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Research report

Prefrontal mediation of the reading network predicts intervention response in dyslexia

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ABSTRACT

A primary challenge facing the development of interventions for dyslexia is identifying effective predictors of intervention response. While behavioral literature has identified core cognitive characteristics of response, the distinction of reading versus executive cognitive contributions to response profiles remains unclear, due in part to the difficulty of segregating these constructs using behavioral outputs. In the current study we used functional neuroimaging to piece apart the mechanisms of how/whether executive and reading network relationships are predictive of intervention response. We found that readers who are responsive to intervention have more typical pre-intervention functional interactions between executive and reading systems compared to nonresponsive readers. These findings suggest that intervention response in dyslexia is influenced not only by domain-specific reading regions, but also by contributions from intervening domain-general networks. Our results make a significant gain in identifying predictive biomarkers of outcomes in dyslexia, and have important implications for the development of personalized clinical interventions.

1. Introduction

Dyslexia is the most prevalent learning disorder, estimated to affect 6–17% of the population (Fletcher, 2009); it is characterized by impaired word reading deficits despite intact cognition and adequate instruction (Lyon et al., 2003). Though studies have identified key interventional targets for dyslexia, current interventions are ineffectual for approximately 2–3% of readers with dyslexia (Mathes et al., 2005). These intervention limitations are due in part to inconsistent behavioral profiles of response prediction (Al Otaiba & Fuchs, 2002; Cho et al., 2015; Fletcher et al., 2011; Miciak et al., 2014, 2015; Stuebing et al., 2015). While studies have identified core reading characteristics that predict response—including phonological awareness, knowledge of the alphabetic

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principle, rapid naming of words, and demographics (Fletcher et al., 2011; Nelson, Benner, & Gonzalez, 2003)—the extent to which response is dependent on baseline executive functions is unclear. The distinction between reading versus executive contributions to prediction is critical, as the answer addresses a fundamental question on the nature of intervention response in learning disabilities: do responsive learners simply have greater baseline cognitive efficacy in domain-specific skills (e.g., reading, math, etc.), or do they have a more intact executive "scaffold" (e.g., working memory, meta-cognition, and planning ability) that provides support for domain-specific skills?

The distinction between executive versus reading contributions consequently has large implications for the development of effective interventions, and potential for identifying additional population sub-groups. Notably, developmental research appears to report paradoxical findings in regard to executive function and its role in educational gains. Broader behavioral studies on school readiness have found that executive functions are indeed critical predictors of school readiness and achievement (Blair & Razza, 2007; Diamond, 2013; St Clair-Thompson & Gathercole, 2006). However, executive function ability is generally not considered to be a good predictor of dyslexia intervention response, with domain-specific skills instead being the best predictors (Cho et al., 2015; Miciak et al., 2015; Stuebing et al., 2015). This discrepancy has partially been attributed to the fact that the extent of executive function contributions may be concealed by overlapping variance with reading-related behavioral metrics (Schatschneider, Fletcher, Francis, Carlson, & Foorman, 2004; Stuebing et al., 2015; Wagner, 1996). This explanation ties nicely into recent work in the psychiatric literature that provides a more nuanced explanation of how executive function may relate to other cognitive functions. This literature has revealed that the *interaction* between executive and other cognitive systems, rather than executive ability alone, is what engenders positive behavioral outcomes (Cole, Anticevic, Repovs, & Barch, 2011; Cole, Repov, & Anticevic, 2014). Thus, as applied to learning outcomes, neuroimaging allows for a window into executive function and reading relationships that may otherwise be obscured, particularly how executive functions may *facilitate* reading systems,[2] and, in this case, how such coordination may predict intervention response in dyslexia. Such knowledge may be critical for understanding how executive systems play a role in intervention response and academic growth more generally.

Previous work in neuroimaging that has examined baseline activation/structure in responders and nonresponders overall characterizes responders as having more intact reading systems that are more like typically developing readers (Farris et al., 2011; Rezaie et al., 2011b, 2011a), including some possible evidence to suggest that responders recruit compensatory right inferior frontal gyrus (IFG; Farris, Ring, Black, Lyon, & Odegard, 2016; Hoeft et al., 2011). However, no one has tested the hypothesis that these more typical reading network connections may be traced to greater utilization of a top-down executive scaffold. In the current study, we apply the concept that the interaction of executive systems with reading systems may also be important for academic outcomes. Specifically, we used functional magnetic resonance imaging (fMRI) to examine neurobiological network *interactions* that predict intervention response. This approach allowed us to move beyond general patterns of response prediction (as have been characterized by Farris et al., 2011; Hoeft et al., 2011; Rezaie et al., 2011a, 2011b; for review see Barquero et al., 2014), and specifically test whether responders have greater baseline utility of executive systems to facilitate activation of typical reading networks. Of particular relevance to the current study was the potential contributions of the frontoparietal control network (FPN)—a neural system known to subserve executive functions including working memory, cognitive control, and attention (Cole, Repov, & Anticevic, 2014; Ptak, 2012). Higher integrity of the FPN has been found to be predictive of better clinical outcomes in neural vulnerabilities in the neural disorder and psychiatric literature (Borstad, Choi, Schmalbrock, & Nichols-Larsen, 2016; Cole et al., 2011). The convergent implication of the FPN across highly disparate disorders has led some to suggest that a healthy FPN regulates other neural systems in a goal-directed manner in both typical and pathological states; worse clinical outcomes may consequently reflect both a primary, disease-specific neural deficit and a secondary failure of the FPN to direct the vulnerable systems (Cole et al., 2011, 2014).

The involvement of the FPN in reading and dyslexia is not unfounded. Behavioral models of word reading offer a few possibilities for when executive areas would be necessary in directing reading processes. For instance, Balota's two-part verification model of lexical decision-making suggests that a reader must engage in executive processes if the familiarity/meaningfulness of a word-form is insufficient to resolve a word-form (Balota & Chumbley, 1984), and more generally that attention processes regulate the necessarily flexible pathways that support lexical access across varying task demands (Balota & Chumbley, 1999). Recent neuroimaging work (not in the context of intervention) has connected subcomponents of these word-reading attentional control processes to areas in the FPN (Ihnen, Petersen, & Schlaggar, 2015), and additional studies have pointed to FPN differences as a marker of dyslexia (Finn et al., 2013; Koyama et al., 2013; Norton et al., 2014). These latter studies include findings of internal connectivity reductions within the FPN in dyslexia (Finn et al., 2013; Koyama et al., 2013), as well as aberrance of specific structures within the FPN. In particular, the left dorsolateral prefrontal cortex (dlPFC)—a structure associated with working memory and the top-down planning/organization of information (Reynolds, O'Reilly, Cohen, & Braver, 2012)—appears to be linked to reading ability. Although not highlighted in their findings, in a seminal study Shaywitz et al. (1998) found overactivation of dlPFC in readers with dyslexia. Others, however, have found that children with dyslexia have different patterns of anomalies in the dlPFC, including hypoactivation compared to reading-matched controls during a phonological decision task

[2] Heretofore we use "reading systems" or "reading networks" to refer to brain areas that are known to contribute to, but may not be specific to, reading, including the putative visual word form area, and areas in the canonical left-lateralized language network such as inferior frontal and middle temporal gyri (see Methods for specific information).

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