MAJOR REVIEW

ACTA NEUROPSYCHOLOGICA Vol. 10, No. 2, 2012, 163-191

Received: 10.01.2012
Accepted: 28.06.2012

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DYSLEXIA RESEARCH AT THE TURN OF THE 21ST CENTURY: BEHAVIOURAL, NEUROIMAGING AND GENETIC FINDINGS

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SUMMARY

Behavioural studies have shown that dyslexics are a heterogeneous population and between-group comparisons are thus inadequate. Some subjects do not develop dyslexia despite having a deficit implicated in this disorder, which points to protective factors. Dyslexia co-occurs with ADHD, DCD, SLI, and SSD, so that future behavioural studies will need to screen and/or statistically control for other disorders. Studies of multiple cases of DPs with other developmental disorders are necessary. Neuroimaging findings show structural and/or functional brain abnormalities in language areas, V5/MT and the cerebellum. Future neuroimaging studies need to investigate the whole reading network and multiple cases. Six dyslexia risk genes have been found, mostly involved in neural migration, which may suggest dyslexia is a deficit of neuronal migration. However, it is not clear how these genes can restrict migration to specific brain areas. As a complex and heterogeneous disorder, dyslexia is likely to be associated with several mutated genes. ADHD and SSD are characterised by genetic risk factors which are partially shared with dyslexia, resulting in comorbidity. Future genetic studies need to focus on identifying other risk genes and pleiotropic genes involved in comorbidities, and linking genotypes implicated in dyslexia with brain structure. Any theory of dyslexia needs to take into account a multitude of risk and protective factors across behavioural, neural and genetic domains.

Key words: developmental dyslexia, neuroimaging, dyslexia risk genes, comorbidity, theories of developmental dyslexia

INTRODUCTION

The last two decades have brought important advances in research on developmental dyslexia (henceforth dyslexia), which have deepened the understanding of this disorder. Firstly, three important behavioural findings have been noted:

- persons with dyslexia (DPs) are a very heterogeneous population;
- some control persons do not develop this disorder despite having a deficit which is recognised as an underlying deficit in dyslexia;
- dyslexia co-occurs with other developmental disorders.

Secondly, neuroimaging studies have shown that DPs exhibit both structural and functional brain abnormalities. Thirdly, two major genetic findings have been reported: specific genes have been found to be implicated in dyslexia, and some genetic findings suggest that the comorbidity of dyslexia with other developmental disorders originates from common genetic aetiological factors.

The main aim of the present study is to provide an overview of the research and issues involved in these major advances, not to present an exhaustive review. The structure of this article is as follows: First, the behavioural findings, which suggest that DPs are a heterogeneous population and show how their cognitive and psychophysical profiles can be accounted for by the competing theories of dyslexia, will be presented mainly through an in-depth discussion of one study. Next, a summary of studies according to which dyslexia co-occurs with other developmental disorders will be reviewed. Then, results on dyslexia using structural and functional neuroimaging techniques will be presented. The genetic findings on dyslexia are then discussed. Finally, the evidence which points to shared aetiology between dyslexia and other developmental disorders will be discussed. A summary and discussion on future directions will close the article.

INDIVIDUALS WITH DYSLEXIA EXHIBIT CONSIDERABLE HETEROGENEITY

There are several definitions of dyslexia, but because many issues regarding this disorder are unresolved, none of them seems satisfactory. A definition by the World Federation of Neurology (1968) is used here: dyslexia is a developmental disorder manifested by difficulty in learning to read despite conventional instruction, adequate intelligence and socio-cultural opportunity. The terms ‘reading disability’, ‘reading deficit’ and ‘reading disorder’ are used here as synonyms of ‘dyslexia’, and the terms: ‘reading impaired’ and ‘reading disabled’ as synonyms of ‘dyslexic’. The prevalence rates for dyslexia range from 5 to 17.5% (Shaywitz, 1998).

Although some past studies have emphasised that the dyslexic population is heterogeneous (Miles, 1993), most studies have focused on one underlying cause, within one theoretical domain, such as:

- the phonological deficit theory (PDT) (Lundberg & Hoien, 2001; Rack, Snowling & Olson, 1992; Snowling, 2000);

- the magnocellular deficit theory (MDT) (Hansen, Stein, Orde, Winter & Talcott, 2001; Stein, 2001; 2003; Stein & Talcott, 1999; Stein, Talcott & Witton, 2001; Stein & Walsh, 1997);
- the cerebellar deficit theory (CDT) (e.g., Fawcett & Nicolson, 1999; Nicolson & Fawcett, 1990; Nicolson & Fawcett, 2008; Nicolson et al., 1999; Nicolson, Fawcett & Dean, 1995; 2001). See Reid (2006b) for a review.

Furthermore, most studies on dyslexia have reported only group differences, so it is not possible to determine what proportion of DPs in a given study exhibited a certain deficit. As emphasised by Reid, Szczerbinski, Iskierka-Kasperek, and Hansen (2007) it is becoming clear that DPs are a heterogeneous population, exhibiting difficulties across a whole range of skills, so that selective focus on a single domain can lead to limited conclusions. At the beginning of the 21st century, however, some research (Ramus et al., 2003; Reid & Szczerbinski, 2002; Reid et al., 2007; White et al., 2006) focused on single and multiple case studies of dyslexia which contrasted with the predictions of the main theories of dyslexia. All of these studies uncovered considerable heterogeneity among DPs.

Reid et al. (2007) presented an unusual study, because it not only focused on group analyses (DPs and controls) and multiple case analyses, but also collected detailed profiles of DPs via interview. The sample was also screened for ADHD (Attention Deficit Hyperactivity Disorder). The between-groups comparison, in line with the findings of Ramus et al. (2003), showed no significant deficit on magnocellular and cerebellar tasks, with significant differences on most phonological tasks. These results provided support for the PDT, but not for the MDT and CDT. In contrast, detailed multiple case analyses, which tested deficits in every participant with dyslexia (DP), relative to controls, revealed that 13.3% of DPs exhibited a visual magnocellular deficit, 26.7% a cerebellar deficit, and 86.7% a phonological deficit. Clearly some participants had more than one deficit. The full appreciation of the heterogeneity of these DPs requires consideration of this overlap. One DP (6.6% of the DPs sample) exhibited phonological and visual magnocellular deficits and a further three (20%) phonological and cerebellar deficits. Nine DPs (60%) had only a phonological deficit, one DP (6.6%) a magnocellular deficit only, and one DP (6.6 %) a cerebellar deficit only.

