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Functional connectivity of the angular gyrus in normal reading and dyslexia

(positron-emission tomography/human/brain/regional/cerebral)

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ABSTRACT The classic neurologic model for reading, based on studies of patients with acquired alexia, hypothesizes functional linkages between the angular gyrus in the left hemisphere and visual association areas in the occipital and temporal lobes. The angular gyrus also is thought to have functional links with posterior language areas (e.g., Wernicke's area), because it is presumed to be involved in mapping visually presented inputs onto linguistic representations. Using positron emission tomography , we demonstrate in normal men that regional cerebral blood flow in the left angular gyrus shows strong within-task, across-subjects correlations (i.e., functional connectivity) with regional cerebral blood flow in extrastriate occipital and temporal lobe regions during single word reading. In contrast, the left angular gyrus is functionally disconnected from these regions in men with persistent developmental dyslexia, suggesting that the anatomical disconnection of the left angular gyrus from other brain regions that are part of the "normal" brain reading network in many cases of acquired alexia is mirrored by its functional disconnection in developmental dyslexia.

Because written language is a relatively recent addition to human communication, and because most of a typical individual's day is not spent reading, it is unlikely that a neural network evolved that is singularly dedicated to this task. Neurons that are activated during reading are also engaged by other cognitive tasks. Thus, it is not surprising that functional neuroimaging studies comparing reading to control tasks (i.e., the subtraction method) have been inconsistent in demonstrating activation of all the crucial nodes of the neural network mediating reading hypothesized from studies of alexic patients, especially the angular gyrus (1–7).

To complement the subtraction technique, we have developed a method for examining the covariance, or functional connectivity, between regions during the performance of individual tasks by using data obtained from positron emission tomography (PET) (8–10). 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 [indexed by regional cerebral blood flow (rCBF)] between network elements. 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 in the two functionally connected regions. The net effect is a large within-task, across-subject correlation in rCBF between the two regions. Note that functional connectivity is not the same as anatomical connectivity, because two regions may be anatomically connected, but not functionally connected during a specific task. On the other hand, if rCBF in two regions is correlated, these regions need not be anatomically linked; their activities may be correlated, for example, because both receive inputs from a third area (for more discussion about these connectivity concepts, see refs. 8, 10, and 11).

Based on lesion studies in many patients with alexia, it has been proposed that the posterior portion of the neural network mediating reading in the left cerebral hemisphere involves functional links between the angular gyrus and extrastriate areas in occipital and temporal cortex associated with the visual processing of letter and word-like stimuli (12–14). The angular gyrus also is thought to have functional links with posterior language areas (e.g., Wernicke's area), because it is presumed to be involved in mapping visually presented inputs onto linguistic representations (15).

To examine the functional connectivity of the angular gyrus during single word reading, we measured rCBF by using [^{15}O]-water and PET in 14 normal male readers and in 17 men with persistent developmental dyslexia (6, 16). Each subject performed two reading tasks [read aloud low frequency exception words (words with irregular spellings), i.e., words that violate phonological rules, thus requiring the reader to rely on orthographic familiarity; read aloud pseudowords, thereby requiring the reader to rely on phonological rules; see Rumsey *et al.* (6) for a fuller discussion]. Functional connectivity was determined by evaluating interregional correlations between rCBF in the angular gyrus and all other brain areas in both normal and dyslexic readers.

MATERIALS AND METHODS

Subjects. Description of the subjects used in this study, details of the PET procedure, and an analysis of the differences in rCBF between normal and dyslexic men, are given in Rumsey *et al.* (6, 16). Concerning the subjects, 17 healthy, right-handed (17) dyslexic men between the ages of 18 and 40 (mean ± SD = 27 ± 8 yr) and 14 normal male readers (25 ± 5 yr), well-matched with respect to education, IQ, and handedness, were scanned; dyslexic men were not lower compared with controls in Full-scale, Verbal, or Performance IQ. All were monolingual native English speakers, and all gave informed consent in writing before participation in the study. All the dyslexic men had a history of reading difficulty, met DSM-IV (18) criteria for developmental reading disorder, and continued to show reading deficits (19).

