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An Intention Manipulation to Change Lateralization of Word Production in Nonfluent Aphasia: Current Status

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Abstract

A review of recent aphasia literature indicates that both the left and right hemispheres participate, under various circumstances, in recovery of language and in treatment response. In chronic aphasias with large lesions and poor recovery of function, the right hemisphere is more likely to demonstrate prominent activity than in cases with small lesions and good recoveries. Extraneous activity during language tasks for aphasia patients may occur in both the left and right hemispheres. Right hemisphere activity during language in aphasia patients is likely to occur in structures homologous to damaged left hemisphere structures. When the left hemisphere is so damaged as to preclude a good recovery, recruitment of right-hemisphere mechanisms in the service of rehabilitation may be desirable. Hence, a treatment with an intention manipulation (complex left-hand movement) was developed for nonfluent aphasia to assist in re-lateralization of language production. A review of existing evidence indicates that the intention manipulation adds value to naming treatments and helps to shift lateralization of language production to right frontal structures. However, wholesale transfer of language function to the right hemisphere does not occur, and residual language knowledge in the left hemisphere also seems vital for relearning of word production. Further research is needed to fully understand the contribution of the intention manipulation to treatment response.

Learning Objective—After reading this article, the reader should be able (1) to cite instances in which left-hemisphere mechanisms support language recovery in aphasia and aphasia treatment, (2) to cite instances in which right-hemisphere mechanisms support such language recovery, and (3) to assess the treatment implications of this information.

Keywords

nonfluent aphasia; rehabilitation; fMRI; neuroplasticity; aphasia treatment; intention

In this paper, I review a treatment that was developed to help patients with nonfluent aphasia focus word production mechanisms in the right lateral frontal lobe. In a broader context, this work was based on a simple assumption: that we (aphasia researchers and clinicians) can develop treatments to engage specific neural substrates in the service of aphasia rehabilitation and that we can use functional brain imaging to ascertain whether such treatments actually do engage the targeted substrates. Over the last 20 years, animal model literature has made it clear that plasticity in the adult brain is the substrate for learning^{1, 2}. Further, adult animals with brain damage can relearn activities to a significant degree if properly trained and neuroplastic changes account for the relearning^{3, 4}. Such findings compel us to understand the neural as well as the cognitive substrates of effective aphasia rehabilitation so that better treatments can

be developed. If we understand the neural substrates, we will be better able to engage them in the service of rehabilitation. As evidenced by an increasing number of functional imaging studies, the need to understand the neural substrates of language in aphasia and mechanisms of rehabilitation clearly has been understood. Yet, progress has been slow and even the simplest interpretations of data can be controversial. The slow progress in understanding the neural substrates of aphasia may explain why few treatments have been developed to target specific neural substrates. Before we can do so, we must know what substrates to target.

Further, although this idea of targeting neural substrates for rehabilitation is relatively simple, implementation of the concept is far from straightforward. I have already noted the literature as yet has yielded few ideas of what substrates should be targeted. Other questions that are likely to arise include: What neural substrates are available to be recruited in the service of rehabilitation? What residual knowledge of language exists, where does it reside, and how can it be used in rehabilitation? How is the existing knowledge connected to potential alternative substrates by neural pathways? What treatment mechanisms can be used to recruit viable substrates for relearning language? Hence, it will be important to understand both how an individual patient's lesion affects potential neural substrates for rehabilitation and the connectivity between them, and how rehabilitation strategies can best engage the requisite substrates. One treatment is unlikely to fit all patients' needs; thus, we will have to understand what treatments to use for different patients.

In this review, I will address several topics. The first is whether or not a case for engaging the right hemisphere in aphasia rehabilitation can be built. While I am convinced that such a case can be made, I am equally convinced that wholesale transfer of all language mechanisms to the right hemisphere is in most instances neither desirable nor practical. A second topic is the definition of intention and how might be useful in rehabilitation. Third, I will describe an intention treatment developed to re-lateralize word production from the left to the right frontal lobe. In particular, I will address existing evidence regarding its efficacy and for what kind of patients it seems to work best. Finally, I will summarize preliminary evidence regarding whether the treatment actually re-lateralizes word production to the right lateral frontal lobe.

