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Research report

No evidence for systematic white matter correlates of dyslexia: An Activation Likelihood Estimation meta-analysis

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ABSTRACT

Dyslexia is a prevalent neurodevelopmental disorder, characterized by reading and spelling difficulties. Beyond the behavioral and functional correlates of this condition, a growing number of studies have explored structural differences between individuals with dyslexia and typically developing individuals. To date, findings remain disparate – some studies suggest differences in fractional anisotropy (FA), an indirect measure of white matter integrity, whereas others do not identify significant disparities. Here, we synthesized the existing literature on this topic by conducting a meta-analysis of Diffusion Tensor Imaging (DTI) studies investigating white matter correlates of dyslexia via voxel-based analyses (VBA) of FA. Our results showed no reliable clusters underlying differences between dyslexics and typical individuals, after correcting for multiple comparisons (false discovery rate correction). Because group comparisons might be too coarse to yield subtle differences, we further explored differences in FA as a function of reading ability, measured on a continuous scale. Consistent with our initial findings, reading ability was not associated with reliable differences in white matter integrity. These findings nuance the current view of profound, structural differences underlying reading ability and its associated disorders, and suggest that their neural correlates might be more subtle than previously thought.

1. Introduction

Developmental dyslexia is a specific type of learning disability characterized by distinct reading and spelling difficulties. The disorder is typically diagnosed in childhood, affecting around 5–7% of school aged children, and can persist into adulthood (Lindgren et al., 1985; Lyon et al., 2003; Sally E. Shaywitz et al., 2008). With heritability estimated to range between 50 and 65% (Habib and Giraud, 2013), dyslexic reading difficulties occur despite appropriate learning environment and adequate resources, and are not attributable to sensory, neurological, psychiatric, intellectual or motivational issues or deficits (Habib and Giraud, 2013; Lyon et al., 2003).

Neuroimaging studies have investigated the neurobiological underpinnings of dyslexia, yielding three key left-hemisphere networks associated with impaired reading. The posterior temporoparietal network has been mainly linked to basic, phoneme level word analysis; the posterior occipitotemporal network, including the visual word form area (VWFA), is commonly associated with word form and fluent reading (Lyon et al., 2003; Shaywitz et al., 2002; Shaywitz et al., 1998; Shaywitz et al., 2008); whereas the anterior network of the inferior frontal gyrus, including Broca's area, is involved in speech pronunciation (Shaywitz et al., 2008). Furthermore, studies by Shaywitz et al. (1998) and Shaywitz et al. (2002) reported underactivation in posterior temporoparietal and occipitotemporal regions while reading and performing phonological tasks in dyslexics, compared to typical readers. Numerous other functional imaging studies across cultures and stages of development have supported these findings (Brunswick et al., 1999; Horwitz et al., 1998; Paulesu et al., 2001; Rumsey et al., 1992; Simos et al., 2000). Shaywitz et al. (1998) and Shaywitz et al. (2002) also observed increased activation of the inferior frontal gyrus, involved in the anterior reading network, among dyslexic compared to typical readers. This hyperactivation is hypothesized to be a compensatory strategy: dyslexic readers use memorization of the structure of words—rather than phonological skills—to read, therefore overengaging frontal brain regions (Shaywitz et al., 2007; Shaywitz et al., 2003), though we should note that these findings have been debated in the literature (Hoeft et al., 2007; Norton et al., 2015; Richlan, 2014; Richlan et al., 2009).

Beyond functional differences, Diffusion Tensor Imaging (DTI) studies have demonstrated impairments in white matter cortical

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connections between regions among dyslexic readers (Vandermosten et al., 2012). DTI allows probing the distance and direction of water molecule movement, producing form and orientation information about the underlying white matter structures (Assaf and Pasternak, 2008; Soares et al., 2013). In some cortical tissues, such as gray matter and cerebrospinal fluid, diffusion is isotropic; that is, water molecules disperse approximately equally in all directions. Conversely, white matter exhibits anisotropic water movement, with water molecules showing various degrees of diffusion in each direction (Assaf and Pasternak, 2008; Emsell et al., 2015; Soares et al., 2013). In typical DTI studies, diffusion images from at least six directions are analyzed using an ellipsoid tensor model—a symmetrical 3x3 matrix. Parallel and perpendicular diffusivities are then calculated and used to estimate properties of underlying tissues. Fractional anisotropy (FA) of the tissue is used most commonly (Assaf and Pasternak, 2008; Soares et al., 2013); FA is measured from 0, isotropic diffusion, to 1, anisotropic diffusion (Assaf and Pasternak, 2008). Other properties include the mean, axial and radial diffusivities (Soares et al., 2013).

Region of interest (ROI) and voxel-based analyses (VBA) can be conducted to compare DTI properties between groups or individuals. In ROI analyses, brain regions defined by *a priori* hypotheses are manually or automatically mapped onto brain images, before the DTI properties of the ROI are averaged within a region and compared across regions. These analyses, however, can be complex, time consuming, and subject to observer and selection biases (Soares et al., 2013; Van Hecke and Emsell, 2015). In contrast, VBA use brain images normalized to a standard brain atlas and smoothed, before computing and comparing DTI properties of each individual voxel. This approach greatly reduces the typical biases of ROI analyses, although this freedom comes at a cost—as VBA is typically less theoretically driven, more drastic corrections for multiple comparisons are often required (Soares et al., 2013; Van Hecke and Emsell, 2015).

