- McBride-Chang, C., & Manis, F. R. (1996). Structural invariance in the associations of naming speed, phonological awareness, and verbal reasoning in good and poor readers: A test of the double deficit hypothesis. *Reading and Writing*, 8(4), 323–339.
- McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences*, 7(7), 293–299.
- McCrory, E. J., Mechelli, A., Frith, U., & Price, C. J. (2005). More than words: a common neural basis for reading and naming deficits in developmental dyslexia?. *Brain*, 128(2), 261-267.
- McNorgan, C., Randazzo-Wagner, M., & Booth, J. R. (2012). Cross-modal integration in the brain is related to phonological awareness only in typical readers, not in those with reading difficulty. *Frontiers in human neuroscience*, 7, 388-388.
- McRobbie, D. W., Moore, E. A., Graves, M. J., & Prince, M. R. (2006). *MRI from Picture to Proton*. Cambridge University Press.
- Merigan, W. H., Byrne, C. E., & Maunsell, J. H. (1991a). Does primate motion perception depend on the magnocellular pathway?. *The Journal of neuroscience*, 11(11), 3422-3429.
- Merigan, W. H., Katz, L. M., & Maunsell, J. H. (1991b). The effects of parvocellular lateral geniculate lesions on the acuity and contrast sensitivity of macaque monkeys. *The Journal of Neuroscience*, 11(4), 994-1001.
- Merigan, W. H., & Maunsell, J. H. (1993). How parallel are the primate visual pathways?. *Annual review of neuroscience*, 16(1), 369-402.
- Mesulam MM. (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol* ; 28: 597–613.
- Meyer, P., Mecklinger, A., Grunwald, T., Fell, J., Elger, C. E., & Friederici, A. D. (2005). Language processing within the human medial temporal lobe. *Hippocampus*, 15(4), 451-459.
- Miller-Shaul, S. (2005). The characteristics of young and adult dyslexics readers on reading and reading related cognitive tasks as compared to normal readers. *Dyslexia*, 11(2), 132–151.

- Mody M., Studdert-Kennedy M., Brady S. (1997) Speech perception deficits in poor readers: Auditory processing or phonological coding? *Journal of Experimental Child Psychology*, 64, 199–231.
- Moe-Nilssen R, Helbostad J, Talcott J, and Toennesen F. (2003) Balance and gait in children with dyslexia. *Experimental Brain Research*, 150: 237–244.
- Monzalvo, K., Fluss, J., Billard, C., Dehaene, S., & Dehaene-Lambertz, G. (2012). Cortical networks for vision and language in dyslexic and normal children of variable socio-economic status. *Neuroimage*, 61(1), 258-274.
- Morais, J., Cary, L., Alegria, J., and Bartleson, P. 1979. Does awareness of speech as a sequence of phones arise spontaneously? *Cognition* 7:323-331.
- Morgan, W. P. (1896). A case of congenital word blindness. *British medical journal*, 2(1871), 1378.
- Morgan, V. L., Mishra, A., Newton, A. T., Gore, J. C., & Ding, Z. (2009). Integrating functional and diffusion magnetic resonance imaging for analysis of structure-function relationship in the human language network. *PLoS One*, 4(8), e6660.
- Morken, F., Helland, T., Hugdahl, K., & Specht, K. (2014). Children with dyslexia show cortical hyperactivation in response to increasing literacy processing demands. *Frontiers in psychology*, 5.
- Morris, R. D., Stuebing, K. K., Fletcher, J. M., Shaywitz, S. E., Lyon, G. R., Shankweiler, D. P., ... & Shaywitz, B. A. (1998). Subtypes of reading disability: Variability around a phonological core. *Journal of educational psychology*, 90(3), 347.
- Muller, A. M., & Meyer, M. (2014). Language in the brain at rest: new insights from resting state data and graph theoretical analysis. *Frontiers in human neuroscience*, 8.
- Muneaux, M., Ziegler, J., Truc, C., Thomson, J., & Goswami, U. (2004). Deficits in beat perception and dyslexia: Evidence from French. *NeuroReport*, 15, 1255–1259.
- Murphy CF, and Schochat E. (2009) How auditory temporal processing deficits relate to dyslexia. *Braz J Med Biol Res* 42(7), 647-54.
- Murphy, K., Birn, R. M., Handwerker, D. A, Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *NeuroImage*, 44(3), 893–905.
- Murphy, K., Birn, R. M., Handwerker, D. A, Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *NeuroImage*, 44(3), 893–905.
- Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of cognitive neuroscience*, 16(7), 1227-1233.

- Nation, K., & Hulme, C. (2011). Learning to read changes children's phonological skills: Evidence from a latent variable longitudinal study of reading and nonword repetition. *Developmental science*, *14*(4), 649-659.
- Nelson, J. R., Benner, G. J., & Gonzalez, J. (2005). An investigation of the effects of a prereading intervention on the early literacy skills of children at risk of emotional disturbance and reading problems. *Journal of Emotional and Behavioral Disorders*, *13*(1), 3-12.
- Nelson, J. R., Stage, S. A., Epstein, M. H., & Pierce, C. D. (2005). Effects of a prereading intervention on the literacy and social skills of children. *Exceptional Children*, *72*(1), 29-45.
- Nelson, J. M. (2015). Examination of the double-deficit hypothesis with adolescents and young adults with dyslexia. *Annals of dyslexia*, *65*(3), 159-177.
- Nergård-Nilssen, T., & Hulme, C. (2014). Developmental dyslexia in adults: behavioural manifestations and cognitive correlates. *Dyslexia*, *20*(3), 191-207.
- Neta, M., Schlaggar, B. L., & Petersen, S. E. (2014). Separable responses to error, ambiguity, and reaction time in cingulo-opercular task control regions. *NeuroImage*, *99*, 59-68.
- Neubert, F. X., Mars, R. B., Thomas, A. G., Sallet, J., & Rushworth, M. F. (2014). Comparison of human ventral frontal cortex areas for cognitive control and language with areas in monkey frontal cortex. *Neuron*, *81*(3), 700-713.
- Newbury, D. F., Monaco, A. P., & Paracchini, S. (2014). Reading and language disorders: the importance of both quantity and quality. *Genes*, *5*(2), 285-309.
- Newbury, D. F., Paracchini, S., Scerri, T. S., Winchester, L., Addis, L., Richardson, A. J., ... Monaco, A. P. (2010). Investigation of Dyslexia and SLI Risk Variants in Reading- and Language-Impaired Subjects. *Behavior Genetics*, 90-104.
- Nicolson, R. I., & Fawcett, A. J. (1990). Automaticity: A new framework for dyslexia research? *Cognition*, *35*(2), 159-182.
- Nicolson, R. I. and Fawcett, A. J. (1994) Reaction times and dyslexia. *The Quarterly Journal of Experimental Psychology*, *47A*, 29-48.
- Nicolson, R. I., Fawcett, A. J., & Dean, P. (1995). Time estimation deficits in developmental dyslexia: evidence of cerebellar involvement. *Proceedings of the Royal Society of London B: Biological Sciences*, *259*(1354), 43-47.
- Nicolson, R. I., Fawcett, A. J., Berry, E. L., Jenkins, I. H., Dean, P., & Brooks, D. J. (1999). Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. *The Lancet*, *353*(9165), 1662-1667.
- Nicolson, R. I., Fawcett, A. J., & Dean, P. (2001). Developmental dyslexia: the cerebellar deficit hypothesis. *Trends in neurosciences*, *24*(9), 508-511.

