Role of the Right and Left Hemispheres in Recovery of Function during Treatment of Intention in Aphasia

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Abstract

Two patients with residual nonfluent aphasia after ischemic stroke received an intention treatment that was designed to shift intention and language production mechanisms from the frontal lobe of the damaged left hemisphere to the right frontal lobe. Consistent with experimental hypotheses, the first patient showed improvement on the intention treatment but not on a similar attention treatment. In addition, in keeping with experimental hypotheses, the patient showed a shift of activity to right presupplementary motor area and the right lateral frontal lobe from pre- to post-intention treatment functional magnetic resonance imaging (fMRI) of language production. In contrast, the second patient showed improvement on both the intention and attention treatments. During pre-treatment fMRI, she already showed lateralization of intention and language production mechanisms to the right hemisphere that continued into post-intention treatment imaging. From pre- to post-treatment fMRI of language production, both patients demonstrated increased activity in the posterior perisylvian cortex, although this activity was lateralized to left-hemisphere language areas in the second but not the first patient. The fact that the first patient’s lesion encompassed almost all of the dominant basal ganglia and thalamus whereas the second patient’s lesion spared these structures suggests that the dominant basal ganglia could play a role in spontaneous reorganization of language production functions to the right hemisphere. Implications regarding the theoretical framework for the intention treatment are discussed.

INTRODUCTION

Intention is selection for execution of one action among competing actions and initiation of the selected action. Intention involves the medial frontal cortex (supplementary motor area [SMA], pre-SMA, rostral cingulate zone), lateral frontal structures, and basal ganglia loops (Heilman, Watson, & Valenstein, 2003). Intention systems support language by facilitating word selection and initiation of speech. Recent data show how intention systems influence language production. Crosson, Benefield, et al. (2003) described a loop consisting of the dominant pre-SMA, dorsal caudate nucleus, and ventral anterior thalamus that is involved in generating words, but not in generating nonsense syllables. Further, Crosson, Sadek, et al. (2001) demonstrated that the dominant pre-SMA is involved in word generation but not in word repetition, and Moore et al. (unpublished data) have demonstrated a similar pattern for the dorsal caudate nucleus. Based on these data, it was concluded that the dominant pre-SMA—dorsal caudate—ventral anterior thalamic loop is involved in activation and selection of preexisting lexical representations during word generation. Specifically, in light of the works of Copland (2003) and Copland, Chenery, and Murdoch (2000), it was suggested that pre-SMA creates a rapid, automatic bias toward selection of a particular word and that the basal ganglia maintain this response bias so that it can influence conscious, top–down processing during word selection.

Crosson, Benefield, et al. (2003) also found robust activity of the nondominant basal ganglia in the absence of significant nondominant frontal activity during word generation but not during nonsense syllable generation. These data suggested that the right basal ganglia mediate suppression of right frontal activity by left pre-SMA during word generation to prevent interference with left-hemisphere processes. The proposed roles of the basal ganglia (i.e., maintaining response biases and suppressing right frontal activity) are consistent with conceptualizations of the basal ganglia as facilitating desired and suppressing undesired...
behaviors (e.g., Mink, 1996; Penney & Young, 1986) and with the bilateral projections of left pre-SMA to the basal ganglia (Inase, Tokuno, Nambu, Akazawa, & Takada, 1999).

These concepts regarding intention and language are applicable to aphasia. First, patients with parietal lesions showed improved language performance when stimuli for language tasks were shifted into ipsilesional hemispace (Coslett, 1999; Anderson, 1996). If manipulation of spatial attention mechanisms improves language performance, then manipulation of intention also could impact language output in aphasia. Second, because nonfluent aphasia is characterized by difficulty initiating and maintaining language output and by word-finding difficulty, we characterize it as a disorder of intention (i.e., a difficulty in selecting words for production and initiating spoken output). For these reasons, the relationship between intention and language systems in nonfluent aphasia must be explored.

In ischemic strokes, middle cerebral artery events causing nonfluent aphasia damage lateral frontal but not medial frontal structures involved in intentional aspects of language. A growing number of studies indicate that good recovery of language functions in nonfluent aphasia is accompanied by greater perilesional than right-hemisphere reorganization, whereas poor recovery is accompanied by greater right-hemisphere than perilesional reorganization (Rosen et al., 2000; Cao, Vikingstad, George, Johnson, & Welch, 1999; Karbe et al., 1998; Heiss et al., 1997). In addressing the intention deficit in severe and persistent cases of nonfluent aphasia, we assume that right frontal activity represents an attempt of right frontal structures to assume language production functions, although other interpretations are possible (e.g., Rosen et al., 2000). Further, although right lateral frontal mechanisms become active in severe nonfluent aphasia, left medial frontal structures remain active during language generation (Karbe et al., 1998). At best, combined left medial frontal and right lateral frontal activity in word production is likely to be an inefficient way to enhance word selection and language initiation. At worst, if interpretation of recent data (Crosson, Benefield, et al., 2005) is correct, left medial frontal structures (i.e., pre-SMA) may suppress right lateral frontal activity (via the right basal ganglia), thus, decreasing the efficiency of its word production processes.

These ideas were the theoretical motivation for development of an intention treatment for patients with chronic, nonfluent aphasia. In this treatment, patients initiate word-finding trials with a complex (multistage) left-hand movement in their left hemispace. Pairing the complex left-hand movement with the naming task is thought to prime a right medial frontal intention mechanism that can enhance word production because this mechanism is located in right pre-SMA adjacent to the region subserving complex left-hand movements (Picard & Strick, 1996). Given the connections between pre-SMA and lateral prefrontal cortex (e.g., Picard & Strick, 1996; Matsuzaka, Aizawa, & Tanji, 1992) and the functional relationship that can be inferred from this linkage, a resulting increase in right pre-SMA activity should enhance right lateral frontal activity as right pre-SMA assumes intention functions for language. The fact that the medial (pre-SMA) activity precedes the lateral frontal activity (Abdullaev & Posner, 1998) also is supportive of the influence of the former on the latter. Preliminary studies of this treatment showed that it enhances performance of nonfluent aphasia patients in picture naming over baseline performance levels (Richards, Singletary, Rothi, Koehler, & Crosson, 2002) and that the intention component (i.e., the complex left-hand movement) is an active component of the treatment for patients with moderate to severe chronic nonfluent aphasia (Richards, Wierenga, et al., 2003). The purpose of the current study was to provide a preliminary test of neuroanatomic assumptions underlying the treatment using pre- and post-treatment functional magnetic resonance imaging (fMRI).

