

## Connectivity–behavior analysis reveals that functional connectivity between left BA39 and Broca’s area varies with reading ability

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**Correlations between temporal fluctuations in MRI signals may reveal functional connectivity between brain regions within individual subjects. Such correlations would be especially useful indices of functional connectivity if they covary with behavioral performance or other subject variables. This study investigated whether such a relationship could be demonstrated in the context of the reading circuit in the brain. The method proved sufficiently powerful to reveal significant correlations between the reading abilities of subjects and the strength of their functional connection between left Brodmann’s area 39 and Broca’s area during reading. This suggests that the disconnection of the angular gyrus previously reported for dyslexic readers is part of a larger continuum in which poor (but nonimpaired readers) also show reduced connectivity to the region. In addition, it illustrates the potential power of paradigms that examine correlations between behavior and functional brain connections.**

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### Introduction

The neural circuitry involved in reading has been investigated extensively using neuroimaging techniques and lesion studies. Specific language areas have been implicated repeatedly, including left inferior frontal gyrus and superior and middle temporal cortex. In addition to the classic language areas, regions in the occipito-temporal and extrastriate cortex, as well as left Brodmann’s area 39 (often referred to as left angular gyrus, although it also includes the posterior superior aspect of the middle temporal gyrus), have been consistently reported to be implicated in reading (Beauregard et al., 1997; Constable et al., 2004; Fiez et al., 1999; Fiez and Peterson, 1998; Pugh et al., 2001).

Neuroimaging activation studies map out brain regions involved in specific cognitive processes, and there is considerable interest in examining the connectivity between those brain areas. Diffusion tensor imaging methods allow the examination of anatomical connectivity, while measurements of interregional correlations in activity patterns (as inferred from functional imaging data) allow assessment of the state-dependent functional connectivity between regions. Functional connectivity does not itself imply a direct, causal influence of one region over the other (otherwise known as effective connectivity), as it is correlational in nature. However, it can provide important insights into the functional relationships between brain areas.

Previous studies have examined the functional connectivity of the angular gyrus during reading. Using positron emission tomography, Horwitz et al. (1998) examined correlations in regional cerebral blood flow between a locus in left BA39 and other parts of the brain during reading tasks and found that the correlations were markedly reduced in dyslexic readers as compared to healthy control subjects. A functional magnetic resonance imaging study (fMRI) then extended this finding by reporting disrupted correlations between activations of left Brodmann’s area (BA39) and activations in posterior reading areas in dyslexic readers specifically for reading tasks involving phonological processing (Pugh et al., 2000). These two studies assessed functional connectivity between brain regions via interregional correlations computed across subjects.

An alternate method for looking at functional connectivity in the brain that has gained popularity more recently is to examine interregional temporal correlations within subjects over time (Biswal et al., 1995; Hampson et al., 2002; Lowe et al., 1998; Xiong et al., 1999). This is the approach used in this study. It has the potential advantage that the strength of functional connection between two regions is assessed for each subject individually and thus theoretically can be related to behavioral variables such as task performance (or other subject variables such as age). To simplify discussion, this particular type of brain–behavior analysis will hereafter be referred to as connectivity–behavior analysis, with the

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intent that connectivity be understood to refer to the strength of specific interregional functional covariations in the brain. If behavioral measures and brain connectivity can be successfully related, such connectivity–behavior analyses could prove extremely useful for investigating a variety of brain functions and/or dysfunctions.

In this work, we hypothesized that correlations in the fluctuations in blood oxygenation level-dependent (BOLD) MRI signals from different parts of the reading circuit could be detected reliably in individual subjects in a reasonable time for scanning. In addition, we hypothesized that the magnitudes of those correlations would covary with behavioral measures of reading ability. A specific aim was to determine whether functional connectivity with left BA39 is related to reading ability in healthy readers. Originally, to allow the most straightforward comparison with previous studies of connectivity between brain areas involved in reading, the intent was to examine correlations between left BA39 and the rest of the brain. However, due to difficulties in functionally localizing this region (interestingly, it only activated reliably in the more skilled readers), maps of functional connectivity to Broca's area were computed instead. The strength of the correlation between reading ability and functional connectivity between Broca's area and left BA 39 was then measured across subjects.

