

Developmental Psychobiology of Reading Disability

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The acquisition of reading serves as a foundational skill for a great deal of later educational and intellectual development. Most children, over the course of several years of formal education and practice, develop specialized perceptual skills that support the fluent and effortless recognition of visual words. Many, however, do not. Impairment in reading skill development is arguably the most prevalent form of learning disability. Substantial and persistent difficulties in the development of reading skill are estimated to impact approximately 5 to 15 percent of the population in the U.S. (Rutter, 1978; Stanovich, 1986). Reading disorder (RD) is typically diagnosed as a clinical disorder under the DSM IV (1994) and characterized by poor reading achievement, quantified by standardized tests of reading accuracy, fluency and comprehension, that falls substantially below expected levels given an individual's chronological age, measured intelligence, and education.

Like many other clinical disorders considered in this special issue, reading disability has been investigated under the framework of developmental psychobiology, which involves understanding the symptoms of clinical disorders that impact mental function by examining the underlying cognitive processes involved, linking these processes to specific brain mechanisms, and characterizing how these factors unfold over the course of development. In reviewing this research, this paper first examines cognitive processes that have been proposed to play a causal role in the complex symptoms of reading impairments. We then review evidence linking core cognitive deficits in reading disability to differences in brain function and structure that exist between individuals with and without reading disability. Beginning with neuroimaging research comparing adults with and without RD, we examine common brain regions implicated at the end state of

reading development. Next, we examine the developmental course of these cognitive and neurobiological factors across a number of recent developmental neuroimaging studies contrasting children with and without reading disability. Several recent studies have combined neuroimaging with cognitive training studies to examine links between improvements in cognitive skills and the accompanying changes in neurobiological processes associated with reading disability. Such studies demonstrate the potential plasticity (i.e. capacity for change) of cortical circuitry linked to reading skills and provide a potential framework for future research to examine causal relationships between intervention efforts and changes in functional brain activity.

Cognitive Deficits in Reading Disability

A significant body of cognitive research has focused on understanding reading disability as a manifestation of more fundamental cognitive deficits that are intrinsic to a child's basic abilities. The past several decades of cognitive research in reading development has provided converging evidence in support of the hypothesis that cognitive deficits in phonological processing abilities play a primary causal role in the development of reading disabilities. Reading disability (i.e. developmental dyslexia) has been systematically linked to impaired performance in several specific tasks that tap phonological processes, such as phonological awareness (the ability to access and flexibly use the speech sounds within syllables, as in rhyming tasks and phoneme blending tasks) (Manis et al 1993), (Bradley & Bryant 1985) verbal short term memory (Jorm 1983, Paulesu et al 2001, Torgesen et al 1988), and rapid naming of common visual stimuli (Denkla & Rudel 1976) (Wolf 1984). Direct links between various

phonological deficits and RD have been shown in adults (Pennington et al 1990) as well as children (National Reading Panel. Washington 2000). These phonological processing deficits have been theorized to have a causal influence on the development of reading skill by impacting the early phases of literacy acquisition (Bradley & Bryant 1983). Evidence in support of this core phonological deficit in RD has been surprisingly consistent across two decades of research.

A host of other cognitive deficits have been demonstrated in subsets of dyslexic adults, but with varying degrees of consistency across studies, and even less consistency in accounting for variance in reading measures (see Ramus, 2003 for recent review). One class of proposed cognitive deficits involves processing rapid temporal information in the auditory modality, with studies suggesting that a primary deficit involving rapid auditory perceptual abilities may underlie previously reported phonological and reading difficulties (Tallal 1980). More contemporary work, however, in both adult dyslexic individuals (Chiappe et al 2002) and children followed longitudinally from kindergarten to Grade 2 (Share et al 2002) show that phonological and reading deficits cannot be reduced to, nor predicted by, more basic deficits in processing rapid auditory information. Furthermore, auditory deficits across studies are estimated to appear in approximately 39% of dyslexics and are generally not specific to the processing of rapid temporal information (Ramus 2003).

Other classes of cognitive deficits that might play a critical role in reading disability include the perceptual mechanisms in vision involving magnocellular processing pathways (Stein 2001b), and the cerebellar-motor functions that impact learning, timing and automaticity (Nicholson et al 2001). Although there is evidence

linking these cognitive deficits to dyslexia, results from a number of extensive replication efforts have raised concerns about the specificity of visual deficits to the magnocellular system, the prevalence of magnocellular and cerebellar processing deficits in dyslexia, and the relationship between the severity of such deficits and actual reading ability (Ramus 2003). One study directly assessed these a wide range of cognitive skills in a single well-characterized group of dyslexic adults. Whereas phonological deficits were present in nearly every case, nearly a third of the sample showed no significant signs of sensory and/or motor deficits (Ramus et al 2003).

Generally speaking, the current state of the literature supports phonological deficits as the dominant core cognitive deficit associated with RD. The influence of other forms of cognitive deficits on RD remains more controversial, both in terms of the relative prevalence and the specific nature by which the proposed cognitive deficit impacts the acquisition and skilled performance of reading. In the following section we examine evidence from neuroimaging studies that seeks to elucidate the relationship between phonological processes and reading disability.

Neuroimaging Studies of Adults with Reading Disability

In vivo brain imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have provided an important approach for investigating activity within specific cortical regions and associated cognitive deficits linked to reading disability. Flowers and colleagues (1991) provided perhaps one of the first empirical links between cognitive operations involved in phonological processing and patterns of functional disruption in left posterior cortical

activity. Adults with childhood histories of RD performed an auditory spelling task while regional cerebral blood flow was imaged in 16 brain regions via a xenon inhalation imaging method (Flowers et al 1991). The results showed reduced activity in posterior temporal regions for subjects with RD relative to non-impaired subjects. The following year, a similar finding was reported in a PET study examining phonological processing impairment using a similar auditory spelling test (Rumsey et al 1992). This finding of less left posterior temporal responsiveness to phonologically demanding tasks in adults with dyslexia relative to non-impaired readers became a central focus of this literature.

