Chapter

Neuroimaging Reveals Heterogeneous Neural Correlates of Reading Deficit in Individuals with Dyslexia Consistent with a Multiple Deficit Model

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Abstract

Neuroimaging has become a powerful way of studying in vivo brain function and structure. The aim here is to comprehensively review Reid's fMRI study which is the first to use a multiple case approach to investigate individual differences among 18 participants with dyslexia (DPs) and 16 control participants (CPs) and to directly test the predictions of the main dyslexia theories on reading deficit. The results show that the neural correlates of reading deficit for all DPs (except one) are consistent with more than one theory, supporting a multiple deficit model. Striking individual differences between DPs were found; even if the neural correlates of reading deficit in two DPs were consistent with the same theory, the affected brain areas could differ. To make progress, research on causes of reading deficit in dyslexia would need to (1) focus on the multiple deficit model, (2) use neuroimaging to test a further refined set of brain areas (including areas hypothesised by other dyslexia theories) in longitudinal designs, (3) control the effects of co-occurring neurodevelopmental disorders, (4) use high-field MRI (including diffusion techniques), multiband fMRI and MEG with optically pumped magnetometers, (5) progress imaging genetics and (6) pursue neuroimaging intergenerational transmission of brain circuity.

Keywords: dyslexia, MRI, fMRI, neuroimaging, individual differences, a multiple case study, co-occurring neurodevelopmental disorders, reading disorder, imaging genetics, multiple deficit model

1. Introduction

1.1 A brief summary of neuroimaging methods and neuroimaging research on the biomarkers of neurological, neuropsychiatric and neurodevelopmental disorders

There are six main neuroimaging methods: magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG) and positron emission tomography (PET). MRI and DTI enable investigation of brain structure,

whereas fMRI, EEG, MEG and PET enable research into brain function. MRI produces high-resolution images of the brain, with clearly distinguishable grey and white matter, ventricles and fibre tracts. DTI is a method which is mainly used to investigate the anatomical structure of the axon tracts and can provide information on the between-regional anatomical connectivity in the brain. An MRI scanner is used to perform DTI which measures the motion and density of the water in the axons. fMRI uses magnetic resonance imaging to measure brain activity by measuring the ratio of oxygenated to deoxygenated haemoglobin, and this value is referred to as the blood oxygen level-dependent (BOLD) effect; brain activity is usually measured in an experimental task, relative to a control task. EEG is an electrophysiological method for recording global electrical activity of the brain. In order to ask questions on how brain activity is modulated in response to a particular task, an event-related potential (ERP) needs to be extracted from the global EEG signal. MEG is a technique which allows the mapping of brain activity by recording the magnetic fields created by the electrical currents of the brain, using very sensitive magnetometers. Finally, PET measures metabolic activity in the brain by monitoring the distribution of a radioactive tracer. As with fMRI, PET relies on the fact that local blood flow increases in active brain areas. Unlike MEG and EEG, fMRI and PET do not directly measure neural events but metabolic changes which are correlated with neural activity. The neuroimaging techniques differ with respect to critical variables in brain mapping, such as spatial and temporal resolution. Spatial resolution is the ability to distinguish two separate objects that are situated close to one another, whereas temporal resolution is the ability to detect two events that happen in close temporal proximity [1]. ERP and MEG have relatively good temporal resolution of milliseconds (0.01 s) but relatively poorer spatial resolution (10 mm). Structural MRI has relatively good spatial resolution; brain structures much smaller than 1 mm can be resolved with this method, including subcortical structures, such as the superior colliculus. DTI's spatial resolution has been improving, and high-spatial-resolution DTI imaging has been reported with a resolution of 1 mm [2]. fMRI is characterised by relatively good temporal resolution of seconds to hundreds of milliseconds and spatial resolution of 4–5 mm. PET has relatively lower spatial (5–10 mm) and temporal (60–1000 s) resolutions [1]. It should be emphasised here that the neuroimaging methods introduced above are subject to steady improvement, with regard to their spatial and temporal resolution and other characteristics; furthermore new neuroimaging methods are being developed. For instance, three more recent neuroimaging methods need to be mentioned here: diffusion kurtosis imaging (DKI) [3], a neuroimaging method that provides independent and additional information (to that acquired with DTI) which indicates the complexity of the microstructural environment of the imaged tissue, neurite orientation dispersion and density imaging (NODDI) [4] (see Section 3.4) and magnetic field correlation imaging (MFC) [5], a neuroimaging technique used for the quantitative assessment of iron within the brain. For more details on neuroimaging methods, see [6–9].

Neuroimaging has become a popular and powerful way of studying in vivo brain function and structure in health and disease. One important branch of neuroimaging is the search for a biomarker in neurological, neuropsychiatric and neurodevelopmental disorders (including dyslexia). For instance, promising strides here have been made using various neuroimaging techniques in Alzheimer's disease (MRI [10], fMRI [11], PET [12] and MEG [13]), schizophrenia (PET [14], EEG [15] and MEG [16]), attention deficit hyperactivity disorder (ADHD) (MEG and structural MRI [17], DKI [18], MRI and MFC [19]) and dyslexia (MEG and structural MRI [17], structural MRI [20], ERPs [21, 22], MEG [23] and fMRI [24]). It should be noted that some of the above cited papers explicitly claim the search for neuroimaging biomarkers, while others do not,

but the results reported can be considered as potential candidates for neuroimaging biomarkers. However, an obstacle to the development of neuroimaging biomarkers in neurodevelopmental disorders, such as dyslexia and ADHD, is sample heterogeneity, due to the phenotypic and aetiological complexity and co-occurrence of other disorders. Therefore, it is likely that no single neuroimaging biomarker (or even multiple biomarkers from the same domain) may be sufficient for reliable and accurate diagnosis of these disorders and there needs to be a shift towards identifying sets of biomarkers, possibly from different domains. The serious problem of sample heterogeneity which is associated with neurodevelopmental disorders was the main reason behind adopting a different approach in Reid's [25] fMRI study reviewed in this chapter.

1.2. Dyslexia and the most researched causal theories of this disorder

'Percy F ... has always been a bright and intelligent boy, quick at games, and in no way inferior to others of his age. His great difficulty has been – and is now – his inability to learn to read. This inability is so remarkable, and so pronounced, that I have no doubt it is due to some congenital defect' [26, p.1378].

This chapter reviews the first fMRI study [25] which used a multiple case approach to investigate reading deficit in participants with similar difficulties to Percy F's struggles described 122 years ago. Such difficulties are nowadays defined as developmental dyslexia (henceforth dyslexia). The above example is only given to illustrate the profound and puzzling literacy difficulties experienced by individuals with dyslexia and not to discuss Morgan's [26] interpretation of reading difficulties as congenital word blindness. It should also be emphasised that despite such profound difficulties when learning to read, most individuals with dyslexia reach a reasonable level of reading ability, becoming compensated DPs.

Dyslexia is one of the most prevalent neurodevelopmental disorders—it affects from 5 to 17.5% of the English-speaking population [27]. DPs exhibit difficulties in learning to read, despite sociocultural opportunities, a scholarly education, adequate conventional instruction and intelligence, as well as intact sensory abilities [28]. It has been demonstrated [29] that the rates of reading disability are higher in boys than in girls. Untreated dyslexia is likely to have a serious impact on the life of an individual, including learning ability, self-esteem, mental health, relationships, social participation, employment and economic status. The vast majority of research on dyslexia has been conducted in English (an unrepresentative language in terms of grapheme-to-phoneme correspondence). More recent research across different languages indicates that dyslexia also occurs in other languages, including languages with an orthographic transparency higher than English [30–32]. Dyslexia is characterised by a strong heritable component [33]. Most research on dyslexia has focused on deficits; however, some publications have explored positive aspects of dyslexia [34]. There is now considerable evidence that dyslexia co-occurs more frequently than by chance with other neurodevelopmental disorders, such as ADHD and developmental coordination disorder (DCD). About 20–42% of reading disabled children also meets the criteria for ADHD [35, 36]. Furthermore, there is growing evidence that some reading impaired individuals exhibit motor difficulties [37, 38]. The prevalence of dyslexia and DCD co-occurrence are relatively high, for example, 63 and 60% in samples in [36] and [38], respectively.

There are three main, most researched causal theories of dyslexia, and each theory postulates a different and single underlying cause of literacy difficulties in dyslexia. A short description of each theory is included below, but the detailed review of these theories is beyond the scope of this chapter; interested readers are referred to the references and to Reid's publication [25]. According to the

phonological deficit theory (PDT) [39–41], phonological deficit is the underlying cause of dyslexia. This means that DPs have a specific impairment in the representation and processing of speech sounds (phonemes) [41] or a deficit in accessing intact phonological representations [42]. According to the PDT, the phonological deficit leads to poor grapheme-to-phoneme conversion and this in turn leads to poor reading. It is claimed that the phonological deficit also manifests itself on the behavioural level by difficulties in phonological fluency [32, 40], phonological awareness [40, 43] and verbal short-term memory [44, 45]. The deficit postulated by the PDT was specified on the biological level as the left (L) perisylvian region abnormality [46] and recently as the L temporoparietal abnormality and L frontal abnormality [47].

The visual magnocellular deficit theory (MDT) [48–50] claims that the underlying cause of literacy problems in dyslexia is not language specific but a more general impairment of the visual magnocellular system with spared parvocellular system. Magnocellular neurons are defined at the level of the retinal ganglion cell which have specific projections to the lateral geniculate nucleus (LGN) in the thalamus. The results in support of the MDT include reduced contrast sensitivity [51], unsteady binocular fixation [48] and a significantly higher threshold for the perception of coherent movement in random-dot kinematograms in DPs than in CPs [52]. The MDT claims that the visual magnocellular system impairment in dyslexia has a genetic origin. According to Stein [48], the clearest genetic result is for linkage to the region on the short arm of chromosome 6 which helps to control the production of antibodies (see also [53, 54] for recent studies showing association between motion deficit and the *DCDC2* gene). The magnocellular system is hypothesised to play an important role in reading and orthographic and phonological representations [48]. First, it subserves the process of image stabilisation and/or letter localisation in words during reading [55]. Second, it affects orthographic knowledge, through reading skill. Third, it affects phonological representations through orthographic representations [48]. For the most recent version of the MDT, see [56].

