In How Children Learn To Read: Cuyrrent Issuses And New Directions In The Integration Of Cognition, Neurobiology And Genetics Of Reading And Dyslexia R Edited by K.R. Pugh and P. McCardle

5 Tools for Multimodal Imaging

W. Einar Mencl, Stephen J. Frost, and Kenneth R. Pugh

Recent years have seen an explosion in the use of functional magnetic resonance imaging (fMRI) for the investigation of the neural bases of cognitive function in general and language processing specifically. However, a broad range of techniques is in use and provides alternate ways of measuring brain activity. It would be wise to attempt to integrate knowledge gained from these myriad techniques to avoid the shortcomings of any one method and to take advantage of the strengths of each. Here, we first relate some initial work on directly combining data from two imaging modalities, fMRI and magnetoencephalography (MEG). Second, several findings of related structural and functional linkages among brain areas are reviewed, with direct implications for skilled and impaired reading.

A STUDY OF BASIC SPEECH PERCEPTION USING fMRI AND MEG

Two broad categories of neuroimaging techniques can be distinguished, each with its own advantages and disadvantages. First, the neuroelectric (EEG/ERP, electroencephalography/event-related potentials) and neuromagnetic (MEG) techniques measure at or above the surface of the scalp, electrical currents stemming from neuronal firing (EEG/ERP) and their associated magnetic fields (MEG). Because these measures are directly responsive to the firing of neurons in real time, the resultant data is time resolved, that is, temporal differences in activations on the order of milliseconds can be recorded and compared. However, since the initial signals are recorded with an array of sensors outside the brain, an integral part of analysis is to estimate which of the many possible sets of source activations is likely to have caused the data recorded at the surface sensors.

Second, whole-brain imaging methods such as positron emission tomography (PET) and fMRI measure tracers or endogenous compounds as they are transported and used throughout the brain. Most useful of these methods is tracking the oxygen levels, or the BOLD (blood-oxygen level dependent) response: Simply, when neurons in an area use oxygen to produce action potential firings, freshly oxygenated blood is rapidly reintroduced to resupply that local area. The proportion of oxygenated to deoxygenated blood can be measured by the MRI scanner across the brain at relatively precise spatial resolutions, commonly at ~3 mm cubes. However, because the signal is driven by the vascular system, and

not directly by the neurons themselves, the BOLD response is a highly temporally smoothed and lagged version of the underlying neuronal firing. The typical response in any given area to a single event, like a brief flash of light, leaves baseline levels at approximately 2 seconds poststimulus, reaches a peak at around 5 seconds, and slowly returns to baseline levels again by 12 to 16 seconds after stimulation. Because of the smearing imposed by the vascular response, the time course of fMRI data does not provide clean information about the timing of neuronal firing on the millisecond level; indeed, BOLD data are typically sampled at very low temporal resolutions, such as every 2 seconds.

A primary inherent difference between fMRI and MEG should now be apparent as a distinction between temporal resolution and spatial resolution. MR imaging allows measurement throughout the entire brain at millimeter spatial resolution, but the signal is terribly temporally impoverished; MEG recording allows millisecond temporal resolution measurement but requires strong assumptions to precisely localize the activation sources. Combining these two measures is a logical next step, and formed the rationale for the following experiment.

In this study (Billingsley-Marshall et al., 2007), we used both fMRI and MEG to measure cortical activations in response to simple spoken words. Researchers in each of these domains have longstanding and routinized methods of analyzing data and localizing the source of activations. The initial approach taken here, then, was to acquire data using each approach on the exact same task in the same set of subjects (in separate sessions), use standard techniques within each laboratory to identify the activation sources, and then directly overlay the findings from both on a single brain image for each subject. By examining the extent of overlap (and differences) in the resulting images, we expected some initial insight into the common and unique contributions of each method.

In both the fMRI and MEG sessions, subjects participated in the same simple task. Immediately prior to imaging, subjects heard a spoken list of 30 common words through headphones. Then during scanning, they heard a randomized sequence of these 30 words ("old" words), mixed with 10 filler words as yet unheard ("new" words). The subject's task was to press a button whenever an old word is heard and not to respond to new words. This process was repeated six times. This experiment was chosen not because it is particularly incisive about cognitive function (although it does permit later investigation of memory function), but rather because it strongly activates the speech perception and language systems, and had already been extensively used in MEG for presurgical planning (Papanicolaou et al., 2004).