Since these initial studies, a number of advances in brain imaging methodology and analysis have provided the opportunity to perform more comprehensive studies of the biological substrates of RD. For example, contemporary imaging methods provide whole brain imaging with voxel-by-voxel based rather than region of interest analysis.

Magnetoencephalography (MEG) studies provide additional information about the time course of activity in various regions on a millisecond timescale. Table 1 summarizes the key findings of the adult neuroimaging studies that involve direct comparisons between RD and non-impaired adults performing cognitive tasks related to reading or phonological processes. (See (McCandliss & Noble in press) for recent review).

----- Table 1 about here -----

Several convergent findings relevant to understanding the neurobiology of reading disability become apparent when reviewing these studies. First, RD subjects show reduced activity in left posterior regions of temporal cortex, commonly including left superior temporal gyrus, as well as other neighboring regions such as left angular gyrus, and left supramarginal gyrus when performing reading or other phonologically

demanding tasks. This central finding is now supported across a wide variety of tasks that target phonological processing regardless of input (auditory words or visual letters) or response modality (i.e. oral pronunciation, button pressing), and suggests that failure to successfully recruit left perisylvian regions when facing phonologically demanding tasks may provide an important neurobiological marker for dyslexia. This result establishes an important connection between findings of core phonological deficits in reading impairments and atypical brain activation patterns associated with phonological processes.

Some studies have been reported in which RD subjects showed greater activity than non-impaired readers in left frontal regions, a pattern hypothesized to reflect alternate strategies that are engaged to compensate for poor phonological skills. Two studies have demonstrated such effects in left frontal regions, specifically within the left inferior frontal gyrus (IFG) (Shaywitz et al 1998) and left insular cortex (Rumsey et al 1997), but this pattern does not appear in the majority of studies.

Another consistent pattern across studies appears within the visual system when examining activity patterns in response to the presentation of visual words. Across studies involving visual presentation of words or word-like stimuli (pseudowords), non-impaired adults show increased activity in the vicinity of left fusiform gyrus (basal temporal region, BA 37) in a way that RD adults do not. This general pattern of group differences in response to visual word forms was present even when task instructions were unrelated to the linguistic properties of the stimuli (Brunswick et al 1999), and was consistently replicated across non-impaired and dyslexic readers of English, French and Italian (Paulesu et al 2001). In a recent review of evidence for the functional

contribution of this region during reading tasks, responses in this region were shown to be sensitive to abstract letter information and to common orthographic patterns, and thus may reflect a form of learned perceptual expertise for reading (McCandliss 2003).

Magnetoencephalography studies present an important complement to PET and fMRI studies by providing information about temporal dynamics of activity over the course of the several hundred milliseconds typically required to recognize a word. While fMRI and PET images provide a detailed map of regions activated by a task, MEG provides the opportunity to investigate the time course of activity within these different brain regions.

Contrasting MEG responses across groups of RD and non-impaired adults has demonstrated several converging insights that are fairly consistent across studies. Early responses to visual words typically occur within 100 msec in posterior occipital areas and are equivalent between reading impaired and non-impaired subjects. MEG sources located in or near the fusiform gyrus region (basal temporal region), show that the earliest differential response between RD and non-impaired subjects viewing a word does not appear until 180 msec after stimulus onset (Salmelin et al 1996a). In non-impaired adult readers, this early MEG response is sensitive to differences between visual words versus a set of control symbol stimuli, but this effect is absent in RD subjects, who show equivalent responses to words and control symbols (Helenius et al 1999). Approximately 200 to 400 msec after stimulus onset, a second group difference emerges over left posterior temporal regions (near superior temporal gyrus), in which non-impaired readers show stronger responses than RD subjects while reading words (Salmelin et al 1996b). This same region also shows differences in MEG responses between RD and non-

impaired subjects in the perception of speech sounds, suggesting a role in phonological analysis (Helenius et al 2002).

Another important finding involves an examination of how activation patterns within certain brain regions act in a coherent fashion during tasks that involve reading. Horwitz and colleagues examined this issue in RD and non-impaired subjects by performing correlational analyses on fMRI data to examine the extent to which angular gyrus activity was correlated with activity in reading-related areas such as the left superior temporal gyrus, and the fusiform gyrus (Horwitz et al 1998). Findings indicated that the strength of such correlations was significantly reduced in RD subjects relative to non-impaired readers.

Together, the available adult neuroimaging literature provides strong converging evidence across a number of paradigms and imaging methodologies toward a neurobiological profile for RD. This profile is marked by both a disruption of the early response to visual words in the left fusiform region, and a tendency toward hypoactivity of posterior temporal regions as subjects engage in a wide range of phonological tasks including reading words and analyzing the sounds within spoken words. Some studies demonstrate clear evidence that RD individuals show increased activity in other regions (relative to non-impaired subjects), potentially reflecting some form of compensatory strategy. However, the size and location of such effects appear to change across paradigms, and such activity may be entirely dependent on the demands of each experiment. In addition to identifying functional disruptions within cortical regions, adult functional neuroimaging also demonstrates that efficient communication between phonological regions and visual word form analysis regions might be impacted in RD

(Horwitz et al 1998).