Similar to the deviance analysis, the data collected in the interview revealed that DPs have heterogeneous and complex profiles of difficulties. Most DPs reported other difficulties, which poses questions of whether the widely used cognitive and psychophysical tests have enough sensitivity and whether they tap into all crucial factors which underlie literacy deficits. For instance, all participants except one reported at least one problem which may be due to cerebellar deficit. Fourteen DPs (including four cases who in the deviance analysis were classified as having only a phonological deficit) complained of visual problems which could be linked to a visual magnocellular deficit, such as unconsciously skipping lines during reading and/or inclination to swap the order of letters within words when reading. These and other findings from the interview further underscore the heterogeneity of the population with dyslexia.

None of the currently investigated theories of dyslexia (the PDT, visual MDT, and CDT) can account for all the cases studied by Reid et al. (2007). Therefore, Reid et al. (2007) put forward an explanation in terms of different sub-types of dyslexia, with different underlying causes, such as a phonological or visual magnocellular or cerebellar deficit (single underlying cause), or a combination of these (multiple underlying causes). The PDT, therefore, accounted for 13 cases (86.7%), the MDT for two cases (13.3%) and the CDT for four cases (26.7%). This included 20% of cases which were accounted for by both the PDT and the CDT and 6.6% of cases which were accounted for by the PDT and MDT. Therefore the multiple case analysis, in contrast to the between-groups analysis, revealed that the DP sample consisted of individuals who had visual magnocellular and cerebellar deficits. The percentages of cases accounted for by the visual MDT and CDT were very similar to those reported by Ramus et al. (2003). Conversely, the studies differ in the percentage of cases accounted for by the PDT, with 86.7% (Reid et al., 2007) versus 100% (Ramus et al., 2003). Note that, since all the DPs in the study by Ramus et al. (2003) exhibited a phonological deficit that was a significant predictor of literacy (while other deficits were not), the authors concluded that this deficit is the underlying cause of dyslexia and the other deficits simply co-occur with dyslexia, having no causal relationship with it. The explanation given by Reid et al. (2007) is similar to an earlier hypothesis (e.g., Doehring, Trites, Patel & Fiedorowicz, 1981), according to which a variety of factors may contribute to reading impairment, such as visual, linguistic, and other deficits. In contrast to the earlier hypothesis, however, Reid et al. (2007) postulate a range of deficits that are more precisely characterised, thanks to work on the underlying causes of dyslexia within the framework of the major theories of dyslexia.

Two criticisms which could be made regarding the account proposed by Reid et al. (2007) are that the magnocellular and cerebellar composite variables (the individual measurements were summarised in composite variables) were not significant predictors of literacy in Reid et al. (2007), therefore it may be argued that they cannot be the underlying cause of dyslexia in the cases studied. However, Reid et al. (2007) emphasise that their results are likely to be affected by the low statistical power of the small sample, and this is also true of the two other studies (Ramus et al., 2003; White et al., 2006). Moreover, not being able to detect a deficit in a behavioural experiment does not mean that such a deficit does not exist on the neurophysiological level. In addition, some data suggest that cerebellar and visual magnocellular deficits may indeed have an impact on literacy skills (Fulbright et al., 1999; Moretti, Bava, Antonello & Torre, 2002; Moretti, Torre, Antonelli, Cazzato & Bava, 2003; Talcott et al., 2002; Turkeltaub, Eden, Jones & Zeffiro, 2002). Second, magnocellular and cerebellar deficits also occur in other populations, such as children with autism, but without reading problems (Ramus et al., 2004) and the unimpaired population. It could be therefore argued that cerebellar and visual magnocellular deficits are neither necessary nor sufficient to cause literacy difficulties (Ramus et al., 2004). However, two DPs studied by Reid et al. (2007) - SER and DM, the former suffering only from a visual magnocellular deficit and the latter suffering only from

a cerebellar deficit - suggest that dyslexia may result from these deficits. This issue, nevertheless, needs to be further addressed with a much larger sample of DPs to maximise the number of DPs with phonological, magnocellular and cerebellar deficits, so that one can test whether these deficits can predict literacy. In fact work on this has already been initiated (Reid, 2006a).

Note also that the supplementary analysis of the data (Reid et al., 2007) revealed that although many more DPs than controls exhibited a phonological deficit, two controls had a phonological deficit (one control also exhibited a phonological deficit in Ramus et al., 2003). This raises the question of how a participant can exhibit a phonological deficit and not have literacy problems. One possible explanation is that if a person exhibits a given deficit, but protective factors operate in their ontogenetic development (Pennington, 2006; Snowling, 2001), literacy problems can be attenuated or prevented. The issue of protective and risk factors suggests that a new chapter in dyslexia research should be started, and the current parsimonious approach needs to be replaced with a different approach which recognises that the causal mechanism underlying dyslexia may be more complex than was expected. This is discussed further in the final section.

DYSLEXIA CO-OCCURS WITH OTHER DEVELOPMENTAL DISORDERS

There is now considerable evidence that dyslexia co-occurs, more frequently than would be expected by chance, with other disorders, such as ADHD, Developmental Coordination Disorder (DCD), SLI (Specific Language Impairment) and SSD (Speech Sound Disorder). Some of this evidence is presented below, together with brief definitions of these disorders.

ADHD is a neurobehavioural disorder manifested by a developmentally inappropriate and persistent pattern of inattention and/or hyperactivity and impulsivity with onset in childhood (American Psychiatric Association, 2000). It is associated with altered brain structure (Carmona et al., 2005; Ellison-Wright, Ellison-Wright & Bullmore, 2008; Filipek et al., 1997; Mostofsky, Reiss, Lockhart & Denckla, 1998) and function (Rubia et al., 1999; Rubia, Smith, Brammer, Toone & Taylor, 2005; Smith, Taylor, Brammer, Toone & Rubia, 2006; Tamm, Menon & Reiss, 2006; Valera, Faraone, Biederman, Poldrack & Seidman, 2005; Lipowska et al., 2008; Pachalska et al., 2007). Heritability estimates for ADHD range from 60-80% (Smalley, 1997). Approximately 25-40% of children with ADHD or dyslexia also have another developmental disorder (August & GarWnkel, 1990; Carroll, Maughan, Goodman & Meltzer, 2005; Dykman & Ackerman, 1991; Semrud-Clikeman et al., 1992; Willcutt & Pennington, 2000). Kaplan, Wilson, Dewey and Crawford (1998) found that 42% of their reading disabled children also met the criteria for ADHD.