Tasks. Two scans obtained during pseudoword reading and two scans during exception word reading were analyzed for the present study. For the pseudoword reading task, subjects were

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Abbreviations: PET, positron emission tomography; rCBF, regional cerebral blood flow; BA, Brodmann area.

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presented one at a time with pseudowords constructed from low frequency rimes, forcing a reliance on phonologic rules (e.g., phalbap, chirl), and asked to read each aloud. In the exception word reading task, subjects viewed low frequency words with irregular spellings and/or inconsistent pronunciations (words that violate phonologic rules and which therefore have to be recognized based on experience; e.g., choir and pharaoh) and were asked to read each word aloud. Stimuli, shown on a computer monitor, were presented self-paced. Dyslexics performed less accurately and more slowly than did controls (16), although the responses of the dyslexics indicated that they were fully engaged in the tasks.

Imaging. A Scanditronix PC2048–15B tomograph (Milwaukee) was used to acquire 15 contiguous axial slices (resolution: in plane, 6.5 mm; axial, 5.5 mm) (6). Earplugs and occlusive sheets were used to minimize extraneous auditory and visual stimulation. Scan slices were obtained from the level of the inferior temporal cortex through the inferior parietal lobe. Ten PET scans were performed, each using a 30 mCi (1 Ci = 37 GBq) bolus injection of $H_2{}^{15}O$; data from only four will be discussed here. An attenuation correction was performed by using a rotating pin source of ^{68}germanium/^{68}gallium. Brain radioactivity was used as an index of rCBF (20).

Data Analysis. PET data were interpolated and spatially normalized (21) into the stereotactic space of the Talairach and Tournoux atlas (22) (final voxel size: 2 mm × 2 mm × 4 mm) and smoothed to 20 mm × 20 mm × 12 mm; values of rCBF for each subject were standardized by dividing rCBF for each voxel by global CBF. Because of smoothing, an individual voxel represents regional activity. Interregional correlations (across subjects) within each condition were calculated (10) between a reference voxel located in the superior temporal sulcus in the region of the angular gyrus [Talairach coordinates $(x, y, z) = (\pm44, -54, +24)$] and all other voxels in the brain; separate correlations were performed for reference voxels in the left and right hemispheres. This voxel was chosen to represent the angular gyrus because its location is centered within the foci of angular gyral activations reported by numerous investigators [e.g., Demonet *et al.* (15) (−48. −52, 28); Howard *et al.* (3) (−50, −48, 8); Price *et al.* (4) (−52, −38, 24); Calvert *et al.* (23) (49, −50, 17); Small *et al.* (24) (−47, −58, 19); Fiez *et al.* (25) (40, −54, 19); Bookheimer *et al.* (2) (−44, −66, 32)].

