

A Meta-analysis of Functional Neuroimaging Studies of Dyslexia

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Reading and phonological processing deficits have been the primary focus of neuroimaging studies addressing the neurologic basis of developmental dyslexia, but to date there has been no objective assessment of the consistency of these findings. To address this issue, spatial coordinates reported in the literature were submitted to two parallel activation likelihood estimate (ALE) meta-analyses. First, a meta-analysis including 96 foci from nine publications identified regions where typical readers are likely to show greater activation than dyslexics: two left extrastriate areas within BA 37, precuneus, inferior parietal cortex, superior temporal gyrus, thalamus, and left inferior frontal gyrus. Right hemisphere ALE foci representing hypoactivity in dyslexia were found in the fusiform, postcentral, and superior temporal gyri. To identify regions in which dyslexic subjects reliably show greater activation than controls, 75 foci from six papers were entered into a second meta-analysis. Here ALE results revealed hyperactivity associated with dyslexia in right thalamus and anterior insula. These findings suggest that during the performance of a variety of reading tasks, normal readers activate left-sided brain areas more than dyslexic readers do, whereas dyslexia is associated with greater right-sided brain activity. The most robust result was in left extrastriate cortex, where hypoactivity associated with dyslexia was found. However, the ALE maps provided no support for cerebellar dysfunction, nor for hyperactivity in left frontal cortex in dyslexia, suggesting that these findings, unlike those described above, are likely to be more varied in terms of their reproducibility or spatial location.

Key words: meta-analysis; dyslexia; functional imaging

Introduction

Developmental dyslexia is a common reading disorder which accounts for 80% of all learning disabilities in the United States (Lerner, 1989; Lyon, 1995a). The cognitive deficits associated with developmental dyslexia have been intensely studied over the last 40 years (for review see Vellutino, Fletcher, Snowling, & Scanlon, 2004). Behavioral studies of

dyslexia suggest that a core deficit in phonological processing, specifically phonemic awareness, underlies problems in the decoding of text (Bruck, 1992; Fletcher *et al.*, 1994; Flowers, 1995; Liberman & Shankweiler, 1991; Morris *et al.*, 1998; Ramus, 2003; Shankweiler, Liberman, Mark, Fowler, & Fischer, 1979; Shaywitz *et al.*, 1999; Shaywitz *et al.*, 2003; Stanovich & Siegel, 1994; Torgesen, 1995; Wagner & Torgesen, 1987). In addition to language, several other domains, such as the visual, auditory, and motor systems, are affected (Eden *et al.*, 1996; Fawcett & Nicolson, 1992; Lovegrove, Heddle, & Slaghuys, 1980; Tallal, 1980).

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Although the criteria that define dyslexia have been refined over time and are now well established (Lyon, 1995b; Lyon, Shaywitz, & Shaywitz, 2003; Shaywitz, Fletcher, & Shaywitz, 1995), the underlying pathology of dyslexia remains uncertain. Neuroimaging technologies provide one approach to determine the neural basis of dyslexia; following the lines of behavioral studies in dyslexia, research using these newer modalities have focused primarily on the study of reading and phonological processing. Neuroimaging methods such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), event-related potentials (ERP), and magnetoencephalography (MEG) have been used in different countries to provide evidence of hypoactivation of the left posterior language system in dyslexia, across different languages (Brunswick, McCrory, Price, Frith, & Frith, 1999; Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Horwitz, Rumsey, & Donohue, 1998; Ingvar *et al.*, 2002; Paulesu *et al.*, 2001; Rumsey *et al.*, 1992; Rumsey *et al.*, 1997b; Salmelin, 1996; Shaywitz *et al.*, 2002; Temple *et al.*, 2000). This hypoactivity has been localized to left posterior parietal cortex (Brunswick *et al.*, 1999; Eden *et al.*, 2004; Flowers *et al.*, under review; Pugh *et al.*, 2000; Rumsey *et al.*, 1997b; Shaywitz *et al.*, 2002; Simos *et al.*, 2000a; Simos *et al.*, 2000b; Temple *et al.*, 2001), inferior occipitotemporal cortex (Brunswick *et al.*, 1999; McCrory, Mechelli, Frith, & Price, 2005; Paulesu *et al.*, 2001; Shaywitz *et al.*, 2002), and superior temporal gyrus (Flowers *et al.*, under review; Paulesu *et al.*, 2001; Paulesu *et al.*, 1996; Rumsey *et al.*, 1997b).

On the other hand, there is some disagreement in the literature regarding certain brain regions. For example, left inferior frontal cortex has been reported by some investigators to be more active in dyslexics (Brunswick *et al.*, 1999; Grünling *et al.*, 2004; Shaywitz *et al.*, 1998), and compensatory mechanisms have been suggested to account for this observation (Shaywitz & Shaywitz, 2005). However, other studies have not found this hyperactivation in

dyslexia (Eden *et al.*, 2004; Rumsey *et al.*, 1994), and there are even reports of hypoactivity in left inferior frontal regions, relative to controls (Flowers *et al.*, under review; Georgiewa *et al.*, 1999; Paulesu *et al.*, 1996; Rumsey *et al.*, 1997b; Shaywitz *et al.*, 2002). Some of the studies showing an absence of frontal hyperactivation in dyslexia were conducted in children and could suggest that dyslexia leads to compensatory mechanisms once adulthood is reached (Shaywitz *et al.*, 2002). However, this age-specific theory does not account for the left inferior frontal gyrus hypoactivity reported for adults in other studies (Flowers *et al.*, under review; Georgiewa *et al.*, 1999; Paulesu *et al.*, 1996; Rumsey *et al.*, 1997b; Shaywitz *et al.*, 2002).

Another area of intense investigation in reading and dyslexia involves the role of the cerebellum. Although traditionally not considered a participant in language, more recent evidence suggests that the cerebellum might play a significant role in reading (Fiez & Petersen, 1998), and that its activity may differ during reading and word repetition tasks in individuals with dyslexia (Brunswick *et al.*, 1999; McCrory, Frith, Brunswick, & Price, 2000). Combined with evidence of cerebellar dysfunction from the behavioral (Nicolson, Fawcett, & Dean, 2001), metabolic (Rae *et al.*, 1998), anatomical (Rae *et al.*, 2002) and functional literature (Nicolson *et al.*, 1999), the cerebellum is considered to play a potential role in reading disability (Ramus, 2003).

In general, discrepancies in the published literature are most likely explained by subtle differences in task paradigms. The neural basis of reading is known to be influenced by task parameters such as duration and frequency of the word presentation (Price, Moore, & Frackowiak, 1996). Subject selection (severity of dyslexia, bilingualism in the subjects, etc.) and proficiency of task performance are also believed to play a role. There have been some investigations into the role of a language's orthography, particularly the consistency by which mapping of sound to print occurs. Notably, Paulesu *et al.* showed that aberrant activity

in left inferior posterior temporal regions was common to French, Italian, and English dyslexics, suggesting that the orthography of the language cannot account for differences in neural activity during reading, at least in alphabetic languages (Paulesu *et al.*, 2001). However, the functional anatomy of dyslexia has proven to be somewhat different in some studies of Asian languages. Siok and colleagues in China found that dyslexia in nonalphabetic languages may have a neural signature distinct from dyslexia in alphabetic languages (Siok, Perfetti, Jin, & Tan, 2004). In sum, the particular population studied, the cognitive tasks employed, and differences in methodology influence functional neuroimaging results. These study-specific factors lead to variable results. Despite this variability, a solid understanding of the neurologic basis of dyslexia can be obtained if an objective approach is employed, which identifies the most robust and consistent functional differences.