DCD (also known as dyspraxia) is a marked impairment in the development of motor coordination. The features of this disorder vary with age. For instance, younger participants may exhibit clumsiness and delays in developmental motor milestones, such as crawling or sitting, whereas older participants may have

problems with playing ball, handwriting and building models. It has been estimated that approximately 6% of 5-11-year-old children have this disorder (American Psychiatric Association, 2000). A few published neuroimaging studies on DCD show that the deficit is associated with functional brain abnormalities (Kashiwagi, Iwaki, Narumi, Tamai & Suzuki, 2009; Querne et al., 2008). There is growing evidence that reading impaired individuals exhibit motor difficulties (Denckla, 1985; Fawcett & Nicholson, 1995; Haslum, 1989; Iversen, Berg, Ellertsen & Tonnessen, 2005; McPhillips & Sheehy, 2004; Miles, 1993; Wolff, Cohen & Drake, 1984). Kaplan et al. (1998) estimated the prevalence of dyslexia and DCD comorbidity to be 63% in their sample.

Individuals with SLI exhibit poor comprehension and/or expression of syntax and semantics. Neuroimaging studies demonstrated brain abnormalities, both functional (Dibbets, Bakker & Jolles, 2006; Hugdahl et al., 2004; Weismer, Plante, Jones & Tomblin, 2005) and anatomical (Gauger, Lombardino & Leonard, 1997; Leonard et al., 2002; Plante, Swisher, Vance & Rapcsak, 1991). There is growing evidence that persons with SLI are also poor at reading and phonological processing (Bishop & Snowling, 2004; Filipek, 1999; Joanisse & Seidenberg, 1998; Lane, Foundas & Leonard, 2001). It has been demonstrated that dyslexia is comorbid with SLI (Catts, Adlof, Hogan & Weismer, 2005; Riccio & Hynd, 1993) and approximately 30% of individuals with dyslexia have also SLI (Riccio & Hynd, 1993).

SSD (also known as articulation or phonological disorder) is characterised by difficulties with spoken language, especially in accurate production of speech sounds in spoken words. The only published structural neuroimaging study (Watkins et al., 2002) of the KE family, where approximately half the members had both SSD and a language impairment, revealed significant brain abnormalities. Extensive behavioural research has demonstrated that individuals who exhibited SSD in childhood are characterised by an increased risk of literacy difficulties (e.g., Aram, Ekelman & Nation, 1984; Bishop & Adams, 1990; Catts, Fey, Tomblin & Zhang, 2002; Hall & Tomblin, 1978; Scarborough & Dobrich, 1990; Snowling, Bishop & Stothard, 2000). These studies showed that approximately 30% of children with SSD develop literacy difficulties.

Although for many years some researchers reported that DPs exhibit a range of difficulties (e.g., Miles, 1993), hardly any studies screened or statistically controlled (by treating them as covariates in ANCOVA) for other developmental disorders. Furthermore, many studies on dyslexia did not report any information about possible comorbid disorders. This is an important issue to be born in mind when interpreting many earlier studies on dyslexia. Examples of results for DPs which have been affected by ADHD have been reported (e.g., Reid & Hansen, 2009; Rochelle, Witton & Talcott, 2009). Clearly, the issue of either screening or statistically controlling for other developmental disorders is of importance for designing new studies on the underlying causes of dyslexia, so that the results are not confounded. Moreover, multiple cases studies of DPs with other comorbid developmental disorders are necessary, so that the interactions between these disorders can be further characterised and understood.

NEUROIMAGING FINDINGS ON DYSLEXIA

Neuroimaging findings on dyslexia belong to two broad categories: structural and functional. Structural neuroimaging studies focus on structural brain abnormalities and use structural Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI). Structural MRI studies are able to investigate only gross anatomical features, because the resolution is insufficient to focus on histological abnormalities. Structural MRI data are often analysed using voxel-based morphometry (VBM), a technique which investigates group differences in grey matter, white matter, or cerebrospinal fluid (CSF) throughout the brain (Ashburner & Friston, 2000). DTI is a relatively new technique which allows one to trace fibre pathways in vivo by imaging the movement of molecules of water in a given direction in the brain (Mori, 2002). By contrast, functional neuroimaging studies are concerned with physiological changes in the brain activity elicited by experimental manipulation, such as reading single words. The studies reported below were run using one of three neuroimaging techniques: fMRI, PET, or MEG. fMRI – functional Magnetic Resonance Imaging is the most widely used technique, and is based on measuring changes in blood flow related to neural activity (Matthews, 2001). PET - Positron Emission Tomography - is an older technique, which utilises radioactively labelled probes that are specific to biochemical pathways in the brain to test regional brain function (Cherry & Phelps, 2002). MEG (Magnetoencephalography) directly measures the electrical currents in neurones with sub-millisecond temporal accuracy (Hämäläinen & Hari, 2002), but has worse spatial resolution than both PET and fMRI.

Many structural MRI studies have reported structural brain differences between DPs and controls across many brain areas. For, instance, focusing on the inferior frontal gyrus, DPs had a significantly larger right than left inferior frontal gyrus (Robichon, Levrier, Farnarier & Habib, 2000) and DPs' left inferior frontal gyrus showed decreased grey matter density (Brown et al., 2001). Silani et al. (2005) reported altered cell density in DPs in the left arcuate fasciculus.

Moving on to the temporal gyrus, decreased grey matter density in DPs, as compared to controls, was reported in:

- the left inferior temporal gyrus (Brown et al., 2001; Vinckenbosch, Robichon & Eliez, 2005);
- the left superior temporal gyrus (Brown et al., 2001);
- the left middle temporal gyrus (Brown et al., 2001; Silani et al., 2005; Vinckenbosch et al., 2005).

Silani et al.'s study also showed an increase of grey matter density in DPs in the left middle temporal gyrus area (BA 37) posterior to that showing reduced grey matter. Furthermore, some studies (Leonard et al., 2001; Leonard et al., 1993) have reported an increased incidence of the presence of a second gyrus posterior to Heschl's gyrus in DPs; however, other studies (Eckert et al., 2003; Green et al., 1999) have not replicated these findings.

For temporo-parietal and occipital regions, the following differences between DPs and controls have been reported:

- significantly larger volumes of left and right hemisphere temporal and parietal areas caudal to the infra-Sylvian fissure (volume measure of the planum temporale and parietale) (Green et al., 1999);
- larger leftward asymmetry in DPs of the planum temporale and parietale (Leonard et al., 2001);
- significantly greater leftward asymmetry of the parietal peri-Sylvian region in DPs as compared to controls (Robichon et al., 2000).

