Tackling the Early Identification of Dyslexia with the Help of Neuroimaging

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Typically, dyslexia is not diagnosed until a child has failed to learn to read as expected, usually in second grade or later. As a result, children with dyslexia must often make up a large gap in reading ability and experience to reach the level of their typically reading peers (Hiebert, 2000). Years of failure to read can lead to reduced self-esteem, depression, and other psychological and clinical implications (Valas, 1999). Furthermore, targeted interventions are most effective when administered in kindergarten and first grade (Torgesen, 2000). Thus, to date, dyslexia is generally diagnosed after the most effective time for intervention has passed, which can be termed the *dyslexia paradox*.

Although several behavioral measures show promise in predicting which children will develop dyslexia even before reading onset (Scarborough, 1998; Schatschneider, Fletcher, Francis, Carlson, & Foorman, 2004), early identification requires a trade-off between specificity (i.e., reducing the rate of misidentifying children as dyslexia risk, who are not) and sensitivity (i.e., reducing the rate of failing to identify children who are at risk) of identification, which can often result in high rates of over/under identification (Gabrieli, 2009). Most recently, studies have employed neuroimaging to enhance the prediction of reading outcomes (Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015). These types of studies utilize magnetic resonance imaging (MRI) because it affords high spatial resolution (i.e., how well you can localize structures in the brain) without being invasive. The advent of neuroimaging methods in the study of early reading development and dyslexia may offer at least two advancements: 1) understanding the underlying mechanism of dyslexia, its origin and developmental trajectories; and 2) improving early identification of at-risk children prior to formal reading instruction. However, high costs, limited availability, and logistical challenges are some of the obstacles to using this instrument in educational settings. Still, brain imaging may prove cost effective in a clinical setting if sensitivity and specificity could be maximized.

This article summarizes the results from MR neuroimaging studies in children before reading instruction begins and critically evaluates the potential of these studies to enhance the identification of children at risk for dyslexia prior to the start of formal reading instruction. First, the neurobiology of typical and atypical reading development will be discussed. Then, evidence from neuroimaging studies that examine children prior to and concomitant with the onset of reading and reading instruction will be presented. Finally, the feasibility of utilizing neuroimaging methods for the early identification of those at risk as well as its implications for educational settings and policy will be critically discussed.

Studying the Reading Brain Using MRI

Structural MRI measurements can provide information about the structural (anatomical) characteristics of the different brain regions (e.g., size and volume of brain structures) within accuracy of a few millimeters. MRI measures differences in magnetic properties of different tissues in the brain. This is done with the help of water molecules, the most abundant molecules in the human body. MR technology utilizes the fact that the hydrogen atoms that make up water molecules interact differently with the magnetic force of the MRI scanner, depending on the properties of the tissue in which the hydrogen atoms are located. For example, structural measures of the gray matter in the brain (i.e., the cell bodies and dendrites of neurons) can inform about the number of neural cells within a particular region.

Diffusion measures such as diffusion tensor imaging (DTI) can inform about the properties of white matter tracts and the size of these tracts. White matter tracts are neural pathways carrying information between different brain areas. Functional magnetic resonance imaging (fMRI) can be used to examine brain function. In most fMRI experiments, participants complete a task in the MR scanner and oxygen changes in local tissues are observed. For example, in a classical phonological task, participants with and without dyslexia may be instructed to decide whether two words they hear start with the same first sound. Brain areas that are involved in the processing of this task use oxygen. Following the consumption of oxygen in these "active" brain areas, the brain reacts by sending more oxygen than originally consumed to the active brain areas. This oxygen change alters the MR signal in a measurable way. The oxygen change during the task is compared to the oxygen change during a control task (e.g., the participants listen to the same words but decide whether they are spoken by the same person). The statistical difference in oxygen change between the experimental and the control task is calculated and the difference is displayed on a brain surface template (the warmer the color the bigger the statistical difference between the experimental and the control task). Thus, fMRI can inform about the magnitude and location of brain activation during one particular task by

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Abbreviations

DTI: Diffusion tensor imaging
FHD+: Familial history of dyslexia
FHD-: Children without familial history of dyslexia
FA: Fractional anisotropy
fMRI: Functional magnetic resonance imaging
MRI: Magnetic resonance imaging

taking advantage of an endogenous tracer (our own oxygenated and deoxygenated blood) and this is used to infer brain activity (Huettel, Song, & McCarthy, 2009).