Using the terminology of Koretz (2002), a “narrative review” of the literature has thus far been the only method by which the findings from neuroimaging studies of dyslexia have been summarized. Such reviews are based on findings that are most dependable across multiple studies (Eden & Zeffiro, 1998; McCrory, 2004; Shaywitz & Shaywitz, 2005; Temple, 2002). However, narrative reviews are susceptible to biases (Koretz, 2002). This problem is compounded by the fact that the choice of anatomic labels applied in studies of brain imaging is somewhat subjective. To address this issue, meta-analytic approaches have recently been applied to published brain imaging findings (Chein, Fissell, Jacobs, & Fiez, 2002; Turkeltaub, Eden, Jones, & Zeffiro, 2002). As in other fields, meta-analyses are a post-hoc combination of results from independent studies, allowing for a better estimation of parameters of interest. To this end, statistically significant effects from different studies are pooled to estimate the spatial location of activation likelihood for specific cognitive functions. For example, Turkeltaub *et al.* developed an objective, quantitative meta-analytic method to deter-

mine consistency across neuroimaging studies, and employed it to identify regions commonly seen during reading in adults (Turkeltaub *et al.*, 2002). This method generates an activation likelihood estimate (ALE) at each voxel. There are numerous advantages to such “systematic reviews” (Koretz, 2002), which have been described in detail by Fox and colleagues (Fox, Laird, & Lancaster, 2005b; Laird *et al.*, 2005b).

Of importance, meta-analytic approaches aid the estimation of concordance across multiple published brain imaging findings and present a principled way of assessing spatial reproducibility. The ALE method and similar methods (Chein *et al.*, 2002) have been used to identify common cortical networks for a range of cognitive functions (Bolger, Perfetti, & Schneider, 2005; Buchsbaum, Greer, Chang, & Berman, 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005; Farrell, Laird, & Egan, 2005; Fox *et al.*, 2005a; Grosbras, Laird, & Paus, 2005; Laird *et al.*, 2005b; Neumann, Lohmann, Derrfuss, & von Cramon, 2005; Owen, McMillan, Laird, & Bullmore, 2005; Petacchi, Laird, Fox, & Bower, 2005; Price, Devlin, Moore, Morton, & Laird, 2005; Tan, Laird, Li, & Fox, 2005). In addition to conducting meta-analysis in alphabetic writing systems (Turkeltaub *et al.*, 2002), the ALE approach has also been used to determine regions of the brain that are universally engaged in readers of English, Chinese and Japanese (Bolger *et al.*, 2005). However, the ALE approach has only recently been implemented to examine and compare findings across the published literature in clinical populations, namely those with stuttering and schizophrenia (Brown, Ingham, Ingham, Laird, & Fox, 2005; Glahn *et al.*, 2005).

The present ALE meta-analysis aims to derive an objective conclusion about the most commonly reported differences in the dyslexic population during tasks involving reading of alphabetic languages. The method employed here includes all coordinates from an eligible experimental contrast, not just regions of particular interest based on trends in the literature. The studies chosen employ PET or fMRI,

and compare dyslexics and typical readers engaged in linguistic tasks that involve the visual presentation of words or letters. This provides a good degree of task consistency across studies, suitable for the meta-analytical approach.

The primary objective of the meta-analysis is to identify the most robust regions of hypo- and hyperactivation in dyslexia. The inclusion of studies that reported on hyper- and hypoactivity in dyslexia using the same paradigms made this possible. We expected to find cross-study agreement for hypoactivity in dyslexia in areas of left posterior brain regions, including parietal cortex, inferior occipitotemporal, and superior temporal gyri. Areas revealed by this meta-analysis can serve the purpose of determining acquisition and analysis strategies in future studies. For example, the location of these areas might be used to conduct region-of-interest analyses, aid in selecting voxels that serve as a “seed” for whole-brain correlations, and help to model the neural correlates predicted for mechanisms of compensation.

Methods

Criteria for Papers Included in the Meta-analysis

We performed a MEDLINE search to identify published fMRI or PET studies comparing dyslexics and normal readers. We limited studies to those using tasks involving reading of alphabetic languages, with visually presented words, pseudowords, or letters in the subjects’ native language. Only studies involving healthy postpubertal dyslexic or nondyslexic teens and adults, with no history of neurologic or psychiatric disorders, matched for age and handedness, were allowed into the analysis. The following studies were excluded: those which did not present stereotactic Talairach (Talairach & Tournoux, 1988) or Montreal Neurological Institute (MNI) coordinates of local maxima (x , y , z) for a direct comparison between normal readers and dyslexics, those that used a region-of-interest rather than voxel-wise analysis, and

those studies whose subjects were prepubertal age.

Nine papers (Brunswick *et al.*, 1999; Flowers *et al.*, under review; Georgiewa *et al.*, 1999; Grünling *et al.*, 2004; Ingvar *et al.*, 2002; McCrory *et al.*, 2005; Paulesu *et al.*, 2001; Paulesu *et al.*, 1996; Rumsey *et al.*, 1997b) met the selection criteria and provided 96 activation foci from a combined total of 171 subjects, in which controls exhibited greater activity than dyslexics. Six of the nine papers reported 75 foci from 159 subjects in which dyslexics showed greater activity than controls.

Summaries of Papers Included in the Meta-analysis

The paradigms employed in the studies included here were generally of two types: either those requiring decisions about visually presented letters, words, and pseudowords; or those requiring explicit reading of visually presented words and pseudowords. Some papers report using both approaches. One meta-analysis included two reports that employed a decision-making task only (Studies 1 and 2 described below), three reports that utilized both a decision-making task and an explicit reading task (Studies 3 to 5), and four reports (Studies 6 to 9) that relied only on paradigms involving explicit reading. Within each meta-analysis the tasks and contrasts between the dyslexic and nondyslexic groups were identical, allowing for easy comparison and clear interpretation of the resultant ALE maps. Each report is described in more detail next.

- (1) A study by Paulesu *et al.* represents the earliest neuroimaging work included in this meta-analysis on the neural basis of dyslexia (Paulesu *et al.*, 1996). PET was used to measure regional cerebral blood flow (rCBF) in five partially compensated adult dyslexics with residual phonological deficits and five control subjects. Subjects made a manual response to specifically defined target stimuli. In the rhyming

paradigm included in this meta-analysis, subjects directed a joystick to indicate when visually presented letters rhymed with “B.” In a short-term memory task employed in the same study, but not included in our meta-analysis, subjects were instructed to indicate whether a probe consonant was present in a preceding group of six consonants. The dyslexics showed reduced activation in Broca’s area (left inferior frontal, BA 6/44) and Wernicke’s area (left superior temporal gyrus, BA 21/22) during the short-term memory task and the rhyming task, respectively. During both tasks, dyslexics showed less activity in the left insula compared to the control group, who activated all three areas during both tasks. Paulesu *et al.* proposed a “disconnection” deficit model for dyslexia in which the insula is critical to integrate anterior and posterior systems for the processing of linguistic stimuli.