According to the cerebellar deficit theory (CDT), the underlying cause of dyslexia is a cerebellar impairment. Cerebellar dysfunction has been linked to problems in (1) motor skills, (2) perception and production in timing tasks, (3) automatisation of motor skill and (4) classical conditioning of the eye-blink response. Dyslexia research has shown that DPs indeed exhibit deficits over a range of functions which rely on cerebellar processing, such as motor skills, including balancing [57], eye-blink conditioning [58] and time estimation [59]. Nicolson et al. [60] put forward a hypothetical ontogenetic causal chain according to which cerebellar deficit could lead to reading difficulties in dyslexia by two routes. The major route claims that cerebellar impairment leads to mild articulatory problems, which lead to an impoverished representation of the phonological characteristics of speech. In turn, this causes difficulties in phonological awareness and subsequently results in difficulties with learning to read. Furthermore, reduced articulation speed leads to reduced working memory. The second route claims that difficulties in reading acquisition stem from a cerebellar deficit which causes problems with automatising skills and knowledge, leading to problems with (1) automatic grapheme-to-phoneme conversion, (2) automatic word recognition, (3) automatic verbal working memory and (4) automatic awareness of the orthographic regularities. Motor problems (also caused by cerebellar impairment) lead to dysgraphia (writing impairment). Additionally, balance deficits are also caused by cerebellar deficit. However, these motor difficulties (except for the articulatory difficulties) and problems with balance do not lead to reading difficulties, but the underlying cerebellar deficit [60].

2. The first neuroimaging study to use a multiple case approach to investigate individual differences among DPs

Most neuroimaging (and behavioural) studies which have been formulated within the main theories of dyslexia have shortcomings (for a review of studies, see [25]). First, they have used group comparisons which can cloud the less frequent differences between DPs and controls (CPs). Second, they mostly investigated a single underlying cause, hypothesised by one theory. Third, the majority of them concentrated on finding a deficit without empirically showing its relationship with reading deficit, which defines dyslexia. For instance, significantly lower BOLD signal in DPs (vs. CPs) was reported [61] in the R cerebellar cortex when learning a new sequence of finger presses and interpreted as support for the CDT. Another study [62] revealed lack of fMRI activation in V5/MT in DPs in contrast to CPs (while participants viewed a coherently moving, low-contrast, random-dot stimulus), and the results were interpreted as being in agreement with the MDT. However, a demonstration of a significant between-group difference on these variables does not show that there is a relationship with reading, even if DPs had a documented reading deficit, and their reading scores significantly differed from the CPs. This is because a given variable may be a correlate or biological marker of dyslexia, which is independent of any reading deficit [63].

The goal of Reid's study [25] was to shed more light on the neural correlates of reading deficit in dyslexia and address the above criticisms: First, by choosing a multiple case study to investigate individual differences among DPs. Second, by contrasting the hypotheses based on each of the main theories, on the neural correlates of the reading impairment, in individual DP (vs. CP), thereby detecting differences which otherwise would have been obscured in the between-group comparison, due to heterogeneity among DPs. The behavioural studies suggest that there are subtypes of dyslexia [32, 40, 64–68], but they cannot be investigated by focusing on one theory. Third, by focusing on a reading task using fMRI - which provides an opportunity to more directly investigate the relationship between the predictions of a given theory and the neural correlates of reading impairment in dyslexia.

2.1 Hypotheses

First, if, as hypothesised by the PDT, the neural correlates of reading deficit in DPs lie within the phonological network, then DPs should show abnormal activation in all or some areas within this network. As the descriptive terms for phonological deficit on the biological level (L perisylvian, L temporoparietal and L frontal regions) were not detailed enough to thoroughly test the PDT on the neural level, a literature review was undertaken [25] and showed that phonological processing (operationalised as phonological awareness, naming and short-term memory) involves many brain areas but it is still unclear what role each area plays in phonological processing. Broadly speaking, the phonological processing network (also validated with the broader literature review presented in [25]) included the following L hemisphere areas: the inferior frontal gyrus (BA44/45)—Broca's area, Wernicke's area (BA22), the middle temporal gyrus (BA21), the insula, inferior parietal lobule (including the angular gyrus (BA39) and the supramarginal gyrus (BA40)), the precentral gyrus PMC (premotor cortex) (BA6), the fusiform gyrus (BA19/37) and the posterior fusiform gyrus. The role of the L posterior fusiform gyrus is unclear, with some researchers advocating its involvement exclusively in orthographic processing [69] and other investigators [70] in mapping orthography onto phonology. The above listed areas were used to test the PDT. To detect abnormality in the neural correlates of the reading impairment of a given DP, not

all the areas involved in phonological processing needed to exhibit atypical activation, because individuals might have differed in the neural implementation of the phonological network and/or in the presence of areas with atypical activation. The PDT also predicts that DPs should not show abnormal activations in the magnocellular system and the cerebellum, as predicted by the MDT and CDT, respectively.

Second, if, as predicted by the MDT, reading impairment in dyslexia is due to magnocellular abnormality, then DPs should show significantly lower activation in the V5/MT. The neuroimaging research on the MDT [62, 71] focused on the V5/MT area because it receives the input predominantly from the magnocellular stream [72]. The involvement of V5/MT in reading was demonstrated in a study by Liederman et al. [55] which showed that a virtual lesion of V5/MT, created by repetitive transcranial magnetic stimulation (rTMS) during reading in CPs, resulted in visual but not phonological errors. Furthermore, there may also be differences between CPs and DPs in other areas within the magnocellular system. In the study reported in [25], three areas in both hemispheres were investigated: the V5/MT, V1 and V2. This is because of (1) significant correlations between fMRI activation in these areas (under low mean luminance moving grating conditions), and reading performance were reported [73] and (2) V1 and V2 could be more reliably localised than the remaining motion-sensitive areas, using available cytoarchitectonic maps [74, 75]. Hypoactivation in L and right (R) V1 and/or in V2 was interpreted as supporting the MDT only if discovered jointly with underactivation in the V5/MT. The V5/MT receives input predominantly from the magnocellular stream [72], but V1 and V2 consist of partially separated magno and parvo cell inputs. Therefore, the underactivation of V1 and V2 may reflect underactivation of either parvo cells or magno cells or a combination of these. Hypoactivation in V1 and/or V2, with no underactivation in the V5/MT, was interpreted as a visual but not a magnocellular deficit. A hypothetical visual deficit theory (VDT) was put forward, and it was argued that in DPs who exhibited underactivation in V1 and/or V2, without hypoactivation of V5/MT, hypoactivation is in agreement with the VDT but not with the MDT.

Third, given, that according to the CDT, the underlying cause of dyslexia is a cerebellar impairment, one would predict that the neural correlates of reading problems in DPs are localised within the cerebellum and therefore DPs should show atypical activation during reading in some regions of the cerebellum. However, the CDT does not specify which cerebellar areas should be affected. As the research reported in [25] investigated reading, the focus there was mainly on the cerebellar language areas. Probably the most reliable results regarding the language areas in the cerebellum come from the meta-analysis by Stoodley and Schmahmann [76]. The areas include the R lobule VI (Hem), R and L Crus I (Hem), R Crus II (Hem), R Vermal lobule VIIAt (R Vermal lobule VI) and L lobule VI (Hem). These areas were selected to test the CDT in DPs' reading. Additionally, some areas were also included, either because they were shown to significantly differ in DPs and CPs (R Vermal lobule VI [20], the L and R Crus II and the paramedian R and L lobule (VIIB) [77]) or because they were activated during silent reading in CPs (L and R Crus I, L and R Crus II, L and R lobule VI and L and R lobule VIIB [78]). Most of these areas overlapped with Stoodley and Schmahmann's [76] regions.

Finally, it needs to be stated that the MDT and CDT also make additional predictions. The MDT postulates that the magnocellular system is important in the acquisition of accurate visual representations of the written, orthographic forms of words and that this is essential to grasp their structure at the phonemic level. Therefore, it has been hypothesised [49] that a deficient magnocellular system could be the underlying cause of deficient phonological representations and therefore of a phonological deficit. Hence it is possible that the hypoactivation in phonological areas (coupled with the hypoactivation in the V5/MT) in DPs during reading is also consistent with

the MDT (and with the PDT, as discussed above). However, the methods used in [25] do not allow for teasing apart whether the hypoactivation in phonological areas (co-occurring with hypoactivation in magnocellular areas) is 'purely phonological' or has been influenced by magnocellular malfunctioning. The hypoactivation in DPs in phonological areas in the presence (but not in the absence) of the hypoactivation of magnocellular areas is interpreted here as being consistent with the MDT (and with the PDT, as specified above). Moving to the CDT, it predicts that a phonological deficit (in phonological awareness and in reading) can be caused by a cerebellar impairment. Therefore it is possible that the hypoactivation in phonological areas (coupled with the hypoactivation in cerebellar areas) in DPs during reading, in Reid's study, may also be consistent with the CDT. However, the methodology used in [25] does not allow for teasing apart these effects. The hypoactivation in DPs in phonological areas in the presence (but not in the absence) of the hypoactivation of cerebellar areas was interpreted in [25] as being consistent with the CDT (and with the PDT, as specified above). It is important to keep in mind, however, that interpreting hypoactivation within the phonological areas as being also consistent with the MDT and CDT holds only if one takes the perspective of the MDT or CDT, respectively. In contrast, from the theoretical perspective of the PDT, such interpretations do not hold.

2.2 Participants

Thirty-eight adult native English speakers from three UK universities took part in Reid's study [25]. They were all right handed, with normal hearing, normal or corrected to normal vision, without clinical ADHD (defined as a score < 70 on the ADHD D index on Conners' scales [79]), without clinical DCD (as defined in DSM-IV [80]) or any other known sensory, neurological, psychiatric or neurodevelopmental disorders. There were indications that DP8 and DP15 may be 'at risk' of clinical DCD (They were the only DPs who responded 'yes' to the question on whether their DCD difficulties significantly interfered with their everyday life). DP8 and DP15 were included in Reid's study [25], but a DCD measure obtained from a questionnaire (based on DSM-IV, Adult DCD Checklist (DANDA—Developmental Adult Neuro-Diversity Association) and questions devised by A. Reid (see [25] for details) was used as a covariate in the fMRI analysis. Furthermore, DP8's and DP15's fMRI data were additionally analysed for possible DCD effects. Four participants were excluded from the analysis (1 CP did not provide a dyslexia diagnosis and 3 DPs because their fMRI data could not be salvaged by the recommended techniques [8]). Eighteen individual DPs and 16 CPs (treated as a control group) were entered into an fMRI multiple case analysis. All DPs (6 males and 12 females; mean age 21.28 years (SD = 3.3)) reported a history of persistent literacy difficulties (mainly with reading) and had a formal diagnosis of dyslexia. Twelve DPs (66.7%) disclosed that literacy problems occurred in one or more of their first-degree relatives. CPs (5 males and 11 females; mean age 21.38 years (SD = 6.03)) had no literacy problems or any other known sensory, neurological, psychiatric or neurodevelopmental disorders. Although the DP and CP groups were matched on years of education, age, handedness, verbal IQ, performance IQ and full scale IQ, this was not always the case in the multiple fMRI case analyses which compared every individual DP to CPs. Hence additionally, age, handedness and FSIQ were used as covariates in these analyses. For more details on participants and other aspects of the study, see [25].