Results were mixed. In both the fMRI and MEG sessions, subjects generally showed activations in response to speech tokens in and around the superior and middle temporal gyri, areas known to support speech perception. However, the spatial agreement between the two measures was much poorer than expected: The mean linear distance between the strongest activated site identified with fMRI versus MEG was 6.3 cm and 5.7 cm for the left and right hemispheres, respectively. Examples of three subjects are shown in Figure 5.1: (a) a subject with some agreement in both left and right temporal cortex; (b) a subject with

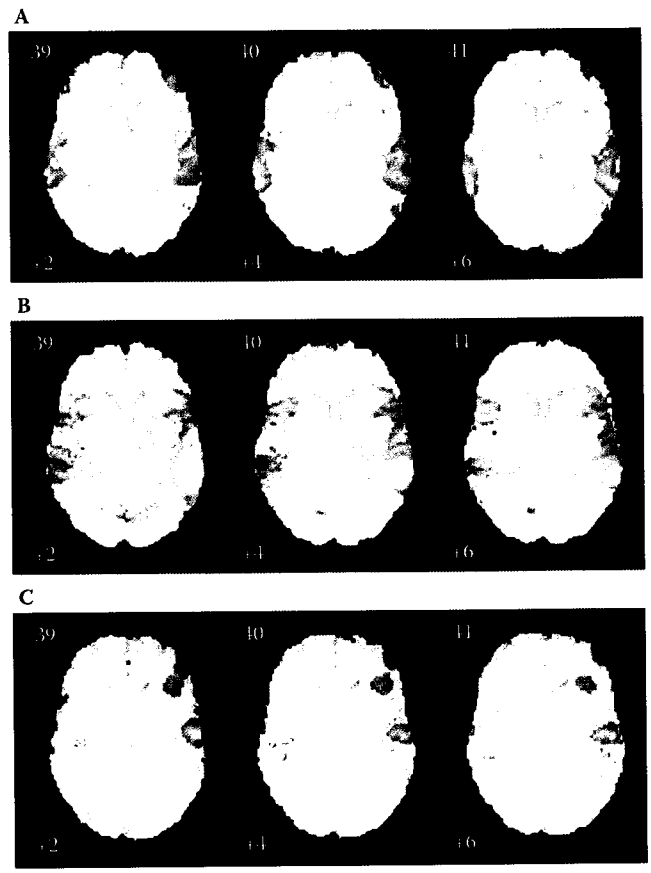

FIGURE 5.1 Results from three subjects showing activations in response to spoken words as measured by fMRI and MEG. The grayscale underlay shows the anatomy at three successive axial slice locations in MNI standard space. The number at the top is slice number within the image; the number at the bottom is the z-coordinate of the slice in MNI space. Red -yellow transparent overlay colors show activated areas recorded with fMRI; blue-purple transparent areas show deactivations. Green-blue solid overlay pixels and clusters indicate activation sources as identified by MEG. Anterior is toward the top of each slice; the right hemisphere is on the left per radiological convention.

good agreement in right temporal cortex but not in the left; and (c) a subject with relatively poor agreement in both hemispheres.

Why might this be the case? Although this initial study was not designed to differentiate among potential causes, several possibilities exist, stemming from specific inherent weaknesses of each method. First, with fMRI, sensitivity varies considerably across the brain. Some areas, particularly medial frontal and inferior temporal, are particularly susceptible to reduction in signal levels caused by nearby borders of tissue, bone, and air cavities. Second, each cube ("voxel") measured with fMRI is relatively large (~3 mm cubed) and contains tens of thousands

of neurons. A small subset of these neurons firing in synchrony may not be enough to produce significant average activation levels in the voxel as a whole. Similarly, the measured activation levels at each voxel are values accrued over a relatively long period of time (typically 2 seconds per image). If a group of neurons fire in a brief burst, as opposed to a sustained manner, the average activation level across the image period may not be enough to reach significance. With MEG, a different set of concerns applies. First, to be detectable with MEG, a group of neurons must fire relatively synchronously, and the cells must be oriented similarly, in a strip or patch of cortex parallel to the surface. This is because the magnetic field generated by each individual neuron's firing is extremely weak and oriented perpendicular to the cell fiber along which the electric potential travels. When a large group of neurons fire, the resulting magnetic fields sum together into a signal strong enough to be observable at the surface if the cells are aligned but can cancel out if misaligned. Similarly, MEG signals are difficult to measure from banks of neurons that are not oriented parallel to the surface (i.e., on the top of a gyrus as opposed to a sulcal wall) or that are deeper within the brain. Second, coordinated timing of the group firing is critical: Asynchronous firing will not generate a large enough magnetic field at any given time to be reliably measured.