- (2) Grünling *et al.* combined data from fMRI and EEG to assess differences between dyslexics and controls (Grünling *et al.*, 2004). Seventeen dyslexics and 21 controls performed a variety of matching tasks, involving letter strings, high frequency words, and pseudowords, similar to the paradigms previously used by Shaywitz and colleagues (Shaywitz *et al.*, 1998). fMRI data gathered when subjects had to decide whether two visually presented pseudowords rhymed (contrasted to letter-string matching) were submitted to the meta-analysis. Grünling and colleagues reported this contrast to reveal hyperactivity in the dyslexics in left and right frontal areas, and hypoactivity in left middle temporal gyrus (BA 21), right superior frontal gyrus (BA 10), and left cuneus (BA 18) compared with controls. The investigators also reported differences in timing of neuronal processing (EEG) between dyslexics and controls.
- (3) In a study using PET-rCBF measurements, Rumsey *et al.* (1997b) examined

17 adult male dyslexics with persistent reading deficits and 14 matched controls during performance of two explicit reading tasks, one phonological (reading aloud of pseudowords such as “chir!”), and the other orthographic (reading aloud of real “exception” words such as “choir”), as well as two decision-making tasks, again one phonological (given two pseudowords such as “bape” and “baik,” which would sound like a read word when spoken) and the other orthographic (given a word and its pseudohomophone such as “hoal” and “hole,” which is a real word) (Rumsey *et al.*, 1997b). The task paradigm was designed to place varying demands on the main deficit thought to account for impaired word recognition in dyslexics, that is, phonological processing. Regions in which dyslexics showed reduced blood flow relative to controls for either the phonological explicit reading or phonological decision-making tasks included bilateral parietal areas (BA 40) and temporal regions (including BA 37, 39, 20, 21, 22, and 42), right pre/postcentral gyrus, and bilateral precuneus. Areas of hyperactivation in the dyslexic group during either the phonological explicit reading or phonological decision-making tasks were found in left inferior occipital gyrus (BA 18), left medial temporal cortex, right insula, left pre/postcentral gyrus, right frontal (BA 10/46), and several subcortical and cerebellar regions. Dyslexics had relative deactivations compared to controls in left inferior frontal cortex (BA 44/45 and 47) for both orthographic tasks. In contrast to the findings from Paulesu *et al.* (1996), Rumsey *et al.* (1997b) found hyperactivation of the left insula in the dyslexic group during real and pseudoword reading. On the basis of the dyslexics’ poor performance during reading, Rumsey *et al.* proposed a compensation hypothesis for the increased activity seen in the left insula in dyslexics as compared to controls.

- (4) In an attempt to address methodological concerns regarding potential performance confounds in earlier studies comparing dyslexics and typical readers, Brunswick *et al.* (1999) designed two reading experiments. Their first experiment, an explicit reading task in which subjects read real or pseudowords aloud was administered. In their second experiment a decision-making “implicit reading” task was used, in which subjects indicated by button press whether or not a real or pseudoword contained an “ascender” letter (for example, l, f, d, or t); a false font condition was used as an active baseline. By including both explicit and implicit reading paradigms, the researchers hoped to differentiate between compensatory activity during explicit reading of words or pseudowords and abnormal activations during implicit processing of these words, respectively. PET was used to measure rCBF in 12 compensated dyslexics with persistent reading deficits and 12 controls (12 in each experiment). During both studies, subjects were exposed to the same number of phonologically simple stimuli designed to minimize performance differences between the two groups. During explicit reading (regardless of word type), several areas showed reduced activation in dyslexics compared to controls, including posterior regions such as left posterior inferior temporal cortex/fusiform gyrus (in and around BA 37) and bilateral medial extrastriate cortex, left subcortical regions, and cerebellum. Left premotor cortex (BA 6/44, Broca’s area), was more active in the dyslexic group relative to controls. Given these findings, Brunswick *et al.* hypothesized that dyslexics may compensate for underactivation of medial extrastriate cortex, a region that may be important for whole-word processing, with increased sublexical articulation mediated by the premotor cortex. Since the second experiment did not require vocalization, the investigators did not predict a similar effect in premotor cortex for implicit reading. Consistent with that hypothesis, the results of the second experiment (based on the decision-making task) were notable for an absence of frontal hyperactivity in dyslexics. Reduced activation was seen only in posterior areas, such as posterior inferior and middle temporal cortex (BA 37/20/21), as well as inferior parietal cortex (BA 40/7).
- (5) In a later paper, Paulesu *et al.* (2001) used PET-rCBF measurements to compare dyslexics and controls during the same explicit and implicit reading paradigm employed by Brunswick and colleagues in order to elucidate specific neurobiological deficits that are consistent across languages with varying orthographic depth (English and French have a deep orthography as the mapping is not as direct as for Italian, which has a shallow orthography). The investigators scanned a group of 12 dyslexics and 12 well-matched controls from three countries: Italy, France, and the UK. Half of the subjects from each country performed the explicit reading task (reading words and pseudowords aloud) and the other half performed an implicit reading task that involved decision-making regarding the presence or absence of an ascender. Although Italian dyslexics performed better than English and French dyslexics on reading measures, dyslexics from each country were equally impaired relative to their respective control groups. Combining the data from the explicit reading study and the decision-making study, four left hemisphere areas proved to be more active in controls compared to dyslexics regardless of word type, task, or language: superior temporal gyrus (BA 22), middle temporal gyrus (BA 21), inferior temporal gyrus (BA 37), and middle occipital gyrus (BA 37). Paulesu *et al.* concluded that dyslexia has a universal

neurobiological basis across alphabet-based languages, but that the behavioral manifestations depend on orthographic depth.

- (6) Georgiewa *et al.* used fMRI to examine brain activity in dyslexics and controls during several tasks designed to place varying demands on phonological skills (Georgiewa *et al.*, 1999). Seventeen adolescent dyslexics and seventeen matched controls performed three silent reading tasks during scanning: letter strings, pseudowords, real words, and a phonological transformation task (similar to pig Latin). Scans from these three conditions were contrasted with passively viewing letter strings. During the tasks which placed the heaviest demands on phonological processing (pseudoword reading and phonological transformation, included in our meta-analysis), reduced activation was seen in left inferior frontal gyrus (BA 44) and thalamus in dyslexics compared with controls. Dyslexics activated the lingual gyrus (BA 18) during real-word reading and superior temporal gyrus (BA 22) during both real- and pseudoword reading to a greater extent than controls. It should be noted that the brain was scanned only within a limited region along the vertical axis (Talairach Z level restricted to the range -15 mm to $+15$ mm), introducing a regional bias to this study. However, the nature of the meta-analytic technique does not preclude the usefulness or validity of the between-group differences reported here, and so available data meeting the inclusion criteria were included.
- (7) To examine differences between dyslexics and controls during language processing, Ingvar *et al.* (200) measured rCBF using PET in 9 adult Swedish-speaking male dyslexics and 9 matched controls. Swedish has a shallower orthography than English. Aloud and silent reading tasks of real words and pseudowords were compared with a resting baseline. During silent real-word reading versus fixation, dyslexics showed more activity than controls in right occipitotemporal cortex (BA 37), whereas controls showed more activity than dyslexics in right dorsolateral prefrontal cortex (BA 10) and right angular gyrus (BA 39). Ingvar suggested that these results support a separate functional compensational processing pathway in dyslexia.
- (8) McCrory *et al.* (2005) sought to identify an abnormal pattern of neural activation in dyslexics common to both reading and naming. During PET scanning, 8 adult dyslexics and 10 controls performed a real-word reading- and picture-naming task (the latter task was not included in the present meta-analysis). Results revealed less activity in left occipitotemporal cortex (BA 37) in dyslexics compared to controls during both tasks, suggesting that reading disability in dyslexia may be related to an underlying deficit in the assignment of phonology to any visual stimuli, and thus may not be specific to words.
- (9) In a recent study, Flowers *et al.* (under review) used fMRI to examine decoding ability in 12 adult dyslexics and 14 matched controls during aloud pseudoword and real-word reading. A direct contrast of the two activation conditions revealed that both dyslexics and controls increase activity in left parietal and bilateral inferior frontal cortex during the more phonologically demanding task, pseudoword reading, whereas left inferior temporal cortex was more active during real-word reading. Regardless of word type (real or pseudowords), compared to controls, dyslexics underactivated bilateral inferior frontal gyri (BA 47), left parietal cortices (BA 40/2), and left inferior temporal cortex (BA 37/20), as well as several right hemisphere regions, including superior temporal gyrus (BA 22), post central gyrus (BA 40/2), and

cerebellum. Orbitofrontal gyrus (47/11), anterior temporal pole (BA 38), right inferior frontal gyrus (BA 44/45), and bilateral thalamus were found to be more active in dyslexics. The results from this main effects analysis were submitted to the meta-analysis. The group-by-task interaction (which was not included in the present meta-analysis) revealed that bilateral parietal and premotor regions as well as left inferior, middle, and superior frontal cortices were more active in controls during pseudoword reading compared with those of dyslexics.

