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Integrating MRI brain imaging studies of pre-reading children with current theories of developmental dyslexia: a review and quantitative meta-analysis

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The neurobiological substrates that cause people with dyslexia to experience difficulty in acquiring accurate and fluent reading skills are still largely unknown. Although structural and functional brain anomalies associated with dyslexia have been reported in adults and school-age children, these anomalies may represent differences in reading experience rather than the etiology of dyslexia. Conducting MRI studies of pre-readers at risk for dyslexia is one approach that enables us to identify brain alterations that exist before differences in reading experience emerge. The current review summarizes MRI studies that examine brain differences associated with risk for dyslexia in children before reading instruction and meta-analyzes these studies. In order to link these findings with current etiological theories of dyslexia, we focus on studies that take a modular perspective rather than a network approach. Although some of the observed differences in pre-readers at risk for dyslexia may still be shaped by language experiences during the first years of life, such studies underscore the existence of reading-related brain anomalies prior to reading onset and could eventually lead to earlier and more precise diagnosis and treatment of dyslexia.

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Introduction

Developmental dyslexia is the most common learning disability, but we do not yet fully understand its core neurobiological cause(s) [1]. MRI brain imaging studies, when performed at an early point in children's reading development, have the potential to validate theories about the etiology of dyslexia by precisely localizing early neurobiological anomalies. Although an increasing number of studies take a network and/or a multivariate pattern analytical approach in identifying differences in dyslexia (e.g. [2,3]), here, we deliberately take a modular perspective and focus on the location of neurobiological anomalies related to dyslexia in order to link findings with etiological theories of dyslexia. We therefore do not include electrophysiological studies, which have higher temporal resolution but typically have lower spatial resolution (for an overview of other behavioral and electroencephalography (EEG) studies see [4,5]).

Much of our understanding of the brain basis of dyslexia comes from MRI studies of adults and older school-aged children, which limits the conclusions that can be drawn regarding the origin of the neurobiological differences in dyslexia. Indeed, learning to read is a dynamic process that depends on brain plasticity as well as implicit and explicit learning. Such learning-induced brain plasticity has been demonstrated in studies of non-literate adults who show both functional and structural changes in reading-related brain regions after learning to read [6]. In addition, findings from MRI studies comparing individuals with dyslexia to both age-matched and younger reading level-matched control groups suggest that some of the brain differences observed in dyslexia can be explained by differences in the amount and quality of reading experience [7]. Hence, neurobiological anomalies in dyslexia observed at later stages of reading development (mainly in left temporo-parietal (TP) and occipito-temporal (OT) regions, [8]) may reflect impoverished or reduced reading experience among those with dyslexia [9] rather than a true biological cause of dyslexia.

Recently, advances in MRI technology and the refinement of child-friendly scanning protocols have made it feasible to study the brain in young children prior to reading onset. At least 16 published studies have used MRI to examine cognitive processes associated with

reading in pre-readers, including those who are at risk for dyslexia, in several independent cohorts [3,10–13•,14–16,17••,18•,19–22,23•,24••]. In this review, we discuss and, for the first time, quantify the location and function of the reported differences in reading-related regions and pathways observed in pre-readers. We then interpret these findings *vis-à-vis* existing etiological theories of dyslexia. These theories vary in their conceptualization of the core deficit in dyslexia, including cognitive-linguistic, perceptual, and meta-cognitive deficit perspectives (for detailed discussion see [25–27]). We focus here on neurobiological findings that relate to theories for which behavioral studies have found differences in preliterate children at high risk compared to low risk for developing dyslexia: specifically theories associated with phonological, orthographic, and lower-level perceptual/attention deficits.

Dyslexia-related differences in pre-readers

Several studies to date have focused on pre-readers who are *at risk* for developing dyslexia because of a family member with dyslexia or because of low performance on standardized behavioral measures that are strongly associated with later reading. Though it would be informative to follow these pre-readers until they could be classified as having dyslexia or typical reading abilities, very few studies have taken this approach. Differences between pre-readers with and without risk for dyslexia have been found across a wide variety of different structural and functional MRI measures [3,12,13•,14–16,17••,18•,21,22,23•,24••]. Differences associated with dyslexia risk are consistently found across studies in four main brain regions: left TP, OT, and cerebellum as well as right parietal which are consistent with a previous structural and functional meta-analysis of children and adults with dyslexia [28] (see meta-analysis of pre-reading studies in Figure 1). These findings of similar anomalies in at risk pre-readers and dyslexic individuals compared to their respective controls provide the first evidence that neurobiological differences observed in adults and children with dyslexia are not purely reading experience-driven, but are more likely related to etiological differences. Other brain regions have also been indicated, though less consistently, across studies. We now turn to examining these findings in greater detail as they relate to theories of the etiology of dyslexia.