Two patients with residual nonfluent aphasia and anomia (A008 and X030) received the experimental intention treatment and a similar attention treatment without the intention component. Based upon the above review, we developed the following hypotheses:

Hypothesis 1. Because nonfluent aphasia is an intentional disorder, these patients will show improvement on the intention but not the attention treatment.

Hypothesis 2. Shifts of pre-SMA and lateral frontal activity from the left to the right hemisphere should be visible through pre- and post-intention treatment fMRI of language production.

RESULTS
Patient A008

Treatment

Generally, A008’s performance was consistent with experimental hypotheses. Performance on the 40 daily treatment probes is plotted in Figure 1. For each treatment, performance on these daily probes was analyzed with the C statistic (Tryon, 1982) for baseline alone and for baseline plus the three treatment phases. For the intention treatment (Figure 1A), baseline performance was stable (Z = 0.38, p > .05), and the patient made significant improvement during treatment (Z = 3.19, p < .01). For the attention treatment (Figure 1C), baseline performance was stable (Z = 1.10, p > .05), but the patient made no significant gains during treatment (Z = 1.55, p > .05). Thus, A008’s
performance was consistent with the hypothesized specificity of improved naming for the intention treatment (Hypothesis 1).

**fMRI for Frontal and Subcortical Activity**

fMRI data for an event-related category–member-generation task were obtained immediately before onset and after completion of the intention treatment series. During the pre-treatment fMRI session, patient A008 generated correct responses to 24 of 45 categories; the average time between category presentation and response was 8.68 sec ($SD = 3.72$). During the post-treatment session, he generated correct responses to 32 of 45 categories; the average time between category presentation and response was 4.80 sec ($SD = 2.39$).

The statistical threshold for significant activity was $R^2 \geq .20$, and only clusters $\geq 150$ µL were interpreted. Figure 2A and C shows activity on coronal images through the frontal lobes for pre- and post-treatment fMRI during word generation, respectively.

For pre-treatment images, activity predominated in left versus the right pre-SMA and activity was relatively equal between the left and right lateral frontal lobes, but for post-treatment images, a dramatic increase in right medial and especially right lateral frontal activity occurred. In Figure 3A, total volumes of significant activity were plotted pre- and post-treatment for the left and right pre-SMA, lateral frontal lobe, basal ganglia, and thalamus. Table 1 displays the percentage of total left plus right hemisphere activity located in the right hemisphere for each region of interest (ROI) and indicates

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**Figure 1.** Performance on treatment probes. Participants were given picture-naming probes daily during baseline and before each treatment session. Intention treatment performance for A008 (A) and for X030 (B) are shown; attention treatment performance is shown for A008 (C) and for X030 (D). In keeping with the first experimental hypothesis, A008 demonstrated significant improvement on treatment probes during the intention treatment (A), but did not show significant improvement on treatment probes during the attention treatment (C). Although X030 also demonstrated significant improvement on treatment probes during the intention treatment (B), the fact that she also showed improvement on treatment probes during the attention treatment (D) was not consistent with the first hypothesis that improved performance would be specific to the intention treatment.
whether the degree of lateralization was significant. Although activity increased in both pre-SMAs from pre- to post-treatment, the increase was proportionately much larger in right than left pre-SMA. For pre-SMA, activity was significantly left lateralized during pre-treatment imaging ($Z = -2.05, p < .05$), but showed no significant lateralization during post-treatment scanning ($Z = -0.53, p > .05$). In contrast, activity in the left lateral frontal lobe dropped slightly from pre- to post-treatment imaging, but activity in the right lateral frontal lobe more than doubled from pre- to post-treatment imaging. There was no significant lateralization of lateral frontal activity during pre-treatment imaging ($Z = -0.99, p > .05$), but a strong predominance of right over left lateral frontal activity occurred during post-treatment imaging ($Z = 5.08, p < .001$).

Within the major ROIs listed in Figure 3A, a description of the specific areas of change from pre- to post-treatment imaging is as follows. During pre-treatment imaging, all left lateral frontal activity was located in the prefrontal cortex, with the bulk of the activity (1202 µL of a total of 1808 µL) located in the superior frontal sulcus. During post-treatment imaging, the bulk of left lateral frontal activity (1010 µL out of a total 1524 µL) shifted to motor cortex. For right lateral frontal cortex, the bulk of pre-treatment activity (1221 µL out of a total 1418 µL) was located in motor cortex, but post-treatment, activity was distributed in motor, premotor, and prefrontal cortex, with the bulk of the activity (2345 µL out of a total 3899 µL) residing in premotor cortex. Other changes in activity involved the emergence of activity in the right dorsal caudate nucleus and in the medial Brodmann’s area 8 bilaterally during post-treatment imaging whereas no such activity was present during pre-treatment imaging. These findings are generally consistent with the second hypothesis in that right pre-SMA activity increased from a subordinate to a nearly equal level of activity from pre- to post-treatment imaging.
post-treatment imaging, and in that lateral frontal activity clearly shifts from equality between hemispheres to right-hemisphere predominance at post-treatment imaging.

**fMRI for Posterior Cortical and Paralimbic Activity**

Figure 3C shows activity in various posterior and paralimbic regions pre- and postintention treatment. Changes in activity from pre- to post-treatment images can be described as follows. During pre-treatment imaging, only two posterior regions demonstrated significant activity: the right parahippocampal gyrus (410 μL) and left visual association cortex (190 μL). By contrast, during post-treatment imaging of word generation, significant activity occurred in the left (831 μL) and right (634 μL) visual association cortices. Activity in the visual areas was not laterализed during post-treatment scanning ($Z = -0.66, p > .05$). In paralimbic cortices, activity occurred in the left (214 μL) and right (376 μL) retrosplenial regions and in the right parahippocampal gyrus (550 μL). Thus, post-treatment paralimbic activity was significantly lateralized to the right hemisphere ($Z = 3.81, p < .001$). During post-treatment scanning, some activity was demonstrated in traditional language areas of the left hemisphere: angular and supramarginal gyri (182 μL) and superior temporal sulcus and superior temporal gyrus (660 μL); however, activity also occurred in the right superior temporal sulcus (494 μL). Thus, activity in the inferior parietal/superior temporal ROIs was not significantly lateralized ($Z = 1.36, p > .05$). During post-treatment scanning, significant activity emerged in the left precuneus (385 μL) that was not apparent on pre-treatment imaging.
Table 1. Percent of Bilateral Activity in Right Hemisphere (Right Total Volume/[Left Total Volume + Right Total Volume])