2.3 Materials, stimuli and fMRI task

The participants were tested using a broad battery of behavioural measures (see [25] for details). The fMRI reading task reported in Reid [25] had three conditions.

Condition 1 consisted of 100 English words (high familiarity, imageability and concreteness, two-syllable, five to seven letters, with regular spelling selected from the MRC psycholinguistic database [81]); Condition 2 contained 100 pseudowords created by the substitution of consonants in the onset or middle of words from Condition 1. Condition 3 (the control condition) consisted of a fixation cross. The fMRI experiment had an event-related design [82] with stimuli from all conditions randomly intermixed. Each stimulus was displayed for 1000 milliseconds, with an interstimulus interval (ISI) of 3000 milliseconds and a stimulus onset asynchrony (SOA) of 4000 milliseconds. The focus in Reid's [25] communication was on word reading which involved the contrast of Conditions 1 and 3.

2.4 fMRI data acquisition

The MRI and fMRI data were acquired at the Aston University MRI Research Centre using a 3 T Trio Siemens scanner equipped with echo planar imaging and a standard eight-channel head coil. A high-resolution structural MRI image was acquired first, followed by fMRI data acquisition during the reading task. For fMRI data, 44 (3 × 3 × 3 mm) slices, covering the whole brain, were acquired every 3 sec (TR = 3000 ms, TE = 30, flip angle = 90, FOVread = 192, FOVphase = 100) for a total of 404 volumes. In the scanner the participants were asked to silently read words and to keep their gaze fixed on the '+' sign shown in the centre of the field of view on the screen. They were asked to read every item carefully because there would be a posttest after the fMRI experiment. The posttest scores were summarised in *d Prime* and entered as covariates into the second-level neuroimaging analysis. To monitor participants' vigilance, they were required to press a response button (with their left index finger) when a black star (displayed during ISI) became red. This occurred on 10% of trials.

2.5 Data preprocessing

SPM5 was used to analyse (and preprocess) the fMRI data. The preprocessing involved realignment, slice timing correction, coregistration, segmentation, normalisation and smoothing [83]. Usually, realignment is run first and slice timing correction second; however, because each volume was acquired in slices in an interleaved fashion, starting from the bottom slice, the order of these two steps was swapped (John Ashburner, email communication, June 4, 2007). The slice timing correction was applied to correct the differences in slice acquisition times. The 'realign' function was used to remove confounds which can arise in the fMRI data from changes in signal intensity over time due to head motion. Realignment parameters were saved for each participant for each session and entered into the design matrix as covariates. A coregistration function was used to coregister the functional (MRI) and the structural (MRI) data so as to maximise their mutual information. A segmentation function was used to segment the structural image according to tissue probability, using default maps, creating grey and white matter images and a bias-field corrected structural image. The data were pooled into the same anatomical space using a spatial normalisation function to put the MRI images into a standard space defined by template images (corresponding to the space defined by the International Consortium for Brain Mapping (ICBM), NIH P-20 project). The data were smoothed with an 8-mm Gaussian kernel.

2.6 Data analysis

In the first-level analysis, the word condition was explicitly modelled. The control condition was implicitly modelled [84]. To avoid confounding the BOLD response

due to the 'Star' stimulus and 'Button Press', they were included in the design matrix as regressors. The shape of the canonical haemodynamic response function (HRF) (SPM5) was used to model the experimental haemodynamic response. Further inclusion of the dispersion and time derivatives was necessary to account for variations in the voxel-to-voxel and subject-to-subject responses, especially in the experiment that involved the DPs characterised by heterogeneity with respect to behavioural and neuroimaging findings. The time derivative allows for the variation in the peak response of plus or minus 1 second, whereas the dispersion derivative allows for the variation in the width of the response by a similar amount [83]. A t-contrast (Word>Fixation Cross) was tested in the first-level analysis. The second-level analysis focused on comparison of a given individual DP and the CPs (treated as a group). Data analysis in the second level involved a two-sample t-test. Two contrasts were tested: CPs > DP (hypoactivation) and DP > CPs (hyperactivation). A number of DPs showed elevated (but non-'clinical') scores on the ADHD and DCD measures in comparison to the CPs; hence these scores were entered into the second-level analysis as covariates. Participants' age, handedness, FSIQ and d Prime scores were also entered into the second-level analysis as covariates, as discussed above.

2.7 ROI analysis (mask)

There is growing evidence that different brain regions, such as BA44 and BA45 are characterised by high inter-participant structural variability [85]. Bearing this in mind, a mask for the ROI analysis was prepared mainly using cytoarchitectonic areas (see note for **Table 1**). The ROI mask consisted of 31 areas. Twenty-nine areas were created as individual ROIs in the AT (V.1.8) [86], and two areas (not available in AT (V.1.8)) were created as individual ROIs in MarsBar (version 0.43) [87]. The ROIs created in MarsBar were coregistered to the ROIs created in the AT (V.1.8). All ROIs were combined (and binarised) into one mask using SPM5. The 31 ROI mask was coregistered in SPM5 (using the resliced option) to the fMRI data before running the ROI analysis. As DPs are usually characterised by considerable heterogeneity, activation in a brain area was considered as supporting a given hypothesis when the probability that a given voxel belonged to that area was 10% or higher [88].

2.8 Results and discussion

The multiple case analysis of DPs' performance on psychometric tests revealed marked heterogeneity among DPs, and this was in line with the previous findings [32, 40, 64–68] (see [25] for details). The neuroimaging results for underactivation in each individual DP, as compared to CPs (CPs > DPs) during word reading relative to the control condition, are shown in **Table 1** and **Figure 1** (see also Appendix B **Table 1** to **18** for MNI coordinates of the BOLD [25]). Hypoactivation is usually assumed to reflect a functional disruption in a system [89]. In the context of the dyslexia theories, hypoactivation in the hypothesised brain areas was interpreted as lending support for these theories. The contrast DP > CPs revealed brain areas which were hyperactivated by a given individual DP (vs. CPs) during word reading, relative to the control condition. Hyperactivation is usually interpreted as a correlate of a compensatory mechanism [89]. Because the dyslexia theories are concerned with a deficit and not compensatory mechanisms, hyperactivation of the brain areas associated with these main theories was not interpreted as evidence of support for them. An inspection of **Table 1** and **Figure 1** reveals that all individuals with dyslexia exhibited heterogeneous and complex patterns of hypoactivation which involved the areas predicted by the dyslexia theories. Five DPs showed overactivation; see text below.

ROI/DP	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
L area 44	+		+	✓	✓	+			+		+			+	+	+		+
L area 45			+															
L area Ig1																		
L area Ig2																		
L area Id1																		
L area 6	+		+	✓			✓		+					+	+	+		+
L IPC PFop																		
L IPC L PFt																		
L IPC PF	+	✓	+	✓										+				+
L IPC PFm			+		✓		✓			+				+		+		+
L IPC PFcm	+																	
L IPC PGa															+			
L IPC PGp	+		+	✓		+		✓	+					+	+		✓	
L area TE3	+			✓										+				+
L MTG	+		+	✓										+		+		+
L FG	+			✓							+	+				+		+
L hOC5																		
R hOC5	+																	
L area 17									+									
R area 17			+					✓	+						+			
L area 18			+						+		+			+				+
R area 18			+	✓			✓	✓	+		+			+		+		+
L Lob. VIIa Cr.I		+	+		+	+	✓	+	+	+	+	+	✓	+	+	+	+	+
R Lob. VIIa Cr.I	+	+	+		+	+	✓	+	+	+	+	+	✓	+	+	+	+	+

ROI/DP	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
L Lob. VIIa Cr.II	+						✓				+	+					+	
R Lob. VIIa Cr.II	+	+	+		+	+	✓	+	+	+	+	+	✓	+	+	+	✓	+
L Lob. VI															+			+
R Lob. VI					+		✓	✓	+	+	+	+		+		+		
R Lob. VI (Ver.)														+				
L Lob. VIIb				✓														
R Lob. VIIb																		

Note: 1–18, a unique number for every participant with dyslexia; the presence of underactivation within ROI in the individual DP is denoted by '+' ($p < .05$ FDR, corrected for multiple comparisons) and '✓' ($p < .001$, uncorrected for multiple comparisons); 31 ROI included in the mask, L area 44 and L area 45 [90] (equivalent to Broca's area L BA44 and L BA45), L areas Ig1, Ig2, Id1 (the posterior insula) [91], L area 6 (the premotor cortex, equivalent to L BA6) [92], L IPC PFop, L IPC L PFt, L IPC PF, L IPC PFm and L IPC PFcm (inferior parietal lobule, these areas approximately cover the region of L BA40 on the supramarginal gyrus with extension into the depth of the Sylvian fissure [93]); L IPC PGa and IPC PGp [94] (inferior parietal cortex, these areas are located approximately at the position of the angular gyrus (BA39), L area TE3 in the lateral part of the superior temporal gyrus, perhaps homologous to BA22 (Wernicke's area) [95], the L middle temporal gyrus (L MTGL) and the L fusiform gyrus (L FG) [96], the L hOC5 and R hOC5 [75] (equivalent to L and R V5/MT), L and R area 17 and area 18 [74] (equivalent to L and R V1 and V2) and nine cerebellar regions (L Lobule VIIa Crus I (Hem), R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus II (Hem), R Lobule VIIa Crus II (Hem), L Lobule VI (Hem), R Lobule VI (Hem), R Lobule VI (Vermis), L Lobule VIIb (Hem) and R Lobule VIIb (Hem) [97]; Lob. denotes lobule; all lobules are hemispheric, except one (R Lob. VI (Ver.)) which is vermal.