There are several limitations, however, inherent in the central paradigm employed in adult neuroimaging studies that directly compare RD and non-impaired groups. Reports of functional differences between reading impaired and non-impaired adults open a number of ambiguities for interpretation. For example, the available evidence does not provide a means of discriminating whether a particular functional disruption *preceded* reading difficulties and is thus more likely to have played a *causal* role, represents a late emerging *response* to childhood difficulties in reading and phonological processing, or represents functional reorganization typically associated with years of successful reading but absent in the case of reading disabilities. Studies that examine only the final adult outcome of long-term developmental processes provide few options for investigating whether a given functional disruption represents a fundamental limit on the level of reading skill one might attain, or acts as a developmental bias that might be counteracted across the development of reading skill. Such limitations can be addressed via a developmental approach that involves children in cognitive testing and neuroimaging studies during the years in which reading skills are initially developing.

Neuroimaging Studies of Children with Reading Disability.

Recent advances in child-friendly, non-invasive imaging procedures, together with a growing interest in the intersection of human development and cognitive neuroscience, have promoted a great deal of progress in imaging the developmental course of several psychiatric disorders (Casey et al 2001). Table 2 highlights key findings from five recent neuroimaging studies of RD children that span a range of development

much closer to the initial emergence of the major symptoms of RD. We consider below how this developmental literature provides new insights into the nature of three central points of convergence from the adult literature: (1) significance of left perisylvian functional disruptions; (2) atypical activation patterns in fusiform gyrus; and (3) other findings of compensatory activity.

Functional disruptions in left perisylvian regions.

Temple and colleagues (Temple et al 2001) scanned a group of 8 to 12-year old RD and non-impaired children using fMRI. They contrasted letter rhyming with visual matching of letters or line segments, based on an adult neuroimaging paradigm (Paulesu et al 1996) that showed hypoactivity in the left superior temporal groups (STG) of children with RD relative to non-impaired children. As summarized in Table 2, results of this child study provided a critical replication of a central finding from the adult literature -- as phonological task demands increase, RD children show less recruitment of left perisylvian regions (including left superior temporal gyrus). This finding was present even when controlling for IQ across groups, suggesting that it is somewhat specific to phonological processing.

A similar effect was found in a large cross-sectional developmental study of 70 RD and 74 non-impaired children ranging in age from 7 to 17 (Shaywitz et al 2002). Cortical responses to two active reading tasks designed to engage phonology and reading skills (pseudoword rhyme match, word category match) compared to a baseline task designed to control for visual stimulation and decision making showed significantly less activity for RD children in a range of areas including the superior temporal gyrus. Other

regions (see Table 2) also showed reduced activity for RD children relative nonimpaired readers, raising the question of specificity in the functional disruption of the left perisylvian region during the development of reading.

In contrast, a comparison of children with and without RD in Germany (Georgiewa et al 1999) showed no evidence to support left perisylvian functional disruption. Instead, evidence from two separate task contrasts that emphasized phonological processes in reading showed reduced activity in left inferior frontal regions for children with RD relative to non-impaired children.

Additional results from a series of developmental MEG studies, however, successfully replicated the central RD adult finding of left posterior functional disruption. One of these studies examined MEG responses to high frequency words from 2nd grade texts (Simos et al 2000a) and another examined MEG responses to a visual pseudoword presented as the first of a pair in a rhyme judgment task (Simos et al 2000b). RD children consistently showed less activation in left perisylvian regions than non-impaired children across both visual reading tasks, generally replicating the adult MEG findings. Furthermore, the RD children showed an atypical pattern of greater recruitment of right perisylvian regions when reading words that was not present in an additional task involving listening to auditory words (Simos et al 2000a).

These studies present support for the hypothesis that one of the most consistent effects found in brain imaging studies of adult dyslexics -- left perisylvian functional disruptions related to phonological processing -- is also present earlier in development, while reading skills are still developing. This finding presents the possibility that functional disruption of left perisylvian regions may play a causal role in

the atypical development of reading skills, and suggests that such findings are not merely a compensatory response or learning effect emerging as a consequence of reading difficulties.

Basal Temporal Regions

Several of the developmental neuroimaging studies presented in Table 2 provide an important contrast with the adult RD literature concerning the left fusiform gyrus within the basal temporal region. As reviewed in the adult MEG studies above, RD and non-impaired readers show different responses to visual words within 200 msec localized to the left basal-temporal region near the fusiform gyrus. This pattern does not emerge, however, in MEG contrasts between RD and non-impaired children. When familiar words are presented, responses in this region are equivalent across these two groups of children, in terms of both signal strength and the latency at which activity in this region reaches its peak (Simos et al 2000a). A similar pattern of results has been reported for pseudowords presented to children in a rhyming task (Simos et al 2000b).

This developmental difference in fusiform findings in RD is potentially informative in understanding the differential roles left perisylvian regions and left fusiform/basal temporal regions play in typical and atypical reading development. In skilled adult readers, responses to words or pseudowords are differentiated from other visual stimuli (i.e. geometric symbols, checkerboards) within 200 msec of stimulus onset (Tarkiainen et al 1999). Such responses represent a form of perceptual expertise in which a region of extrastriate cortex has become sensitive to the visual features of letters, and potentially to abstract patterns of information that govern how letters are grouped

together into visual word forms. It has been proposed that the perceptual expertise that supports such early responses to visual words and pseudowords develops slowly over the course of several years before reaching skilled adult levels (see (McCandliss 2003) for review). Under this developmental framework, the functional responses of fusiform gyrus to words that differentiate RD and non-impaired adults represents differences in learning over the course of years of literacy experience rather than a form of functional abnormality in left fusiform gyrus regions *per se*.