Phonological deficit theory

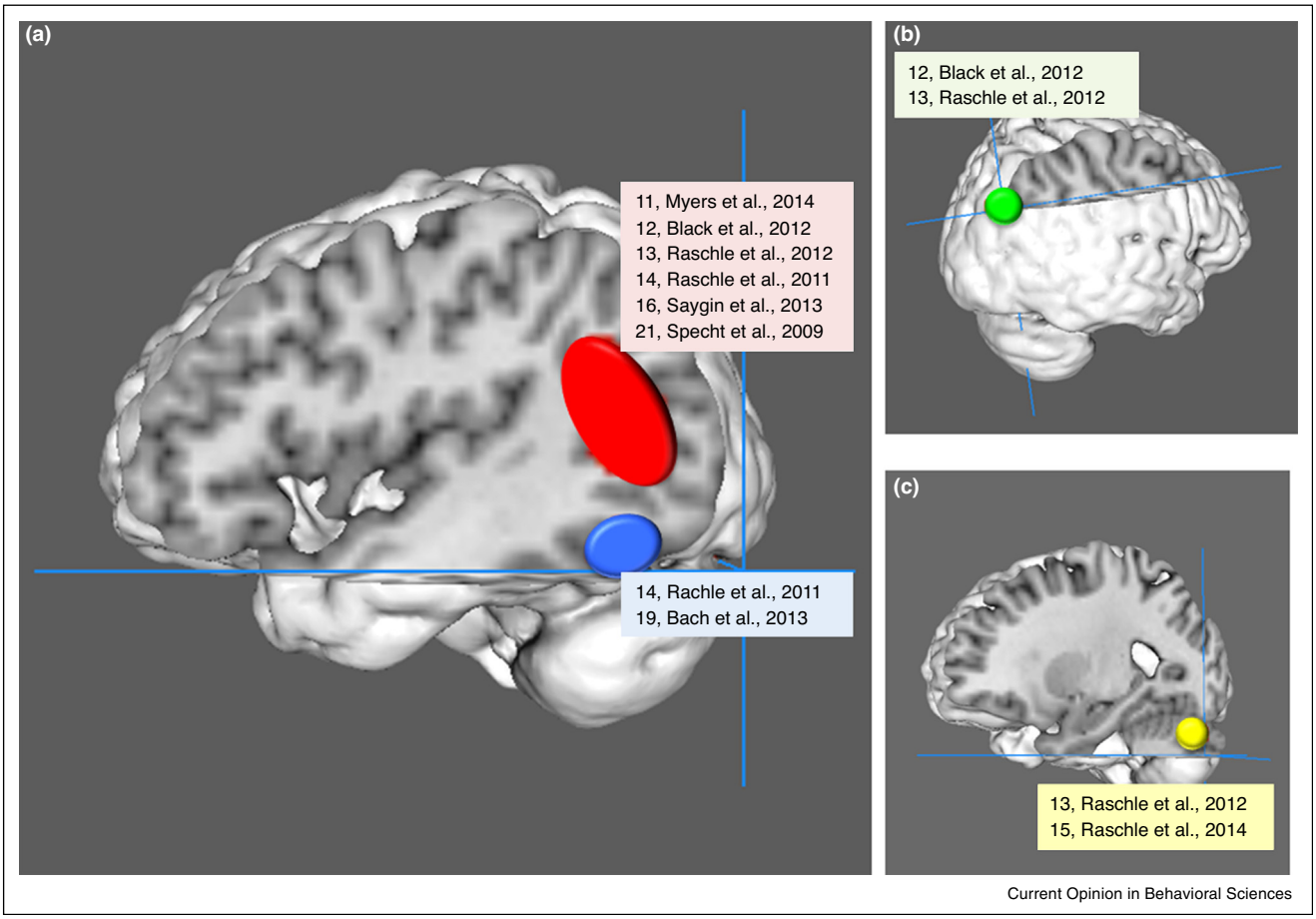
A deficit in phonological processing, and especially in phonological awareness (i.e. the ability to process and manipulate the sound structure of words), is widely recognized as an underlying cause of dyslexia [25,29]. The phonological deficit theory is supported by behavioral evidence from longitudinal studies showing pre-reading phonological deficits [30], and from phonological training studies yielding improved reading [31].