## Method

### Subjects

Nineteen native English-speaking, literate, right-handed adults with no reported psychiatric diagnoses or history of reading or learning disability participated in the study. Subjects ranged in age from 18–48. There were ten men and nine women. All subjects gave informed consent in accordance with a protocol reviewed and approved by the Human Investigations Committee of the Yale School of Medicine.

### Reading tests

Four subtests of the WIAT-II were administered to subjects in a separate session from the scan. These included the word reading (WR), pseudoword decoding (Pseud), spelling (Sp), and reading comprehension (RC) subtests.

### Imaging protocol

Subjects were scanned in a Siemens 3 T Trio scanner. The session began with a localizing scan, followed by the acquisition of sixteen 6 mm T1-weighted axial slices (parallel to the AC–PC line with 4 slices below it). Eight functional runs were then collected with slices in the same locations as the anatomical T1-weighted data. A T2\*-sensitive gradient-recalled, single shot echo-planar pulse sequence was used for the functional scanning (TR = 1 s, TE = 30 ms, flip angle = 90, FOV = 220<sup>2</sup> mm, 64<sup>2</sup> acquisition matrix). Each functional run involved the acquisition of 260 volumes. The first six volumes taken in each scanning run were discarded, and the remaining 254 were used for analyses. In addition, for other purposes (not discussed in this paper), one run of diffusion tensor imaging data was collected, and a high-resolution volumetric anatomical scan was collected.

### Experimental protocol during scanning

Each subject participated in eight functional imaging runs. Two of these consisted of block design paradigms, alternating between sentence-reading blocks (comprised of 3 sentences each presented for 6500 ms and separated by a 500 ms pause) and resting blocks (defined as eyes open with a blank screen). Two of the functional runs consisted of simply the rest condition. Two runs were performed with the subject engaged in continuous reading in which sentences with subject–relative clauses (SR sentences) were presented, and two runs consisted of continuous reading in which sentences with object–relative clauses (OR sentences) were presented. The sentence stimuli were designed so that for each sentence with a subject–relative clause, a matched sentence with an object–relative clause was created using the same words. Subjects were divided into two groups, and the stimuli were split between the groups so that one sentence from each pair was presented to each group. Thus, although each subject only read one sentence from each pair, all subjects were exposed to the same vocabulary as well as the same number of sentences of each type. The order of runs was counterbalanced across participants subject to the constraint that for each pair of steady-state runs, one occurred after a resting scan (or an anatomical scan in which subjects also rested with their eyes open), and the other occurred after a continuous reading run. This constraint was designed to equalize the effects of context across subjects and conditions because effects of preceding cognitive activity on resting correlations have previously been reported in individual subjects (Waites et al., 2005).

### Data analyses

#### Preprocessing

All data were first motion corrected using the SPM99 algorithm with signal correction to remove motion correlated effects (<http://www.fil.ion.ucl.ac.uk/spm/>). A spatial Gaussian filter with a width of 6.875 mm (2 pixels) full-width at half maximum was applied to the data. Pixels with a median value below one-fifth of the maximum median pixel value were set to zero to remove pixels with very low signal levels (such as those outside the brain, or those in very severe signal drop-out areas). For the data used in correlational analyses, several additional preprocessing steps were taken. First, using sinc interpolation, the data from each slice were adjusted for slice acquisition time. Second, a low-pass filter (cutoff of 0.1 Hz) was applied to the data (this is a standard preprocessing step for functional connectivity analyses).

#### Activation analyses (block design paradigm)

Images were assigned to resting or reading blocks after adjusting for hemodynamic delay (hemodynamic response was assumed to be present from four seconds after the onset of a block until 2 s after the end). For each subject, a *t* test was then performed at each pixel comparing signal level during reading blocks to signal level during resting blocks, yielding *t* maps of activation for each subject. These *t* maps were used to functionally define the reference regions to be used for correlational analysis. The Broca's area reference region for each subject was defined to be the 30 most activated pixels in left Brodman's areas 44 or 45. In addition to the *t* maps for each subject, a map of percent signal change across conditions was computed.