- Niessing, J., Ebisch, B., Schmidt, K. E., Niessing, M., Singer, W., & Galuske, R. A. W. (2005). Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 309(5736), 948–51.
- Niogi, S. N., & McCandliss, B. D. (2006). Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. *Neuropsychologia*, 44(11), 2178-2188.
- Norton, E. S., Black, J. M., Stanley, L. M., Tanaka, H., Gabrieli, J. D., Sawyer, C., & Hoeft, F. (2014). Functional neuroanatomical evidence for the double-deficit hypothesis of developmental dyslexia. *Neuropsychologia*, 61, 235-246.
- Novick, J. M., Kan, I. P., Trueswell, J. C., & Thompson-Schill, S. L. (2009). A case for conflict across multiple domains: Memory and language impairments follow damage to ventrolateral prefrontal cortex. *Cognitive Neuropsychology*, 26, 527–567.
- Odegard, T. N., Farris, E. A., Ring, J., McColl, R., & Black, J. (2009). Brain connectivity in non-reading impaired children and children diagnosed with developmental dyslexia. *Neuropsychologia*, 47(8), 1972-1977.
- Olofsson, A., & Lundberg, I. (1985). Evaluation of long term effects of phonemic awareness training in kindergarten: illustrations of some methodological problems in evaluation research. *Scandinavian Journal of Psychology*, 26, 21–34.
- Olulade, O. A., Gilger, J. W., Talavage, T. M., Hynd, G. W., & McAteer, C. I. (2012). Beyond phonological processing deficits in adult dyslexics: atypical fMRI activation patterns for spatial problem solving. *Developmental neuropsychology*, 37(7), 617-635.
- Olulade, O. A., Flowers, D. L., Napoliello, E. M., & Eden, G. F. (2013). Developmental differences for word processing in the ventral stream. *Brain and language*, 125(2), 134-145.
- Olulade, O. A., Flowers, D. L., Napoliello, E. M., & Eden, G. F. (2015). Dyslexic children lack word selectivity gradients in occipito-temporal and inferior frontal cortex. *NeuroImage : Clinical*, 7, 742–754.
- O'Reilly, J. X., Beckmann, C. F., Tomassini, V., Ramnani, N., & Johansen-Berg, H. (2010). Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cerebral cortex*, 20(4), 953-965.
- Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging. *Human Brain Mapping*, 25, 46 –59.
- Papadopoulos, T. C., Georgiou, G. K., & Kendeou, P. (2009). Investigating the double-deficit hypothesis in Greek: findings from a longitudinal study. *Journal of Learning Disabilities*, 42(6), 528–547.

- Parker, G. J. M., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A. M., Ciccarelli, O., & Lambon Ralph, M. A. (2005). Lateralization of ventral and dorsal auditory-language pathways in the human brain. *NeuroImage*, *24*(3), 656–66.
- Parrila, R., Kirby, J. R., & McQuarrie, L. (2004). Articulation rate, naming speed, verbal short-term memory, and phonological awareness: Longitudinal predictors of early reading development? *Scientific Studies of Reading*, *8*(1), 3-26.
- Parrila, R., Georgiou, G., & Corkett, J. (2007). University Students with a Significant History of Reading Difficulties: What Is and Is Not Compensated?. *Exceptionality Education International*, *17*(2), 195-220.
- Pasquini, E. S., Corriveau, K. H., & Goswami, U. (2007). Auditory processing of amplitude envelope rise time in adults diagnosed with developmental dyslexia. *Scientific Studies of Reading*, *11*, 259–286.
- Paulesu, E., Frith, U., Snowling, M., Gallagher, A., Morton, J., Frackowiak, R. S., & Frith, C. D. (1996). Is developmental dyslexia a disconnection syndrome?. *Brain*, *119*(1), 143-157.
- Paulesu, E., Danelli, L., & Berlinger, M. (2014). Reading the dyslexic brain: multiple dysfunctional routes revealed by a new meta-analysis of PET and fMRI activation studies. *Frontiers in human neuroscience*, *8*.
- Pavidou, E.V. and Williams, J.M. (2010) Developmental Dyslexia and implicit learning: Evidence from an AGL transfer study. *Procedia - Social and Behavioral Sciences* *2*(2), 3289–3296.
- Pecini, C., Biagi, L., Brizzolara, D., Cipriani, P., Di Lieto, M. C., Guzzetta, A., ... & Chilosi, A. M. (2011). How many functional brains in developmental dyslexia? When the history of language delay makes the difference. *Cognitive and Behavioral Neurology*, *24*(2), 85-92.
- Pennington, B.F. & Lefly, D.L. (2001) Early reading development in children at family risk for dyslexia. *Child Development* *72*, 816–833.
- Pennington, B. F., Cardoso-Martins, C., Green, P. A., & Lefly, D. L. (2001). Comparing the phonological and double deficit hypotheses for developmental dyslexia. *Reading and Writing*, *14*(7-8), 707-755.
- Pennington, B. F., Santerre-Lemmon, L., Rosenberg, J., MacDonald, B., Boada, R., Friend, A., ... & Olson, R. K. (2012). Individual prediction of dyslexia by single versus multiple deficit models. *Journal of abnormal psychology*, *121*(1), 212.
- Perfetti, C. A., Beck, I., Bell, L., & Hughes, C. (1987). Phonemic knowledge and learning to read are reciprocal: a longitudinal study of first-grade children. *Merrill-Palmer Quarterly*, *33*, 283–319.
- Pernet, C., Andersson, J., Paulesu, E., & Demonet, J. F. (2009). When all hypotheses are right: a multifocal account of dyslexia. *Human brain mapping*, *30*(7), 2278-2292.

- Perry, C., Ziegler, J. C., & Zorzi, M. (2010). Beyond single syllables: Large-scale modeling of reading aloud with the Connectionist Dual Process (CDP++) model. *Cognitive psychology*, *61*(2), 106-151.
- Peschke, C., Ziegler, W., Eisenberger, J., & Baumgaertner, A. (2012). Phonological manipulation between speech perception and production activates a parieto-frontal circuit. *NeuroImage*, *59*(1), 788–99.
- Peterson, R. L., & Pennington, B. F. (2012). Developmental dyslexia. *The Lancet*, *379*(9830), 1997-2007.
- Peterson, R. L., Pennington, B. F., & Olson, R. K. (2013). Subtypes of developmental dyslexia: testing the predictions of the dual-route and connectionist frameworks. *Cognition*, *126*(1), 20–38.
- Peterson, R. L., & Pennington, B. F. (2015). Developmental dyslexia. *Annual review of clinical psychology*, *11*, 283-307.
- Petrides, M. (2006) Broca's area in the human and the non-human primate brain. In Grodzinsky, Y. & Amunts, K. (Eds), *Broca's Region*. Oxford University Press, New York, pp. 31–46.
- Petrides, M. & Pandya, D.N. (2009) Distinct parietal and temporal pathways to the homologues of Broca's area in the monkey. *PLoS Biol.*, *7*, e1000170.
- Peyrin, C., Démonet, J. F., N'Guyen-Morel, M. A., Le Bas, J. F., & Valdois, S. (2011). Superior parietal lobule dysfunction in a homogeneous group of dyslexic children with a visual attention span disorder. *Brain and language*, *118*(3), 128-138.
- Peyrin, C., Lallier, M., Demonet, J. F., Pernet, C., Baciú, M., Le Bas, J. F., & Valdois, S. (2012). Neural dissociation of phonological and visual attention span disorders in developmental dyslexia: fMRI evidence from two case reports. *Brain and language*, *120*(3), 381-394.
- Platt, M. P., Adler, W. T., Mehlhorn, A. J., Johnson, G. C., Wright, K. A., Choi, R. T., ... Rosen, G. D. (2013). Embryonic disruption of the candidate dyslexia susceptibility gene homolog *Kiaa0319*- like results in neuronal migration disorders. *Neuroscience*, *248*, 585–93.
- Plaut, D. C., McClelland, J. L., Seidenberg, M. S., & Patterson, K. (1996). Understanding normal and impaired word reading: computational principles in quasi-regular domains. *Psychological review*, *103*(1), 56.
- Plessen, K. von, Lundervold, A., Duta, N., Heiervang, E., Klauschen, F., Smievoll, A. I., ... & Hugdahl, K. (2002). Less developed corpus callosum in dyslexic subjects—a structural MRI study. *Neuropsychologia*, *40*(7), 1035-1044.
- Poblano, A., Valadéz-Tepec, T., de Lourdes Arias, M., & García-Pedroza, F. (2000). Phonological and visuo-spatial working memory alterations in dyslexic children. *Archives of Medical Research*, *31*(5), 493-496.

