

## NOTES AND DISCUSSION

### Different Neural Circuits Subserve Reading before and after Therapy for Acquired Dyslexia

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Rehabilitative measures for stroke are not generally based on basic neurobiological principles, despite evidence from animal models that certain anatomical and pharmacological changes correlate with recovery. In this report, we use functional magnetic resonance imaging (fMRI) to study in vivo human brain reorganization in a right handed patient with an acquired reading disorder from stroke. With phonological dyslexia, her whole-word (lexical) reading approach included inability to read nonwords and poor reading of function words. Following therapy, she was able to read nonwords and function words, and preferred a decompositional (sub-lexical) strategy in general. fMRI was performed during a reading task before and after treatment. Prior to therapy, her main focus of brain activation was in the left angular gyrus (area 39). After therapy, it was instead in the left lingual gyrus (area 18). This result suggests first that it is possible to alter brain physiology with therapy for acquired language disorders, and second, that two reading strategies commonly used in normal reading use distinct neural circuits, possibly reconciling several conflicting neuroimaging studies of reading. © 1998 Academic Press

## INTRODUCTION

Rehabilitative measures for stroke are generally based on empirical concepts of functional outcome rather than on basic neurological principles. While there is some knowledge about neuropharmacological and neuroanatomical changes that take place after stroke and during stroke recovery, clinical rehabilitation does not generally use this information. Some of the at-

The authors gratefully acknowledge the support of NIH-NIDCD under Grant CD R01-3378-01. Special thanks also to R. Berndt, M. Burton, D. Davis, D. Emge, M. Forbes, C. Genovese, R. Gullapalli, A. Haendiges, P. Hlustik, G. Hoffman, M. McNeil, C. Mitchum, A. Solodkin, and R. Wellington.

tempts to alter the course of neurobiological recovery in animal models (Feeney, Gonzalez, & Law, 1982) and humans (Crisostomo, Duncan, Propst, Dawson, & Davis, 1988; McNeil, Doyle, Spencer, Goda, Flores, & Small, 1997; Small, 1994) have shown promise, but have not yet demonstrated the potential to have a major impact.

The advent of functional neuroimaging permits *in vivo* neuroanatomical investigation in humans, thus opening up many possibilities for stroke rehabilitation research that were not previously available. One potentially important application of this new method is in the study of treatment, where the state of the art depends on empirical assessments of functional outcome, rather than on any theory of neurobiological mechanism. In the present single case study, we applied this technology to the investigation of neuroanatomical reorganization accompanying treatment of an acquired reading disorder in a woman with stroke.

From the framework of cognitive neuropsychology, reading syndromes include those primarily affecting visual processing and others that involve "central" neural processes subsequent to vision. These central syndromes include surface dyslexia, phonological dyslexia, and deep dyslexia (Friedman, 1988; McCarthy & Warrington, 1990).

In surface dyslexia, patients read by using the spelling to sound rules of their language. This becomes noticeable when they use this strategy on irregularly spelled words that do not follow the rules. In phonological dyslexia, patients do the opposite, and read whole words at a time, without invoking spelling to sound correspondences. This becomes evident when patients try to read uncommon words, or in the psychology laboratory, when they are asked to read non-words that have spellings that are consistent with the rules of their language. Since they are only capable of reading whole words at a time, uncommon words and non-words are difficult (or impossible) to read. Many of these patients also have difficulties with words without straightforward semantic interpretations, such as function words. Deep dyslexia combines semantic paralexia with the phonological problems. The anatomy of the central dyslexias remains uncertain, despite a number of case reports including neuropathological or neuroradiological findings (McCarthy & Warrington, 1990).

In this report, we discuss a functional neuroimaging study of a patient with phonological dyslexia and her treatment for spelling to sound conversion deficits (see Flores et al. (1997) for a discussion of the treatment method). The hypothesis was that successful treatment of phonological dyslexia with supervised training of word and nonword reading is accompanied by changes in the neuroanatomical substrate of reading. Imaging was conducted with functional magnetic resonance imaging both before and after therapy. Significant changes took place both in the patient's behavior and in the brain, thus representing an exciting example of how behavioral rehabil-

TABLE 1  
Schedule of fMRI Scans and Relationship to Therapy

fMRI Scan	Time (days)	Baseline testing and treatment time points
1	$t = 0$	Beginning of baseline testing
2	$t = 14$	End of baseline testing and beginning of treatment
3	$t = 38$	End of treatment

itative therapy, motivated by theoretically elaborated cognitive neuropsychological models, can have a direct effect on functional brain organization after stroke.