### Functional connectivity maps

The reference time-course for a given subject was computed by averaging the time-course across all 30 pixels in their functionally defined Broca's reference region during the resting runs. That reference time-course was then correlated with the time-course of every other pixel in the brain within each resting run, after removing the effects of the mean time-course of the slice in which the pixel was located. The removal of slice mean alleviates artifacts arising from cardiac and respiratory pulses that arrive during part of the volume collection and which tend to elevate correlations between slices collected next to one another in time.

The resulting resting correlations were averaged across the two resting runs and transformed to an approximately Gaussian distribution via Fisher's transformation. By fitting the distribution with a Gaussian and adjusting for mean and standard deviation, the data were transformed to a standard normal distribution (see Hampson et al., 2002; Lowe et al., 1998). This yielded a map representing the strength of resting correlations to Broca's area in terms of standardized  $z$  values.

Using the same methods, a map of correlations during the SR sentence-reading condition was obtained for each subject, as well as a map of correlations during the OR sentence-reading condition. For simplification and because correlations were so similar in the two sentence-reading conditions, a map of correlations during all sentence-reading runs was also created (by averaging correlations across all four reading runs prior to transforming the correlations to a  $z$  distribution) and used for ROI analyses and connectivity-behavior analyses. Individual subjects' maps of correlations during reading are displayed thresholded at  $z = 3$  after cluster filtering to remove clusters of less than 3 adjacent pixels.

### Composite functional connectivity maps

For each subject, the  $z$  transformed resting correlation map was transformed to Talairach space. At each pixel in Talairach space, the distribution of  $z$  values across subjects for that pixel were compared (using a two-tailed  $t$  test) to a distribution with a mean of zero, to yield a map of the significance of resting correlation across subjects. Similarly, composite maps of correlations in the SR reading and OR reading conditions were computed. Composite maps are displayed thresholded at  $P < 0.001$  (uncorrected) after cluster filtering to remove clusters of less than 10 adjacent pixels.

### ROI analyses

The Broca's area ROI included left Brodmann's areas 44 and 45. The left BA39 ROI was defined to include all of left Brodmann's area 39, including the angular gyrus and the superior posterior aspect of the medial temporal gyrus (this definition is consistent with that used for the left angular gyrus in Pugh et al., 2000). The left occipito-temporal ROI was defined to include both lateral and medial cortex at the junction of the occipito-temporal lobes below  $z = 0$ , including portions of Brodmann's areas 37, 19, and 20. The  $z$  values in the Talairach transformed maps of correlations (or the percent signal change across the Talairach transformed activation maps) were averaged across anatomically defined ROIs in each subject. For each ROI, the distribution of these average values across subjects was then compared to a normal distribution with a mean of zero (using a two-tailed  $t$  test)

to determine the significance of the correlation (or activation) of that region for that condition.

### Connectivity-behavior analyses

Correlations were computed across subjects between raw scores on each reading subtest, and the average of the  $z$  transformed correlations in a given ROI of the Talairach transformed map of correlations with Broca's area in the resting and continuous sentence-reading conditions separately. For the contrast between reading runs and resting runs, the spatial average of the correlation in the ROI was first subtracted across conditions in each subject, and that difference was then correlated with reading skill. All correlations were first transformed to  $z$  values using the equation:  $z = (N - 3)^{0.5} \log_e((1 + r)/(1 - r))/2$  with  $N = 19$ , and the  $P$  value was then computed as  $P = 2 * (1 - \text{CDF}(|z|))$ , where CDF represents the cumulative distribution function (that is, the area under a standard normal Gaussian curve to the left of that  $z$  value).

### Analysis comparing good readers to poor readers

First, a composite reading score was computed for each subject using the standard WIAT-II procedure (this method combines word reading, pseudoword reading, and reading comprehension measures into one composite score). The subject with the median composite score was included with the good subjects as his percentile score was above the 50th percentile. This yielded ten good and nine poor subjects with all good subjects scoring over the 50th percentile and all poor subjects scoring below 50th percentile. The strength of correlations to Broca's area within the angular gyrus ROI was computed for each subject as described above, and these values were compared across groups using a two-tailed  $t$  test.

