

The Neurobiological Basis of Reading Fluency

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Abstract This chapter shall provide an overview of reading fluency research in the past two decades. We will first discuss fluency deficits and then discuss the genetic and brain behavior activation patterns associated with reading fluency deficits in individuals with dyslexia. Finally, we will present data from special abnormal populations with a specific fluency deficit.

Keywords Dyslexia • Fluency • Malformations • Genetics • Reading • Periventricular nodular heterotopia

1 Introduction

To most of us, the act of reading seems as natural and automatic as driving. We read effortlessly and rapidly. We read to learn new information or review familiar material. For many of us, reading itself is one of the greatest pleasures available. For a significant number of children, however, learning to read is similar to deciphering a highly enigmatic code. It is estimated that 5–17% of the population, despite having adequate intelligence and schooling, has some type of reading disability. This population is typically referred to as having developmental dyslexia, which is the

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most common reading disability. Defining features include difficulties in accurate and/or fluent word reading. Alternatively, struggling readers who can read single words without difficulty can show challenges instead in connected text reading fluency or comprehension (Georgiou, Das, & Hayward, 2009; Katzir et al., 2006). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) subsumes reading disabilities under the diagnostic label of Specific Learning Disorder (SLD). SLD includes disabilities in reading accuracy, fluency, or comprehension; spelling; written expression; or mathematics reasoning (American Psychiatric Association [APA], 2013). The formal diagnostic definition for Specific Learning Disorder is summarized as follows:

Difficulties in learning and using academic skills, as indicated by the presence of at least one symptom ... that have persisted for at least 6 months, despite the provision of interventions that target those difficulties. The affected academic skills are substantially and quantifiably below those expected given the individual's chronological age, and cause significant interference with academic or occupational performance, or with activities of daily living. The learning difficulties begin during school-age years but may not become fully manifest until the demands for those affected academic skills exceed the individual's limited capacities. The learning difficulties are not better accounted for by intellectual disabilities, uncorrected visual or auditory acuity, other mental or neurological disorders, psychosocial adversity, lack of proficiency in the language or academic instruction, or inadequate educational instruction. When more than one academic domain is impaired, each one should be coded individually. For example, when reading is impaired, one must specify if the deficit is in word reading accuracy, reading rate/fluency, or reading comprehension (APA, 2013, p. 66–67).

According to the DSM-5, Dyslexia is an alternative term used to refer to a pattern of learning difficulties characterized by problems with accurate and/or fluent word recognition, poor decoding and poor spelling abilities. When using this term, it is important also to specify any additional difficulties presented, such as difficulties with reading comprehension or math reasoning (APA, 2013, p. 67).

Most notably, in comparison to previous versions of the DSM, the current definition puts a distinct emphasis on reading fluency. Reading fluency has been defined as “a level of accuracy and rate where decoding is relatively effortless...and where attention can be allocated to comprehension” (Wolf & Katzir-Cohen, 2001, p. 219). It is debated whether reading fluency difficulties are independent from or a consequence of difficulties in reading accuracy (Breznitz, 2006; Chang et al., 2007; Katzir, Kim, Wolf, Morris, & Lovett, 2008).

In this chapter, we compare two clinical groups of readers that reveal distinct perspectives on reading fluency: readers with developmental dyslexia and individuals with periventricular nodular heterotopia (PNH). This latter group shows distinct difficulties in reading fluency concomitant with a specific brain malformation of cortical development that is associated with seizures. These reader groups can offer a unique perspective into the necessary and sufficient anatomical and functional characteristics of the brain to support fluent reading.

We present current cognitive and neuroscientific findings in reading disabilities research based on these reader groups as they inform our understanding of reading fluency. We will conclude by suggesting that a comparison across groups holds the

promise of revising current models of reading development and reading difficulties. Most importantly, understanding the different pathways to development and breakdown of reading fluency in the reader groups will serve as an important stepping-stone toward the assessment and remediation of these problems in diverse populations with developmental disabilities.

2 Background on Reading Disabilities: Epidemiology and Heritability

Reading is a dynamic skill that depends on both exposure and brain maturation. A recent longitudinal study among children with typical reading skills revealed links between cortical volume and componential reading skills in rapid naming, word reading accuracy and fluency in reading (Houston et al., 2014). Volume reductions in the left parietal and frontal cortical brain regions over time are associated with better performance on rapid naming, word reading and fluency. This finding suggests that cortical circuits that are tuned and efficient over time are associated with stronger reading skills.