Activation Likelihood Estimate Method

We used the activation likelihood estimate (ALE) method to perform the meta-analyses (Turkeltaub *et al.*, 2002). To ensure that all input coordinates were in the same standard anatomical space, we avoided mixing Talairach coordinates with MNI coordinates (Brett, Christoff, Cusack, & Lancaster, 2001; Brett, Johnsrude, & Owen, 2002). We treated the foci of activity as coordinates of MNI space if a study (1) used a version of SPM (Wellcome Department of Cognitive Neurology, London, UK) that officially employs the MNI templates (SPM96 or later) and did not apply a conversion to Talairach space, or (2) used some other template-based software with an MNI template to perform spatial normalization (e.g., Automated Image Registration [AIR] of Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998). All coordinates thought to be reported using the Talairach coordinates were converted to MNI space (Brett, 1999), thereby bringing all studies into a common coordinate system.

With all foci in MNI space, we submitted the coordinates to two separate ALE meta-analyses: one to identify locations in the brain where control groups showed greater task-related activity than the dyslexic groups (Controls > Dyslexics: 96 foci from 9 papers,

14 contrasts; Table 1), and a second analysis to reveal the reverse, that is, where dyslexics demonstrated more activity than controls (Dyslexics > Controls: 75 foci from 6 papers, 10 contrasts; Table 2). For each of these two meta-analyses, a spatial smoothing factor of 14.1 mm FWHM was used. Ten thousand (10,000) randomizations were performed to estimate the null ALE distribution (Turkeltaub *et al.*, 2002). To account for multiple comparisons, an ALE threshold was selected by controlling the false discovery rate at a level of 0.0001 (Genovese, Lazar, & Nichols, 2002; Laird *et al.*, 2005a).

After thresholding each ALE map, local maxima were identified, their MNI coordinates converted to Talairach coordinates (Brett, 1999), and their anatomical labels were assigned using the atlas of Talairach and Tournoux (Talairach & Tournoux, 1988). The relative contribution of each study to each ALE local maximum was calculated (Tables 3 and 4). For visualization purposes, the thresholded ALE maps were overlaid on a structural MRI scan in MNI space and displayed in 2D (axial slices captured in MEDx) as well as 3D volume renderings (VolView, Kitware, Clifton Park, NY, USA).

Results

Controls > Dyslexics

The meta-analysis for Controls > Dyslexics revealed nine distinct clusters of suprathreshold voxels in the ALE map, the largest of which had two local maxima (Table 5). The local maxima in the left hemisphere were located in precuneus (BA 31), middle occipital gyrus (BA 37), fusiform gyrus (BA 37), inferior parietal lobule (BA 40), superior temporal gyrus (BA 22), thalamus (pulvinar), and inferior frontal gyrus (BA 47/11). In the right hemisphere, the ALE analysis identified foci in fusiform gyrus (BA 20), postcentral gyrus (BA 2), and superior temporal gyrus (BA 21). 2D slices at the level of the

TABLE 1. Characteristics of the Nine Papers Included in the Meta-analysis for Controls > Dyslexics

Study	Year	Imaging	Task type	Response modality	Word type	Baseline	# of foci	Uncorrected threshold	Dyslexics (N)				Controls (N)				Native language		
									Total	Male	RH	Mean age	Total	Male	RH	Mean Age			
1	Paulesu	1996	PET	Decision (rhyme)	Button press	Aloud	Single letters	Korean shape decision	6	$P < .05$	5	5	5	5	5	5	25.2	27.2	English
2	Grünling	2004	fMRI	Decision (rhyme)	Button press	Aloud	Pseudo	Letter-string matching	3	$P < .01$	17	NA	17	14	21	NA	14	13	German
3a	Rumsey	1997	PET	Decision (phonological)	Button press	Silent	2 pseudo	Fixation	12	$P < .01$	17	17	17	27	14	14	14	25	English
4a	Brunswick	1999	PET	Decision (orthographic)	Button press	Aloud	1 real	Fixation	11	$P < .01$	17	17	17	27	14	14	14	25	English
5	Paulesu	2001	PET	Decision (ascender)	Button press	Aloud	Real + pseudo	False font	6	$P < .001$	6	6	6	24.5	6	6	6	24.5	English
3b	Rumsey	1997	PET	Explicit + decision	Both	Aloud	Real + pseudo	Rest + false font	4	$P < .001$	12	12	12	~24	12	12	12	~24	English
4b	Brunswick	1999	PET	Explicit phonological	Aloud	Aloud	Pseudo	Fixation	14	$P < .01$	17	17	17	27	14	14	14	25	English
6	Georgiewa	1999	fMRI	Explicit reading	Silent	Silent	Exception real	Rest (eyes closed)	11	$P < .01$	17	17	17	27	14	14	14	25	English
7	Ingvær	2002	PET	Explicit reading	Silent	Silent	Real + pseudo	Letter-string reading	14	$P < .01$	6	6	6	23	6	6	6	23.2	English
8	McCloskey	2005	PET	Explicit reading	Aloud	Aloud	Pseudo	Letter-string reading	2	$P < .001$	17	8	17	13.6	17	8	17	14.4	German
9	Flowers	Under review	fMRI	Explicit reading	Aloud	Aloud	Real	Letter-string reading	2	$P < .001$	17	8	17	13.6	17	8	17	14.4	German
							Teal	Rest (eyes open)	3	$P < .001$	9	9	9	20-26	9	9	9	20-28	Swedish
							Real	False font (saying "yes")	1	$P < .001$	8	8	8	20	10	10	10	20	English
							Real + pseudo	Fixation	18	$P < .001$	12	9	10	43.7	14	10	13	40.7	English

TABLE 2. Characteristics of the Six Papers Included in the Meta-analysis for Dyslexics > Controls

Study	Year	Imaging	Task type	Response modality	Word type	Baseline	# of foci	Uncorrected threshold	Dyslexics (N)				Controls (N)				
									Total	Male	RH	Mean age	Total	Male	RH	Mean Age	
1 Grütling	2004	fMRI	Decision (rhyme)	Button press	Pseudo	Letter-string matching	31	$P < .01$	17	?	17	14	21	?	21	13	German
2a Rumsey	1997	PET	Decision phonological	Button press	2 pseudo	Fixation matching	10	$P < .01$	17	17	17	27	14	14	14	25	English
2b Rumsey	1997	PET	Decision orthographic	Button press	1 real; 1 pseudo	Fixation	6	$P < .01$	17	17	17	27	14	14	14	25	English
			Explicit phonological	Aloud	Pseudo	Fixation	7	$P < .01$	17	17	17	27	14	14	14	25	English
			Explicit orthographic	Aloud	Exception real	Fixation	8	$P < .01$	17	17	17	27	14	14	14	25	English
3 Brunswick	1999	PET	Explicit reading	Aloud	Real + pseudo	Rest (eyes closed)	1	$P < .001$	6	6	6	23	6	6	6	23.2	English
4 Georgiewa	1999	fMRI	Explicit reading	Silent	Pseudo	Letter-string reading	1	$P < .01$	17	8	17	13.6	17	8	17	14.4	German
			Transformation	Silent	Real	Letter-string reading	2	$P < .01$	17	8	17	13.6	17	8	17	14.4	German
5 Ingvar	2002	PET	Explicit reading	Silent	Real	Rest (eyes open)	3	$P < .001$	9	9	9	20-26	9	9	9	20-28	Swedish
6 Flowers	Under review	fMRI	Explicit reading	Aloud	Real + pseudo	Fixation	18	$P < .001$	12	9	10	43.7	14	10	13	40.7	English