Table 1.
Brain areas (ROI) underactivated in individual DPs (CPs > DPs).

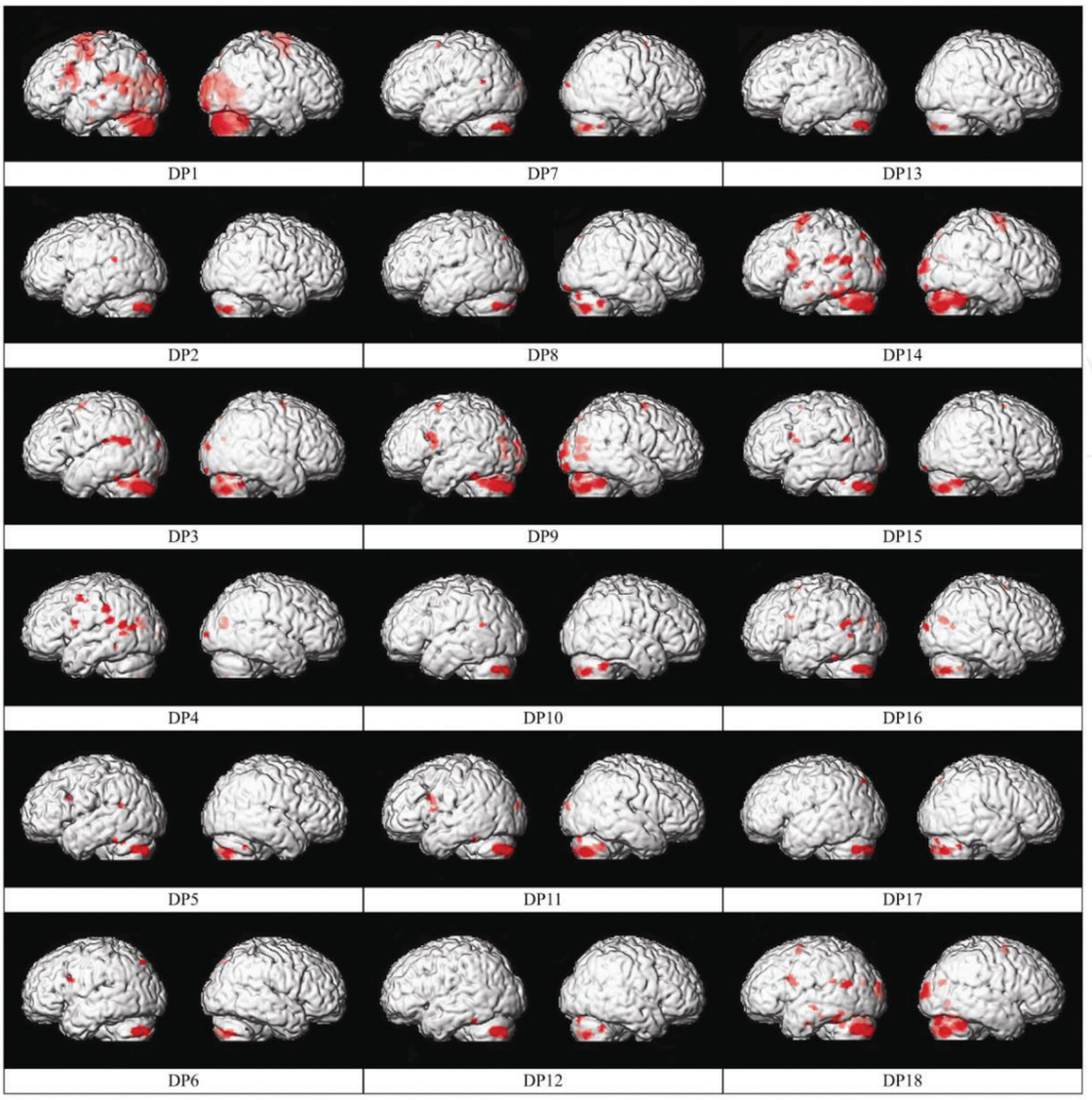

Figure 1.
Clusters of underactivation (CPs > DP) for individual DPs. Underactivation is superimposed on a volume-rendered brain (a spatially normalised anatomical image for an individual DP). Cluster size threshold $k \geq 6$. An ROI mask was applied; see Section 2.7 and note for **Table 1**.

The main goal of the research reported in [25] was to shed more light on the underlying reading impairment (which defines dyslexia) in adult DPs, as hypothesised by the PDT, MDT and CDT, with special focus on individual differences among DPs. When the hypotheses based on the three main theories of dyslexia were contrasted in the same DPs, the neural correlates of word reading deficit were consistent with the PDT in 17 cases (94.4%), with the CDT in 18 cases (100%) and in 1 case (5.5%) with the MDT. Furthermore, the reading deficit of 10 cases (56%) was consistent with the VDT but not with the MDT.

A more detailed inspection of the neuroimaging results for reading revealed that when hypotheses based on the three main theories are tested in individual DPs, DPs showed complex and heterogeneous patterns of underactivation in the brain regions predicted by the dyslexia theories. For instance, DP1 showed hypoactivation in eight areas predicted by the PDT (L area 6 (BA6), L area 44 (BA44), L middle temporal gyrus (BA21), L fusiform gyrus (BA19/37), L TE 3 (part of BA22), L IPC (PF) (BA40), L IPC (PFcm) (BA40) and L IPC (PGp) (BA39)), one area hypothesised by the MDT (R hOC5 (V5/MT)) and three areas predicted by the CDT (R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus II (Hem) and R Lobule VIIa Crus II (Hem). DP10 exhibited hypoactivation in one area hypothesised by the PDT (L IPC

(PFm) (BA40)) and four areas predicted by the CDT (L Lobule VIIa Crus I (Hem), R Lobule VIIa Crus I (Hem), R Lobule VIIa Crus II (Hem) and R Lobule VI (Hem)). In contrast, DP13 hypoactivated only areas predicted by the CDT (L Lobule VIIa Crus I (Hem), R Lobule VIIa Crus I (Hem) and R Lobule VIIa Crus II (Hem)) (see **Table 1** and **Figure 1** for the other cases).

Moreover, the neuroimaging data exhibited a high degree of individual differences. Even if the neural correlates of reading disorder in two DPs were consistent with the same theory, the neural correlates in those DPs could differ. For instance, within the framework of the PDT, DP6 showed hypoactivation in the L area 44 (BA44) and L IPC (PGp) (BA39); DP10 exhibited hypoactivation in L IPC (PFm) (BA40), whereas DP12 hypoactivated L FG (fusiform gyrus). This is also the case for the neural correlates of reading deficit hypothesised by the CDT. For instance, DP1 showed hypoactivation in R Lobule VIIa Crus I (Hem), L Lobule VIIa Crus II (Hem) and R Lobule VIIa Crus II (Hem); DP14 hypoactivated L Lobule VIIa Crus I (Hem), R Lobule VIIa Crus I (Hem), R Lobule VIIa Crus II (Hem), R Lobule VI (Hem) and R Lobule VI (Vermis), whereas DP4 showed hypoactivation only in L Lobule VIIb (Hem). The traditional approach, based on group comparison where only between-group differences (DPs vs. CPs) were tested, could not reveal the individual differences among DPs as shown in [25].

The results revealed considerable individual differences in patterns of hypoactivation within the reading network among DPs, which are unexpected in the context of the between-group comparison studies, which have dominated neuroimaging research on dyslexia. Nevertheless, they are perhaps less surprising if one considers the fact that reading is a relatively new (less than 6000 years old) cultural invention in human evolutionary history. It requires areas which evolved for vision, language and associative learning. Reading acquisition is an exercise in brain plasticity; the goal of which is to create an efficient reading network which enables the unimpaired reader to get from visual precept to meaning in approximately 250 milliseconds [98]. As in the ontogenetic development of an individual, a number of brain regions need to be 'adapted' for reading; it is perhaps not surprising that in different DPs, different components may be deficient.

Five (28%) DPs in the study [25] exhibited hyperactivation. Similar to the patterns of underactivation, overactivation differed in different DPs. DP4 exhibited overactivation in L area 6, L insula (Ig2), L IPC (PFm), L IPC (PGa), L area 17, R area 17, L area 18 and R area 18, R Lobule VIIa Crus I (Hem) and L Lobule VI (Hem). DP5 hyperactivated L area 17 and R area 18. DP8 overactivated L insula (Id1) and L area 18. DP13 show hyperactivation in L area 6, L middle temporal gyrus and L area 17. Finally, DP17 exhibited overactivation in L fusiform gyrus, insula (Id1) and L Lobule VIIb (Hem). All results for ROI analyses at $p < 0.001$ (uncorrected for multiple comparisons), except for DP4's results at $p < 0.05$ (FDR). Overactivation in some DPs in the areas hypothesised to show underactivation in DPs by the PDT indicates that a compensatory network is not limited to the frontal regions, as suggested by a number of studies based on group comparisons (for instance, see [89]), but involves brain regions distributed across the phonological reading network. Cerebellar and secondary and/or primary visual areas were overactivated in two and four DPs, respectively, suggesting the existence of a potential compensatory network within these brain regions.

An important common characteristic of the dyslexia theories (the PDT, MDT and CDT) investigated in [25] is the assumption that a single underlying deficit is necessary and sufficient to cause symptoms of dyslexia: phonological, or visual magnocellular, or cerebellar, respectively. As mentioned above, one of the limitations of research on dyslexia is that it has mostly investigated one theory in a given sample of DPs. The findings reported in [25] reveal that if one investigates

individual DPs, comparing the predictions of all the main dyslexia theories, the neural correlates of reading for all DPs (except one DP) were in agreement with the hypotheses based on more than one theory. In the sample reported in [25], the neuroimaging results for one case (5.6%) were in agreement with the PDT, MDT and CDT and for another case with only the CDT. The results for six cases (33.3%) were in agreement with the PDT and CDT and the findings for 10 cases (55.6%) with the PDT, CDT and VDT. The results for all, but one DP, supported a multiple deficit model.