The strength of using structural MRI measures in dyslexia research is that they are task-independent and therefore can be replicated more consistently and reliably across studies and populations. This is especially important for clinical application (Gabrieli et al., 2015). MRI is especially suitable for infants or young children, since infants can be asleep during the measurements and young children can be engaged with a movie. The strength of fMRI is that it measures task-dependent activation, thereby allowing brain activity to be examined in response to a subject's performance on a particular cognitive or perceptual task.

Conducting MRI studies in young children is not an easy endeavor (Raschle et al., 2012). Common challenges include parental and child anxiety (e.g., concern about the noisy, constricted, and unfamiliar environment), technical limitations (e.g., availability of child-appropriate equipment), and analysis challenges (e.g., how to deal with head movement). For anyone who has interacted with young children, the central problem of using a tool that is easily corrupted by movement is evident. This is especially challenging when using MRI with infants and preschoolers. In infants, researchers utilize a natural sleep protocol (Raschle et al., 2012), striving to replicate the child's normal bedtime routines as closely as possible by scanning during their regular nap time, setting a familiar and soothing environment in the imaging suite (e.g., including rocking chair, crib, dim lights), and encouraging the parents to perform the regular sleep routines in the suite (e.g., nursing). With young children, a child-friendly theme (e.g., setting an engaging story and animations for the tasks, projecting movies) and terminology (e.g., the MRI machine may be called a "brain camera"), as well as incentives to ensure the child's motivation are used. Practicing lying still prior to the session in a mock scanner, reinforcing the importance of minimizing movement, and having someone next to the child during the entire session are several techniques that have proven particularly useful to minimizing in-scanner motion. Using these methods, MRI data on thousands of young children and infants have been collected around the world.

The Development of the Typical Reading Brain

The reading brain consists of multiple neural structures that form a complex functional and structural network through a child's experience with language and reading (Dehaene, 2009). The emergence of this network starts as early as in utero, when babies are exposed to the muffled sounds of speech. As young as 6 months, infants are already able to distinguish their speech sounds from those of other languages (Kuhl et al., 2006). The ability to recognize and distinguish among native speech sounds is called phonological processing. Phonological processing relies on the function of the auditory system located in the left superior temporal regions (Figure 1) in the brain.

As children gain expertise in processing the sounds of their language, they begin gaining a metacognitive understanding of the intricacies of speech. The ability to manipulate speech by forming rhymes or taking words apart to form other words is called phonological awareness. Left temporoparietal and inferior frontal regions (Figure 1) are involved in phonological awareness as well as phonological processing (Pugh et al., 2001).

When children enter school, or shortly beforehand, they begin learning that speech sounds have visual representations called letters. Learning the form of letter strings and words is supported by higher-order visual recognition systems in the occipitotemporal region (Figure 1) often termed the *visual word form area* (Dehaene, 2011). As children master the letter-to-sound correspondences, the link between visual recognition regions and the temporoparietal phonological awareness regions strengthens (Pugh et al., 2000). Through repeated experiences with a given word, children learn to automatically identify the word as a whole, and reading proceeds more fluently from the visual word recognition areas to meaning areas commonly located in the middle temporal lobe and in the inferior frontal gyrus (Cutting et al., 2006).

As such, fluent reading relies on automatic identification of familiar words and the ability to efficiently decode unfamiliar words. Fluent reading is additionally governed by global cognitive mechanisms, such as attention and executive control (Breznitz, 2006). Reading comprehension requires, among other things, lexical and background knowledge, correct utilization of linguistic cues, and inference and reasoning skills (Just, 2013). Many brain regions, especially the inferior frontal areas (Figure 1), participate in these higher cognitive abilities (Price, 2000). This sequence of reading development in the brain is a simplification, both of the timeline of reading development, as many skills are gained in parallel, and of the complex neural processes that occur in the brain to make reading possible. The understanding of how reading development occurs in the brain is still fairly limited. Even more limited is the understanding of how these processes differ in the brains of individuals with dyslexia. A preliminary sketch, however, has been made possible by the advent of neuroimaging technology, such as MRI.