## Results

As mentioned in the Introduction, the block design sentence-reading task did not consistently activate left BA39 in all subjects. This was surprising at first, but examination of the data revealed that subjects that had low scores on the reading tests were generally the individuals who had little or no activation of BA39. Indeed, activation of this region was highly correlated with reading ability. The correlations between left BA39 activation and reading ability were significant for three of the four reading skills tested (WR:  $P < 0.02$ , Pseud:  $P < 0.004$ , RC:  $P < 0.003$ ). Therefore, Broca's area (which could dependably be localized in all subjects) was selected as the reference region for correlational analyses. This region was significantly activated by the block design reading task ( $P < 0.00001$ ), and its activation was not correlated with reading ability.

The correlations to Broca's area at rest revealed patterns of functional connectivity consistent with the known reading circuitry. Not surprisingly, the composite map of resting correlations (Fig. 1a) reveals strong correlations with areas adjacent and homologous to Broca's area, extending up into premotor cortex and down into ventral IFG (BA47). In addition, a large distinct swath of correlation is seen extending bilaterally from the superior and middle temporal gyri ventrally through the lateral occipito-temporal junction. Strong positive correlations are also apparent in bilateral medial occipito-temporal cortex, and in the medial frontal gyrus, and weaker loci are seen in the left hemisphere in BA 40, at the lateral occipito-parietal

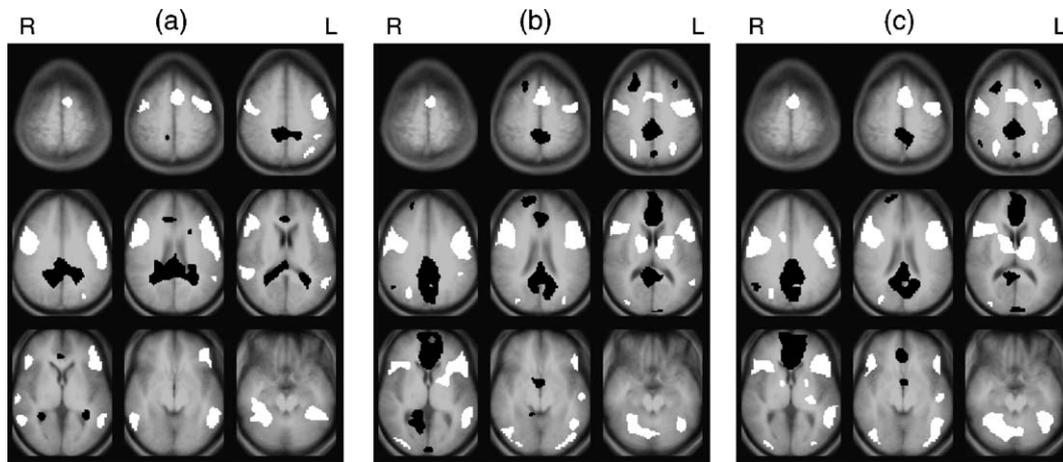


Fig. 1. Composite maps of correlations to Broca's area ( $P < 0.001$  threshold): (a) Correlations during rest. (b) Correlations during continuous reading of sentences with subject–relative clauses (SR sentences). (c) Correlations during continuous reading of sentences with object–relative clauses (OR sentences). Positive correlations are white, negative correlations are black.

junction, and in the angular gyrus. Negative correlations are apparent in the anterior and posterior cingulate cortices (negative correlations are also seen in other areas but these may be due to motion artifacts lining the ventricles). Although the composite map shows only a small correlation between Broca's area and left BA39, likely due to variability in the spatial location of the BA39 peak across subjects, ROI analysis indicates that the correlation to the left BA39 was significant ( $P < 0.004$ ).