## METHODS

A 42-year-old right-handed woman had a large left fronto-temporal ischemic stroke at the age of 25 with severe aphasia and hemiplegia. Despite significant recovery in spoken language, reading remained a major problem. The patient demonstrated a pattern of reading consistent with phonological dyslexia; her reading of common (high frequency) words was better than uncommon words, and she could not read nonwords. She read function words poorly. She did not make semantic paralexical errors. We performed therapy using supervised (teacher assisted) learning of grapheme to phoneme correspondences (GPCs) through exemplars. During therapy, the patient learned to read nonwords. She was observed by the therapist to decompose words into parts in order to read them, and to apply this strategy more generally than actually necessary (Flores et al., 1997).

fMRI is a task-dependent activation method, and thus requires comparison of two functional brain states, an "active" condition and a "control" condition (Donders, 1868/1969; Sergent, Zuck, Lévesque, & MacDonald, 1992; Sternberg, 1969). The active condition was a reading version of the Token Test (De Renzi & Vignolo, 1962; McNeil & Prescott, 1978), specifically designed for functional imaging studies, in which the subject decides whether or not a visually presented sentence (e.g., "The red square is above the green circle") describes a picture containing an array of colored tokens. The passive condition consisted of false font text and (the same) visually presented tokens, in which the subject was asked to respond true if the picture showed any squares above any circles and false otherwise. fMRI scans were performed before and after treatment as shown in Table 1. Informed consent was obtained from the subject in accordance with the policies and with the approval of the Institutional Review Board for Biomedical Research of the University of Pittsburgh.

During each trial, active and control tasks were presented alternately for 60 seconds each for 8 minutes. During each 60 second presentation of one task, eight functional images were collected, for a total of 64 images in each trial. Of these, 32 were collected during the main task and 32 during the control task. Each scanning session consisted of four separate trials of stimulus presentation, in which two different sets of sentences and pictures were employed. These corresponded to subtests 6 and 8 of the Revised Token Test (McNeil & Prescott, 1978), adjusted for use in reading and for neuroimaging experiments. The total data analyzed thus consisted of 128 scans acquired during performance of the main task and 128 scans acquired during performance of the control task. The actual time series of scan acquisition consists of 8 scans of one task followed by 8 scans of the other, in a repetitive pattern for a total of 16 condition pairs.

Functional imaging employed the spiral k-space method (Noll, Cohen, Meyer, & Schneider,

1995) on a 1.5 T GE Signa scanner with a standard clinical head coil. One complete multi-shot (four spirals) scan of the entire brain (20 slices) was performed in 7.5 seconds. Images were obtained in the sagittal plane with a 7 mm interslice interval and a 3.7 mm resolution in the imaging plane. Movement artifacts were minimized at scan time with head immobilization. Part of the image analysis pathway also employed image registration (Woods, Cherry, & Mazziotta, 1992) for further compensation of movement artifact as well as MR angiography, which was used to exclude the presence of vascular artifacts.

Each imaging session consisted of four eight-minute experimental runs, yielding four time series of data, consisting of 64 time points at each voxel location in the image (24 slices). Since each time series was collected at a different time (between 8 and 24 minutes apart), the MRI scanner could experience signal drift and the subject could change location. Thus the first analysis step was to normalize each time series to a zero mean and to apply a detrending procedure to remove changes in the baseline signal (Cox, 1997), and the second step was to co-register all the images together using the 3D version of the automated image registration algorithm (Woods et al., 1992).

The four resulting time series were concatenated together, and a reference sinusoidal waveform was cross-correlated with the concatenated time series (Bandettini, Jesmanowicz, Wong, & Hyde, 1993). The cross-correlation was performed with sine waves offset by 0, 7.5, 15, 22.5, and 30 degrees (0, 2.5, 5, 7.5, 10 seconds) and the best match retained to account for hemodynamic lag (Bandettini et al., 1993).

A correlation coefficient threshold of  $r = 0.45$  was used for all further analyses of the data of all three imaging sessions. In order to reduce false positives and to minimize the effects of multiple comparisons, a minimum cluster size threshold (using a 3D neighborhood of 28 voxels) of 4 voxels (4 voxels = 98.4 mm<sup>3</sup>) was used. The active regions shown in the tables all meet this criterion. The total activation numbers, used to show fractional activations, are shown including all voxels regardless of minimum cluster size.

## RESULTS

The main results of the study are summarized in Tables 2 and 3 and Figs. 1–3. Several features of these results are important for the understanding of phonological dyslexia and its treatment. First, the primary site of activation at the two time points prior to treatment is the angular gyrus of the left inferior parietal lobule (Brodmann's area 39). This activation is highly robust and is consistent with historical literature on visual language processing (Dejerine, 1891). The fractional activation in this region increased during the period of baseline testing, when the patient was exposed to a large number of words but not given any instruction on sublexical reading. The center of the left angular gyrus activation during this period of whole word (lexical) reading was at Talairach coordinates (−51, −64, 36) (Scan 1).