- Poelmans H., Luts H., Vandermosten M., Boets B., Ghesquiere P., Wouters J. (2011). Reduced sensitivity to slow-rate dynamic auditory information in children with dyslexia. *Res. Dev. Disabil.* 32, 2810–2819.
- Ponten, S. C., Bartolomei, F., & Stam, C. J. (2007). Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clinical neurophysiology*, 118(4), 918-927.
- Powell, D., Stainthorp, R., Stuart, M., Garwood, H., & Quinlan, P. (2007). An experimental comparison between rival theories of rapid automatized naming performance and its relationship to reading. *Journal of Experimental Child Psychology*, 98(1), 46-68.
- Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., ... & Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron*, 72(4), 665-678.
- Price, C. J. (2012). A review and synthesis of the first 20years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage*, 62(2), 816-847.
- Price, C. J., & Devlin, J. T. (2011). The Interactive Account of ventral occipitotemporal contributions to reading. *Trends in Cognitive Sciences*, 15(6), 246–253.
- Prull, M. W., Gabrieli, J. D., & Bunge, S. A. (2000). Age-related changes in memory: A cognitive neuroscience perspective.
- Pugh, K. R., Shaywitz, B. A., Shaywitz, S. E., Constable, R. T., Skudlarski, P., Fulbright, R. K., ... & Gore, J. C. (1996). Cerebral organization of component processes in reading. *Brain*, 119(4), 1221-1238.
- Pugh, K. R., Mencl, W. E., Shaywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Constable, R. T., ... & Liberman, A. M. (2000). The angular gyrus in developmental dyslexia: task-specific differences in functional connectivity within posterior cortex. *Psychological science*, 11(1), 51-56.
- Pugh, K. R., Mencl, W. E., Jenner, A. R., Katz, L., Frost, S. J., Lee, J. R., ... & Shaywitz, B. A. (2001). Neurobiological studies of reading and reading disability. *Journal of communication disorders*, 34(6), 479-492.
- Puolakanaho, A., Ahonen, T., Aro, M., Eklund, K., Leppänen, P. H., Poikkeus, A., ... Lyytinen, H. (2007). Very early phonological and language skills: Estimating individual risk of reading disability. *Journal of Child Psychology and Psychiatry*, 48(9), 923–931.
- Qi, T., Gu, B., Ding, G., Gong, G., Lu, C., Peng, D., ... & Liu, L. (2015). More bilateral, more anterior: Alterations of brain organization in the large-scale structural network in Chinese dyslexia. *Neuroimage*, 124, 63-74.
- Qiu, D., Tan, L.-H., Zhou, K., & Khong, P.-L. (2008). Diffusion tensor imaging of normal white matter maturation from late childhood to young adulthood: voxel-wise evaluation of mean diffusivity, fractional anisotropy, radial and axial diffusivities, and correlation with reading development. *NeuroImage*, 41(2), 223–32.

- Quaglino, V., Bourdin, B., Czernasty, G., Vrignaud, P., Fall, S., Meyer, M. E., ... de Marco, G. (2008). Differences in effective connectivity between dyslexic children and normal readers during a pseudoword reading task: an fMRI study. *Clinical Neurophysiology*, *38*(2), 73–82.
- Raberger T and Wimmer H. (2003) On the automaticity/cerebellar deficit hypothesis of dyslexia: Balancing and continuous rapid naming in dyslexics and ADHD children. *Neuropsychologia*, *41*: 1493–1497.
- Rae, C., Harasty, J. A., Dzendrowskyj, T. E., Talcott, J. B., Simpson, J. M., Blamire, A. M., ... & Richardson, A. J. (2002). Cerebellar morphology in developmental dyslexia. *Neuropsychologia*, *40*(8), 1285-1292.
- Ram-Tsur R, Faust M, Caspi A, Gordon CR, and Zivotofsky AZ. (2006) Evidence for ocular motor deficits in developmental dyslexia: Application of the double-step paradigm. *Investigative Ophthalmology and Visual Science*, *47*: 4401–4409.
- Ramnani, N. (2006). The primate cortico-cerebellar system: anatomy and function. *Nature Reviews Neuroscience*, *7*(7), 511-522.
- Ramus, F., Rosen, S., Dakin, S. C., Day, B. L., Castellote, J. M., White, S., & Frith, U. (2003). Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults. *Brain*, *126*(4), 841-865.
- Ramus, F. (2004). Neurobiology of dyslexia: A reinterpretation of the data. *TRENDS in Neurosciences*, *27*(12), 720-726.
- Ransby, M. J., & Swanson, H. L. (2003). Reading comprehension skills of young adults with childhood diagnoses of dyslexia. *Journal of Learning Disabilities*, *36*(6), 538–555.
- Raschle, N. M., Chang, M., & Gaab, N. (2011). Structural brain alterations associated with dyslexia predate reading onset. *Neuroimage*, *57*(3), 742-749.
- Raschle NM, Zuk J, Gaab N. (2012) Functional characteristics of developmental dyslexia in left-hemispheric posterior brain regions predate reading onset. *Proc Natl Acad Sci* *109*(6):2156-61.
- Raschle NM, Stering PL, Meissner SN, Gaab N. (2014) Altered neuronal response during rapid auditory processing and its relation to phonological processing in prereading children at familial risk for dyslexia. *Cereb Cortex*. *24*(9):2489-501.
- Ray, N. J., Fowler, S. S., & Stein, J. F. (2005). Yellow Filters Can Improve Magnocellular Function: Motion Sensitivity, Convergence, Accommodation, and Reading. In S. Ramat, D. Straumann (Eds.), *Clinical and basic oculomotor research: In honor of David S. Zee* (pp. 283-293). New York, NY US: New York Academy of Sciences.
- Raymond, J. L., Lisberger, S. G., & Mauk, M. D. (1996). The cerebellum: a neuronal learning machine? *Science*, *272*(5265), 1126.