The Atypical Reading Brain

Dyslexia is a neurobiological condition and is associated with atypicalities in various brain areas within the reading network. Genetic predisposition for dyslexia is thought to affect early brain development resulting in neural alterations in brain regions important for reading (Figure 1: gray matter and Figure 2: white matter; Galaburda, 2006). It remains debated which brain characteristics of dyslexia are a result of reduced reading practice and which predate the onset of reading instruction. Studies that have demonstrated that children with dyslexia exhibit brain differences even when compared to reading-level-matched children (i.e., younger children without dyslexia who read at the same level [Hoeft et al., 2006]) and studies

that have shown these differences in prereading children with genetic risk of dyslexia (Im, Raschle, Smith, Grant, & Gaab, 2015; Langer et al., in press; Raschle, Chang, & Gaab, 2011; Raschle, Stering, Meissner, & Gaab, 2013) suggest that at least some of the brain characteristics of dyslexia are hereditary and are not the outcome of experience.

Do Brain Alterations in Dyslexia Predate Reading?

In order to identify which brain differences within the reading circuit predate reading failure, and thus could contribute to causing it, it is important to study brain differences in young children before reading instruction ensues. Consequently, given the strongly hereditary nature of dyslexia (Grigorenko, 2004), affecting approximately 50% of children with a first-degree relative (an older sibling or a parent) with dyslexia (Finucci, 1983; Grigorenko, 2004), many studies focus on comparing prereading children with a familial history of dyslexia (FHD+) with children without familial history (FHD-) to investigate the neural markers of dyslexia. Other studies determine risk based on poor performance on behavioral measures of early literacy. Below, the results from MR neuroimaging studies in young children before they are exposed to explicit reading instruction will be summarized.

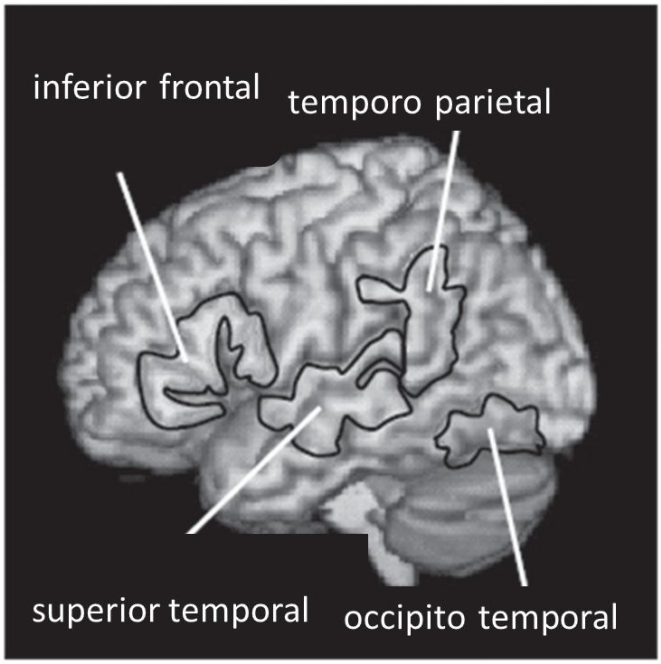

Figure 1. Brain regions important for reading that are commonly found to be associated with atypical function or structure in dyslexia.

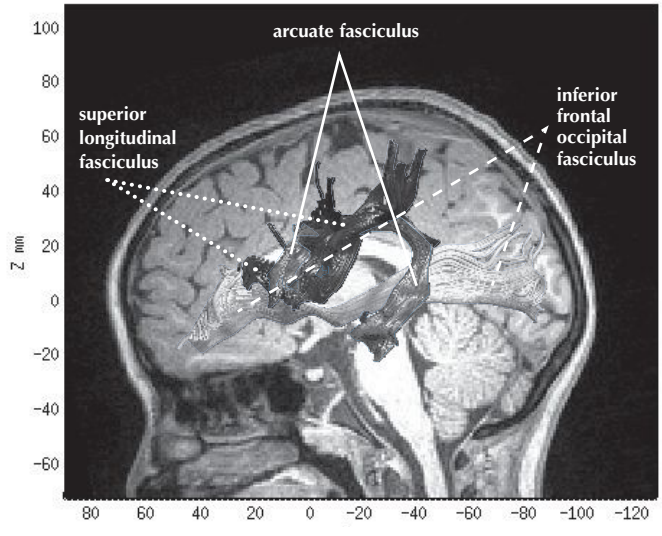

Figure 2. White matter pathways important for reading: arcuate fasciculus (*blue*), inferior frontal occipital fasciculus (*light blue*), superior longitudinal fasciculus (*blue-black*).