Additionally, decreased grey matter density in DPs has been observed in the left and right angular gyrus in the parietal lobe (Brown et al., 2001). Significantly lower grey matter density in DPs has been noted in the right medial occipital lobe and left occipital lobe (Brown et al., 2001).

Finally, focusing on findings for the cerebellum, significantly smaller grey matter volume in DPs than controls has been reported across the following areas:

- the bilateral anterior cerebellum (Kronbichler et al., 2008);
- the left semilunar lobule (Brown et al., 2001; Eckert et al., 2003);
- the right semilunar lobule (Brown et al., 2001).

Moreover, it has been reported (Rae et al., 2002) that DPs, in contrast to controls, exhibit grey matter symmetry of the left and right cerebellum. Finally, Pernet, Poline, Demonet and Rousselet (2009), using a newly devised method, reported that the grey matter of the right cerebellar declive (and the right lentiform nucleus) differentiated DPs and controls in such a way that 100% of DPs fell outside the 95% confidence interval boundaries of controls.

The first DTI study (Klingberg et al., 2000) showed bilateral differences in white matter in the temporo-parietal region in adult DPs, as compared to controls. The findings were interpreted in terms of weakened connectivity between frontal and temporo-parietal areas in DPs. A further study (Deutsch et al., 2005) with dyslexic children replicated these results.

Moving on to functional neuroimaging studies, most of these have been done within the PDT, with fewer studies on the MDT and the CDT. The studies which provide support for the PDT can be divided into two categories: studies which investigated phonological processing, such as phoneme rhyming and naming, and studies which focused on single word reading. The former will be discussed first.

Paulesu et al. (1996) investigated the performance of DPs in the covert consonant rhyming task, and reported that DPs exhibited significantly less activation than controls in the right supplementary motor area (BA 6), the left premotor cortex (BA 6), the left superior temporal gyrus (BA 21/22), the left insula and right striatum. The authors interpreted their findings in terms of weak connectivity between anterior and posterior language areas. Shaywitz et al. (1998) used the consonant rhyming task with a large sample of teenagers and adults with dyslexia. It was found that DPs exhibited significantly less activation in posterior areas: the posterior superior temporal gyrus (Wernicke's area), the angular gyrus (BA 39) and the striate cortex (BA 17). Conversely, when performing the same

task, DPs exhibited significantly more activation in the inferior frontal gyrus than controls. Focusing on naming, McCrory, Mechelli, Frith and Price (2005) investigated in a PET study whether there is a common neurological impairment for naming and reading deficits in DPs. The results revealed that, despite their intact behavioural performance, DPs exhibited significantly less activation in the left occipito-temporal area during naming and reading. The authors concluded that the left occipito-temporal area cannot be specific to orthographic processing, as claimed earlier (Cohen et al., 2000; Cohen et al., 2002; Cohen et al., 2003), but must be involved in a more general deficit in binding visual with phonological information (see also Price & Devlin, 2003).

Moving on to fMRI studies of single word-reading, it should be emphasised that it is beyond the scope of this paper to review them systematically. Here only a brief outline is presented and the reader is referred to reviews by Price and Mechelli (2005) and Pugh et al. (2000). The reading network, as revealed by neuroimaging studies, consists of three main subsystems in the left hemisphere: the ventral system (occipito-temporal), the dorsal system (temporo-parietal) and the anterior system. The ventral system includes the inferior occipito-temporal/fusiform area and extends anteriorily into the middle and inferior temporal gyri. The dorsal system includes the angular gyrus, supramarginal gyrus and Wernicke's area (BA 22). Finally, the anterior system is placed in the posterior aspects of the inferior frontal gyrus. Also, there is emerging evidence (Fulbright et al., 1999; Turkeltaub et al., 2002) that the cerebellum is part of the reading network.

Broadly speaking, neuroimaging studies of reading in DPs have demonstrated under-engagement of both the left dorsal and left ventral areas (Brunswick, McCrory, Price, Frith & Frith, 1999; Paulesu et al., 2001; Pugh et al., 2000; Salmelin, Service, Kiesila, Uutela & Salonen, 1996; Shaywitz et al., 1998). The under-activation of the occipitotemporal/fusiform region and three dorsal regions has also been reported in children (at the end of nursery) who had not mastered some important stages in learning to read (Sarkari et al., 2002). Regarding the cerebellum, Brunswick et al. (1999) reported that while reading aloud, DPs, in comparison to controls, exhibited less activation in the left cerebellum. In summary, the authors of the above cited studies interpreted their results as support for the PDT.

Three neuroimaging studies reported support for the MDT, whereas one did not. Eden et al. (1996) and Demb, Boynton and Heeger (1997; 1998) reported support for the MDT. Eden et al. (1996) demonstrated, in an fMRI study, that the presentation of moving stimuli in a motion coherence task did not elicit the same activation in V5/MT in DPs as in controls. In contrast, the presentation of stationary visual patterns elicited equivalent activations in V1/V2 and the extrastriate cortex in both groups (Eden et al., 1996). In two subsequent fMRI studies, Demb, Boynton and Heeger (1997; 1998) found that DPs exhibited significantly lower responses than controls in MT+ (and other extrastriate areas, including V1) when responding to low mean luminance, moving gratings. DPs' deficit as early as V1 is in line with the claim, based on anatomical data from the lateral geniculate nucleus (LGN), according to which a magnocellular deficit is precortical (Living-

stone, Rosen, Drislane & Galaburda, 1991). In contrast, Vanni, Uusitalo, Kiesila, and Hari (1997) reported in a MEG study that both high and low contrast motion stimuli elicited similar activation in V5 in DPs and controls. This result contrasts with the fMRI neuroimaging studies, and it is not clear what underlies this difference. It may be due to different samples of DPs, different experimental stimuli, or different techniques used, with MEG, in contrast to fMRI, being able to pick up small and transient changes in neuronal synchrony.

Most of the support for the CDT from neuroimaging studies comes from the structural brain abnormalities reviewed above, and there are only a few fMRI studies within the CDT. Nicolson et al. (1999) demonstrated, in an fMRI study, that brain activation in adult DPs (relative to controls) was significantly lower in the right cerebellar cortex when they were learning a new sequence of finger presses and in the right cerebellar cortex (and the left cingulate gyrus) when they were performing a pre-learnt sequence of finger presses. A recent fMRI study (Baillieux et al., 2009), which used a noun-verb association paradigm, revealed that while controls exhibited activation in the frontal and parietal lobes, and posterior areas of the cerebellar hemispheres, DPs exhibited activation mostly in the cerebellar cortex (hemispheric lobule VI, VII; vermal lobules I, II, III, IV, VII; and Crus I, II).