In the SR and OR sentence-reading conditions (Figs. 1b and c respectively), the composite maps of correlation to Broca's area are remarkably similar (there is nothing present in a contrast map of the two reading conditions at this threshold). For this reason, and because distinctions between the two sentence types are not relevant to the purposes of this paper, correlations to Broca's area in the two reading conditions combined were used for ROI analyses and for connectivity–behavior correlations. As in the resting condition, the maps obtained during continuous reading reveal strong correlations between Broca's area and adjacent and homologous regions, extending up into premotor cortex and down into ventral IFG (BA47). There is also a large swath of correlation extending from the left superior and middle temporal gyri ventrally through the left lateral occipito-temporal junction (and correlation in homologous occipito-temporal cortex), although the correlation in superior and middle temporal cortex is more lateralized than in the resting condition. Also similar to the resting condition are strong positive correlations in bilateral medial occipito-temporal cortex (spreading into the cerebellum) and in the medial frontal gyrus. Despite these many similarities, there are some differences between the maps obtained during reading and those obtained during rest. The most dramatic of these are a pronounced correlation between Broca's area and bilateral subcortical regions (primarily in the lenticular nucleus and adjacent parts of the thalamus) in both reading conditions that is not apparent at rest, as well as correlations in lateral extrastriate areas bilaterally, and a large increase in the negative correlations between Broca's area and the cingulate cortices in the sentence-reading conditions. There are also some small activations and deactivations that differ across conditions. Interestingly, ROI analysis does not reveal a significant correlation between left BA39 and Broca's area during continuous reading. This is likely due to disrupted connectivity in the less skilled readers during reading, given the connectivity–behavior patterns described below.

Results from the connectivity–behavior analyses examining correlations between the functional connectivity of left BA39 and Broca's area and the various reading skills are summarized in Table 1. In the resting state, the strength of connection between left BA39 and Broca's area was slightly correlated with scores on the four reading subtests, but this correlation only reached a significance of  $P < 0.05$  for one of the four reading subtests (RC) and was not significant after correcting for twelve multiple comparisons. However, in the sentence-reading condition, the correlations between this interregional brain connection and reading skills were pronounced. For all four reading subtests, the correlation to functional connection strength during reading was significant after correcting for twelve multiple comparisons. Some increase in significance of connectivity–behavior correlations in the sentence-reading condition relative to the resting condition might be due to increased power in this condition (given that there was twice as much data as for the resting condition), therefore, a contrast between conditions was performed that controlled for these differences in power. The third column of Table 1 presents the correlation between the difference in the strength of the brain connection in the reading condition compared to the resting condition and performance on the four reading subtests. All four reading subtests demonstrated significance at an uncorrected level, and the pseudoword reading subtest was significant at the corrected level (the word reading subtest was also approaching significance at the corrected level). There was no significant correlation between subject age and the strength of left BA39–Broca's area connectivity in either condition or between subject age and the

Table 1

Connectivity–behavior data: significance of correlation (uncorrected  $P$  value) between reading subtest performance and left BA39–Broca's area functional connectivity (FC)

Reading subtest	FC at rest	FC during sentence reading	Change in FC from resting to reading
WR	–	0.002 <sup>a</sup>	0.007
Sp	–	0.004 <sup>a</sup>	0.01
Pseud	–	0.003 <sup>a</sup>	0.004 <sup>a</sup>
RC	0.03	0.001 <sup>a</sup>	0.024

<sup>a</sup> Indicates significance after correction for multiple comparisons.

change in this connection strength across condition. In addition, there was no significant effect of gender on this functional connection in either condition and no significant effect of gender on the change in this connection across conditions.

If the functional connectivity between Broca's area and all the other major reading-related brain areas showed similar patterns of disruption during reading in poor readers, it would suggest that the poor readers may simply have failed to participate in the reading task during the continuous reading scans. To investigate this possibility, connectivity between Broca's area and left occipito-temporal cortex was examined. Left occipito-temporal cortex (OTC) has been repeatedly implicated in reading (Fiez and Peterson, 1998) and was found to be specifically activated by reading in contrast to auditory language processing (Constable et al., 2004). Broca's area was strongly correlated with left OTC during reading ( $P < 0.00003$ ), and the increase in connectivity between Broca's area and left OTC during the reading condition relative to the resting condition was also significant ( $P < 0.03$ ). There was no significant correlation between any of the four reading scores and the strength of the connection between Broca's area and left OTC during reading, and there was no significant correlation between any of the four reading scores and the change in connectivity between Broca's area and left OTC across conditions (i.e., reading vs. rest). In summary, participants, regardless of reading ability, exhibited strong connectivity between Broca's area and occipito-temporal cortex during the sentence-reading runs, and this connectivity was significantly greater than at rest.