- Read, C., Zhang, Y., Nie, H., & Ding, B. (1986). The ability to manipulate speech sounds depends on knowing alphabetic spelling. *Cognition*, *24*, 31–44.
- Regtvoort, A. G., & van der Leij, A. (2007). Early intervention with children of dyslexic parents: Effects of computer-based reading instruction at home on literacy acquisition. *Learning and individual differences*, *17*(1), 35-53.
- Reid, A. a., Szczerbinski, M., Iskierka-Kasperek, E., & Hansen, P. (2007). Cognitive profiles of adult developmental dyslexics: Theoretical implications. *Dyslexia*, *13*(1), 1–24.
- Reilhac C, Peyrin C, Démonet JF, Valdois S. (2013) Role of the superior parietal lobules in letter-identity processing within strings: fMRI evidence from skilled and dyslexic readers. *Neuropsychologia* *51*(4) :601-12.
- Reiter, A., Tucha, O., & Lange, K. W. (2005). Executive functions in children with dyslexia. *Dyslexia*, *11*(2), 116-131.
- Richards, T., Stevenson, J., Crouch, J., Johnson, L. C., Maravilla, K., Stock, P., ... & Berninger, V. (2008). Tract-based spatial statistics of diffusion tensor imaging in adults with dyslexia. *American Journal of Neuroradiology*, *29*(6), 1134-1139.
- Richards, T. L., & Berninger, V. W. (2008). Abnormal fMRI connectivity in children with dyslexia during a phoneme task: Before but not after treatment. *Journal of neurolinguistics*, *21*(4), 294-304.
- Richardson, U., Thomson, J. M., Scott, S. K., & Goswami, U. (2004). Auditory processing skills and phonological representation in dyslexic children. *Dyslexia: An International Journal of Research and Practice*, *10*, 215–233.
- Richlan, F., Sturm, D., Schurz, M., Kronbichler, M., Ladurner, G., & Wimmer, H. (2010). A common left occipito-temporal dysfunction in developmental dyslexia and acquired letter-by-letter reading? *PLoS One*, *5*(8), e12073.
- Richlan, F., Kronbichler, M., & Wimmer, H. (2013). Structural abnormalities in the dyslexic brain: a meta-analysis of voxel-based morphometry studies. *Human Brain Mapping*, *34*(11), 3055-3065.
- Richlan, F. (2014). Functional neuroanatomy of developmental dyslexia: the role of orthographic depth. *Frontiers in human neuroscience*, *8*, 347.
- Rimrodt, S. L., Clements-Stephens, A. M., Pugh, K. R., Courtney, S. M., Gaur, P., Pekar, J. J., & Cutting, L. E. (2009). Functional MRI of sentence comprehension in children with dyslexia: beyond word recognition. *Cerebral Cortex*, *19*(2), 402-413.
- Rimrodt, S. L., Peterson, D. J., Denckla, M. B., Kaufmann, W. E., & Cutting, L. E. (2010). White matter microstructural differences linked to left perisylvian language network in children with dyslexia. *Cortex*, *46*(6), 739-749.
- Ritchie, S. J., Della Sala, S., & McIntosh, R. D. (2011). Irlen colored overlays do not alleviate reading difficulties. *Pediatrics*, *128*(4), e932-e938.

- Roach N. W., Edwards V. T., Hogben J. H. (2004). The tale is in the tail: an alternative hypothesis for psychophysical performance variability in dyslexia. *Perception* 33, 817–830.
- Robichon, F., & Habib, M. (1998). Abnormal callosal morphology in male adult dyslexics: Relationships to handedness and phonological abilities. *Brain and language*, 62(1), 127-146.
- Robichon, F., Levrier, O., Farnarier, P., & Habib, M. (2000). Developmental dyslexia: atypical cortical asymmetries and functional significance. *European Journal of Neurology*, 7(1), 35-46.
- Rosen S. (1992). Temporal information in speech: acoustic, auditory and linguistic aspects. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 336, 367–373.
- Rosen, S. (2003). Auditory processing in dyslexia and specific language impairment: Is there a deficit? What is its nature? Does it explain anything? *Journal of Phonetics*.
- Ross, J., Burr, D., & Morrone, C. (1996). Suppression of the magnocellular pathway during saccades. *Behavioural brain research*, 80(1), 1-8.
- Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*, 52(3), 1059-1069.
- Rumsey, J. M., Donohue, B. C., Brady, D. R., Nace, K., Giedd, J. N., & Andreason, P. (1997). A magnetic resonance imaging study of planum temporale asymmetry in men with developmental dyslexia. *Archives of Neurology*, 54(12), 1481-1489.
- Russeler J, Gerth I, and Munte TF. (2006) Implicit learning is intact in adult developmental dyslexic readers: Evidence from the serial reaction time task and artificial grammar learning. *Journal of Clinical and Experimental Neuropsychology*, 28: 808–827.
- Sandak, R., Mencl, W. E., Frost, S. J., & Pugh, K. R. (2004). The neurobiological basis of skilled and impaired reading: Recent findings and new directions. *Scientific Studies of reading*, 8(3), 273-292.
- Saur, D., Kreher, B.W., Schnell, S., Kummerer, D., Kellmeyer, P., Vry, M.S., Umarova, R., Musso, M., Glauche, V., Abel, S., Huber, W., Rijntjes, M., Hennig, J. & Weiller, C. (2008) Ventral and dorsal pathways for language. *Proc. Natl. Acad. Sci. USA*, 105, 18035–18040.
- Scerri, T. S., Morris, A. P., Buckingham, L. L., Newbury, D. F., Miller, L. L., Monaco, A. P., ... & Paracchini, S. (2011). DCDC2, KIAA0319 and CMIP are associated with reading-related traits. *Biological psychiatry*, 70(3), 237-245.
- Schaffler T., Sonntag J., Hartnegg K., Fischer B. (2004) The effect of practice on low-level auditory discrimination, phonological skills, and spelling in dyslexia. *Dyslexia* 10, 119–130.

- Schatschneider, C., Carlson, C. D., Francis, D. J., Foorman, B. R., & Fletcher, J. M. (2002). Relationship of rapid automatized naming and phonological awareness in early reading development implications for the double-deficit hypothesis. *Journal of learning disabilities, 35*(3), 245-256.
- Schlaggar, B. L., & McCandliss, B. D. (2007). Development of neural systems for reading. *Annual Review of Neuroscience, 30*, 475–503.
- Schmahmann, J. D. (1996). From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Human brain mapping, 4*(3), 174-198.
- Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain, 121*(4), 561-579.
- Schmahmann JD, Pandya DN. (2006) Fiber pathways of the brain. New York: Oxford University Press.
- Schneider, W., Kuespert, P., Roth, E., & Vise, M. (1997). Short- and long-term effects of training phonological awareness in kindergarten: evidence from two German studies. *Journal of Experimental Child Psychology, 66*, 311–340.
- Schurz, M., Wimmer, H., Richlan, F., Ludersdorfer, P., Klackl, J., & Kronbichler, M. (2015). Resting-State and Task-Based Functional Brain Connectivity in Developmental Dyslexia. *Cerebral Cortex, 25*(10), 3502-3514.
- Share DL, Jorm AF, Maclean R, Matthews R (2002) Temporal processing and reading disability. *Reading and Writing 15*, 151–178.
- Share, D (2008) On the Anglocentricities of Current Reading Research and Practice: The Perils of Overreliance on an "Outlier" Orthography. *Psychology Bulletin.134* (4): 584-615.
- Shanahan MA, Pennington BF, Yerys BE, Scott A, Boada R, Willcutt EG, et al.(2006) Processing speed deficits in attention deficit/ hyperactivity disorder and reading disability. *Journal of Abnormal Child Psychology, 34*: 585–602.
- Shastry, B. S. (2007). Developmental dyslexia: an update. *Journal of Human Genetics, 52*(2), 104-109.
- Shaywitz, S. E., Shaywitz, B. A., Pugh, K. R., Fulbright, R. K., Constable, R. T., Mencl, W. E., ... & Katz, L. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proceedings of the National Academy of Sciences, 95*(5), 2636-2641.
- Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Mencl, W. E., Fulbright, R. K., Skudlarski, P., ... & Gore, J. C. (2002). Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biological psychiatry, 52*(2), 101-110.
- Shaywitz, S. E., Shaywitz, B. A., Fulbright, R. K., Skudlarski, P., Mencl, W. E., Constable, R. T., ... & Lyon, G. R. (2003). Neural systems for compensation and persistence: young adult outcome of childhood reading disability. *Biological psychiatry, 54*(1), 25-33.