Developmental dyslexia is best described as a heterogeneous group of disorders, with several underlying explanations for distinct subtypes of reading disabled students (Katzir, 2001). Dyslexia is both heritable and familial. Family history is one of the most important risk factors; 23–65% of children who have a parent with dyslexia are also identified with reading difficulties. The percentage of dyslexic siblings out of all children identified with dyslexia is approximately 40% (see Shaywitz & Shaywitz, 2005, for a further review). The variance of reading skills explained by genetic factors is high, with heritability estimates ranging from 40 to 80% (Schumacher, Hoffmann, Schmä, Schulte-Körne, & Nöthen, 2007).

The rates of heritability and identification rates in dyslexia remain inconsistent. Barbiero et al. (2012) identified prevalence rates of dyslexia in Italian speaking children aged 8–10 to be around 3%. In another study of English speakers, prevalence of dyslexia was found to be 9% among school-aged children (aged 8–17) and even 28% among participants from selected families with one member already suffering from dyslexia. Other findings indicated that when one of the parents is dyslexic, 22–35% of the children are affected too (Saviour, Padakannaya, Nishanimutt, & Ramachandra, 2009). In summary, while there is agreement that dyslexia is a neurological condition with some genetic basis, there is great variation in reports of prevalence and heritability of dyslexia. These may be related to the identification measures used, language spoken in the study and age of the children included in the sample. Thus, while significant advances have been made at understanding the brain, behavioral and genetic basis of dyslexia, there is not yet a clear universal genetic marker that is agreed upon for the phenomenon.

The prominent theory of the cause of dyslexia affirms common clinical observations of educators and psychologists that many children who cannot read have defi-

cits in the phonological processing system. Phonological processes are those involved in the representation, analysis, and manipulation of information specifically related to linguistic sounds from the level of the individual speech sound, or phoneme, all the way to the level of connected text. That is, children with dyslexia have difficulty developing an awareness that words, both written and spoken, can be broken down into smaller units of sounds, such as phonemes, onsets, rhymes and syllables (Wolf & Kennedy, 2003).

Neuroimaging work has provided converging lines of evidence in support of the phonological deficit theory. Neurofunctional research has shown that a deficit in integrating letters and speech-sounds among readers with dyslexia is one of the proximate causes of reading and spelling failure (Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009) and it may bridge the gap between phonological processing deficits and problems in learning to read (Burman & Booth, 2006). A considerable body of evidence indicates that dyslexic readers exhibit disruption primarily, but not exclusively, in the neural circuitry of the left hemisphere serving language (see Houston et al., 2014, for review).

A neuroimaging study using functional magnetic resonance imaging (fMRI) (Hoeft et al., 2007) measured brain activation during a word rhyme judgment task and gray matter morphology in dyslexic adolescents, and compared the results to the results of an age-matched group and a reading-matched group younger than the dyslexic group. Results showed that hyper-activation in frontal and sub-cortical brain regions was related to current reading ability, independent of dyslexia, while hypo-activation in left posterior regions was related to dyslexia itself. Furthermore, one of the brain regions that exhibited hypo-activation in dyslexia, the left inferior parietal lobe (IPL), also exhibited a reduction of gray matter in dyslexia. This study distinguished between regions associated with dyslexia specifically (posterior regions) and those recruited for groups of lower reading competence relative to a stronger reading group (frontal regions).

Another fMRI study demonstrated hemispheric activation differences between dyslexic readers and typical readers during lexical decision tasks (regular words, irregular words, pseudo-words) (Waldie, Haigh, Badzakova-Trajkov, Buckley, & Kirk, 2013). Specifically, the results showed hypo-activation in the left posterior areas and over-activation in the right hemisphere among dyslexic readers. This study highlighted the reliance of struggling readers on a right hemisphere system that serves a compensatory role.

Reduced activation in left hemispheric networks (including parieto-temporal and occipito-temporal regions) during phonological processing among readers with dyslexia already exists in young pre-literate children with familial risk for dyslexia (Raschle, Zuk, & Gaab, 2012). Brain activity within those brain regions shows a positive correlation with phonological processing skills among children with or without familial risk for dyslexia. This study suggests that children's functional systems tuned to language sounds can be vulnerable before reading instruction given familial history, though the percent of children who go on to have difficulties remains undetermined.