<table>
<thead>
<tr>
<th>Structure</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral frontal</td>
<td>0.439</td>
<td>0.719***</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Pre-SMA</td>
<td>0.254*</td>
<td>0.465</td>
<td>0.912***</td>
<td>0.798</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>–</td>
<td>–</td>
<td>0.000</td>
<td>0.151***</td>
</tr>
<tr>
<td>Thalamus</td>
<td>–</td>
<td>–</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Inferior parietal/ superior temporal</td>
<td>–</td>
<td>0.370</td>
<td>–</td>
<td>0.086***</td>
</tr>
<tr>
<td>Visual cortex</td>
<td>0.000</td>
<td>0.433</td>
<td>0.460</td>
<td>0.783**</td>
</tr>
<tr>
<td>Paralimbic cortex</td>
<td>1.000</td>
<td>0.812***</td>
<td>0.618</td>
<td>–</td>
</tr>
</tbody>
</table>

Although binomial tests could not be done on ratios of 1.000 or 0.000, they also should be considered highly significant.

*p < .05, **p < .01, ***p < .001 that activity is significantly lateralized (i.e., deviates from .500 according to binomial equation).

Patient X030

Treatment

Generally, X030’s performance departed from assumptions underlying experimental hypotheses. For the intention treatment (Figure 1B), performance over the last eight baseline sessions was stable (Z = 0.30, p > .05), and the patient made significant improvement during treatment (Z = 5.40, p < .01). However, for the attention treatment (Figure 1D), performance was stable over the last eight baseline sessions (Z = 0.90, p > .05), and the patient also made significant gains during treatment (Z = 5.16, p < .01). Thus, unlike A008, X030’s performance was not consistent with Hypothesis 1. Specifically, she made improvement on both the intention and attention treatments rather than exclusively on the intention treatment.

fMRI for Frontal and Subcortical Activity

fMRI data for the event-related category–member-generation task were obtained immediately before onset and after completion of the intention treatment series. During pre-treatment fMRI, patient X030 gave correct responses to 41 of 45 items on the category–member-generation task, and the average time between category presentation and response was 6.11 sec (SD = 2.37). During the post-treatment session, she gave correct responses to 44 of 45 items, and the average time between category presentation and response was 6.74 sec (SD = 1.76). Clusters of activity with $R^2 \geq 0.20$ and volume \(\geq 150\) µl were interpreted. Figure 2B and D shows activity on coronal images through the frontal lobes for pre- and post-treatment fMRI of word generation, respectively. Figure 3B shows total volumes of significant activity pre- and post-treatment for the major divisions of the frontal lobe and subcortical nuclei, and Table 1 displays the percentage of total left and right hemisphere activity that was located in the right hemisphere for each ROI.

Even for preintention treatment images, activity clearly predominated in the right versus the left medial and lateral frontal lobe. Activity within specific areas of the larger ROIs from Figure 3B and changes in activity from pre- to post-treatment imaging can be described as follows. During pre-treatment scanning, all lateral frontal activity was in the right hemisphere and pre-SMA activity also was significantly right lateralized (Z = 3.71, p < .001). In the right lateral frontal lobe, the bulk of the activity (935 µl of a total of 1413 µl) was in the motor cortex, with remaining activity residing in the inferior frontal sulcus. pre-treatment, activity also appeared in right SMA (156 µl), the right dorsal medial thalamus (408 µl), and the left dorsal caudate nucleus (191 µl). Although frontal activity continued to be 100% right lateralized post-treatment, the degree of pre-SMA lateralization was no longer significant. There was a decrease in both right lateral frontal and right pre-SMA activity (Figure 3B) after treatment. Right frontal activity was limited to motor cortex post-treatment, and activity appeared in the right dorsal caudate nucleus (321 µl) that was not present before treatment. Left basal ganglia activity increased 10-fold, occupying foci in the dorsal caudate nucleus (1353 µl), putamen (575 µl), and nucleus accumbens (193 µl). Thus, basal ganglia activity was significantly left lateralized post-treatment (Z = 5.47, p < .001). Activity in the right thalamus (152 µl) shifted from the dorsal medial nucleus to the pulvinar, and activity appeared in left SMA that had not been present before treatment.

fMRI for Posterior Cortical and Paralimbic Activity

Activity within specific areas of the larger ROIs from Figure 3B and changes in activity from pre- to post-treatment imaging can be described as follows. pre-treatment, posterior cortical activity was dominated by the visual system, including primary visual cortex, first-order visual association cortex, and the ventral visual stream (Figure 3B). There were 2080 µl of activity in left-hemisphere visual cortex and 1772 µl of activity in right-hemisphere visual cortex, yielding no significant lateralization pre-treatment (Z = −0.69, p > .05). In addition, right primary and first-order auditory association cortex demonstrated activity pre-treatment (549 µl). Other regions of posterior cortical activity during pre-treatment imaging included the left (181 µl) and right (455 µl) superior parietal lobe. Paralimbic regions of activity included the left (257 µl) and right (416 µl) retrosplenial cortex, yielding no significant lateralization of paralimbic activity during pre-treatment imaging (Z = −0.74, p > .05).
After treatment, there was a shift of posterior cortical activity into traditional language areas of the dominant hemisphere. Specifically, there was a large amount of activity in the left supramarginal and angular gyri (997 µL) and in the left superior temporal gyrus (639 µL). Although some activity occurred in the right supramarginal gyrus (153 µL) during post-treatment imaging, activity in the inferior parietal/superior temporal ROI was significantly lateralized to the left hemisphere (Z = −5.47, p < .001). Activity in the visual cortex was reduced in both the left (191 µL) and the right (969 µL) hemispheres, compared with pre-treatment levels and was significantly lateralized to the right hemisphere (Z = 2.49, p < .01). There was no paralimbic activity during post-treatment scanning, but there was activity in the right parietal lobe (394 µL) outside of the inferior parietal lobule.

DISCUSSION

Patient A008’s findings were consistent with experimental hypotheses. In keeping with the hypothesis that patients with residual nonfluent aphasia would benefit from the intention but not the attention treatment, his performance on daily treatment probes improved on the intention but not the attention treatment. Consistent with the second experimental hypothesis, he demonstrated shifts in lateralization of frontal functions from pre- to postintention treatment fMRI sessions. Pre-SMA activity shifted from strongly lateralized to the left hemisphere to nearly equal left and right hemisphere activity, and lateral frontal activity shifted from relatively equal activity between the hemispheres to activity strongly lateralized to the right hemisphere.