In adults and school-age children, phonological processing has repeatedly been associated with a left-lateralized network including the TP region (including the supramarginal gyrus, planum temporale, and superior temporal gyrus) as well as inferior and superior frontal regions ([32,33], for a meta-analysis see [34]). Anomalies in the left TP region (Figure 1a; shown in red) are consistently observed in dyslexia, including decreased functional activation [35,36] as well as atypical gray matter volume [37] and white matter organization [38]. These robust differences in the left TP region are often interpreted as neural evidence for the phonological deficit theory, yet such a causal interpretation needs validation in pre-readers, especially given the fact that some studies comparing dyslexic readers with reading-matched and age-matched controls have not found differences in this area [39] whereas others have [7].

Several MRI studies in pre-readers at risk for dyslexia also observe different neural organization in left TP regions in the children [3,12,13•,14,16,21,22,24••]. Further, gray and white matter volume in left TP regions predict later reading skills [11,40]. Importantly for validation of the phonological deficit theory, left TP anomalies in at-risk pre-readers have been associated with participants' phonological processing difficulties; functional MRI (fMRI) studies in both English and Norwegian children show that left TP is hypoactivated in at-risk compared to typically-developing pre-readers during a phonological processing task [13•] and in beginning readers during an alphabetic decoding reading task [21]. In addition, two independent diffusion MRI studies found that phonological awareness scores were correlated with organization of the left arcuate fasciculus, a white matter tract that connects TP and frontal regions [16,18•]. Thus, it may not be only a local anomaly in TP cortex *per se*, but different functional and structural connectivity between TP and other reading-related regions that give rise to phonological difficulties [41,42•,43].

Together with evidence from fMRI studies of skilled readers [34], these data suggest that the link between phonological processing and left TP seems to be established prior to reading and might remain present throughout reading development. Yet, in contrast to adults, pre-readers seem to recruit a more distributed network of regions for phonological processing which includes left OT and cerebellar as well as right hemisphere areas [14,18•,21] (see also Figure 1 panel b and c), although these additional regions seem less consistently impaired in pre-readers at risk for dyslexia. Further, based on the few studies to date that followed at-risk pre-readers and examined whether these differences are markers of which children develop dyslexia, the involvement of TP regions are not fully clear. One study found no significant differences in left TP cortical thickness among pre-readers who later developed dyslexia versus those who did not;

Figure 1



Regional differences in pre-readers that are related to familial or behavioral risk for dyslexia, or to later reading outcome, revealed by meta-analysis. Only coordinate-based studies are included in this figure (Refs. [12,13,14•,15–17,18••,20–23]; no coordinates are available from Refs. [3,19•,24•,25••]). Studies and corresponding reference numbers contributing to each cluster are listed in the figure. Analyses were performed in Ginger ALE 2.3. A cluster is identified when reported by multiple studies with a cluster-level significance threshold of $P < .01$ (10,000 permutations). The circles are drawn proportional to the size of the cluster, which reflects the variability in location within the cluster and not necessarily the strength of the effect. **(a)** The red cluster represents the left temporo-parietal (TP) region (center at Montreal Neurological Institute (MNI) coordinates −46, −61, 14, with 5 sub-peaks within the cluster). The blue cluster is the left fusiform gyrus in the occipito-temporal (OT) region (−44, −57, −15). **(b)** The green cluster is in the right parietal lobe (45, −71, 33). **(c)** The yellow cluster is in the left cerebellum (−26, −79, −27).

significant group differences were observed in other more sensory regions [17••]. The number of pre-readers who later developed dyslexia in this study was small (N = 7), however [44]. Another study found that children with family history of dyslexia differed from controls in the organization of the left arcuate fasciculus; further, the trajectory of left arcuate development over time predicted their later reading ability [24••]. In sum, though our meta-analysis identified left TP abnormalities in pre-readers at risk for dyslexia, future studies should further investigate the precise role of this region in reading development.

