Predicting Responsiveness to Reading Intervention with fMRI

By

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To children who struggle with reading.

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CHAPTER I

INTRODUCTION

Children who are at-risk for reading difficulties (RD) lag behind their peers in academic achievement and this achievement gap may grow over time (Morgan, Farkas, & Hibel, 2008; Stanovich, 1986), resulting in a lifelong condition that negatively impacts academic achievement, employment opportunities, and social interaction. Consequently, remediating reading difficulties is a paramount goal of education, requiring research that disentangles the causes and symptoms of reading difficulties and develops effective treatment.

RD can involve difficulties with reading at the word level or language processing level. Some children have specific comprehension difficulties (e.g., Cain & Oakhill, 2006; Hulme & Snowling, 2011), while children with word level difficulties (decoding and/or word recognition) may have comprehension difficulties largely as a result of word-level deficits (e.g., Garcia & Cain, 2013; Gough & Tunmer, 1986). In the general population, estimates of reading difficulty in children at the word level (often referred to or thought of as synonymous with dyslexia) range from 6 to 17% (Fletcher, 2009) and these children typically have a phonological processing deficit (S. E. Shaywitz & Shaywitz, 2005; Torgesen et al., 1999). Children with word-level difficulties tend to be identified during the early elementary years (Nation & Snowling, 1997; Shankweiler et al., 1999), though some do not experience difficulties until late elementary or middle school years (Catts, Compton, Tomblin, & Bridges, 2012; Compton, Fuchs, Fuchs, Elleman, & Gilbert, 2008; Leach, Scarborough, & Rescorla, 2003; Lipka, Lesaux, & Siegel, 2006). To minimize the reading deficits that may otherwise impede their progress, children with RD need evidence-based reading intervention.

Responsiveness to Reading Intervention

Behavioral interventions have been found effective in remediating reading difficulties in some, but not all, individuals with RD (Al Otaiba & Fuchs, 2002; Compton et al., 2012; Foorman, Francis, Fletcher, Schatschneider, & Mehta, 1998; Torgesen, 2000; Torgesen et al., 1999; Vaughn et al., 2009; Vellutino et al., 1996). Interventions that are effective for most children involve explicit instruction and address the reading components of phonological awareness, phonics, fluency, vocabulary, and comprehension (Bus & van IJzendoorn, 1999; National Reading Panel, 2000; Swanson, 1999; Vaughn, Gersten, & Chard, 2000). One-on-one explicit, intensive intervention that emphasizes phonemic awareness and decoding skills has been show to enhance word level reading (Torgesen et al., 1999). Interestingly, even short-term intensive intervention can lead to gains in reading. For example, one study (McGuiness, McGuiness, & McGuiness, 1996) showed increased reading scores after only 12 hours of 1:1 reading instruction. Another study (Truch, 2003), compared two reading programs in which participants received up to 80 hours of instruction, and though gains continued throughout intervention, the largest gains occurred in the initial 12 hr of instruction.

Determining which children will and will not readily respond to intervention could inform resource allocation such that children who are not likely to respond well could receive more intensive or individually targeted instruction sooner. A review by Al Otaiba and Fuchs (2002) determined that the majority of children who exhibit low responsiveness to intervention have a phonological awareness deficit, and other deficiencies may include problems with phonological retrieval or encoding, verbal ability, behavior, and developmental delays. These findings are generally supported by meta-analyses showing that individual responsiveness to intervention can be influenced by problem behaviors, phonological awareness, alphabetic principle, memory, and IQ (Nelson, Benner, & Gonzalez, 2003), and that pre-intervention differences in real word identification, word attack, and reading comprehension are predictive of gains following intervention (Tran, Sanchez, Arellano, & Swanson, 2011). More recent studies have provided further evidence for identifying intervention responders. These include a study that found inadequate responders in Response to Intervention (RTI) Tier 3 (intensive instruction) showed impairment on language measures, particularly phonological awareness (Denton et al., 2013). Another study found that when categorizing nonresponders on decoding and fluency criteria, and comparing with responders and typically achieving students phonological awareness was the strongest contributor to group differentiation, with rapid letter naming, syntactic comprehension/working memory, and vocabulary also contributing (Fletcher et al., 2011). A study which used profile analysis to compare responders and nonresponders in word-level reading skills (word identification, word attack, sight word fluency, phonemic decoding fluency) as well as cognitive skills (rapid naming, sound matching, listening comprehension, vocabulary, matrix reasoning, attention) found elevation effects for responders across pre-intervention profiles (Toste et al., 2014). Despite these results suggesting differences in behavioral profiles for responders and nonresponders, a recent meta-analysis of studies that used baseline learner characteristics such as oral language, phonological awareness, rapid naming, spelling/orthographic processing, and working memory to predict growth over intervention yielded small effect sizes in predicting growth curve slope or gain, suggesting that extensive testing beyond baseline reading assessments adds little to predictive ability (Stuebing et al., 2014). Though most investigations have studied the early grades (K-2), a few studies have examined intervention responsiveness in middle and high school. Interestingly, a study of adolescent inadequate responders found that patterns of strengths and weaknesses do not serve as good markers of responsiveness (Miciak, Fletcher, Stuebing, Vaughn, & Tolar, 2014). In summary, though there appears to be some applicability of using behavioral measures to predict responsiveness to intervention, a clear profile of that predicts responsiveness has not been found based upon behavioral measures.

Perhaps some of the difficulty in predicting responders and non-responders to intervention lies in the complexity of the problem. Scores on behavioral assessments may be the result of the interplay of underlying factors, such that two individuals could have the similar behavioral scores for differing reasons. This complexity includes biological factors that influence cognitive factors which in turn influence behavior, all three of which are impacted by an individual’s environment (Frith, 2001). This means that an individual’s neurophysiology (underlain by genotype and gene expression) affects the individual’s cognitive skills and receptivity to instruction. Yet, influences on behavior extend beyond biology and cognition, as environment can have an impact at multiple levels. Instruction, as part of the individual’s environment, can vary in emphasis, quality, and dosage and is only one of numerous environmental factors (e.g., nutrition, home life, stress) that could have downstream impacts on responsiveness to intervention. All of these components interact to yield behavioral scores that may represent the level of performance at a given time, but may not provide a complete profile for predicting responsiveness to intervention. So, understanding the behavioral profile of differential intervention response is necessary and useful, but further characterization of the underlying causes requires the exploration of neurobiology.

Reading Difficulties and Neurobiology

Though extensive literature has characterized the behavioral aspects associated with RD, the underlying cognitive causes of RD are not fully elucidated and are currently under investigation. RD in the general population appears to be part of a normally distributed continuum of reading ability (Fletcher & Lyon, 2008; Vellutino, Fletcher, Snowling, & Scanlon, 2004). Growing evidence indicates that the behavioral symptoms of RD are associated with anomalous underlying neurobiology which may be distributed along a continuum as well or perhaps diverges from that of typical readers in different ways according to the type of reading deficit as some structural evidence suggests (Leonard & Eckert, 2008). This underlying neurobiology is likely influenced by multiple factors—genetics (Miller & McCardle, 2011), training/instruction (Brem et al., 2010; Chein & Schneider, 2005), nutrition (Gomez-Pinilla, 2008), epigenetics (Day & Sweatt, 2011; Sweatt, 2009) and possibly other factors beyond those mentioned (Vaynman & Gomez-Pinilla, 2006). The interplay of these factors creates variability in RD and adds complexity to diagnosis and treatment. Understanding the learning process at the neurobiological level and how this process may differ for individuals with RD may therefore improve outcomes in the future for those with RD. Of particular importance is neural plasticity related to RD.

The capacity to develop neural pathways and adapt to cognitive demands is the essence of neural plasticity. Changes in electrical impulses, chemical signaling, and neuronal growth underlie the behavioral aspects of learning. Describing the candidate mechanisms of neuroplasticity in detail is beyond the scope of this paper but to illustrate the complexity of processes involved in neuroplasticity we describe some of what is known and refer the reader to several excellent review papers. At the synaptic level, long-term potentiation (LTP) of the postsynaptic neuron in response to repeated presynaptic stimuli is widely believed to be a primary mechanism of long-term memory and learning (Lynch, 2004). LTP can lead to synaptic modifications that result in enhanced signal transmission (Cooke & Bliss, 2006). Though short-term synaptic modification does not require protein synthesis, long-term synaptic changes seem to require protein synthesis and these long-term changes are considered to be the cellular correlates of learning and memory (Kandel, 2001). Beyond enhancement of synaptic connections through LTP, gray matter structural mechanisms of neuroplasticity include neurogenesis, axon sprouting, dendritic branching (and synaptogenesis), gliogenesis and glial modifications, and angiogenesis (Zatorre, Fields, & Johansen-Berg, 2012). As numerous gene products are believed to be involved in learning and memory and protein synthesis appears to be required for long-term memory storage, regulation of gene expression is likely to be important in learning processes. Epigenetic mechanisms include histone modification (Day & Sweatt, 2011) and post-transcriptional regulation of gene expression by microRNAs (Bredy, Lin, Wei, Baker-Andresen, & Mattick, 2011). Clearly, learning and memory are complex events at the cellular and molecular levels. Yet, what does this mean for children with learning disabilities? Perhaps these processes differ for individuals with RD compared to typically achieving peers. An inefficiency in one mechanism of the intricate processes involved in storing and retrieving information could adversely affect learning. Such neurobiological differences could explain why some children absorb new knowledge effortlessly while others not only struggle to grasp new concepts, but may also have great difficulty in retaining and consolidating information.

If a characterizable neurobiological anomaly underlies poor response to instruction, identifying these individuals and developing an appropriate intervention could possibly compensate for the deficiency. To illustrate, a critical molecular process related to long-term memory is the effect that CREB (cAMP response element binding protein) has on genetic transcription. CREB is stimulus-inducible in neurons and involved in long-term memory by influencing protein synthesis (Lonze & Ginty, 2002). In a mouse study, long term memory was adversely affected by CREB gene disruption, yet, interestingly, the learning deficit was overcome by increasing the time between the training events (Kogan et al., 1996). That is, modifying the behavioral training compensated for a molecular deficiency. Perhaps identifying underlying dysfunction in functional activity can lead to a specific intervention. Of course, the challenge lies in understanding these differences and perhaps addressing them in a more prescriptive manner that may be tailored based on behavioral and neurobiological measures. Whatever the deficiencies may be, characterizing those deficiencies through investigative techniques is a step in the process toward targeted remediation.

Neuroimaging is a tool that can be used to explore brain activity and can make a valuable contribution to understanding plasticity and learning. Brain activity not only indirectly reflects the underlying tissue structure and physiology (as neurons must be present and functioning to exhibit activity), but also represents which areas of the brain are actively engaged when presented with stimuli of interest. Numerous studies have used imaging techniques to explore brain activity associated with specific cognitive tasks. A growing number of studies are exploring various aspects of reading to determine how the brain accomplishes the complex task of reading. Further investigations are concerned with how the brain differs in functional activity between skilled readers and readers who struggle. Thus far, relatively few studies have explored neurobiology and reading intervention, and the need to gain additional knowledge in this area provided the impetus for the current study.

The primary intent of this study was to examine the relation between functional activity in the brain prior to reading intervention and behavioral responsiveness to the intervention. The study explored the use of pre-intervention fMRI scans in predicting how well children with reading difficulties (RD) responded to a short-term reading intervention based on word-level reading measures. Exploring this relationship may provide insight into what type of pre-intervention functional profile may respond well to intensive, short-term, phonics-based interventions.

The following chapter is a review of the literature relevant to the study. First, an overview of the brain regions believed to be involved in reading is provided. Second, the methods of conducting the systematic review of neuroimaging and reading intervention are provided, including inclusion criteria and the article search procedures. Third, we report the results of the literature review and discuss the findings. Finally, we summarize the review and describe how it is related to the current study. This literature review has been published separately from the current study and its findings (Barquero, Davis, & Cutting, 2014).

CHAPTER II

LITERATURE REVIEW

Brain Regions Involved in Reading

Studies with unimpaired adult readers have revealed a left hemisphere reading network comprised of three areas: a ventral posterior region, a dorsal posterior region, and an anterior region (Pugh et al., 2000, 2001; Schlaggar & McCandliss, 2007; S. E. Shaywitz & Shaywitz, 2008). The posterior ventral region is located in an inferior occipito-temporal area. This area appears to be involved in visual processing and recognition of words (Cohen, Dehaene, Chochon, Lehericy, & Naccache, 2000; Dehaene & Cohen, 2011; McCandliss, Cohen, & Dehaene, 2003; Price, 2012; Pugh et al., 2000) as even letters and pseudoletters elicit a response in this region (Levy et al., 2008). The posterior dorsal region is comprised of the posterior superior temporal gyrus (pSTG), supramarginal gyrus (SMG), and angular gyrus (AG) and appears to be involved in phonological processing, transforming orthographic representations to phonological representations, and semantic processing (Price, 2012; Pugh et al., 2000; S. E. Shaywitz et al., 1998; Temple, 2002). The anterior region is located in and around the inferior frontal gyrus (IFG). The IFG appears to be involved in phonological processing (Levy et al., 2008) and may be involved in articulatory recoding such that phonological input is converted to speech-gesture articulation output (Pugh et al., 2000, 2001) and semantic processing (Price, 2012). The studies establishing these regions have largely focused on single word reading. However, studies exploring reading comprehension have found left SMG and AG (Constable et al., 2004) and bilateral middle and superior temporal gyri (Cutting et al., 2006) to be activated by typical readers during comprehension tasks.

While imaging studies of reading in children indicate a large amount of overlap with adults in activation, there are some differences. Some evidence indicates that over the course of development, activation in some more dispersed areas attenuates with age while increases with age are more focal, and these changes are largely independent of performance (Brown et al., 2005; Schlaggar & Church, 2009). For example, adults show less activation of left supramarginal and angular gyri, areas involved in phonological processing (Church, Coalson, Lugar, Petersen, & Schlaggar, 2008). This suggests that children are more actively engaged in using phonology to analyze words as they read, whereas adults have developed such automaticity in word reading that increased use of these phonological processing areas is no longer required. In contrast, adults showed increased activity in frontal and parietal regions thought to be involved in attention and top-down cognitive control (Brown et al., 2005; Schlaggar & Church, 2009). It is important to consider developmental changes in functional activity when reflecting on whether reading difficulties are more related to a delay in development or to dysfunctional reading networks that encourage development of compensatory mechanisms. Another recent finding in functional developmental changes is that sensitivity to visually presented words (i.e. activation response to detecting a word among progressively decreasing visual noise) increases over the school-age years in the left posterior occipito-temporal sulcus (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011). This may imply a more refined usage of an area used in visual word reading.

Over the past two decades, numerous studies have reported differences in brain function during reading tasks for people with reading problems relative to controls with typical reading achievement and several narrative reviews have highlighted the commonalities among studies

(Démonet, Taylor, & Chaix, 2004; McCandliss & Noble, 2003; Pugh et al., 2000; Sandak, Mencl, Frost, & Pugh, 2004; Schlaggar & McCandliss, 2007; B. A. Shaywitz et al., 2004; S. E. Shaywitz & Shaywitz, 2005). The functional differences between RD and typical readers are generally characterized by reduced activity in left hemisphere regions for RD. Reviews of the literature have indicated that RD involves a dysfunction of the aforementioned three-region reading network: general underactivation of L temporo-parietal region (including superior temporal gyrus) and ventral occipito-temporal (including lateral extrastriate, fusiform, and inferior temporal gyrus) and overactivation of the L inferior frontal gyrus (IFG). This overactivation of the L IFG has been presumed to be due to compensatory articulatory effort and evidence that contradicts this portion of the accepted model has recently emerged (Richlan, 2012). Though less consistent than reduced left hemisphere activation, some studies have also reported increased right hemisphere activation that may signify compensatory activity for people with RD during reading tasks (Eden et al., 2004; Rimrodt et al., 2009; Sarkari et al., 2002; S. E. Shaywitz et al., 1998; Simos, Fletcher, Sarkari, Billingsley, et al., 2007a) and this compensatory activity may develop as early as second grade (Bach et al., 2010). Adding further complexity, there is evidence that, at times, typical readers exhibit less brain activation in reading areas than do readers with RD. Rimrodt et al (Rimrodt et al., 2009) found that adolescents with RD activated more than typical readers in the left middle and superior temporal gyri when reading incongruent sentences, perhaps suggesting more effortful processing of nonmeaningful sentences. Pugh et al (Pugh et al., 2008a) found through manipulating stimuli that for non-impaired adolescent readers, factors that make the word easier to process were associated with relatively reduced activation. However, for readers with RD facilitative factors were associated with increased activation in the same areas, “suggesting that the LH reading circuitry in adolescent RD is poorly trained but not wholly disrupted" (Pugh et al., 2008a). Less activation may at times be reflective of knowledge consolidation. If cognitive processing is less effortful, then the resulting efficiency may mean less functional activity. Though evidence is limited, some studies have shown that typically achieving novice performers can exhibit increased activation, yet following training or practice, decreased activation is observed (Chein & Schneider, 2005; Little & Thulborn, 2006; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008).

While the value of the narrative reviews cannot be discounted, meta-analysis provides a statistical approach to synthesizing across studies. In a meta-analysis of adults with reading disabilities compared to controls, reduced activation was reported for left hemisphere ventral occipitotemporal cortex, inferior parietal cortex, superior temporal gyrus, inferior frontal gyrus, and thalamus (Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008). Another recent meta-analysis, which included both children and adults with reading disabilities, identified underactivation in the left hemisphere inferior parietal, superior temporal , middle and inferior temporal, and fusiform regions and also reported underactivation in the L IFG that coincided with overactivation in the primary motor cortex and anterior insula (Richlan, Kronbichler, & Wimmer, 2009). In a meta-analysis that compared adults with RD and children with RD, showed similar results except that temporoparietal underactivation was seen only for adults with RD, not for children with RD (Richlan, Kronbichler, & Wimmer, 2011).These meta-analyses are consistent with the literature reviews in identifying a dysfunctionally underactivating left hemisphere network in RD. However, the meta-analyses indicate the presence of underactivation of the L IFG in RD rather than the overactivation assumed in the narrative reviews (Richlan, 2012). The meta-analysis would appear to constitute a consensus across studies, yet appropriate caution should be used when interpreting meta-analyses. Due to the necessary requirement of coordinates of activation to perform functional meta-analysis, not all relevant studies may be included in the analysis. Hence, both the meta-analytic approach and the narrative literature review provide insight into understanding differences between typical readers and those with RD.

Arising from the growing evidence of RD brain activity differences are questions surrounding how reading instruction can impact individuals with RD at the neurobiological level. In addition, questions arise regarding the relation of neurobiological differences and responsiveness to intervention. To address these questions, a systematic review of the functional imaging literature associated with reading intervention is presented below. The review is focused upon studies that explored functional activity differences before, during, and after intervention including studies that examined responsiveness to intervention and associated functional imaging. Included in the review are recent studies published since earlier summaries and reviews (Noble & McCandliss, 2005; Richards, Aylward, Field, et al., 2006; B. A. Shaywitz, Lyon, & Shaywitz, 2006; S. E. Shaywitz, Morris, & Shaywitz, 2008). In this paper detailed examination is limited to fMRI and MEG. However, it should be noted that in addition to fMRI and MEG reading intervention has been explored with other methods and modalities. Structural imaging studies have included diffusion tensor imaging (DTI) (Davis et al., 2010; Gebauer et al., 2011; Keller & Just, 2009) and voxel based morphometry (VBM) (Krafnick, Flowers, Napoliello, & Eden, 2011). Functional activity studies have used event related potential (ERP) (Hasko, Groth, Bruder, Bartling, & Schulte-Körne, 2014; Lovio, Halttunen, Lyytinen, Näätänen, & Kujala, 2012; Molfese, Fletcher, & Denton, 2013; Spironelli, Penolazzi, Vio, & Angrilli, 2010), magnetic resonance spectroscopy (MRS) (Richards et al., 2000, 2002) and using transcranial magnetic stimulation treatment (Costanzo, Menghini, Caltagirone, Oliveri, & Vicari, 2012; Turkeltaub et al., 2012).

Inclusion Criteria

To obtain studies that examined brain activity associated with reading intervention, six inclusion criteria were stipulated. First, only peer-reviewed, primary research studies were included. Second, only studies with at least some participants designated as having reading difficulties, reading disabilities, dyslexia, or at-risk status for reading difficulties were included. For studies that used imaging to predict future reading scores, the designation of reading difficulties could be determined at posttest. Case studies were excluded. Third, the reading difficulty must have been idiopathic in nature and not the result of head trauma, stroke, or illness. Fourth, the studies were required to describe reading-related instruction that occurred during the experiment. Fifth, the studies were required to include neuroimaging in the modalities of either fMRI or MEG and the experimental design must associate the imaging with the reading instruction. Sixth, the functional imaging task must have been a reading task or a task of reading-related skill (e.g., letter sound matched to visual letter).

Article Search

Two search strategies were employed to identify relevant studies and these searches were current as of January 2013. First, searches were conducted using two electronic databases, *PubMed* and *Web of Science.* The *Web of Science* search input was (TS=((reading disability OR dyslexia OR reading difficulty) AND (neuroimaging OR fMRI OR brain activation) AND (reading intervention OR reading instruction OR reading treatment))) AND Document

Types=(Article). The *PubMed* search input was ((("reading"[MeSH Terms] OR "reading"[All Fields]) AND disability[All Fields]) OR ("reading"[MeSH Terms] OR "reading"[All Fields]) AND difficulty[All Fields]) OR ("dyslexia"[MeSH Terms] OR "dyslexia"[All Fields]) AND (("neuroimaging"[MeSH Terms] OR "neuroimaging"[All Fields]) OR ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "fmri"[All Fields]) OR (("brain"[MeSH Terms] OR "brain"[All Fields]) AND activation[All Fields])) AND ((("reading"[MeSH Terms] OR "reading"[All Fields]) AND ("Intervention (Amstelveen)"[Journal] OR "Interv Sch Clin"[Journal] OR "intervention"[All Fields])) OR (("reading"[MeSH Terms] OR "reading"[All Fields]) AND ("teaching"[MeSH Terms] OR "teaching"[All Fields] OR "instruction"[All Fields]))). The *Web of Science* search yielded 75 articles. The *PubMed* search yielded 49 articles. The resulting 124 articles were examined and those that did not meet criteria were systematically eliminated (Fig 1) (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). Next, using references from studies that met inclusion criteria, additional studies were considered. Additionally, Google Scholar searches were performed to locate papers that have cited some of the studies that met inclusion criteria.