In contrast, patient X030’s findings were not consistent with our hypotheses. Contrary to the first experimental hypothesis, she showed improved performance on daily treatment probes for both the intention and attention treatments. Further, during pre-treatment imaging, lateral frontal activity was already completely lateralized to the right hemisphere, with no significant left and a large volume of right lateral frontal activity, and pre-SMA activity was nearly completely lateralized to the right hemisphere, with a large volume of right pre-SMA activity and only marginal left pre-SMA activity. Post-treatment, although this patient showed a reduction in right frontal activity, lateral frontal activity still was completely right lateralized. However, lateralization of pre-SMA activity to the right hemisphere no longer reached significance (too few acquisition voxels were involved in either hemisphere to reach significance). Based on different patterns of performance on treatment probes and on different patterns of frontal activity during pre- and post-treatment fMRI, we conclude the two patients demonstrated different underlying mechanisms for improvement during treatment. Thus, theoretical assumptions of the intention treatment must be reexamined. To guide further investigation of this treatment, we developed hypotheses to explain the performance of both patients.

Three hypotheses are presented to account for these data; subsequently, the supporting evidence for each hypothesis will be discussed. (1) The novel treatment for intention in aphasia that the two patients received relies on two phenomena. The first phenomenon is transfer of language production procedures to the right frontal lobe. The second phenomenon is formation of associations between newly established procedures for word production in the right frontal cortex and existing lexical–semantic knowledge in the posterior left hemisphere. (2) If the basal ganglia in the left hemisphere are intact, they can participate in the suppression of left lateral frontal activity, facilitating the transfer of language production procedures to the right frontal lobe. (3) For the intention treatment to work in nonfluent aphasia, it is necessary to tap preserved lexical–semantic knowledge in posterior left-hemisphere structures.

The Two Phenomena Responsible for Treatment Effects

Patient A008’s performance was representative of both phenomena responsible for treatment change. Before treatment, his word-production performance was dominated by left- as opposed to right-hemisphere activity in pre-SMA, and lateral frontal activity was split relatively equally between the hemispheres. After treatment, there was a clear dominance of right over left lateral frontal activity during word production as well as a substantial increase in right pre-SMA activity. This pattern suggests the patient was transferring language production mechanisms to the right frontal lobe. Further, the inability to improve when the intention component (i.e., complex left-hand movement) was removed during the attention treatment demonstrated his dependence on the intention component of treatment to enhance learning in word production. He also showed recruitment of posterior perisylvian cortex during post-treatment imaging, although this activity was not lateralized.

Patient X030’s performance was representative primarily of the second phenomenon in which associations were established between motor patterns in the right frontal region and lexical–semantic knowledge. Before treatment, lateral frontal activity already was completely right lateralized, and pre-SMA activity was strongly right lateralized. After treatment, although right lateral frontal activity decreased, it still was entirely right lateralized, although lateralization of pre-SMA activity to the right hemisphere was no longer significant. Indeed, we believe that reduction of right lateral frontal and pre-SMA activity from pre- to postintention treatment may have indicated an increased efficiency of language production mechanisms within the right hemisphere.
Utilization of preserved left-hemisphere lexical–semantic knowledge was manifested in X030 by engagement of left posterior perisylvian mechanisms (supramarginal, angular, and superior temporal gyri) only after and not before completion of the intention treatment. These regions have long been thought to be involved in lexical–semantic processing (e.g., Alexander, 2003). This analysis for patient X030 raises two questions. The first is why language production activity is right lateralized before treatment. The second is how the intention treatment facilitated recruitment of existing lexical–semantic knowledge in the left posterior perisylvian cortex.

**Suppression of Left Frontal Activity through the Left Basal Ganglia**

A major difference between the two patients that bears upon the first question was that X030’s lesion did not encompass the left basal ganglia and thalamus, whereas A008’s lesion destroyed these structures almost completely. Could the intact left basal ganglia and thalamus have allowed X030 to transfer language production mechanisms to the right frontal lobe even before the treatment intended to provoke this transfer? Although the status of the dominant basal ganglia usually has been ignored in functional imaging studies of language after stroke, Kim, Ko, Parrish, and Kim (2002) addressed this issue. Although they used fMRI of silent language generation during which both correct and incorrect responses mostly likely were imaged, their findings were consistent with our pre-treatment data. Specifically, the three patients with left fronto-temporal lesions and intact basal ganglia showed strongly lateralized right frontal activity. Lesion location and fMRI lateralization of frontal activity are consistent with those of X030. On the other hand, Kim et al.’s three patients with left basal ganglia plus fronto-temporal lesion showed bilateral frontal activity. This lesion location and lateralization of frontal functions are consistent with those of A008. Thus, taken together, our pre-treatment findings and the findings of Kim et al. indicate that lateralization of language production to the right hemisphere occurs in patients whose lesions are confined to left fronto-temporal cortex, whereas frontal activity is not lateralized in patients whose lesions also subsume the left basal ganglia. This pattern suggests that an intact left basal ganglia may somehow permit the natural transfer of language production mechanisms to the right frontal lobe without a treatment specifically designed to facilitate this shift. How do the left basal ganglia permit shift of language production mechanisms to right frontal cortex?

Before treatment, X030 demonstrated activity in the left dorsal caudate nucleus during word production. As noted above, the nondominant basal ganglia are suspected to mediate suppression of right frontal activity in neurologically normal subjects during word production (Crosson, Benefield, et al., 2003). This notion is consistent both with known bilateral connections between pre-SMA and the basal ganglia (Inase et al., 1999) and with the notion that the basal ganglia suppress “unwanted” behaviors (Mink, 1996; Penney & Young, 1986). It follows that the left basal ganglia could participate in suppressing left frontal activity in a patient with nonfluent aphasia, which in turn would facilitate transfer of language production to right frontal mechanisms. This interpretation raises the question of why left basal ganglia activity would increase so dramatically during postintention treatment imaging for X030, spreading to the left putamen and nucleus accumbens, as well as continuing in the left dorsal caudate nucleus. It is possible that when left posterior perisylvian mechanisms (supramarginal, angular, and superior temporal gyri) are invoked to establish associations between new right frontal word production patterns and existing left-hemisphere lexical–semantic knowledge, there is a tendency for these left posterior perisylvian mechanisms also to activate left frontal mechanisms because of premorbid association processes. In this case, it would be necessary to enhance left basal ganglia activity to effectively suppress the tendency to activate left frontal mechanisms. (Remember that these posterior left perisylvian mechanisms were not active before treatment for X030.) Indeed, it should be noted that such diffuse activity of the nondominant basal ganglia is the usual state of affairs for neurologically normal persons during word production (Crosson, Benefield, et al., 2003).