Second, although this inferior parietal site of activation remains after training, it is much less prominent, with the most active site of activation being the area of the left lingual gyrus (BA 18). This region of activation is very reliable over the course of four experimental runs, and is consistent with PET studies of single word processing (Petersen, Fox, Posner, Mintun, & Raichle, 1988). The center of the left lingual gyrus activation during this period of phonological (sub-lexical) reading was at Talairach coordinates (−16, −79, −10) (Scan 3).

TABLE 2

Characteristics of Brain Activation Patterns in Phonological Dyslexia before and after Learning Grapheme Phoneme Correspondences

Hemisphere	Sign	Anatomical region	Volume	Fraction	Brodman
Scan 1: Before baseline testing					
L	+	Supplementary motor area	0.12	0.17	6/m
L	+	Lateral premotor area	0.25	0.33	6/l
L	+	Angular gyrus	0.37	0.50	39
Scan 2: After baseline testing and before therapy					
L	+	Supplementary motor area	0.22	0.12	6/m
L	+	Lateral premotor area	0.37	0.21	6/l
L	+	Pre-cuneate area	0.17	0.10	7
L	+	Angular gyrus	0.57	0.32	39
L	+	Lingual gyrus	0.37	0.21	18li
R	+	Prefrontal cortex	0.10	0.05	46
R	-	Middle temporal gyrus	0.15	0.08	22
Scan 3: After therapy					
L	+	Precentral gyrus	0.10	0.06	4
L	+	Lateral premotor area	0.25	0.16	6/l
L	+	Pre-cuneate area	0.10	0.06	7
L	+	Angular gyrus	0.10	0.06	39
L	+	Cuneate gyrus	0.17	0.11	18cu
L	+	Lingual gyrus	0.69	0.44	18li
R	+	Cuneate gyrus	0.15	0.10	18cu
R	-	Middle temporal gyrus	0.37	0.24	22

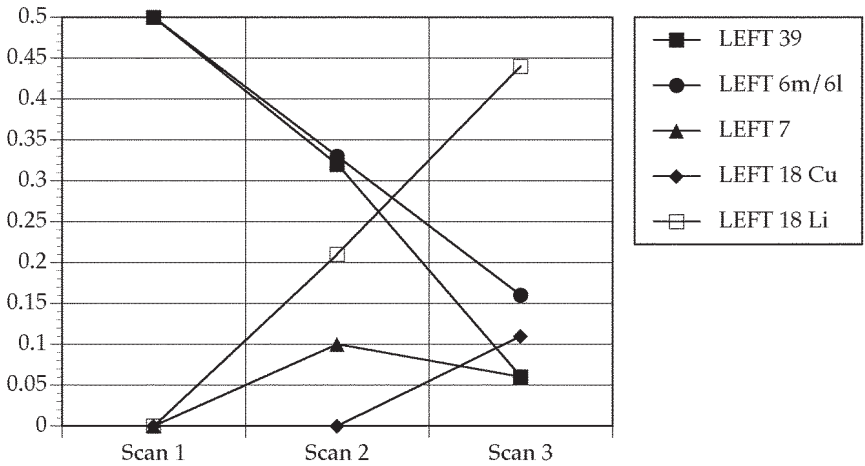
*Note.* Key: Hemisphere: Left (L) or Right (R); sign: Positive activation (+) or negative activation (-); anatomical region: Gyrus and/or functional region; volume: shown in cubic centimeters; for conversion to voxels, divide by 0.0246 cc<sup>3</sup> or 24.6 mm<sup>3</sup>, the size of one voxel (1.875 × 1.875 × 7); Fraction: Fraction of total positive activation in the brain (negative activation is also expressed in terms of the total positive activation for perspective); Brodman: Brodman's areas.