Can the right hemisphere assume language functions in aphasia?

The intention treatment that I shortly will discuss is predicated on two ideas. The first is that right-hemisphere mechanisms are sometimes the optimal substrate for rehabilitation. Specifically, when damage to left frontal language mechanisms for language production and surrounding cortex are so heavily damaged that even after recovery and traditional therapy word finding is substantially compromised, right frontal mechanisms may be the optimal frontal component for relearning word production. The second idea is that lateralization of language is not a passive process and is influenced, among other things, by attention and intention mechanisms. Specifically, word production can be influenced by activating intention (action-oriented) mechanisms in the left and right hemispheres. In this section, I discuss evidence supporting the first idea. In the next section, I will address evidence supporting the second idea. For recent, extensive literature reviews on left- and right-hemisphere participation in language and rehabilitation for aphasia patients, I refer readers to our recent reviews on the topic^{5, 6}. Below, I summarize this literature.

Some of the best evidence for participation of the right hemisphere in the language of aphasia patients is over 100 years old. In the century before the last one, Barlow⁷ and Gowers⁸ both reported cases of aphasia caused by left-hemisphere lesion. In both instances, patients showed some degree of language recovery after their left brain lesions but lost further language function when right-hemisphere lesion subsequently ensued. Basso and colleagues⁹ used standardized aphasia testing to establish this phenomenon in a small number of cases who demonstrated

aphasia after left hemisphere lesion and subsequently demonstrated deterioration of language after right-hemisphere lesion. Similarly, Kinsborne¹⁰ also demonstrated that some patients with chronic aphasia lose language function when their right hemisphere is anesthetized during Wada tests. What do these data mean? In the rush to interpret compelling functional images, such lesion and Wada data are often forgotten or cast aside, but they are powerful indicators of right hemisphere function. Loss of language function when right-hemisphere function is permanently or temporarily interrupted strongly suggests that right-hemisphere mechanisms are playing some role in language. Nonetheless, the data do not necessarily signal a wholesale shift of language to the right-hemisphere. They merely indicate that some right-hemisphere mechanism is playing a crucial role in language.

Before I review functional neuroimaging studies regarding the neural substrates of language and rehabilitation in aphasia, I must address one weakness of functional neuroimaging: Activity in a particular structure on functional neuroimaging does not necessarily indicate that the structure is critical for the task at hand. For example, because inhibitory activity at the synaptic level is based on release of inhibitory neurotransmitters, inhibitory activity generates increased metabolic demands that result in increased activity on functional neuroimaging that is indistinguishable from excitatory activity. Hence, in some cases, activity on functional neuroimaging could be a sign that a structure is being inhibited instead of excited^{11, 12}. In some instances, the effects of inhibitory neurotransmitters can be seen at the target structure instead of at the structure where the cell bodies responsible for the inhibitory activity reside (see Mitchell¹³ for a good example). Perhaps a more important possibility is that activity in a specific structure actually may interfere with an ongoing cognitive process. For example, Rosen et al.¹⁴ raised the possibility that right-hemisphere activity during language in aphasia may actually interfere with language functions.

The work of Naeser and colleagues¹⁵ speaks to this latter possibility. They briefly described some pilot work they performed with repetitive transcranial magnetic stimulation (rTMS) to inactivate the anterior (pars triangularis) and posterior (pars opercularis) right-hemisphere counterparts to Broca's area. Inactivation of right pars triangularis resulted in decreased picture-naming latency and increased accuracy, but inactivation of right pars opercularis resulted in increased naming latency and decreased accuracy. Naeser et al.¹⁵ turned their observations into a treatment for word finding in nonfluent aphasia. They showed that inactivation of pars triangularis with rTMS daily for 10 days over two weeks led to improvement in naming that continued eight months after rTMS ended. Do these data indicate that, contrary to the above lesion studies, no right-hemisphere structure plays a role in word production in aphasia? No, they do not. Remember that in Naeser et al.'s pilot study inactivation of right pars opercularis led to increased naming latency and decreased accuracy. Instead the data indicate that activity in some right-hemisphere structures may impede language recovery, but activity in other structures may facilitate naming. Hence, Naeser et al.'s concept of over-activation of the right hemisphere does not imply that no right-hemisphere structure is important for language in aphasia, and her study does not necessarily contradict the lesion and Wada data presented in the previous paragraph. Put together, however, the data do indicate that in aphasia, some right-hemisphere activity may be beneficial for and other right-hemisphere activity may detract from language functions. It also should be pointed out that Naeser et al.'s¹⁵ study was performed with a small number of subjects (N = 4) and that the degree to which findings can be generalized to all patients with nonfluent aphasia must be determined by replication with a large sample.