TABLE 3. Relative Contributions of Each Contrast to Each ALE Local Maximum for Controls > Dyslexics

	Precuneus (BA 31)	Left inferior temporal gyrus (BA 37)	Left fusiform gyrus (BA 37)	Left inferior parietal lobule (BA 40)	Left superior temporal gyrus (BA 22)	Left thalamus	Left inferior frontal gyrus (BA 47/11)	Right fusiform gyrus (BA 20)	Right postcentral gyrus (BA 2)	Right superior temporal gyrus (BA 21)
1 Paulsen, 1996					(1%)					
2 Grünling, 2004					9%					
3a Rumsey, 1997	34%	(1%)	32%	36%	33%		32%	33%		26%
4a Brunswick, 1999		18%	36%	36%	(2%)		41%			25%
5 Paulsen, 2001		32%	19%	(1%)	(1%)					
3b Rumsey, 1997	47%		(1%)		24%			36%	60%	27%
4b Brunswick, 1999	19%	(4%)	(5%)	26%	29%	46%	27%	31%	39%	22%
6 Georgiewa, 1999		34%				27%				
7 Ingvar, 2002										
8 McCrory, 2005		11%	(5%)							
9 Flowers Experiments	3	4	3	3	4	3	3	3	(1%)	2

Note: Values in parentheses are below the cutoff of 7%.

TABLE 4. Relative Contributions of Each Contrast to Each ALE Local Maximum for Dyslexics > Controls

		Right thalamus	Right insula (BA 13)
1	Grünling, 2004		14%
2a	Rumsey, 1997	(8%) 20%	33%
2b	Rumsey, 1997		20%
		35%	33%
3	Brunswick, 1999		
4	Georgiewa, 1999		
5	Ingvar, 2002		
6	Flowers Experiments	38% 3	4

Note: Values in parentheses are below the cutoff of 10%.

maxima are shown in Figure 1, and 3D volume renderings are shown in Figure 2. The relative contributions of the fourteen contrasts to each of these local maxima are shown in Table 3. Ideally, each local maximum would have been derived from equal contributions from all contrasts (Turkeltaub *et al.*, 2002), each providing 1/14th of the total probability at the local maximum; therefore, values less than 7% are shown in parentheses in Table 3.

Dyslexics > Controls

The meta-analysis results for Dyslexics > Controls showed only two distinct clusters of suprathreshold voxels in the ALE map, one in the right insula (BA 13) and the other in the right thalamus. The estimated locations for the local maxima are shown in Table 6. 2D slices at the level of the two local maxima are shown in Figure 3, and a 3D volume rendering of the right hemisphere is shown in Figure 4. The relative contributions of the ten contrasts are shown in Table 4; values less than 1/10 are shown in parentheses.

Discussion

Altogether, the two meta-analyses examining differences in brain activity during reading

TABLE 5. The Ten Local Maxima Found after Thresholding the ALE Map for Controls > Dyslexics

Estimated localization of local maximum	MNI coordinates of local maximum			ALE local maximum within cluster (10^{-3})	Cluster size (voxels)
	X	Y	Z		
Left precuneus (BA 31)	-4	-76	28	5.55	32
Left inferior temporal gyrus (BA 37)	-48	-58	-10	7.52	843
Left fusiform gyrus (BA 37)	-48	-42	-22	7.01	
Left inferior parietal lobule (BA 40)	-46	-44	26	5.82	42
Left superior temporal gyrus (BA 22)	-52	-36	8	7.29	155
Left thalamus	-18	-24	10	7.09	133
Left inferior frontal gyrus (BA 47/11)	-22	32	-4	5.68	30
Right fusiform gyrus (BA 20)	48	-34	-26	6.28	51
Right postcentral gyrus (BA 2)	50	-26	32	5.76	30
Right superior temporal gyrus (BA 21)	44	-22	-4	8.49	190

Note: The two local maxima in left inferior temporal gyrus and left fusiform gyrus were both located in the largest cluster of contiguous suprathreshold voxels, which contained 843 voxels.

between dyslexics and controls, revealed twelve foci that distinguished these two diagnostic groups. The Controls > Dyslexics meta-analysis confirmed that dyslexic readers tend to underactivate numerous regions in left hemisphere posterior cortex as well as three regions in the right hemisphere. Specifically, in the left hemisphere, ALE maps suggest that dyslexic readers showed hypoactivity in portions of the extrastriate (BA 37 and 31), inferior parietal (BA 40) and inferior frontal (BA 47/11) cortices, as well as the pulvinar of the thalamus. Dyslexic readers also underactivated bilateral superior temporal cortex (BA 21 and 22) as well as right hemisphere post central gyrus (BA 2), and right fusiform gyrus (BA20). In the second meta-analysis, examining Dyslexics > Controls, ALE maps revealed a high likelihood of overactivation in two right hemisphere regions in the dyslexics: anterior insula (BA 13) and lateral posterior thalamus.

In addition to the location of these foci, the ALE analysis also provides information on the statistical significance of the ALE value, its spatial extent and the number of studies that contributed to the focus. These will be taken into consideration next, as our findings are discussed in the context of the functional anatomy of reading.

Posterior Ventral Regions Postulated to Mediate Addressed Phonology

Many studies have suggested that portions of the left ventral visual processing stream, including the inferior temporal and lingual/fusiform gyri, have a role in the direct mapping of orthographic information to the corresponding phonological representation (Binder *et al.*, 2003; Brunswick *et al.*, 1999; Fiebach, Friederici, Muller, & von Cramon, 2002; Hagoort *et al.*, 1999; Herbster, Mintun, Nebes, & Becker, 1997; Rumsey *et al.*, 1997b). Indeed, some call a large area of the extrastriate region the “visual word form area” (Cohen *et al.*, 2000; McCandliss *et al.*, 2003). However, it is debatable whether the function of this region is confined to the processing of words and word-like stimuli, and there is recent evidence that its overall function is phonological retrieval, whether of language-related or object stimuli (McCrorry *et al.*, 2005; Price & Devlin, 2003). Nevertheless, a frequent finding has been of relatively less activity (including deactivation relative to a contrast condition) among dyslexics as compared to controls in the left ventral extrastriate region (Brunswick *et al.*, 1999; Flowers *et al.*, under review; Georgiewa *et al.*, 1999; Paulesu *et al.*, 2001; Rumsey *et al.*, 1997b).