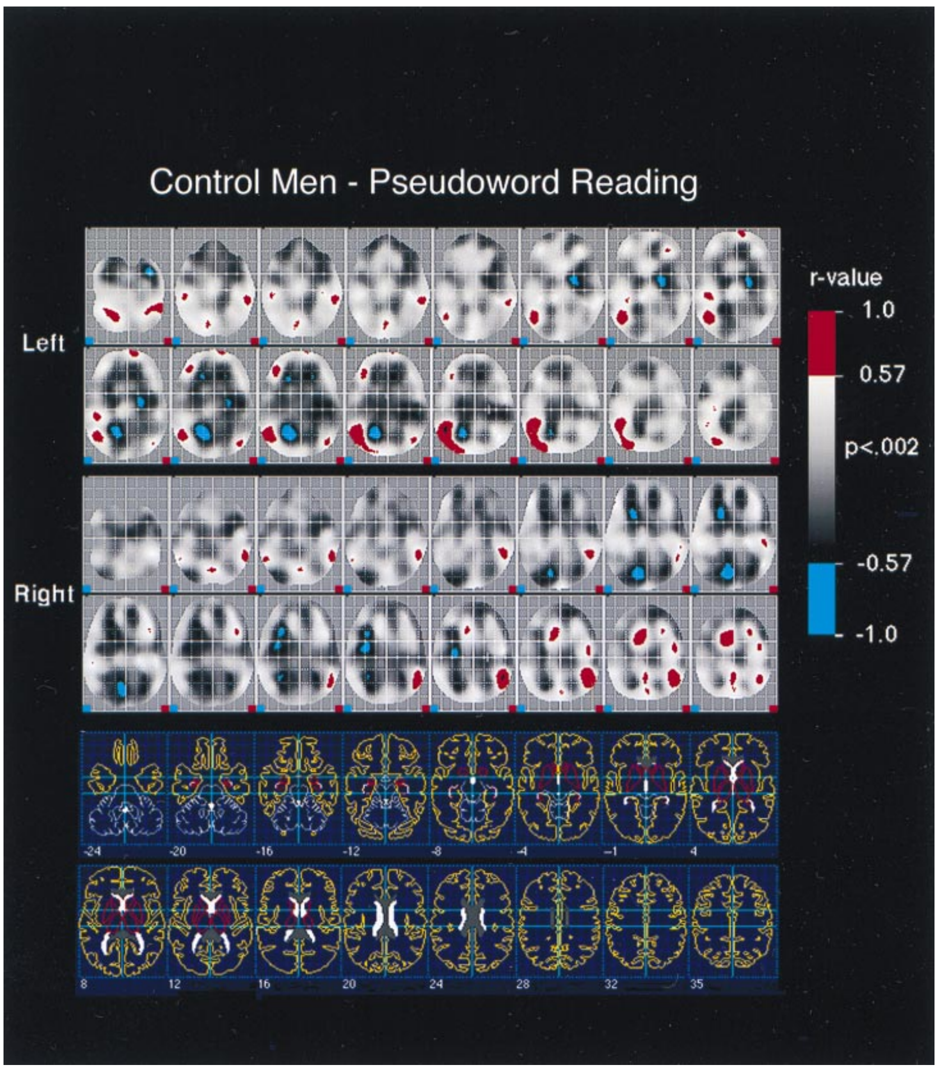

FIG. 1. Correlation coefficients in controls during pseudoword reading between standardized rCBF in a reference voxel in the angular gyrus with standardized rCBF in all other brain voxels. Shown are transaxial slices in stereotactic space of the Talairach atlas (22) (left side of the brain is on the left side of the images), modified anatomic drawings of which are shown at the bottom of the figure; the grid from the Talairach atlas is superimposed over each slice. The numbers in the drawings correspond to the distance (mm) of each slice from the intercommissural plane. The reference voxels, shown as the black dots on the 24-mm slice, have Talairach coordinates (±44, −54, 24). Value of the correlation coefficient is given by the gray scale (see color bar), with those that are significantly ($P < 0.002$, two-tailed test) >0 in red, and those significantly <0 in cyan.

Table 1. Local maxima for angular gyrus correlations

Region	Brodmann area	Tx	Ty	Tz	Correlation
Pseudoword reading: Control men					
Superior occipital	19	−30	−78	28	0.76
Lateral occipital (MT)	19/37	−40	−66	4	0.76
Inferior frontal	45	−36	30	16	0.70
Cerebellum		−22	−62	−24	0.65
Precentral	4	−32	−18	44	0.64
Fusiform	20	−46	−34	−20	0.63
Superior temporal	22	−48	−34	8	0.62
Hippocampal/fusiform	37	−34	−38	0	0.60
Lingual	18	−6	−76	−12	0.60
Cerebellum		−14	−78	−20	0.59
Exception word reading: Control men					
Pre/postcentral	3/4	−32	−20	44	0.72
Cerebellum		−8	−74	−16	0.71
Superior occipital	19	−32	−76	28	0.70
Fusiform	19/37	−48	−64	−12	0.66
Cerebellum		−46	−62	−20	0.65
Cerebellum		−32	−62	−24	0.65
Inferior parietal lobule	19/40	−30	−64	40	0.63
Fusiform	37	−50	−46	−20	0.59

Shown are the Talairach (22) coordinates and values of the correlation coefficients for the local maxima in the left hemisphere for positive correlations with standardized rCBF for a voxel in the left angular gyrus with Talairach coordinates (Tx, Ty, Tz) = (−44, −54, 24). inf., inferior; med., medial; sup., superior.