Orthographic deficit theory

Fluent reading also depends on orthographic processing, that is, the ability to identify written letter patterns and words as whole units (rather than letter by letter). As orthographic knowledge is chiefly acquired by repeated and successful phonological decoding of words [45], orthographic problems in dyslexics are often considered secondary to a primary phonological deficit. However, some studies show that orthographic processing might be an independent cause of dyslexia, as it predicts word reading ability after controlling for phonological processing [46,47]. In parallel to the left TP region's involvement in phonological processing, the left ventral OT area, including the fusiform gyrus, plays a key role in orthographic processing in skilled readers [48,49]. In a subsection of the OT region often referred to as the visual word form area (VWFA), activation to words is reduced among individuals with dyslexia relative to controls [50].

In pre-readers and early readers at risk for dyslexia, the left OT region shows reduced gray matter volume [14], different patterns of anatomical folding [23•], reduced functional activation [21], and reduced connectivity to frontal regions [18•]. Furthermore, among a small sample of pre-readers, activation in the OT region to words and symbols predicted later reading ability beyond the contribution of behavioral and EEG measures [19]. Among children who could read beginning words, this area showed activation for words that must be remembered as wholes because of their irregular spelling pattern, but not for words that could be decoded based on grapheme–phoneme correspondences [21].

Although many studies suggest involvement of the left OT region in orthographic processing, it is not yet clear how specialized this region is for orthographic processing early in reading development. Indeed, studies of pre-readers have found that phonological awareness skills relate to left OT structure [14], function [13•] and connectivity patterns [18•]. In addition, performing an orthographic task activates regions beyond left OT including bilateral TP, frontal and parietal regions in pre-readers and early readers [3,13•,17••,21]. More longitudinal studies, starting at the pre-reading stage, should be conducted to validate whether neural specialization for reading-related cognitive functions is something that is only established after reading acquisition.

Theories based on perceptual and other deficits

Theories based on perceptual deficits generally do not deny that cognitive-linguistic problems characterize dyslexia; however, they assert that these phonological and orthographic deficits are caused, in turn, by lower-level deficits. In pre-readers, perceptual deficit theories have not been frequently investigated using MRI methods. One study [15] found that pre-readers at risk for dyslexia showed hypoactivation in pre-frontal regions during processing of nonlinguistic auditory stimuli with rapid frequency transitions. Activation during this rapid auditory processing task was correlated with phonological awareness, suggesting a link to reading ability through that process. Indirect support for perceptual theories also comes from the aforementioned study that showed reduced cortical thickness in primary auditory and visual areas in a small sample of pre-readers who were later diagnosed with dyslexia [17••]; however, no behavioral or functional MRI data were provided in that study to support a direct link with perceptual abilities. Therefore, further investigation of perceptual theories by means of MRI studies in pre-readers is needed in order to confirm whether atypical neural processing of perceptual information is a precursor and cause of dyslexia. Other perceptual theories including deficits in visual–spatial attention [51] and neural coding of auditory stimuli [52] have been validated in pre-readers, but have not yet been investigated using MRI.

In contrast, theories based on other deficits have been tested using MRI in older children and adults, but not yet in pre-readers. Deficits in auditory/temporal sampling, which may account for deficits in reading speed and accuracy in dyslexia, have been observed [53,54]. There is also evidence for the double-deficit hypothesis [55], which suggests that weaknesses in either rapid automatized naming (RAN) or phonological awareness can cause dyslexia, and that those with both deficits are the most severely impaired readers. Functional activation and connectivity patterns in these groups are consistent with this hypothesis [56]. In terms of brain structure, white matter tracts relating to PA have been identified, but no measures of tract organization have yet consistently been associated with RAN [16,18•].

Limitations of current evidence in pre-readers

Although the MRI studies of pre-readers reviewed here provide hints about the validity of the different etiological models, interpretation in terms of causal effects is limited by a few shortcomings. First, prenatal and early developmental and environmental effects also shape many of the processes underlying reading and the brain. Efforts to scan infants, for whom these differences are more minimal, are already underway and may provide new insights into these questions. Second, a more comprehensive assessment of parental influences might lead to a better understanding of the genetic and environmental mechanisms underlying dyslexia [57]. For example, it may be the case that parents with dyslexia provide different quality or quantity of reading-related input to their child, though behavioral studies suggest that such differences have a modest effect on behavioral indices of reading and language development [58]. Third, the modulating role of orthographic depth is not examined in the current review due to a small number of MRI studies in pre-readers per language. Although a recent meta-analysis of cognitive studies indicated that differences in phonemic awareness between pre-readers with and without familial risk were not dependent on orthographic depth [58], a meta-analysis on fMRI studies in school-aged children and adults with dyslexia did show a modulating effect in phonological-related regions such as left TP, with dyslexic hypoactivation only present in shallow orthographies [59].