For patient A008, damage to the left basal ganglia and thalamus would not allow for such a “natural” transfer of word production processes. Instead, priming right-hemisphere intention mechanisms with a left-hand movement was necessary to facilitate this transfer. Further, the inability to suppress left lateral frontal mechanisms through the left basal ganglia allows left lateral frontal activity to continue after treatment, even in the face of dramatic increases in right frontal activity. With the continuation of left lateral frontal activity, massive activation of right lateral frontal mechanisms may be necessary to minimize interference of residual left frontal activity with word production. Regarding posterior perisylvian activity, it is of interest that, like lateral frontal activity for A008, it was not lateralized. Perhaps, massive right lateral frontal activity after treatment tends to engage other connected cortices in the right hemisphere. From a therapeutic standpoint, it is important for therapists to know that some patients may require the intention mechanism to continue progress in word production treatment whereas others eventually may be able to learn without this component in treatment. A008 was not able to continue improvement without the complex left-hand movement during the attention treatment, whereas X030 continued to improve after this intention component was removed during the attention treatment. If our hypothesis is correct, the extent of basal ganglia lesion may predict whether the intention component is necessary.
to continue producing the treatment effect. This issue should be addressed in future studies.

Utilization of Existing Left-Hemisphere Lexical–Semantic Knowledge

Cato, Parkinson, Wierenga, and Crosson (2004) showed that auditory–verbal comprehension scores predict treatment success for the intention treatment that our patients received. Left inferior parietal structures (supramarginal and angular gyri) and the superior temporal gyrus play a critical role in the lexical–semantic knowledge underlying auditory–verbal comprehension (Alexander, 2003). Neither A008 nor X030 invoked significant activity in these left posterior perisylvian structures during word production before treatment, but both patients showed activity in these structures after the intention treatment. Thus, it seems reasonable to conclude that these structures played some role in treatment gains. We hypothesize that left anterior production and posterior perisylvian mechanisms not only are intimately linked during normal language activities but also share lexical–semantic code. When this code is maintained in left posterior perisylvian cortex, it can act as a template to establish new synaptic connectivity necessary to link emerging language production activities with appropriate lexical–semantic representations.

Caveats and Alternative Explanations

Based upon comparison of pre- and post-treatment fMRI of language generation, we modified basic assumptions of the intention treatment. Because these modifications are based upon findings from only two cases, they must be considered hypotheses awaiting confirmation by further studies. Under such circumstances, it is appropriate to consider limitations and potential alternative explanations for the findings.

One potential limitation is that for patients with chronic aphasia, we lack knowledge regarding stability of fMRI activity in word-generation tasks. In particular, we know of no studies repeating similar tasks across multiple sessions in patients with chronic nonfluent aphasia. However, some data are available regarding repeated performance of word-generation tasks in young neurologically normal participants. When such subjects repeat a verb-generation task, left prefrontal, left posterior temporal, and medial frontal activity evident during initial performance decrease after nine repetitions of the task when the same stimuli were used each time to cue verb generation (Petersen, van Mier, Fiez, & Raichle, 1998; Raichle et al., 1994). At the same time, activity in the insula and surrounding sylvian cortex increases with practice. These changes were specific to the stimuli used in the repeated task because when new stimuli were introduced, the pattern of activity is similar to the first trial of the repeated presentations. Further, because the number of stereotyped responses increased across trials, the authors attributed the changes in distribution of neural activity to the fact that the responses became more automatic across task repetitions with the same cues. Findings of Cardebat et al. (2003) suggest that such changes may occur with fewer repetitions and even when repeated trials are separated by several months. van Turennout, Bielamowicz, and Martin (2003) noticed similar changes with visual object naming, with the addition that left basal ganglia activity also increased with repetition. Similar findings across these studies raise the question of whether the current findings could be attributed to repeated presentations of the word-generation task during pre- and post-treatment fMRI sessions.

We believe that such effects are unlikely to account for the changes demonstrated by our patients for the following reasons. First, the data of Raichle et al. (1994) strongly suggest that the effects of repeated task performance occur because responses become more automatic as the task becomes practiced with a specific set of stimuli. Such effects are unlikely to occur in aphasia patients. If responses in aphasic patients easily became automatic with repetition, retraining vocabulary would occur much more rapidly than it does in actuality. Second, the pattern of change in our aphasic patients does not replicate that of the studies mentioned above. Activity does not shift from frontal and temporal regions to insular and sylvian cortex as it does with task repetitions for normal participants (Cardebat et al., 2003; van Turennout et al., 2003; Petersen et al., 1998; Raichle et al., 1994). Indeed, activity in the posterior superior temporal lobe, which occurs primarily during initial trials of word generation in normal subjects (Petersen et al., 1998; Raichle et al., 1994), is present only after training in our aphasic subjects. The increase in basal ganglia activity occurring after repeated naming trials is in the language dominant hemisphere for neurologically normal subjects (van Turennout et al., 2003), but it is in the hemisphere opposite of frontal activity in our subject X030. The location and greater extent of basal ganglia activity in the hemisphere opposite from frontal language production mechanisms is consistent with the findings of Crosson, Benefield, et al. (2003) in normal word generation.