Correlations between standardized rCBF for each reference voxel in the left and right angular gyri and standardized rCBF in all other voxels in the brain, evaluated by using a program written in MATLAB (Mathworks, Natick, MA) (10), were determined separately for the two tasks (pseudoword and exception word reading), and for the two groups (normal and dyslexic men). For each analysis, an individual's data were entered as if each of the two scans corresponding to the same experimental condition provided new data, and then a correction for repeated measures was performed (26). In effect, a partial correlation coefficient was calculated, with scan number partialled out. Thus, for the normal group there are 25 degrees of freedom (two scans, 14 subjects) for each correlation coefficient, if considered individually; for the dyslexic group (17 subjects), there are 31 degrees of freedom. Results for an individual correlation coefficient are considered statistically meaningful at the $P < 0.001$ level (one-tailed t test); critical r values are 0.57 for controls and 0.52 for dyslexic men (note that for functional connectivity studies a proper balance between type I and II errors is essential, because one does not want to ignore important network relationships; thus, choosing overly conservative P values is inadvisable). Results were displayed using ANALYZE (Mayo Clinic, Rochester, MN).

Local maxima were identified as voxels that had a higher absolute value of the correlation coefficient (or Z value; see below) than any other voxel in a 10 mm × 10 mm × 12 mm (5 × 5 × 3 voxels) space centered on that voxel (27). Their locations are expressed as coordinates (x = left/right; y = anterior/posterior; z = superior/inferior) and Brodmann areas (BA) based on the atlas of Talairach and Tournoux (22). To test