Qualitative and quantitative work by educators and psychologists has led to the extension of the phonological deficit view of dyslexia and broadened our understanding and treatment of reading disorders. Inevitably, in a process as complex as reading, reductionist hypotheses cannot explain all sources of reading difficulty. Some children elude diagnosis, classification, and sometimes treatment. Subtyping classification represents not a new, but rather an ongoing, effort to address the heterogeneity of reading disabled populations and to understand children who do not fit conventional theories of breakdown. Such research differs from those on reading disabilities which tacitly or explicitly operate within a model of general homogeneity, i.e., where single factors are assumed to explain reading failure (Badian, 1997; Carver, 1997; Kirby, Parrila, & Pfeiffer, 2003; Lovett, 1987; Lovett, Steinbach, & Frijters, 2000; Manis, Doi, & Bhadha, 2000; McGrath et al., 2011; Wolf & Bowers, 1999).

Current research in cognitive neuroscience has complemented behavioral work extending beyond phonological processing deficits as explanatory frameworks for reading disabilities. Naming speed deficits are considered to be an alternative and a complement to phonological deficits (Jones, Branigan, & Kelly, 2009; Wolf & Bowers, 1999). That is, impaired readers are slow to retrieve the names of very familiar letters and numbers. A naming speed deficit reflects difficulty in the processes underlying the rapid recognition and retrieval of visually presented stimuli. Debate exists whether rapid letter naming is a kind of phonological processing task, or whether it taps additional cognitive and linguistic processes that are not accessed within phonological processing tasks (Wagner, Torgesen, & Rashotte, 1999), supporting the notion that phonological and naming-speed deficits are independent factors, each contributing separately to reading development. A growing body of research demonstrates that there are discrete groups of children with reading disabilities characterized by either naming-speed or phonological processing deficits, or by combined deficits in both areas (Araújo, Pacheco, Faísca, Petersson, & Reis, 2010; Badian, 1997; Compton, DeFries, & Olson, 2001; Manis et al., 2000; Powell, Stainthorp, Stuart, Garwood, & Quinlan, 2007; Wolf & Bowers, 1999).

Advances in neuroimaging techniques offer the opportunity to investigate the neuroanatomical systems that are engaged in rapid serial letter- and word-reading. These techniques may provide insight into lines of evidence for the role and relationship between neural structures involved in rapid naming and reading. A study using fMRI suggests that the same factors that are related to the connections of visual representations to phonological information are also activated in rapid letter recognition (Misra, Katzir, Wolf, & Poldrack, 2004). In this study, a collaborative team of neuroscientists and educators used the theoretical framework suggested by Wolf and Bowers (1999) and applied it to neuroimaging research in skilled readers. They found that in skilled readers, the neurological underpinnings of phonological processing and rapid letter naming differ. These findings suggest that phonological processing and rapid letter naming are discrete cognitive processes that have different relationships to reading.

In a study of the neural correlates of reading fluency, the findings of Christodoulou et al. (2014) offer a hypothesis for reading fluency deficits in dyslexia. Specifically,

brain regions involved in semantic retrieval and semantic representations failed to be fully engaged for comprehension at rapid reading rates in adults with dyslexia. This finding is consistent with patterns of hypoactivation for posterior brain networks in dyslexia for reading words. This work has expanded our understanding of neural systems supporting reading by identifying atypical recruitment of neural systems and correlates with reading behaviors in dyslexia.

In summary, a range of neurobiological investigations, examining multiple linguistic and cultural groups, has documented the intrinsic disruption of neural systems for reading and dyslexia across languages and cultures (Grigorenko 2001; Lyon, Shaywitz, & Shaywitz, 2003; Paulesu et al., 2001; Pollack, Luk, & Christodoulou 2015; Vellutino, Fletcher, Snowling, & Scanlon, 2004). Collectively, these studies have contributed to our general understanding of the brain regions and processes involved in normal and impaired reading. A considerable body of evidence indicates that children with a reading disability exhibit both subtle structural differences as well as differences in neural circuitry when compared to non-impaired readers (Berninger & Richards, 2002). However, there is no definitive brain marker, either structural or functional, of dyslexia. Instead, these combined studies give a better picture of brain differences between normal and dyslexic readers as a group (Katzir & Pare-Balagov, 2006).

3 Dyslexia as a Disorder of Cerebral Cortical Development

There has long been evidence that dyslexia may be associated with subtle abnormalities of cortical development. In the 1980s, Galaburda and colleagues reported several developmental abnormalities in brains of patients with dyslexia, including an absence of the normal asymmetry of the planum temporale, foci of ectopic neurons in the molecular layer of perisylvian cortex, and foci of glial scarring (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Humphreys, Kaufmann, & Galaburda, 1990). Across multiple reports, subtle structural abnormalities have been seen in high-resolution imaging studies of dyslexic patients' brains, although there are few consistent, reproducible anatomical findings (Habib, 2000). Candidate genes have been identified at chromosomal loci linked to dyslexia susceptibility, and some of these encode proteins thought to be important either in axonal pathfinding or in neuronal migration during brain development (Hannula-Jouppi et al., 2005; Meng et al., 2005).