A second potential weakness is the lack of knowledge regarding how changes in cerebrovascular autoregulation in stroke patients affect hemodynamic responses (HDRs) in blood oxygen level-dependent (BOLD) fMRI. Some data suggest that negative BOLD responses occur when areas of compromised circulation are activated during behavioral tasks (Röther et al., 2002). Because the deconvolution program used for the current analyses makes no a priori assumptions about the shape of the HDR, it is capable of detecting such negative BOLD responses. Clearly more research needs to be done regarding the prevalence and nature of changes in BOLD response in stroke patients.
Another potential weakness of the current study is the use of a task for the fMRI studies (word generation) that differs from the primary treatment task (picture naming). Indeed, in many treatments for word finding, better results are clearly produced for trained as opposed to untrained items (Raymer & Rothi, 2000) within the same tasks (i.e., generalization can be limited). It should be remembered, however, that the intention treatment in the current study was designed to use an intentional mechanism (initiation of word-finding trials with a complex left-hand movement) to leverage a shift of language productions mechanisms to the right hemisphere. To the degree the treatment is successful in accomplishing that goal, it should produce generalization across items and tasks. Preliminary analyses from studies of the intention treatment indicate that generalization to untrained items occurs in the vast majority of patients who receive the treatment. Also germane to the current discussion is the fact that A008 demonstrated considerable improvement in the fMRI word-generation task from pre- to post-treatment scans. Although the improvement of X030 was less in absolute terms, she was within four items of maximum performance during her pre-treatment fMRI session. Thus, data regarding the intention treatment support the concept of generalization of training to untrained items and tasks. Further, use of a task for fMRI scanning that is different from the treatment task has a significant advantage. At the post-treatment fMRI session, patients have experienced the task only once before, in the pre-treatment scanning session, whereas if the same task was used for scanning as for treatment, subjects would have experienced the task 31 times before the post-treatment scanning session. In instances when the fMRI task exposure is so dense, it is much more likely that mere exposure to the task, which may have nothing to do with neuroplasticity, will influence differences between pre- and post-treatment fMRI findings.

A final caveat relates to the order of treatments. In both cases, the intention treatment was given before the attention treatment. There was no control for treatment order in these case studies. Thus, it is possible that the intention treatment drove picture-naming performance for A008 high enough that it left little room for improvement during the attention treatment or that the effects of the intention treatment were necessary before X030 could benefit from the attention treatment. Although the present design does not allow us to address such issues, it is worth noting that analyses on which we are based is not a modification of the original assumptions on which the intention treatment was based and must be subjected to further empirical scrutiny to ascertain their veracity.

**METHODS**

**Patients**

Two patients with residual nonfluent aphasia and moderate anomia received the intention and attention treatments. Both patients were right-handed premorbidly and were determined from medical records by a speech/language pathologist to have nonfluent aphasia during the subacute period between 2 and 4 weeks postonset of thromboembolic stroke. Patients gave written informed consent separately for the treatments and the scanning sessions in accordance with procedures established by the University of Florida Health Science Center Institutional Review Board. Other details regarding each patient are as follows.

**Patient A008**

This patient was a 47-year-old man whose cerebral vascular accident secondary to left middle cerebral artery ischemia occurred 4 years before initiation of treatment. Selected scores from the Western Aphasia Battery (Kertesz, 1982), the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), and the Florida Semantics Battery (Rothi, Raymer, Maher, Greenwald, & Morris, 1991) just before treatment are shown in Table 2.

We have developed a novel treatment of intention for nonfluent aphasia. The treatment was based upon specific assumptions regarding neuroplasticity: First, after a critical amount of damage to language production mechanisms in left frontal cortex, right frontal cortex offers a superior substrate for rehabilitation. Second, a manipulation of intention, initiating picture-naming trials with a complex left-hand movement, can catalyze transfer of language production functions to right frontal cortex. Findings from the two patients of the current study indicate that patterns of neuroplasticity may vary between patients, depending on lesion location. The following hypotheses are offered to account for the current findings. (1) The intention treatment of the current study relies on two phenomena, transfer of language production functions to the right frontal lobe and formation of associations between newly established right frontal word production mechanisms and existing lexical–semantic knowledge in the posterior perisylvian cortex of the left hemisphere. (2) If the basal ganglia in the left hemisphere are intact, they can participate in the suppression of left lateral frontal activity, facilitating the transfer of language production functions to the right frontal lobe, even before treatment. (3) For the intention treatment to work in nonfluent aphasia, it is necessary to tap preserved lexical–semantic knowledge in posterior left-hemisphere structures. These hypotheses represent a modification of the original assumptions on which the intention treatment was based and must be subjected to further empirical scrutiny to ascertain their veracity.

**Conclusion**

We have developed a novel treatment of intention for nonfluent aphasia. The treatment was based upon specific assumptions regarding neuroplasticity: First, after a critical amount of damage to language production mechanisms in left frontal cortex, right frontal cortex offers a superior substrate for rehabilitation. Second, a manipulation of intention, initiating picture-naming trials with a complex left-hand movement, can catalyze transfer of language production functions to right frontal cortex. Findings from the two patients of the current study indicate that patterns of neuroplasticity may vary between patients, depending on lesion location. The following hypotheses are offered to account for the current findings. (1) The intention treatment of the current study relies on two phenomena, transfer of language production functions to the right frontal lobe and formation of associations between newly established right frontal word production mechanisms and existing lexical–semantic knowledge in the posterior perisylvian cortex of the left hemisphere. (2) If the basal ganglia in the left hemisphere are intact, they can participate in the suppression of left lateral frontal activity, facilitating the transfer of language production functions to the right frontal lobe, even before treatment. (3) For the intention treatment to work in nonfluent aphasia, it is necessary to tap preserved lexical–semantic knowledge in posterior left-hemisphere structures. These hypotheses represent a modification of the original assumptions on which the intention treatment was based and must be subjected to further empirical scrutiny to ascertain their veracity.

**METHODS**

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with moderate anomia and periodic difficulty in initiating speech. Auditory comprehension was relatively intact. His lesion (Figure 4a) included the left frontal operculum and insula inferiorly. At a higher level, the lesion included the frontal and temporal opercula and prefrontal cortex beyond the frontal operculum. Superiorly, the parietal operculum and the fronto-parietal region above the level of the insula were involved. The lesion extended deep into the left hemisphere to encompass the caudate and lentiform nuclei and most of the thalamus.

Patient X030

This patient was a 48-year-old woman whose cerebral vascular accident secondary to left middle cerebral artery ischemia occurred 8 months before entry into the treatment protocol. Selected scores from the Western Aphasia Battery, Boston Naming Test, and Florida Semantics Battery just before treatment are shown in Table 2. The patient had a moderate residual nonfluent aphasia with a moderate anomia and periodic difficulty in initiating speech. Auditory comprehension was relatively intact. Her lesion (Figure 2B) included the left frontal operculum near its junction with the insula and the temporal and parietal opercula. It extended into the fronto-parietal region above the level of the insula. In contrast to patient A008, X030’s lesion spared the caudate nucleus, lentiform nucleus, and thalamus.

Anomia Treatments

Each patient received both the intention treatment that was developed as a treatment for anomia in nonfluent aphasia and a similar treatment, without the intention component, that manipulated spatial attention. Both patients received the intention treatment followed by the attention treatment. These experimental treatments can be described as follows.