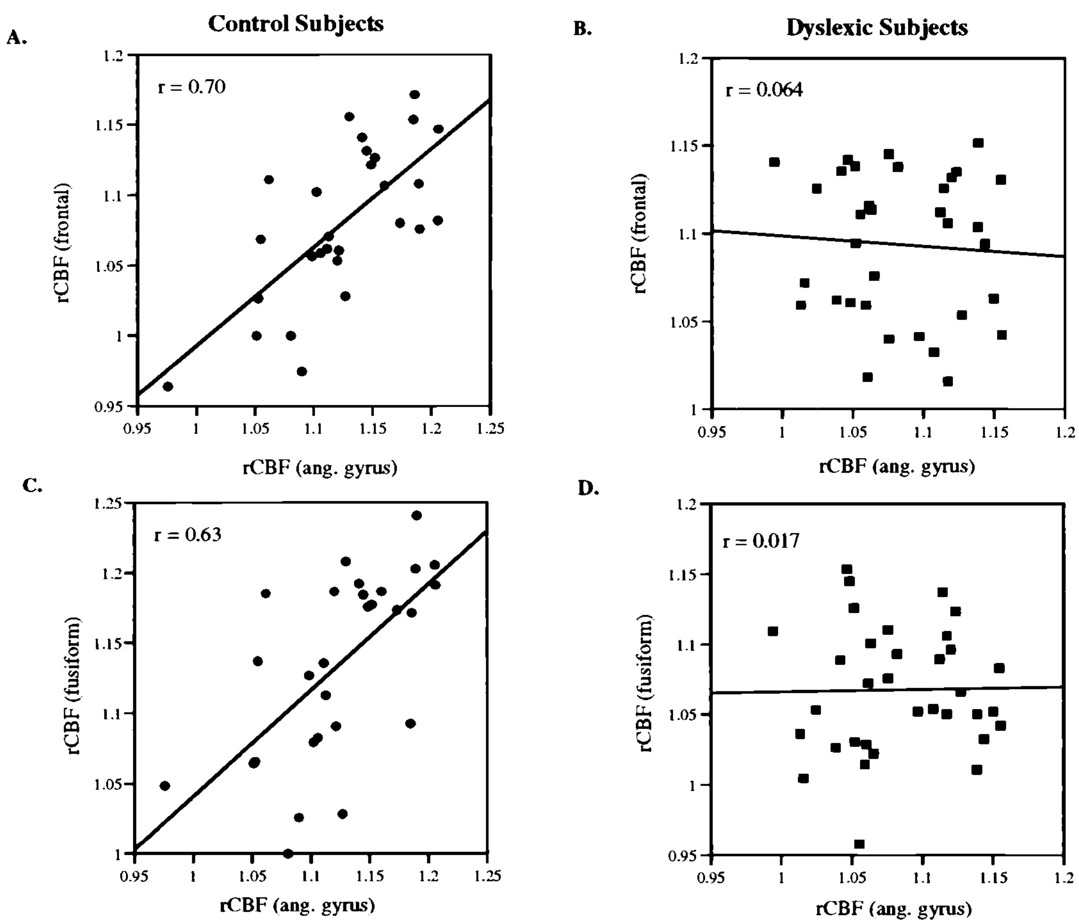

FIG. 2. Scatter plots showing rCBF in the left angular gyrus (Talairach coordinates −44, −54, 24) vs. rCBF in left inferior frontal cortex (*A* and *B*) and left fusiform gyrus (*C* and *D*) during pseudoword reading. A and C present data in normal subjects, B and D in the dyslexic patients. The Talairach location for frontal cortex is the local maximum shown in Table 1 (−36, 30, 16); for the fusiform location, it is also the Table 1 local maximum (−46, −34, −20). The values of each correlation coefficient is given in the upper left of each plot.

whether correlation coefficients at each voxel were significantly different in the dyslexic group compared with the normal group, each correlation was converted by the Fisher r-to-Z-transformation into a quantity whose distribution is approximately normal (28); a normal variate (Z statistic) was used to compare these transformed quantities. Two correlation coefficients were accepted as significantly different from each other at the $P < 0.01$ level.

RESULTS

Fig. 1 shows the functional connectivity of the left and right angular gyri (BA39) in normal readers during the pseudoword reading task. Large positive correlations were found between the left angular gyrus and extrastriate visual areas in occipital and temporal cortex in the left hemisphere (locations in Talairach coordinates of the local maxima for the significant correlations are given in Table 1). These regions include an area at the junction of BA 19 and 37 that frequently includes the motion processing area V5/MT (29), and areas in the lingual and fusiform gyri (BA 18 and 20, respectively) that have been shown to be activated during visual stimulation with letter and word-like stimuli (3, 6, 30–32). Also strongly correlated with standardized rCBF in the left angular gyrus is rCBF in the posterior portion of the left superior temporal gyrus (BA 22), part of Wernicke's area. Finally, there was a significant positive correlation with blood flow in or just anterior/superior to Broca's area in the left inferior frontal gyrus (BA 45). Fig. 2 shows scatter plots for two of these correlations.

In contrast to these findings, when the reference voxel was placed in the right hemisphere, as opposed to the left, positive correlations with right hemisphere homologues of the above regions were either not significant, or else [in the case of the foci in the middle temporal gyrus (BA 21) and Wernicke's area (BA 22)] smaller in extent. No significant positive correlations were found with rCBF in fusiform or lingual gyri, the BA 19/37 junction, or inferior frontal cortex.

During exception word reading, rCBF in the left angular gyrus showed a pattern of significant positive correlations with rCBF in left lingual and fusiform gyri similar to that seen during pseudoword reading (see Table 1), although significance was just missed for the foci in Wernicke's area and inferior frontal cortex (for normal readers during exception word reading, the correlation coefficient for the voxel in Wernicke's area (−48, −34, 8) was $r = 0.40$, $P < 0.05$; for the voxel near Broca's area (−36, 30, 16) was $r = 0.47$, $P < 0.01$.

In the subjects with dyslexia, as Fig. 3*A* (and Fig. 2 *B* and *D*) illustrates, rCBF in the left angular gyrus showed no significant