Data were gathered from articles, supplemental material, and from other works referenced in the paper as needed (e.g.,detailed descriptions of participants or interventions published separately from imaging analysis). Efforts were made to include information describing participant groups, neuroimaging techniques, and reading interventions.

Literature Review Results

The literature search resulted in 22 studies that met criteria for inclusion in the descriptive literature review (Fig 1). The studies are presented in chronological order with their participant groups, interventions used, and intervention dosages in Table 1. The imaging modalities, functional tasks, and imaging findings are listed in Table 2.

Figure 1. Flow diagram of literature review article exclusion

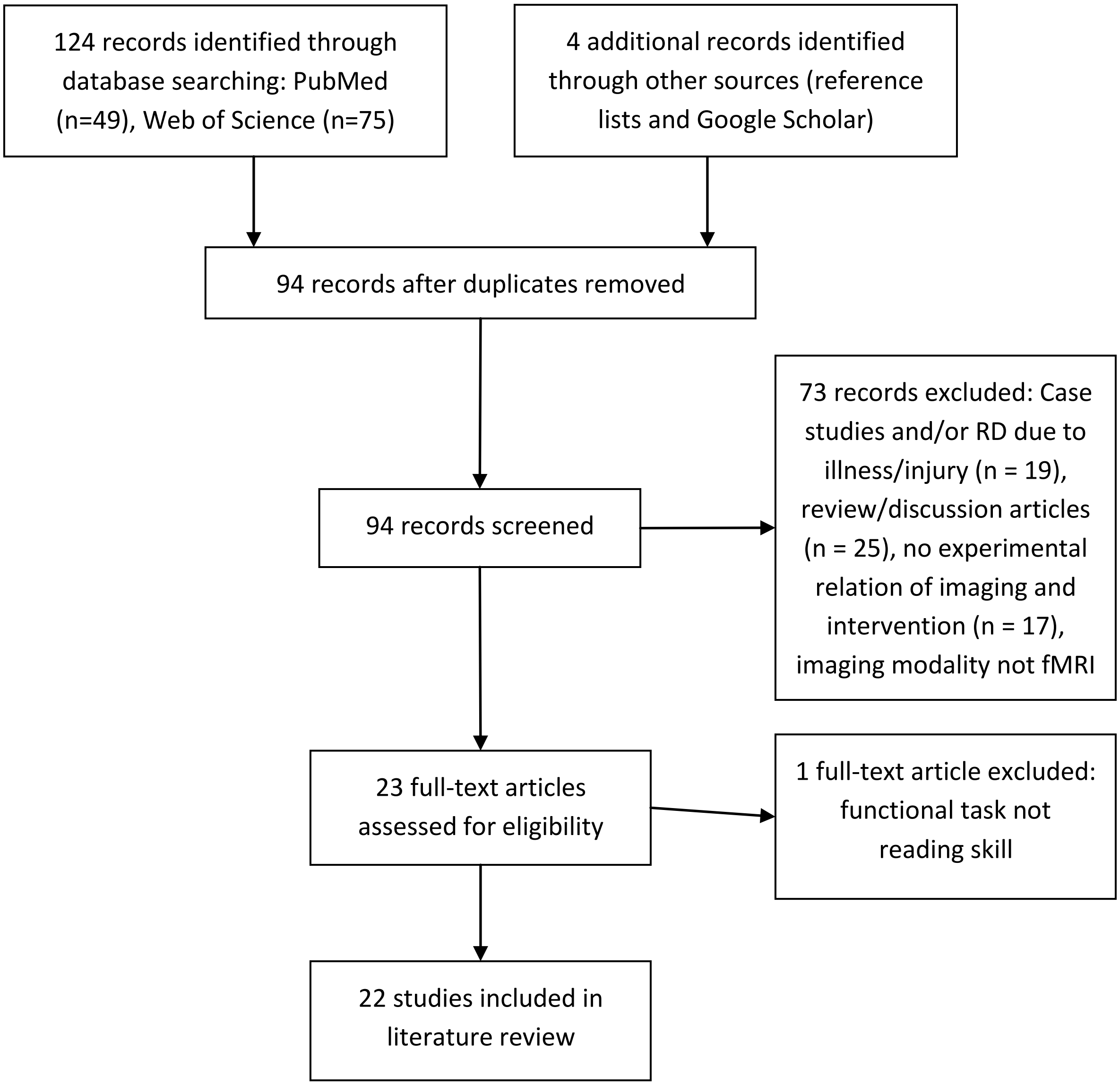


Table 1. Participant groups and interventions in literature review.

Study	RD N	CT N	Age	Intervention	Dosage
Simos et al, 2002	8; 6 received Phono-Graphix, 2 received Lindamood Phonemic Sequencing	8	7-17 yrs	Phono-Graphix (Read America, Orlando FL) Lindamood Phonemic Sequencing (Lindamood-Bell, San Luis Obispo, CA)	80 hrs: 1-2 hr/day over 8 wk
Aylward et al, 2003	10	11	139.1 (9.8) months, 137.5 (7.9) months	Instruction in linguistic awareness, alphabetic principle, fluency, and reading comprehension	28 hrs: 2hr/day over 14 session days (3 wk)
Temple et al., 2003	20	12	8-12 yrs	Fast ForWord Language (Scientific Learning Corporation, Oakland, CA)	100 min/day, 5 days/wk, average 27.9 days
Eden et al., 2004	19 total; 9 received intervention	19	adults, RD 44.0 (9.4), CT 41.1 (9.7)	Multisensory instruction including sound awareness, letter-sound association, articulatory feedback administered by Lindamood-Bell Learning Corporation staff	3 hr/day, 8 wks, avg 112.5 hr total
Shaywitz et al., 2004	49 total; 37 received experimental intervention, 12 received community intervention	28	6.1 - 9.4 yrs; RD experimental 7.9 (0.5), RD community 8.1 (0.6), CT 8.0 (0.5)	Experimental intervention (Blachman, Schatschneider, Fletcher, & Clonan, 2003)included sound-symbol associations, blending, timed reading for fluency, oral reading, dictation	50 min/day for 8 months

Simos, et al., 2005	16; 13 responders, 3 non-responders	17	5.6-7.2 yrs at baseline (Low risk group 5.6-6.5, High risk group 6.0-7.2) 6.4-8.1 yrs at posttest (Low risk 6.4 – 7.5, High risk group 7.0 – 8.1)	Proactive Reading and Responsive Reading (Mathes et al., 2005)	40 min/day, 5 day/wk for 8 months
Richards et al., 2006	18; 8 orthographic treatment, 10 morphological treatment	21	RD 130.8 months, CT 132.6 months	Instruction in alphabetic principle, composition, and either orthographic spelling treatment or morphological spelling treatment	28 hr total: 2 hr/day for 14 sessions over 3 wk
Hoeft et al., 2007	64 struggling readers (identified by teachers, many had scores in average range)	-	10.0 (1.09) yr	Power4Kids Reading Initiative. Many participants received 1 of 4 interventions, but there was no significant effect of intervention on decoding scores.	about 6 months during schoolyear
Richards et al., 2007	20; 11 phonological treatment, 9 nonphonological treatment	10 nonphonological treatment	RD phonological 137.7 (10.00) months, RD nonphonological 134.60 (11.10) months, CT 128.60 (8.00) months	Phonological treatment included explicit written language instruction using phonological working memory, phoneme-grapheme correspondences in spelling, and science report writing (Berninger et al., 2007). Nonphonological treatment included nonverbal virtual reality supported science problem solving (Winn et al., 2006)	24 hrs total—8 sessions over 2 wks with 3hr/session
Simos, Fletcher, Sarkari, Billingsley-Marshall, et al, 2007	15	-	7-9 years	Phono-Graphix(McGuiness et al., 1996) and Read Naturally (Ihnot, Mastoff, Gavin, & Hendrickson, 2001)	16 weeks total: 2 hr/day for 8 wks Phono-Graphix, 1 hr/day for 8 wks Read Naturally

Simos, Fletcher, Sarkari, Billingsley, et al., 2007	15; 8 responders, 7 nonresponders (same as Simos, et al., 2007 above)	10	7-9 years	Phono-Graphix (McGuiness et al., 1996) and Read Naturally (Ihnot et al., 2001)	16 weeks total: 2 hr/day for 8 wks Phono-Graphix, 1 hr/day for 8 wks Read Naturally
Meyler et al., 2008	23 (possible overlap with Hoeft, et al., 2007)	12	5th grade	Power4Kids project used four programs: Corrective Reading, Wilson Reading, Spell Read Phonological Auditory Training (PAT), Failure Free Reading	100 hrs total over 6 months
Odegard et al., 2008	12 total: 6 responders, 6 nonresponders	6	10 - 14 yrs	Take flight: A comprehensive intervention for students with dyslexia (Avrit et al., 2006)	90 min/day, 4 days/wk for 2 school years
Richards& Berninger, 2008	18 (same as Richards et al., 2006)	21	RD 130.8 months, CT 132.6 months	Instruction in alphabetic principle, composition, and either orthographic spelling treatment or morphological spelling treatment	28 hrs total--14 sessions over 3 wks with 2hr/session;
Davis et al., 2011	10 total: 5 responders, 5 nonresponders	4	7.5 (0.43) yrs	Intervention consisted of sight word reading, letter sound practice, decoding practice, and reading for fluency.	45 min, 3 days/wk, 17 weeks
Farris et al., 2011	10 total: 5 responders, 5 nonresponders (same as Odegard et al., 2008)	5	10 - 14 yrs	Take flight: A comprehensive intervention for students with dyslexia (Avrit et al., 2006)	90 min/day, 4 days/wk for 2 years

Hoeft et al., 2011	25	20	RD 14.0 (1.96) CT 11.0 (2.57)	*This study did not provide an intervention.*11 participants received some form of intervention, but no differences were observed for intervention.	-
Rezaie et al., 2011a	20 total: 10 Adequate Responders (AR), 10 Inadequate Responders (IR)	20	Adequate Responders 158 ± 7 months, Inadequate Responders 153 ± 11 months, CT 151 ± 11 months	Instruction included word study, fluency, vocabulary, comprehension (Vaughn et al., 2010)	45-50 min/day over 1 schoolyear
Rezaie et al., 2011b	27 total: 16 AR, 11 IR (possible overlap with Rezaie, et al., 2011a)	23	Adequate Responders 159 ± 9 months, Inadequate Responders 156 ± 16 months, CT 153 ± 12 months	Instruction included word study, fluency, vocabulary, comprehension (Vaughn et al., 2010)	45-50 min/day over 1 schoolyear
Yamada et al, 2011	7 (at-risk)	7 (on-track)	At-risk 5.6 (0.2) yrs, On-track 5.7 (0.3) yrs	Early Reading Intervention (Kame'enui & Simmons, 2003)	30 min/day, 3 months
Gebauer Fink, Kargl et al., 2012	20 total (poor reading and spelling): 10 Treatment (TG), 10 Waiting Group (WG)	10	10-15 yrs, (*M* = 11.80; *SD*= 1.58)	Morpheus: a computer-aided morpheme-based spelling training in German (May, Vieluf, & Malitzky, 2000)	Daily handwritten and computer homework, 1/wk instructor-guided courses for 2 hr, over 5 wks.
Bach et al., in press	6 poor readers (group classification made at follow-up)	11	Poor Readers 6.33 ± 0.19 yr, Normal Readers 6.35 ± 0.29 yr	Graphogame: a computerized training game teaching grapheme-phoneme correspondences in German (Lyytinen, Erskine, Kujala, Ojanen, & Richardson, 2009; Lyytinen, Ronimus, Alanko, Poikkeus, & Taanila, 2007; Saine, Lerkkanen, Ahonen, Tolvanen, & Lyytinen, 2011)	321.5 ± 124.3 min over 8 wk

Table 2.Imaging and findings in literature review studies.

Study	Imaging	Imaging task	Principle Findings
Simos et al., 2002	MSI, Pre/Post	Pseudoword rhyme-matching	Pre-intervention underactivation of left posterior STG in RD group increased to level of controls at post-intervention. Control group did not change over time. Additionally, RD showed pre-intervention overactivation of R STG.
Aylward et al., 2003	fMRI, Pre/Post	Letter-Phoneme Matching (with Letters Only Matching control task) Comes From Morpheme Mapping (with Synonym Judgment control task)	Pre-treatment RD underactivated in L MFG, IFG, MTG, ITG, R SFG, and bilateral superior parietal regions during phoneme mapping and in L MFG, R superior parietal and fusiform/occipital area during morpheme mapping. No differences between groups at post-scan due to increased activity for RD group and decreased activity for controls.
Temple et al., 2003	fMRI, Pre/Post	Rhyme Letters (phonological), Match Letters (nonphonological), Match Lines (nonletter)	Following treatment, RD had increased activity in \L IFG, anterior cingulate, ITG, MTG/angular, hippocampal, and lingual gyri, R anterior cingulate, MFG, insula/IFG, SFG, MTG, posterior cingulate/precuneus, parieto-occipital sulcus, and bilateral anterior thalamus. These increases were not present in CT.
Eden et al., 2004	fMRI, Pre/Post	Sound Deletion (aurally presented words), Word Repetition (aurally presented)	Post intervention, Group × Session interaction revealed increases in L IPL (BA 4 0), intraparietal sulcus (BA 40/7), fusiform/parahippocampal gyrus (BA 37), hippocampal gyrus, thalamus, and MFG (BA 46), R posterior STS/G (BA 22/39), SPL (BA 7), IPL (BA 40), IFG (45/46), inferior postcentral gyrus (BA 43), medial frontal cortex (BA 10/11/47), and inferior MFG (BA 11).

Shaywitz et al., 2004	fMRI, Pre/Post/1yr follow-up	Matching Letter Name (audio) to Letter (visual), Audio tone/Visual symbol control task	Immediately following treatment, RD experimental intervention group showed increased activation compared to RD community intervention in L IFG and MTG and decreased activation in the R caudate nucleus. One year after treatment ended, the RD experimental intervention group had increased activation in bilateral IFG, LSTS, posterior MTG/ITG/ anterior middle occipital gyrus, inferior occipital gyrus, and lingual gyrus, and decreased activation in R MTG and caudate nucleus.
Simos et al., 2005	MSI, Pre/Post	Letter-sound naming, pseudoword reading	Grade × Group interactions revealed reduction in onset latency in the bilateral occipito-temporal region and increased onset latency in the L IFG for responders.
Richards et al., 2006	fMRI	Orthographic mapping, morpheme mapping with/ without phonological shift, Phoneme mapping	Following intervention, the orthographic treatment group showed increased activation in R IFG and posterior parietal region to levels that no longer differed from control group.
Hoeft et al,. 2007	fMRI (and VBM)	Real-word rhyme judgment	Combining fMRI and VBM with behavioral scores predicted word attack skills better than behavioral or imaging alone. Regions predicting posttest word decoding scores included R fusiform gyrus, fusiform/mid occipital gyrus, and LMTG as positive predictors and R MFG as a negative predictor.
Richards et al., 2007	fMRI, Pre/Post	Pseudoword visual decoding, aural match, and aural repeat	Following intervention, Group x Time interaction for visual-decode/aural-match contrast showed nonphonological group increased activation in L occipital cortex (BA 19) to the level of CT, whereas phonological group continued to underactivate. The aural-repeat/aural-match contrast revealed decreased activation for the phonological group to levels resembling CT in L SMG and postcentral gyrus

Simos, Fletcher, Sarkari, Billingsley-Marshall et al., 2007	MEG, Pre/Mid/Post	Timed reading of increasingly difficult words	Changes included increased degree of activity in bilateral posterior MTG (BA 21), decreased onset latency in LMTG (BA 21) and R lateral occipitotemporal region (BA 19/37), and increased onset latency in premotor cortex.
Simos, Fletcher, Sarkari, Billingsley, et al., 2007	MEG, Pre/Mid/Post	3-letter pronounceable nonwords (visually presented)	No notable activation differences between responders and nonresponders at baseline. Following intervention, responders showed increased duration of activity in the L posterior STG, SMG, and angular gyrus. The nonresponders showed increased duration of activity in R temporoparietal and bilateral frontal areas. Responders showed changes in the sequence of activation to more closely resemble CT by initiating in extrastriate, followed by temporoparietal, and then frontal areas and this temporal profile was not apparent in nonresponders.
Meyler et al., 2008	fMRI, Pre/Post/1yr Followup	Visual presentation of sentences with sense-nonsense judgment	Pre-intervention, RD underactivated in L mid occipital/angular, IPL/postcentral, SPL/sup occipital, MFG, R IPL/SMG, SMG/IPL and overactivated in anterior and posterior SMA. Post-treatment, RD activated more than CT in L putamen and R insula/IFG and CT were greater than RD in L SPL/superior occipital and MFG. At follow-up the treatment group showed greater activation than CT in L postcentral gyrus, insula/putamen, insula, SFG/cingulate, anterior SFG, anterior and middle cingulate, thalamus, and cerebellum (vermis), R postcentral gyrus, putamen/insula, SFG/SMA, anterior cingulate, posterior cingulate, precuneus, and cerebellum (vermis).

Odegard et al., 2008	fMRI, Post	Phoneme-grapheme matching, tone-symbol	Following treatment, L inferior parietal showed increased activation in controls relative to non-responders, R inferior frontal showed greater activation in responders relative to non-responders and controls, R middle temporal showed greater activation in non-responders relative to responders and controls
Richards & Berninger, 2008	fMRI, Pre/Post	Phoneme Mapping	Before treatment, children with dyslexia showed higher functional connectivity than controls from L IFG to bilateral MFG and SMA, L precentral gyrus, and R SFG. Following treatment, RD showed no difference from controls in L IFG seed point.
Davis et al., 2011	fMRI, Post	Letter-sound matching	Responders showed greater activation in the L STG (BA 22) relative to nonresponders. Responders activated more that controls in L MTG/Angular (BA39)
Farris et al., 2011	fMRI, Post	Phoneme-grapheme matching, tone-symbol	Following treatment, responders were equivalent to controls in functional connectivity between L and R inferior frontal lobes, and nonresponders exhibited less functional connectivity.
Hoeft et al., 2011	fMRI (and DTI), Pre	Rhyme judgment	fMRI activity in the R IFG (BA 44, inferior operculum) together with DTI of the R superior longitudinal fasciculus predicted responsiveness with 72% accuracy. Whole-brain multivariate patterns of brain activation (fMRI) predicted reading gains with >90% accuracy. Areas contributing to classification with positive correlation: R IFG (operculum), insula, lingual gyrus, precuneus/MTG/occipital, culmen of cerebellum, L IFG (triangularis), SFG, MFG. Negative correlation: L IFG/Insula, precentral gyrus, SFG/SMA, IPL, posterior cingulate/cuneus/calcarine, L superior/middle occipital gyri, L midbrain, R lingual/fusiform

Rezaie et al., 2011a	MEG, Pre	Word reading	At baseline, adequate responders showed increased activity in the L MTG, L STG, L ventral occipitotemporal regions, and R medial temporal cortex relative to inadequate responders. Activity in these regions predicted improvement in real word reading efficiency above predictions of reading accuracy or fluency.
Rezaie et al., 2011b	MEG, Pre	3-letter pronounceable nonwords	Pre-intervention activity was higher for adequate responders compared to inadequate responders in L SMG and angular gyrus and bilateral STG and MTG. Pre-intervention activity in L SMG, STG, and angular gyrus was positively correlated with post-intervention gains in fluency scores.
Yamada et al., 2011	fMRI, Pre/Post	One-back task with letters and letter-like stimuli	Pre-treatment at-risk group underactivated in L ITG, superior lateral occipital cortex, and thalamus, R SFG, anterior cingulate, posterior superior STG, and temporal/fusiform cortex, occipital pole, and amygdala, bilateral IFG, frontal orbital cortex (ORB), MTG, SMG, precentral cortex, SPL, supracalcarine cortex, and putamen. The at-risk group overactivated in R frontal orbital cortex (medial to the underactivation listed above). Posttreatment the at-risk group overactivated in L IFG, frontal pole, SPL, and occipital pole, R SFG, SMG, ACC, MFG, planum temporale, frontal operculum, precuneus, postcentral gyrus, lateral occipital cortex, and lingual gyrus and bilateral precentral gyrus and paracingulate region and underactivated in L superior lateral occipital cortex.

Gebauer, Fink, Kargl et al., 2012	fMRI, Pre/Post	Correctly spelled words, misspelled words, pseudowords	Treatment group showed increased activation following treatment in R posterior cingulate, L MTG, ITG, hippocampus, and parahippocampal region during pseudoword reading. The waiting group showed increases in R lateral occipital cortex and middle temporal cortex during all three conditions. CT showed increases in bilateral middle temporal and occipito-temporal regions. Group × Session interaction revealed increased activation for the training group in the bilateral parahippocampal area and cerebellum. The waiting group showed increased activation in bilateral precuneus and cerebellum, L frontal pole, and R lateral occipital cortex and parieto-temporal region..
Bach et al., in press	fMRI (and ERP), at Post-training used for predicting reading 2 years later	Word/symbol processing	fMRI and ERP data combined with behavioral measures at kindergarten significantly improved prediction of reading skill at second grade over behavioral measures alone. For fMRI, activity in L visual word form area (fusiform) ROI correlated with gains in letter knowledge.

Note. The terms *overactivated* and *underactivated* are used in reference to control groups. IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, STG = superior temporal gyrus, STS = superior temporal sulcus, MTG = middle temporal gyrus, ITG = inferior temporal gyrus, SMG = supramarginal gyrus, IPL = inferior parietal lobule, SPL = superior parietal lobule, SMA = supplementary motor area, ACC = anterior cingulate cortex.

