CHAPTER 15

Early Atypical Brain Development in Developmental Dyslexia

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SUMMARY

Significant technological advances since the publication of the Geschwind-Galaburda Hypothesis (GGH; Geschwind & Galaburda, 1985a, b, c) have made it possible to examine brain development in the living human brain. Results across numerous studies suggest atypical early structural and functional brain development in children with a familial risk or a diagnosis of developmental dyslexia, although the sensitivity and specificity of the observed brain changes is still under investigation. Atypical brain development is seen in both hemispheres of the brain, although the strongest effects are observed in regions within the left hemisphere. In addition, research suggests that there may be a network in the right hemisphere in some at-risk children that facilitates the development of typical reading skills. Overall, research results since the mid-1980s partially support the GGH, but they show a more complex picture of how children's brains develop and its hemispheric specialization. The GGH has triggered a vast amount of work on early brain development in learning disorders and has led to a developmental neurobiological approach to studying dyslexia. This approach combines behavioral and brain research and will continue to play a crucial role in the development of effective strategies for early identification and intervention. Most important, it may help to reduce the devastating clinical, psychological, and social consequences of developmental dyslexia.

INTRODUCTION

No viable methods were available for noninvasive in vivo measuring of brain activation and brain structure with high spatial precision when Norman Geschwind and Albert Galaburda (1985a, b, c) published their seminal theory on the neurobiological mechanisms of cerebral lateralization and the role of these mechanisms in developmental disorders such as dyslexia. The advent of magnetic resonance imaging (MRI) technology allowed for safe and comprehensive investigation of typical and atypical neuroanatomy across perceptual and cognitive domains, including reading (Raschle et al. 2009; Raschle et al., 2012). Extensive discoveries have been made on the neurobiological basis of developmental dyslexia since the mid-1990s (Gabrieli, 2009; Norton, Beach, & Gabrieli, 2015), and Geschwind and Galaburda's original reports from postmortem studies of individuals with dyslexia were

affirmed: Differences in brain anatomy can be observed in individuals with developmental dyslexia across the developmental timeline.

The vast majority of these studies, however, were conducted in school-age children and adults diagnosed with developmental dyslexia. The limitation of this approach was alluded to in the GGH: "Although genetic factors are important, we will lay stress on several factors that, in the course of development, both prenatal and postnatal, modify the direction and extent of these structural differences" (Geschwind & Galaburda, 1985a, p. 428). The main limitation of neuroimaging studies in children who had already been instructed in reading (e.g., second graders and older) is that they represented both the innate neurobiological deficits in the brains of readers with dyslexia and the consequences of environmentally driven neuroplasticity (i.e., the conflated effects of struggling to learn to read) (Goswami, 2015). Several etiological mechanisms (e.g., genetics, neurobiology, perceptual and cognitive deficits, and environment) can contribute to reading failure (Ozernov-Palchik, Yu, Wang, & Gaab, 2016). Examining the contributing factors across all stages of the developmental trajectory of learning to read, from birth to adulthood, is important to understanding the etiology of developmental dyslexia.

This chapter briefly reviews the neurobiological factors of developmental dyslexia and summarizes research findings from MRI studies of pre-reading children at risk for dyslexia. The studies are connected with two GGH predictions—atypical brain development and atypical lateralization in developmental dyslexia.

STRUCTURAL AND FUNCTIONAL BRAIN ATYPICALITIES IN DYSLEXIA

Developmental dyslexia has been associated with atypicalities in brain regions important for reading. MRI studies in children and adults with developmental dyslexia commonly demonstrate reduced gray matter volume and cortical thickness, as well as hypoactivation in bilateral temporoparietal and inferior frontal and left occipito-temporal networks (Ozernov-Palchik et al., 2016). Furthermore, atypical functional and structural connectivity among these regions has been demonstrated (e.g., Boets et al., 2013; Horwitz, Rumsey, & Donohue, 1998; Morken, Helland, Hugdahl, & Specht, 2017; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010; Stanberry et al., 2006; van der Mark et al., 2011). Brains of individuals with developmental dyslexia have further been characterized by reduced asymmetry in posterior brain regions important for language processing, such as the planum temporale or other areas surrounding the sylvian fissure (e.g., Altarelli et al., 2014; Galaburda, Menard, & Rosen, 1994).