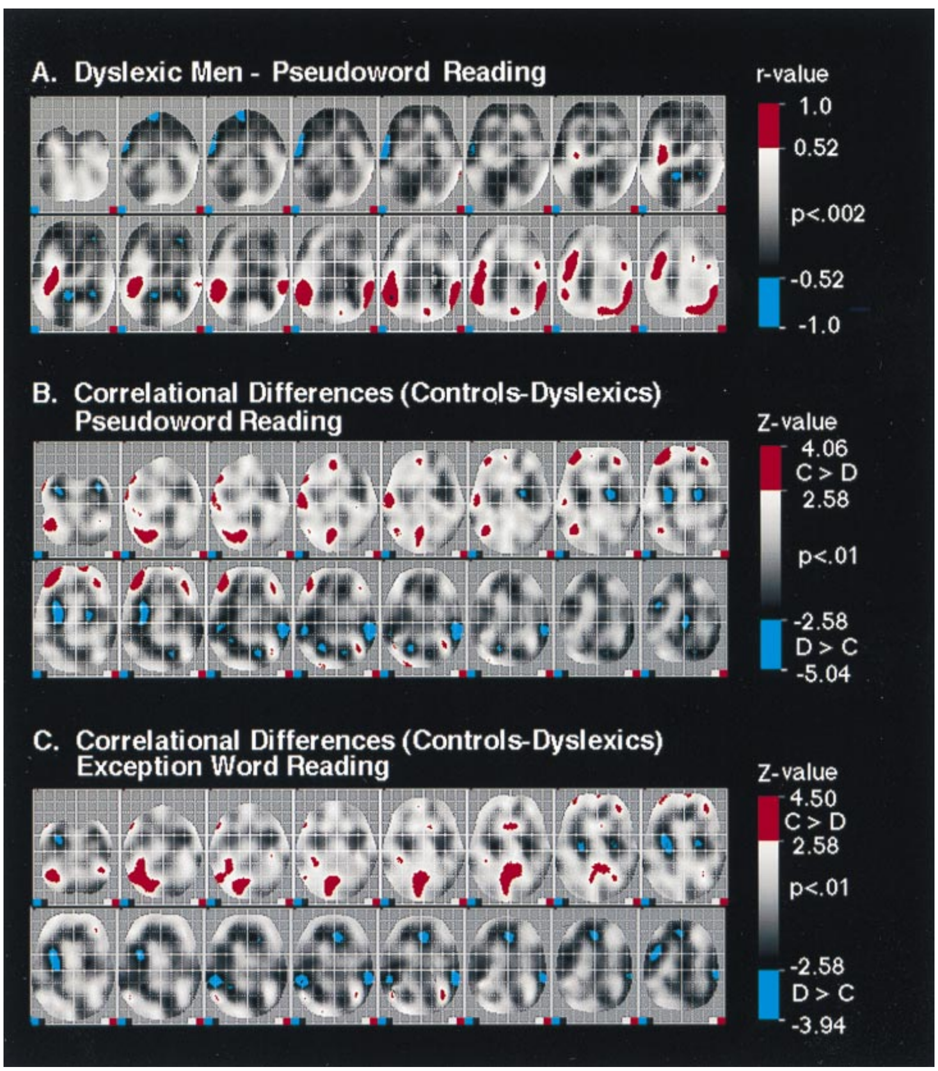

FIG. 3. (*A*) Correlation coefficients with a reference voxel in the left angular gyrus in dyslexic men during pseudoword reading; see the caption to Fig. 1 for details. (*B* and *C*) Z values corresponding to a voxel-by-voxel comparison of the correlation coefficients in controls and dyslexic men during pseudoword (*B*) and exception word (*C*) reading; each voxel's Z value compares the correlation coefficient between standardized rCBF in that voxel with that in the left angular gyrus (−44, −54, 24). The gray scale indicates the value of Z (see color bar); red denotes regions where the correlations were significantly larger ($P < 0.01$) in controls than in the dyslexic men; cyan denotes regions where they were significantly smaller.

Table 2. Local maxima for angular gyrus correlational differences between controls and dyslexics

Region	Brodmann area	Tx	Ty	Tz	*Z*
Pseudoword reading: Controls–dyslexic men					
Inferior frontal	46	−36	36	12	4.06
Cerebellum		−8	−74	−12	3.59
Middle temporal	21	−52	−18	−8	3.49
Cerebellum		−30	−76	−20	3.29
Inferior temporal	37	−34	−62	0	3.28
Cerebellum		−38	−56	−24	3.15
Middle temporal	21	−50	4	−24	3.13
Subcallosal gyrus	25	−6	36	−12	3.12
Inferior temporal	20	−56	−10	−20	3.01
Superior temporal	38	−46	14	−20	2.99
Occipital gyrus	19	−26	−86	24	2.85
Fusiform gyrus	20	−38	−38	−20	2.65
Exception word reading: Controls–dyslexic men					
Lingual gyrus	18	−10	−74	−12	4.50
Cerebellum		−36	−58	−24	3.69
Fusiform gyrus	37	−32	−46	−20	3.17
Superior temporal	38	−48	14	−20	2.97
Fusiform gyrus	37	−34	−38	−8	2.95
Middle frontal	10	−30	56	4	2.88
Inferior frontal	10	−34	48	0	2.73