To summarise: the neuroimaging studies within each theoretical framework - the PDT, visual MDT and CDT – have revealed some evidence in support of the corresponding deficits in dyslexia: phonological, visual magnocellular and cerebellar, respectively. Furthermore, they have uncovered many structural and functional brain abnormalities in DPs, as compared to controls. However, these studies, with very few exceptions (e.g., Eden et al., 1996), involved only group comparisons, so it is unclear what proportion of DPs exhibited a given structural and/or functional brain abnormality.

GENETIC FINDINGS ON DYSLEXIA

The underlying cause of dyslexia has also been addressed on the genetic level. For many years it has been noted that dyslexia runs in families, implicating a genetic basis (Hallgren, 1950; Thomas, 1905). However, this is insufficient to prove a genetic basis for this disorder, since family members also share the same environment. Therefore, scientists have studied MZ (monozygotic) twins (who have almost identical genetic material) and DZ (dizygotic) twins (who share approximately half of their genes). It is also assumed that both types of twins share the same environment. Therefore, if MZ twins' reading ability is more similar than DZ twins' reading ability, it suggests that genetic factors play a role in reading ability. This pattern of results was found in a pioneering study of a large sample of twins involved in the Colorado Learning Disabilities Research Center. A concordance rate (identity of traits within twins) for dyslexia of 38% was reported in DZ twins, as compared to 68% in MZ twins (DeFries & Alarcon, 1996). The same research group developed the DeFries-Fulker regression (DF) method, based on direct analysis of continuous indices of severity, which tests whether DZ co-

twins exhibit more similarity to the control population. This method also provides estimates of heritability, defined as variation which can be attributed to genetic factors (DeFries & Fulker, 1985). A heritability of approximately 50% (±11%) for reading disability was estimated (DeFries & Gillis, 1993). For a more detailed history of genetic research on dyslexia see Fisher and Smith (2001) and Pennington and Olson (2004); for definitions of genetic terms see Pennington and Olson (2004) and Rédei (2003).

In the early 1990s, molecular genetics research, which aims to establish which genes are implicated in dyslexia, started to grow rapidly. One of the most popular techniques used in these studies is linkage analysis. This analysis relies on the fact that genes which lie close to each other on a given chromosome have a tendency to be inherited together. In linkage analysis, researchers search genetic material from given family members for chromosomal zones which have been co-inherited at above chance levels. Two types of linkage analysis have been used, for single and complex gene disorders respectively. In the former type, linkage can be determined using a few families with many relatives, in which co-transmission of a DNA marker allele and disorder can be traced (Plomin, DeFries, McClearn & McGuffin, 2008). In the latter, linkage can be detected by examining allele sharing for pairs of affected relatives (Plomin et al., 2008).

Each non-sex chromosome has a number, with 1 denoting the largest and 22 the smallest chromosome. Every chromosome has one long (q) and one short (p) arm; 2p denotes the short arm of chromosome 2. Each arm consists of morphologically defined regions which are numbered consecutively starting from the centromere (an area between the two arms of a chromosome), e.g., 2p1, 2p2 etc. The notation '2p12-p16' denotes a location on the shorter arm of chromosome 2, including regions: 12, 13, 14, 15 and 16. Regions on five chromosomes have been implicated by linkage studies of dyslexia. Because of space constraints, only results which have been reduplicated at least once are reported here. These include regions on:

- chromosome 2 (Fagerheim et al., 1999; Fisher, Francks, Marlow et al., 2002; Petryshen, Kaplan, Hughes, Tzenova & Field, 2002);
- chromosome 3 (Fisher, Francks, Marlow et al., 2002; Nopola-Hemmi et al., 2001);
- chromosome 6 (Cardon et al., 1994; 1995; Fisher et al., 1999; Gayan et al., 1999; Grigorenko et al., 1997; Grigorenko, Wood, Meyer & Pauls, 2000; Smith, Kimberling & Pennington, 1991);
- chromosome 15 (Fulker et al., 1991; Grigorenko et al., 1997; Schulte-Korne et al., 1998; Smith et al., 1991; Smith, Kimberling, Pennington & Lubs, 1983);
- chromosome 18 (Fisher, Francks, Marlow et al., 2002) (this paper included UK and US samples and a further replication set).

Recently, molecular genetics has started an exciting new chapter in dyslexia research, identifying some individual genes implicated in dyslexia. So far, six such genes have been identified in some of the loci reported in linkage analyses:

- DYX1C1, on the long arm of chromosome 15 (15q21);

- KIAA0319, on the short arm of chromosome 6 (6p22);
- DCDC2, also on the short arm of chromosome 6 (6p22);
- ROBO1, on the short arm of chromosome 3 (3p12);
- C2ORF3 and MROL19, on the short arm of chromosome 2 (2p12-p16).

DYX1C1 was identified by mapping the chromosome translocation breakpoint. Initially, DYX1C1 had been implicated in dyslexia in a group of Finnish families (Taipale et al., 2003), but not in English or Italian families (Bellini et al., 2005; Marino et al., 2005; Scerri et al., 2004). More recently, however, Marino et al. (2007) reanalysed their sample reported in 2005, and found that DYX1C1 influences a broader phenotypic definition of dyslexia in Italian families. A significant linkage was observed with 'single letter backward span'. Similar results were obtained from a German study (Dahdouh et al., 2009), where DPs' short-term memory scores mainly contributed to the implication of DYX1C1. Finally, Massinen (2009) reported a novel finding that DYX1C1 is involved in the regulation of estrogen receptors, and may therefore affect brain development and regulation of cognitive functions. DYX1C1 is expressed in the brain, but also other organs (e.g. lungs, kidneys). It can be found in cortical neurones and glial cells in the adult human brain. The role of DYX1C1 has been investigated in RAN interference (RANi) studies with animals. Neuronal migration (movement of neurones during foetal brain development when they migrate to find their final locations in the brain) into the cortical plate of the neocortex was disrupted by knockdown of Dyx1c1 in embryonic rat brain (lower case denotes a homologous gene in an animal) (Wang et al., 2006). Furthermore, a subsequent study (Rosen et al., 2007) reported results for the brains of adult rats that had Dyx1c1 function disrupted *in utero*. The results revealed blocked migration of some neurones into the cortical layer and over-migration of a larger neuronal population to supragranular layers, as well as heterotopias (clusters of un-migrated neurons) in the cortical molecular layer, similar to those reported for adults with dyslexia (Galaburda, Sherman, Rosen, Aboitiz & Geschwind, 1985). Some animals exhibited hippocampal malformations that may have resulted from mis-migrated cortical neurones.