Brain Atypicalities in Preschoolers at Risk for Dyslexia

A key question in research on the neural basis of dyslexia concerns which brain characteristics of developmental dyslexia may be related to the cause

of the reading difficulty versus the result of reduced reading experience due to struggles in learning to read. In order to investigate this question, we conducted a series of longitudinal and cross-sectional studies in children who are prereaders and infants with hereditary risk for developmental dyslexia. Studies estimate a 50% risk for developing dyslexia in children with a first-degree relative with the disorder (Ziegler et al., 2005); therefore, this group provides a unique opportunity to examine early, genetically and prenatally determined atypicalities in brain development, as well as disentangle brain characteristics in developmental dyslexia that are postnatally determined.

Structure and Function

We demonstrated hypoactivation in bilateral occipito-temporal and left temporo-parietal regions during phonological processing in an investigation of children who are prereaders with a family history for developmental dyslexia (FHD+) and without (FHD–) (Raschle, Stering, Meissner, & Gaab, 2013; Raschle, Zuk, & Gaab, 2012). In addition, reduced gray matter volume indices in bilateral occipito-temporal and temporo-parietal regions were observed in FHD+ compared to FHD– preschoolers, and gray matter indices in these left-hemispheric regions were positively correlated with prereading skills (Raschle, Chang, & Gaab, 2011). We also observed significantly decreased similarity (compared to typical developing children) in the sulcal basin area in left temporo-parietal and occipito-temporal regions in children with developmental dyslexia as well as younger FHD+ preschoolers (Im, Raschle, Smith, Grant, & Gaab, 2015). The degree of similarity of sulcal patterns correlated positively with reading performance, supporting the idea of atypical early brain development in developmental dyslexia starting in utero because sulcal pattern is primarily determined prenatally (Chi, Dooling, & Gilles, 1977; Kostovic & Vasung, 2009).

Structural Connectivity

We demonstrated atypical development of white matter pathways, specifically of the arcuate fasciculus (AF) and the inferior and superior longitudinal fasciculi (ILF and SLF, respectively), from the prereading to the fluent reading stage in FHD+ compared to FHD– children (Wang et al., 2017). An automated fiber quantification (AFQ) method (Yeatman, Dougherty, Myall, Wandell, & Feldman, 2012) was employed in this DTI study to quantify the fractional anisotropy (FA) of multiple nodes along the three tracts of interest important for reading. The FA development rate of the left AF significantly differed between children who subsequently developed into good or poor readers, and was positively correlated with gains in reading performance. The rate of FA development in the SLF together with familial risk and prereading performance further predicted reading fluency subsequently once the children entered elementary school.

In addition, hemisphere lateralization of the three tracts was examined. FHD+ children showed right lateralization in AF at the prereading and the beginning reading stages, whereas FHD− children showed left lateralization in AF, with the group differences being most prominent at the prereading stage. This result supports previous studies that showed reduced leftward asymmetry in posterior white matter regions and the AF in children with reading deficits (Niogi & McCandliss, 2006; Vandermosten et al., 2015). We conducted another study (Project READ) of prereaders in collaboration with researchers at the Massachusetts Institute of Technology and demonstrated that children who had lower phonological awareness scores had significantly reduced volume and fractional anisotropy of the left AF but not in other tracts (Saygin et al., 2013). These findings indicate atypical white matter development associated with hereditary and behavioral risk for dyslexia. It further supports reduced left lateralization in white matter tracts important for reading development in individuals with dyslexia.

Studies from other laboratories have corroborated our findings of atypical white matter development in developmental dyslexia using various methods (Black et al., 2012; Clark et al., 2014; Myers et al., 2014; van Herten et al., 2008; Vandermosten et al., 2015). For example, in one study in Dutch speakers, FHD+ kindergartners demonstrated significantly reduced FA in the left inferior fronto-occipital fasciculus (IFOF), and increased FA in IFOF bilaterally was associated with phonological awareness (Vandermosten et al., 2015).