In sum, whereas MEG is relatively more sensitive to brief, synchronous group neuronal firing, fMRI is more sensitive to asynchronous firing and also to activations from cells at any orientation. Subsequent investigations will need to specifically address these individual questions, for instance, by using higher resolution fMRI scanning (to discriminate neuronal firing on gyral peaks versus sulcal walls), and relating fMRI and MEG results back to single-unit recording studies (to discriminate group synchronous versus asynchronous activity).

RELATING ANATOMIC CONNECTIVITY AND FUNCTIONAL CONNECTIVITY

Two distinct types of connectivity are being aggressively investigated in the field. The first is *anatomic connectivity*, the locations and characteristics of white matter fiber tracts (axons) that connect cortical areas and serve as the communication conduit for action potentials between neurons. Historically, histological postmortem studies were the primary method of assessing white matter tracts in the human brain, a time-consuming process with limited applicability for looking at neural development. With the advent of MRI, however, scan sequences have been developed for indirectly imaging white matter tracts in vivo. These sequences depend on the natural random diffusion tendencies of water molecules within the brain: They tend to preferentially travel up or down longitudinally within and alongside nerve fibers and do not tend to travel crosswise across fiber tracts because they are physically impeded from doing so. The directional tendencies of water diffusion thus provide a measure that can be used to recreate the location and orientation of fiber tracts in the human brain, and MRI scans employing

diffusion tensor imaging protocols (diffusion tensor imaging, or DTI) can now measure these signals.

Second is *functional connectivity*, broadly defined as correlations between remote neurophysiological events, that is, activations (Friston, 1994; Horwitz et al., 1992). The correlations measured in functional connectivity analyses are commonly assumed to reflect causal relationships among processing sites—in its most simple form, activated neurons in one area fire action potentials that travel down axons and cause activations at the remote site. Areas that participate in correlated activity are likely candidates for processing nodes performing distinct functions in a larger network; conversely, absence of correlations between two areas suggests that they are not cooperatively engaging in support of the same cognitive function. Since these analyses are correlation based, they do not prove a direct causal relationship. For instance, a third cortical area may be independently driving the activation in the two observed sites, which then show correlated responses. Still, correlational analysis remains popular because it is readily available and highly suggestive of network architecture, and true causal analyses require either acquisition of additional specific types of data or assumption-laden a priori specification of a processing model.

Linking data about anatomic connectivity and functional connectivity then, should result in a tighter picture of the neural systems underlying reading and reading disability: anatomic connectivity provides information about the underlying hardware available, and functional connectivity informs us as to the way these communication lines are being used for interregional communication. What follows is a restricted review of studies toward this goal.

A growing number of studies are converging on one particular locus for a white matter anomaly in developmental dyslexia. Initially, Klingberg et al. (2000) reported that in a sample of 12 adults (6 good readers and 6 poor readers), measures of diffusion in white matter ("anisotropy") in the left temporoparietal region were significantly correlated with reading ability. This correlation held both across the entire sample as well as within the subgroups of good and poor readers. Klingberg et al. interpreted their findings as reflecting an increased coherence in the microstructure of the white matter tracts in this area in good readers. Subsequently, two studies nearly simultaneously extended this finding to encompass children as well. Deutsch et al. (2005) showed that in 14 children (7 good readers and 7 poor readers) anisotropy in this left temporoparietal region again correlated with several measures of reading ability, spelling, and rapid naming. Beaulieu et al. (2005) reported a similar finding in a broad sample of 32 children (28 average and above average reading ability and 4 below average): Anisotropy in the left temporoparietal region again correlated with reading ability. Niogi and McCandliss (2006) reported on a larger sample of 31 children (20 good readers and 11 poor readers) and replicated the earlier results: Anisotropy within the left temporoparietal area again correlated with reading scores.

Initial interpretation of these findings (Klingberg et al., 2000) suggested the precise locus to be the arcuate fasciculus, a fiber tract that connects inferior frontal cortex (Broca's area) and posterior superior temporal cortex (Wernicke's area),

and as such has long been suspected to play a role in reading and reading disability. Following studies allowed the possibility that the difference lies near the boundary of the arcuate fasciculus and the corona radiata, a tract that connects nearby cortical areas to the cerebellum, thalamus, and brain stem (Deutsch et al., 2005). Finally, Dougherty et al. (2007) proposed another possible interpretation, that "exuberant growth" of the posterior portion of the corpus callosum serves to displace fiber tracts in the arcuate fasciculus and/or corona radiata, and the intrusion of differently oriented tracts results in the decreased measures of fiber coherence in this area.