KIAA0319 was identified as a dyslexia risk gene by positional association studies (Cope et al., 2005; Francks et al., 2004). The results have been replicated also with a sample from Wales (Harold et al., 2006). Moreover, it has also been reported that there are significant associations between KIAA0319 and reading skill in the general population (Paracchini et al., 2008). KIAA0319 expression is specific to the brain. In the adult human brain, the highest level of its expression is in the amygdala, cerebral cortex, hippocampus, putamen, dentate gyrus, and cerebellum (Paracchini et al., 2006). KIAA0319 encodes a protein which seems to function at the cell-surface; it regulates adhesion and interactions between adjacent neurones (Francks et al., 2004; Paracchini et al., 2006). Animal tests (using RNAi) revealed that down-regulation of Kiaa0319 in rat neocortex *in utero* resulted in reduced migration of neurones, with some neurones having abnormal orientation along the radial glial fibres that guide migrating neurones.

DCDC2 was first identified as a dyslexia risk gene in a positional association study (Meng et al., 2005). Association with dyslexia has also been replicated in German samples (Schumacher et al., 2006; Wilcke et al., 2009). DCDC2 is expressed in many organs, including the brain. Within the brain, it is expressed in the entorhinal cortex, amygdala, hypothalamus, hippocampus, and most importantly for any association with reading, in the inferior and medial temporal cortices. Down-regulation of Dcdc2 in rat brain *in utero* resulted in disrupted neuronal migration in the neocortex (Meng et al., 2005). The effect of *in utero* down-regulation of Dcdc2 in rat brain, investigated postnatally, showed hippocampal malformations, a bimodal cortical neuron migration pattern in both over-migrated and under-migrated neurons, and periventricular heterotopias (Burbridge et al., 2008). In contrast to DYX1C1, heterotopias in the cortical molecular layer were not found for DCDC2. DCDC2 codes for a cytoplasmic protein which resembles a protein coded for by DCX that has been implicated in deficits in neuronal migration in double cortex syndrome and lissencephaly (Gleeson et al., 1998).

ROBO1 was implicated as a dyslexia risk gene by mapping of the chromosomal translocation breakpoint in a four-generation Finnish family, where 27 members (out of 74) had dyslexia (Hannula-Jouppi et al., 2005). Normally, dyslexia is characterised by complex inheritance (Fisher & DeFries, 2002); however, in this family a single damaged gene acted in dominant fashion. ROBO1 is a homologous gene of the gene found in the fruit fly which has been implicated in cortical dendritic guidance and inter-hemispheric axon guidance (Hannula-Jouppi et al., 2005). It also encodes a receptor for proteins which guide cellular migration.

Finally, MRPL19 and C2ORF3 were implicated as dyslexia risk genes by positional candidate association mapping (Anthoni et al., 2007). C2ORF3 is expressed in the hippocampus, thalamus, hypothalamus, and all cortices (Anthoni et al., 2007). In contrast, MRPL19 has lower expression in these areas. MRPL19 expression in the brain is mostly correlated with that of KIAA0319. On the other hand, C2ORF3's expression in the brain correlates with that of DYX1C1, DCDC2 and ROBO1 (Anthoni et al., 2007). Currently it is not clear whether MRPL19 and C2ORF3 influence neural development.

Is dyslexia a neural migration disorder?

As four out of six genes currently implicated in dyslexia appear to have a role in neural migration or neuronal guidance, the question arises as to whether dyslexia is a neural migration disorder. Indeed, a working model of the underlying causes of dyslexia based on this explanation has been put forward (Galaburda, 2005; Galaburda, LoTurco, Ramus, Fitch & Rosen, 2006). One problem for this model is that for abnormalities, such as ectopias and microgyri, to cause dyslexia – a specific reading disorder – they have to be restricted to particular brain areas: the left perisylvian cortex, in the case of PDT. Interestingly, cytoarchitectonic abnormalities in DPs have been also found in post-mortem studies in LGN (in the thalamus), the left medial geniculate nucleus (LMGN) (Livingstone et al., 1991) and the cerebellum (Finch, Nicolson & Fawcett, 2002), and they provide some

support for the visual and auditory MDT and CDT, respectively. However, the assumption under which abnormalities in LGN and LMGN cause a visual/auditory magnocellular deficit have been challenged by some data from animal models. For instance, newborn rats with microgyri across their cortices later develop abnormalities in the LMGN. Therefore the direction of causality seems to be in the opposite direction, and cortical abnormalities produce abnormalities in LMGN (Galaburda, 1999). As the genes implicated so far in dyslexia appear to have a general function in neuronal migration and guidance, it is unlikely that they can restrict migration to these specific areas. It is more likely that some additional mechanisms are involved. Clearly, further research is needed.

A few notes of caution on how to interpret molecular genetic discoveries for dyslexia

It must be made clear that the genes described above are not 'dyslexia genes'. Firstly, these genes, except for KIAA0319, are also expressed in organs other than the brain, and therefore their role is not limited to neuronal migration and neuronal guidance. Secondly, the genes implicated in dyslexia can also be found in similar forms in other species, such as rats and mice. Thirdly, as most labs investigating these genes have focused on them in the context of dyslexia, it is not clear whether they are involved in other cognitive processes, such as mathematical abilities and IQ. Fourthly, these genes are involved in general developmental processes, such as neuronal migration, consequently they are not directly coding for any behaviour, including reading.

According to Fisher (2006), using a phrase such as 'a gene for dyslexia' is a common misunderstanding, and comes from the time when there was no molecular genetic perspective. He further states that it is erroneous to interpret the correlation between genetic and phenotypic variation as a straightforward linear relationship between specific genes and behaviour. He argues that the interpretation of genetic findings in dyslexia needs to be grounded in the appreciation that the biology and appearance of a given organism results from complex ontogenetic events which take place over time and are influenced by stochastic and environmental processes, and an understanding of a gene in the molecular perspective. The definition of a gene as a 'specific functional unit of DNA (or RNA) potentially transcribed into RNA or coding for protein' (Rédei, 2003) makes it clear that genes work on the molecular level and code for organic compounds made of amino acids. Fisher (2006) emphasises that using the phrase 'a gene, allelic variants of which influence a person's risk of developing dyslexia' is clearer and therefore preferable.