Differences in brain structure

Across several studies conducted in young children prior to the onset of reading instruction, a consistent finding has emerged: FHD+ prereading children demonstrate neural atypicalities in the same regions as older children and adults with dyslexia. For example, the Boston Longitudinal Dyslexia Study (at Boston Children's Hospital) evaluated FHD+ and FHD- children the summer before kindergarten using extensive behavioral and MRI measures. Results indicated that some of the brain alterations in children at higher risk for developing dyslexia are most likely genetically rather than experientially driven (Raschle, Chang, & Gaab, 2011). FHD+ children, as compared to FHD- children, demonstrated reduced gray matter volume in regions within the reading circuit (i.e., occipitotemporal and temporoparietal regions). Confirming the importance of these regions for early-reading development, there was an association between gray matter volume in these regions and performance on a rapid automatized naming measure. However, it is important to note that in this study it is still unclear which of these children will develop a reading disability. Therefore, it is important to evaluate these children again in later grades when reading can be evaluated and a diagnosis of dyslexia can be made.

In another study, the sulcal patterns (the arrangement, number, and size of primary cortical folds) of the same group of children with a family history of dyslexia as well as a new sample of older children with dyslexia were characterized (Im et al., 2015). Sulcal pattern has been hypothesized to relate to optimal organization of cortical function and white matter connectivity. Sulcal pattern is largely determined during prenatal development and does not change much after birth; as such this measure provides excellent insights into when during development brain differences may have arisen. Results demonstrated atypical sulcal patterns in temporoparietal and occipitotemporal regions in FHD+ compared to FHD- prereaders, and the same patterns were observed in older children with dyslexia. This suggests that at least some of the brain characteristics of dyslexia are present at birth, but studies in infants are needed in order to confirm this working hypothesis.

The findings from the BOLD Study are supported by those from other investigators in California, Germany, and Norway. Researchers in California conducted a more in-depth examination of the two components of gray matter volume: surface area and cortical thickness in early reading children (Black et al., 2012). Surface area, similar to sulcal pattern, is thought to develop prenatally, while cortical thickness changes across

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development and is more environmentally driven. Hoeft and colleagues observed an association between the maternal history of reading failure and reduced cortical surface area within the temporoparietal regions. Their findings suggest that brain alterations in dyslexia are be primarily associated with maternally transmitted genes but further study needs to replicate these findings.

A longitudinal study in typically reading German first graders demonstrated that more gray matter volume in the left superior temporal gyrus at first grade was associated with greater gains in reading proficiency between first and second grade (Linkersdörfer et al., 2014). This suggests that variation in brain structure can impact the development potential of reading early in schooling. Another longitudinal study in Norwegian prereading children with and without a familial risk of reading problems examined the children's behavioral performance in the beginning of kindergarten and their brain structure in the spring of first grade (prior to reading instruction), third grade, and sixth grade (Clark et al., 2014). Retrospective analysis revealed that those first graders who eventually received a diagnosis of dyslexia (in sixth grade) had a significantly thinner cortex in several low-level auditory, visual and executive functioning regions in first grade, but not in the areas associated with reading. Significantly thinner cortex within the reading network was not observed until sixth grade. As suggested by some researchers (e.g., Galaburda et al., 2006), these findings indicate that early brain alterations in dyslexia are in more basic sensory regions impairing the proper acquisition of phonological and orthography knowledge, and only arise in the reading network as the consequence of poor reading. This finding of the delayed emergence of atypicalities in the reading network, however, contradicts those of other studies that found differences in the reading regions prior to reading onset (e.g., Im et al., 2015; Langer et al., in press; Raschle, Chang, & Gaab, 2011). Future longitudinal studies with larger sample sizes are needed to resolve this question.