- Shaywitz, B. A., Skudlarski, P., Holahan, J. M., Marchione, K. E., Constable, R. T., Fulbright, R. K., ... & Shaywitz, S. E. (2007). Age-related changes in reading systems of dyslexic children. *Annals of neurology*, *61*(4), 363-370.
- Shmuel, A., Augath, M., Oeltermann, A., & Logothetis, N. K. (2006). Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nature Neuroscience*, *9*(4), 569–77.
- Silani, G., Frith, U., Demonet, J. F., Fazio, F., Perani, D., Price, C., ... & Paulesu, E. (2005). Brain abnormalities underlying altered activation in dyslexia: a voxel based morphometry study. *Brain*, *128*(10), 2453-2461.
- Siok, W. T., Niu, Z., Jin, Z., Perfetti, C. A., & Tan, L. H. (2008). A structural–functional basis for dyslexia in the cortex of Chinese readers. *Proceedings of the National Academy of Sciences*, *105*(14), 5561-5566.
- Skeide, M. A., Kirsten, H., Kraft, I., Schaadt, G., Müller, B., Neef, N., ... & Friederici, A. D. (2015). Genetic dyslexia risk variant is related to neural connectivity patterns underlying phonological awareness in children. *NeuroImage*, *118*, 414-421.
- Skottun, B. C. (2000). The magnocellular deficit theory of dyslexia: the evidence from contrast sensitivity. *Vision research*, *40*(1), 111-127.
- Smith-Spark, J., Fisk, J., Fawcett, A., & Nicolson, R. (2003). Investigating the central executive in adult dyslexics: Evidence from phonological and visuospatial working memory performance. *European Journal of Cognitive Psychology*, *15*(4), 567-587.
- Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., ... Beckmann, C. F. (2009). Correspondence of the brain’s functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–5.
- Smith, S. M., Vidaurre, D., Beckmann, C. F., Glasser, M. F., Jenkinson, M., Miller, K. L., ... Van Essen, D. C. (2013). Functional connectomics from resting-state fMRI. *Trends in Cognitive Sciences*, *17*(12), 666–82.
- Snook, L., Paulson, L.-A., Roy, D., Phillips, L., & Beaulieu, C. (2005). Diffusion tensor imaging of neurodevelopment in children and young adults. *NeuroImage*, *26*(4), 1164–73.
- Snowling, M., Chiat, S., & Hulme, C. (1991). Words, nonwords and phonological processes. Some comments on Gathercole, Willis, Emslie and Baddeley. *Applied Psycholinguistics*, *12*, 369–373.
- Snowling, M., Nation, K., Moxham, P., Gallagher, A., & Frith, U. (1997). Phonological processing skills of dyslexic students in higher education: a preliminary report. *Journal of Research in Reading*, *20*(1), 31–41.
- Snowling, M. (1998). Dyslexia as a Phonological Deficit: Evidence and Implications. *Child Psychology and Psychiatry Review*, *3*(1), 4–11.

- Snowling, M.J. (2000). *Dyslexia* (2nd edn). Oxford: Blackwell.
- Snowling, M. J., Gallagher, A., & Frith, U. (2003). Family risk of dyslexia is continuous: Individual differences in the precursors of reading skill. *Child Development, 74*(2), 358–373
- Snowling, M. et al. (2007) Outcomes in adolescence of children at family-risk of dyslexia, *Journal of Child Psychology & Psychiatry, 48*, 609–618.
- Snowling, M.J. & Hulme, C. (2015). Disorders of reading, mathematical and motor development. In Thapar's et al. (Eds.), *Rutter's Child and Adolescent Psychiatry*.
- Solan, H.A. et al. (2004) M-cell deficit and reading disability: a preliminary study of the effects of temporal vision-processing therapy. *Optometry 75*, 640–650.
- Song, S.-K., Sun, S.-W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Demyelination Revealed through MRI as Increased Radial (but Unchanged Axial) Diffusion of Water. *NeuroImage, 17*(3), 1429–1436.
- Song, S.-K., Yoshino, J., Le, T. Q., Lin, S.-J., Sun, S.-W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage, 26*(1), 132–40.
- Specht, K., Hugdahl, K., Ofte, S., Nygård, M., Bjørnerud, A., Plante, E., & Helland, T. (2009). Brain activation on pre-reading tasks reveals at-risk status for dyslexia in 6-year-old children. *Scandinavian journal of psychology, 50*(1), 79-91.
- Sperling A, Lu Z-L, and Manis F. (2004) Slower implicit categorical learning in adult poor readers. *Annals of Dyslexia, 54*: 281–303.
- Stam, C. J., Nolte, G., & Daffertshofer, A. (2007). Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. *Human brain mapping, 28*(11), 1178-1193.
- Stanberry, L. I., Richards, T. L., Berninger, V. W., Nandy, R. R., Aylward, E. H., Maravilla, K. R., ... & Cordes, D. (2006). Low-frequency signal changes reflect differences in functional connectivity between good readers and dyslexics during continuous phoneme mapping. *Magnetic resonance imaging, 24*(3), 217-229.
- Stanovich, K., Cunningham, A. E., and Feeman, D. J. 1984. Intelligence, cognitive skills and early reading progress. *Reading Research Quarterly 19*:278-301.
- Stein, J. F. (1994). Developmental dyslexia, neural timing and hemispheric lateralisation. *International Journal of Psychophysiology, 18*(3), 241-249.
- Stein, J., & Walsh, V. (1997). To see but not to read; the magnocellular theory of dyslexia. *Trends in neurosciences, 20*(4), 147-152.
- Stein, J., Talcott, J., & Walsh, V. (2000). Controversy about the visual magnocellular deficit in developmental dyslexics. *Trends in cognitive sciences, 4*(6), 209-211.

- Stein JF, Richardson AJ, and Fowler MS. (2000) Monocular occlusion can improve binocular control and reading in dyslexics. *Brain*, 123: 164–170.
- Steinbrink C, Groth K, Lachmann T, Riecker A. (2012) Neural correlates of temporal auditory processing in developmental dyslexia during German vowel length discrimination: an fMRI study. *Brain Lang.* 121(1): 1-11.
- Stoodley CJ, Fawcett AJ, Nicolson RI, and Stein JF. (2005) Impaired balancing ability in dyslexic children. *Experimental Brain Research*, 167: 370–380.
- Stoodley CJ and Stein JF. (2006) A processing speed deficit in dyslexic adults? Evidence from a peg-moving task. *Neuroscience Letters*, 399: 264–267.
- Stoodley, C. J., Hill, P. R., Stein, J. F., & Bishop, D. V. M. (2006). Auditory event-related potentials differ in dyslexics even when auditory psychophysical performance is normal. *Brain Research*, 1121, 190–199.
- Stoodley CJ, Harrison EP, and Stein JF. (2006) Implicit motor learning deficits in dyslexic adults. *Neuropsychologia*, 44: 795–798.
- Stoodley CJ, Ray NJ, Jack A, and Stein JF. (2008) Implicit learning in control, dyslexic, and garden-variety poor readers. *Annals of the New York Academy of Sciences*, 1145: 173–183.
- Stoodley, C. J., & Schmahmann, J. D. (2009). Functional topography in the human cerebellum: a meta-analysis of neuroimaging studies. *Neuroimage*, 44(2), 489-501.
- Stoodley, C. J. (2012). The cerebellum and cognition: evidence from functional imaging studies. *The Cerebellum*, 11(2), 352-365.
- Strehlow U., Haffner J., Bischof J., Gratzka V., Parzer P., Resch F. (2006) Does successful training of temporal processing of sound and phoneme stimuli improve reading and spelling? *European Child and Adolescent Psychiatry*, 15, 19–29.
- Stuart, M. (1995). Prediction and qualitative assessment of five- and six-year-old children's reading: a longitudinal study. *British Journal of Educational Psychology*, 65, 287–296.
- Sunseth, K., & Bowers, P. G. (2002). Rapid Naming and Phonemic Awareness: contributions to reading, spelling, and orthographic knowledge. *Scientific Studies of Reading*, 6(4), 369–400.
- Surányi, Z., Csépe, V., Richardson, U., Thomson, J. M., Honbolygó, F., & Goswami, U. (2009). Sensitivity to rhythmic parameters in dyslexic children: A comparison of Hungarian and English. *Reading & Writing*, 22, 41–56.
- Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol*, 4(6), e1000100.
- Swan, D., & Goswami, U. (1997a). Picture naming deficits in developmental dyslexia: The phonological representations hypothesis. *Brain & Language* 56, 334-353.