**Intention Treatment**

As noted above, the intention treatment was designed to prime right-hemisphere mechanisms for intention, which in turn would facilitate participation of right lateral frontal mechanisms in word production. The treatment was divided into three phases of 10 sessions each, and a different set of 50 words (pictures) was trained during each phase. One treatment session was given daily, 5 days per week. During all phases, the patient was seated with a computer monitor directly in front of her/him. (1) During Phase 1, each treatment trial began with the presentation of a flashing star (approximately 2.5 × 2.5 cm) at the center of the monitor and a 1000-Hz tone. To initiate presentation of a line drawing for naming, the patient lifted a lid on a small box located to his/her left with her/his left hand and pressed a button located within the box. The tone and star disappeared when the button was pressed, and after a delay of 2 sec, a black-and-white line drawing appeared in the center of the monitor. Patients were given 20 sec to name the stimulus. If the patient correctly named the picture, the trial terminated. If the patient did not respond or incorrectly named the picture,

Table 2. Preintention Treatment Language Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>A008</th>
<th>X030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Aphasia Battery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>summary measures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aphasia quotient</td>
<td>79.6/100</td>
<td>81.4/100</td>
</tr>
<tr>
<td>Spontaneous speech total</td>
<td>16/20</td>
<td>14/20</td>
</tr>
<tr>
<td>Comprehension total</td>
<td>172/200</td>
<td>196/200</td>
</tr>
<tr>
<td>Repetition total</td>
<td>80/100</td>
<td>86/100</td>
</tr>
<tr>
<td>Naming total</td>
<td>72/100</td>
<td>83/100</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>50/60</td>
<td>44/60</td>
</tr>
<tr>
<td>Florida Semantics Battery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>naming</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral picture naming</td>
<td>24/32</td>
<td>27/32</td>
</tr>
<tr>
<td>Written picture naming</td>
<td>2/32</td>
<td>19/32</td>
</tr>
<tr>
<td>Naming to definition</td>
<td>20/32</td>
<td>21/32</td>
</tr>
</tbody>
</table>

*aAll 60 items on the Boston Naming Test were given to patients; otherwise, the administration was standard.

*bOn the naming subtests of the Florida Semantics Battery, 32 of the 120 items were selected for administration.

![Figure 4. T1-weighted MRIs. Both patients showed lesions of left perisylvian cortex (described in text), but these structural images through the level of the basal ganglia show that A008 had almost total destruction of the left basal ganglia, whereas these structures (white arrows) were intact for X030. A008 also had significant damage of the thalamus, and again, X030 had no thalamic damage. PUT = putamen; CN = caudate nucleus; THAL = thalamus. The left hemisphere is on the left side of the images.](http://www.mitpressjournals.org/doi/pdfplus/10.1162/0898929053279487)
the therapist named the picture while making a nonsymbolic circular gesture with the left hand. The subject repeated the correct picture name aloud while making this gesture. (2) Phase 2 was the same as Phase 1, except during the initiation of treatment trials, the 1000-Hz tone was eliminated. (3) During Phase 3, treatment trials began with a flashing star appearing at the center of the monitor. The patient performed a nonsymbolic circular gesture with the left hand. Once this gesture was performed three times, a line drawing to name appeared at the center of the monitor. Otherwise, treatment trials were the same as in Phases 1 and 2.

Attention Treatment

The attention treatment was based on work by Coslett (1999), which demonstrated that language performance for some patients improved when stimuli for language tasks were moved into their ipsilesional hemispace. Because this manipulation of spatial attention worked only for patients whose lesions extended well into the parietal lobe, this treatment was expected to work only for patients with fluent aphasias. Like the intention treatment, the attention treatment was divided into three phases of 10 sessions each, and a different set of 50 words (pictures) was trained during each phase. One treatment session was given daily, 5 days/week. During all phases, the patient was seated with a computer monitor 45° to the left of his/her midline, and the therapist was seated to the left of and slightly behind the patient. The three treatment phases can be described as follows. (1) During Phase 1, pictures to be named appeared on the left side of the computer monitor. Patients were instructed to turn their head to face toward the computer monitor when they heard a 1000-Hz tone. Then, a fireworks-like stimulus appeared on the left side of the monitor for 4 sec. When the tone and fireworks disappeared, a line drawing immediately appeared on the left side of the monitor. Patients were given 20 sec to name the stimulus. If the patient named the picture correctly, the trial ended. If the patient did not respond or named the picture incorrectly, then the therapist modeled the correct response and instructed the patient to repeat the word. (2) During Phase 2, the fireworks display that accompanied the tone was eliminated. Otherwise, treatment trials were the same as in Phase 1. (3) During Phase 3, the 1000-Hz tone at trial onset was shortened to 0.5 sec, and after the tone stopped, the computer screen remained blank for approximately 4 sec before the picture appeared at the center of the monitor. Otherwise, treatment trials were the same as in Phases 1 and 2.

Treatment Probes

For each treatment, a set of 40 probe items was constructed to monitor treatment progress. The 40 items in each probe set were composed of 10 line drawings from each treatment phase, for a total of 30 drawings, and 10 line drawings that were not trained in any treatment phase. During pre-treatment baseline sessions and before each treatment session during every phase of treatment, the entire set of 40 items was administered. During naming of these probe items, no treatment intervention was performed. Before treatment, at least eight baseline sessions were performed for each treatment. No treatment session followed administration of the probe set during baseline. Baseline sessions continued until the C statistic (Tryon, 1982) indicated that no significant increase in performance occurred for the last eight baseline sessions. Once stable baseline performance was achieved according to this criterion, treatment was initiated. Improvement across treatment was assessed by applying Tryon’s (1982) C statistic to the entire time series for the treatment probes (i.e., baseline probes plus probes for all three treatment phases).

Stimuli

All stimuli for the 50-item treatment sets and the 40-item probe sets consisted of black-and-white line drawings. These drawings were selected to represent low-frequency words (0–5 occurrences per million) according to Frances and Kucera (1982). Low-frequency items were chosen to ensure that these patients, who had moderate anomia, would not demonstrate ceiling effects at the beginning of treatment.