Can it also be said that some left-hemisphere activity may be beneficial for and other left-hemisphere activity may detract from language functions in aphasia? Specifically, is it possible that some left-hemisphere activity may impede language function in aphasia? There is some indirect evidence that this may be the case. In a doctoral dissertation performed in our

laboratory, Parkinson¹⁶ studied whether degree of lesion in 29 cortical and subcortical structures predicted improvement during action and object naming treatments that contained semantic components. Subjects were 15 patients with chronic aphasia and anomia due to left-hemisphere lesion. Location of left-hemisphere lesion was not a selection criterion. Patients received one of two treatments emphasizing semantic components. Degree of lesion was determined by 2 operators trained to a high degree of reliability ($r = .89$) using Naeser and colleagues' system^{17–19}. Raters were blind to treatment outcome; differences in ratings were resolved by consensus. For purposes of data reduction, degree of lesion in three composite regions of interest was determined by adding scores from structures within the three regions: anterior (frontal) cortex, posterior perisylvian cortex, and basal ganglia. (However, correlations between outcome and degree of lesion in the individual structures were consistent with those of the composite regions.) Because degree of basal ganglia lesion and degree of frontal lesion affected treatment outcome in different ways and because many patients had lesions in both structures, the effects of basal ganglia lesion on the relationship between treatment improvement and frontal lesion (and vice versa) were controlled with partial correlation. Partial correlations indicated a negative relationship between degree of basal ganglia lesion and improvement in both action naming ($r = -0.785$) and object naming ($r = -0.749$). In other words, the greater the degree of basal ganglia lesion is, the worse the patient does in treatment. This finding was not too surprising because it has been known for some time that patients with left basal ganglia lesion in addition to left cortical lesion show more persistent aphasias than patients with similar cortical lesions alone²⁰. However, it is the frontal findings in which we are most interested for purposes of this discussion. Partial correlations showed a positive relationship between degree of left frontal lesion and improvement in both action naming ($r = 0.821$) and object naming ($r = 0.858$). In other words, the greater the degree of frontal lesion is, the better the patient does in treatment. This finding is counter-intuitive. Why should patients with larger frontal lesions do better in treatment than patients with smaller frontal lesions? It must be remembered that these patients had chronic aphasias. Patients who had small lesions and showed good recoveries would not have had the level of deficit that would qualify them for the study. Hence, the inclusion criteria, dictated a sample of patients whose recovery was not optimal and would tend to have larger lesions. In these cases, one possible interpretation is that perilesional cortex in the frontal lobe was producing a poor quality (noisy) output that competed with areas in the dominant or previously nondominant hemisphere that had greater potential for participating in the process of relearning words. Larger frontal lesions would tend to destroy perilesional cortex with the potential for interfering with a more functional reorganization. The important point for our discussion is that this study indicates that left- as well as right-hemisphere regions may have the potential for interfering with relearning of language processes in aphasia.

Another study suggests that activity in left frontal cortex of aphasia patients can interfere with language functions. Monti et al.²¹ applied transcranial direct current stimulation (tDCS) to the left frontotemporal cortex of patients with nonfluent aphasia. Cathodal stimulation, thought to suppress cortical function, improved naming accuracy, but anodal stimulation, thought to enhance cortical activity, had no effect on naming accuracy. Cathodal occipital stimulation also had no effect on naming. Although this study was done on a small number of patients ($N = 6$), it does suggest that left frontal activity can impede naming performance in some patients with aphasia and, therefore, is consistent with the findings of Parkinson¹⁶.