Descriptively synthesizing across studies, key findings by anatomical region are presented below. Numerous brain regions were found to be associated with reading intervention in these studies. These regions included not only frontal, temporo-parietal, and occipital cortex, but also sublobar and subcortical areas.

Frontal Areas

Frontal areas were reported in multiple studies. While IFG findings were reported most, findings included other frontal areas as well.

Inferior frontal gyrus. The IFG was found to be associated with intervention across multiple studies. Following reading intervention, previously underactivating L IFG in RD more closely resembled controls (Aylward et al., 2003; B. A. Shaywitz et al., 2004; Temple et al., 2003) with one study showing underactivation of at-risk children shifting to overactivation following intervention (Yamada et al., 2011). Interestingly, another study (Richards & Berninger, 2008) found that children with RD showed higher functional connectivity than controls for the L IFG as related to R and L supplemental motor areas and L precentral gyrus as well as R superior frontal gyrus. Following intervention, no difference was observed between children with RD and controls. An additional functional connectivity study (Farris et al., 2011) similarly found that L and R inferior frontal connectivity was the same following treatment for RD as compared to controls, but in somewhat of a contrast, found that nonresponders to intervention showed less functional connectivity than did responders. Another study (Hoeft et al., 2011) found that activity in the pars triangularis of the L IFG was positively correlated with reading gains, whereas L IFG/Insula activity was negatively correlated. To summarize, it seems that L IFG involvement may be that of underactivation prior to intervention relative to controls, followed by normalization after treatment. However, there is not complete consensus among the studies in this review.

The right IFG is also prominent in findings related to intervention. Prior to treatment, at-risk children showed underactivation in R IFG (Yamada et al., 2011). Activation increases in R IFG were seen following intervention (Eden et al., 2004; Meyler et al., 2008; Temple et al., 2003) and at follow-up (B. A. Shaywitz et al., 2004) and considered to be normalized to the level of controls (Richards, Aylward, Berninger, et al., 2006). Prior to treatment, higher R IFG activity predicted higher reading gains for children with RD (Hoeft et al., 2011). Following treatment, responders exhibited greater R IFG activation than did nonresponders and controls (Odegard, Ring, Smith, Biggan, & Black, 2008). Nonresponders showed increased duration of activity in bilateral frontal areas (Simos, Fletcher, Sarkari, Billingsley, et al., 2007a), and exhibited less functional connectivity between left and right inferior frontal regions than did responders and controls (Farris et al., 2011).

Additional frontal areas. While the IFG was the most consistently involved region in intervention, other frontal regions emerged in some studies with several studies presenting results in superior frontal and middle frontal gyri. Prior to intervention, children with RD showed underactivation in R superior frontal gyrus (Aylward et al., 2003) and increases in activation were seen following treatment (Temple et al., 2003) and at follow-up (Meyler et al., 2008). Activity in the L superior frontal gyrus (SFG) was positively correlated in predicting response to intervention (Hoeft et al., 2011). At follow-up to intervention, children with RD showed increased activation in L SFG/cingulate (Meyler et al., 2008). Prior to intervention, children with RD showed underactivation in L middle frontal gyrus (Aylward et al., 2003) and L MFG activity contributed to whole-brain multivariate patterns that predicted responsiveness to intervention

(Hoeft et al., 2011). Pre-treatment activation levels in R MFG negatively correlated with posttest decoding scores (Hoeft et al., 2007). Following intervention, children with RD exhibited increased levels of activation in R MFG (Temple et al., 2003; Yamada et al., 2011) whereas adults showed increased activation in R and L middle frontal gyrus (Eden et al., 2004). More isolated frontal lobe findings include at-risk children underactivating in bilateral frontal orbital cortex at pre-treatment (Yamada et al., 2011) and responders showing increased dorsolateral prefrontal activation(Simos et al., 2005).

Temporo-parietal Areas

The most commonly reported temporo-parietal areas were STG and MTG. Other regions also produced findings in some studies.

STG and MTG. Some consistencies emerged among studies in temporo-parietal areas, particularly in the superior temporal and middle temporal gyri. Before treatment, participants with RD showed underactivation relative to controls in posterior STG and temporo-parietal cortex that increased or normalized to the level of controls after intervention (B. A. Shaywitz et al., 2004; Simos et al., 2002; Temple et al., 2003; Yamada et al., 2011). Increased L STG activation was evident at follow-up as well (Simos et al., 2002; Yamada et al., 2011). Responders to intervention showed greater activation than nonresponders in L STG prior to treatment (Rezaie et al., 2011a, 2011b) and following treatment (Davis et al., 2011). Also, responders to treatment showed increased duration of activity in posterior L STG and the L hemisphere sequence of activation changed for responders such that temporoparietal areas activated prior to frontal areas, such that after treatment responders much more closely resembled (Simos, Fletcher, Sarkari, Billingsley, et al., 2007a). In young children considered at-risk for RD, underactivation was seen in the R posterior STG prior to treatment. In adults, increases in R posterior STG/angular gyrus activation were seen following treatment (Eden et al., 2004). While in one MEG study, responders exhibited bilateral temporal-parietal activation (Simos et al., 2005), another study showed nonresponders having increased R temporo-parietal activation (Simos, Fletcher, Sarkari, Billingsley, et al., 2007a). Because of the lesser spatial resolution of MEG, these areas are more general than in fMRI.

Though the STG seemed to be the temporo-parietal region with the most consistent findings across studies, the middle temporal gyrus (MTG) also emerged in findings from several studies. At pre-treatment, relative underactivation of the L MTG was seen, with activation increases observed following treatment (Aylward et al., 2003; Gebauer et al., 2012; B. A. Shaywitz et al., 2004; Simos, Fletcher, Sarkari, Billingsley-Marshall, et al., 2007). As for responsiveness, higher L MTG activity was predictive of better response to intervention (Hoeft et al., 2007; Rezaie et al., 2011a) and responders activated more than controls in L MTG/Angular gyrus following intervention(Davis et al., 2011). In addition to the L MTG, increases in activation were also shown for RD in the R MTG following treatment (Simos, Fletcher, Sarkari, Billingsley-Marshall, et al., 2007; Temple et al., 2003). However, one study (B. A. Shaywitz et al., 2004) found that R MTG activity was higher in RD at pre-treatment than at follow-up and another study (Odegard et al., 2008) found that after treatment non-responders showed greater activation relative to controls and responders in R MTG. In addition, one study found that responders had increased activity at baseline in R mesial temporal cortex, an area not identified in other studies (Rezaie et al., 2011a).

Other temporo-parietal areas. Though less consistent across studies than the STG and MTG findings, activity in other temporo-parietal areas, including inferior temporal gyrus, inferior parietal lobule, supramarginal gyurs (SMG), and angular gyrus, was associated with reading intervention in a few studies. In the inferior temporal gyrus (ITG), children with RD underactivated in the L hemisphere relative to controls at baseline, a difference that was no longer present following treatment (Aylward et al., 2003), a finding in congruence with Gebauer, Fink, Kargl et al (Gebauer et al., 2012) that showed increased activation in L ITG for poor spellers/readers at post-intervention.In adults, increases in activation were seen following treatment in R and L inferior parietal lobule and left intraparietal sulcus (Eden et al., 2004). At pretreatment, at-risk children underactivated in bilateral supramarginal gyri, and following treatment activated more than controls in R SMG (Yamada et al., 2011). Pre intervention L SMG and angular gyrus activity positively correlated with post-intervention fluency gains (Rezaie et al., 2011b). Following intervention, responders showed increased activation of L SMG (Simos, Fletcher, Sarkari, Billingsley, et al., 2007a) and activated more than controls in L MTG/Angular (BA 39). Adults showed increased activity following intervention in R superior temporal/Angular (BA 22/39) (Eden et al., 2004).

Occipital and Fusiform

Children with RD underactivated in the occipital/fusiform region (Aylward et al., 2003) and superior lateral occipital cortex (Yamada et al., 2011) prior to intervention. Baseline activation in the R fusiform and R fusiform/mid occipital gyri positively correlated with later decoding scores (Hoeft et al., 2007). At baseline, children who were responders to intervention showed greater activation than non-responders in L ventral occipitotemporal region (Rezaie et al., 2011a).Post treatment L fusiform activation positively correlated with future gains in letter knowledge for young children (Bach, Richardson, Brandeis, Martin, & Brem, n.d.). Following intervention, increases in activation were seen in adults in the L fusiform gyrus (Eden et al., 2004) and in children in the L lingual gyrus (Temple et al., 2003). Onset latency increased in R lateral occipitotemporal cortex (Simos, Fletcher, Sarkari, Billingsley-Marshall, et al., 2007). Of interest, the only region in which children who were on track for typical reading achievement activated more than at-risk children who had received treatment was in the L superior lateral occipital cortex (Yamada et al., 2011). At one year follow-up, increased activation was seen in occipitotemporal regions for children with RD (B. A. Shaywitz et al., 2004).

Pre/postcentral Areas

Limited evidence indicates possible differences in activity in precentral and postcentral gyri associated with intervention. Following treatment, children considered at-risk for RD showed increased activity relative to controls in L precentral gyrus (Yamada et al., 2011). Responders exhibited increased onset latency (Simos, Fletcher, Sarkari, Billingsley-Marshall, et al., 2007) of premotor cortex. Increases were seen in R inferior postcentral gyrus (BA 43) in adults following intervention (Eden et al., 2004) and in bilateral postcentral gyrus in children at follow-up (Meyler et al., 2008).

Subcortical Areas

Post-intervention increases in activation were found in adults with RD in the L hippocampal gyrus (Eden et al., 2004). Increases in thalamus activity were observed in the left hemisphere following intervention for adults (Eden et al., 2004), bilaterally for children following intervention (Temple et al., 2003), and in L hemisphere for children at follow-up (Meyler et al., 2008). Following treatment, children with RD showed increased activation in L putamen relative to controls (Meyler et al., 2008). At follow-up in the same study increased activation was seen in L and R insula/putamen.

Sublobar/medial Cortex.

Though findings are limited in these areas, several studies reported findings in the insulae and other sublobar or medial areas.

Insula. Following treatment, increased activation was seen in R insula/IFG (Meyler et al., 2008; Temple et al., 2003) and at follow-up in bilateral insula/putamen (Meyler et al., 2008). Prior to intervention, bilateral insular activity contributed to predicting response to intervention with a positive correlation for R insula and a negative correlation for L insula (Hoeft et al., 2011).

Additional sublobar/medial areas. Prior to intervention, the R precuneus contributed to prediction of responsiveness (Hoeft et al., 2011). At treatment follow-up, children with RD showed greater activation than controls in R precuneus (Meyler et al., 2008). Children with RD showed greater activation than controls in R anterior cingulate after treatment (Yamada et al., 2011) and at follow-up (Meyler et al., 2008). Prior to treatment, L posterior cingulate activation was negatively correlated in whole-brain multivariate patterns predicting responsiveness to intervention (Hoeft et al., 2011). At post-intervention, poor spellers/readers showed increased activation in R posterior cingulate cortex. At treatment follow-up, children with RD showed greater activation than controls in R posterior cingulate (Meyler et al., 2008).

Review Discussion

Though relatively few studies have examined the neurobiology associated with reading intervention and differing methodologies have been employed, some commonalities among studies have emerged in this review. This descriptive literature review revealed that across studies, reading intervention may be associated with differential activation in bilateral IFG, STG, MTG, MFG, and SFG, as well as bilateral occipital regions, postcentral gyri, inferior parietal lobule, and insulae, among others. In almost all of these regions, differences involve underactivation for RD prior to intervention with relative increase following intervention. These results seem to be consistent with literature that describes underactivation in these areas for RD relative to typical readers and points toward normalization through remediation.

Not all of the patterns that emerged across these intervention studies were consistent with previous literature addressing imaging of RD. Several studies in this review indicated underactivation of L IFG prior to intervention for RD. Interestingly, while these findings are similar to that revealed in meta-analyses of RD (Richlan, 2012) they are in contrast to the accepted model of L hemisphere dysfunction that includes L IFG overactivation in RD as a compensatory mechanism for underactivating temporo-parietal and occipito-temporal regions (Pugh et al., 2000, 2001). In the studies we reviewed, reading intervention was generally associated with increased L IFG activation to normalizing levels. However, as one study (Yamada et al., 2011) showed overactivation in the L IFG (among other areas) in RD following intervention, there may be support for the conventional model of RD overactivating L IFG subsequent to intervention. One proposed hypothesis that would account for this pattern is that of an inverted U activation curve (Pugh et al., 2008b). In this model, children with RD may have a different starting point on the curve when performing a reading task. They may start at (and remain longer) at the low point of activation. With intervention, they may exhibit increased activation in relevant areas. In contrast, unimpaired readers may start out with higher activation, but over repeated exposures or training will decrease in activation. While still speculative, the inverted U should be considered when conducting imaging studies with RD, even if the study is not directly concerned with intervention as perhaps undocumented or inadvertent treatment could be underlying increased activity.

In addition to exploring the differences in activity associated with intervention, this review identified studies that examined predictors of intervention response and differences among responders and nonresponders. Individuals may vary in their neurobiological receptiveness to training or instruction. Exploring these differences may eventually facilitate the targeting of intervention to individual needs. A few studies have begun the investigation of neural predictors of reading improvement in children with RD. Baseline fMRI activity in the R IFG predicted reading growth in one study that did not include a specific intervention (Hoeft et al., 2011). More specifically, they found that brain measures were more predictive of reading gains for adolescents with dyslexia than were behavioral measures, with greater activation in the R IFG during rhyme-judgment predicting greater reading improvement over the next 2 ½ years. In another study, baseline L MTG, L STG, L ventral occipitotemporal, and R medial temporal cortex MEG activity predicted response to intervention (Rezaie et al., 2011a). In this study of adolescent struggling readers, Rezaie et al. (2011a) reported that brain activity prior to intervention was predictive of behavioral response to a year-long intervention that emphasized vocabulary, comprehension, word study, and fluency, with higher MEG activity in L middle, superior temporal, and ventral occipitotemporal and R medial temporal cortex predicting better response (as demonstrated by word reading efficiency) than was predicted by pre-intervention reading accuracy or fluency measures alone (Rezaie et al., 2011a). These areas overlap with the previously discussed posterior areas involved in reading. In general, this suggests that adolescents with neurobiological profiles more closely resembling typically achieving readers are more likely to respond well to intervention.

The studies which looked at differential responsiveness and post-intervention imaging indicated that children who demonstrate behavioral response as evidenced by increased standardized test scores exhibited higher activation in left middle temporal and posterior superior temporal areas (Davis et al., 2011; Simos et al., 2006) and left inferior parietal region (Odegard et al., 2008) following intervention as compared to children who did not respond to intervention. Nonresponders (a year after intervention) had increased right middle temporal lobe during a letter-sound task (Odegard et al., 2008). Functional connectivity data indicate that responders and non-impaired readers exhibit connectivity between inferior frontal regions that is absent in nonresponders (Farris et al., 2011). Identifying these patterns of responders and nonresponders may provide insight into determining if these children are somehow at an optimal state to grow or unknowingly primed to respond to intervention, so that the lesser responders can be moved into that zone.

This review has its limitations. First among these is the limited number of studies that have explored neuroimaging and reading intervention. Even within these studies there are shared participants (i.e., appears to be identical groups or overlap among studies as noted in Table 1), such that this review is fairly limited in the number of unique participants. Also, due to the limited number of studies, the review included studies that differed in several respects. For instance, one study with adult participants was included, though it has been established that adults and children differ in reading activation in both typical readers and those with RD (Brown et al., 2005; Church et al., 2008; Richlan, 2012). In addition, the review included studies that greatly differed in treatment type and treatment dosage. Clearly, if differences in functional activity are related to treatment, type and dosage of treatment would be important factors.

Additionally, though the focus was on RD, definitions of RD (or being at-risk for RD) are not entirely consistent and the definition of RD varied by study.

A further limitation is that this review did not consider the statistical thresholds for imaging analysis used by each experiment. Not all studies approach data analysis in the same way, which presents a concern when synthesizing across studies. In some instances, journal articles do not provide all details of their methods and analyses. In more recent years, a call for more explicit description of experiment methodology and data analysis has occurred (Poldrack et al., 2008). As the functional imaging field has grown and evolved, reporting of methods and results have generally improved with the understanding of what information is necessary to the reader. This is a natural progression for a field in its infancy, so it is with this perspective that shortcomings in earlier works are acknowledged as likely due to limitations of the time. Nonetheless, it is important to state that at least one study appears to have used an uncorrected significance threshold and in several of the studies the reporting of methodology and statistical analysis is somewhat opaque. Thus, the current analyses are somewhat limited by the analyses performed in the original studies. Nevertheless, meta-analytic techniques are useful in identifying commonalities across studies and could add validity to studies that did not use stringent statistics if the results are consistent across studies.

Another limitation of this study is that task difficulty is not addressed. Task difficulty may have an effect on functional activity and this effect may differ depending on reading proficiency. As one study (Pugh et al., 2008b) showed, factors that make words easier to read (i.e., frequency, imageability, consistency) result in higher activation in reading related brain areas for RD while non-impaired readers exhibit, reduced activation. Interestingly, there is indication that even in a resting state condition, proficient readers show activation in reading networks (Koyama et al., 2010). This is an area of research that needs further exploration.

Another important consideration is that age-related differences were not directly examined. Gray matter development is not uniform. Rather, while areas involved in basic function such as motor and sensory areas mature early, areas involved in executive function, attention, and motor coordination mature later, with areas involving spatial orientation, speech and language development maturing in-between (Gogtay et al., 2004). As stated previously, functional changes occur over the course of development as well (Schlaggar & Church, 2009). As such, when considering activity in a certain region of the brain, it is worthwhile to consider the typical course of functional activity in that region.

Despite the limited number of studies and the disparate methods of experiments included due to this low number, this analysis provides a start for examining reading intervention and neuroimaging. While acknowledging the limitations, the current review results suggest that there are differences in brain activity associated with intervention.

Summary and Application to Current Study

The literature regarding neuroimaging and reading intervention is limited. In particular, very few studies have explored responsiveness to intervention. Fewer of these have sought to determine pre-intervention neuroimaging profiles that respond well (or less well) to intervention and none examined responsiveness to intensive, short-term intervention. The general aim of the proposed study is address this gap in the literature by characterizing neurobiological profiles that respond well to controlled, one-to-one, short-term intervention. A specific aim derived directly from the literature review is to determine through region of interest (ROI) analyses whether the same regions found to predict responsiveness to reading intervention in previous studies are predictors of response to controlled, intensive, short-term intervention. In addition to exploring a different dose and intensity of intervention than previous literature, the whole brain analyses in the proposed study provides superior spatial resolution when compared to the MEG analyses of two of the previous studies (Rezaie et al., 2011a, 2011b).

Purpose of the Study

The purpose of this study was to expand the existing literature base regarding functional imaging and reading intervention by using fMRI data to predict responsiveness to intensive, short-term reading intervention. Similar to previous imaging studies (Davis et al., 2010, 2011), we first considered the behavioral responsiveness of children with RD who received intervention. Reading growth was examined within the context of the larger study (Barquero, Sefcik, Cutting, & Rimrodt, in press) and was based the primary outcome variable designated in ClinicalTrials.gov, the Woodcock-Johnson-III (WJ-III) Basic Reading (Woodcock, McGrew, & Mather, 2001) composite score for word-level reading skills. Then, for the current study, we used a subset of children in the larger study who had participated in the MRI portion of the study and had usable scans. Participants were designated to responsiveness category (Responders or Nonresponders) based upon WJ-III Basic Reading change scores. After the two groups were established, we went back and compared whole brain functional activity during a word-reading task that had been performed prior to the intervention. We then analyzed these functional scans at the whole brain and ROI levels to determine whether they are predictive of behavioral response to intervention. Finally, we sought to categorize Responders and Nonresponders using multivariate patterns of behavioral and functional imaging data. More specifically, the study was designed to explore the following four research questions.

Research Questions and Hypotheses

Research question one: Is intensive, short-term reading intervention associated with reading growth? We hypothesized that short-term, one-on-one, reading intervention using evidence-based practices would result in increased reading scores. If increased scores were observed at posttest, an alternative hypothesis would be that effects were due to testing practice. To explore this, we compared behavioral change scores of participants receiving intervention with those of participants who were wait-listed for intervention (did not receive intervention between pre- and posttest).

Research question two: Can responsiveness to reading intervention be predicted from pre-intervention fMRI scanning? We hypothesized that children who responded well to reading intervention would exhibit a functional profile at pre-scan that differed from children with relatively poor response to the intervention. This pre-intervention functional profile could be emblematic of predisposition to intervention responsiveness.

Research question three: How do the functional imaging profiles of Responders and Nonresponders compare to typically developing participants? We hypothesized that Responders would more closely resemble typical readers in their functional activity and Nonresponders would exhibit a more dissimilar profile.

Research question four: If pre-intervention fMRI scans are predictive of intervention response, can multivariate patterns analysis (MVPA) of imaging data be used to sort Responders and Nonresponders; if so, how does this compare to MVPA of behavioral data? It was hypothesized that pre-intervention functional activity patterns could be used to discriminate

Responders and Nonresponders, and that such patterns might be superior to multivariate patterns of behavioral measures.

CHAPTER III

METHODS

In this chapter, the methods of the study are presented. First, the participants, recruitment methods, and consenting procedures are described. Next, behavioral testing and reading interventions are explained. Then, the neuroimaging procedures are described. Finally, data analysis procedures are provided.

Participants

Participants were selected as part of a larger study conducted at Kennedy Krieger Institute and Vanderbilt University and data were collected from 2006 until early 2013.The larger study recruited participants with and without neurofibromatosis type 1 (NF1) as well as participants with and without RD. Behavioral and intervention results of the larger study are presented in a separate publication (Barquero, et al., in press). The current study included children ages 8-14 years with either typical reading development or RD who completed pretest measures including an fMRI scan. All selected participants for the study were required to meet criteria for either the RD group or the typically developing group (TD) as described in the following sections. Of participants who were categorized as RD, some were randomly selected for wait-list status (RD-WL) and received intervention after posttest. For the current study, groups included RD (*n* = 23), TD (*n* = 15), and RD-WL (*n* = 16). Following intervention, the RD group was divided into Responders (*n* = 13) and Nonresponders (*n* = 10) as described in the Data Analysis section.