Summary of Findings in Preschoolers

Taken together, these results suggest that some of the structural and functional brain characteristics observed in children with developmental dyslexia predate the onset of formal reading instruction, indicating that developmental dyslexia may originate from genetically driven altered organization of primarily left-hemispheric cortical areas, but also to the right-hemispheric, temporo-parietal and occipito-temporal regions. These genetic risks interact reciprocally with a multitude of postnatal factors involved in the development of the reading circuitry, causing the neurobiological and behavioral outcomes observed in developmental dyslexia (see Ozernov-Palchik et al., 2016; van Bergen, van der Leij, & de Jong, 2014). More important, these alterations in preschool children can significantly enhance the prediction of later reading outcomes (Bach, Richardson, Brandeis, Martin, & Brem, 2013; Puolakanaho et al., 2007) or even outperform behavioral variables (Maurer et al., 2009).

BRAIN ATYPICALITIES IN INFANTS AT RISK FOR DYSLEXIA

Because most of the earliest MRI studies were conducted in preschoolers, it remains unclear whether the early brain differences in developmental

dyslexia are present at birth or develop in conjunction with the key stages of language development. Longitudinal MRI studies beginning in infancy are needed to better understand the emergence of the developmental dyslexia phenotype and the specific brain subsystems involved. Strong evidence for the prenatal origin of some brain atypicalities in developmental dyslexia has been provided by several studies showing atypical neural responses in FHD+ infants within a few days of birth. For instance, alterations in neural responses to speech sounds have been observed using event-related potentials in FHD+ infants (e.g., Lyytinen et al., 2004; Molfese, 2000; van Herten et al., 2008). More important, these alterations differentiated infants subsequently diagnosed with developmental dyslexia from those who developed typical reading skills (e.g., Molfese, 2000). We have shown that the previously observed white matter alterations in the left AF in children at risk for developmental dyslexia (Wang et al., 2016) can be detected in FHD+ at 5–17 months of age (Langer et al., 2015). The DTI data were collected using the natural sleep paradigm developed in our lab (Raschle, Zuk, Ortiz-Mantilla et al., 2012), and infants' language skills were assessed in infancy and at age 4. An AFQ analysis revealed significantly lower FA in the central portion of the left AF for FHD+ compared with FHD– infants. FA in the left AF correlated with expressive language skills and vocabulary at age 4 in a subsequent preliminary analysis (Figuccio, Wang, Liederman, & Gaab, 2016). It is important to note, however, that it remains to be determined which of these infants will subsequently develop developmental dyslexia.

BRAIN ATYPICALITIES IN THE RIGHT HEMISPHERE: MECHANISMS OF COMPENSATION?

Genetic predisposition for dyslexia is not deterministic, and about 50% of children with familial risk for reading problems will develop average or above average reading skills (Snowling, Muter, & Carroll, 2007), but the protective factors and compensatory mechanisms at play are largely unknown (Pammer, 2014). Neuroimaging studies suggest an increased recruitment of right-hemispheric regions in compensated individuals with dyslexia and in response to interventions (e.g., Barquero, Davis, & Cutting, 2014; Chiarello, Lombardino, Kacinik, Otto, & Leonard, 2006). In a DTI study of prereaders from our lab (Wang et al., 2017), FHD+ children who subsequently developed typical reading skills showed a significantly higher rate of FA development in the temporo-parietal segments of the right SLF compared with those FHD+ children who subsequently developed into poor readers, suggesting the emergence of an alternate network for reading in these children. In another study of middle- and high-schoolers, adolescents with dyslexia showed significant correlations between reading improvement within a 2.5 year period and functional activation in right-hemispheric frontal regions as well as FA in the right SLF. Moreover, the activation pattern in the right frontal areas predicted with

92% accuracy which individual children improved their reading scores over a 2½-year time period (Hoeft et al., 2011).