Table 2 also provides results of a brain-behavior correlation analysis in children that include a range of RD and non-impaired children spanning the ages of 7 to 18 (Shaywitz et al 2002). This analysis revealed a significant relation between reading skill (as measured by decoding ability) and the degree of activity in left fusiform gyrus during word and pseudoword reading tasks. Children with the highest level of reading skill tended to have the most robust activity in the region centered on the left fusiform gyrus. Importantly, this relationship held true both for RD and non-impaired children, suggesting that the degree to which this region responds to visual words changes over the course of skill acquisition. Thus, improvements in reading skill lead to increased activity in this regions in response to visual words.

Regions of increased activity in RD.

The patterns of increased cortical recruitment in RD can also be informative for understanding atypical development. The developmental studies summarized in Table 2 provide insight into cortical areas that RD children recruit more than non-impaired children as well as areas they recruit less. As was seen in a review of adult imaging studies, similarly a review of the child imaging studies show inconsistent regions of

greater activity for RD children across different activation paradigms. For example, while both adults and children with RD showed increases in left inferior frontal regions in a study by Temple et al. (2001), other studies have shown the opposite effect (Georgiewa et al 1999).

In MEG studies, children with RD show a robust group tendency to recruit right perisylvian regions to a greater extent than either their non-impaired counterparts and to their own recruitment of left perisylvian regions. This pattern was consistent across two independent MEG studies that involved reading high frequency familiar words and reading pseudowords, respectively. In an additional experiment that involved listening to high frequency words, however, RD and non-impaired children showed equivalent responses in left and right superior temporal gyrus regions, suggesting that the group differences are somewhat specific to reading.

A somewhat similar pattern emerged from brain-behavior correlation analysis from the Shaywitz et al. child study. Negative correlations were evident between reading skill and the magnitude of activity in right occipito-temporal regions. This effect was characterized by the poorest readers showing an increased tendency to recruit right hemisphere regions when reading familiar words and making semantic category judgments (Shaywitz et al 2002). A similar negative correlation between reading skill and the right fusiform gyrus has been replicated in a group of non-impaired children 6 to 22 years of age (Turkeltaub et al 2003).

Across several studies summarized in Table 2, children with reading disability show reliable patterns of atypical recruitment, typically involving right hemisphere homologues of brain regions critical for skilled reading. These robust patterns of right

hemisphere recruitment are not present in the adult literature, suggesting that this pattern of right hemisphere recruitment in RD subjects maybe be specific to earlier stages of reading development.

In general, childhood neuroimaging studies of reading impairments provide several key insights into the nature of the central findings from the adult literature. First, it appears that patterns of compensatory activity change rather dramatically over the course of development, such that compensatory patterns in young or reading disabled children involve right perisylvian regions and/or right occipito-temporal regions (including right fusiform), a pattern that is absent in adults with reading disability, who tend to show increased activity in left frontal regions. Developmental data on patterns of activity in the left basal temporal regions suggest that the adult findings for functional differences between RD and non-impaired adults may reflect a gradually developing form of perceptual expertise related to developing reading skills. Such learning is perhaps not unlike expertise in face processing described by Scott & Nelson (see this volume). Finally, the developmental data indicate that functional disruptions of left perisylvian regions may act as an early, persistent, and potentially causal factor over the course of development of reading disability. This conclusion, however, is somewhat limited by the fact that most of the children in these developmental studies had already been exposed to several years of formal schooling and reading experience before entering each study.

Infant Studies of Speech Processing and Risk for RD

One line of developmental research on reading impairments has begun to examine potential evidence for functional abnormalities early in the development of cortical

systems related to phonology via event-related Potential (ERP) responses to speech sounds in infants. A longitudinal study conducted in Finland (Guttorm et al 2001) examined 3-5 day old infants' ERP responses to simple speech sounds. This study utilized the high heritability rates associated with reading disability (Gayan & Olson 2001) to contrast groups of infants with and without familial risk for RD. Familial risk (parental history for reading disability) for RD consistently yields actual incidence of reading deficits in more than one-third of high-risk children (Gilker, 1991; Pennington, 2001). Group contrasts showed distinct ERP effects for children with a familial risk of reading disability, characterized by greater amplitudes and extended durations of ERP responses over right hemisphere sites for particular speech stimuli (e.g., "ga").

A similar 8-year longitudinal study (Molfese 2000) examined the relationship between ERP responses to speech sounds in infancy and reading abilities in these same children 8 years later. This study started with no *a priori* data on differences between infants, but instead employed multivariate discriminant function analyses to relate childhood reading scores to amplitude and latency estimates for infant ERP recordings. The analyses were capable of classifying infants, on the basis of their ERP data, into one of three childhood outcome groups (control, poor, or dyslexic) with greater than 75% accuracy. Findings from these studies provide clear evidence that reading impairments are accompanied by some form of subtle functional disruption related to speech processing that is present very early in development.

Anatomical Contributions

Based on the notion that regional cellular properties influence computational specialization in local networks, several research efforts have attempted to link functional disruptions in cortical regions to cellular abnormalities in these regions. Evidence for cellular differences have been reported, but are typically based on small sample sizes (i.e. $n < 10$). Nonetheless, several post mortem case studies have revealed ectopias, dysplasias and microgyria (Galaburda et al 1985), glial scarring (Humphreys et al 1990) and minicolumn abnormality (Casanova et al 2002) in the perisylvian regions of a set of previously diagnosed dyslexics. However, such findings are not exclusive to these regions, as cell size differences between dyslexics and controls have also been reported in left primary visual cortex (Jenner et al 1999), lateral and medial geniculate nucleus (see (Cestnick & Coltheart 1999) and (Stein 2001a) for discussion) and most recently, cerebellar regions (Finch et al 2002).