Recruitment and Inclusion Criteria

Participants were recruited through flyers distributed in the community and to physician offices and advocacy groups, advertisements in local parent magazines, and recruitment sites including Vanderbilt Kennedy Center Study Finder and ClinicalTrials.gov. All participants met the following inclusion criteria: 1) English as a first language; 2) normal hearing and normal vision, or vision corrected with glasses; 3) no history of major psychiatric illness; 4) no history of known neurological disorder such as traumatic brain injury, cerebral palsy, or epilepsy; 5) no history of a developmental disability; and 6) upon screening, a standard score of ≥70 on Full Scale IQ, Verbal Comprehension Index, or Perceptual Reasoning Index of the Wechsler Intelligence Scale for Children–IV (WISC-IV; Wechsler, 2003). Participants were not excluded for ADHD, though participants who could not remain motionless in a mock scanner practice session were excluded from scanning. Each participant gave written consent at the beginning of the study, with procedures carried out in accordance with the university's Institutional Review Board. Participants received $50 for completing pretest assessments and $50 for completing posttest assessments. The reading interventions were provided as part of the study and at no cost to the participants. Participant families were provided with cognitive and reading skill assessment scores for standardized tests that were part of the study.

Parents/guardians of participants contacted the research group and completed a telephone screening evaluation to gather background information and to answer questions regarding inclusionary and exclusionary criteria. If criteria were met, the participant visited the research site and completed a behavioral assessment screening session. Screening and exclusion criteria for the larger study are described elsewhere (Barquero et al., in press). For the current study, the RD and TD categories included only participants who had no contraindication to MRI (e.g., orthodontic braces, claustrophobia), consented to undergoing the MRI session, were able to complete the MRI session, and did not exhibit excessive head motion. Because the RD-WL group is only included in the behavioral analysis for this portion of the study, we did not exclude RD-WL participants who did not complete the MRI session.

Behavioral Assessment

Screening

In the screening session, in addition to the aforementioned Wechsler Intelligence Scale for Children–IV (WISC-IV; Wechsler, 2003), participants received word-level reading measures that were used for category (RD or TD) designation. Categories were defined using the Woodcock-Johnson–III (WJ-III) Letter-Word Identification (LWID) and Word Attack (WA) subtests (Woodcock, McGrew, & Mather, 2001), the Wechsler Individual Achievement Test-II Word Reading subtest (WIAT-II; Wechsler, 2001), and the Word Identification and Spelling Test (WIST; Wilson & Felton, 2004). Participants were categorized in the RD group if obtaining a standard score less than 90 (below 25th percentile) for WJ-III LWID, WJ-III WA, WIAT-II Word Reading, or the Word Identification subtest of the WIST (Wilson & Felton, 2004). Though categorization as RD required only 1 low score, all but 3 of the 23 RD participants in this study had at least 2 low scores on word-level screening measures. Further, many of the scores fell substantially below the 25th percentile cut score. Participants were categorized in the TD group if they obtained a score of greater than or equal to a standard score of 96 (40th percentile) for the average of WJ-III LWID, WJ-III Word Attack, WIAT-II Word Reading, and WIST Word Identification subtest with all scores above a standard score of 90 for these subtests.

Pretest

Following screening, participants received a battery of reading-related assessments as described in the Measures section. Phonological skills were assessed with the Comprehensive Test of Phonological Processing (CTOPP; Wagner, Torgesen, & Rashotte, 1999). Receptive and expressive language skills were evaluated with the Clinical Evaluation of Language Fundamentals (CELF 4; Semel, Wiig, & Secord, 2003). Word-level reading and decoding efficiency was measured with Test of Sight Word Reading Efficiency (TOWRE; Torgesen et al., 1997). Sound-symbol and spelling skills were assessed tested with the Word Identification and Spelling Test (WIST; Wilson & Felton, 2004). Reading accuracy, rate, and comprehension were measured with the Gray Oral Reading Test (GORT-4; Wiederholt & Bryant, 2001). Contextual fluency was measured with the Test of Silent Contextual Reading Fluency (TOSCRF; Hammill, Wiederholt, & Allen, 2006). Attention was rated by parents with the Conners' Rating Scale-Revised (Conners, 2002). Executive function was rated by parents with the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) and evaluated with Elithorn mazes (Wechsler, 2003) and the Delis Kaplan Executive Function System tower test (Delis, Kaplan, & Kramer, 2001). Handedness was evaluated with the Edinburgh Handedness Inventory (Oldfield, 1971)

Posttest

Posttest measures were administered using the alternate forms when available to those used in pretest. Participants received the posttest battery 3-13 days after pretest. Posttest battery included CTOPP, TOWRE, GORT-4, and TOSCRF in addition to WJ-III LWID and WJ-III WA.

Measures

Rapid naming. The Rapid Letter Naming subtest from the Comprehensive Test of Phonological Processing (CTOPP; Wagner, Torgesen, & Rashotte, 1999) requires participants to name six letters (*a, c, k, n, s, t*) randomly arranged as 36 stimulus items. Two trials are administered and the score is the total seconds to complete the two trials. Test-retest reliability for this subtest is 0.72 for children between 8 and17 years of age. The CTOPP Rapid Digit Naming subtest requires the participant to name six numbers (*2, 3, 4, 5, 7, 8*) randomly arranged as 36 stimuli. Two trials are administered and the score is the total seconds to complete the two trials. Test-retest reliability for this subtest is 0.80 for children between 8 and17 years of age. The Rapid Naming Composite consists of Rapid Letter Naming and Rapid Digit Naming, with test-retest reliability of 0.79.

Phonological awareness. In the Elision subtest of the CTOPP (Wagner et al., 1999) students are required to repeat a stimulus word minus a syllable or phoneme (e.g., "say *pancake* without saying *cake*" or "say *bold* without saying /b/"). The test-retest reliability of the Elision is 0.79 for students between ages 8 and 17 years. The Blending Words subtest of the CTOPP has the participant listen to audio recordings isolated sounds and then blend the sounds to form a word (the participant hears "/n/, /ō/", then says "*no*"). The test-retest reliability for Blending Words is 0.72 for children between 8 and17 years of age. The Phonological Awareness Composite consists of Elision and Blending Words, with test-retest reliability of 0.84.

Phonological memory. The Memory for Digits subtest of the CTOPP (Wagner et al., 1999) requires the participant to listen to a series of digits presented by audio recording and then repeat the series. Increasingly long series are presented. Test-retest reliability is 0.83 for children between 8 and17 years of age. In the Nonword Repetition subtest the participant listens to increasingly long pseudowords (3 to 15 phonemes) presented by audio recording. The participant repeats each pseudoword as it is presented. Test-retest reliability is 0.75 for children between 8 and17 years of age. The Phonological Memory Composite is comprised of Memory for Digits and Nonword Repetition, with a test-retest reliability of 0.86.

Comprehension. Reading comprehension was measured using the Gray Oral Reading Test (GORT-4; Wiederholt & Bryant, 2001). The GORT-4 requires participants to read passages of increasing difficulty and answer multiple-choice questions about the passages. Interform reliability is 0.78.

The WJ-III Passage Comprehension requires participants to read sentences or very short passages and provide a missing word represented by a blank space. Test-retest reliability across age groups is 0.92.

Rate. The GORT-4 (Wiederholt & Bryant, 2001) rate subtest consists of measuring the time taken to orally read each passage. Interform reliability is 0.91.

Accuracy. The GORT-4 (Wiederholt & Bryant, 2001) accuracy subtest involves the tester recording the number of errors in the oral reading of increasingly difficult passages. Interform reliability is 0.91.

Word reading. The Word Reading subtest of the Wechsler Individual Achievement Test (WIAT II; Wechsler, 2005) is an untimed test that requires participants to orally read lists of words. For lower grade levels identification of letters and sounds and phoneme blending is included. Test-retest reliability averaged across age groups is 0.98.

The Letter Word Identification Subtest of the Woodcock Johnson III (WJ-III; Woodcock et al., 2001) is an untimed measure that requires participants to orally identify letters and read real words. This measure was scored with the Normative Update (McGrew, Schrank, & Woodcock, 2007). Test-retest reliability averaged across age groups is 0.95.

The Word Identification and Spelling Test (WIST; Wilson & Felton, 2004) Word Identification subtest presents participants with high frequency sight words to read aloud. The first list of words are regularly spelled and the second list are irregularly spelled. The test-retest reliability coefficient is .98.

Spelling. The WIST (Wilson & Felton, 2004) spelling subtest requires participants to listen to dictated familiar words with both regular and irregular spellings and write the word with correct spelling. Test-retest reliability is .97.

Sound-symbol correspondence. The WIST (Wilson & Felton, 2004) Sound-Symbol Knowledge subtest requires participants to produce the correct sounds that correspond to written letters or common orthographic groupings of letters (sound patterns). Test-retest reliability is .97.

Sight word reading efficiency. The Test of Sight Word Reading Efficiency (TOWRE: SWE, Torgesen et al., 1997) is a norm-referenced measure of sight word reading accuracy and fluency. Participants are presented with a list of 104 words with increasing difficulty and read aloud as many as possible in 45 sec. Test-rest reliability for the 10-18 year old range is .83 to .92.

Phonemic decoding efficiency. The Test of Phonemic Decoding Efficiency (TOWRE: PDE, Torgesen et al., 1997) is a norm-referenced measure of decoding accuracy and fluency. Participants are presented with a list of 63 decodable pseudowords increasing in difficulty and read aloud as many as possible in 45 sec. Test-rest reliability for the 10-18 year old range is .83 to .92.

Decoding. The Word Attack Subtest is an untimed measure that requires participants to pronounce decodable pseudowords. This measure was scored with the Normative Update (McGrew et al., 2007). Test-retest reliability is 0.83 across age groups.

Word level composites. The WJ-III Basic Reading composite is comprised of WJ-III LWID and WJ-III WA. Test-retest reliability across age groups is 0.95.

Language skills. Subtests of the Clinical Evaluation of Language Fundamentals (CELF 4; Semel, Wiig, & Secord, 2003) were used to obtain composite scores for Receptive and Expressive Language. Test-retest reliability across age groups is 0.89 for Receptive Language and 0.92 for Expressive Language.

Silent reading fluency. In the Test of Silent Contextual Reading Fluency (TOSCRF; Hammill, Wiederholt, & Allen, 2006), participants are presented with passages of text containing only uppercase letters and with no spaces or punctuation. Participants are instructed to draw lines to separate the words of the increasingly long passages for three minutes. Test-retest correlation exceeds .80 for the age range of the study.

Full scale IQ. The Wechsler Intelligence Scale for Children (Wechsler, 2003) provides a measure of full scale IQ through compilation of four indexes: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. The reliability coefficient for full scale IQ is .97 across the age range.

Executive function. The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) Parent Form includes 86 items on which parents rate a child’s behavior using a three-point scale (never, sometimes, often). The items regard the behaviors Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor, Inhibit, Shift, Emotional Control. Ratings yield composite indexes for Metacognition, Behavior Regulation, and Global Executive. Test-retest correlations range from .72 to .84.

In Elithorn mazes (Wechsler, 2003), participants are required to navigate a path (using a pencil) through a maze without backtracking. The reliability coefficient for this test is .75 across the age range.

In the Delis Kaplan Executive Function System tower test (Delis et al., 2001), participants are required to build a tower of differing sized discs within certain rule constraints. Participants are timed and the number of disc moves and the number of rule violations are counted during test performance.

Behavior. The Conners' Parent Rating Scale—Revised Long Form (Conners, 2002) includes 80 items on which parents rate their child using a scale from 0 (not at all) to 3 (very much or very often) on behaviors that comprise indexes of Anxious/Shy, Inattentive, and Hyper/Impulsive. Test-retest reliability coefficients range from .47 to .85.

Handedness. The Edinburgh Handedness Inventory (Oldfield, 1971) provides participants with a list of activities (e.g., writing, throwing) for which they indicate their preferred hand for performing the activity. A quotient for laterality is calculated by subtracting the number of left hand preferences from the number of right hand preferences, diving by the total, and multiplying by 100. Negative scores (ranging from <-40 to -100) are considered to indicate lefthandedness. Positive scores (ranging from >40 to 100) are considered to indicate righthandedness. More neutral scores (-40 to 40) are considered to indicate ambidexterity or mixed handedness.

Intervention

RD participants were assigned to one of two tutorial reading interventions and received 15 hours of one-to-one instruction. Participant families were offered the choice of receiving intervention over 3 consecutive workdays for 5 hours per day, or over 5 consecutive workdays for 3 hours per day. Most participants completed the intervention in three days, with five hours of contact time per day. Participants were randomly assigned to reading intervention, with allowances for scheduling limitations (tutor availability). Both interventions incorporated systematically structured, research-based principles of reading instruction, largely derived from Orton-Gillingham (Orton, 1937) methods. Treatment A emphasized a multisensory approach to strengthen sound-symbol correspondence. Treatment B focused more upon building automaticity through repetition. The sequence of activities in each intervention was standardized across participants, but the pace of instruction was modified based on participant needs.

Treatment A used a combination of visual, auditory, and kinesthetic/tactile strategies to teach phonological awareness and sound-symbol correspondences. Participants received explicit instruction in the distinct features of vowel and consonant phonemes. Graphemes were represented on color-coded plastic chips that were used to teach phoneme-grapheme correspondences and to facilitate word building. Syllables were introduced in a prescribed sequence and supported with visual cues from color-coded chips and kinesthetic cues with hand signals. Sound blending skills were practiced by using a finger to circle graphemes on plastic chips and then drawing circles around syllables in print. Strategies for generalizing these skills to phrases and sentences in print were explicitly taught. Tutors periodically assessed progress and used assessments to inform the responsive instructional pace and scope. A total of 9 participants with RD completed Treatment A and had useable scan data.

Treatment B used visual strategies to train sound-symbol correspondences to the point of automaticity. Participants practiced visually identifying orthographic patterns on worksheets and performed repeated timed drills of sounds and words to develop automaticity. Orthographic patterns and syllables were taught in a prescribed sequence. Vowels and vowel combinations were introduced with corresponding pictures as visual cues. Participants progressed through the program developing automaticity at each level: identifying graphemes, reading phoneme-grapheme correspondences, reading single words, and reading from controlled text. A total of 14 participants with RD completed Treatment B and had useable scan data.

Participants who were wait-listed for intervention (RD-WL) received intervention after completing posttesting. As such, these participants served as the intervention control group. There were 16 RD-WL participants with behavioral data. Because the design and research questions of the current study did not require RD-WL scans, the RD-WL group was included only in the behavioral analysis and not in the imaging analysis.

Behavioral testing and reading interventions were administered by research staff and graduate students who were trained to a high level of fidelity. Behavioral assessments were independently double-scored and double-entered into the database. All testing and tutoring sessions were audio-recorded and a random sample was evaluated for treatment fidelity. In addition, a sample of tutoring sessions were observed and fidelity checklists completed by the observer to ensure fidelity.

MRI Session

Scanning

All fMRI scans were acquired at either the Kennedy Krieger Institute (KKI) in Baltimore, Maryland, United States, or at Vanderbilt University Institute of Imaging Science (VUIIS) in Nashville, Tennessee, United States, on a 3.0 T Philips Achieva MR scanner with an 8-channel head coil. Scans were performed at KKI in the years 2006-2009 and at VUIIS in the years 2010-2013. The functional task for this study was part of an MRI scanning session that included 2 additional functional tasks for participants 8-9 years of age and 3 additional functional tasks for participants aged 10-14 years in addition to structural imaging. The total time in the scanner was less than 1 hr for participants 8-9 years of age and less than 1.5 hr for participants 10-14 years of age.

Functional imaging used a single-shot echo planar sequence to acquire 40 slices (transversely oriented, ascending order, 3mm thick with a 1-mm interslice gap). Task sessions consisted of 2 runs, each 3 minutes and 40 seconds (94 dynamics per run). Other relevant imaging parameters for the functional images are TE=30 msec (for optimal BOLD contrast at 3T), 75 degree flip angle, TR=2200 msec, FOV 240 x 216 x 159 mm, and a reconstruction matrix size of 128×128 yielding 1.88×1.69×3.00 mm voxels.

fMRI Task: Single-word Reading

In this task, participants viewed individual words that appeared in the center of the screen. The stimuli consisted of real words (80%) and decodable pseudowords (20%). Both real words and pseudowords ranged from three to six letters in length. For each stimulus, the participant decided whether it was a real word (indicated by right-thumb button press) or a pseudoword (indicated by left-thumb button press). Words varied in the following dimensions:

regular/irregular, high/low frequency, and concrete/abstract. This was an event related design, with two separate runs, each consisting of 50 “words.” Stimuli were presented in random order, with each stimulus appearing on the screen for 2000 ms, with a jittered blank inter-stimulus interval ranging in duration from 1000ms to 3000 ms (mean 2000 ms). For each trial, reaction time and accuracy were measured. During each run, three 10 second periods of crosshair fixation were included to provide a baseline.

Data Analysis

Defining Responders and Nonresponders.

The difference between posttest and pretest for WJ-III Basic Reading scores was used as the measure of responsiveness. The treatment group was divided at a growth cut score of 3 W-score points to establish relative responsiveness and delineate Responder and Nonresponder groups. A cutscore that results in unequal groups for Responders and Nonresponders has been used in a previous neuroimaging study (Rezaie et al., 2011b), and for an intervention that shows an effect makes more sense than using a median split that would fail to capture potential Responders with gains below the median (i.e., participants with 3 or 4 point gains in W score) in the Responder group. One participant with a markedly negative change in Basic Reading (a decrease of 24 W points, which was 3.2 standard deviations below the mean change score for all participants) was excluded from analyses. Another point of note, of the 3 RD participants that were categorized as RD based upon a low score on a single measure, 2 were Nonresponders and 1 was a Responder.

Behavioral Measures Analysis.

All participants included in analyses had WJ-III LWID and WA scores. For other measures, missing data were replaced with the mean. SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used to make group comparisons to determine whether growth was associated with treatment (versus no treatment) as evidenced by WJ-III Basic Reading W scores at pretest and posttest. First, a repeated measures ANOVA was conducted across categories, RD, RD-WL, and TD. Next, a repeated measures ANOVA was performed for Responders, Nonresponders, RD-WL, and TD. Then, a repeated measures ANOVA was conducted to compare growth between Treatment A and Treatment B. Because W scores are not normed for age, we included age as a covariate in all repeated measures ANOVAs for WJ-III Basic Reading. As attention and executive function could potentially impact intervention responsiveness, we performed additional analyses including parent ratings on Conners Inattentive (Conners, 2002), Dupaul Attention (DuPaul, Power, Anastopoulos, & Reid, 1998), and BRIEF Metacognitive Index (Gioia et al., 2000) as additional covariates.

fMRI Behavioral Task

Button press responses to word and pseudoword stimuli presented during the fMRI scan were analyzed for response time and accuracy of response. Accuracy is reported as A′ values in the Results section. A′ is defined as follows:

$$A' = 0.5 + \frac{(\text{hit rate-false alarm rate}) \times (1 + \text{hit rate - false alarm rate})}{4 \times \text{hit rate } (1 - \text{false alarm rate})}$$

where,

$$\text{hit rate} = \frac{\text{true positives}}{\text{true positives + false negatives}}$$

$$\text{false alarm rate} = \frac{\text{false positives}}{\text{false positives + true negatives}}$$

For the purposes of response accuracy, true positives were real word stimuli for which the participant correctly pressed the right-hand thumb button. Accordingly, false positives were real word stimuli for which the participant incorrectly pressed the left thumb button. In turn, true negatives were pseudoword stimuli for which the participant correctly pressed the left thumb button. False negatives were pseudoword stimuli for which the participant incorrectly pressed the right-hand thumb button.

fMRI Scan Analysis.

Raw images from the scanner were converted to Nifti format and then realigned using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm/). Motion related outlying volumes for each participant were identified using Artifact Detection Tools (ART) (Whitfield-Gabrieli, 2009). Using a motion threshold of 3mm translation and 3° rotation, participants with ≥20% of the total volumes exceeding this threshold were excluded from analyses. Of 19 TD participants with scan data, 4 were excluded due to excessive motion. Of 26 RD participants with scan data, 2 were excluded due to excessive motion.

All functional data were analyzed using MATLAB 2013a (The MathWorks, Natick, Massachusetts, United States) and SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). At the individual level, functional data were corrected for slice timing, aligned to the mean functional image, normalized to MNI space using the EPI template, and spatially smoothed with an 8-mm FWHM Gaussian filter. The first-level regression model included estimated hemodynamic response (HRF) for each condition and the six motion parameters (translational and rotational *x*, *y*, *z*) with the outlying volumes as determined by ART (Whitfield-Gabrieli, 2009) added to the design matrix as regressors of no interest. Individual contrast maps were created to establish relative activation for the task condition, Single Word Reading (both conditions) versus Baseline.

Second-level analyses used MATLAB 2013a (The MathWorks, Natick, Massachusetts, United States) and SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/). Individual contrasts were entered into the following group-level analyses. First, using the behavioral responsiveness definition to establish Nonresponders and Responders, whole brain group contrasts were performed for Single Word Reading versus Baseline. To account for multiple comparisons (i.e., control for Type I error), thresholds of uncorrected significance and cluster size were determined by Monte Carlo simulations performed with AFNI 3dClustSim, setting an alpha level of .05 and taking into account voxel size and image dimensions. Two-sample t-test contrasts were performed first to determine how Responders and Nonresponders each differed from TD at baseline, followed by how Responders and Nonresponders differed from each other. Scan site (KKI or VUIIS) was included as a covariate. Next, to explore responsiveness as a continuous variable, behavioral responsiveness in the form of WJ-III Basic Reading change score was entered as a covariate in a general linear model of activation, and scan site was entered as a covariate of no interest. Results were visualized and regions identified using the xjView toolbox (http://www.alivelearn.net/xjview).