In the secondary analysis, in which subjects were divided into two groups of readers, good and poor, and connectivity in the groups was compared directly (rather than looking at correlations with continuous variables representing reading skills), ROI analysis revealed that good readers had a significant positive correlation between Broca's area and left angular gyrus both at rest ( $P < 0.003$ ) and during reading ( $P < 0.01$ ). Poor readers, on the

other hand, had positive correlations between Broca's area and left angular gyrus that were not significant in either condition. Most importantly, there were significant differences in the strength of the Broca's area—left BA 39 connection between the good and poor readers at rest ( $P < 0.04$ ) and during reading ( $P < 0.03$ ). Although these findings were dependent on the criteria used for categorization of the readers, the finding of significant group differences in the reading condition was relatively robust. For example, if the reader with the median composite reading score was categorized as a poor reader rather than a good reader (resulting in ten poor and nine good readers), then the difference between groups dropped below significance in the resting condition ( $P < 0.13$ ) but was still highly significant in the reading condition ( $P < 0.0071$ ).

To illustrate the connectivity patterns in individual readers during reading, maps of connectivity to Broca's area are shown for four individual subjects (two poor readers and two good readers) in Fig. 2. Subjects are ordered from left to right with increasing composite reading score. Here, we can see that although Broca's area is correlated with Wernicke's area in all four individuals (apparent in the more ventral slice shown in the bottom row), its correlation with left BA 39 varies with reading ability.

## Discussion

The correlations found between left BA39 activation and reading ability were pronounced. As a result, we could not functionally localize left BA39 in the poor readers. However, the strong correlation of activation in this region with reading ability is an interesting discovery. Angular gyrus/BA39 activation has been previously reported to be diminished in dyslexic subjects (Shaywitz et al., 1998) across a range of reading tasks. However, to our knowledge, activation of the angular gyrus/BA39 during reading has not been previously reported to be related to reading ability in healthy readers. Activation in left BA39 has been found in many different reading paradigms. It has been suggested that this brain region is involved in a variety of reading-related tasks including cross-modal conversion (Booth et al., 2003), semantic access (Binder et al., 2003), character-to-phonological conversion in letter perception (Callan et al., 2005), access to the visual orthographic lexicon (Joubert et al., 2004), and the processing of syntactically complex portions of a sentence (Caplan et al., 2001). The findings reported here that left BA39 activation during sentence reading is correlated with reading skills could thus be interpreted in a variety of ways. For example, if this region is the locus of the visual orthographic lexicon as suggested by Joubert et al. (2004), the correlation could arise because better readers directly access a visual lexicon while poor readers rely more on orthographic to phonological decoding.

The composite map of resting correlations to Broca's area revealed a set of brain areas known to be involved in reading including superior and middle temporal cortex, medial and lateral occipito-temporal areas, and, to a lesser degree, left BA39. This is in contrast to a previous report of resting correlations to Broca's area (Hampson et al., 2002) in which connectivity with the superior temporal gyrus was strong, but other reading-related areas were absent. This is not surprising, given that Broca's area in this study was functionally localized based on a reading task, whereas in the earlier Hampson et al. (2002) study, the region was functionally localized based on an auditory language task. The difference in the circuits identified