- Swan, D., & Goswami, U. (1997b). Phonological Awareness Deficits in Developmental Dyslexia and the Phonological Representations Hypothesis. *Journal of Experimental Child Psychology* 66(1), 18-41.
- Swanson, H. L., Trainin, G., Necochea, D. M., & Hammill, D. D. (2003). Rapid naming, phonological awareness, and reading: A meta-analysis of the correlation evidence. *Review of Educational Research*, 73(4), 407-440.
- Swanson, H. L., Zheng, X., and Jerman, O. (2009). Working memory, short-term memory, and reading disabilities: a selective meta-analysis of the literature. *J. Learn. Disabil.* 42, 260–287. doi: 10.1177/0022219409331958.
- Szalkowski, C. E., Fiondella, C. G., Galaburda, A. M., Rosen, G. D., Loturco, J. J., & Fitch, R. H. (2012). Neocortical disruption and behavioral impairments in rats following in utero RNAi of candidate dyslexia risk gene Kiaa0319. *International Journal of Developmental Neuroscience* 30(4), 293–302.
- Talcott J. B., Witton C., McLean M. F., Hansen P. C., Rees A., Green G. G. R., et al. (2000). Dynamic sensory sensitivity and children's word decoding skills. *Proc. Natl. Acad. Sci.* 97, 2952–2957.
- Talcott, J. B., Witton, C., Hebb, G. S., Stoodley, C. J., Westwood, E. A., France, S. J. et al. (2002). On the relationship between dynamic visual and auditory processing and literacy skills; results from a large primary-school study. *Dyslexia*, 8, 204– 225.
- Talcott, J. B., Gram, A., Van Ingelghem, M., Witton, C., Stein, J. F., & Toennesen, F. E. (2003). Impaired sensitivity to dynamic stimuli in poor readers of a regular orthography. *Brain and Language*, 87, 259–266.
- Tallal P. and Piercy. M. (1973) Developmental aphasia: rate of auditory processing and selective impairment of consonant perception. *Neuropsychologia*, 12, 83–93.
- Tallal, P. (1980) Auditory temporal perception, phonics, and reading disabilities in children. *Brain and Language* 9, 182–198.
- Tammimies, K., Vitezic, M., Matsson, H., Le Guyader, S., Bürglin, T. R., Ohman, T., ... Tapia-Páez, I. (2013). Molecular networks of DYX1C1 gene show connection to neuronal migration genes and cytoskeletal proteins. *Biological Psychiatry*, 73(6), 583–90.
- Tarkar, A., Loges, N. T., Slagle, C. E., Francis, R., Dougherty, G. W., Tamayo, J. V, ... Omran, H. (2013). DYX1C1 is required for axonemal dynein assembly and ciliary motility. *Nature Genetics*, 45(9), 995–1003.
- Tanaka, H., Black, J. M., Hulme, C., Stanley, L. M., Kesler, S. R., Whitfield-Gabrieli, S., ... & Hoeft, F. (2011). The brain basis of the phonological deficit in dyslexia is independent of IQ. *Psychological science*, 22(11), 1442-1451.
- Taylor, J. S. H., Rastle, K., & Davis, M. H. (2013). Can cognitive models explain brain activation during word and pseudoword reading? A meta-analysis of 36 neuroimaging studies. *Psychological Bulletin*, 139(4), 766.

- Temple, E., Poldrack, R. A., Salidis, J., Deutsch, G. K., Tallal, P., Merzenich, M. M., & Gabrieli, J. D. (2001). Disrupted neural responses to phonological and orthographic processing in dyslexic children: an fMRI study. *Neuroreport*, *12*(2), 299-307.
- Thompson, P. A., Hulme, C., Nash, H. M., Gooch, D., Hayiou-Thomas, E., & Snowling, M. J. (2015). Developmental dyslexia: predicting individual risk. *Journal of Child Psychology and Psychiatry*, *56*(9), 976-987.
- Thomson, J. M., Fryer, B., Maltby, J., & Goswami, U. (2006). Auditory and motor rhythm awareness in adults with dyslexia. *Journal of Research in Reading*, *29*, 334-348.
- Tomasi, D., & Volkow, N. D. (2012). Resting functional connectivity of language networks: characterization and reproducibility. *Molecular psychiatry*, *17*(8), 841-854.
- Torgesen, J. K., Wagner, R. K., Rashotte, C. A., Herron, J., & Lindamood, P. (2010). Computer-assisted instruction to prevent early reading difficulties in students at risk for dyslexia: Outcomes from two instructional approaches. *Annals of dyslexia*, *60*(1), 40-56.
- Torppa, M., Eklund, K., van Bergen, E., & Lyytinen, H. (2015). Late-emerging and resolving dyslexia: A Follow-up study from age 3 to 14. *Journal of abnormal child psychology*, *43*(7), 1389-1401.
- Tournier, J., Calamante, F., & Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *NeuroImage*, *35*(4), 1459-72.
- Tournier, J.-D., Calamante, F., Gadian, D., & Connelly, A. (2004). Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage*, *23*, 1176-1185.
- Tournier, J.-D., Yeh, C., Calamante, F., & Cho, K. (2008). Resolving crossing fibres using constrained spherical deconvolution: validation using diffusion-weighted imaging phantom data. *Neuroimage*, *42*, 617-625.
- Tournier, J., Calamante, F., & Connelly, A. (2012). MRtrix: diffusion tractography in crossing fiber regions. *International Journal of Imaging Systems and Technology*, *22*(1), 53-66.
- Trecy, M. P., Steve, M., & Martine, P. (2013). Impaired short-term memory for order in adults with dyslexia. *Research in Developmental Disabilities*, *34*(7), 2211-2223.
- Treiman, R., & Baron, J. (1983). Phonemic analysis training helps children benefit from spelling-sound rules. *Memory and Cognition*, *11*, 382-389.
- Tuch, D. S. (2004). Q-ball imaging. *Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *52*(6), 1358-72.
- Turkeltaub, P. E., Gareau, L., Flowers, D. L., Zeffiro, T. A., & Eden, G. F. (2003). Development of neural mechanisms for reading. *Nature neuroscience*, *6*(7), 767-773.

- Turken, U., & Dronkers, N. (2011). The neural architecture of the language comprehension network: converging evidence from lesion and connectivity analyses. *Frontiers in Systems Neuroscience*, 5(February), 1–20.
- Uchikawa, K., & Sato, M. (1995). Saccadic suppression of achromatic and chromatic responses measured by increment-threshold spectral sensitivity. *JOSA A*, 12(4), 661–666.
- Vaessen, A., Gerretsen, P., & Blomert, L. (2009). Naming problems do not reflect a second independent core deficit in dyslexia: Double deficits explored. *Journal of experimental child psychology*, 103(2), 202–221.
- Valente, E. M., Rosti, R. O., Gibbs, E., & Gleeson, J. G. (2014). Primary cilia in neurodevelopmental disorders. *Nature Reviews. Neurology*, 10(1), 27–36.
- Valk S. L., Di Martino A., Milham M. P., Bernhardt B. C. (2015). Multicenter mapping of structural network alterations in autism. *Hum. Brain Mapp.* 36, 2364–2373.
- van Bergen, E., de Jong, P. F., Regtvoort, A., Oort, F., van Otterloo, S. G., & van der Leij, A. (2011). Dutch children at family risk of dyslexia: Precursors, reading development, and parental effects. *Dyslexia* 17(1), 2–18.
- van Bergen, E., de Jong, P. F., Plakas, A., Maassen, B., & van der Leij, A. (2012). Child and parental literacy levels within families with a history of dyslexia. *Journal of Child Psychology and Psychiatry*, 53(1), 28–36.
- van Ermingen-Marbach M, Pape-Neumann J, Grande M, Grabowska A, Heim S. (2013) Distinct neural signatures of cognitive subtypes of dyslexia: effects of lexicality during phonological processing. *Acta Neurobiol Exp* 73(3):404-16.
- van den Bos, K. P., Zijlstra, B. J., & Spelberg, H. C. (2002). Life-span data on continuous-naming speeds of numbers, letters, colors, and pictured objects, and word-reading speed. *Scientific Studies of Reading*, 6(1), 25–49.
- Van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, 20(8), 519–34.
- Van der Mark, S., Bucher, K., Maurer, U., Schulz, E., Brem, S., Buckelmüller, J., ... & Brandeis, D. (2009). Children with dyslexia lack multiple specializations along the visual word-form (VWF) system. *Neuroimage*, 47(4), 1940–1949.
- Van der Mark, S., Klaver, P., Bucher, K., Maurer, U., Schulz, E., Brem, S., ... & Brandeis, D. (2011). The left occipitotemporal system in reading: disruption of focal fMRI connectivity to left inferior frontal and inferior parietal language areas in children with dyslexia. *Neuroimage*, 54(3), 2426–2436.
- Van Dijk, K. R. A., Hedden, T., Venkataraman, A., Evans, K. C., Lazar, S. W., & Buckner, R. L. (2010). Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *Journal of Neurophysiology*, 103(1), 297–321.