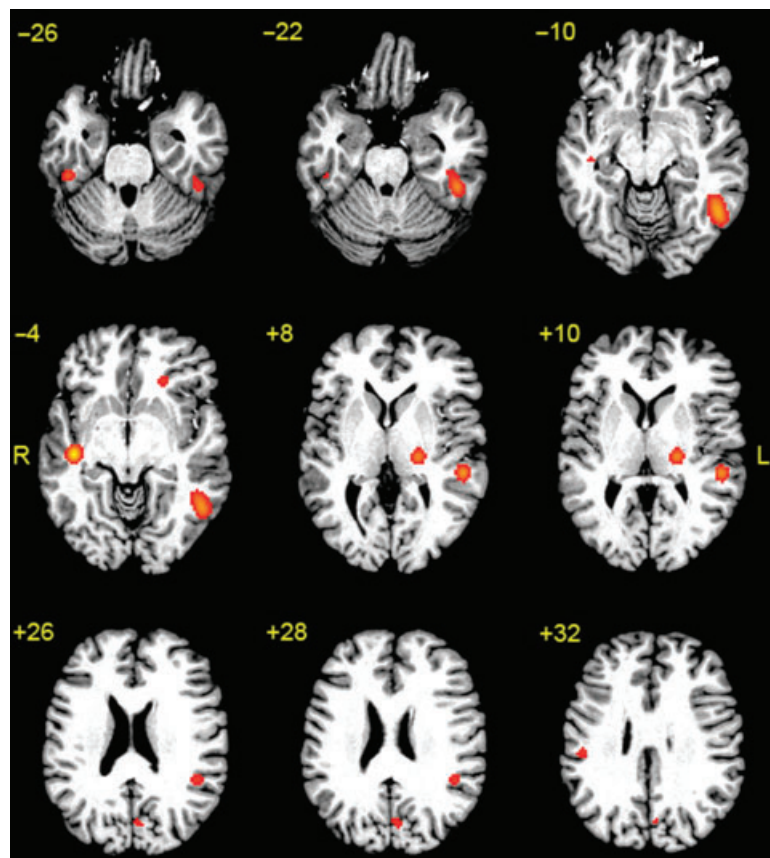


Figure 1. 2D axial slices depicting the ten ALE local maxima for Controls > Dyslexics (Table 5). All images are presented in radiologic convention (subject left = image right) and MNI coordinates in the inferior-superior (Z) plane are provided in the upper left corners of each image. The ALE maps reveal differences in left hemisphere precuneus (BA 31), middle occipital gyrus (BA 37), fusiform gyrus (BA 37), inferior parietal lobule (BA 40), superior temporal gyrus (BA 22), thalamus (pulvinar), and inferior frontal gyrus (BA 47/11). In the right hemisphere, the ALE analysis identified foci in fusiform gyrus (BA 20), postcentral gyrus (BA 2), and superior temporal gyrus (BA 21).

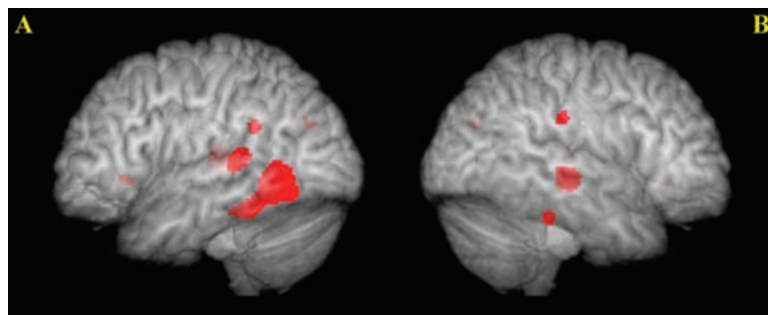


Figure 2. 3D volume rendering of the thresholded ALE map for Controls > Dyslexics, seen from the left (A) and right (B) sides. ALE values located closer to the surface (which are more lateral) appear as a more solid red, whereas those further away (more medial) appear as a lighter red.

TABLE 6. The Two Local Maxima Found after Thresholding the ALE Map for Controls > Dyslexics

Estimated localization of local maximum	MNI coordinates of local maximum			ALE local maximum within cluster ($\times 10^{-3}$)	Cluster size (voxels)
	X	Y	Z		
Right thalamus	14	-20	12	6.09	66
Right insula (BA 13)	34	18	2	7.10	113

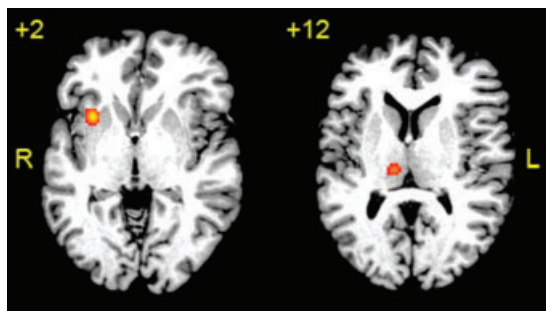


Figure 3. 2D axial slices revealing the location of the two local maxima for the Dyslexics > Controls meta-analysis: right insula (BA 13) and right thalamus (for corresponding coordinates see Table 6; subject left = image right).

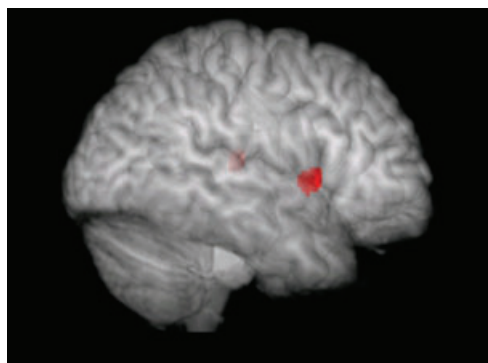


Figure 4. 3D volume rendering of the thresholded ALE map for Dyslexics > Controls, seen from the right side.

In the Control > Dyslexic meta-analysis, seven experiments were identified where dyslexics underactivated the left ventral extrastriate cortex (BA 37). Three of these contrasts contributed to the left fusiform gyrus finding, and four to the left inferior temporal gyrus finding, making this the most robust outcome of the analysis. The contrasts that elicited these findings were varied, and included implicit and

explicit reading of words and pseudowords as well as orthographic and phonologic decisions. This task-invariant hypoactivity has also been linked to a robust difference in brain structure within this region in individuals with dyslexia drawn from a variety of different countries (Silani *et al.*, 2005). A significant ALE value in the left precuneus (BA31/23) suggests that hypoactivity in dyslexia during reading in some instances extends to the medial aspect of the left posterior cortex.

Underactivation by dyslexics in a more anterior portion of the fusiform region (BA 20) was also found, but this time in the right hemisphere (contributed by three experiments), suggesting the presence of right as well as left ventral extrastriate deficiency associated with dyslexia. This result is consistent with a finding of right BA 20 hypoactivity in dyslexia during an auditory sound manipulation task (Eden *et al.*, 2004). It is possible that the ventral streams of both hemispheres are compromised in dyslexia, with a behavioral deficit attributed to the right hemisphere (e.g. face processing, which is more subtle than that observed for word processing) (Tarkiainen, Helenius, & Salmelin, 2003).

Posterior Dorsal Regions Postulated to Mediate Assembled Phonology

Grapheme–phoneme correspondence, the mapping of the written representations of words onto their associated sounds (“assembled phonology”), is the principal defining characteristic of dyslexia and found to be impaired throughout the lifespan (Bruck, 1992; Fletcher *et al.*, 1994; Flowers, 1995; Liberman & Shankweiler, 1991; Lyon, 1995b; Lyon *et al.*,

2003; Morris *et al.*, 1998; Ramus, 2003; Shankweiler *et al.*, 1979; Shaywitz *et al.*, 1995; Shaywitz *et al.*, 1999; Shaywitz *et al.*, 2003; Stanovich & Siegel, 1994; Torgesen, 1995; Wagner & Torgesen, 1987). Several functional imaging studies of dyslexia entered into the meta-analysis have independently reported underactivation in superior/middle temporal and inferior parietal regions believed to mediate assembled phonology. For example, dyslexics were found to have reduced activation in the left superior temporal gyrus/inferior parietal lobule (usually incorporating the supramarginal gyrus, BA 40) during implicit reading of either real words or pseudowords relative to false font strings or during overt word reading relative to visual fixation (Brunswick *et al.*, 1999). The same observation has also been made during overt pseudoword reading, relative to real-word reading (Flowers *et al.*, under review), and during phonological and orthographic overt reading as well as during silent decision making (relative to visual fixation) (Rumsey *et al.*, 1997b).