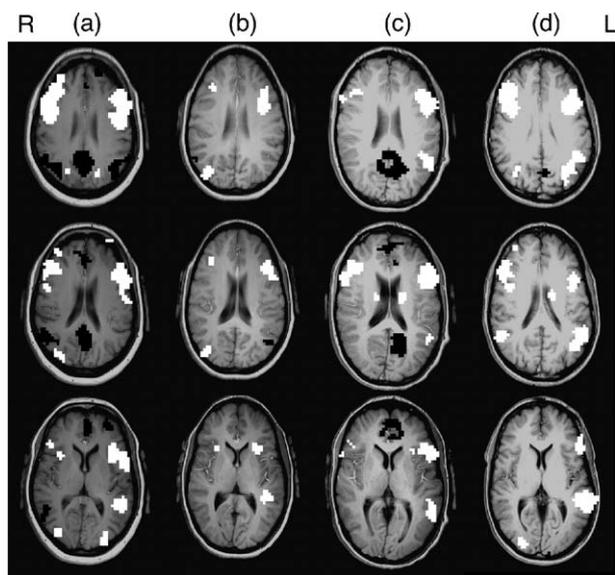


Fig. 2. Maps of correlations to Broca's area during continuous reading runs from four individual subjects ( $z = 3$  threshold). Each column represents one subject, and they are ordered from left to right with increasing composite reading scores. The first two subjects (a and b) were classified as poor readers and the second two (c and d) as good readers. Positive correlations are white, negative correlations are black.

in these two studies illustrates how functionally localizing a reference region for correlational analyses can be a powerful tool for identifying specific circuits.

The basis of resting state correlations is still not understood, although there is a good deal of evidence that they are consistent with known circuitry in the brain. One possibility is that regions with strong connectivity track each other's neural activity even when they are not activated, *per se*, and that their blood flow patterns are somewhat synchronized as a result. Another possibility is that there is some mechanism in the brain for phase-locking blood flow (independent of neural activity) between highly connected regions. It is also possible that inter-regional correlations may arise between functionally related regions in a given functional circuit because the circuit (as a whole) varies in the degree of its activation. That is, even at rest certain brain circuits may become intermittently activated, and this intermittent activation could result in correlations between all regions in those circuits. Of course, there could be multiple factors contributing to the observed correlations. If it is the case that inter-regional correlations arise predominantly because various brain circuits are intermittently activated at rest, then the strength of the correlation between brain areas in a circuit may not be indicative of the internal structure of the circuit. Instead, areas that activate strongly when the circuit comes on will be more strongly correlated with each other, regardless of their direct relationship within the circuit. In many brain systems, the possibility of intermittent activation at rest is not only possible but very probable. For example, it would be surprising if the language or memory systems were not intermittently activated at rest. However, the reading circuit is one for which there is no obvious reason for intermittent activation at rest (not many people imagine reading text when resting). The findings of this study that resting correlations can be used to delineate the reading circuitry is thus more difficult (although certainly not impossible) to explain solely in terms of an intermittently activated cognitive circuit. As resting correlations in other circuits in the brain (particularly those with no obvious reasons for becoming intermittently activated at rest) are studied, the basis of these resting correlations may become clearer.

The major focus of this study, however, was to examine connectivity–behavior relationships during reading. Connectivity–behavior analyses revealed strong correlations between reading skill and the strength of the functional connection between Broca's area and left BA39 during continuous reading. This suggests that the findings of reduced connectivity between the angular gyrus/BA39 and other reading-related brain areas in dyslexic readers (Horwitz et al., 1998; Pugh et al., 2000) may be part of a more general phenomenon in which angular gyrus/BA39 connectivity is reduced in poorer readers (regardless of whether they are specifically classified as dyslexic). A recent study using psychophysiological interactions reported that training subjects to pronounce nonnative letters resulted in an increase in functional connectivity between left BA39 and several other areas, including left superior temporal gyrus and left occipital gyrus, when subjects were exposed to those letters in a 2-back task (Callan et al., 2005). Taken in conjunction with the findings of the current study, this strongly suggests that connectivity of left BA39 during reading is related to reading level, regardless of whether it is experience or impairment that is influencing that level. It is important to note, however, that the study reported here did not investigate the connectivity between left BA39 and other posterior reading areas, and thus, it remains to be determined how the strength of those

functional connections are related to reading ability in healthy readers.