TABLE 3

Left Hemisphere Activation Volume by Regions

Brodman area	Scan 1	Scan 2	Scan 3
Areas 6m/6l	0.37 (0.50)	0.59 (0.33)	0.25 (0.16)
Area 7	0.00 (0.00)	0.17 (0.10)	0.10 (0.06)
Area 18 cu	0.00 (0.00)	0.00 (0.00)	0.17 (0.11)
Area 18 li	0.00 (0.00)	0.37 (0.21)	0.69 (0.44)
Area 39	0.37 (0.50)	0.57 (0.32)	0.10 (0.06)
Other (7, 8, 9, 46)	0.00 (0.00)	0.00 (0.00)	0.10 (0.06)

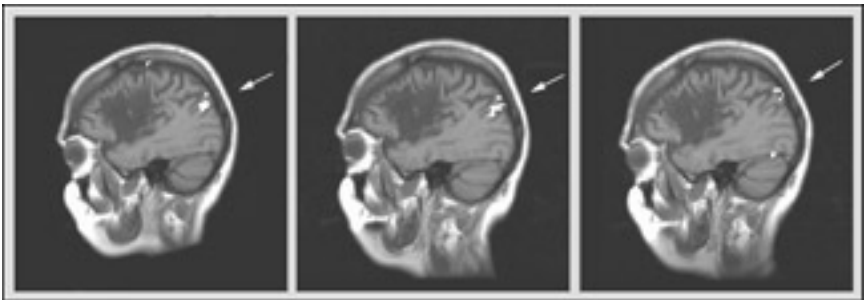
*Note.* Volumes are the regional volumes in cc<sup>3</sup> (see previous legend); in parentheses are the fractions of total positive brain activation. Brodman's areas 6m and 6l refer respectively to the medial and lateral portions of premotor area 6; areas 18 cu and 18 li refer respectively to the cuneate and lingual portions of visual area 18.



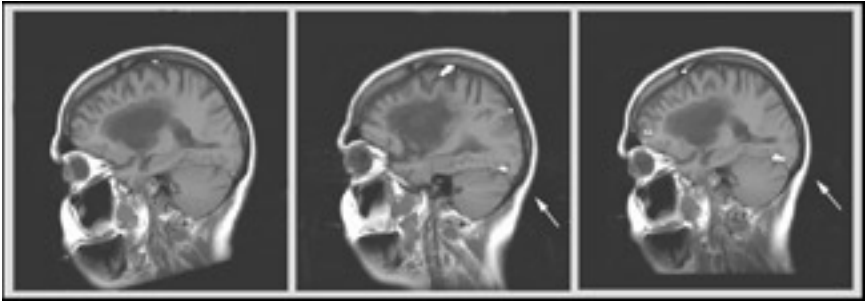
**FIG. 1.** Graph showing changes in fractional activation of five regions of interest over the course of baseline testing (scans 1–2) and treatment (scans 2–3). Numbers shown in the legend are Brodmann areas, with area 6 including medial and lateral portions, and area 18 divided into cuneate and lingual portions.

## DISCUSSION

The present study demonstrates that in the case of a specific neuropsychologically defined syndrome and a theoretically motivated treatment method, functional MRI can assess the neuroanatomical changes that accompany successful behavioral therapy in aphasia. In the case of our patient with phonological dyslexia, fMRI showed that learning how to make grapheme to phoneme correspondences led to functional neuroanatomical changes. With decreased use of whole word (lexical) reading strategies came decreased



**FIG. 2.** Activation in the inferior parietal lobule (a) before baseline testing; (b) after baseline testing and before therapy; and (c) after therapy. All regions have cluster size  $\geq 4$  and  $r \geq 0.45$  and are indicated by arrows.



**FIG. 3.** Activation in the lingual gyrus (a) before baseline testing; (b) after baseline testing and before therapy; and (c) after therapy. All regions have cluster size  $\geq 4$  and  $r \geq 0.45$  and are indicated by arrows (except for (a) which has no activation in that region). Note that scan (b) also shows activation in lateral premotor cortex.

reliance on the dominant left angular gyrus (50% of total activation in scan 1; 6% of total activation in scan 3); and with greater use of decompositional (phonological; sublexical) reading strategies came increased reliance on the dominant left lingual gyrus (44% of total activation in scan 3; 0% of total activation in scan 1).

In the primary sensory and motor cortices of animals, relevant experience changes cortical structure/function relationships. The present study shows an analogous change in human language reorganization. Several common features of anatomy and physiology underlie these changes in both cases: First is that functional encodings in the cerebral cortex are dynamic; second is that functional anatomy changes by unmasking existing circuits and altering synaptic connectivity; and third is that experience of the subject can induce these changes.

The dynamic nature of these functional encodings is best demonstrated by the experience-induced functional anatomical changes that occur rapidly (Gilbert, 1992). These changes take place through the "unmasking" of circuits that follow pre-existing anatomical connections (Jacobs & Donoghue, 1991), and have been postulated to explain fast reorganization in motor, sensory, and visual systems after stroke (Das & Gilbert, 1995; Jacobs & Donoghue, 1991; Kaas, Krubitzer, Chino, Langston, Polley, & Blair, 1990; Keller, Weintraub, & Miyashita, 1996). On the longer time frame (i.e., months or years), axonal sprouting and synaptogenesis may mediate more substantial anatomical changes and concomitant improvements in recovery (Gilbert, 1992).