Other researchers have selectively examined morphologic differences in particular brain structures by quantifying variations in size, shape, and asymmetry of entire brain regions. For example, the planum temporale has been a natural region of interest for investigations of abnormalities in language and reading acquisition, as this structure is involved in the early analysis of the spectrotemporal structure of words. Located in auditory association cortex at the posterior end of the Sylvian fissure, the planum temporale is engaged in the analysis of spectrotemporal patterns (Griffiths & Warren 2002). While leftward dominance in planum temporale asymmetry is consistently reported in non-impaired subjects (Preis et al 1999, Shapleske et al 1999, Steinmetz 1996, Tetzner et al 1972), reduced planum temporale asymmetry has been reported in dyslexics

across a number of studies (and for review, see Habib 2000, Larsen et al 1990, Morgan & Hynd 1998). However, persistent discrepancies in this literature have led to a host of recent studies that have provided improvements in sample sizes, quantification of subject characteristics, and methods for quantifying brain regions. These studies have yielded no significant differences between groups of RD and non-impaired adults (Eckert et al 2002, Eckert et al 2003, Hugdahl et al 2003, Leonard et al 2001). Although such null findings cannot rule out the possibility of brain structure differences in RD, such differences are likely to be expressed as biases that fall within the normal range of the non-impaired population, and are likely present in only a subset of RD subjects. An important future direction in this work will examine the possibility that morphological variations in multiple brain regions may each contribute a small, but additive, influence on reading ability. One such study examined whole-brain morphological comparisons and more refined phenotypes of dyslexia ((Leonard et al 2002). Leonard and colleagues illustrate that different multivariate anatomical criteria are related to different fundamental deficits at different stages of development. (Leonard et al 2002).

Another important area of research on potential structural differences between RD and non-impaired subjects involves the examination of white matter tracts connecting various brain regions associated with reading and phonology. Diffusion Tensor Imaging (DTI) is sensitive to biological properties of white matter tracts by measuring the degree to which water molecules diffuse along the direction of coherent white matter tracts, rather than in random directions (a measure called fractional anisotropy, Wiestmann et al 1999). Recently DTI measurements of white matter tracts in bilateral perisylvian regions have shown sensitivity to group differences between adults with and without a history of

childhood RD (Klingberg et al 2000). In left perisylvian regions, the degree of fractional anisotropy was positively correlated with standardized reading scores across the entire range of skill levels.

As discussed above, developmental evidence may play an important role in elucidating the causal relationship between reading skill and neurobiological measures. Two preliminary reports of previously unpublished data have recently replicated this effect in children, suggesting that white matter tract differences precede rather than follow reading impairments (Dougherty et al 2003, Nagy et al 2002).

Intervention Studies

Given the social significance of developing reading skills in children, rigorous cognitive studies of reading intervention have been abundant. Many studies provide evidence that support the basic claim that children with mild to severe reading impairments can benefit significantly from intervention techniques that involve explicit training and support in phonological awareness and alphabetic decoding skills (Foorman 1998) (Torgesen 2001, Vellutino 1996)). Such interventions have been shown to produce dramatic improvements for children with reading impairment over the course of 1 to 2 semesters of focused intervention.

---Table 3 about here---

Reading intervention studies can be combined with neuroimaging techniques in children to address questions about the inherent limitations or plasticity of observed functional patterns of activity associated with dyslexia. Furthermore, examining the functional reorganization that takes place over the course of an intervention may provide

insight into the nature of how an intervention achieves its effect. While some intervention approaches may have a direct impact on the core deficits and the associated abnormal patterns of functional activity, others may achieve their effects by recruiting compensatory mechanisms. Furthermore, given that RD children exhibit a tendency of both underactivating some regions involved in normal reading function and overactivating other regions in relation to typically developing readers, an intervention could act to normalize these regions. Accordingly, interventions would presumably increase activity in regions they fail to properly employ, and/or reduce the level of activity in regions that are not typically associated with skilled performance of the task. It is possible that a successful intervention may not reflect such changes due to selection of activation paradigms that fail to capture the critical aspects of cognitive improvement. Table 3 summarizes the details of three recently published studies that combine phonological interventions directed toward children with reading impairments with neuroimaging measures applied both before and after intervention.

One of the first imaging intervention studies (Simos et al 2002) used MEG to examine neural changes during the visual pseudoword rhyming task described above (Simos et al 2000b) over a two month intervention period. Eight reading impaired children showed pre-test MEG measures that replicated the pattern of group differences demonstrated in their previous study -- the reading impaired group demonstrated both smaller responses over left superior temporal gyrus regions and larger responses over right superior temporal gyrus regions in relation to an age-matched control group of non-impaired readers. Following a 2-month intervention period involving 80 hours of direct intervention with one of two commercial packages (*Phono-Graphics* and *Lindamood*

Phoneme Sequencing), each child showed large improvements in reading scores. Mean standardized reading scores progressed from the 5th percentile before the intervention to the 50th percentile afterwards. Such gains are generally consistent with published response rates to well-structured tutorial intervention programs (Torgesen 2001). Following intervention, the reading impaired children showed significant changes in MEG responses to pseudowords, including both increases in left superior temporal gyrus activity and a decrease in right superior temporal gyrus activity. The 8 non-impaired children who did not participate in the intervention demonstrated stable MEG responses over a similar time span.

In an fMRI study conducted using the letter rhyme task described above (Temple et al 2001), Temple et al. (2003) measured changes in functional activity in a group of reading impaired children participating in a 6-week intervention program (45 hours total). The intervention phase included a commercial computer-training program (*Fast ForWord Language*) in conjunction with a special school curriculum for children with dyslexia. This combination resulted in significant reading improvements. Pretest fMRI results indicated that reading impaired children showed reduced temporal-parietal activity and inferior frontal activity relative to controls. Changes in post-test fMRI results were widespread for the reading impaired children, including over 14 brain regions in addition to regions showing shared changes with the non-impaired group. These regions included a subset typically involved in phonological processes, as well as several regions that are not (i.e. cingulate, hippocampus). The magnitude of activation changes in left temporo-parietal regions correlated with improvements in oral language, although no such correlation with reading improvements was found.