Supporters of the PDT may argue that the neural correlates of reading in all cases (except for DP13) are in agreement with the core deficit, as hypothesised by the PDT and that the hypoactivation in the cerebellum and/or magnocellular areas in these DPs just co-occurs with dyslexia. As highlighted above, contrary to previous studies, Reid's study [25] investigated the more direct link between reading deficit in DPs and the predictions of the main dyslexia theories on the neural level by using an fMRI reading task. Hence it seems reasonable to interpret the findings of hypoactivation in the areas hypothesised by the PDT and the CDT, in the same DP, as lending support to the claim that reading in a given DP is consistent with the predictions of both theories and therefore both phonological areas and cerebellar areas contribute to the reading impairment in a given DP and the CDT deficit is not just co-occurring with no causal effect on reading deficit (as argued by the protagonists of the PDT). The same reasoning also applies to DPs who exhibited underactivation in both phonological and visual/magnocellular areas.

Taking into consideration the additional predictions of the CDT (discussed above), it might be the case that the underactivation in phonological areas in all DPs (except DP13) is also consistent with the CDT (and with the PDT), but this holds only from the perspective of the CDT and not the perspective of the PDT. Finally, it is also possible that the underactivation in phonological areas in DP1 is also in line with the additional predictions of the MDT (discussed earlier); however, this is true only from the perspective of the MDT and not from the perspective of the PDT (see Section 3.1 for further discussion).

A single deficit model has been dominant for many years in the research on dyslexia and other neurodevelopmental disorders. Each dyslexia theory postulates a different and single underlying cause of dyslexia. However, a single deficit model, although parsimonious and straightforward to test, has limitations. For instance, it cannot explain cases which exhibit a single deficit but do not have a reading disorder. Such cases have been reported in longitudinal studies involving children 'at risk' of dyslexia [99]. Reid et al. [32] also reported cases of adult CPs, who, although exhibiting a phonological deficit, did not have a reading impairment. Furthermore, the single deficit model cannot account for the more frequent than chance co-occurrence of other neurodevelopmental disorders with dyslexia (see below for a further discussion). Therefore, Pennington [100] formulated a multiple deficit model (MMD). The MMD recognises the fact that there are multitudes of environmental and genetic risk factors and that they do not operate independently. It is possible that they are correlated with each other or that they share effects of gene-by-environment interaction, or genes may interact with each other as they are part of the genetic system. The model does not specify the causal connections between the levels of analyses, including feedback loops from the behavioural level to the neural system level (or even to the aetiology level). The strength and existence of causal connections need to be resolved empirically [100]. Multidisciplinary research on the underlying causes of reading disorder in dyslexia within the MDM holds significant promise.

3. Future directions

3.1 Neuroimaging studies testing a further refined set of brain areas (including areas hypothesised by other dyslexia theories) in longitudinal designs

Research on the brain areas involved in language processing and reading, including those areas hypothesised by the main theories of dyslexia, is active. For instance, there is now growing evidence of the involvement of subcortical brain areas in reading and language skills [101, 102]. Also new research has been reported for the MDT. For instance, a high-resolution proton density-weighted MRI study [103] revealed that L LGN (but not R LGN) was significantly smaller in volume and differed in shape in vivo in DPs (vs. CPs). These results are consistent with the MDT, and future neuroimaging research testing the MDT needs to include LGN as an ROI in a neuroimaging study on reading deficit in DPs. Furthermore, there are other theories of dyslexia, for instance, the auditory MDT [48] and the low-frequency phase-locking mechanism deficit theory [104]. Further research on the underlying reading deficits in dyslexia, using a refined set of brain areas (including also areas hypothesised by the other theories of dyslexia), is warranted, and it is argued below that longitudinal designs are indispensable here.

The study presented in [25] investigated reading in adult DPs in an fMRI task. Although such studies are valuable as they provide insight into the neural correlates of reading in a mature system, it is possible that the adult neural system may have been significantly or partially altered due to compensatory mechanisms. Given that reading is a learned skill that is acquired through instruction and practice over a relatively long period of time, it is likely that brain-based findings are going to be dynamic, and therefore longitudinal neuroimaging studies, starting with newborns with familial risk of dyslexia, are indispensable in tracking the developmental trajectory of reading deficits in dyslexia. Longitudinal studies may also be successful in testing the additional predictions of the CDT and MDT which could not be resolved in Reid's study [25].

3.2 Controlling the effects of co-occurring neurodevelopmental disorders

The current research indicates that co-occurrence of neurodevelopmental disorders is most likely more common than cases of 'pure' disorders [36]. A detailed history was taken in Reid's study [25] from participants regarding different disorders, and measures were collected for ADHD and DCD and entered into the fMRI analyses as covariates. This procedure ensured that the results were not confounded by these variables. Furthermore, the supplementary fMRI analyses showed that two DPs (11%) who were identified as possibly being at risk of clinical DCD exhibited underactivation in the areas consistent with DCD, but the underactivated areas for DP8 and DP15 differed (see [25] for details). These findings underscore the co-occurrence of these neurodevelopmental disorders and heterogeneity among participants who are at risk of clinical DCD.

There is growing evidence that dyslexia may co-occur with other disorders, such as specific language impairment (SLI), speech sound disorder (SSD), autism spectrum disorder (ASD), dyscalculia, conduct disorder, oppositional defiant disorder, anxiety, depression and disruptive, impulse-control and conduct disorders (CDs). Currently the relationship between these disorders and dyslexia is unclear [105]. It should be emphasised here that, although some efforts, especially more recently, are made to control the effects of some co-occurring disorders, the effects of some other co-occurring disorders are not controlled for in dyslexia studies. Therefore there is an urgent need for future research on the underlying causes of reading

deficit in dyslexia to control for the effects of the co-occurring disorders either by the exclusion of cases with such disorders or by collecting appropriate data (including genetic data, where available) to be used as covariates in the analyses.

The issue of co-occurring disorders is complex and can be further underscored by an observation that a person with a given neurodevelopmental disorder (e.g. dyslexia) may have first-degree relatives diagnosed with different neurodevelopmental disorders, for example, one with ADHD and another with DCD (Deborah Dewey, personal communication, July 2, 2015). It is currently unclear why this is the case, but it may suggest that genes that affect one neurodevelopmental disorder are also likely to affect other neurodevelopmental disorders [106]. The field of molecular genetics of co-occurring neurodevelopmental disorders is young. However, some findings have already suggested that common single-nucleotide polymorphisms on a number of chromosomes increase susceptibility to both dyslexia and SLI [107]. Research investigating generalist gene hypothesis [106], de novo gene mutations [107] and pleiotropic effects [108], using state-of-the-art molecular technologies, such as high-throughput genotyping and next-generation sequencing of whole genomes, holds the promise of providing important answers here. In summary, molecular genetics of co-occurring neurodevelopmental disorders makes progress in identifying genetic components which increase the susceptibility to more than one neurodevelopmental disorder. The more is known here, the easier it would be to also control the genetic component in experimental work. It must be emphasised that co-occurrence of neurodevelopmental disorders cannot be ignored in the future research on dyslexia because it is a potentially serious confound which is likely to distort results. See, for instance [109, 110], for findings which show that ADHD symptoms mediate deficits in developmental dyslexia.

3.3 Using a variety of imaging tools in dyslexia research

A promising way forward in dyslexia research would be to test individual DPs (or samples of DPs as homogenous, as possible, with respect to behavioural and genetic profiles) using various neuroimaging techniques, in addition to fMRI, which would allow for a fuller characterisation of DPs' neural profiles, including the neural correlates of reading deficit. Some attempts have already been made; for instance, a recent study [111] used structural MRI, diffusion MRI and probabilistic tractography to investigate the structural connections of the visual sensory pathway in dyslexia in vivo. The results revealed altered structural connectivity in DPs in the direct pathway between the L LGN and L V5/MT but not between the L LGN and L V1. Another study [112] combined fMRI with multi-voxel pattern analysis and functional and structural connectivity analysis of DTI data in adult DPs. The results revealed that phonetic representations in the L and R auditory cortex were intact, whereas anatomical and functional connections found between these areas and the L inferior frontal gyrus were disrupted, suggesting an access deficit.

Another fruitful way forward would be to ask novel questions using neuroimaging. Pugh et al. magnetic resonance spectroscopy (MRS) study [113] was the first to test the role of multiple metabolites in developing readers. The authors reported an inverse relationship between both glutamate and choline and reading ability, such that higher concentrations of these metabolites were associated with lower reading scores. Given that heightened levels of glutamate can reflect hyperexcitability [114], whereas heightened levels of choline are associated with abnormal white matter organisation [115], the results reported in [113] suggest potential links between abnormal white matter organisation and reading deficit and hyperexcitability and reading deficit in atypical brain development and reading acquisition. The findings reported in [113] are cited (among others) in support of a recently formulated neural noise hypothesis (NNH) of dyslexia (see [116] for details).

Finally, recent MRI advances, such as multiband fMRI [117] and high-field MRI [118], promise to increase the spatial and/or temporal resolution of MRI and fMRI. Also, recent developments of more sophisticated diffusion MRI techniques, such as neurite orientation dispersion and density imaging (NODDI), hold promise of new insights into white matter structure and organisation in DPs (see Section 3.4 for further discussion of this). Furthermore, new developments in MEG also look promising. For instance, advanced preprocessing techniques which enable decomposition of the signal into components with origin inside and outside the head increase the signal-to-noise ratio by approximately 100%, enabling therefore even one-trial measurements with the standard MEG systems (e.g. whole head 306 Elekta or 275 CTF channel systems). Furthermore, optically pumped magnetometers (which allow MEG sensors to get closer to the head) should considerably increase the signal-to-noise ratio of MEG [119]. As the defining characteristic of dyslexia is impaired reading—a skill characterised by extremely rapid and interlocked processing events—it is likely that MEG (with its relatively high temporal resolution) would play a particularly important role in providing valuable insights into the underlying causes of reading deficit in this neurodevelopmental disorder. In summary, the advances discussed above offer new possibilities in dyslexia research, so that dyslexia endophenotypes can be investigated with higher spatial and temporal resolution, increasing the chance of elucidating the underlying causes of reading disorder in dyslexia, as well as reliable biomarkers for dyslexia.

3.4 Imaging genetics

The neuroimaging data undoubtedly provide a description of endophenotypes in dyslexia, but they do not offer an explanation of what causes such endophenotypes. As discussed above, Reid's study [25] contrasted, on the neural level, the explanatory frameworks of the main dyslexia theories, but an explanation at the genetic level was not investigated (as genetic data were not available for the studied DPs). Given findings on dyslexia within the fields of molecular genetics and imaging genetics, it is likely that the heterogeneity among DP's phenotypes and endophenotypes reported in [25] is due in part to dyslexia risk genes.