Region of Interest Analysis

ROIs were selected based on previous literature that examined prediction of intervention response and included L MTG (Rezaie et al., 2011a, 2011b), R MTG (Rezaie et al., 2011b), L STG (Rezaie et al., 2011a, 2011b), R STG (Rezaie et al., 2011b), L Angular gyrus (Rezaie et al., 2011b), L SMG (Rezaie et al., 2011b) L fusiform (Rezaie et al., 2011a), L VWFA located within the fusiform gyrus (Bach et al., n.d.), and R IFG (Hoeft et al., 2011). Anatomical ROIs were defined using the Automated MNI Atlas Label (AAL) in the WFU PickAtlas toolbox (http://fmri.wfubmc.edu/research/PickAtlas). The .mat ROI files were converted to Nifti (.nii) format using MarsBaR (http://marsbar.sourceforge.net/) for use in subsequent analyses. Using the coordinates provided in previous literature for R IFG (Hoeft et al., 2011) and VWFA (Bach et al., n.d.), we used MarsBaR to construct spherical ROIs, each with a 10mm radius. Group contrasts for each ROI were conducted in SPM8 and included scan site as a covariate.

As with the whole brain analyses, we input each ROI into AFNI 3dClustSim (http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) which performed alpha probability simulations to compute the probability of obtaining false positive clusters resulting from noise within a given ROI. AFNI 3dClustSim generated a table of p-values and the cluster size (number of voxels) necessary to survive statistical correction. For the two ROIs that were created by constructing spheres around a point, the 10-mm radius allowed Afni 3dClustSim to generate significance thresholds for the ROI analysis, whereas 5-mm spheres do not have sufficient volume and resulted in a warning message in Afni 3dClstSim. Hence, we did not use any spheres of 5-mm radius.

Multivariate Pattern Analysis

We performed MVPA analysis in Matlab using the MVPA Toolbox (Hoeft et al., 2011) downloaded from brainLENS (brainlens.org; last update of toolbox 02/26/2013). To conduct these analyses, we first created a class vector, designating Responders as “+1” and Nonresponders as “-1”. We then constructed a matrix of behavioral measures with the participants in rows and behavioral standard scores in columns. The support vector machine (SVM) analysis used these data to conduct a training phase in which data from previously designated groups was used to define a hyperplane that best divided the groups (Orrù, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012). The training phase was followed by leave-one-out cross-validation to minimize chances of overfitting of the data and to maximize chances that models would generalize to other data sets (Hoeft et al., 2011). Recursive feature elimination was employed, iteratively excluding 30% of the measures at a time, such that only measures that best contribute to the pattern were included in the final model.

The fMRI MVPA analyses used the same class vector as used with the behavioral measures to designate Responder status. An additional vector was constructed to designate scan site (KKI or VUIIS) for input as a regressor of no interest. For each ROI that reached significance in the previously described ROI analysis, the activation was extracted for each participant. A matrix was constructed with participants in rows and the ROI voxels in columns. After regressing out the effect of scan site, the matrix was normalized across subjects. Next, principal component analysis (PCA) was performed to reduce the dimensions of the data (Hoeft et al., 2011), as each ROI was comprised of numerous voxels (range of 498 to 4942). Each of these ROI matrices was then subjected to SVM analysis.

CHAPTER IV

RESULTS

Behavioral Analysis

Pretest

The results of word level measures that were used to categorize participants as RD or TD are shown by group in Table 3. Additionally, the WJ-III Basic Reading composite scores are listed by groups, along with the group change scores that were used on an individual basis to categorize participants as Responders and Nonresponders. ANOVAs showed significant group differences for all pretest word-level measures. Post-hoc analyses revealed that at pretest, TD significantly outperformed RD and RD-WL on all word-level measures. No difference was observed between RD and RD-WL. Responders and Nonresponders differed at pretest only for WJ-III Word Attack, for which Nonresponders scored higher. For overall groups (TD, RD, RD-WL), Basic Reading change scores did not reach significance ($p = .089$), but Responders showed statistically significant growth over Nonresponders. The more extensive behavioral battery is provided in Table 4.

fMRI behavioral task

Results for in-magnet behavioral responses are shown in Table 5. TD outperformed RD in both accuracy and response time. Responders were significantly faster in their responses than were Nonresponders, but did not differ in accuracy.

Table 3. Word-level measures used for designation of Reading Difficulty and Typically Developing status.

	All Participants								RD Subgroups					
	RD		RD-WL		TD				Non-Responders		Responders			
	n=23		n=16		n=15				n=10		n=13			
Measure	M	SD	M	SD	M	SD	*p*	η^2	M	SD	M	SD	*p*	η^2
Screening/Pretest														
WIAT Word Reading (ss)	81.3	10.0	80.3	12.6	106.2	12.5	.000[a]	.51	79.1	10.9	83.0	9.4	.367	.04
WIST Word ID (ss)	62.0	19.3	65.0	18.7	103.0	7.8	.000[a]	.55	57.2	15.9	65.7	21.5	.309	.05
WJ-III NU LWID (ss)	82.6	9.3	80.1	13.0	105.7	9.4	.000[a]	.53	83.5	10.5	81.8	8.6	.681	.01
W	463.8	30.3	462.4	28.9	508.8	21.8	.000[a]	.36	458.0	28.1	468.2	32.3	.436	.03
WJ-III NU WA (ss)	86.2	8.7	85.0	7.2	102.8	9.1	.000[a]	.47	91.3	5.9	82.3	8.6	.010	.28
W	477.0	17.8	475.8	15.7	504.3	11.1	.000[a]	.40	482.0	14.6	473.2	19.6	.246	.06
WJ-III NU BR (ss)	83.0	8.6	80.9	9.6	104.6	9.3	.000[a]	.57	86.2	8.2	80.6	8.5	.127	.11
W	470.4	22.4	469.1	20.2	506.5	14.7	.000[a]	.42	470.1	20.4	470.6	24.7	.958	.00
Posttest														
WJ-III NU LWID (ss)	83.4	11.1	80.8	13.4	103.5	10.3			80.9	11.4	85.4	10.8		
W	465.5	34.6	464.1	30.7	505.7	18.3			452.0	31.3	475.9	34.5		
WJ-III NU WA (ss)	89.7	6.6	84.6	5.9	103.9	8.0			91.4	6.3	88.5	6.8		
W	483.5	14.5	475.7	11.4	506.9	9.1			482.8	13.2	484.1	15.9		
WJ-III NU BR (ss)	85.2	9.1	81.1	9.1	103.9	9.5			84.6	9.4	85.7	9.2		
W	474.5	23.8	469.9	18.7	506.3	12.6			467.4	21.9	479.9	24.6		
Pretest-Posttest Change														
WJ-III NU BR (ss)	2.2	4.2	0.3	4.4	-0.7	3.3	.089	.09	-1.6	2.6	5.1	2.6	.000	.64
W	4.1	7.8	0.9	7.9	-0.3	4.6	.150	.07	-2.7	4.9	9.3	4.9	.000	.62

[a] TD > RD and RD-WL, p<.001

[b] RD > RD-WL, p = .024

[c] RD > RD-WL, p = .056, not significant

WIAT=Wechsler Individual Achievement Test, WJ-III NU=Woodcock Johnson-III Normative Update, LWID=Letter Word Identification, WA=Word Attack, BR=Basic Reading, WIST=Word Identification and Spelling Test ss=standard score, W=W score

Table 4. Demographic information and assessment scores by group.

	All Participants								RD Subgroups					
	RD (n=23)		RD-WL (n=16)		Typically Developing (n=15)				Non-Responders (n=10)		Responders (n=13)			
Measure	M	SD	M	SD	M	SD	*p*	η^2	M	SD	M	SD	*p*	η^2
Age	10.4	2.0	10.6	2.1	10.1	1.7	.800	.01	9.9	2.1	10.8	1.9	.275	.06
Gender	F11 M12		F5 M11		F6 M9		.583		F3 M7		F8 M5		.133	
Edinburgh Handedness	R19 Amb4		R13 Amb3		R11 Amb4		.772		R8 Amb2		R11 Amb2		.772	
WISC FSIQ	90.9	10.3	86.9	12.9	101.5	11.6	.002[a,b]	.21	91.1	10.9	90.8	10.2	.926	.00
Conner's Parent AS (T)	52.3	9.2	49.8	7.7	55.3	13.5	.329	.04	56.1	9.2	49.3	8.3	.077	.14
Conner's Parent HI (T)	54.6	13.6	60.2	12.9	56.4	9.6	.389	.04	58.7	14.4	51.5	12.6	.213	.07
Conner's Parent Inatt (T)	58.0	14.2	58.6	12.2	57.7	13.2	.982	.00	64.2	14.1	53.2	12.8	.063	.16
BRIEF Parent BRI (T)	49.0	9.3	56.1	10.6	52.7	11.5	.116	.08	50.0	10.2	48.2	8.9	.661	.01
BRIEF Parent MCI (T)	56.4	12.5	57.0	11.9	55.3	14.4	.934	.00	62.6	11.7	51.5	11.2	.031	.20
DKEFS Tower	9.7	2.9	7.8	3.4	9.8	2.8	.094	.09	10.0	3.5	9.5	2.5	.713	.01
Elithorn Maze	8.5	3.5	7.0	3.0	10.1	3.2	.043[d]	.12	7.3	3.6	9.5	3.3	.149	.10
Pretest														
CTOPP PA (ss)	89.7	11.3	82.9	14.4	99.6	14.8	.004[b,c]	.20	91.3	12.8	88.4	10.4	.556	.02
CTOPP PM (ss)	87.4	9.8	88.5	8.2	91.6	13.4	.473	.03	85.9	10.6	88.5	9.4	.546	.02
CTOPP RN (ss)	85.9	9.7	84.0	11.4	98.0	17.8	.007[a,b]	.18	83.8	11.5	87.6	8.2	.366	.04
CELF Receptive (ss)	86.7	15.6	81.3	14.6	94.2	13.6	.059	.11	89.3	18.4	84.8	13.4	.502	.02
CELF Expressive (ss)	86.5	15.3	84.5	13.4	99.5	11.7	.007[a,b]	.18	86.4	15.9	86.6	15.5	.974	.00
TOWRE SWE (ss)	81.3	9.4	82.8	14.0	101.9	15.9	.000[a,b]	.34	77.1	7.3	84.5	9.8	.057	.16
TOWRE PDE (ss)	82.2	5.7	77.5	8.5	100.9	13.8	.000[a,b]	.52	82.9	5.4	81.7	6.1	.626	.01
WIST Sound Symbol (ss)	70.7	11.2	69.6	9.8	94.3	13.0	.000[a,b]	.49	73.7	11.5	68.3	10.8	.263	.06
WIST Spelling (ss)	71.7	10.5	71.2	12.0	98.1	15.0	.000[a,b]	.50	68.1	9.4	74.4	10.8	.158	.09
GORT Accuracy (sc)	4.6	2.4	5.0	2.5	10.0	3.3	.000[a,b]	.45	3.8	2.0	5.2	2.6	.195	.08
GORT Rate (scaled)	5.0	2.3	6.0	2.5	10.3	3.3	.000[a,b]	.42	4.3	1.9	5.6	2.6	.179	.08
GORT Comprehension (sc)	8.2	2.9	7.6	3.0	10.2	3.7	.060	.10	8.1	2.6	8.3	3.2	.842	.02
TOSCRF (ss)	80.0	8.8	78.4	8.5	94.4	12.5	.000[a,b]	.33	76.8	8.8	82.4	8.4	.135	.10

Posttest														
CTOPP PA (ss)	92.7	11.8	87.4	14.4	102.2	13.5	.010[b,c]	.17	95.2	15.2	90.8	8.4	0.382	.04
CTOPP PM (ss)	91.0	9.9	88.4	12.4	94.2	13.0	.380	.04	91.0	12.1	91.0	8.3	1.000	.00
CTOPP RN (ss)	85.1	11.0	80.3	11.3	95.2	18.0	.010[b,c]	.16	80.8	12.4	88.5	8.7	.097	.13
TOWRE SWE (ss)	80.5	9.8	81.8	14.1	103.7	13.3	.000[a,b]	.42	75.3	7.2	84.5	9.9	.022	.23
TOWRE PDE (ss)	79.3	6.2	74.8	10.4	100.2	12.1	.000[a,b]	.56	79.6	6.4	79.0	6.4	.825	.00
GORT Accuracy (scaled)	4.8	2.5	4.6	2.4	10.9	2.9	.000[a,b]	.55	4.4	2.4	5.0	2.7	.609	.01
GORT Rate (scaled)	4.8	2.5	5.4	3.0	10.7	3.8	.000[a,b]	.42	3.8	1.9	5.6	2.7	.079	.14
GORT Comprehension (sc)	8.5	2.8	7.8	2.5	11.7	3.3	.001[a,b]	.25	8.2	2.5	8.7	3.0	.691	.01
TOSCRF (ss)	85.8	12.2	82.3	9.7	101.1	13.2	.000[a,b]	.31	82.5	14.0	88.4	10.6	.262	.06

[a]TD > RD *p* < .01, [b]TD > RD-WL, *p* < .01, [c]TD > RD *p* < .05, [d]TD > RD-WL, *p* < .05

Amb = ambidextrous, ss=standard score, sc=scaled score, T= T-score, WISC=Wechsler Intelligence Scale for Children, AS=Anxious/Shy, HI=Hyper/Impulsive, Inatt=Inattentive, BRI=Behavioral Regualtion Index, MCI=Metacognition Index, BRIEF=Behavior Rating Inventory of Executive Function, CTOPP=Comprehensive Test of Phonological Processing, PA=Phonological Awareness, PM=Phonological Memory, RN=Rapid Naming,CELF=Clinical Evaluation of Language Fundamentals, TOWRE=Test of Word Reading Efficiency, SWE=Sight Word Efficiency, PDE=Pseudoword Decoding Efficiency, WIST=Word Identification and Spelling Test, GORT=Gray Oral Reading Test, TOSCRF=Test of Silent Contextual Reading Fluency

Table 5. fMRI task accuracy and response time by group.

	All Participants						RD Subgroups					
	RD n=23		Typically Developing n=15				Non-Responders n=10		Responders n=13			
Measure	M	SD	M	SD	*p*	η^2	M	SD	M	SD	*p*	η^2
Accuracy (A')	0.83	0.17	0.93	0.07	0.03	.12	0.78	0.21	0.870	0.130	0.228	.07
Response Time (ms)	968.20	117.21	903.68	97.46	0.09	.08	1029.33	89.16	921.18	117.12	0.024	.22

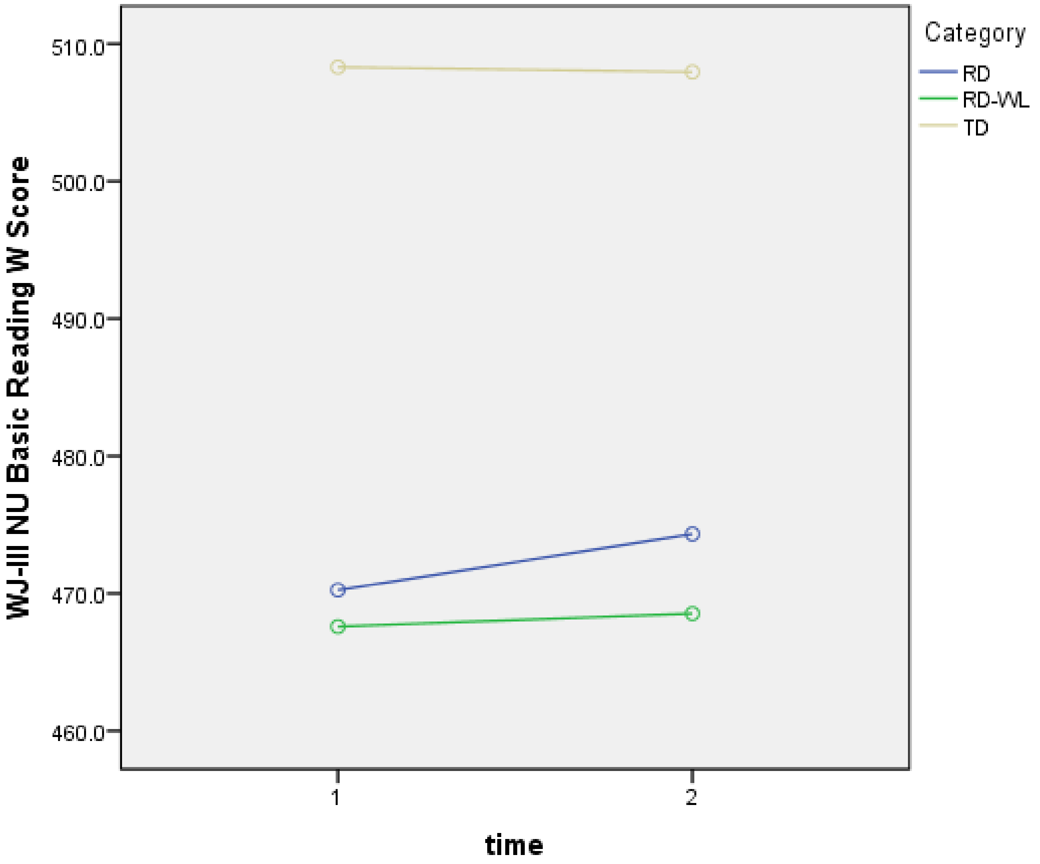
Word-level reading change

Intervention results for the larger study showed significant effect of treatment on word-level skills and are reported separately (Barquero et al., in press). To evaluate the smaller sample included in the current study, a repeated measures ANOVA was performed to test intervention effect on word level reading skills using WJ Basic Reading W scores, comparing RD (n =23), RD-WL (n= 16) and TD (n = 15) while covarying on age. At both pretest and posttest, W scores met the assumption of normality for all groups as determined by Shapiro-Wilk test (p>0.05). No outliers were detected by inspection of SPSS boxplots. Results indicated a non-significant category × time interaction, *F*(2, 50), = 1.984, *p* = .148; however, η_p^2 =.074 indicated a small-to-medium effect size (Fig 2). The main effect of category was significant (p<.001, η_p^2 =.592) but the main effect of time was not significant (p=.352, η_p^2 =.017) and the age × time interaction was not significant *F*(1, 50), = 0.434, *p* = .513, η_p^2 =.009. When including attention and executive function as additional covariates, the category × time interaction was significant, *F*(2, 45), = 3.453, *p* = .040. Post-hoc analyses reveal that RD showed significant gains (*p*=.002), while RD-WL (*p*=.794) and TD (*p*=.491) did not.

To confirm that Responders showed a significant gain relative to other groups, an additional repeated measures ANOVA for WJ-III Basic Reading was conducted with the RD group divided into Responders (n=13) and Nonresponders (n=10) and comparing RD-WL (n=16) and TD (n=15) and covarying on age. Results indicated a significant responder group × time interaction, *F*(3, 49), = 10.695, *p* < .001, with η_p^2 =.396 indicating a large effect size (Fig 3). The main effect of time neared significance, *F*(1, 49)=3.998, *p*=.051, η_p^2 =.075. The main effect of responder status was significant *F*(3,49)=23.733, *p* <.001, η_p^2 =.592. (The additional analysis that included ratings of attention and meta-cognition as additional covariates showed similar results with group × time interaction, *F*(3, 45), = 10.143, *p* < .001). Post hoc pairwise comparisons revealed that only Responders exhibited a significant increase from pretest to posttest (*p*<.001), in contrast to no change for RD-WL (*p*=.487), and TD (*p*=.770) and Nonresponders (*p*=.105). In this analysis all groups met the assumption of normality as assessed by Shapiro-Wilk (*p* >.05) at both pretest and posttest. However, there were two low outliers and one high outlier at pretest, all within the Responder group; none of these were extreme outliers as determined by inspection of boxplots. At posttest, one of the pretest low outliers remained a low outlier, otherwise there were no outliers in the posttest data. To justify including these outliers, we reran the analysis with the 3 outliers excluded. No difference was observed in outcome: group × time interaction, *F*(3, 46), = 9.681, *p* < .001, with post-hoc analyses showing significant gain for Responders alone.

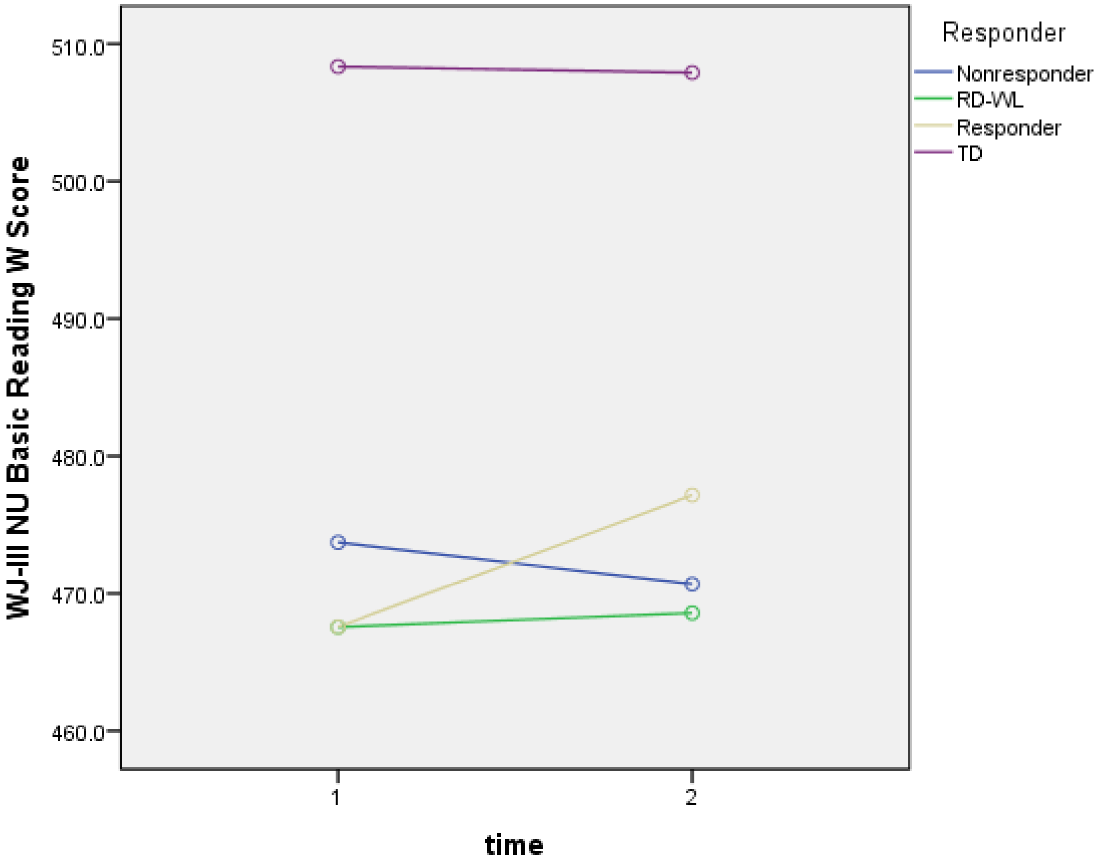
The small sample size necessitated the combining of treatment groups upon establishing no difference for which treatment was received. Of the 13 Responders, 6 received Treatment A and 7 received Treatment B. Of the 10 Nonresponders, 3 received Treatment A and 7 received Treatment B. A Fisher's exact test revealed that differences in the distributions were not significant (*p* =.669) To determine whether the two treatments differed in growth, a repeated measures ANOVA was conducted comparing Treatment A (*n*=9) and Treatment B (*n*=14) and covarying for age. Treatment × time was not significant (*p*=.701). These results are congruent with the larger sample results, and indicate that combining the two treatments for analyses is acceptable.