Functional cortical reorganization seems to depend on the nature of practice, rather than simply on its presence (Nudo, Wise, SiFuentes, & Milliken, 1996; Taub, Miller, Novack, Cook, Fleming, Nepomuceno, et al., 1993). Our patient with phonological dyslexia was trained using a particular method of supervised training with exemplars of words and nonwords. This training

successfully taught her to read by a sublexical route (Flores et al., 1997), and with fMRI, it was possible to show that the functional neuroanatomy of her reading accompanied this change in behavior.

Within the framework of the cognitive theories of reading, (at least) two mechanisms are postulated, one involving visual decomposition and conversion of small visual components to their verbal syllabic counterparts (grapheme to phoneme conversion), and the second incorporating whole word recognition (Coltheart, Curtis, Atkins, & Haller, 1993). The patient described here was able to read well using the whole word route prior to any therapy, but was not able to use the decompositional route. After therapy, she was able to decompose words into constituent graphemes and successfully read these strings that are not supported by either frequent occurrence or lexical semantics. In fact, after therapy, the patient was noted by the research therapist to do this as a general strategy when trying to read (Flores et al., 1997).

The nature of this functional reorganization might have been expected on the basis of neuropsychological theory regarding the central dyslexias. Previous functional neuroanatomical research on single word reading has implicated two different areas in the processing of single words presented visually. The first such study, performed using PET technique, suggested that the left medial extrastriate cortex played a special role in processing words and pseudo-words and not false font strings or consonant clusters (Petersen et al., 1988; Petersen, Fox, Snyder, & Raichle, 1990). A subsequent study, incorporating a task design aimed at eliminating the contributions of phonological processing, suggested that the left posterior superior temporal gyrus, adjacent to "the classical location of visual word forms, namely the angular gyrus", plays the primary role in visual word processing (Howard, Patterson, Wise, Brown, Friston, Weiller, et al., 1992). This reaffirmed a long-standing belief in neurology about the localization of "visual word forms" (Dejerine, 1891), and was subsequently replicated using fMRI technique (Small, Noll, Perfetti, Hlustik, Wellington, & Schneider, 1996).

An important finding of the present study is that it may help reconcile these two apparently conflicting PET studies of single word reading. The patient described here undoubtedly used a whole word reading strategy prior to therapy. This is the only strategy available to patients with phonological dyslexia, and was used exclusively by this patient at the time of the first two fMRI scans. It is possible that between the first and second scans, when the patient was exposed to many words as part of baseline testing of reading, she developed some subtle improvement in phonological reading. However, based on formal testing and intuitive observation, this was not a profound improvement.

The area of activation present during reading prior to therapy is very close to the area implicated in single word reading in neurological tradition (Dejerine, 1891; Dejerine, 1892) and neuroimaging studies (Howard et al., 1992; Small et al., 1996). This area showed decreased activation after ther-



apy—could it be particularly important to the whole word reading mechanism? The occipital area present after therapy includes significant overlap with the left medial extrastriate region that activated in the original PET study of single word reading (Petersen et al., 1988) and was found later to become active only for strings in which a graphemic decomposition was possible (Petersen et al., 1990). Since our patient preferred a decompositional strategy at all times after therapy (often using her finger or an index card to mark visually the graphemic components of presented strings), the imaging results suggest that the functional brain reorganization in this patient led to unmasking of circuits in the occipital cortex that are ordinarily employed as the initial stages in phonological (decompositional) reading.

Two additional findings will not be discussed at length. First is the involvement of medial and lateral supplementary motor areas in the present reading task, which declined over time. Although these areas have not generally been present in studies of single word reading, they may reflect the processing of entire sentences when timing issues play a larger role. Second is the increasing de-activation of the right middle temporal gyrus over time. It might be speculated that deactivation of some right hemisphere regions homologous to important language areas in the left hemisphere is required for successful phonological reading.

The present study demonstrates that therapy for phonological dyslexia, which changed reading from a whole word to a decompositional approach, leads to specific changes in the pattern of brain activation, predicted by neuropsychological theory and previous neuroimaging studies of normal subjects. For aphasia therapy, this result suggests that specific therapeutic methods can alter the neurophysiology of language. For basic cognitive neuroscience, this result may help understand two neuroimaging studies of single word reading in terms of current theory in the neuropsychology of reading. Finally, this study suggests a fundamental relationship among cognitive neuropsychological theory, aphasia therapy, and basic neuroscience.

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