I can now review the functional imaging evidence on neuroplasticity in recovery and treatment for aphasia. It will be helpful to have a contextual framework for reviewing this literature. Explicitly or implicitly, many investigators approach this literature with the following question: Is it the right hemisphere or is it the left hemisphere that is responsible for recovery of language in aphasia? Framing the question in this fashion implies that the answer should rest entirely in one hemisphere or the other. In other words, the answer should lie at one of two extremes: all

relevant activity is in the right hemisphere versus all relevant activity is in the left hemisphere. Such an approach discounts the middle ground between the extremes in which there are a number of scenarios where both hemispheres could contribute to language in aphasia. Further, if we look for an answer only at one of the two extremes, a review of the literature confuses us because support for both positions could be found. Hence, a better way to approach the literature is to ask the following question: When do left-hemisphere mechanisms contribute to language in aphasia, and when do right-hemisphere mechanisms contribute? Framing the question this way allows us to find an answer at either of these extremes but also allows for considerable ground between the two extremes.

To the degree we can assume that activity seen on functional imaging is largely contributory to language functions, we can draw the following general conclusions. First, evidence can be found that left-hemisphere structures support language in aphasia^{22–27}. However, evidence can also be found that right-hemisphere structures support language in aphasia^{28–31}. If we look at the whole continuum of possibilities and not the extremes, these data suggest that depending upon circumstances, both hemispheres may be involved in language functions in aphasia. But, can we further define under what circumstances left-hemisphere mechanisms are involved and in what circumstances right-hemisphere mechanisms are involved in language in aphasia? Based on currently available literature, there are at least two circumstances in which the hemisphere participating can be predicted. (1) With relatively small lesions, recovery from aphasia generally is good and perilesional activity in the left hemisphere appears to be the more active substrate. With relatively large lesions, recovery generally is poor and activity in the right hemisphere seems to play a large role in language^{14, 32–36}. (2) Shifts in function to the right-hemisphere often occur in homologues of damaged left-hemisphere areas^{31, 37–40}. This evidence suggests that participation (or at least activation) of right-hemisphere structures is dependent what structures in the left hemisphere are damaged. Perhaps a more important implication is that engagement (or activation) of the right hemisphere can be selective. In such instances, wholesale transfer of language to the previously nondominant hemisphere does not occur, a point I will detail further in our discussion of the intention treatment.

To this point, the neuroimaging studies I have discussed have been largely cross-sectional studies examining activity underlying language processes at a single time point. Serial measurements addressing how the two hemispheres participate in aphasia treatment effects is less prolific. By and large, the patterns seen in the cross-sectional studies can be found on a smaller scale in the treatment studies. For example, Wierenga et al.⁴¹ studied activity during sentence generation in two patients with relatively small lesions who were undergoing syntactic mapping treatment. Their changes in activity across treatment were almost exclusively in the left hemisphere, which is consistent with cross-sectional data indicating that patients with small lesions tend to reorganize function to the left hemisphere. Musso et al.⁴² gave patients with temporoparietal lesions a treatment emphasizing language comprehension. Changes in activity in the right temporal lobe during language comprehension correlated with improvement in comprehension during training, which is consistent with cross-sectional literature indicating that right-hemisphere areas that become active are homologues of the damaged areas. Additional evidence of both left-hemisphere⁴³ and right-hemisphere⁴⁴ participation in rehabilitation gains exist.

Hence, the functional neuroimaging evidence suggests that both the left and right hemispheres may be involved in recovery or rehabilitation for aphasia, especially when taken into consideration with other evidence discussed above. As damage to the left hemisphere becomes greater, activity in the right hemisphere increases. To the degree this is an indication of participation in language functions, we can surmise that greater damage in the left hemisphere will predict greater attempts by the right hemisphere to compensate. However, there may also be some degree of specificity in that the right-hemisphere areas that are recruited are

homologues of damaged left hemisphere areas. I will discuss our own research on a novel intention treatment shortly, but before I do, the concepts of attention and intention must be discussed.

What are attention and intention and how do they influence language?

A good way to begin the discussion of attention and intention is with the observation of the Russian anatomist, Betz⁴⁵, that the telencephalon, like the spinal cord, could be divided into two complementary parts: a posterior compartment dealing with sensation and an anterior compartment dealing with action. In other words, the temporal, parietal, and occipital lobes are organs of sensation and perception, and the frontal lobes are the organ of action. Likewise, our ability to focus cognitive resources, can be divided into two components: attention and intention.