Although the exact location and nature of the white matter tract differences is not yet resolved, the replication of the general effect still invites interpretation with reference to the classic "disconnection syndrome" hypothesis (Dejerine, 1892; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Geschwind, 1965). This approach suggests that it is impaired communication among areas, as opposed to impaired functioning of these areas themselves, that results in reading disability.

Which cortical areas are important for reading? In truth, vast portions of cortex are engaged in full sentential reading, which places demands not only on word identification but also on higher level processing of syntax, semantics, and memory. Given that the core deficit in developmental dyslexia appears to be relatively constrained to single word identification, we can restrict our attention here to a smaller set of regions, primarily in the left hemisphere, implicated by a large body of research (for a review, see Pugh et al., 2001).

1. The area at the junction of the temporal and parietal cortex, posterior to Wernicke's area and including portions of the angular gyrus and supramarginal gyrus, is suggested to employ rule-based analysis, generally enacting grapheme-to-phoneme rules. This area is hypothesized to strongly subserve early reading, when these rules are learned and practiced.
2. At the juncture of the inferior occipital and temporal lobes lies an area often referred to as the ventral word form area or VWFA. This area appears to develop with reading experience to serve as a rapid word-recognition area (Shaywitz et al., 2002), although the extent to which its internal processing is based primarily on visual/orthographic features or also incorporates other aspects of linguistic structure (i.e., phonology, morphology) is still under investigation.
3. An anterior region centered in the inferior frontal gyrus, and including Broca's area, is typically active when phonological manipulations are required; one hypothesized function is for recoding phonological representations into a form applicable for output to speech.

Next, we review the growing literature on functional connectivity among these regions (and others) in developmental dyslexia.

The earliest neuroimaging study to examine functional connectivity in dyslexia was reported by Horwitz, Rumsey, and Donohue (1998). They examined 31 adult men (14 good readers and 17 dyslexics) with positron emission tomography

(PET) while they read single words and pseudowords. Importantly, PET imaging is similar to fMRI in that it relies on a vascular measure, regional cerebral blood flow (rCBF). Each subject provides a small number of images that reflect summed activity over a large period of time (i.e., minutes). For typical analysis, images are subtracted from one another to isolate areas that are more or less active in each task or group of subjects. Here, this analysis was complemented by a new method: "The main assumption of this method is that subject-to-subject differences in using a systems-level neural network result in strongly correlated neural activity ... Some subjects may find the task easier than others and thus use the network somewhat less, with the result that there is less rCBF in two functionally connected regions; other subjects use the network more, resulting in more rCBF ... the net result is a large within-task, across-subject correlation in rCBF between the two regions" (Horwitz et al., 1998, p. 8939). Indeed, their results showed that across the set of good readers there were strong correlations between the left angular gyrus and several other reading-related sites, including the inferior frontal gyrus, areas of the extrastriate cortex, and temporal lobe. In contrast, the group of dyslexic subjects did show significant correlations between the angular gyrus and these target sites. This suggests that communication among these regions is impaired in the poor readers.

Pugh et al. (2000) followed up on these findings with data from a similar study of adult dyslexics (Shaywitz et al., 1998). Here, a larger sample of 61 unremediated dyslexic adults (32 good readers and 29 dyslexics) was examined with fMRI while they performed multiple different tasks designed to progressively tap the component processes of single word reading: visual-spatial processing (line orientation judgment), orthographic analysis (letter case match), simple phonological transcoding (letter name rhyme judgment), complex phonological sequencing (nonword rhyme judgment), and semantic processing (word relatedness judgment). Connectivity analysis centered on the angular gyrus showed a similar pattern of results as the earlier Horwitz et al. (1998) study. Posterior left hemisphere cortical areas, including striate, extrastriate, and the posterior temporal lobe, showed strong and significant correlations to the angular gyrus in good readers while they were rhyming nonwords—the task that places the highest demands on rule-based grapheme-to-phoneme mapping. By contrast, the dyslexic group showed weak and nonsignificant correlations among these regions. Connectivity analysis (also using the Horwitz across-subjects method) on data from the single-letter rhyme task, however, showed a different pattern: Both groups exhibited reasonable connectivity among these posterior areas. This pattern suggests that connections among these areas may be weak in dyslexics and insufficient to support proficient transcoding of grapheme strings (nonwords), yet additionally implies that they are not completely disrupted and can still support simpler phonological processes.