Shown are the Talairach coordinates and Z values for local maxima in the left hemisphere where the correlation coefficient was significantly larger ($P < 0.01$) in controls than in dyslexic men.

positive correlations with rCBF in many of the above regions during pseudoword reading, including Broca's region, BA 19/37, or regions in fusiform or lingual gyrus (as seen in Fig. 3*A* on the $z = 8$ mm slice, there is a region of significant correlation that extends into the superior temporal area that we have identified as Wernicke's area, probably due to data smoothing; however, the local maximum for this region is located in or near the transverse temporal gyrus (Talairach coordinates −40 −36 12) and thus most likely represents primary/secondary auditory cortex). As shown in Fig. 3*B*, these differences were marked; correlations for these regions with left angular gyral rCBF were significantly smaller in the dyslexic group than in controls (see Table 2 for local maxima of the significant differences). This also was the case during exception word reading (Fig. 3*C*).

DISCUSSION

There are two important findings in this study of the functional connectivity of the angular gyrus during single word reading. (*i*) Many features of the classic neurological model for reading (12–14), which was based on lesion studies, were found in the normal readers in this functional imaging study. In particular, we have demonstrated strong functional linkages of the left angular gyrus with areas of visual association cortex in occipital and temporal lobe known to be activated by words and word-like stimuli (1–4, 6). Furthermore, during pseudoword reading, the left angular gyrus also was functionally linked to a region in the left superior and middle temporal gyri that is part of Wernicke's area, and to an area in frontal cortex in or near Broca's region. This latter task, where explicit grapheme-to-phoneme transformations are required, would be predicted to engage more fully the interaction of the angular gyrus with other network elements. The fact that correlations between rCBF in the right angular gyrus and extrastriate visual areas in the right hemisphere were not significant indicates that the strong functional connectivity of the angular gyrus observed during reading is more pronounced in the left hemisphere than in the right. Unlike PET analyses that have employed the more traditional "subtraction paradigm," where a reading task is compared with a control task, our results were obtained by investigating the relationship between regional functional activities solely during performance of the reading tasks. Thus, our results are not confounded by what neurons in the angular gyrus might be doing during the control condition.

(*ii*) In men with developmental dyslexia, the strong functional linkages between the left angular gyrus and other left hemisphere regions involved in normal reading were absent, suggesting a functional disconnection of the left angular gyrus from visual areas, from Wernicke's area, and from inferior frontal cortex. Altered rCBF in left parietal cortex has been reported in dyslexia in several studies (7, 16, 33, 34). In addition, Rumsey *et al.* (35) have shown in these subjects that left angular gyral rCBF during single word reading was positively correlated with level of reading skill in the controls, whereas these same correlations were negative in the dyslexic men. Thus, although better reading skill was associated with higher rCBF in controls, in dyslexic men, higher rCBF was associated with more impaired reading (i.e., those dyslexic men who had compensated to some degree used this region less than those who had not), further suggesting an important role for this region in developmental reading disorder.

The loss of functional connectivity in dyslexia between the left angular gyrus and the occipitotemporal region containing V5/MT is interesting in that several reports have suggested a fundamental abnormality in the magnocellular system, of which V5/MT is a part (36), in developmental dyslexia (37, 38). A recent functional magnetic resonance imaging study (39) demonstrated a failure to activate the V5/MT region in response to a moving stimulus in a subset of our dyslexic subjects.

Because the PET data that were used to determine correlations reflect integrated activity over a time interval of about 30–60 sec, the presence of large correlations across subjects indicates that each control subject was using essentially the same systems-level network for performance of these reading tasks. The absence of these large correlations in the dyslexic men demonstrates that as a group they were not using the same network as controls. Each subject has compensated to some degree over his lifetime for a dysfunctional network in the left hemisphere. Whether the functional disconnection of the angular gyrus observed here represents a fundamental problem in dyslexia or is simply the result of compensation awaits further research. Nevertheless, our results suggest that there is a close correspondence between the altered functional connectivity of the left angular gyrus in developmental dyslexia and the anatomical disconnection of this region from other brain areas that are part of the "normal" reading network in acquired alexia.

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