Attention is one of the most studied concepts in cognitive neuroscience. Modern definitions of attention owe much to William James⁴⁶; indeed, our definition is basically the same as James'. Attention is the ability to focus on one among multiple competing incoming sources of information for cognitive processing. Hence, as James pointed out, the construct of attention implies withdrawing consideration from some things in order to deal effectively with another. Since attention deals with incoming information, it is a sensory-perceptual construct describing the regulation of perceptual processes. One often studied phenomenon in the neuropsychology is attention to left and right hemispace. Hemispace can be determined by body midline, midline of the head, or midline of gaze, with the opposite hemisphere controlling attention to left and right hemispaces. Because attention involves perceptual processing, it acts upon cortex in the temporal, parietal, and occipital lobes. The posterior cingulate cortex, parietal lobes, and thalamus are involved in attention⁴⁷.

Intention refers to the ability to select one among several competing actions for execution and the initiation of that action. Fuster⁴⁸ refers to this phenomenon as executive attention, but it is the same concept. Similar to Heilman and colleagues (2003), I prefer the term intention because it emphasizes that intention is not simply a subset of attention. As pointed out by Fuster, "intention" is grossly understudied in comparison to attention. The great irony of this fact is that attention is often entrained to intention; Nadeau and Crosson⁴⁹ referred to this phenomenon as intentionally guided attention. Suppose, for example, that you have chosen to pour a cup of coffee and have initiated that action. Unless you wish to make a mess or scald your leg, you must attend to the location of the cup. The intention to pour a cup of coffee determines the stimuli to which you must attend to successfully complete the action. Intention as well as attention has spatial components related to side of space, side of body, and direction of movement, with the left- versus right-sided action controlled by the opposite hemisphere. Because intention controls action, it primarily acts through anterior portions of the cortex, i.e., the frontal lobes. Intentional mechanisms per se involve the medial frontal cortex and basal ganglia⁴⁷.

How can these constructs be applied to language? First, when we speak, we often have choices of which word we will use to convey a concept. If I talk about our dog, I can refer to him as the dog, Toby, our dachshund, our pet, etc., but I must select one. Or, if I ask you to name a bird, you must choose one of the many varieties of birds that you know. This application of the concept of intention seems fairly obvious. However, what may not be so obvious, is that spatial components of intention and attention may affect language. For example, Coslett⁵⁰ demonstrated that language performance in some stroke patients could be improved by moving stimulation into the good hemisphere, i.e., the hemisphere ipsilateral to the patient's lesion. This phenomenon only applied to patients with parietal lesions, and it worked with left- or right-hemisphere strokes. These facts suggest that it was the engagement of intact attention

mechanisms that affected language performance. If such a simple manipulation of spatial attention could affect language performance for patients with parietal lesions, my colleagues and I also wondered if an intention manipulation could affect language output in patients with anterior lesions and if such a manipulation might be used in treatment.

Can an intention manipulation be used to improve word production in aphasia?

Hence, we developed a treatment that used an intention manipulation. The intention manipulation involved initiating picture naming trials with a complex left-hand movement. Briefly, the patient was seated directly in front of a computer monitor, with a box on the left side of the monitor (i.e., in the patient's left hemispace). The complex left-hand movement involved opening the lid of the box on the patient's left side with the left hand, finding the correct button on an apparatus inside the box, and pressing the button with the left hand. The button press caused a picture to appear on the computer monitor. If the patient named the picture correctly, they proceeded to the next picture naming trial. However, if the patient made an error, they had to make a circular gesture with the left hand while repeating the correct name of the object after the therapist. Thus, the correction procedure also was initiated with a complex left-hand movement. These procedures have been described in more detail by ⁵¹. The idea behind the treatment was that the complex left-hand movement would activate intention mechanisms in the right hemisphere, which in turn would activate right lateral frontal mechanisms that could participate in language production. Through pairing the movement repeatedly with picture naming, right lateral frontal mechanisms eventually would assume word production functions. Because the treatment involved intention, it was thought that it would affect primarily frontal mechanisms. Since nonfluent aphasia most frequently affect word production mechanisms in the left frontal lobe whereas as fluent aphasia more commonly affect posterior mechanisms, this treatment with the intention manipulation was targeted for nonfluent aphasia.