A comprehensive review regarding the genetics of dyslexia (see Scerri & Schulte-Körne, 2010) revealed dyslexia risk chromosomal loci, like *DYX1*, *DYX2*, *DYX3*, *DYX5* and *DYX8* (e.g. Chapman et al., 2004; Grigorenko et al., 2003; Marlow et al., 2003; Schumacher et al., 2008; Tzenova, Kaplan, Petryshen, & Field, 2004). A novel approach, then, to the neurobiological study of dyslexia and other learning disabilities is to investigate the phenotypes of known malformations of cortical development (MCDs), neurological disorders in which the usual process of cerebral

cortical development is disrupted during embryonic and fetal life (Barkovich, Kuzniecky, Jackson, Guerrini, & Dobyns, 2005).

Given the histopathological and genetic findings described above, the study of those malformations associated with neuronal migration problems may be particularly relevant to our understanding of the relationship, if any, between dyslexia in the broad population and developmental abnormalities of the cerebral cortex.

4 Periventricular Nodular Heterotopia (PNH): A Rare Brain Malformation

Periventricular nodular heterotopia (PNH), a disorder of neuronal migration that in some cases is associated with specific genetic mutations, might provide us exclusive insights, as it is a rare disorder that is linked to focal deficits in reading fluency (Reinstein, Chang, Robertson, Rimoin, & Katzir, 2012). PNH is one of a number of DBMs, or developmental brain malformations (Barkovich et al., 2005), associated with seizures. With the advent of high-resolution neuroimaging, and in particular the widespread use of magnetic resonance imaging (MRI) in patients with epilepsy, the diagnosis of MCDs is becoming more common in clinical medicine. In fact, MCDs are now recognized to be a relatively prevalent cause of seizure disorders (Sisodiya, 2004).

During embryonic and early fetal life, progenitor cells called neuroblasts proliferate deep in the brain along the lateral ventricles, which are intracerebral spaces filled with cerebrospinal fluid. These progenitor cells divide, giving rise to cells that are destined to become cortical neurons. However, these cells must first migrate from the proliferative zones that are adjacent to the ventricles outward toward the surface of the brain in order to begin populating what will soon become the multi-layered cerebral cortex. The failure of groups of neurons to migrate to their proper destination leads to misplaced, or heterotopic, regions of gray matter in the mature brain. In PNH, nodules anywhere from a few millimeters to more than one centimeter in diameter are present along the walls of the lateral ventricles bilaterally. These nodules contain neurons that are morphologically normal but appear to have failed to migrate properly to the cortical surface (Eksioglu et al., 1996; Ferland et al., 2009; Fox et al., 1998). In some cases the nodules are so large and numerous that they become confluent, forming a continuous string of gray matter along the ventricles.

Classic bilateral PNH has been associated with mutations in the Filamin A (*FLNA*) gene (Fox et al., 1998; Robertson, 2005). This gene encodes an actin-cross linking protein (filamin) that is expressed in multiple different organ systems during development and plays a critical role in cell locomotion. In the developing nervous system, it appears to be important for neuronal migration, although it may also have effects on the neuroepithelial lining of the ventricles and on the cerebral vascula-

ture. Females with mutations in the *FLNA* gene on one of their two copies of the X chromosome typically demonstrate the classic PNH appearance on brain MRI, and can pass on the condition to 50 % of their daughters. Most mutations in *FLNA*, when passed on to sons (who have only one copy of the X chromosome), are thought to result in prenatal lethality and spontaneous abortion, although certain mutations and patterns of somatic mosaicism can result in liveborn male children who may have classic PNH or other abnormalities (Guerrini et al., 2004). Researchers have demonstrated the presence of a number of variant forms of PNH associated with abnormalities such as hydrocephalus and microcephaly; these appear to have different genetic etiologies (Sheen et al., 2004a, b).

The histopathological and genetic characteristics of PNH have been known for a number of years. Despite this, it has only been in recent years that a detailed behavioral study of PNH patients has been undertaken, and in fact it is perhaps the cognitive and intellectual abilities of PNH patients that are the most surprising aspect of this condition. Although classic PNH appears to represent a quite widespread abnormality of neuronal migration, patients with this condition have generally been found to be of normal intelligence (d'Orsi et al., 2004). In fact, most are not diagnosed until adolescence or later, when seizures develop and an MRI of the brain is obtained.