A third intervention study (Aylward et al 2003) also showed evidence of changes in neuroimaging profiles for reading impaired children following an intervention. The intervention involved 28 hours of intervention that included activities that stress “linguistic awareness, alphabetic principle, fluency, and reading comprehension”, which resulted in an improvement in standard scores on a measure of reading novel words. A task assumed to isolate grapheme-phoneme mapping processes was used to probe the effects of treatment on changes in brain activity. In pretest measures, fourteen general brain regions showed less activity in the children with RD, relative to non-impaired children, demonstrating a lack of specificity in the task that potentially complicates interpretation of changes. The intervention group demonstrated no significant change in areas previously associated with phonology and reading, such as left perisylvian regions and left fusiform gyrus regions. Some patterns of changes were reported across a number of other cortical regions, although statistical limitations did not allow clear differentiation of whether such changes reflected significant increases in the RD group or significant decreases in the non-impaired group. The non-specific nature of the pre-test activation patterns, and the ambiguities in the nature of the changes that occurred for both groups underscores the importance of well-developed and validated probe tasks in characterizing intervention-based changes in activity.

Together, the convergent result across these initial intervention/neuroimaging studies stand as form of proof-of-concept demonstration that functional activation differences between RD and non-impaired readers may in some cases prove to be quite malleable in response to effective therapeutic interventions. Such findings demonstrate the degree to which activation patterns, under some circumstances, may change

dramatically over the course of relatively short-lived experiences. The Simos et al., (2003) and Temple et al., (2003) studies demonstrated that significant change can be induced within the very same cortical regions that have been consistently implicated in adult and child neuroimaging studies, as well as within structural/anatomical studies, with interventions. These findings suggest the possibility that interventions can serve to counteract a dominant psychobiological phenotype of reading disability—the tendency for hypoactivation of left perisylvian regions during phonological processing.

MEG methods provide an additional source of information for assessing the impact of intervention, in the form of timing information at the millisecond level. In the Simos et al. (2003) study, signs of functional disruption in left superior temporal gyrus persisted even after remediation, as the peak latency of this effect was over 230 msec slower than the non-impaired group even after the intervention. It is possible that this effect taps into aspects of functional disruptions that are more difficult to change through short-term intervention, such as the fluency of phonological operations.

These initial studies represent a new research paradigm for investigating the relationship between specific interventions and specific changes in cortical activity. In theory, such paradigms could allow specific causal relationships between therapeutic interventions and changes in cortical activation patterns associated with core processing deficits in reading disability.

The specific inferences that can be drawn from these three initial studies are limited by a number of factors, however. For example, none of the three studies included key controls that would be crucial for establishing a causal link between the intervention activities and observed changes in cortical activity, such as a reading impaired control

group randomized to an alternate intervention. Other challenges involve the selection of appropriate functional activation paradigms, and the specificity of results obtained during pre and post-test measures. In the case of the Aylward et al (2003) study, the pretest task failed to specifically isolate cortical regions established as critical for grapheme-phoneme processing, or to demonstrate clear evidence for changes within phonological and graphemic analysis regions for the intervention group. In contrast, the other two studies employed tasks that had been validated previously by contrasts between RD and non-impaired children and adults, and have been found to isolate regions associated with reading and phonological processing. An additional limitation to interpretation comes in the form of intervention results that are non-specific. In the Temple et al. study, the fact that a large number of regions throughout diverse brain regions showed significant changes presents challenges for understanding the specific relationship between improvements in ability and changes in particular brain regions. Identifying changes specifically associated with critical improvements in targeted cognitive skills may require additional development of assessment tasks.

A third complication is illustrated by the nature of the pre-test contrast in the Simos et al study. The complexity of the visual pseudoword rhyming task may have precluded these children with severe reading disability from engaging in any attempt at phonological analysis. In fact, pretest mean accuracy was at chance performance (51.1%), and thus the pretest task provides no evidence for the types of mental operations the children were engaging, with the possible exception of the increased recruitment of right superior temporal gyrus regions. If this low performance accuracy reflects a complete disengagement in the phonological aspects of the task, perhaps due to an

inability to read the pseudowords of the task, then interpretations mandated by the evidence of cortical changes are rather limited.

Overcoming such methodological issues will require a better characterization of the relationship between performance and activation in both RD and non-impaired children (for discussion see (Schlaggar et al 2002), and the development of tasks that will allow direct comparison between RD and non-impaired children performing at comparable levels. One methodological advance that has already been extensively employed in developmental studies of reading disability involves contrasting RD children with a younger control group matched for overall reading ability (Goswami & Bryant 1989). Inclusion of such a control group in developmental imaging studies would provide a basis for characterizing pre-test differences in children with RD as developmental delays that are similar to the typical development of reading versus qualitatively different patterns of development.

In summary, the last decade of research on reading disability has produced a great deal of evidence at the cognitive, neural systems, and cellular levels of analysis. Cognitive research has identified a core phonological processing deficit in associated with reading disability in both adults and children, as well as host of other cognitive difficulties that show substantially weaker relationships with reading disability. Neuroimaging research relates adult reading disability to particular functional disruptions within and between cortical regions associated with processing visual and phonological information important to reading. Adults with reading disability produce a wide range of cortical responses that diverge from non-impaired readers, including a tendency under-recruit left perisylvian regions and over-recruit left frontal regions during phonologically

demanding tasks, and a tendency to show reduced responses to visual words in left basal temporal regions. Some of these phenomena appear to be linked to differences in cellular populations, including subtle disruptions in perisylvian regions that include white and gray matter disruptions, and may also relate to morphological differences in the shape and size of particular gyri.