To verify that correlations between left BA39-Broca's area connectivity and reading ability were the result of disrupted functional connections in the less skilled readers (alternately, they could arise from a negative correlation in less skilled readers that was absent in the better readers), an analysis that divided the group into two categories of readers (poor and good) was also conducted. This approach has several disadvantages relative to the correlational approach. First, it discards information regarding how good or how poor a reader is in the process of categorization (and thus can result in less power). Second, in the case of correlations to a continuous variable such as this, it depends upon a somewhat arbitrary division between higher and lower values of that variable, where the dividing point has no real meaning, but where the results can depend upon the placement of that point. In the manner in which it was implemented here, there was an additional drawback that information regarding the separate reading skills was combined into one measure of overall reading ability and information was lost regarding how specific skills were related to functional connectivity. However, this analysis allowed verification of connectivity patterns in each subject group separately and thus provided a more direct comparison to results of previous studies examining dyslexic readers (Horwitz et al., 1998; Pugh et al., 2000). The results confirmed that good readers had a positive correlation between left BA39 and Broca's area during reading, and that this correlation was significantly decreased in the poor readers and thus confirmed that the disconnection found in dyslexic readers between these areas is part of a more general phenomenon in which less skilled readers show decreased connectivity.

Interestingly, the correlations between reading skills and left BA39-Broca's connectivity were less pronounced in the resting condition than in the sentence-reading condition, and the change in strength of connection across conditions was related to reading skill (in particular, the change in connectivity was significantly correlated with pseudoword reading ability, its correlation with word reading scores was approaching significance, and it showed some correlation with both of the other measures). This suggests that the connectivity disruption associated with the less skilled readers was more pronounced in the sentence-reading condition than at rest. Such findings are relevant in the context of the assertion by Pugh et al. (2000) that connectivity to angular gyrus/BA39 is not entirely disrupted in dyslexic readers but rather is functionally disrupted only for specific processing tasks (particularly, those involving phonological assembly according to Pugh et al., 2000), while remaining intact for other processing tasks. A similar effect of functionally specific disconnection appears to be present in less skilled, but healthy readers. As the sentence-reading condition involves many cognitive processes in addition to phonological assembly, our results are not specific regarding the precise functional process associated with connectivity disruption, but they do support the possibility that the connection may not be disrupted in an absolute sense (as the resting connections are relatively intact). An intriguingly parallel finding was also reported in a 1977 EEG study of children (Evans, 1977). In that study, a configuration of cortical coupling associated with reading skill was identified, and the presence or absence of that configuration was found to differentiate good from poor readers during reading. During other tasks, however, the presence or

absence of that configuration was less discriminating (particularly during rest and during a session in which compound flash/click stimuli were presented). The change in configuration across conditions was most prominent in the poor readers, suggesting that healthy connection patterns were somehow particularly disrupted in that group during reading, and relatively intact during other task conditions. Although there are obviously important differences between that EEG study in children and the fMRI study of adult connectivity described here, the congruence of findings is encouraging.

One limitation of this study is that in-magnet performance was not controlled. A design that involved collecting performance data was avoided as any motor response during the reading runs would introduce serious confounds into the interregional correlations. Thus, one concern is that the less skilled readers may not have attended to the stimuli because they found reading effortful and thus unpleasant. If this was the case, a pattern of disconnection throughout the reading circuit related to weaker reading abilities would be expected. In contrast, we found that the observed pattern of functional disconnection related to reading ability was regionally specific. In particular, a high correlation between Broca's area and occipito-temporal cortex during reading was found that was independent of reading ability. This suggests that all subjects were engaging their reading circuit. Although all subjects reported they were able to read the sentences in the time presented, there was still likely variability in their levels of processing, and less skilled readers may have failed to co-activate brain areas involved in the later stages of reading comprehension as a result. Therefore, interpretation of these results must bear in mind that the relationship between connectivity and reading skill could be either performance or strategy related.

Given that this study of connectivity–behavior relationships identified significant relationships between reading ability and brain connections with less than 20 subjects, each participating in a standard imaging session, it appears that connectivity–behavior analysis holds great potential for investigating cognitive brain function. However, the problem of multiple comparisons in such studies is challenging. For example, if examining a circuit with six component brain areas, there are fifteen pair-wise functional connections to be considered. Correlating the strengths of these connections with four behavioral variables then yields sixty pair-wise correlations. Clearly, the multiple comparisons problem easily becomes unwieldy in connectivity–behavior analyses and can undermine confirmatory analyses when clear, specific hypotheses are not made a priori.

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