Functional Magnetic Resonance Imaging Task

To image word production, patients were given a category–member-generation task during pre- and post-treatment fMRI sessions. At the beginning of a trial, patients heard a single category (e.g., “birds”), and they attempted to generate aloud a single exemplar for that category (e.g., “eagle”). Category–member generation was chosen as the experimental task over simple object naming because previous research showed that pre-SMA activity was optimal in the former as opposed to the latter (Crosson, Sadek, et al., 2001). Patients were instructed at all times to look at a fixation point outside the scanner, visible through the mirror attached to the head coil, and not to think of any words to themselves between trials. A minimally active baseline task (visual fixation) was chosen to optimize activity in language-related brain structures (Newman, Twieg, & Carpenter, 2001). Length of trials and intertrial intervals (ITIs) were selected so that HDRs were not contaminated by head motion from spoken responses in subsequent trials. In this way, artifacts due to head motion were limited to the initial segment of the HDR. Five experimental runs of nine trials each were given. Trials were 9.96 sec...
(6 images) in length to allow the anomic patients adequate time to generate a response. ITIs varied in length to mitigate low-frequency artifacts that occur in BOLD contrast fMRI (Zarahn, Aguirre, & D’Esposito, 1997) and to facilitate data analysis using deconvolution. One ITI was 14.94 sec (9 images) in length, three were 16.60 sec (10 images), two were 18.26 sec (11 images), and two were 19.92 sec (12 images). These ITI lengths were interspersed between trials in a pseudorandom fashion. The initial interval before the first trial was 21.58 sec (13 images) and the terminal interval after the last trial was 14.94 sec (9 images) in length. Thus, each run was 276.26 sec long. Stimuli were recorded onto CD and played with volume at an individually determined maximum comfort level to patients via a Commander XG Audio System (Resonance Technology). Patient responses were recorded to a laptop computer (Gateway) using CoolEdit software (Syntrillium Software). Responses were scored for accuracy off-line, and the precise onset time of each response was recorded so that it could be used in image analysis.

**Image Acquisition**

fMRI data were acquired with a 3-T Signa LX scanner (General Electric) with a dome-shaped quadrature radio frequency coil (MRI Devices). Thirty-two contiguous sagittal slices covering whole brain were acquired using a one-shot spiral sequence (1660 msec TR; 18 msec TE; 70° flip angle; 64 x 64 matrix; 200 mm FOV; 4 mm thickness). Images were acquired in the sagittal plane because the smallest out-of-plane head motion during speech typically occurs with acquisitions in the sagittal plane (Barch et al., 1999). An additional 9 images (14.94 sec) were added to the beginning of the run to allow MR signal to reach equilibrium. Anatomic images were obtained using a T1-weighted spoiled GRASS sequence (23 msec TR; 6 msec TE; 25° flip angle; 256 x 192 matrix; 1.5 mm thickness; 124 slices, FOV = 240 mm). Foam padding limited head motion during scanning.

**Image Analysis**

Image analysis was performed with AFNI (Cox, 1996) and programs developed in our laboratory. Using a three-dimensional rigid body registration, functional images were aligned to a base image from the functional volume acquired closest in time to structural images. Linear trends in the time series of each run were removed, and five runs then were concatenated. Voxels in which the standard deviation exceeded the mean signal intensity by more than 8% were excluded from the analysis to mitigate large vessel effects and other artifacts. AFNI’s deconvolution was used to estimate the HDR for correct responses only. Deconvolution began at the image in which a correct response was initiated and included 26.5 sec (16 images) of signal. The estimated HDR obtained by this process was then convolved with the temporal sequence of correct responses and tested for goodness of fit against the original time series using a multiple correlation ($R^2$).

The time series in each voxel was corrected for residual motion artifacts using a refinement of the selective detrending procedure developed in our laboratory (Gopinath, 2003). This procedure estimates residual-motion-related artifacts by selecting deconvolved responses (DRs) from several voxels outside the brain with high $R^2$ values, and estimates potential HDRs of different temporal onset by selecting voxels within gray matter with high $R^2$ values and with rise to peak and return to baseline of approximately 9–12 sec. When the DR in a voxel showed no correlation ($r < .50$) with any of the estimated motion artifacts, no detrending was done in the voxel. When the DR correlated ($r \geq .50$) with one or more of the estimated motion artifacts but not with any HDR estimate, the times series within the voxel was detrended for the entire estimated artifact with which its estimated DR showed the highest correlation. When the DR from a voxel correlated with both artifact and HDR estimates, then the time series within the voxel was detrended only for the first three time points of the estimated artifact with which its DR showed the highest correlation. This methodology has proven superior to other available detrending techniques described in the literature when both sensitivity and specificity are considered (Gopinath, 2003). Once the selective detrending procedure was applied to time series on a voxel by voxel basis, the deconvolution analysis was repeated, and new $R^2$ values were obtained for each voxel.

Before analysis of pre- and post-treatment functional MR images, images were equated for sensitivity to BOLD response across sessions on a voxel by voxel basis using a procedure developed in our laboratory. In brief, this procedure used the residual variance from the deconvolution analysis to estimate the noise structure of pre- and post-treatment images. Different known amounts of signal were added to the noise for both image sets, and detection probability curves (fraction of voxels in the data set activated as a function of $R^2$) at each of the different levels of signal added were generated for each data set. These detection probability curves then were used to equate the pre-treatment and post-treatment $R^2$’s for sensitivity.

After correction for motion-related artifacts and equating for sensitivity, images were converted to $1 \times 1 \times 1$-mm voxels in Talairach coordinate space (Talairach & Tournoux, 1988). A statistical threshold of $R^2 \geq .20$ and a contiguity threshold of volume $\geq 150$ µl were used to select areas of activity for interpretation so that the possibility of interpreting false positive activity was minimized. Anatomic localization was determined by visual inspection of images with occasional assistance of the Talairach atlas (Talairach & Tournoux, 1988).
& Tournoux, 1988). Broad ROIs were specified for further analysis and included the pre-SMA, lateral frontal cortex, basal ganglia, thalamus, inferior parietal lobule/superior temporal gyrus, visual cortex (from primary visual cortex to the visual association cortex of the inferior temporal lobe), and paralimbic cortex (parahippocampal gyrus and retrosplenial cortices). Because the goal of the intention treatment was to shift activity from the left to the right medial and lateral frontal lobe, statistical analyses focused on lateralization of activity in the various broad ROIs. When one of the broad ROIs listed above demonstrated activity in both hemispheres, a binomial equation was applied to determine if the distribution of active voxels departed significantly from the expectation of equal distribution between the hemispheres.

Acknowledgments

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The data reported in this experiment have been deposited in the fMRI Data Center (www.fmridc.org). The accession number is 2-2004-117P2.

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Crosson et al. 405