Figure 2. Repeated measures ANOVA of WJ-III NU Basic Reading W scores by category



Covariates appearing in the model are evaluated at the following values: Age = 10.4015

Figure 3. Repeated measures ANOVA of WJ-III NU Basic Reading W score by responder status.



Covariates appearing in the model are evaluated at the following values: Age = 10.4015

Imaging Analysis

Whole Brain Analysis

Using SPM8, whole brain group comparisons (TD v RD, TD v Responders, TD v Nonresponders, Responders v Nonresponders) were conducted for single word reading > baseline. To account for multiple comparisons, 3dClustSim performed Monte Carlo simulations to determine cluster size and image significance level for alpha level .05. Clusters that survived this threshold are presented in Tables 6-9and the resulting images are presented in Figures 4-7. All significant relative activations were positive (i.e, TD showed only increased activation relative to RD, Responders, and Nonresponders; Responders showed only increased activation relative to Nonresponders). To explore responsiveness as a continuous variable rather than a dichotomous variable, we used multivariate regression. In SPM8, we entered all RD scans (first-level contrasts of word reading>baseline, n=23) and input WJ-III Basic Reading change in W score along with scan site as covariates. We used the same thresholding (p=0.05) as used for the group comparisons. Clusters that survived this threshold are presented in Table 10 and the resulting image is presented in Figure 8.

Table 6. Significant clusters for TD>RD during single word reading task

Cluster Size (2x2x2 mm voxels)	Region	MNI Coordinates x	y	Z	t-value	Brodmann Areas (≥40 voxels)
1666						21, 37, 18, 19, 20
	L Middle Temporal Gyrus	-52	-52	0	3.25	
		-48	-36	-14	3.23	
	L Middle Occipital Gyrus	-40	-60	0	3.24	
		-32	-74	6	3.10	
	L Fusiform Gyrus	-32	-64	-14	3.07	
		-34	-32	-20	2.99	
986						8, 6, 9
	L Middle Frontal Gyrus	-26	26	44	3.39	
		-28	22	44	3.38	
		-30	26	30	3.20	
		-32	8	50	2.99	
	L Precentral Gyrus	-36	2	32	3.34	
862						40, 39
	L Angular Gyrus/Inferior Parietal Lobule	-46	-66	40	3.73	
754						40
	R Angular Gyrus	48	-54	38	3.19	
	R Inferior Parietal Lobule	58	-58	40	3.11	
		54	-56	40	3.11	
	R Superior Temporal Gyrus	36	-38	16	3.10	
	R Supramarginal Gyrus/Angular Gyrus	48	-50	32	3.03	
566						31, 23
	R Posterior Cingulate/Precuneus	4	-58	22	3.31	
	L Posterior Cingulate/Precuneus	-4	-58	18	3.30	
	L Subgyral/Cuneus	-14	-58	24	3.10	

Note: Local maxima shown for t-value ≥ 2.99 and > 4mm apart. Threshold values for an alpha level of .05 were calculated by Afni 3dClustSim to be p = .02, k = 538.

Table 7. Significant fMRI clusters for TD>Responders during single word reading task

Cluster Size (2x2x2 mm voxels)	Region	MNI Coordinates x	y	Z	t-value	Brodmann Areas (≥ 40 voxels)
938						24, 23
	R Cingulate Gyrus	12	-26	30	4.02	
	L Cingulate Gyrus	-8	-20	32	4.02	
		-16	-8	44	3.30	
		-16	-24	36	3.22	

Note: Local maxima shown for t-value ≥ 2.99 and > 4mm apart. Threshold values for an alpha level of .05 were calculated by Afni 3dClustSim to be p = .02, k = 538.

Table 8. Significant fMRI clusters for TD>Nonresponders during single word reading task

Cluster Size (2x2x2 mm voxels)	Region	MNI Coordinates x	y	Z	t-value	Brodmann Areas (≥40 voxels)
2657						37, 19, 18, 20
	L Fusiform Gyrus	-30	-68	-16	4.21	
		-34	-34	-24	4.01	
		-36	-36	-20	3.96	
		-42	-62	-14	3.64	
		-40	-50	-20	3.29	
		-36	-54	-18	3.19	
		-30	-64	-4	3.16	
	L Middle Occipital Gyrus	-54	-68	-8	4.11	
	L Inferior Frontal Gyrus	-52	-48	-28	3.86	
	L Inferior Occipital Gyrus	-44	-78	-8	3.81	
		-50	-74	-10	3.39	
	L Cerebellum	-36	-64	-24	3.41	
	Vermis	-2	-70	-6	3.14	
1297						34, 21, 28, 38, 20
	R Amygdala	18	4	-18	5.26	
	R Middle Temporal Gyrus	60	0	-32	4.50	
		46	4	-24	3.79	
	R Temporal Pole/MTG	36	8	-34	3.38	
		52	18	-32	3.01	
	R Temporal Pole/STG	52	20	-24	3.20	
	R Fusiform Gyrus	40	-20	-22	3.01	
867						
	R Cerebellum	10	-44	-52	3.57	
	L Cerebellum	-16	-48	-48	3.48	

		-16	-44	-50	3.42	
850						
	L Superior Frontal Gyrus	-26	-2	68	3.74	
	L Precentral Gyrus	-34	-20	62	3.48	
	L Middle Frontal Gyrus	-26	10	60	3.05	
668						31, 23, 7
	L Cuneus	-14	-58	24	3.46	
	R Precuneus	8	-54	24	3.28	
		2	-58	30	3.19	
	L Precuneus	-6	-60	18	3.18	
644						37
	R Cerebellum	22	-54	-24	3.42	
	R Parahippocampal Gyrus	26	-30	-14	3.02	
622						40
	L Inferior Parietal Lobule	-40	-46	54	3.55	
		-36	-58	52	3.08	

Note: Local maxima shown for t-value ≥ 2.99 and > 4mm apart. Threshold values for an alpha level of .05 were calculated by Afni 3dClustSim to be p = .02, k = 538. Maxima not defined in WFU aal PickAtlas are not included in table.

Table 9. Significant fMRI clusters for Responders>Nonresponders during single word reading task

Cluster Size (2x2x2 mm voxels)	Region	MNI Coordinates			t-value	Brodmann Areas (≥40 voxels)
		x	y	z		
3882						20, 38, 21, 28, 37, 34, 36
	R Parahippocampal Gyrus	20	8	-26	4.66	
		28	-4	-36	3.47	
	R Cerebellum	52	-58	-34	4.57	
		22	-54	-24	4.44	
		50	-52	-32	4.27	
		38	-44	-28	3.84	
		36	-50	-26	3.50	
		40	-68	-36	3.11	
	R Fusiform	42	-20	-22	4.21	
		30	-10	-34	3.70	
	R Temporal Pole, STG	32	16	-26	3.64	
	R Hippocampus	28	-32	-8	3.62	
	R Middle Temporal Gyrus	48	4	-22	3.52	
		58	2	-28	3.39	
	R Temporal Pole, MTG	52	18	-32	3.45	
		56	14	-22	3.15	
	R Inferior Temporal Gyrus	46	-8	-34	3.13	
2004						6, 40, 3, 2, 7
	L Precentral Gyrus	-32	-4	64	4.18	
		-34	-16	62	3.06	
	L Postcentral Gyrus	-42	-42	58	4.03	
		-50	-22	52	3.39	
		-50	-16	54	3.36	

		-48	-22	46	3.31	
		-44	-28	64	3.14	
	L Supramarginal	-58	-30	34	3.66	
	L Superior Frontal Gyrus	-20	-4	58	3.39	
	L Inferior Parietal Lobule	-36	-38	46	3.11	
871						37, 19, 20
	L Fusiform Gyrus	-38	-38	-22	4.69	
		-36	-46	-22	3.63	
	L Inferior Temporal Gyrus	-44	-62	-10	3.72	
		-52	-62	-10	3.28	
	L Inferior Occiptal Gyrus	-38	-74	-4	3.16	
	L Cerebellum	-34	-64	-30	3.03	
708						
	L Cerebellum	-8	-48	-56	4.19	
		-14	-42	-54	3.51	
	R Cerebellum	6	-50	-52	3.08	
668						
	L Parahippcampal Gyrus	-24	-18	-30	3.03	

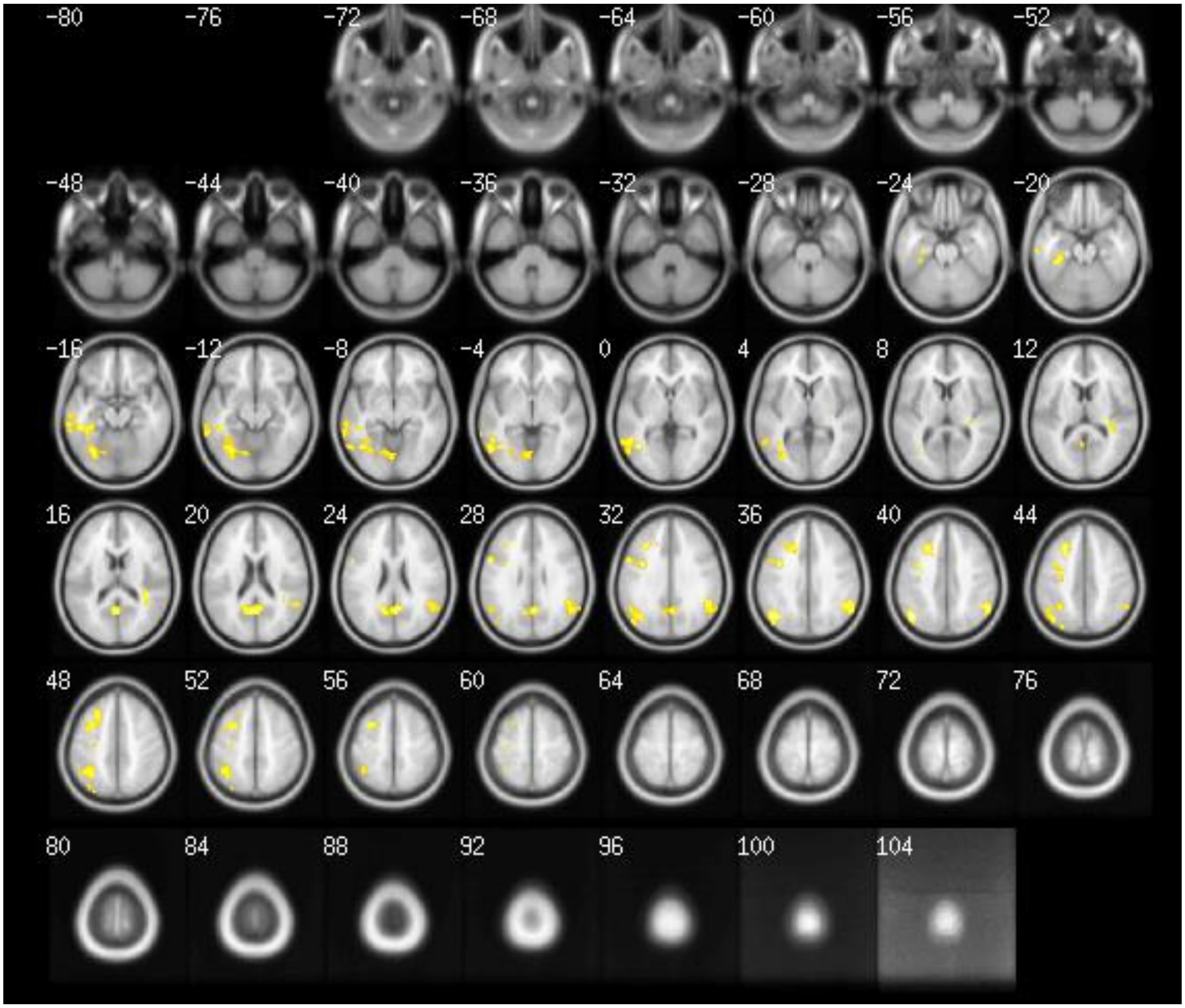
Note: Local maxima shown for t-value ≥ 2.99 and > 4mm apart. Threshold values for an alpha level of .05 were calculated by Afni 3dClustSim to be p = .02, k = 538. Maxima not defined in WFU aal PickAtlas are not included in table.

Table 10. Significant clusters for RD group regressing on Basic Reading change score.

Cluster Size (2x2x2 mm voxels)	Region	MNI Coordinates x	y	z	t-value	Brodman Areas (≥40 voxels)
874						40, 2, 3
	L Inferior Parietal Lobule	-46	-42	56	4.07	
		-48	-24	48	3.59	
		-38	-36	50	3.50	
		-44	-30	64	3.38	
	L Supramarginal	-58	-28	32	3.12	
	L Inferior Parietal Lobule	-26	-48	54	3.11	
768						20
	R Cerebellum	24	-56	-24	3.72	
		18	-52	-24	3.45	
		38	-42	-30	3.32	
		52	-58	-34	3.03	
	R Fusiform	44	-34	-20	2.99	

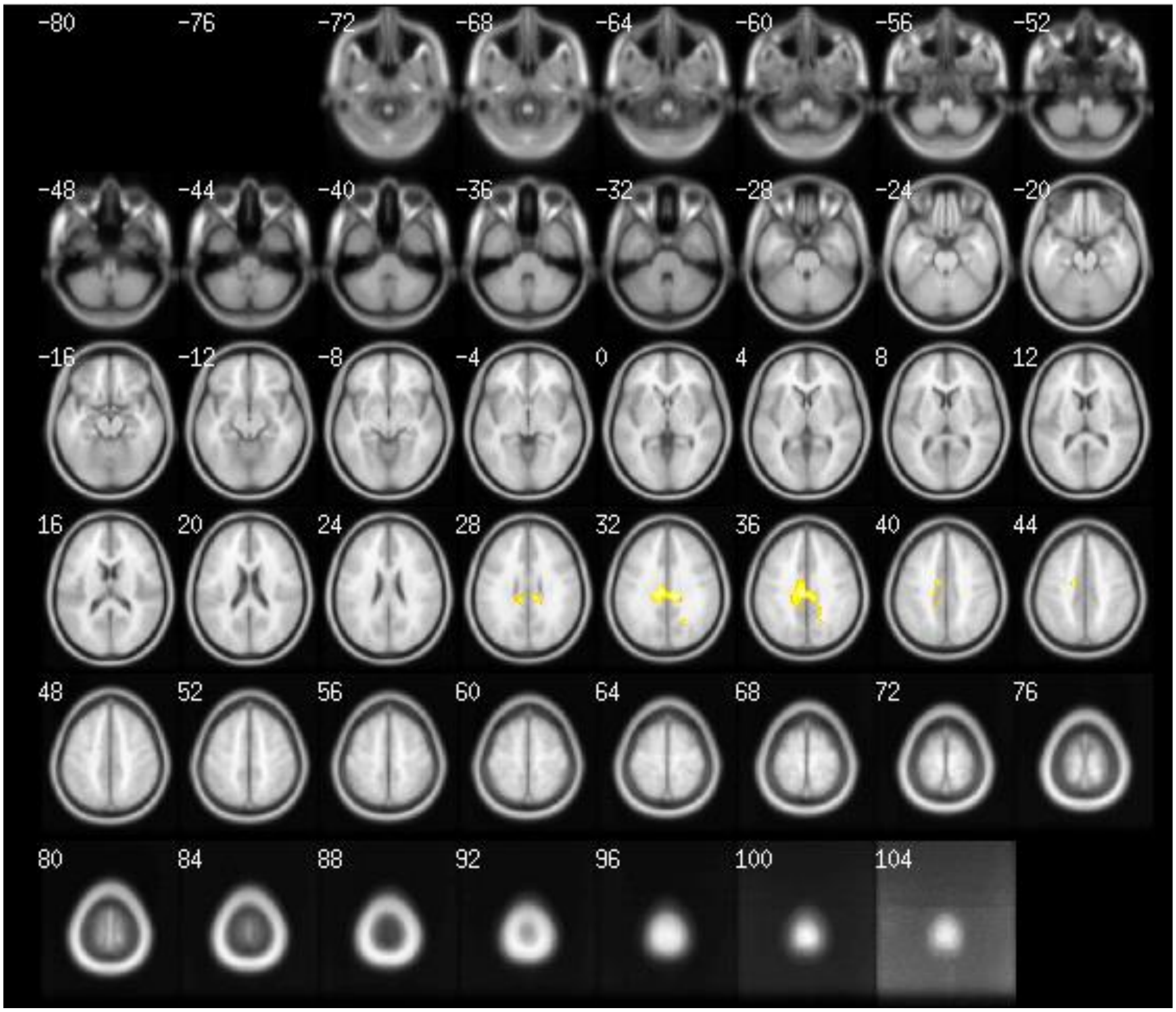
Note: Local maxima shown for t-value ≥ 2.99 and > 4mm apart. Threshold values for an alpha level of .05 were calculated by Afni 3dClustSim to be p = .02, k = 538.

Fig. 4. Whole brain group comparison TD (n=15) versus RD (n=23) for word reading > baseline.



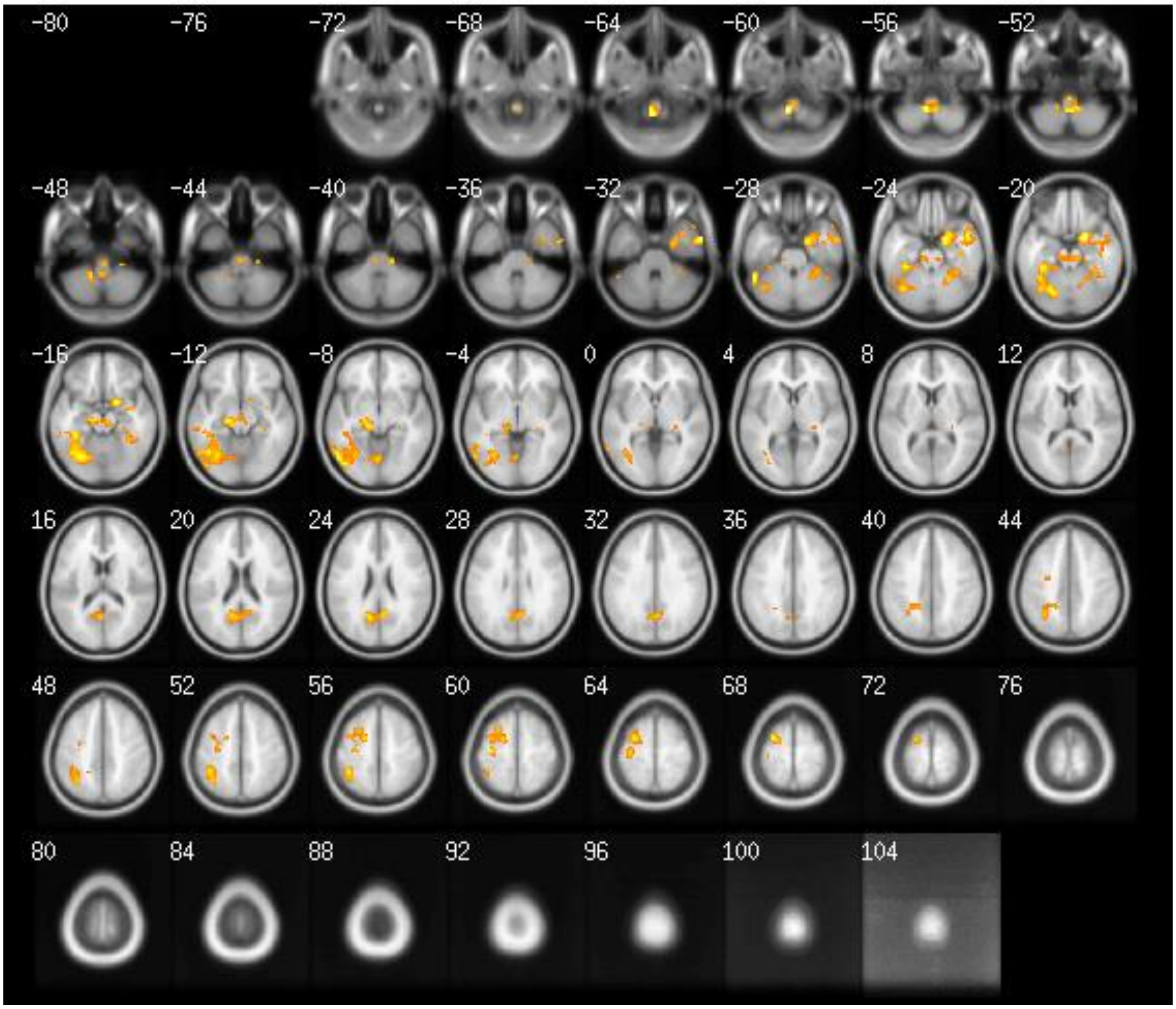
p<0.05 (image threshold at p=0.02, k=538 per 3dClustSim)

Fig. 5. Whole brain group comparison TD (n=15) versus Responders (n=13) for word reading > baseline.