Throughout this review, we argue that characterizing the causal relationships between these various findings and exploring the implications of these findings for intervention is significantly facilitated by examining the *development* of these differences between RD and non-impaired readers. Evidence from infant ERP studies demonstrate that some aspects of reading disability, specifically those associated with early responses to speech sounds, are associated with differences between infants with and without familial risk for RD. As these differences in brain activity precede any substantial exposure to language, they are presumably the result of neuroanatomical biases attributed to genetic variance.

Neuroimaging evidence from children at the age in which reading ability and disability first emerge as stable traits reveals a number of important similarities and differences to the adult literature that are potentially instructive. First, children with RD show the same general pattern of reduced activity in left perisylvian regions in response to phonological demands, suggesting that such atypical patterns may reflect a somewhat stable characteristic of RD responses spanning from infancy to adulthood. In contrast, response patterns in left fusiform gyrus to visual words are similar across children with and without RD, suggesting that the adult difference may be more associated with developmental changes that occur between late childhood and adulthood. We propose

that late emerging differences between RD and non-impaired individuals reflect differences in perceptual expertise associated with years of successful or unsuccessful reading experience, akin to other forms of extensive experience that have been found to modify fusiform responses to classes of stimuli.

Finally, examination of childhood differences between RD and non-impaired patterns of brain activity reveal patterns of compensatory activity that are not found in adults, including increased recruitment in right perisylvian and right fusiform areas. Although the cognitive implications of such patterns of activity are not currently known, such findings demonstrate that compensatory patterns of activity associated with RD change dynamically across the development of reading skills.

In closing, we observe that the initial studies that have examined the impact of intensive intervention on cortical responses in childhood RD have demonstrated a considerable degree of plasticity in such responses, especially within areas shown to be hypoactive in the processing of phonological information in childhood and adulthood RD. Carefully engineered intervention protocols appear to counteract the neurobiological biases demonstrated in developmental studies of RD, producing significant changes in reading achievement as well as changes in patterns of cortical activity. Although a host of methodological limitations currently prevent the establishment of direct causal relationships between the prescribed intervention activities and the observed changes in cortical activity, many of these challenges have been addressed successfully in other imaging studies and other intervention studies. This research may soon provide a framework for systematically studying the causal relationships between intervention techniques designed to stress particular principles, such

as increasing children's attention to the relationship between graphemes and phonemes within word forms, and changes within cortical activation patterns typically associated with reading disability.

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Table 1

Authors/ Method	Subjects	Stimuli	Active Task	Control	Key Findings		
					Type of effect	Group Effect	Region
Rumsey et al. (1992), PET (49 regions examined)	NI (n=14) RD (n=14)	Auditory word pairs Tones	Rhyme matching: auditory words	Intensity matching: tones	Active > control	NI > RD	L Sup. Temp region
Paulesu et al (1996) PET	NI (n=5) RD (n=5)	Letter pairs Korean character pairs	Letter name rhyme matching	Visual similarity (Korean characters)	Active > control	NI > RD	L STG L Insula
Rumsey et al (1997) PET	NI (n=14) RD (n=17)	Visual words, pseudowords	Read aloud	Fixation	Active > control	NI > RD	Post. Temporal (including L STG) L Fusiform L Inf. Parietal
						RD > NI	L Insula
Horwitz et al (1998) PET	NI (n=14) RD (n=17) (same sample as Rumsey, 1997)	Words, pseudowords	Read aloud	Fixation	Correlation w/ angular gyrus activity and other regions	NI > RD	L STG Fusiform/Lingual Inf. frontal areas
Shaywitz et al (1998) FMRI (17 ROIs based on previous studies)	NI (n=32) RD (n=29)	Stimulus – Task Pairings Line segments Letter strings Pseudowords Words	Orientation match Letter case matching Rhyme matching Category matching	Each task served as a control for the next in the hierarchy	Increasing activity with increasing task demands in the hierarchy	NI > RD	L STG Angular gyrus Striate Cortex-BA 17
						RD > NI	IFG
Paulesu et al (2001) PET	NI (n=36) RD (n=36) x 3 language groups (French., English., Italian.)	Words, pseudowords	Explicit (read aloud) (n= 18 RD, 18 NI) Implicit (feature judgment) (n=18 RD, 18 NI)	Baseline False fonts	Conjunction analysis of explicit and implicit task contrasts showing group effects	NI > RD All 3 language groups	L STG L mid-Temporal L Fusiform/ L mid-Occipital

Table 1

Table 1

Brunswick et al (1999) PET	NI (n=6) RD.-remediated (n=6)	Words, pseudowords	Read aloud (Explicit reading)	Rest, eyes closed	Active > control	NI > RD	Fusiform/Lingual gyrus (BA 37) Cerebellum
						RD > NI	Pre-motor areas
	NI (n=6) RD -remediated (n=6)	Words, pseudowords, false fonts	Feature Detection (Implicit reading)	Rest, eyes closed	Active > control	NI > RD	Basal temporal region (including fusiform gyrus) L inf. parietal. L inf. temporal L mid-temporal
Salmelin et al, (1996) MEG	NI (n=8) RD (n=6)	Words, nonwords	Silent reading with infrequent probe trial	Prestimulus baseline	Stimulus locked response: 180 msec.	NI > RD	L. posterior source (near BA 37)
					Stimulus locked response 200-400 msec	NI > RD	L Temporal lobes (near STG)
Helenius et al, (1999) MEG	NI (n=10) RD (n=12)	Words, geometric symbol strings, Presented in different levels of visual noise	Passive viewing with infrequent probe trial	Pre-stimulus baseline	Stimulus locked response: 100 msec.	NI = RD	Sources within early visual regions
					Words > symbols at 180 msec	NI > RD	Sources near basal temporal region (including Fusiform gyrus)
Helenius et al, (2002) MEG	NI (n=10) RD (n= 9)	Speech: syllables with short or long gaps between onset and rime	Passive listening Active discrimination of rare deviant syllables	Pre-stimulus baseline	Amplitude of response within 100 msec to deviant syllable (both tasks)	RD > NI	L STG
		Non-speech;, rapid pairs of simple tones, complex sounds	Passive listening Active discrimination,	Pre-stimulus baseline	Stimulus locked responses	NI = RD	L/R STG