- Van Ingelghem M., Boets B., van Wieringen A., Onghena P., Ghesquiere P., Vandebussche E., et al. (2005). An auditory temporal processing deficit in children with dyslexia? in *Children With Learning Disabilities: A Challenge to Teaching and Instruction* eds Ghesquiere P., Ruijsenaars A. J. J. M., editors. (Leuven: University Press;), 47–63.
- Vandermosten, M., Boets, B., Wouters, J., & Ghesquière, P. (2012). A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neuroscience & Biobehavioral Reviews*, 36(6), 1532-1552.
- Vandermosten, M., Boets, B., Poelmans, H., Sunaert, S., Wouters, J., & Ghesquière, P. (2012). A tractography study in dyslexia: neuroanatomic correlates of orthographic, phonological and speech processing. *Brain*, 135(3), 935-948.
- Vandermosten, M., Poelmans, H., Sunaert, S., Ghesquière, P., & Wouters, J. (2013). White matter lateralization and interhemispheric coherence to auditory modulations in normal reading and dyslexic adults. *Neuropsychologia*, 51(11), 2087-2099.
- Vandermosten, M., Vanderauwera, J., Theys, C., De Vos, A., Vanvooren, S., Sunaert, S., ... & Ghesquière, P. (2015). A DTI tractography study in pre-readers at risk for dyslexia. *Developmental cognitive neuroscience*, 14, 8-15.
- Varvara, P., Varuzza, C., Sorrentino, A.C.P., Vicari, S., & Menghini, D. (2014). Executive functions in developmental dyslexia. *Frontiers in Human Neuroscience*, 8(120), 1–8.
- Vaughn, S., Mathes, P., Linan-Thompson, S., Cirino, P., Carlson, C., Pollard-Durodola, S., ... & Francis, D. (2006). Effectiveness of an English intervention for first-grade English language learners at risk for reading problems. *The Elementary School Journal*, 107(2), 153-180.
- Velay JL, Daffaure V, Giraud K, and Habib M. (2002) Interhemispheric sensorimotor integration in pointing movements: A study on dyslexic adults. *Neuropsychologia*, 40: 827–834.
- Vellutino, E, and Scanlon, D. 1988. Phonological coding, phonological awareness, and reading ability: Evidence from a longitudinal and experimental study. In K. Stanovich (ed.). *Children's Reading and the Development of Phonological Awareness*. Detroit: Wayne State University Press.
- Verhagen, W., Aarnoutse, C., & Van Leeuwe, J. (2008). Phonological awareness and naming speed in the prediction of Dutch children's word recognition. *Scientific Studies of Reading*, 12(4), 301-324.
- Vidyasagar TR1, Pammer K. (2010) Dyslexia: a deficit in visuo-spatial attention, not in phonological processing. *Trends Cogn Sci*. 14(2):57-63.
- Vidyasagar, T. R. (2013). Reading into neuronal oscillations in the visual system: implications for developmental dyslexia. *Frontiers in Human Neuroscience*, 7, 811.

- Vigneau, M., Beaucousin, V., Herve, P. Y., Duffau, H., Crivello, F., Houde, O., ... & Tzourio-Mazoyer, N. (2006). Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *Neuroimage*, *30*(4), 1414-1432.
- Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *Journal of neurophysiology*, *100*(6), 3328-3342.
- Vinckenbosch, E., Robichon, F., & Eliez, S. (2005). Gray matter alteration in dyslexia: converging evidence from volumetric and voxel-by-voxel MRI analyses. *Neuropsychologia*, *43*(3), 324-331.
- Vourkas, M., Micheloyannis, S., Simos, P. G., Rezaie, R., Fletcher, J. M., Cirino, P. T., & Papanicolaou, A. C. (2011). Dynamic task-specific brain network connectivity in children with severe reading difficulties. *Neuroscience letters*, *488*(2), 123-128.
- Vukovic, R. K., & Siegel, L. S. (2006). The double-deficit hypothesis a comprehensive analysis of the evidence. *Journal of Learning disabilities*, *39*(1), 25-47.
- Vukovic, R. K., Wilson, A. M., & Nash, K. K. (2004). Naming speed deficits in adults with reading disabilities: a test of the double-deficit hypothesis. *Journal of Learning Disabilities*, *37*(5), 440-450.
- Waber D, Marcus D, Forbes P, Bellinger D, Weiler M, Sorenson L, et al. (2003) Motor sequence learning and reading ability: Is poor reading associated with sequencing deficits? *Journal of Experimental Child Psychology*, *84*: 338-354.
- Wager, T. D., Jonides, J., & Reading, S. (2004). Neuroimaging studies of shifting attention: a meta-analysis. *NeuroImage*, *22*(4), 1679-93.
- Wagner, R., and Torgesen, J. 1987. The nature of phonological processing and its causal role in the acquisition of reading skills. *Psychological Bulletin* *101*:192-212.
- Wagner, R. K., Torgesen, J. K., & Rashotte, C. A. (1994). Development of reading-related phonological processing abilities: new evidence of bidirectional causality from a latent variable longitudinal study. *Developmental Psychology*, *30*, 73-87.
- Wagner, R. K., Torgesen, J. K., Rashotte, C. A., Hecht, S. A., Barker, T. A., Burgess, S. R., ... & Garon, T. (1997). Changing relations between phonological processing abilities and word-level reading as children develop from beginning to skilled readers: a 5-year longitudinal study. *Developmental psychology*, *33*(3), 468.
- Wang J., Fan L., Zhang Y., Liu Y., Jiang D., Zhang Y., Yu C., Jiang T. 2012. Tractography-based parcellation of the human left inferior parietal lobule. *Neuroimage* *63*:641-652.
- Wang, L., Saalman, Y. B., Pinsk, M. A., Arcaro, M. J., & Kastner, S. (2012). Electrophysiological low-frequency coherence and cross-frequency coupling contribute to BOLD connectivity. *Neuron*, *76*(5), 1010-20.