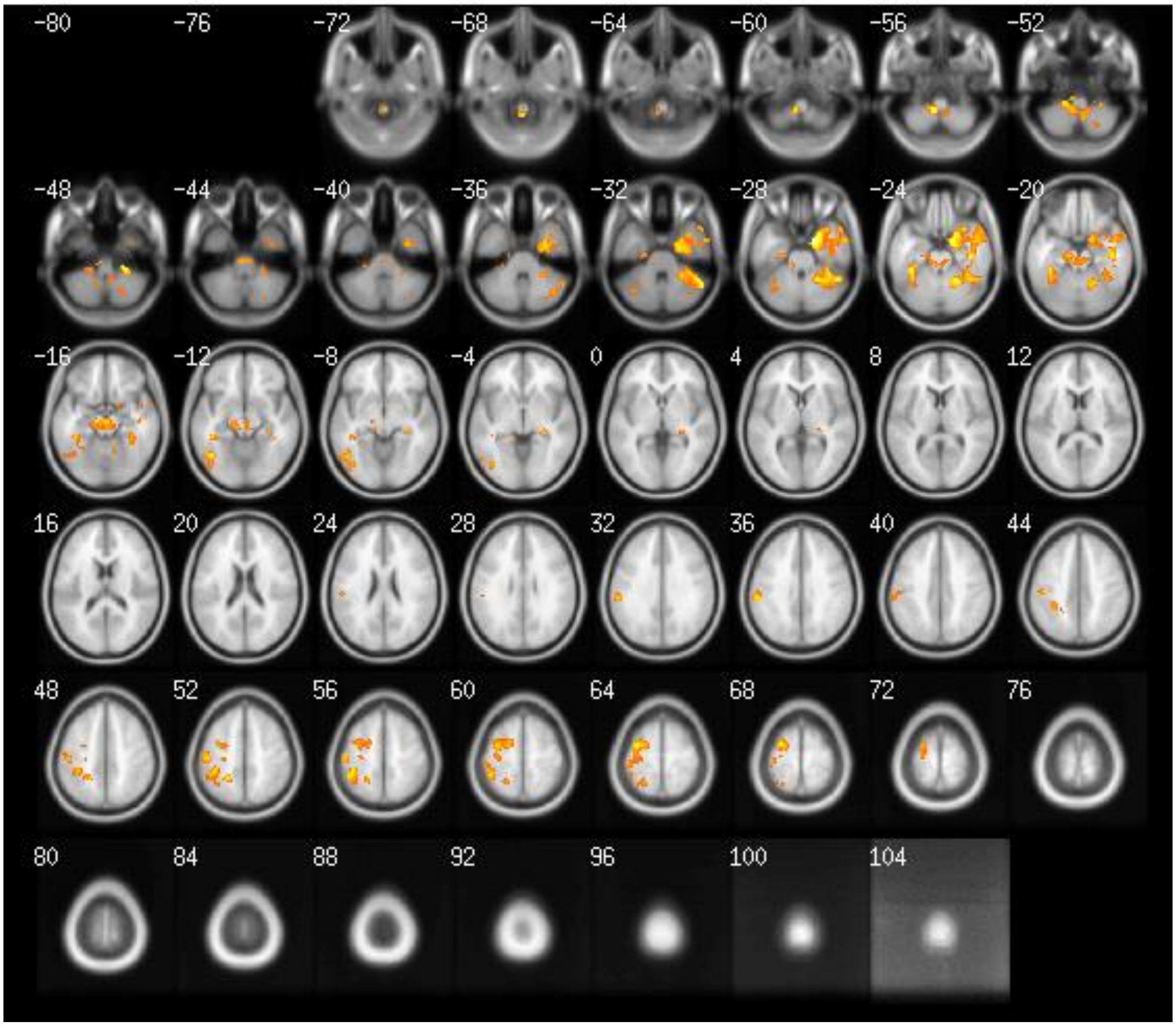
$p<0.05$ (image threshold at $p=0.02$, $k=538$ per 3dClustSim)

Fig. 6. Whole brain group comparison TD (n=15) versus Nonresponders (n=10) for word reading > baseline.



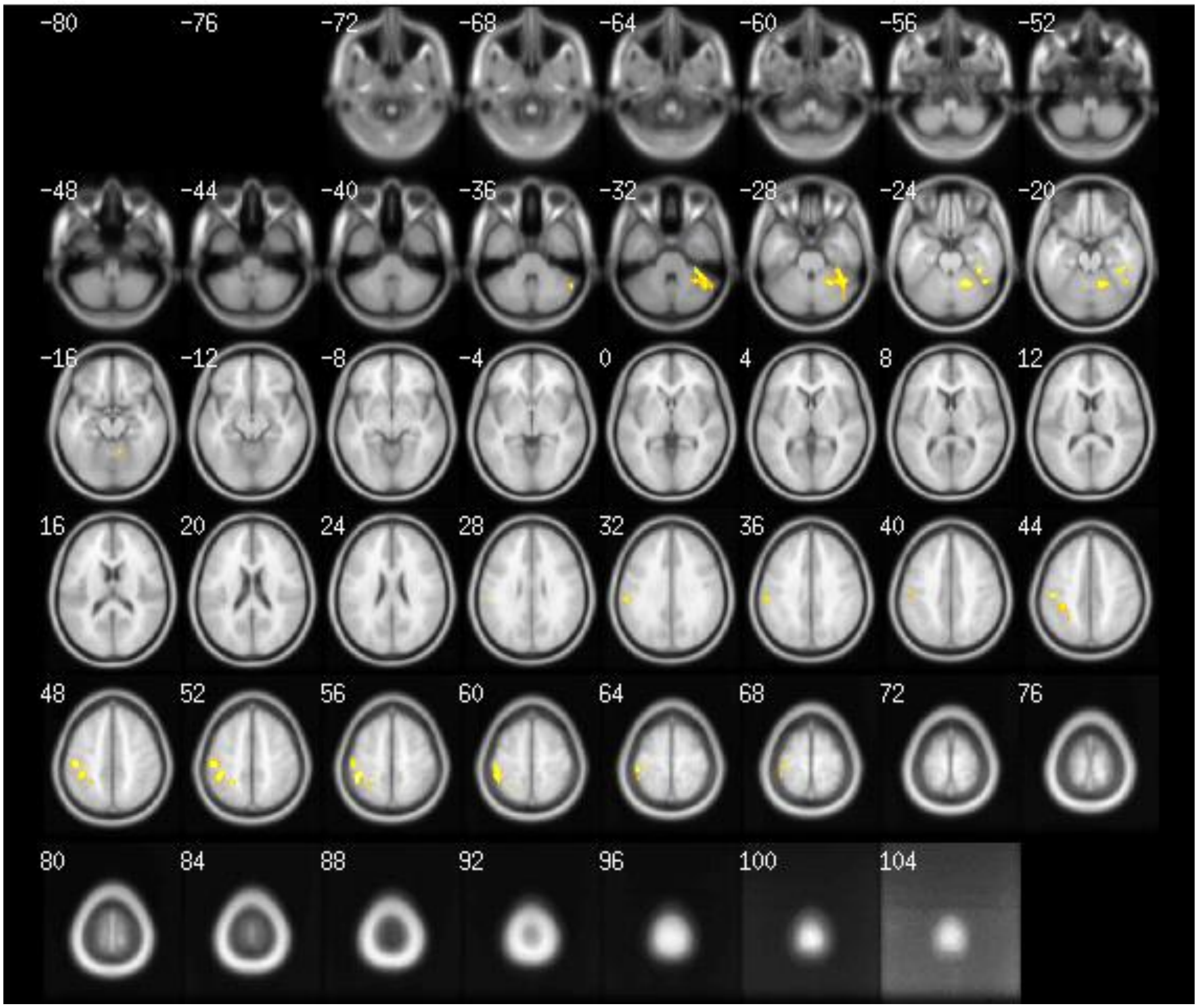
p<0.05 (image threshold at p=0.02, k=538 per 3dClustSim)

Fig. 7. Whole brain group comparison in Responders (n=13) versus Nonresponders (n=10) for word reading > baseline.



$p<0.05$ (image threshold at $p=0.02$, $k=538$ per 3dClustSim)

Fig. 8. Whole brain multiple regression showing WJ-III NU Basic Reading W score change for the RD group (including scan site as a covariate of no interest)



p<0.05 (image threshold at p=0.02, k=538 per 3dClustSim)

ROI Analysis

ROI analyses were conducted on literature-based ROIs. The comparisons by responder status (TD v Responders, TD v Nonresponders, Responders v Nonresponders) are presented in Table 11 and Figures 9-16. Significance thresholds were set at p=0.05 and cluster and significance levels were determined by 3dClustSim. All significant relative activations were positive (i.e, TD showed only increased activation relative to Responders and Nonresponders; Responders showed only increased activation relative to Nonresponders).

Table 11. Region of interest analysis

	TD v Responder	TD v Nonresponder	Responder v Nonresponder
Region	*p*	*p*	*p*
Anatomically Defined			
L Angular Gyrus			
L Fusiform Gyrus		<.001	<.001
L Middle Temporal Gyrus	<0.05		
L Superior Temporal Gyrus			
L Supramarginal Gyrus		<.001	<.01
R Middle Temporal Gyrus			<.01
R Superior Temporal Gyrus			
10mm Spheres			
Visual Word Form Area		<.001	<.05
R Inferior Frontal Gyrus			

Fig 9. Left fusiform region of interest for TD > Nonresponders during single word reading task.

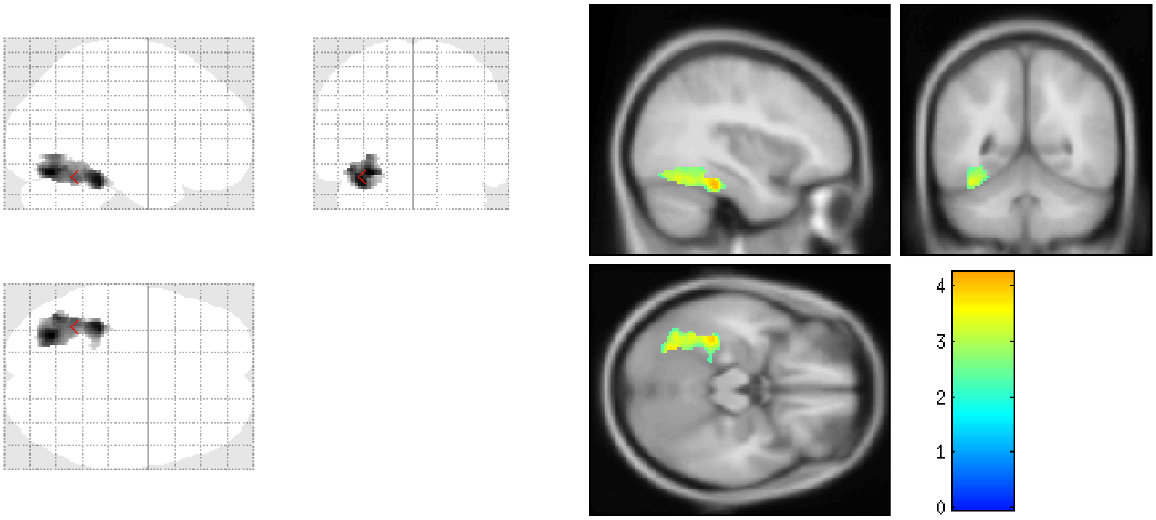


Fig 10. Left fusiform region of interest for Responders > Nonresponders during single word reading task.

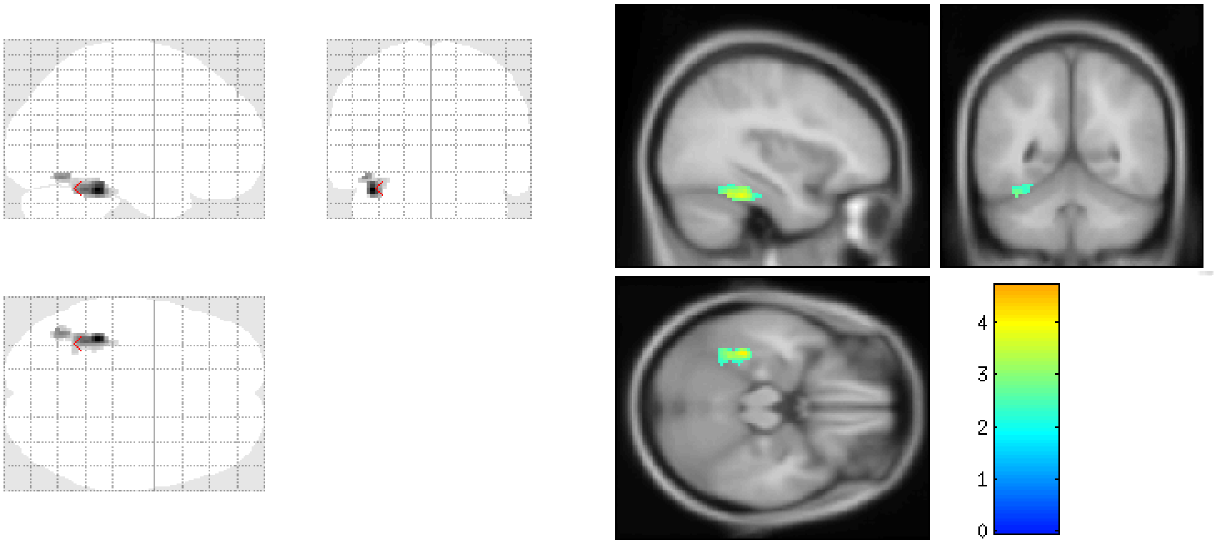


Fig. 11.Visual Word Form Area region of interest, 10mm sphere with center at MNI -42 -54 -17 (Bach et al., n.d.), for TD > Nonresponders during single word reading task.

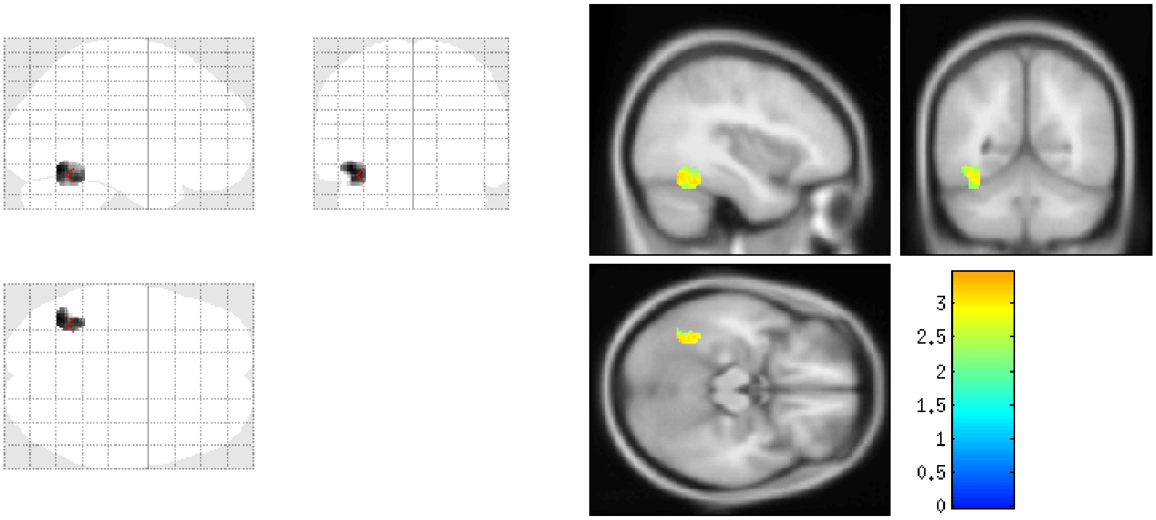


Fig. 12. Visual Word Form Area region of interest, 10mm sphere with center at MNI -42 -54 -17 (Bach et al., n.d.), for Responders > Nonresponders during single word reading task.

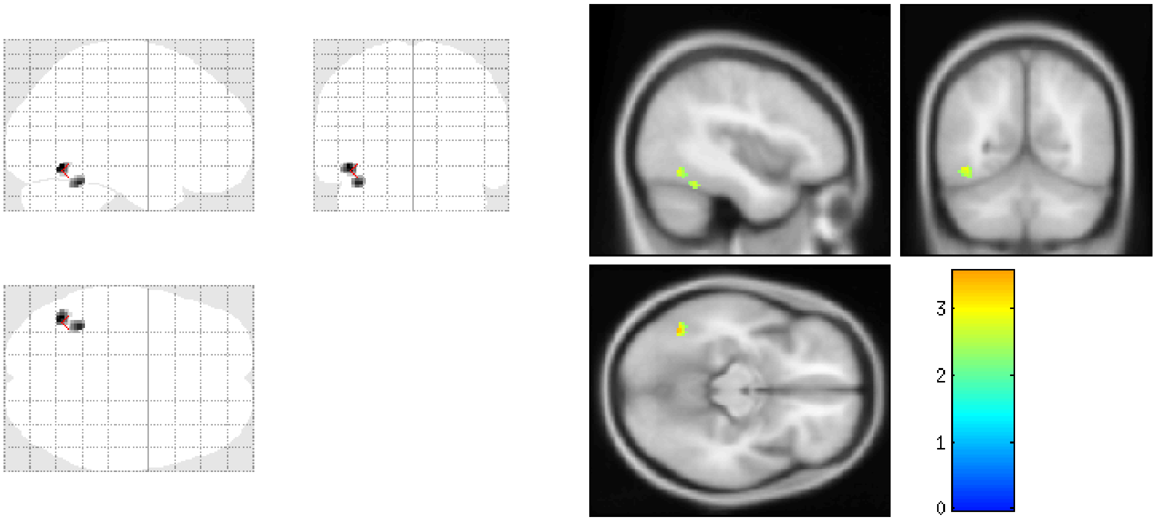


Fig 13. Left supramarginal gyrus regiojn of interest for TD > Nonresponders during single word reading task.

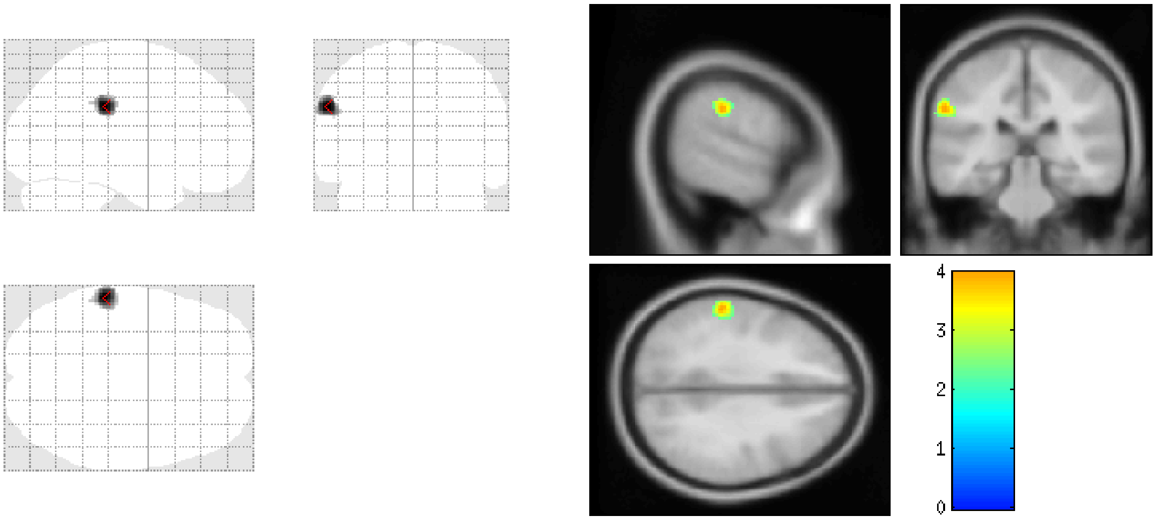


Fig. 14. Left supramarginal region of interest for Responders > Nonresponders during single word reading task.

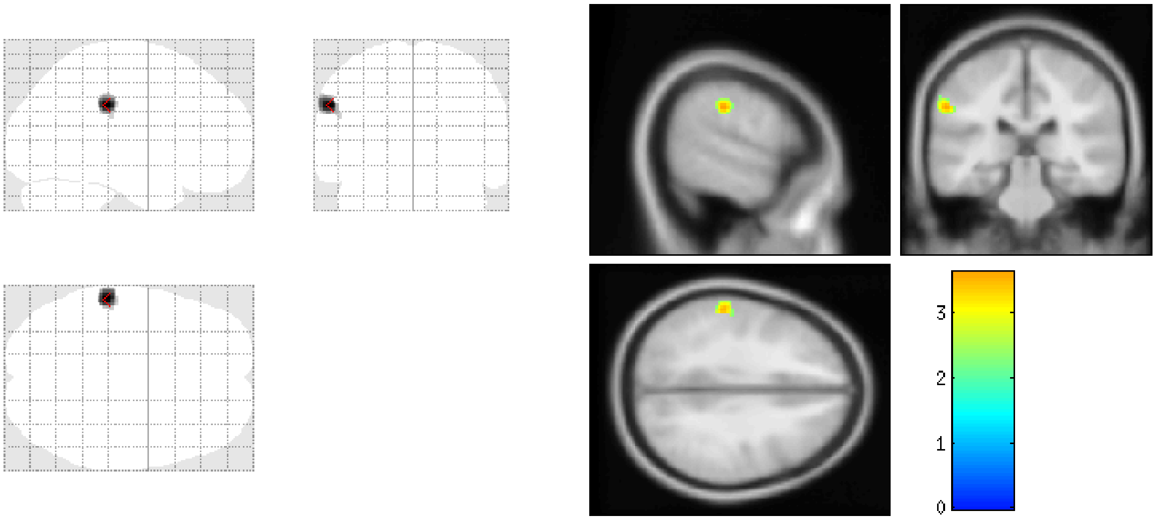


Fig. 15. Left middle temporal gyrus region of interest for TD > Nonresponders during single word reading task.