Hampson et al. (2006) used a different method of assessing functional connectivity with fMRI. While in the scanner, subjects simply read full sentences on the screen for repeated 4 minutes sessions, and a full functional MR image was gathered every second. For each subject separately, the image-to-image time course of activity levels in Broca's area was extracted. This time series was then

correlated with the time course of other targeted areas in the brain to assess functional connectivity. The individual subject-by-subject measures were then averaged to obtain composite connectivity scores. Across subjects in general, Broca's area correlated with other areas in the reading system, including posterior aspects of the superior and middle temporal lobes, and the inferior occipitotemporal junction. Most striking, when individual reading subtest scores were compared to these connectivity scores, a clear relationship was found: subjects with lower reading scores showed lower connectivity values between Broca's and the angular gyrus; subjects with higher reading scores showed higher connectivity. This study presents the first report of network connectivity measures within single subjects predicting reading ability.

In an attempt to assess connectivity among a larger set of regions in the reading network, we employed a multivariate connectivity analysis on data gathered from a large set of children (Mencl et al., 2003; Shaywitz et al., 2002). This sample of 144 children was initially scanned while performing several reading-related tasks, including reading real words. For subsequent analysis, we split the sample into older good readers ($N = 27$; mean age, 13.5 years; mean Woodcock–Johnson Word Attack (WJWA) score, 519); younger good readers ($N = 47$; mean age, 9.4 years); older dyslexic readers ($N = 46$; mean age, 14.9 years); and younger dyslexic readers ($N = 24$; mean age, 10.1 years). This allowed us to compute across-subjects functional connectivity measures within each group separately and then compare these measures by age cohort and reading ability in order to identify region-to-region connections within the reading network that change as a function of age and skill. We first isolated primary regions of interest, including Broca's area, a medial and lateral aspect of the inferior occipitotemporal area, the temporoparietal area, and the anterior cingulate gyrus. Initial targeted univariate analyses examined the correlations between the occipitotemporal area and Broca's area in each of the groups. Although all groups showed a numerically positive correlation between these two sites, it was largest and only reached significance in the older good readers. We also observed a weak replication of findings reviewed earlier (Hampson et al., 2006; Horwitz et al., 1998; Pugh et al., 2000): Correlations between the angular gyrus and the occipitotemporal area were numerically stronger in both the younger and older good readers than in the dyslexic groups, although the direct comparisons between reader groups did not reach significance.

Clearly, analysis of this large number of possible bivariate correlations, and the group differences among them, presents analytical problems. We therefore applied a multivariate analysis (partial least squares, or PLS; McIntosh, Bookstein, Haxby, & Grady, 1996) to group these correlations into sets, or components, that change together by age or subject group. These components represent sets of linkages among areas that change together and can be interpreted as shifts in the reading network at a systems level. The first component from this analysis shows group loadings (Figure 5.2b) that reflect a connectivity pattern that increases with age in the nonimpaired readers (a negative loading for the young cohort and a positive loading for the older cohort). Group loadings for the two dyslexic age cohorts are

nearer to zero, indicating that this component is not strongly expressed in those subjects. The brain loadings (Figure 5.2a) among a set of areas indicate a positive shift in connectivity in the older cohort, relative to the younger cohort, specifically including the connection between Broca's area and the left occipitotemporal area (yellow connection between LBR and LOT; see the figure caption for full details), and between the left occipitotemporal area and the angular gyrus. This reflects the difference observed in the initial univariate analyses: an increase in functional connectivity between these two areas in the older cohort of good readers, compared to the younger cohort. One negative shift should be noted, that