So far, six genes have been identified as implicated in dyslexia, and there are indications from the linkage studies that more genes will be discovered. A question which springs to mind is this: why are there so many genes implicated in dyslexia, whereas only one gene in disorders such as Huntington's disease or phenylketonuria? Huntington's disease and phenylketonuria are rare disorders which occur in approximately 1 in 20,000 and 1 in 10,000, respectively, and are

the result of a single mutated gene (Plomin et al., 2008). In contrast, as discussed earlier, dyslexia is a very heterogeneous disorder (Ramus et al., 2003; Reid & Szczerbinski, 2002; Reid et al., 2007; White et al., 2006) with much higher prevalence, ranging from 1 in 20 to 1 in 6 (Shaywitz, 1998), and encompasses a disorder of reading – a highly complex cognitive function which relies on many integrated cognitive processes. Although a single gene mutation may be associated with dyslexia, as in the case of ROBO1, such cases should be rare. Furthermore, the presence of a ROBO1 gene mutation may also involve other factors that significantly increase the risk of developing dyslexia. It is likely that most cases of dyslexia will be associated with several mutated genes, each contributing a portion to an individual's risk of developing this disorder (Fisher, 2006).

Genetics points to shared aetiology between dyslexia and several other developmental disorders

As has been stressed earlier, dyslexia co-occurs with other developmental disorders, more often than would be expected by chance. One of the goals of behavioural and molecular genetics is to determine whether there is any genetic overlap between these comorbid disorders. The focus will be on two comorbidities: with ADHD and SSD. So far, no genetic overlap has been reported for dyslexia and DCD, or dyslexia and SLI (Pennington & Bishop, 2009).

Comorbidity between dyslexia and ADHD – cognitive and genetic overlap

Regarding cognitive overlap, Willcutt, Pennington, Olson, Chhabildas and Hulslander (2005) reported that a dyslexia group, an ADHD group, and a dyslexia and ADHD group exhibited deficits of similar magnitude on linguistic and non-linguistic measures of speed of processing. Furthermore, in a follow up study (Shanahan et al., 2006), the authors found evidence for speed of processing as a cognitive risk factor which is shared by both ADHD and dyslexia. Cognitive deficits specific to ADHD (behavioural inhibition) and to dyslexia (phonological processing) were also found (Willcutt et al., 2001).

Genetic overlap tests are generally used to investigate whether the relation between two traits is greater in MZ than DZ twins. If it is greater, then it is called 'bivariate heritability' for the two traits. This means that some of the genetic influence on trait one is the same as the genetic influence on trait two. Some studies (Light, Pennington, Gilger & DeFries, 1995; Stevenson, Pennington, Gilger, DeFries & Gillis, 2006; Willcutt, Pennington & DeFries, 2000) reported bivariate heritability for reading disorder and ADHD. Higher bivariate heritability estimates (45%) were reported for the inattention subtype and reading disability (Willcutt et al., 2000) than for the hyperactivity/impulsivity subtype and reading disorder (5%).

A pioneering molecular genetic study on ADHD and reading comorbidity found that the dyslexia risk locus on chromosome 6p22 is also implicated in ADHD (Willcutt et al., 2002). A straightforward explanation here would be to postulate a pleiotropic gene. A more recent molecular genetic study (Couto et al., 2009)

tested this hypothesis by investigating whether the genes associated with reading disorders on chromosome 6 - DCDC2/VMP and KIAA0319/TTRAP - are also associated with ADHD. The results reported by Couto et al. revealed strong association for both inattention and hyperactivity/impulsivity subtypes of ADHD with the markers in the 6p22 region, which is in line with the findings of Willcutt et al. (2002). However, Couto et al. were not able to determine which exact gene is specific to ADHD. A much stronger association was found for the DCDC2/VMP region than for the KIAA0319/TTRAP region. Furthermore, no overlap for ADHD and reading skills markers was found, which does not replicate Willcutt et al. (2002). This may be because only 31 individuals with ADHD out of 264 probands (persons through which a family study of the inheritance of a human trait is initiated) and 55 siblings were diagnosed with reading disability.

Loo et al. (2004) reported support for both common and unique genetic effects in ADHD and reading deficit. Loci that uniquely contributed to variation in reading were mapped on chromosomes 2p, 8p, and 15q. Common loci contributing to both reading disorders and ADHD were found on chromosome 16p, 17q and possibly on 10p. The findings for 16p and 17q replicated earlier findings for the same data set (Fisher, Francks, McCracken et al., 2002; Ogdie et al., 2003; Smalley et al., 2002). A more recent study (Wigg et al., 2008) further investigated an association of ADHD with the region on chromosome 15q. Wigg et al. (2008) found that ADHD was not associated with DYX1C1, but six markers in the PRTG (Protogenin) gene showed association with ADHD. There was no association for reading measures and the PRTG or DYX1C1 genes, which may be due to insufficient variation of the trait in the sample used. Finally, Doyle et al. (2008) reported a region on chromosome 3 (3q13) which exhibited a suggestive linkage with the inattention subtype of ADHD and a range of neurocognitive traits. Interestingly, 3q13 overlaps with the region which contains the ROBO1 gene (Nopola-Hemmi et al., 2001).

Comorbidity of dyslexia and SSD – cognitive and genetic overlap

Initially, some researchers postulated that SSD and dyslexia are the same disorder, but differ in the severity of the underlying phonological deficit. If the phonological deficit is severe, it first manifests as SSD and later as dyslexia. Conversely, if it is not severe, it does not manifest itself as SSD, but later produces dyslexia. The assumption here is that reading relies on more mature phonological representations than speech (Pennington, 2006). However, there are some important findings that do not support this hypothesis. First, research by Snowling et al. (2000) identified SSD children with a phonological deficit that persisted into adolescence, who did not develop dyslexia. Secondly, Tunick (2004, cited by Pennington, 2006) found that probands with SSD and probands with dyslexia exhibited a deficit of similar magnitude on a phonological awareness measure, relative to controls. Interestingly, probands with SSD were significantly better than DPs on rapid serial naming, which may indicate a protective factor in some participants with SSD who do not later develop dyslexia.