A detailed behavioral study of PNH was undertaken to test the hypothesis that the cortical developmental abnormality would result in cognitive deficits in PNH patients that could be identified by expert neuropsychological testing, but might spare performance on tests of general intelligence. This work demonstrated that heterotopia patients share similar behavioral profiles to developmental dyslexia patients (Chang et al., 2007). Both groups had impaired reading fluency and phonological processing difficulties, but only the dyslexic group had significant lower phonological processing skills compared to normal readers. There was no significant difference in IQ scores between the groups. Using diffusion tensor imaging (DTI; a noninvasive, MRI-based method that allows for analysis of white matter microstructure and visualization of fiber tracts), the researchers revealed that PNH was associated with specific, focal disruptions in white matter microstructure and organization in the vicinity of gray matter nodules. The degree of white matter integrity correlated with reading fluency in PNH patients. Hence, the degree to which long cortico-cortical fiber tracts are affected may be the factor that influences reading performance among PNH patients.

A study by Reinstein et al. (2012) has presented a mother and daughter pair who suffers from bilateral widespread gray matter heterotopia, both diagnosed with a specific mutation in *FLNA* gene and the same X-chromosome inactivation. Their results revealed different reading and cognitive profiles. Both of them had normal verbal IQ and intact phonological processing skills, but the mother had significant impairments in reading fluency and reading comprehension, whereas the daughter had no fluency or comprehension problems. The mother's profile is consistent with previous findings of impaired reading fluency and intact phonological skills among periventricular heterotopia patients (e.g., Chang et al., 2007). The unique findings of Reinstein et al. (2012) lead to the assumption that the same genetic mutation and

similar heterotopia anatomy may result in different effects on cortical circuits, hence, differentiated cognitive outcomes among distinct patients.

Evidence indicates that regions of nodular heterotopia in a developmental brain malformation have connectivity to other regions of gray matter in the brain, most commonly to discrete regions of cerebral cortex that immediately overlie the heterotopia themselves (Christodoulou et al., 2012). This study identified white matter fiber tracts that appear to mediate structural connectivity between heterotopia and some brain regions, and illustrated that these regions are also highly functionally correlated, as determined by resting-state blood oxygenation level-dependent (BOLD) imaging.

Further research has provided evidence of functional brain activation within periventricular nodules in PNH participants during reading related tasks (Christodoulou et al., 2013). Standard behavioral tasks that related to reading are associated with the activation of heterotopia across multiple anatomical locations in PNH participants using a strict statistical threshold. Their results represent a systematic demonstration that heterotopic gray matter can be metabolically co-activated in PNH.

5 Clinical and Research Implications

The work described above has important implications for the clinical care of patients with developmental brain malformations. It must be recognized that even malformations felt not to adversely affect cognitive function may in fact have specific learning disabilities or other limited cognitive impairments associated with them. These would only be evident upon detailed neuropsychological assessment. In these situations, clinicians should have a low threshold for arranging detailed cognitive testing. The identification of any such disabilities may warrant the institution of early interventions in school-age children who have been diagnosed with MCDs, in addition to the medical care they may be receiving for seizures and other clinical manifestations of their brain malformation.

The results of the PNH studies also suggest that a more detailed structural study of PNH patients' brains, with particular attention to gray matter volume, cerebral cortical thickness, and white matter microstructure may prove particularly illuminating in the search for the underlying neuroanatomical basis of the reading disability in this population. These types of detailed anatomical studies can now be undertaken using computational post-processing methods applied to neuroimaging data acquired from live human subjects, a key innovation given the dearth of post-mortem brain tissue available in this and similar conditions. Detailed functional imaging studies, using BOLD functional MRI techniques, may help to shed light on the neural basis of the reading disability in PNH, particularly in the context of the numerous fMRI studies of dyslexic patients that have demonstrated alterations in the usual left hemisphere networks that appear to be responsible for reading (Shaywitz & Shaywitz, 2005).

6 Conclusions

In the end, a focus on the cognitive and functional consequences of disruptions in cerebral cortical development may allow insights from a relatively select group of patients with rare disorders to aid our understanding of, and approach to, the much larger population of children and adults with learning disabilities. In particular, data from more detailed behavioral studies of the reading problems faced by PNH patients may hold the promise of allowing us to refine our current models of reading development and reading breakdown. Ultimately, an increased appreciation of the neurobiological basis of reading disability, both in those with uncommon developmental brain disorders and more commonly in the wider population of dyslexics, will be one step toward the proper evaluation and remediation of children and adults with developmental disabilities.

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