Differences in white matter connectivity

Reading, like other cognitive functions, relies on the robustness of the specific white matter fiber bundles that connect different brain regions. White matter consists of axons, the "tails" of the neural cells, which transmit signals from one brain cell to another. These tracts are analogous to "highways" between cortical areas that enable fast information flow. Fractional anisotropy (FA) is one measure that quantifies the quality/integrity of these fibers and it has been debated which property of the fiber leads to reduced FA/integrity (e.g., myelin, the insulation of the fiber, the number of fibers or crossing fibers). Using the "highway" analogy, this can be compared to the smoothness of the highways or how many lanes it has or whether it has any crossing streets. One particularly important tract for reading is the arcuate fasciculus that connects the temporoparietal region important for phonological processing with the inferior frontal regions important for language comprehension and high-level synthesis of linguistic information (Wandell, 2013). A longitudinal study by researchers at Boston Children's Hospital and Massachusetts Institute of Technology revealed that kindergarteners with poor phonological awareness have reduced arcuate fasciculus volume and reduced fractional anisotropy (Saygin et al., 2013).

A study in Dutch-speaking prereading kindergarteners also demonstrated a positive association between phonological awareness and the FA of the arcuate fasciculus and another tract, the inferior frontal occipital fasciculus that connects the visual word form area in the occipitotemporal region (the region of the brain that is thought to specialize in visual processing of letters and words) and inferior frontal regions (Vandermosten et al., in press). This study also demonstrated significant reduction in FA in the left inferior frontal occipital fasciculus in FHD+ children as compared to FHD- children, suggesting that white matter abnormalities in the left reading networks may predate reading onset. Importantly, the Gaab team at Boston Children's Hospital have demonstrated that these white matter atypicalities may already be present in as early as infancy. In their study, FHD+ infants showed reduced FA in several parts of the arcuate fasciculus, compared to FHD- infants (Langer et al., in press). Furthermore, higher FA in these regions was associated with better language skills in all infants. However, one needs to keep in mind that only 50% of these infants will develop a reading impairment and future studies need to track these infants longitudinally to establish the sensitivity and specificity of these observations.

Overall, the literature so far has demonstrated that some structural gray and white matter alterations seem to predate reading onset. Due to the significant impact of environmental factors, such as language and literacy exposure (even prior to reading instruction) on brain development, additional MRI studies originating in infancy and examining the developmental timeline from infancy to elementary school or even beyond are needed. This will help to characterize the underlying neural mechanisms of dyslexia and its developmental trajectories, and will be highly valuable in establishing causality.

Differences in brain function

fMRI Activation in Response to Auditory/Phonological Processing

Several studies have suggested that the functional brain alterations (as measured with fMRI) in children with a diagnosis of dyslexia can also be observed in prereading children with a familial risk of dyslexia. For instance, the Boston Longitudinal Dyslexia Study has revealed that FHD+ preschoolers compared to FHD- preschoolers already show reduced neural activation during a first-sound matching task (e.g., deciding whether the words *cat* and *car* heard inside the scanner start with same sound or different sound) in the left occipitotemporal and temporoparietal regions. Furthermore, reduced activation in the left prefrontal regions, which are important for auditory working memory, has been shown in these FHD+ preschoolers during a task in which they listened to rapid compared to slow

onsets of artificial syllables (Raschle, Stering, Meissner, & Gaab, 2013; Raschle, Zuk, & Gaab, 2012). Brain activation in these tasks correlated with behavioral performance on preliteracy measures (e.g., rapid automatized naming and phonological awareness). Taken together, these findings suggest aberrant neural processing of auditory and phonological information in dyslexia prior to the onset of reading instruction.