Moving on to genetic findings, it was established (Lewis, 1990; Lewis, Ekelman & Aram, 1989) that SSD and dyslexia run in the same families. Tunick and Pennington (2002), using a twin design, established that SSD and dyslexia are also co-heritable. Following the report on the candidate gene for dyslexia on chromosome 3 (Nopola-Hemmi et al., 2001), Stein et al. (2004) investigated, in a molecular genetic study, whether there were any common genetic influences on SSD and dyslexia linked to chromosome 3. Their results suggested that measures common to SSD and dyslexia are pleiotropically influenced by a quantitative trait locus on chromosome 3. Smith, Pennington, Boada and Shriberg (2005) extended the study of Stein et al. (2004) by investigating whether SSD is also linked to other loci implicated in dyslexia, such as those on chromosomes 6 and 15. They found that the SSD phenotype was linked to dyslexia loci on these chromosomes, including DYX1C1, again implying a pleiotropic operation of involved genes.

In the context of dyslexia and its comorbidity with other disorders, some attention should be given to Plomin and Kovas' (2005) generalist genes hypothesis, according to which genes associated with deficits of reading, language and mathematics are generalists in three ways:

- First, genes that influence these disabilities also influence normal variation in learning.
- Second, genes that influence a given characteristic of a learning disability also influence other characteristics of this disability.
- Third, genes that influence a given learning disability are in all probability influencing other learning disabilities.

This hypothesis, if supported by future studies, will have significant implications for the understanding of dyslexia and its comorbidity with other disorders.

In summary, the cognitive and genetic results for comorbidity of dyslexia and ADHD, and dyslexia and SSD, can be accounted for in terms of partly different and partially shared cognitive and genetic risk and protective factors. Disorders such as ADHD or SSD are a product of an interaction of multiple cognitive and genetic risk and protective factors, some of which are shared with other disorders, such as dyslexia (Pennington, 2006). The genetic results on SSD seem more coherent, whereas the ADHD results are less clear-cut, which may be because dyslexia and ADHD belong to different diagnostic groupings and/or ADHD has at least two subtypes. This warrants further research.

SUMMARY AND FUTURE DIRECTIONS

The findings reported here demonstrate significant progress within the last two decades in research on dyslexia. Investigation of these areas in the past has been either neglected or impossible without technological developments, especially in neuroimaging and molecular genetics.

Although the issue of heterogeneity among DPs has been raised in the past, no systematic approach has been taken which would involve multiple case studies. At the beginning of the 21st century, this problem has been addressed by

a single case study and three multiple case studies (Ramus et al., 2003; Reid & Szczerbinski, 2002; Reid et al., 2007; White et al., 2006), which contrasted the predictions of the main theories of dyslexia. All four studies uncovered much heterogeneity among DPs. To account for the findings on heterogeneous profiles of DPs, Reid et al. (2007) put forward an explanation in terms of single underlying causes (phonological or visual magnocellular, or cerebellar) and multiple underlying causes (cerebellar and phonological, and magnocellular and phonological). Furthermore, in a supplementary analysis, Reid et al. (2007) identified two control participants who did not exhibit dyslexia, despite having a phonological deficit. This brings up an important issue of how it is possible to have an impairment that is a widely accepted causal factor underlying dyslexia, which nevertheless does not develop. To discuss this in some depth, it has to be appreciated that many complex processes and factors take place during ontogenetic development. Some of these factors will be risk factors, such as phonological deficit, and some, such as good language skills and individualised reading and spelling instruction, will act as protective factors. A given person will not develop dyslexia if the protective factors outweigh the risk factors. Future behavioural research needs to investigate risk and protective factors in the context of the ontogenetic development of DPs. The current parsimonious approach needs to be replaced with an approach which recognises that the underlying cause/s of dyslexia may be more complex than was expected.

The neuroimaging studies have revealed both structural and functional brain abnormalities in DPs. These findings undoubtedly complement the behavioural studies, clearly showing differences between DPs and controls on the neural level. Nevertheless, they have shortcomings, and three important issues for future research need to be highlighted here:

First, although most of these studies show between-group differences, there are many studies which do not provide an explanation for these differences. Consequently future neuroimaging studies must be strongly theoretically grounded.

Second, as it is becoming clear that reading involves a whole network of brain areas, investigations of differences between DPs and controls need to take into account the whole reading network. One promising way of addressing this would be to measure differences between groups in effective connectivity of the reading network, which allows one to determine the interactions between the relevant brain regions (Büchel & Friston, 2001).

Third, the vast majority of neuroimaging studies are based on group comparisons, so it is unclear what proportion of DPs has a given abnormality. Clearly multiple case neuroimaging studies of DPs are a necessary future goal.

Molecular genetic studies have revealed six dyslexia risk genes. As four of them appear to have a role in neural migration, some researchers have postulated that dyslexia is a deficit of neuronal migration; however, it is not currently clear how genes with such general function could restrict migration to specific brain areas. It is likely that more dyslexia risk genes will be discovered, because, as is becoming clear, dyslexia is a highly heterogeneous and complex disorder.

Furthermore, dyslexia manifests as difficulty with reading - a highly complex cognitive function which relies on many well integrated cognitive processes. It must be appreciated therefore, that the process of mastering this skill is under the influence of a multitude of factors, some of which are risk factors (e.g., genes implicated in dyslexia), and some of which are protective factors (e.g. good language skills). Therefore, carrying a mutated allele of one or more dyslexia risk genes will put a given person at risk, but whether this person will develop dyslexia will depend on the interactions between the risk and protective factors. A further complication comes from the findings that some genes which are implicated in dyslexia are also implicated in other developmental disorders, such as ADHD and SSD. Therefore these are pleiotropic genes and they put a person at risk from both disorders. Again, whether this person will develop both disorders, or only one disorder, or none, will depend on the interaction of many risk and protective factors, some of which are genetic and some environmental. Hence any model of the underlying causes of dyslexia must consider the risk and protective factors that operate in ontogenetic development to produce a DP with unique genetic, cognitive, and behavioural characteristics. Finally, due to advances in molecular genetics and neuroimaging techniques, the unique possibility has arisen to link genotype with brain structure. Making this link is of importance for uncovering the influence of allelic variation on the brain and understanding how deficits such as dyslexia are inherited. Genetic effects on brain structure can be tested with twin or familial experimental designs (Thompson, Mega & Toga, 2002).

The 21st century has brought many discoveries crucial for understanding dyslexia. However, it is likely that this is just the tip of the iceberg, and most crucial discoveries are still to be made. The findings across the three domains indicate that any theory of the underlying causes of dyslexia needs to rely on multiple case studies and has to take into account a multitude of risk and protective factors across behavioural, neural and genetic domains. Undoubtedly, this is an exciting time, when considerable technological and conceptual advancements promise discovery of the mechanisms underlying dyslexia.

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