Our meta-analytic results are consistent with the converging findings of the literature. In an early rCBF study, the posterior superior temporal cortex was reported to be underactivated in dyslexics who carried out an orthographic task (Flowers, Wood, & Naylor, 1991). Subsequently, others have reported similar findings in superior and middle temporal gyri (BAs 21, 22, 42). For example, underactivation by dyslexics has been found during either a rhyming task relative to a shape-similarity task or during word reading relative to baseline (Paulesu *et al.*, 1996), when contrasting rhyming pseudowords with letter strings (Grünling *et al.*, 2004), and during phonological or orthographic reading or decision-making tasks compared to a visual fixation baseline (Rumsey *et al.*, 1997b). However, the meta-analytic results are incongruent with reports of greater activation in the superior and middle temporal gyri in dyslexics (Georgiewa *et al.*, 1999), suggesting that there may be variability in this region as a function of task demands or language of the participants.

In the meta-analysis, three contrasts from one paper (Rumsey *et al.*, 1997b) accounted for the majority of the contribution to the meta-analytic finding in the left inferior parietal lobe, and therefore this cannot be considered a consistent finding across the nine papers. Also, as Rumsey *et al.* pointed out, the dyslexic participants in their study exhibited markedly impaired behavioral performance, leading to a much more widespread pattern of activation and deactivation. Thus, contrast maps between their dyslexic and nondyslexic groups must be interpreted with caution. As has been discussed extensively by McCrory and others (e.g., 2004), it is unclear how impaired behavioral performance and variable performance as a consequence of self-paced tasks affects the activation results. If control subjects were to perform the same tasks at a lower level of accuracy and with slower reaction times, the task-related activity is likely to be somewhat different. This has been demonstrated in studies where inter-stimulus intervals were parametrically modulated (Price *et al.*, 1996).

It is noteworthy that in the study by Rumsey and colleagues, two of the tasks employed were orthographic in nature, suggesting that the inferior parietal region is involved in both phonological and orthographic processes. As pointed out by Rumsey and colleagues in a study of typical readers (Rumsey *et al.*, 1997a), the attempts to distinguish separate pathways that subservise the “direct” orthographic route versus the “indirect” phonological route have not been as successful as might be predicted by theoretical models of reading (Coltheart, Curtis, Atkins, & Haller, 1993). Nevertheless, these results suggest that during reading, dyslexic readers are deficient in recruiting essential left hemisphere language-related regions around the temporoparietal junction.

Turning to the opposite hemisphere, while some studies have previously shown right inferior parietal (BA 40) (Rumsey *et al.*, 1997b), angular gyrus (BA 39), or superior parietal region (BA 7) (Grünling *et al.*, 2004) to be underactivated by dyslexics, our meta-analysis found

no robust concordance in this region. Instead, we found a high likelihood for hypoactivity in dyslexics in the right superior temporal gyrus (BA 21). This result is consistent with those observed in studies of dyslexia that involve reading of printed words (Flowers *et al.*, under review) and repetition of spoken words (McCrorry *et al.*, 2000).

Neither ALE analysis revealed differences in the cerebellum, suggesting that even if the cerebellum is involved in linguistic tasks (Fiez & Petersen, 1998), there is no robust evidence of a cerebellar deficit in dyslexia during reading as has been found for motor learning (Nicolson *et al.*, 1999).

Anterior Regions Postulated to Mediate Word Production and Semantic Processing

The left inferior frontal gyrus has been proposed to mediate articulatory recoding of phonological information, and activation of this area during a variety of reading and phonological processing tasks has been widely reported. Dorsal and ventral subdivisions are implicated for phonological processes and semantic processes, respectively (Brunswick *et al.*, 1999; Fiez, Balota, Raichle, & Petersen, 1999; Hagoort *et al.*, 1999; Herbster *et al.*, 1997; Pol-drack *et al.*, 1999; Pugh *et al.*, 1996; Rumsey *et al.*, 1997b; Zurowski *et al.*, 2002). The inferior frontal region, and specifically Broca's area (BA 44/45/46), is more commonly related to prevocalization programs for word production (Brunswick *et al.*, 1999; Dietz, Jones, Gareau, Zeffiro, & Eden, 2005; Hagoort *et al.*, 1999; Xu *et al.*, 2001). The left ventral inferior frontal gyrus (BA 47) is believed to be involved in the retrieval and maintenance of semantic representations, making semantic decisions, and holding semantic material in working memory (Brunswick *et al.*, 1999; Rumsey *et al.*, 1997b; Shaywitz *et al.*, 1998).

Both under- and overactivation of the left inferior frontal cortex have been reported in dyslexia. Overactivation in BA 44/45 and

BA 44/6 (premotor cortex) in dyslexics compared to controls during phonological decision-making tasks has been proposed to represent compensation to counteract deficits in phonological processing normally mediated by posterior cortical regions (Brunswick *et al.*, 1999; Grünling *et al.*, 2004; Shaywitz *et al.*, 1998). However, reading aloud has been associated with under activation in the left and simultaneous overactivation in the right frontal cortex by dyslexics (Flowers *et al.*, under review; Georgiewa *et al.*, 1999). Still other studies have found no differences in activation between dyslexics and controls in the inferior frontal gyrus during rhyming (Paulesu *et al.*, 1996), reading aloud of words and pseudowords (Brunswick *et al.*, 1999), and phonological and orthographic tasks (Rumsey *et al.*, 1997b). In our meta-analysis of Controls > Dyslexics, three of the four contrasts from a single paper (Rumsey *et al.*, 1997b) made the majority contribution to underactivation in the left inferior frontal gyrus associated with dyslexia (see Table 3). It is noteworthy that the original study reported several regions within the left frontal cortex that demonstrated relative "deactivations" in the dyslexic group when contrasting the orthographic tasks with the resting baseline (Rumsey *et al.*, 1997b). Since this region is located in the ventral subdivision associated with semantic processes (BA 47/11), the result of the meta-analysis suggests that dyslexics underutilize semantic processes when reading, perhaps because of a lifelong history of insufficient reading experience. There was no evidence of overactivation in the left inferior frontal gyrus, a finding that in previous reports has been suggested to be "compensatory" (Shaywitz *et al.*, 1998). Nor did the ALE maps suggest any areas of relatively enhanced activity located in regions homotopic to those left hemispheric areas that demonstrated hypoactivity in the dyslexics.

The meta-analyses revealed overactivation by dyslexics in the right insula; four contrasts from two papers (Rumsey *et al.*, 1997b; Grünling *et al.*, 2004) contributed to this finding

(Table 4). One interpretation for an increased likelihood for dyslexics to engage the anterior insula is the aversive nature of reading for individuals who have continuously suffered reading failure. The anterior insula, which receives input from the autonomic nervous system, has been shown to increase activity in response to aversive visual stimuli (Kosslyn *et al.*, 1996). This theory could be tested directly by examining task-related activity in dyslexics during the processing of words and adverse stimuli. Neither of the two meta-analyses revealed differences in the left insular area. Previous reports in this region have been mixed, with Paulesu and colleagues (1996) reporting left insular underactivation thought to represent an anterior-posterior connectivity failure, whereas Rumsey *et al.* (1997b) proposed that the overactivation observed in the left anterior insula by dyslexics during overt reading represented compensation.