fMRI Activation in Response to Orthographic Processing

While the role of phonological deficit in dyslexia is widely accepted, the importance of orthographic processing is less clear. While atypical orthographic processing has been shown for school-aged children and adults with dyslexia (e.g., Temple et al., 2001), it has been suggested that these deficits are the consequence of a more limited reading experience in individuals with dyslexia (Olulade, Napoliello, & Eden, 2013). Two studies to date, both defining risk based on behavioral measures (not family history), have investigated whether atypical processing of letter-form representations is associated with dyslexia risk and can be observed as early as kindergarten/early elementary school. In one study, at-risk kindergarten children demonstrated reduced activation for letters (Yamada, 2011). In another study in Norwegian 6-year-old children, the at-risk group demonstrated reduced activation to sight words (words that are recognized automatically without decoding) in the occipitotemporal regions important for reading (Specht et al., 2009). These findings suggest that distinct patterns of neural activation in response to print in children at risk for dyslexia can be observed as early as kindergarten/early elementary school. However, since both studies examined behavioral rather than genetic risk for dyslexia, differences in processing orthographic stimuli may be related to environmental rather than hereditary influences (such as limited print exposure).

Can MRI Measures Enhance the Prediction of Reading Outcomes?

While the previous section described studies that aimed to identify brain precursors of dyslexia, this section will summarize the studies that have utilized MRI data in young children to predict reading outcome. Although there are multiple studies that utilize electroencephalography in infants and young children to predict later reading outcome (e.g., Guttorm, Leppänen, Hämäläinen, Eklund, & Lyytinen, 2010; Molfese, 2000; van der Leij, 2013), the number of MRI prediction studies in young children in preschool or kindergarten is still very limited. One longitudinal study by Fumiko Hoeft investigated the degree to which white-matter development predicts reading outcomes (Myers et al., 2014). Behavioral and DTI data were collected on English-speaking children in kindergarten and third grade. Reading in third grade was associated with developmental increases in white matter volume in 2 left temporoparietal regions. Specifically, white matter volume in the left arcuate fasciculus and another tract accounted for a unique 21.6% of variance in third-grade reading, even when controlling for environmental factors and preliteracy performance. Together, the behavioral and brain measures accounted for 59% of variance in third-grade reading outcomes.

A Swiss fMRI study demonstrated that activation in response to words in the visual word-form region (occipitotemporal region) in kindergarteners explained 17% of unique variance, above behavioral measures, in second-grade reading performance (Bach, Richardson, Brandeis, Martin, & Brem, 2013). All measures combined explained 84% of variance. These findings offer further evidence for the importance of print selectivity in the occipitotemporal region for reading development even prior to formal reading instructions. Thus, a small number of studies to date demonstrated that MRI measures can enhance the accuracy of reading outcome prediction in young prereading children.

Are We There Yet? An Evaluation of Evidence

MRI studies in prereading children and beginning readers have provided evidence for the presence of brain alterations early in development and prior to formal reading instruction. These alterations are similar to those observed in older children with a diagnosis of dyslexia and may reflect the differential developmental trajectory of reading brain networks as the result of genetic predisposition for dyslexia. However, more evidence is needed in order to determine whether these early brain alterations are only present in subsequent poor readers or can also be observed in children with a familial risk who develop into good readers. The latter would suggest that brain markers are not reliable indicators of reading outcomes, but rather an endotype and therefore relatively unspecific and irrelevant for the development of reading.

Nevertheless, these alterations may serve as early biomarkers of risk for dyslexia one day, but their sensitivity and specificity are still unclear. It is important to note that to date it is not possible to reliably identify brain alterations characteristic for dyslexia in a single subject and it is unclear whether this will be possible in the near future (or ever). Thus, we are still far away from a brain-based diagnostic tool (if we will ever have one) and the limited number of studies, small sample sizes, differences in criteria for defining dyslexia, heterogeneity of symptoms reported for dyslexia, and differences across orthographies are some obstacles that we still need to overcome. Furthermore, while neural measures enhance the overall prediction accuracy of behavioral measures, their additional contribution is moderate and may not warrant the high costs and logistical problems associated with using MRI with young children (yet).

Nevertheless, we need to invest our resources in the improvement of early identification tools. Identifying the neurobiology and the underlying mechanisms of dyslexia, as well as establishing reliable behavioral and/or brain markers of dyslexia, is important for the early identification of children at risk. This, in turn, would allow for targeted intervention early in schooling (or even before, prior to years of reading failure), and ultimately resolve the dyslexia paradox. Preventing the spiraling effects of the waiting-to-fail approach has tremendous implications for children and their families, as well as society at large.

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