Two main avenues of research have been pursued using DTI, employing both ROI and VBA approaches. First, studies have investigated significant differences in FA between dyslexic and typical readers. Two pioneer studies, Klingberg et al. (2000) and Deutsch et al. (2005), identified significant differences in FA in the temporoparietal regions of both hemispheres among small samples of dyslexic and typical reading adults and children, respectively. Lower FA values in the left temporoparietal region among dyslexics compared to typical readers have been further corroborated in subsequent studies (Carter et al., 2009; Rimrodt et al., 2010; Steinbrink et al., 2008), yet despite this apparent convergence, the reported differences within this region vary considerably (Vandermosten et al., 2012). More problematic perhaps, Keller and Just (2009) were unable to replicate these findings in an intervention study, instead reporting lower FA in an anterior region, the left anterior centrum semiovale. Similarly, Koerte et al. (2016) found no significant differences in FA when controlling for false positives adequately. Studies have also found a variety of significant differences in other brain regions, including the superior and inferior frontal regions, precuneus, insula and occipital region in the left hemisphere, superior corona radiata, splenium of the corpus callosum and throughout the right hemisphere (Carter et al., 2009; Deutsch et al., 2005; Frye et al., 2008; Niogi and McCandliss, 2006; Rimrodt et al., 2010; Steinbrink et al., 2008). In addition, Richards et al. (2008) found 45 clusters of significant FA differences between dyslexics and typical readers across the whole brain. Taken together, these findings highlight the wide discrepancies reported in the literature.

Besides group differences contrasting dyslexics with typical readers, additional studies have identified regions where FA values significantly correlate with performance on reading tasks. Numerous studies report positive correlations between FA in the left temporoparietal area of dyslexic or typical readers and reading ability, measured by a range of reading measures (e.g., word reading, pseudo word reading or phonological reading tasks; Beaulieu et al., 2005; Deutsch et al., 2005; Klingberg et al., 2000; Lebel et al., 2013; Nagy et al., 2004; Odegard et al., 2009; Steinbrink et al., 2008). Similar to the aforementioned literature on group contrasts, however, specific locations within these regions differ considerably between studies (Vandermosten et al., 2012). For example, positive correlations between reading ability and FA have been noted in the superior corona radiata, longitudinal fasciculi, external capsule, centrum semiovale and language areas of the left hemisphere, and bilateral inferior and temporofrontal regions, illustrating the wide variability in results (Deutsch et al., 2005; Keller and Just, 2009; Niogi and McCandliss, 2006; Rimrodt et al., 2010; Steinbrink et al., 2008; Zhang et al., 2014). Finally, negative correlations between reading ability and FA in the posterior/temporal corpus callosum have also been reported (Dougherty et al., 2007; Frye et al., 2008; Odegard et al., 2009; Zhang et al., 2014).

These discrepancies highlight the need to comprehensively examine the variability in brain regions linked to dyslexia. Using Activation Likelihood Estimation (ALE), a technique that determines convergence of activation probabilities across studies (Eickhoff et al., 2009; Eickhoff et al., 2012), Vandermosten et al. (2012) performed a meta-analysis and found that a large cluster (704 mm^3) centered at -29, -17, 26 near the left temporoparietal region, across three DTI studies of correlative and difference that employed VBA. A smaller cluster near the inferior frontal gyrus, centered at -26, 26, 18 was also identified, although less reliably. However, this ALE meta-analysis only examined coordinates where significant differences between dyslexic and typical readers were identified, with particular combinations of studies that created difficulties in interpretation. The software the authors used, GingerALE, has also been updated since, including to correct problems that had a to increase the rate of false positives (Eickhoff et al., 2017). Lastly, further correlational research has been conducted since initial publication of the meta-analysis in 2012, suggesting a possible gap in the current literature, and a need to systematically summarize and quantify the relationship between developmental dyslexia and white matter connections. To address these limitations, we conducted a meta-analysis that consisted of two phases. In Phase 1, we focused on differences in FA, assessed via VBA, between dyslexic and typical readers. Phase 2 of the meta-analysis was restricted to correlations between reading ability and VBA studies of FA.

2. Results

2.1. Study selection and characteristics

All details regarding study selection are outlined in Fig. 1 (Phase 1) and Fig. 2 (Phase 2). Table 1 details the characteristics and demographics of participants included, and the findings of group differences in FA for each study (Phase 1). Table 2 reports the same information for correlations between FA and reading ability (Phase 2).

2.2. Synthesis of results

Two analyses were run in Phase 1. The analysis of 47 foci from 5 experiments (99 subjects), where FA was significantly greater in typical compared to dyslexic readers, yielded no significant clusters when using a FDR correction of 0.05. Similarly, the analysis of 17 foci from 2 experiments (52 subjects), where FA was significantly greater in dyslexic compared to typical readers, produced no significant clusters when using a FDR correction of 0.05.