Imaging genetics offers a bridge between behavioural measures and the brain. Relatively direct connections have been made between (1) brain function and dyslexia risk genes and (2) brain anatomy and dyslexia risk genes [120]. As a full summary of studies on imaging genetics in DPs (and in CPs) is beyond the scope of this chapter, interested readers are referred to the relevant reviews [102, 121]. Findings on brain function and genes associated with dyslexia are briefly summarised first. Cope et al.'s study [122] reported the strongest association between an fMRI activation for a reading task in the L anterior inferior parietal lobe and tandem repeat BV677278 in *DCDC2*. Another fMRI study [123], involving CPs and a reading task, reported that (1) single-nucleotide polymorphisms (SNPs) rs6980093 and rs7799109 (in *FOXP2*) were associated with variations of activation in the L frontal cortex and (2) SNP rs17243157 in the *KIAA0319/TTRAP/THEM2* locus was associated with asymmetry in the functional activation of the superior temporal sulcus. Wilcke et al.'s fMRI study [124] revealed a significant main effect for 'genetic risk' of *FOXP2* variant (rs12533005-G) in a temporoparietal area (significantly lower activation in the 'at risk of dyslexia' group than in the 'non-at-risk' group in the angular and supramarginal gyri). A MEG study [125] reported that DPs with a weakly expressing haplotype of *ROBO1* exhibited defective interaural interaction and the extent of the deficit correlated with the *ROBO1* expression level. Finally, another MEG study [126] reported that about half of DPs exhibited significantly higher levels of variability in their cortical responses to auditory and visual stimuli

in several brain areas of the reading network. A positive and significant relationship between the degree of neural variability in the primary auditory cortex across both DPs and CPs and the number of risk alleles at rs6935076 in *KIAA0319* was found, supporting the link between *KIAA0319* and neural variability.

Moving to studies which focused on brain structure and dyslexia risk genes, four publications need to be mentioned. A voxel-based morphometry (VBM) study [127] showed that participants with high genetic risk variants in *TNFRSF1B* exhibited significantly lower grey matter (GM) probability in Heschl's gyrus/posterior superior temporal sulcus (HG/pSTS) but significantly higher GM probability in pSTS and the converse was true for participants with low genetic risk variants in *TNFRSF1B*. A structural MRI study [128] reported that *DYX1C1*, *DCDC2* and *KIAA0319* contained SNPs that significantly correlated with white matter volume in the L temporoparietal area and that white matter volume influenced reading ability in a general population sample. Finally, two studies need to be briefly discussed here—both using DTI. It should be noted that DTI (and a more sophisticated diffusion MRI techniques, such as NODDI, mentioned above, which provides more specific markers of brain tissue microstructure than standard indices from DTI) could become particularly important neuroimaging techniques in dyslexia research when combined with genetic measures because there is evidence that suggests that some dyslexia risk candidate genes (e.g. *DCDC2, KIAA0319, DYX1C1, FOXP2* and *CNTNAP2*) are involved in neuronal migration (a period in brain development during which young neurons 'look' for their final destination in the brain; this process requires stringent controls that are genetically governed) and/or neurite outgrowth [102]. Such genes (together with the environment and gene-by-environment interaction) may contribute to shaping the brain's white matter structure which can be inferred from the results obtained from MRI diffusion techniques. One of the first studies [129], which combined genetic, DTI (and behavioural) measures, reported that *MRPL19/C2ORF3* was associated with general cognitive ability in DPs and participants with SLI. Also associations between white matter structure measured using DTI and genotypes at the *MRPL19/C2ORF3* (in an independent sample) were found in the posterior corpus callosum and cingulum connecting the temporal, parietal and occipital areas. More recently, a voxel-based DTI study [130] revealed that DPs with a deletion in *DCDC2*/intron 2 compared to CPs exhibited significantly lower fractional anisotropy (FA) in a number of L hemisphere areas (including superior longitudinal fasciculus, arcuate fasciculus, inferior longitudinal fasciculus, optic radiation, corpus callosum, inferior cerebellar pedunculus and two R hemisphere areas (superior longitudinal fasciculus and corpus callosum)), indicating anatomical abnormalities of these white matter structures.

Although imaging genetics is a relatively young field and most findings need to be replicated, endophenotypes uncovered by imaging genetics hold promise for building a link between the behavioural and genetic characteristics of DPs [131]. Currently, however, the imaging genetics results are insufficient to obtain a full picture of the underlying causes of reading deficit in dyslexia. Advancement of imaging genetics in dyslexia needs to proceed in three major ways. First, new hypothesis-driven imaging genetic studies must be designed to investigate the function of neuronal migration (and other) genes and their relationships with well-characterised cognitive and sensory vulnerability and to find connections between such susceptibility variants and neuroanatomical endophenotypes [102]. The integration of specific behavioural, imaging and genetic data may result in the identification of brain areas with gene and behavioural specific effects or with widespread effects [102]. Second, although valuable results have emerged from known dyslexia risk genes, they cannot test other genetic impacts on the overall reading deficits in dyslexia. Therefore, sequencing studies and genome-wide association studies (GWAS) are needed, so that new genes associated with risk of dyslexia can

be discovered and their role tested in the neuroimaging studies, providing a fuller picture of phenotypes and endophenotypes in dyslexia [121]. Such attempts have already started; for instance, a GWAS [132] reported that mismatch negativity (MMN) (which reflects automatic speech deviance processing and is abnormal in DPs) was significantly associated with an intergenic SNP on chromosome 4q32.1. This SNP is hypothesised to have a potential effect on the expression of *SLC2A3*—a gene that encodes a neuronal glucose transporter. The results suggest a possible trans-regulation effect on *SLC2A3*, which might cause glucose deficits in DPs and this in turn may account for DPs' attenuated MMN response. Third, as behavioural deficits overlap across neurodevelopmental disorders, it is of importance to include in the imaging genetics genes associated with different co-occurring disorders, including dyslexia. Such attempts have already been reported in dyslexia with respect to, for instance, *FOXP2* [124]—a gene originally associated with developmental verbal dyspraxia and included in imaging genetics in this disorder [133].

3.5 Neuroimaging intergenerational transmission of brain circuity

Intergenerational transmission is defined as 'the transfer of traits from parents to offspring, including genetic and non-genetic influences. For example, the impact of prenatal effects (e.g. parent nutrition and in utero environment) as well as postnatal rearing effects and other environmental factors could lead to epigenetic or behavioural changes in the offspring, which are thereby intergenerationally transmitted' [134, p. 644]. Intergenerational neuroimaging is a new approach which uses neuroimaging to investigate the relationship of cognitive and neural phenotypes between children and their parents. It holds the promise of shedding light on the ontogeny of complex neurodevelopmental disorders, including dyslexia. One of the major goals of neuroimaging intergenerational transmission of brain circuity in such disorders is to dissociate the different sources of intergenerational effects on the brain circuity on dyslexia by contrasting parent–child pairs from natural conception, adoptive families and in vitro fertilisation (IVF). Such designs have a potential in addressing many important questions in dyslexia research, including (1) intergenerational effects on the brain structure and function (including those supporting reading ability) and (2) the impact of gender-specific effects at the prenatal stage (especially important as dyslexia is more prevalent in males [29]), including the effects of prenatal testosterone levels on brain development, epigenetic effects of estrogen on dyslexia risk genes and gender-specific transmission patterns in reading-related brain circuits in individuals who haven't yet learnt to read [135].

4. Conclusion

The results from the first neuroimaging study to use a multiple case approach to investigate individual differences among DPs [25], reviewed here, revealed that DPs are characterised by marked heterogeneity and complexity in the neural correlates of their reading deficit; even if the reading deficit of two DPs was consistent with the same theory, their affected brain areas could differ. The results further show that the neural correlates of reading deficit for all (except one) DPs were consistent with more than one theory, supporting a multiple deficit model. It is suggested that future research on causes of reading deficit in dyslexia, to make significant progress, would need to (1) focus on the multiple deficit model [100], (2) use neuroimaging to test a further refined set of brain areas (including areas hypothesised by other dyslexia theories) in longitudinal designs, (3) control the effects of co-occurring neurodevelopmental disorders, (4) use different imaging tools

(high-field MRI (including diffusion techniques), multiband fMRI and MEG with optically pumped magnetometers), (5) progress imaging genetics and (6) pursue the neuroimaging intergenerational transmission of brain circuity.

Acknowledgements

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The Lord Dowding Fund financed the MRI scanning for Reid's study [25]. Thanks are due to the participants and to Joel Talcott, Liz Wilkinson, Simon Eickhoff, the Aston Neuroimaging Group and the FIL Methods Group for help and advice with various aspects of the study [25].

Conflict of interest

The author declares no conflict of interest.