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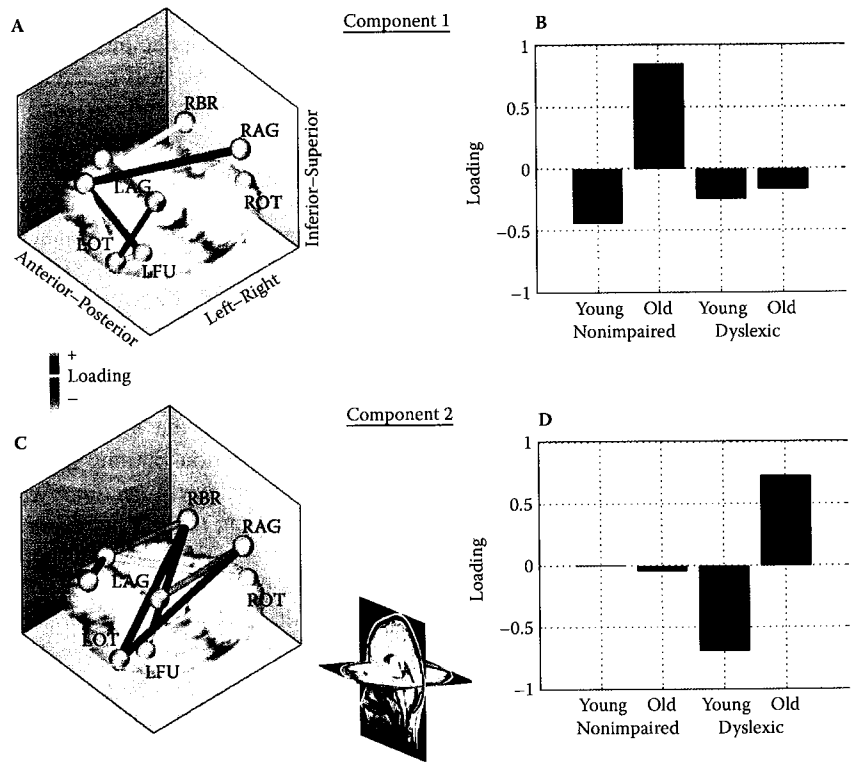

FIGURE 5.2 Results from the PLS analysis of connectivity in four groups of children. Top two panels: (a) brain loadings and (b) group loadings for the first component. Bottom two panels: (c) brain loadings and (d) group loadings for the second component. The eight regions of interest are shown as green spheres. Brain loadings between areas are shown as connecting tubes: red to yellow indicate positive changes on connectivity; purple to blue indicate negative changes in connectivity. The 3-D inset at the bottom shows the orientation of the schematic brains in (a) and (c). LBR, left hemisphere (LH) Broca's area; RBR, right hemisphere (RH) Broca's area homologue; ACG, anterior cingulate gyrus; LTP, LH temporoparietal area; LOT, LH occipitotemporal area; LFU, LH fusiform area; RTP, RH temporoparietal area; ROT, RH temporoparietal area.

between the anterior cingulate gyrus and the left angular gyrus. This effect suggests a reduction in the involvement of the anterior cingulate gyrus in the older cohort. The second component shows group loadings (Figure 5.2d) that indicate a developmental shift in the dyslexic subjects, with near-zero loadings for the good readers. Brain loadings (Figure 5.2c) show a dramatically different set of changes in connectivity: Broadly, the left occipitotemporal and fusiform areas are increasing connectivity with *right hemisphere* homologues of regions in the reading system. Further, the anterior cingulate gyrus shows higher connectivity to bilateral inferior frontal gyrus and to the right hemisphere occipitotemporal area. Clearly, interpretation of these entire patterns of correlational shifts would be difficult and fraught with assumptions. However, the prominent aspects of these results make sense with reference to the theorized roles of the regions involved. First, older good readers increase the functional linkage between the occipitotemporal area and Broca's area, suggesting an increased integration of the skill-based input site with the frontal output system with age. Second, the older dyslexic readers increase linkage of the anterior cingulate gyrus into the reading network, highly suggestive of a more attentionally demanding, effortful style of reading. Further, the increased linkage of the occipitotemporal areas with right hemisphere regions is compatible with earlier observations of the engagement of the contralateral hemisphere for alternative processing strategies in dyslexics (c.f. Shaywitz et al., 2002). This analysis thus presents an initial attempt to integrate knowledge of the processing roles of cortical regions with functional connectivity analysis at the level of the reading network as a whole.

In summary, research on white matter connectivity appears to be converging on a relatively small zone for differences in dyslexia—the left posterior temporoparietal cortex. Research on the functional connections among regions suggests more numerous differences, yet strongly implicates connections with posterior regions as well, particularly connections involving the left hemisphere angular gyrus, the occipitotemporal area, and Broca's area. One testable hypothesis for future work is that the functional connectivity differences observed in dyslexia—even between remote regions—are a result of degraded information transfer through the specific white matter tracts identified by anatomic studies. Finally, relating the hypothesized processing roles of these regions to available anatomic and functional connectivity data provides the elements for specifying more precisely a neurological basis of developmental dyslexia.

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