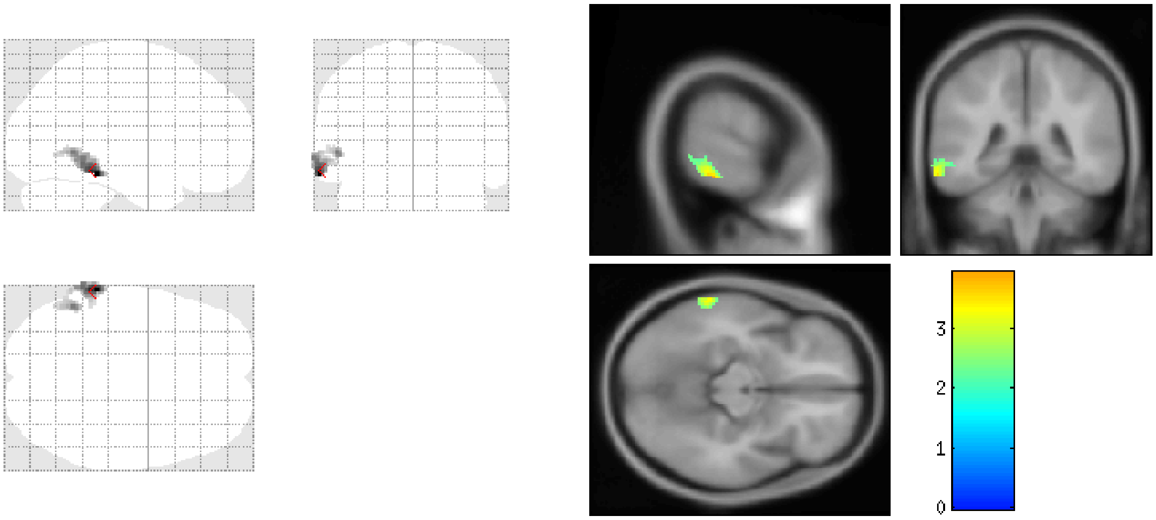
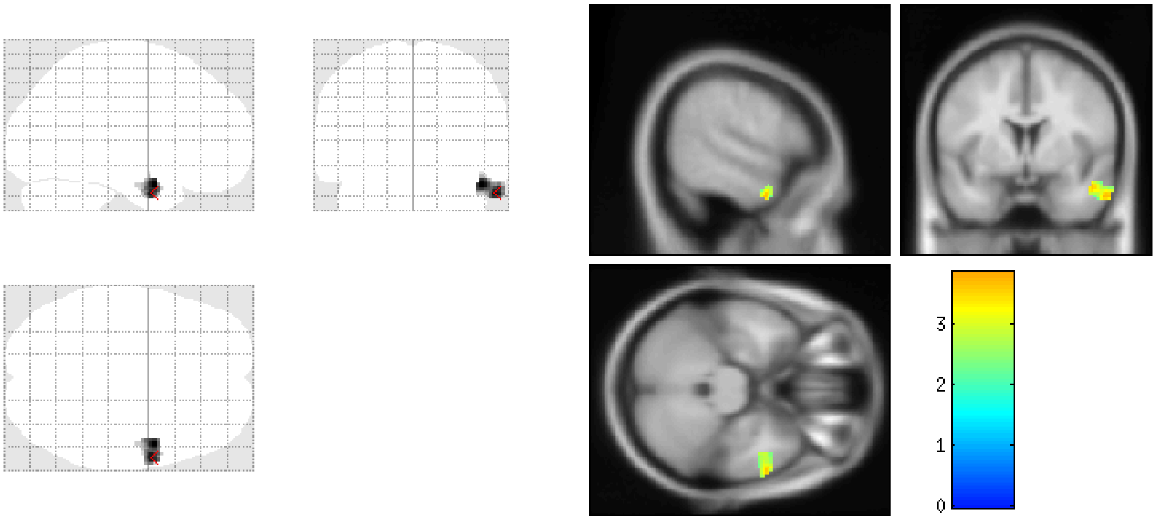


Fig. 16. Right middle temporal gyrus region of interest for Responders > Nonresponders during single word reading task.



MVPA

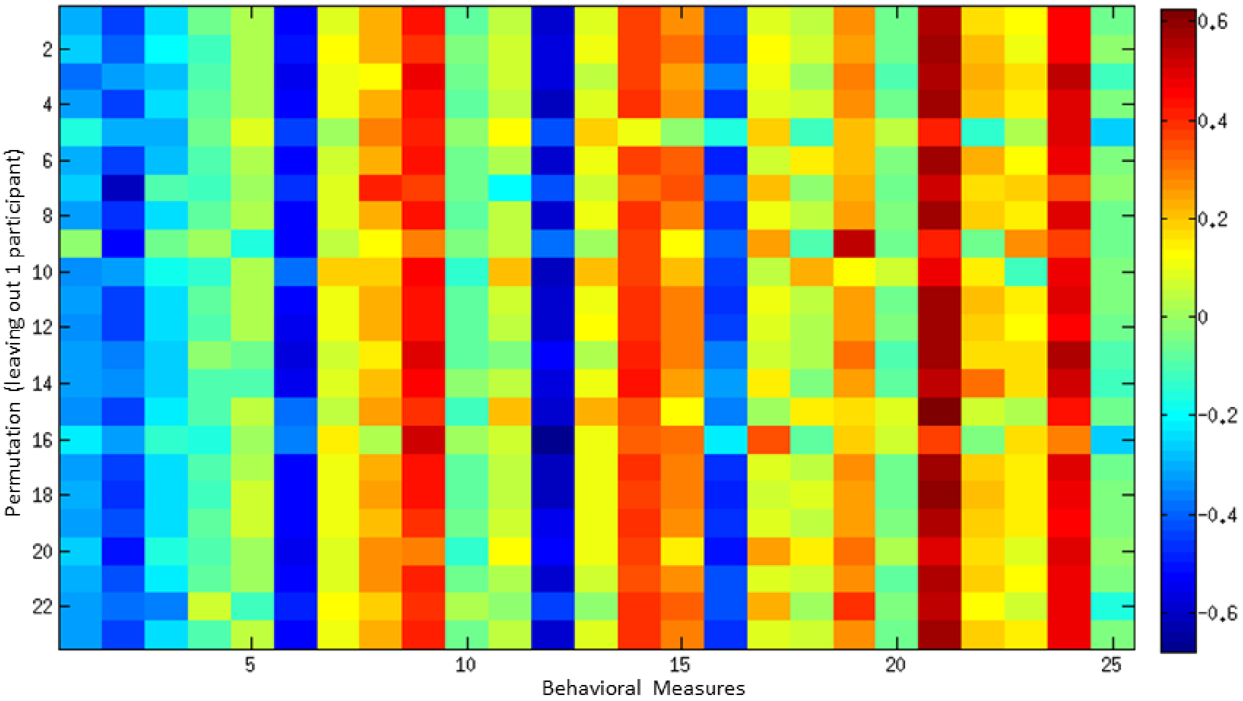
Using the MVPA toolbox, the support vector machine run with leave-one-out analysis and fixed target recursive feature elimination revealed that the behavioral measures alone successfully classified Responders and Nonresponders with an accuracy of 87% (see Table 12, Fig 17). Using imaging data covaried on scan site and applying a gray matter mask, whole brain MVPA classified Responders and Nonresponders with 70% accuracy. Entering values extracted from the L fusiform and performing principle component analysis successfully classified participants by responder status with 74 % accuracy. When combining L fusiform and behavioral measures, accuracy was 83%. No other ROI that was explored based on ROI results (L SMG, R MTG, or L VWFA using the previously described 10mm sphere) performed well in discriminating groups.

Table 12. Multivariate pattern analysis results.

Feature	Accuracy	Sensitivity	Specificity	PPV	PNV
Behavioral (25 measures) RFE	87.0	84.6	90.0	89.4	85.4
Whole brain gray matter PCA	69.6	84.6	50	62.9	76.5
L Fusiform PCA	73.9	76.9	70.0	71.9	75.2
L Supramarginal Gyrus PCA	43.5	46.5	40.0	43.5	42.6
L Middle Temporal Gyrus PCA	43.5	53.8	30.0	43.5	39.4
R Middle Temporal Gyrus PCA	60.9	69.2	50.0	58.1	61.9
L Superior Temporal Gyrus PCA	60.9	69.2	50.0	58.1	61.9
R Superior Temporal Gyrus PCA	60.9	69.2	50.0	58.1	61.9
VWFA (Bach et al., 2011) PCA	43.5	53.8	30.0	43.5	39.4

Note: RFE = fixed target recursive feature elimination, PCA = principle component analysis, PPV = predictive positive value, PNV = predictive negative value

Fig. 17. Multivariate pattern analysis of 25 behavioral measures for predicting Nonresponsiveness to reading intervention



Measures:
1 = CTOPP Phonological Awareness
2 = CTOPP Phonological Memory
3 = CTOPP Rapid Naming
4 = CELF Expressive Language Composite
5 = CELF Receptive Language Composite
6 = TOWRE Sight Word Efficiency
7 = TOWRE Phonemic Decoding Efficiency
8 = WJ-III NU Letter Word Identification
9 = WJ-III NU Word Attack
10 = WJ-III NU Passage Comprehension
11 = WIST Sound Symbol Knowledge
12 = WIST Spelling
13 = GORT Accuracy
14 = GORT Rate
15 = GORT Comprehension
16 = TOSCRF
17 = WISC-IV FSIQ
18 = CBCL Attention
19 = Conners Parent Anxious Shy
20 = Conners Parent HyperImpulsive
21 = Conners Parent Inattentive
22 = BRIEF Parent Behavioral Regulation
23 = BRIEF Parent Metacognition
24 = DKEFs Tower Total Achievement
25 = WISC Elithorn Perceptual Maze

Note: This figure depicts the weights for identifying Nonresponders in each leave-one-out cycle Warm colors indicate positive weights and cool colors are negative weights, such that positive (warm) weightings reflect higher scores in Nonresponders and negative (cool) weights reflect higher scores in Responders. Conners and BRIEF measures are reported in T scores, and accordingly a low score is more favorable than a high score.

CHAPTER V

DISCUSSION

Summary of Findings

This study was an exploration of using fMRI to predict responsiveness to a short-term, intensive reading intervention. Participants with RD were designated as Responders or Nonresponders to reading intervention and were compared with typically developing and no-treatment RD control participants. At pretest, Responders and Nonresponders were not significantly different on most behavioral measures. However, interestingly, Responders were significantly *lower* in decoding skills as evidenced by WJ-III Word Attack scores. Though this difference was somewhat surprising and differed from previous literature (Tran et al., 2011), decoding skills were heavily emphasized in the intervention programs we used and perhaps participants with lower word attack achievement were poised to gain more through interventions targeting decoding weakness; however, these gains could also be attributed to regression to the mean as discussed in the subsequent limitations section. For the battery of behavioral measures administered, the only other significant difference between Responders and Nonresponders was in parent rating of executive function. Responders were rated higher by their parents for meta-cognitive ability, a strength that could be beneficial when learning reading skills and could impact intervention response. Additionally, Responders were faster than Nonresponders in their fMRI task responses, which could be indicative of an additional underlying strength. However, it is difficult to conclude that Responders have faster processing speed as they did not perform significantly better on timed behavioral measures.

The study was designed to answer four research questions. The first question was to establish whether the reading interventions that we implemented resulted in word-level reading gains. Results indicated a small-to-medium overall effect size for the two interventions (which were pooled as there were no differences in intervention effect). Though the word-level gains were not statistically significant for the sample included in these analyses, the current study used a subgroup (participants with neuroimaging data) of a larger intervention group that did exhibit significant gains (Barquero et al., in press), suggesting that the treatment was effective for word level skills. Additionally, in the current study there was a small-to-medium effect size observed for treatment, which may be considered a very reasonable effect for such a short-term intervention. Of note, Responders did exhibit statistically significant gains relative to the other groups. Furthermore, when including ratings of attention and meta-cognitive skills as covariates, significant gains were shown for treatment and not for non-treatment groups.

The second research question we addressed regarded the prediction of intervention response using pre-intervention fMRI scans. Whole brain comparisons of a single word reading task revealed differences between Responders and Nonresponders to intervention, including but not limited to reading-related areas such as L fusiform, L ITG, L middle occipital gyrus, LMTG, L IPL, L SMG, L SFG. An additional analysis that included word-level change score as a continuous variable showed that, with increased change in WJ-III BR W score, activation increased in areas including R cerebellum, R fusiform, L IPL, L SMG, and L postcentral gyrus (note that L postcentral gyrus activation may have been related to pressing the response button with the right-hand thumb with increased accuracy). ROI analyses of regions selected based upon previous literature revealed differences between Responders and Nonresponders in the VWFA and L fusiform, L SMG, and R MTG. No differences were found in R IFG, L/R STG, L

MTG, or L Angular. The L fusiform and VWFA have been shown in several studies (Cohen, Dehaene, Naccache, et al., 2000; Dehaene & Cohen, 2011; McCandliss et al., 2003) to be associated with visual word presentation, though activation in this area is not limited to visual word stimuli (Price & Devlin, 2003). Additional evidence of the importance of the VWFA in reading comes from a case study in which a discrete ischemic stroke in the anterior VWFA resulted in alexia in the absence of visual or language impairment (Turkeltaub et al., 2014). Of further interest, there is growing evidence that this area shows increased activity following reading intervention (Eden et al., 2004; Heim, Pape-Neumann, van Ermingen-Marbach, Brinkhaus, & Grande, 2014). The single word reading task in the current study contains stimuli that are congruent with stimuli that seem to evoke increased activation in this area. Though few studies have explored prediction to intervention response through functional imaging, our results in the L fusiform appear to be in agreement with at least two previous studies that showed VWFA or L fusiform activation as predictive of intervention response (Bach et al., n.d.; Rezaie et al., 2011a). As for the differences observed in the L SMG, that region is generally thought to be involved in phonological processing (Church, Balota, Petersen, & Schlaggar, 2011) and a meta-analysis has shown that L SMG appears less active in dyslexia (Richlan et al., 2009). Accordingly, our findings showing increased activation in Responders in L SMG are reasonable when viewed in the context of previous studies. In addition to VWFA and L SMG, L and R MTG showed higher activation in Responders than in Nonresponders. The L MTG has been found to underactivate in RD (Richlan et al., 2011), so it makes sense that more Nonresponders would activate less in this area than Responders. A previous MEG study also showed increased bilateral MTG activation for Responders relative to Nonresponders (Rezaie et al., 2011a).

The third research question asked whether Responders and Nonresponders differ from typically developing readers. We hypothesized that Responders would more closely resemble TD than would Nonresponders. In general, the results supported this hypothesis. In the whole brain analysis, we found differences between TD and Nonresponders in multiple regions, some of which are reading related such as L fusiform, L middle occipital gyrus, L MTG, L ITG, L MFG, LSFG, in addition to L precuneus, L posterior cingulate, R/L cerebellum, R/L parahippocampal gyrus, R MTG. R STG, R fusiform, R ITG, R/L thalamus. Although there were some differences in frontal regions, there were no significant differences in L IFG, a region of the reading network. We found that differences between Responders and TD were significant only in bilateral cingulate gyri, primarily in the mid-cingulate and extending into posterior cingulate. It is unclear why this area would exhibit higher activation in typically achieving readers over responders. The middle to posterior cingulate has been shown to be activated in semantic and language tasks (Torta & Cauda, 2011) and Responders may have a deficit in this area relative to typical readers. Of particular interest, the differences that were evident in the reading network when comparing typically achieving controls to Nonresponders were absent in the comparison of typically achieving controls to Responders. This may indicate a lesser deficit at the neurobiological level in Responders, and a more severe and impactful deficit for Nonresponders as indicated by both behavioral and imaging results. In addition, or perhaps alternatively, Responders may have readily shown improvement with the intensive intervention because they had not previously received instruction adequate to their needs, whereas the reading problems of Nonresponders may be truly resistant to evidence-based treatment.

The final research question concerned how predicting response to intervention with neuroimaging compared to prediction with behavioral measures. Using MVPA analysis, we determined that for the current sample, the multivariate pattern generated when entering 25 behavioral measures and the multivariate pattern of the principle components of L fusiform activation were both predictive of intervention outcome. However, no additional predictive ability was gained upon combining the two approaches. These MVPA results should certainly be interpreted with caution as they are somewhat at odds with the only previous study to use a similar approach. In that study (Hoeft et al., 2011), which did not include a controlled intervention, the multivariate pattern resulting from the input of 17 behavioral measures did not predict long-term (2.5 yrs) reading growth above the level of chance. However, Hoeft et al (2011) found prediction of reading outcome using MVPA of whole brain fMRI activation exceeded 90%. In addition, the same study revealed that activation in the R IFG in combination with DTI fractional anisotropy values for the R superior longitudinal fasciculus (including the arcuate fasciculus) was predictive of long-term reading outcome at 72%. Our study did not find MVPA of whole brain fMRI activation to be as strongly predictive of short-term intervention response (70%), but did find that behavioral measures were predictive (87%) as was activation of the L fusiform gyrus to a lesser degree (74%). While our study adds to the literature by examining short-term, controlled reading intervention in conjunction with a broad battery of reading-related measures as well as employing a reading task during functional imaging, additional studies of this sort must be performed before substantive conclusions can be drawn.

Limitations

The first limitation of this study is the small sample size and the consequent low power. Accordingly, despite a small-to-medium effect size for treatment, growth associated with treatment was not significant. To maximize our sample, we pooled participants receiving two different interventions. Pooling the two interventions seemed justifiable in this study because, despite receiving different intervention programs, all participants received the same amount of one-on-one instructional time, and the emphases of the two interventions had substantial overlap (e.g., letter-sound knowledge, fluency development). Furthermore, there was no statistical difference in the word-level growth associated with each intervention, so the two interventions were considered comparable. Small samples are not unusual in neuroimaging studies. As evidenced in the literature review, studies of reading intervention and neuroimaging have shown significant neurobiological results with group sizes comparable to those of the current study (Aylward et al., 2003; Bach et al., n.d.; Davis et al., 2011; Eden et al., 2004; Farris et al., 2011; Gebauer et al., 2012; Odegard et al., 2008; Rezaie et al., 2011b; Richards et al., 2007; Simos, Fletcher, Sarkari, Billingsley-Marshall, et al., 2007; Simos, Fletcher, Sarkari, Billingsley, et al., 2007b; Yamada et al., 2011). The results of our neuroimaging analyses did show significant differences, many of which agreed with previous findings.

A second limitation of this study is the possible concern of regression to the mean. We designated participants as RD based upon (a minimum of) one score below the 25th percentile on a word reading or word attack measure, whereas the designation as TD was dependent upon multiple measures, and therefore likely to be a more reliable designation. It is conceivable that a participant could have an isolated poor performance on one measure and be included in the RD group, only to have the aberrant score regress toward the mean at posttest, with the appearance of growth in response to intervention. This could in turn potentially account for the somewhat surprising lack of difference in neurobiology between Responders and TD as it would mean that some Responders were miscategorized and should have been considered TD. However, as previously noted, only 3 participants (2 Nonresponders, 1 Responder) were categorized as RD based upon a single low score.

A third limitation is that there was no reasonable way to control for previous instruction (which, of course, is the case in many behavioral intervention studies, and almost universal in neuroimaging intervention studies but nevertheless important to mention). Participants in the study were from multiple backgrounds and school systems and previous reading instruction varied greatly. An obvious potential conclusion from this study is that Responders are in truth TD who have received poor instruction in the past and benefitted from the explicit instruction provided by the interventions. This is another possible explanation for the minimal differences in functional activation observed between Responders and TD.

Conclusions

This study is an exploration of using neurobiology to predict behavioral responsiveness to an intensive, short-term reading intervention. Behavioral measures, though clearly useful, have not yet been found to fully predict who will respond to evidence-based, intensive intervention. Perhaps the underlying neurobiology of reading difficulty is an important piece of information in characterizing the severity of the deficits. We sought to elucidate a pre-intervention profile of functional activity in the brain that distinguished Responders from Nonresponders.

Our results suggest that the functional activity of Responders largely resembles that of TD while Nonresponders appear to be distinctly different from both TD and Responders. Somewhat surprisingly, all differences between TD and Nonresponders that reached significance showed hypoactivation in Nonresponders. Of particular interest were differences in areas previously shown to be associated with word reading. The L fusiform gyrus, which includes the VWFA, is an area that exhibits activity during visual presentation of words and seems to play a role in word recognition. In our data, Nonresponders appear to have inadequate activation in the L fusiform. Clearly, if activation of this region is required for efficient word reading, hypoactivation of this area would be problematic for word-level skills. Likewise, hypoactivation in the temporoparietal region, including SMG could be a disadvantage. This area has been associated with linking orthography and phonology, an important component of decoding, again possibly impacting word-level reading skills. While we observed hypoactivation in some key areas of the reading network, we detected no potential compensatory activity in either Responders or Nonresponders. Implications of this are unclear, since we did not detect compensatory activity in Responders either.

A few previous studies have explored prediction of reading growth using through differing methodology. Business-as-usual (no controlled intervention employed) growth has been investigated with DTI and fMRI and using behavioral measures and MVPA, demonstrating prediction of outcome (Hoeft et al., 2011). Another fMRI study explored using post-intervention fMRI to predict future growth in reading (Bach et al., n.d.). An ERP study has shown that behavioral prediction of long-term reading can be enhanced by ERPs obtained at preschool (Maurer et al., 2009). Finally, MEG studies have shown promise in predicting intervention outcome (Rezaie et al., 2011a, 2011b). Yet, to our knowledge, this is the first study to use pre-intervention fMRI activity to characterize Responders and Nonresponders to subsequent controlled intervention, and comparing those with typically developing readers Additionally, this is the first fMRI study to use a short-term intervention study design. Thus, findings enrich the literature in an important way and add to the science concerning the potential usefulness of neuroimaging as a predictive tool in the context of academic interventions.

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