Finally, and most importantly, most MRI studies to date have examined pre-readers at-risk for dyslexia but have not followed up to establish which of these children actually develop dyslexia (but see [17••,24••]). (Some longitudinal studies using EEG, which is less expensive and easier to acquire than MRI, have taken this approach [60,61].) It remains therefore to be determined whether the pattern of brain anomalies observed in at-risk pre-readers will be the same in the subset who actually develop dyslexia. At-risk children who become typical readers display subtle problems in phonemic awareness, but these problems are less severe than the deficits among

at-risk pre-readers who do develop dyslexia [58]. Therefore, it might be that left TP anomalies, which are typically associated with phonemic awareness, will be more severe in the at-risk pre-readers who eventually develop dyslexia. Longitudinal follow-up of the at-risk pre-readers, allowing classification according to later reading outcome, may significantly improve our understanding of neural risk factors related to dyslexia.

Conclusion

The purpose of this review was to examine whether dyslexia-related anomalies can be detected with MRI prior to reading onset, and whether taking a modular perspective of brain function and identification of the anomalous locations can inform theories on the etiology of dyslexia. The most consistent findings across studies are differences in left TP brain regions between at-risk pre-readers and controls. Because left TP is associated with phonological processing, this provides substantial support for the phonological deficit theory. Differences in left ventral OT regions are also observed prior to reading onset, though less consistently. Finally, some evidence is also provided for an early deficit in perceptual regions, especially in the auditory domain [15,17••].

It is important to highlight that several studies indicate early connectivity differences in at-risk pre-readers [3,16,18•]. One possibility is that structural connectivity differences give rise to differences in function; a recent study found that even before the VWFA is selective for letters and words in pre-readers, structural connectivity 'fingerprints' in kindergarten children of varying reading ability predicted location of the VWFA 2.5 years later [62]. This finding suggests that inefficient communication and coordination between cortical regions prior to reading instruction could shape neural activation during reading. Insufficient functional and structural connectivity among the regions of the reading network may give rise to the complex behavioral deficits seen in dyslexia, such as difficulty with rapid naming and reading fluency.

Given the complexity of reading and variety of profiles observed in dyslexia, considering each etiological theory in isolation may be a too simplistic a view. As multi-componential models suggest, it is very unlikely that a single underlying causal factor drives the heterogeneous patterns of reading difficulties across individuals with dyslexia [63••]. Dyslexia is perhaps more accurately conceptualized as a complex interaction of different risk and protective factors, and the weighting of each of these factors can vary across different individuals with dyslexia. It may be that inefficient auditory and phonological neural systems cause reading difficulties in one individual with dyslexia, but another individual may struggle as a result of predominant visual-orthographic integration problems. In addition, genetic, environmental, and metacognitive factors can modulate these risks [58].

Educators and clinicians should consider that brain differences in dyslexia are present before children learn to read, and thus that waiting for these problems to resolve on their own is inefficient. However, at the moment, brain measures are insufficiently sensitive and specific at the individual level to aid in early diagnosis. Future studies using MRI and other brain imaging technologies may reveal early, reliable and cost-effective biomarkers of dyslexia. Until then, the most efficient approach is still examination of a combination of early, comprehensive behavioral assessments and demographic information such as family history, followed by intervention that is designed to ameliorate the individual's particular areas of difficulty.

Conflict of interest

Nothing declared.

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This is one of the only studies that followed pre-readers longitudinally in order to differentiate which children developed dyslexia. Although results should be interpreted with caution due to the small samle size (n = 7 pre-readers who developed dyslexia), neuroanatomical anomalies were observed. More specifically, MRI measures of cortical thickness at pre-reading age were significantly different among those who did versus did not develop dyslexia, not in the traditional reading network, but in regions that support lower-level visual and cognitive processing. Differences in the reading network between the groups were only evident after reading acquistion at age 11, suggesting that such differences are driven by differential reading experience.

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In a large group of pre-readers (n = 71), diffusion MRI was used to study the links between white matter organization and behavioral and familial markers of dyslexia. The study confirmed associations between the bilateral arcuate fasciculus and phonological processing, and additionally showed early involvement of ventral tracts related to familial risk.

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