Although the meta-analytic findings in the left inferior frontal gyrus (Table 3) may be consistent with the literature, this focus was derived mostly from a single paper (Rumsey *et al.*, 1997b). Further, the dyslexic participants in this study did not perform the task to the same level of proficiency as the nondyslexics, again leading to the same problems of data interpretation as discussed above for the left inferior parietal cortex. Task performance was not considered as a criterion for inclusion during the selection process for the meta-analysis, but it is known to play a potential role in modulating brain activity, especially in studies of clinical populations (Price & Friston, 1999).

Subcortical Grey Matter

Both over- and underactivation in the thalamus has been reported during reading and phonological tasks. Brunswick *et al.* (1999) found that dyslexics had reduced activation relative to control subjects in the left thalamus during implicit reading, regardless of word type (real words or pseudowords). For both phonological processing (nonwords ver-

sus letter strings) as well as phonological awareness (phonological transformation versus letter strings), Georgiewa *et al.* reported left thalamic signal decreases in dyslexics compared to controls (Georgiewa *et al.*, 1999). Conversely, several studies have reported greater activation in the left thalamus in dyslexics when reading either real words or pseudowords (Flowers *et al.*, under review), when reading real words silently (Ingvar *et al.*, 2002), or during phonological pronunciation (Rumsey *et al.*, 1997b).

The Controls > Dyslexics meta-analysis identified the pulvinar region of the left thalamus as an area underactivated by dyslexics, as a result of two contributing papers (Table 3). The pulvinar of the thalamus is connected to striate and extrastriate cortex (Bender, 1981) and the superior temporal cortex (Galaburda & Eidelberg, 1982), consistent with underactivation in those regions. The second meta-analysis examining Dyslexics > Controls identified the lateral posterior region of the thalamus in the opposite (right) hemisphere to be relatively more active in dyslexics. This is a region that is connected to medial parietal cortex, but its role in dyslexia is harder to explain. Further, the ALE meta-analytic method together with the spatial smoothing applied in the original analyses do not result in resolution sufficient to justify a strong neuroanatomical interpretation of a small structure such as the thalamus. Rumsey and colleagues' (1997b) orthographic decision-making result contributed 20% to the meta-analytic finding in right thalamus. Two tasks from the same paper resulted in activations near the right caudate, which also contributed to the meta-analytic finding in right thalamus: 8% from the phonological decision-making task and 35% from the orthographic pronunciation task. The remainder (38%) was contributed by a right thalamic finding from a study in our group (Flowers *et al.*, under review). Although the opposite polarity of the ALE values for the left and right thalami are intriguing, the interpretation of these findings, based on the size of the thalamus, altogether require some caution.

Studies Not Included in the Meta-analysis

As described in the Methods section, there were several PET or fMRI studies of dyslexic and typical readers engaged in reading tasks that did not meet the criteria for inclusion in this meta-analysis. Although the exclusions were largely made on the basis of age (postpubertal, for the purpose of increasing the homogeneity among the studies) and on technical constraints (published spatial coordinates were necessary to enter the data in the meta-analysis), it is worth considering whether the ALE maps reported here reflect the findings from those studies that were not included. Only two studies using visual word presentation in adults were excluded (Gross-Glenn *et al.*, 1991; Shaywitz *et al.*, 1998). These generally demonstrated underactivity in dyslexics in the left occipital regions (including lingual and fusiform gyri) and the angular gyrus, and overactivity of the right parietal and inferior occipital temporal cortex. These findings are consistent with the generally held view of left hemisphere deficits of assembled and addressed phonology and right hemisphere compensation in dyslexia (Pugh *et al.*, 2000).

The studies described so far have focused on reading, and they therefore employed visually presented words. Since dyslexics have difficulties in isolating and manipulating the constituent sounds of spoken language, several investigations have used auditory stimuli. These studies, five conducted in adults (Eden *et al.*, 2004; Flowers *et al.*, 1991; Ruff, Marie, Celsis, Cardebat, & Demonet, 2003; Rumsey *et al.*, 1992; Temple *et al.*, 2000) and one in children (Corina, San Jose-Robertson, Guillemin, High, & Braun, 2003), largely employed rhyming paradigms. Two of these reported underactivation in dyslexia in right inferior frontal regions (Ruff *et al.*, 2003; Rumsey *et al.*, 1992), but they differed in their findings in the right extrastriate cortex: one study demonstrated overactivity (Rumsey *et al.*, 1992) and another underactivity in dyslexics (Eden *et al.*, 2004). Of importance,

none of the adult studies using auditory stimuli demonstrated differences between dyslexics and controls in the left extrastriate region, even though this brain region is the site of greatest difference in dyslexia when visually presented paradigms are used. The only pediatric study of dyslexia using an auditory tasks found left extrastriate overactivation in dyslexics during a phonological judgment task (Corina *et al.*, 2001).

While our ALE results are based on adult subjects and cannot be generalized to pediatric populations, we can informally examine the concordance with the published literature of children with dyslexia. Five studies in which children performed reading or phonological (largely rhyming) tasks in response to visually presented stimuli yielded widespread activation differences (Aylward *et al.*, 2003; Backes *et al.*, 2002; Georgiewa *et al.*, 2002; Shaywitz *et al.*, 2002; Temple *et al.*, 2001): dyslexics underactivated multiple left frontal, temporal, and parietal regions *as well as* their right hemisphere homologues. This symmetry differs from the largely left-lateralized findings of the adult meta-analysis. In addition, one study reported left posterior occipital hypoactivity in dyslexia (Shaywitz *et al.*, 2002). A finding consistent with our meta-analysis in adults was a finding of greater activation in the left thalamus in non-impaired children (Temple *et al.*, 2001). Finally, numerous regions were found to be overly active in dyslexics compared to controls, especially in the left inferior frontal/anterior insular/anterior superior temporal regions, and in the right inferior posterior regions (Aylward *et al.*, 2003; Georgiewa *et al.*, 2002; Temple *et al.*, 2001).

Together, the studies not included in the meta-analysis are consistent with the more focused findings generated by meta-analyses. The most salient difference is that studies of children report more widespread differences in activation, including the right hemisphere. This might be predicted from developmental studies of reading (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003) and could be investigated

in future meta-analyses once sufficient numbers of pediatric studies are available.

Conclusions

The ALE method, a coordinate-based, voxel-wise meta-analytic method, has been used widely to identify the most robust findings regarding the primary neuroanatomical substrates for a variety of cognitive tasks. Here we used the ALE approach to examine published studies of adults with dyslexia. The likelihood for controls to show more task-related activity compared to dyslexics was greatest in left hemisphere posterior ventral, inferior parietal/temporal, and inferior frontal cortices, as well as the right fusiform, postcentral, and superior temporal gyri. The highest ALE values and greatest convergence among studies for this comparison was found in left extrastriate cortex (inferior temporal gyrus) in BA 37. The Dyslexics > Controls meta-analysis revealed a right hemisphere overactivation by dyslexics in the right thalamus, and a less robust finding in the anterior aspect of the right insula. We found no evidence for hyperactivation in left frontal cortex in adult dyslexia, nor for cerebellar differences. Future meta-analyses in studies involving children will help elucidate age-specific effects that distinguish dyslexic and nondyslexic readers.

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Conflicts of Interest

The authors declare no conflicts of interest.

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