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References

[1] Mazziotta JC. Time and space. In: Toga AW, Mazziotta JC, editors. Brain Mapping: The Methods. San Diego, USA: Academic Press; 2002. pp. 33-46

[2] Kamali A et al. Diffusion tensor tractography of the mammillothalamic tract in the human brain using a high spatial resolution DTI technique. Scientific Reports. 2018;**8**(1):5229

[3] Steven AJ, Zhuo J, Melhem ER. Diffusion kurtosis imaging: An emerging technique for evaluating the microstructural environment of the brain. American Journal of Roentgenology. 2014;**202**(1):W26-W33

[4] Zhang H et al. NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage. 2012;**61**(4):1000-1016

[5] Jensen JH et al. Magnetic field correlation imaging. Magnetic Resonance in Medicine. 2006;**55**(6):1350-1361

[6] Hanson SJ, Bunzl M, editors. Foundational Issues in Human Brain Mapping. Kindle Edition. Cambridge, MA: MIT Press; 2010

[7] Jones DK, editor. Diffusion MRI. Theory, Methods and Applications. Oxford: Oxford University Press; 2011

[8] Poldrack RA, Mumford JA, Nichols TE. Handbook of Functional MRI Data Analysis. Cambridge: Cambridge University Press; 2011

[9] Toga AW, Mazziotta JC, editors. Brain Mapping: The Methods. 2nd ed. San Diego, USA: Academic Press; 2002

[10] Frisoni GB et al. Preliminary evidence of validity of the revised criteria for Alzheimer disease diagnosis: Report of 2 cases. Alzheimer Disease and Associated Disorders. 2010;**24**(1):108-114

[11] Wagner AD. Early detection of Alzheimer's disease: An fMRI marker for people at risk? Nature Neuroscience. 2000;**3**(10):973-974

[12] Nobili F et al. Unawareness of memory deficit in amnestic MCI: FDG-PET findings. Journal of Alzheimer's Disease. 2010;**22**(3): 993-1003

[13] Josef Golubic S et al. MEG biomarker of Alzheimer's disease: Absence of a prefrontal generator during auditory sensory gating. Human Brain Mapping. 2017;**38**(10):5180-5194

[14] Bose SK et al. Classification of schizophrenic patients and healthy controls using [18F] fluorodopa PET imaging. Schizophrenia Research. 2008;**106**(2-3):148-155

[15] Taylor JA et al. Auditory prediction errors as individual biomarkers of schizophrenia. Neuroimage: Clinical. 2017;**15**:264-273

[16] Bowyer SM et al. Potential biomarkers of schizophrenia from MEG resting-state functional connectivity networks: Preliminary data. Journal of Behavioral and Brain Science. 2015;**5**(01):1-11

[17] Serrallach B et al. Neural biomarkers for dyslexia, ADHD, and ADD in the auditory cortex of children. Frontiers in Neuroscience. 2016;**10**:324

[18] Adisetiyo V et al. Attention-deficit/hyperactivity disorder without comorbidity is associated with distinct atypical patterns of cerebral microstructural development. Human Brain Mapping. 2014;**35**(5):2148-2162

[19] Adisetiyo V et al. Multimodal MR imaging of brain iron in attention deficit hyperactivity disorder: A noninvasive biomarker that responds to psychostimulant treatment? Radiology. 2014;**272**(2):524-532

[20] Pernet CR et al. Brain classification reveals the right cerebellum as the best biomarker of dyslexia. BMC Neuroscience. 2009;**10**:67

[21] Guttorm TK et al. Newborn event-related potentials predict poorer pre-reading skills in children at risk for dyslexia. Journal of Learning Disabilities. 2010;**43**(5):391-401

[22] Maurer U et al. Impaired tuning of a fast occipito-temporal response for print in dyslexic children learning to read. Brain. 2007;**130**(Pt 12):3200-3210

[23] Salmelin R, Helenius P, Service E. Neurophysiology of fluent and impaired reading: A magnetoencephalographic approach. Journal of Clinical Neurophysiology. 2000;**17**(2):163-174

[24] Perrachione TK et al. Dysfunction of rapid neural adaptation in dyslexia. Neuron. 2016;**92**(6):1383-1397

[25] Reid AA. An fMRI multiple case study of the neural correlates of reading deficit in individuals with developmental dyslexia: Theoretical implications. In: Asher-Hansley V, editor. Advances in Neuroimaging Research. New York: Nova Science Publishers; 2014. pp. 1-119

[26] Morgan P. A case study of congenital word blindness. British Medical Journal. 1896;**7**:1378-1379

[27] Shaywitz SE. Current concepts: Dyslexia. The New England Journal of Medicine. 1998;**338**:307-312

[28] World Health Organization. The International Classification of Diseases. Classification of Mental and Behavioural Disorders. Vol. 10. Geneva: World Health Organization Publications; 1993

[29] Rutter M et al. Sex differences in developmental reading disability: New findings from 4 epidemiological studies. Journal of the American Medical Association. 2004;**291**(16):2007-2012

[30] Goulandris N, editor. Dyslexia in Different Languages. Cross-Linguistic Comparisons. London: Whurr; 2003

[31] Reid AA. Developmental dyslexia: Evidence from Polish. In: Joshi RM, Aaron PG, editors. Handbook of Orthography and Literacy. Mahwah: LEA; 2006. pp. 249-274

[32] Reid AA et al. Cognitive profiles of adult developmental dyslexics: Theoretical implications. Dyslexia. 2007;**13**:1-24

[33] Poelmans G et al. A theoretical molecular network for dyslexia: Integrating available genetic findings. Molecular Psychiatry. 2011;**16**(4):365-382

[34] Nicolson R. Positive Dyslexia. Sheffield, UK: Rodin Books; 2015

[35] Germano E, Gagliano A, Curatolo P. Comorbidity of ADHD and dyslexia. Developmental Neuropsychology. 2010;**35**(5):475-493

[36] Kaplan BJ et al. DCD may not be a discrete disorder. Human Movement Science. 1998;**17**:471-490

[37] Fawcett AJ, Nicholson RI. Persistent deficits in motor skill of children with dyslexia. Journal of Motor Behaviour. 1995;**27**:235-240

[38] Iversen S et al. Motor coordination difficulties in a municipality group and in a clinical sample of poor readers. Dyslexia. 2005;**11**(3):217-231

[39] Frith U. Paradoxes in the definition of dyslexia. Dyslexia. An International Journal of Research and Practice. 1999;**5**(4):192-214

[40] Ramus F et al. Theories of developmental dyslexia: Insights from a multiple case study of dyslexic adults. Brain. 2003;**126**(Pt 4):841-865

[41] Snowling MJ, Caravolas M. Developmental dyslexia. In: Gaskell MG, editor. The Oxford Handbook of Psycholinguistics. Oxford: Oxford University Press; 2007. pp. 667-683

[42] Ramus F, Szenkovits G. What phonological deficit? The Quarterly Journal of Experimental Psychology. 2008;**61**:129-141

[43] Olson R et al. Specific deficits in component reading and language skills: Genetic and environmental influences. Journal of Learning Disabilities. 1989;**22**:339-349

[44] Paulesu E et al. A cultural effect on brain function. Nature Neuroscience. 2000;**3**(1):91-96

[45] Wang S, Gathercole SE. Working memory deficits in children with reading difficulties: Memory span and dual task coordination. Journal of Experimental Child Psychology. 2013;**115**(1):188-197

[46] Frith U. Brain, mind and behaviour in dyslexia. In: Hulme C, Snowling M, editors. Dyslexia: Biology, Cognition and Intervention. London: Whurr Pulbishers Ltd; 1997. pp. 1-19

[47] Hulme C, Snowling MJ. Developmental Disorders of Language, Learning and Cognition. Chichester, UK: Wiley-Blackwell; 2009

[48] Stein J. The magnocellular theory of developmental dyslexia. Dyslexia. 2001;**7**(1):12-36

[49] Stein J. Visual motion sensitivity and reading. Neuropsychologia. 2003;**41**:1785-1793

[50] Stein J, Walsh V. To see but not to read: The magnocellular theory of dyslexia. Trends in Neurosciences. 1997;**20**(4):147-152

[51] Lovegrove WJ et al. Contrast sensitivity functions and specific reading disability. Neuropsychologia. 1982;**20**:309-315

[52] Hansen PC et al. Are dyslexics' visual deficits limited to measures of dorsal stream function? Neuroreport. 2001;**12**(7):1527-1530

[53] Cicchini GM et al. Strong motion deficits in dyslexia associated with DCDC2 gene alteration. The Journal of Neuroscience. 2015;**35**(21):8059-8064

[54] Gori S et al. The DCDC2 intron 2 deletion impairs illusory motion perception unveiling the selective role of magnocellular-dorsal stream in reading (dis)ability. Cerebral Cortex. 2015;**25**(6):1685-1695

[55] Liederman J et al. The role of motion direction selective extrastriate regions in reading: A transcranial magnetic stimulation study. Brain and Language. 2003;**85**(1):140-155

[56] Stein J. The current status of the magnocellular theory of developmental dyslexia. Neuropsychologia. 2018

[57] Fawcett AJ, Nicolson RI. Performance of dyslexic children on cerebellar and cognitive tests. Journal of Motor Behavior. 1999;**31**(1):68-78

[58] Nicolson RI et al. Eyeblink conditioning indicates cerebellar abnormality in dyslexia. Experimental Brain Research. 2002;**143**(1):42-50

[59] Nicolson RI, Fawcett AJ, Dean P. Time estimation deficits in developmental dyslexia: Evidence of cerebellar involvement. Proceedings of the Biological Sciences. 1995;**259**(1354):43-47

[60] Nicolson RI, Fawcett AJ, Dean P. Developmental dyslexia: The cerebellar deficit hypothesis. Trends in Neurosciences. 2001;**24**(9):508-511

[61] Nicolson RI et al. Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. Lancet. 1999;**353**(9165):1662-1667

[62] Eden GF et al. Abnormal processing of visual motion in dyslexia revealed by functional brain imaging. Nature. 1996;**382**(6586):66-69

[63] Frith C, Frith U. A biological marker for dyslexia. Nature. 1996;**382**:19-20

[64] Heim S et al. Cognitive subtypes of dyslexia. Acta Neurobiologiae Experimentalis (Wars). 2008;**68**(1):73-82

[65] Menghini D et al. Different underlying neurocognitive deficits in developmental dyslexia: A comparative study. Neuropsychologia. 2010;**48**(4):863-872

[66] Snowling MJ. Specific disorders and broader phenotypes: The case of dyslexia. The Quarterly Journal of Experimental Psychology. 2008;**61**(1):142-156

[67] Zoubrinetzky R, Bielle F, Valdois S. New insights on developmental dyslexia subtypes: Heterogeneity of mixed reading profiles. PLoS One. 2014;**9**(6):e99337

[68] Reid AA. Cognitive profiles of individuals with dyslexia: Insights from a large sample study. Paper presented at the 57th Annual Conference of the IDA. Indianapolis, USA; 2006

[69] Cohen L, Dehaene S. Specialization within the ventral stream: The case for the visual word form area. NeuroImage. 2004;**22**(1):466-476

[70] Price CJ, Devlin JT. The myth of the visual word form area. NeuroImage. 2003;**19**(3):473-481

[71] Vanni S et al. Visual motion activates V5 in dyslexics. Neuroreport. 1997;**8**(8):1939-1942

[72] Watson JDG et al. Area V5 of the human brain: Evidence from a combined study using positron emission tomography and magnetic resonance imaging. Cerebral Cortex. 1993;**3**:79-94

[73] Demb JB, Boynton GM, Heeger DJ. Functional magnetic resonance imaging of early visual pathways in dyslexia. The Journal of Neuroscience. 1998;**18**(17):6939-6951