It is not yet clear from these studies whether recruitment of a right-hemispheric network emerges in response to environment and intervention in some children or whether innate characteristics of this network predispose certain children to respond well to environmental enrichment and explicit instruction, which may facilitate the development of a right-hemispheric reading network. Indeed, a study from our lab showed that activation during a phonological task in anterior right-hemispheric structures exhibited a significantly stronger correlation with home literacy variables in FHD+ compared with FHD– children (Powers, Wang, Beach, Sideridis, & Gaab, 2016), which may suggest emerging right-hemispheric networks in children who are genetically at risk in response to certain environmental inputs that act as protective factors. Future studies are needed to determine whether these alterations are present at birth or emerge over time.

INTEGRATING RESULTS FROM HUMAN NEUROIMAGING INTO THE GESCHWIND-GALABURDA HYPOTHESIS: A FIRST ATTEMPT AND NEXT STEPS

The GGH (Geschwind & Galaburda, 1985a, b, c) has been an influential theoretical framework aimed at integrating clinical observations on handedness, learning variants, immune disorders, and male–female differences into a unified neurobiological framework (see Chapter 1). The GGH postulated that developmental dyslexia is a product of atypical neuronal migration and impeded development of the left hemisphere due to genetic risk factors and the prenatal (in utero) environment. The GGH was based on postmortem findings that suggest brain atypicalities in posterior left hemispheric perisylvian regions in individuals with developmental dyslexia (Galaburda, Sherman, & Rosen, 1985) as well as observations of increased prevalence of learning disabilities in left-handed individuals (Geschwind & Behan, 1982). This chapter provided comprehensive evidence that some brain alterations characteristic for developmental dyslexia can be observed as early as infancy and preschool and specifically in children at hereditary risk for developmental dyslexia (which underlines the need to examine the specificity of these characteristics). This evidence supports the pathway between gene alterations and the range of sensorimotor, perceptual, and cognitive characteristics reported for developmental dyslexia proposed by Galaburda and colleagues (Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006). Specifically, variant function of genes linked to developmental dyslexia affects cortical development by disrupting in utero neuronal migration, axonal growth, and/or synaptic transmission, resulting in atypical cortico-cortical and cortico-thalamic circuits.

The GGH also proposed that in utero changes in testosterone impede left lateralization in developmental dyslexia, resulting in reduced

left-hemispheric asymmetry in the perisylvian regions supporting language development. Interestingly, the findings reviewed here suggest fundamental differences in the development of brain regions supporting reading in individuals with dyslexia, which are primarily observed in the left-hemispheric regions but certainly span both hemispheres. One could hypothesize that variant functions in dyslexia susceptibility genes, alternative genes (Hu, Chahrour, & Walsh, 2014), or atypical hormone levels, as suggested by the GGH, trigger the development of these reduced asymmetries, which, in interaction with the environment, could benefit the development of compensatory mechanisms in children at familial risk. More specifically, due to genetic influences, some children with a familial risk may be less lateralized, enabling them to recruit right-hemispheric networks for specific task demands more easily through increased interhemispheric exchange. This is in line with studies showing increased integrity of the posterior corpus callosum (splenium) in individuals with dyslexia (Frye et al., 2008; Hasan et al., 2012; Odegard, Farris, Ring, McColl, & Black, 2009), which may promote increased interhemispheric transfer and the development of alternative (compensatory) networks.

CONCLUSION

Current results suggest early atypical brain development in children with developmental dyslexia, although the sensitivity and specificity of specific brain alterations need to be determined. It has been further demonstrated that early brain atypicalities in developmental dyslexia are bilaterally distributed but exhibit stronger effects in left-hemispheric structures, and there may be a right-hemispheric compensatory network in some children with a familial risk who subsequently develop into good readers. These findings highlight the significance and potential of a developmental focus starting in early infancy to address the etiology and developmental trajectories of developmental dyslexia. A developmental, neurobiological perspective needs to play a crucial role in developing effective early identification strategies and reducing the clinical, psychological, and social consequences of reading failure. Such a perspective could also inform the development of early interventions prior to important brain network pruning and myelination stages. Understanding the complex etiology of developmental dyslexia will be essential to inform and improve the training of teachers, school psychologists, and other clinicians to reliably recognize and optimize the learning contexts for individual learners; this ultimately could lead to personalized education similar to the model of personalized medicine (Butterworth & Kovas, 2013).

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