- Warren, J.E., Wise, R.J. & Warren, J.D. (2005) Sounds do-able: auditory-motor transformations and the posterior temporal plane. *Trends Neurosci.*, **28**, 636–643.
- Watson, B. U. (1992). Auditory temporal acuity in normally achieving and learning disabled college students. *Journal of Speech & Hearing Research*, *35*, 148–156.
- Watson, B. U., & Miller, T. K. (1993). Auditory perception, phonological processing, and reading ability/disability. *Journal of Speech & Hearing Research*, *36*, 850–863.
- Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of “small-world” networks. *Nature*, *393*(6684), 440–2.
- Wedeen, V. J., Wang, R. P., Schmahmann, J. D., Benner, T., Tseng, W. Y. I., Dai, G., ... de Crespigny, a J. (2008). Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *NeuroImage*, *41*(4), 1267–77.
- Weiner, S. H. (1994). Effects of phonemic awareness training on low and middle achieving first graders’ phonemic awareness, decoding, and reading ability. *Journal of Reading Behavior*, *26*, 277–300.
- Westerhausen, R., Kreuder, F., Dos Santos Sequeira, S., Walter, C., Woerner, W., Wittling, R. A., ... Wittling, W. (2006). The association of macro- and microstructure of the corpus callosum and language lateralisation. *Brain and Language*, *97*(1), 80–90.
- White, S., Milne, E., Rosen, S., Hansen, P., Swettenham, J., Frith, U., & Ramus, F. (2006). The role of sensorimotor impairments in dyslexia: A multiple case study of dyslexic children. *Developmental Science*, *9*, 237–255.
- Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, *2*(3), 125–41.
- Wig, G. S., Schlaggar, B. L., & Petersen, S. E. (2011). Concepts and principles in the analysis of brain networks. *Annals of the New York Academy of Sciences*, *1224*(1), 126–46.
- Wilkins, B., Lee, N., Gajawelli, N., Law, M., & Leporé, N. (2014). Fiber estimation and tractography in diffusion MRI: Development of simulated brain images and comparison of multi-fiber analysis methods at clinical b-values. *NeuroImage*. doi:10.1016/j.neuroimage.2014.12.060
- Willcutt, E. G., Pennington, B. F., Olson, R. K., Chhabildas, N., & Hulslander, J. (2005). Neuropsychological analyses of comorbidity between reading disability and attention deficit hyperactivity disorder: In search of the common deficit. *Developmental neuropsychology*, *27*(1), 35-78.
- Wimmer, H., & Goswami, U. (1994). The influence of orthographic consistency on reading development: Word recognition in English and German children. *Cognition*, *51*(1), 91-103.

- Wimmer H, Mayringer H, and Raberger T. (1999) Reading and dual-task balancing: Evidence against the automatization deficit explanation of developmental dyslexia. *Journal of Learning Disabilities*, 32: 473–478.
- Wimmer, H., & Schurz, M. (2010). Dyslexia in regular orthographies: manifestation and causation. *Dyslexia*, 16(4), 283-299.
- Wimmer, H., Schurz, M., Sturm, D., Richlan, F., Klackl, J., Kronbichler, M., & Ladurner, G. (2010). A dual-route perspective on poor reading in a regular orthography: an fMRI study. *Cortex*, 46(10), 1284-1298.
- Witton, C., Talcott, J. B., Hansen, P. C., Richardson, A. J., Griffiths, T. D., Rees, A. et al. (1998). Sensitivity to dynamic auditory and visual stimuli predicts nonword reading ability in both dyslexic and normal readers. *Current Biology*, 8, 791–797.
- Witton, C., Stein, J. F., Stoodley, C. J., Rosner, B. S., & Talcott, J. B. (2002). Separate influences of acoustic AM and FM sensitivity on the phonological decoding skills of impaired and normal readers. *Journal of Cognitive Neuroscience*, 14, 866–874.
- Wolf, M. (1984). Naming, reading, and the dyslexias: A longitudinal overview. *Annals of Dyslexia*, 34, 87-115.
- Wolf, M., & Bowers, P. G. (1999). The double-deficit hypothesis for the developmental dyslexias. *Journal of educational psychology*, 91(3), 415.
- Wolf, M., Goldberg O'Rourke, A., Gidney, C., Lovett, M., Cirino, P., & Morris, R. (2002). The second deficit: An investigation of the independence of phonological and naming-speed deficits in developmental dyslexia. *Reading and Writing: An Interdisciplinary Journal*, 15(11/2), 43–72.
- Wolf, R. C., Sambataro, F., Lohr, C., Steinbrink, C., Martin, C., & Vasic, N. (2010). Functional brain network abnormalities during verbal working memory performance in adolescents and young adults with dyslexia. *Neuropsychologia*, 48(1), 309-318.
- Wolff, P. H., Michel, G. F., Ovrut, M., & Drake, C. (1990a). Rate and timing precision of motor coordination in developmental dyslexia. *Developmental Psychology*, 26(3), 349.
- Wolff, P. H., Michel, G. F., & Ovrut, M. (1990b). Rate variables and automatized naming in developmental dyslexia. *Brain and language*, 39(4), 556-575.
- Wright B.A., Lombardino L.J., King W.M., Puranik C.S., Leonard C.M., Merzenich M.M. (1997) Deficits in auditory temporal and spectral resolution in language-impaired children. *Nature*, 387, 176–178.
- Wright, C. M., & Conlon, E. G. (2009). Auditory and visual processing in children with dyslexia. *Developmental Neuropsychology*, 34, 330–355.

- Xiang, H.-D., Fonteijn, H. M., Norris, D. G., & Hagoort, P. (2010). Topographical functional connectivity pattern in the perisylvian language networks. *Cerebral Cortex (New York, N.Y. : 1991)*, *20*(3), 549–60.
- Yamada, Y., Stevens, C., Dow, M., Harn, B. A., Chard, D. J., & Neville, H. J. (2011). Emergence of the neural network for reading in five-year-old beginning readers of different levels of pre-literacy abilities: An fMRI study. *Neuroimage*, *57*(3), 704-713.
- Yang, J., Shu, H., McCandliss, B. D., & Zevin, J. D. (2013). Orthographic influences on division of labor in learning to read Chinese and English: Insights from computational modeling. *Bilingualism: Language and Cognition*, *16*(02), 354-366.
- Yap, R. L., & van der Leij, A. (1994). Testing the automatization deficit hypothesis of dyslexia via a dual-task paradigm. *Journal of learning disabilities*, *27*(10), 660-665.
- Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. a, & Ben-Shachar, M. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *Journal of Cognitive Neuroscience*, *23*(11), 3304–17.
- Yopp, H. (1988). The validity and reliability of phonemic awareness tasks. *Reading Research Quarterly*, *23*, 159–176.
- Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: identifying differences in brain networks. *Neuroimage*, *53*(4), 1197-1207.
- Zeffiro, T., & Eden, G. (2001). The cerebellum and dyslexia: perpetrator or innocent bystander?: Comment from Thomas Zeffiro and Guinevere Eden to Nicolson et al. *Trends in Neurosciences*, *24*(9), 512-513.
- Zeng, L.-L., Wang, D., Fox, M. D., Sabuncu, M., Hu, D., Ge, M., ... Liu, H. (2014). Neurobiological basis of head motion in brain imaging. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(16), 6058–62.
- Zhang, Y.-J., Lu, C.-M., Biswal, B. B., Zang, Y.-F., Peng, D.-L., & Zhu, C.-Z. (2010). Detecting resting-state functional connectivity in the language system using functional near-infrared spectroscopy. *Journal of Biomedical Optics*, *15*(4), 047003.
- Zhang, S., & Li, C. S. R. (2014). Functional clustering of the human inferior parietal lobule by whole-brain connectivity mapping of resting-state functional magnetic resonance imaging signals. *Brain connectivity*, *4*(1), 53-69.
- Zhou, W., Xia, Z., Bi, Y., & Shu, H. (2015). Altered connectivity of the dorsal and ventral visual regions in dyslexic children: a resting-state fMRI study. *Frontiers in Human Neuroscience*, *9*, 495.
- Zhu, L., Fan, Y., Zou, Q., Wang, J., Gao, J. H., & Niu, Z. (2014). Temporal reliability and lateralization of the resting-state language network. *PloS one*, *9*(1), e85880.