[74] Amunts K et al. Brodmann's areas 17 and 18 brought into stereotaxic space-where and how variable? NeuroImage. 2000;**11**(1):66-84

[75] Malikovic A et al. Cytoarchitectonic analysis of the human extrastriate cortex in the region of V5/MT+: A probabilistic, stereotaxic map of area hOc5. Cerebral Cortex. 2007;**17**(3):562-574

[76] Stoodley CJ, Schmahmann JD. Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. NeuroImage. 2009;**44**:489-501

[77] Finch AJ, Nicolson RI, Fawcett AJ. Evidence for a neuroanatomical difference within the olivo-cerebellar pathway of adults with dyslexia. Cortex. 2002;**38**(4):529-539

[78] Fulbright RK et al. The cerebellum's role in reading: A functional MR imaging study. American Journal of Neuroradiology. 1999;**20**(10):1925-1930

[79] Conners CK, Erhardt D, Sparrow EP. Conners' Adult ADHD Rating Scales (CAARS). New York: MHS; 1999

[80] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Washington, DC: American Psychiatric Association; 1994

[81] Coltheart M. The MRC psycholinguistic database. Quarterly Journal of Experimental Psychology. 1981;**33A**:497-505

[82] Donaldson DI, Buckner RL. Effective paradigm design. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI. An Introduction to Methods. Oxford, UK: Oxford University Press; 2001. pp. 177-195

[83] Friston KJ, Statistics I. Experimental design and statistical parametric mapping. In: Toga AW, Mazziotta JC, editors. Brain Mapping: The Methods. San Diego, USA: Academic Press; 2002. pp. 605-631

[84] Glaser DE. Experimental Design. Talk Given at the Statistical Parametric Mapping Course. London: Wellcome Department of Imaging Neuroscience; 2006

[85] Amunts K et al. Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space–the roles of Brodmann areas 44 and 45. NeuroImage. 2004;**22**(1):42-56

[86] Eickhoff SB et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage. 2005;**25**(4):1325-1335

[87] Brett M, et al. Region of interest analysis using an SPM toolbox. In: Proceedings of the 8th International Conference on Functional Mapping of the Human Brain; 2002. Available on CD-ROM in NeuroImage; Vol 16 No 2: Sendai, Japan

[88] Heim S et al. Interaction of phonological awareness and 'magnocellular' processing during normal and dyslexic reading: Behavioural and fMRI investigations. Dyslexia. 2010;**16**(3):258-282

[89] Shaywitz SE et al. Functional disruption in the organization of the brain for reading in dyslexia. Proceedings of the National Academy of Sciences of the United States of America. 1998;**95**(5):2636-2641

[90] Amunts K et al. Broca's region revisited: Cytoarchitecture and intersubject variability. The Journal of Comparative Neurology. 1999;**412**(2):319-341

[91] Kurth F et al. Cytoarchitecture and probabilistic maps of the human posterior insular cortex. Cerebral Cortex. 2009;**20**: 1448-61

[92] Geyer S. The Microstructural Border Between the Motor and the Cognitive Domain in the Human Cerebral Cortex. Wien: Springer; 2003

[93] Caspers S et al. The human inferior parietal lobule in stereotaxic space. Brain Structure and Function. 2008;**212**(6):481-495

[94] Caspers S et al. The human inferior parietal cortex: Cytoarchitectonic parcellation and interindividual variability. NeuroImage. 2006;**33**(2):430-448

[95] Morosan P et al. Multimodal architectonic mapping of human superior temporal gyrus. Anatomy and Embryology. 2005;**210**:401-406

[96] Tzourio-Mazoyer N et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage. 2002;**15**:273-289

[97] Diedrichsen J et al. A probabilistic MR atlas of the human cerebellum. NeuroImage. 2009;**46**(1):39-46

[98] Pugh KR. Neuroimaging studies of skilled reading and reading disability. Paper presented at the 57th Annual Conference of the IDA. Indianapolis, USA; 2006

[99] Pennington BF. Using genetics and neuropsychology to understand dyslexia and its comorbidities. Paper presented at the 8th BDA International Conference. Harrogate, UK; 2011

[100] Pennington BF. From single to multiple deficit models of developmental disorders. Cognition. 2006;**101**:385-413

[101] Krishnan S, Watkins KE, Bishop DV. Neurobiological basis of language learning difficulties. Trends in Cognitive Sciences. 2016;**20**(9):701-714

[102] Mascheretti S et al. Neurogenetics of developmental dyslexia: From genes to behavior through brain neuroimaging and cognitive and sensorial mechanisms. Translational Psychiatry. 2017;**7**(1):e987

[103] Giraldo-Chica M, Hegarty JP, Schneider KA. Morphological differences in the lateral geniculate nucleus associated with dyslexia. Neuroimage: Clinical. 2015;**7**:830-836

[104] Goswami U. A temporal sampling framework for developmental dyslexia. Trends in Cognitive Sciences. 2011;**15**(1):3-10

[105] Hendren RL et al. Recognizing psychiatric comorbidity with reading disorders. Frontiers in Psychiatry. 2018;**9**:101

[106] Plomin R, Kovas Y. Generalist genes and learning disabilities. Psychological Bulletin. 2005;**131**(4):592-617

[107] Deriziotis P, Fisher SE. Speech and language: Translating the genome. Trends in Genetics. 2017;**33**(9):642-656

[108] Mascheretti S et al. Complex effects of dyslexia risk factors account for ADHD traits: Evidence from two independent samples. Journal of Child Psychology and Psychiatry. 2017;**58**(1):75-82

[109] Gooch D, Snowling M, Hulme C. Time perception, phonological skills and executive function in children with dyslexia and/or ADHD symptoms. Journal of Child Psychology and Psychiatry. 2011;**52**(2):195-203

[110] Wimmer H, Mayringer H, Raberger T. Reading and dual-task balancing: Evidence against the automatization deficit explanation of developmental dyslexia. Journal of Learning Disabilities. 1999;**32**(5):473-478

[111] Muller-Axt C, Anwander A, von Kriegstein K. Altered structural connectivity of the left visual thalamus in developmental dyslexia. Current Biology. 2017;**27**(23):3692-3698 e4

[112] Boets B et al. Intact but less accessible phonetic representations in adults with dyslexia. Science. 2013;**342**(6163):1251-1254

[113] Pugh KR et al. Glutamate and choline levels predict individual differences in reading ability in emergent readers. The Journal of Neuroscience. 2014;**34**(11):4082-4089

[114] Carrey N et al. Glutamatergic changes with treatment in attention deficit hyperactivity disorder: A preliminary case series. Journal of Child and Adolescent Psychopharmacology. 2002;**12**(4):331-336

[115] Gass A, Richards TL. Serial proton magnetic resonance spectroscopy of normal-appearing gray and white matter in MS. Neurology. 2013;**80**(1):17-18

[116] Hancock R, Pugh KR, Hoeft F. Neural noise hypothesis of developmental dyslexia. Trends in Cognitive Sciences. 2017;**21**(6):434-448

[117] Todd N et al. Evaluation of 2D multiband EPI imaging for high-resolution, whole-brain, task-based fMRI studies at 3T: Sensitivity and slice leakage artifacts. NeuroImage. 2016;**124**(Pt A):32-42

[118] De Martino F et al. Frequency preference and attention effects across cortical depths in the human primary auditory cortex. Proceedings of the National Academy of Sciences

of the United States of America. 2015;**112**(52):16036-16041

[119] Boto E et al. A new generation of magnetoencephalography: Room temperature measurements using optically-pumped magnetometers. NeuroImage. 2017;**149**:404-414

[120] Reid AA. Developmental dyslexia–a critical review of imaging-genetics studies. Poster presented at the 22th Annual Meeting of the OHBM. Geneva, Switzerland; 2016

[121] Eicher JD, Gruen JR. Imaging-genetics in dyslexia: Connecting risk genetic variants to brain neuroimaging and ultimately to reading impairments. Molecular Genetics and Metabolism. 2013;**110**(3):201-212

[122] Cope N et al. Variants in the DYX2 locus are associated with altered brain activation in reading-related brain regions in subjects with reading disability. NeuroImage. 2012;**63**(1):148-156

[123] Pinel P et al. Genetic variants of FOXP2 and KIAA0319/TTRAP/THEM2 locus are associated with altered brain activation in distinct language-related regions. The Journal of Neuroscience. 2012;**32**(3):817-825

[124] Wilcke A et al. Imaging genetics of FOXP2 in dyslexia. European Journal of Human Genetics. 2012;**20**(2):224-229

[125] Lamminmaki S et al. Human ROBO1 regulates interaural interaction in auditory pathways. The Journal of Neuroscience. 2012;**32**(3):966-971

[126] Centanni TM et al. Increased variability of stimulus-driven cortical responses is associated with genetic variability in children with and without dyslexia. Developmental Cognitive Neuroscience. 2018;**34**:7-17

[127] Mannel C et al. Working-memory endophenotype and dyslexia-associated genetic variant predict dyslexia phenotype. Cortex. 2015;**71**:291-305

[128] Darki F et al. Three dyslexia susceptibility genes, DYX1C1, DCDC2, and KIAA0319, affect temporo-parietal white matter structure. Biological Psychiatry. 2012;**72**(8):671-676

[129] Scerri TS et al. The dyslexia candidate locus on 2p12 is associated with general cognitive ability and white matter structure. PLoS One. 2012;**7**(11):e50321

[130] Marino C et al. The DCDC2/intron 2 deletion and white matter disorganization: Focus on developmental dyslexia. Cortex. 2014;**57**:227-243

[131] Carrion-Castillo A, Franke B, Fisher SE. Molecular genetics of dyslexia: An overview. Dyslexia. 2013;**19**(4):214-240

[132] Roeske D et al. First genome-wide association scan on neurophysiological endophenotypes points to trans-regulation effects on SLC2A3 in dyslexic children. Molecular Psychiatry. 2011;**16**(1):97-107

[133] Liegeois F et al. Language fMRI abnormalities associated with FOXP2 gene mutation. Nature Neuroscience. 2003;**6**(11):1230-1237

[134] Ho TC et al. Intergenerational neuroimaging of human brain circuitry. Trends in Neurosciences. 2016;**39**(10):644-648

[135] Hoeft F, Hancock R. Intergenerational transmission of reading and reading brain networks. In: Galaburda A, editor. Dyslexia and Neuroscience. Brookes Publishing; Baltimore, USA. 2018