NI=non-impaired; RD= reading disability IFG=inferior frontal gyrus; L=left; R=right; STG=superior temporal gyrus;

Table 1

Table 2

<i>Authors/ Method</i>	<i>Subjects</i>	<i>Stimuli</i>	<i>Active Task</i>	<i>Control Task</i>	<i>Key Finding</i>				
					<i>Effect</i>	<i>Group Effect</i>	<i>Areas</i>		
Shaywitz, et al., (2002) fMRI	NI (n=74 age 7-17) > 39%ile decoding	Visual stimuli unique to each task.	Pseudowords: rhyme match	Line segments: Orientation match	Active (both tasks) > control	NI > RD	LH and RH perisylvian, and frontal regions		
	RD (n=70 age 7-18) <25%ile decoding		Words: category match				Positive correlation of brain activity (active>control) and decoding skill	All subjects combined	Left basal temporal (including L Fusiform)
Temple et al., (2001) fMRI	NI (n=15 age 8-12)	Line segments	Rhyme match letters	Visual match letters	Active > control	NI > RD	L perisylvian (including L STG) L occipito-parietal		
	RD (n=24 age 8-12)	Letter pairs					RD > NI	L IFG	
				Visual match letters	Visual match line segments	Active > control	NI > RD	L mid/sup occipital R precuneous cingulate,	
Simos et al., (2000a) MEG	NI (n=10 age 8-16) > 80%ile decoding	Pseudoword pairs (visually presented)	Rhyme match	Pre-stimulus baseline.	Strength of magnetic source solution	NI > RD	Left Perisylvian		
	RD (n=11 age 10- 17) < 30%ile decoding							RD > NI	Right Perisylvian
								NI = RD	Left Basal Temporal regions (including Fusiform Gyrus)

Table 2

Table 2

Simos et al, (2000b) MEG	NI (n=8 age 8-16) > 80%ile decoding	High frequency words (from 2 nd grade texts)	Visual word recognition	Pre-stimulus baseline	Strength of magnetic source solution	RD	Perisylvian sources: Right > Left
	RD (n=10 age 10- 17) < 30%ile decoding					NI	Perisylvian sources: Left > Right
						NI =RD	Left basal temporal (near fusiform gyrus)
Georgiewa et al., (1999) FMRI	NI (n=17 age 14)	<u>Stimulus - task Hierarchy</u>			Pseudowords > symbol strings	NI > RD	Left IFG
	RD (n=17 age 14) German	Symbol strings	Passive viewing				
		Pseudowords	Silent reading				
		Frequent words	Silent reading				
		Frequent words	Move onset to end, add "ein" (silently)		Phoneme manipulation task (words) > passive viewing (symbols)	NI > RD	Left IFG
RD=reading-disability; NI=non-impaired; STG=superior temporal gyrus; IFG=inferior frontal gyrus; L=left; R= right;							

Table 2

Table 3

Authors	Subjects	Intervention	Behavioral Outcome	Neuroimaging Results	
				Pre-test	Post-Test
Simos et al., (2003)	NI (no intervention) (n=8, 1/8 ADD) RD (intervention) (n=8, 6/8 ADD) Age 7-17	<i>Phono-Graphics</i> (n=6) or <i>Lindamood Phoneme Sequencing</i> (n=2) phonological awareness programs (80 hours)	Large improvements on standardized reading test (no control group)	MEG: rhyme judgment for pairs of visually presented pseudowords NI > RD in sources near L STG RD > NI in sources near R STG	RD: Increases in RD activity in L STG, decrease in right homologue stable pre-post responses
Temple et al., (2003)	NI (no intervention) (n=12) RD (intervention) (n= 20) Age 8-12	<i>Combined Treatment: Fast Forward</i> --adaptive auditory training for rapid	Moderate improvements in word reading, decoding and passage comprehension (no control group)	fMRI: rhyming letters v. matching letters: NI > RD in Left Perisylvian Regions (i.e. as in. Temple et al., 2000).	Excluding all areas of NI change showed increases in 14 unique brain regions within left and right hemispheres, including left temporal parietal region, and BA 37 (near fusiform gyrus). Changes in temporal parietal activation correlated with changes in auditory language skill not reading.
Aylward et al., (2003)	NI (no intervention) (n = 11, 10) Age 11	Syllable and phoneme awareness, decoding activities, reading (28 hours) v. no intervention NI control	Moderate improvements in decoding skill (no control group)	fMRI: same/diff phoneme judgment for graphemes within pseudowords, v. identity judgment for two consonant strings. NI > RD (stronger in left hemisphere) for frontal (inf, mid, sup), parietal (sup, inf), temporal regions (inf, mid, AG) and fusiform gyrus.	Post-test group differences diminished associated with both increases in and decreases in NI (control) for mid frontal gyrus, and superior parietal areas.

IFG=inferior frontal gyrus; L=left; NI=non-impaired; p=posterior; PR=poor readers; R=right; RD=reading-impaired; STG=superior temporal gyrus; TAC=Task Activation Contrast; AG=Angular Gyrus

Table 3