The first question to be answered was whether such an intention mechanism had any value in treatment. As an initial attempt to probe this question, Richards et al. ⁵² demonstrated that the treatment increased naming performance over a stable baseline performance in three chronically nonfluent patients. Generalization from trained to untrained words occurred for all patients. These results were seen as encouraging, though not definitive because of the limited number of subjects and the simple experimental design. A study with a larger number of subjects and greater experimental control was needed to provide more convincing evidence of efficacy. Hence, Crosson et al. ⁵¹ gave this intention treatment to 34 patients with chronic nonfluent aphasia. A treatment with an attention manipulation also was developed to serve as a comparison treatment. This attention treatment involved moving pictures to be named into their left hemispace, similar to what Coslett ⁵⁰ did in a single session. Although it was expected that this attention manipulation could have some therapeutic value, it was hypothesized that the intention treatment would be a more powerful therapeutic tool to improve naming in nonfluent patients because it was designed to address production mechanisms in the frontal lobes, which usually are involved in nonfluent aphasia.

In the Crosson et al. study ⁵¹, patients were divided into two groups in accordance with their ability to name correctly 40 items, whose target names were balanced for their frequency of occurrence in the English language. Moderately to severely impaired patients were defined as those able to name correctly 20% or more of the items, and profoundly impaired patients were defined as those able to name less than 20% correctly. The average age of the sample was 58.96 years, there was no significant difference in age between groups. Patients received three treatment phases, each consisting of 10 sessions. Each of the treatment phases used a different set of 50 pictures for training, and different pictures were used for the two treatments. Treatment

was given daily, five days per week. A set of probe items consisted of 40 pictures: 10 items from phase 1, 10 items from phase 2, 10 items from phase 3, and 10 items that were never trained during any phase. These items were given during a baseline phase and prior to each treatment session to track treatment progress. No manipulation of intention or attention occurred during probe trials, and errors were not acknowledged or corrected. To control for the possibility of improvement in naming simply due to repetition of words, patients were required to demonstrate a stable (non-increasing) baseline performance for probes before treatment was initiated. Each patient received both treatments in a cross-over design, counterbalanced for order of treatment presentation. The difference between percent of probes correctly named in each phase and percent of probes correctly named during baseline served as the measure of outcome. Order had no significant effect on outcome.

For the profoundly impaired patients, about half of the patients benefited from each of the treatments, and group analysis indicated that there were no differences in benefits between treatments, though on the average, patients benefited from both treatments. In contrast, 89% of moderately to severely impaired patients benefited from the intention treatment, and 85% benefited from the attention treatment. In the group analysis there was a significant group by treatment interaction (Figure 1), indicating that patients relearned words faster during the intention treatment than the attention treatment. Hence, on the average, the intention treatment appeared to provide a slight advantage in relearning words compared to the attention treatment for the moderately to severely impaired patients. It also should be noted that generalization of treatment effects was the rule rather than the exception. As a group, moderately to severely impaired patients demonstrated significant generalization to untrained items for both treatments; 85% of individual patients demonstrated generalization for the intention treatment, and 68% of patients demonstrated generalization for the attention treatment. About half of the profoundly impaired patients demonstrated generalization for both treatments, as they did for the entire probe set.

In summary, the intention treatment provides a slight but significant advantage for relearning of words in the moderately to severely impaired group. Such advantage is not seen in the profoundly impaired patients. Improved relearning of words was accompanied by generalization to never-trained words. It is worth asking if there were any hints as to why the intention treatment did not produce differentially beneficial results in the profoundly impaired group. In this regard, it should be noted that the profoundly impaired group not only showed differences in naming scores from moderately to severely impaired patients, they also showed significantly lower Western Aphasia Battery (WAB) scores (mean WAB Aphasia Quotient for profoundly impaired patients = 25.53, SD = 12.16; mean WAB Aphasia Quotient for moderately to severely impaired patients = 67.95, SD = 7.63) $p < .001$. In a small subsample of the 34 patients having volumetric MRI scans ($n = 9$), Cato et al.^{53, 54} showed that poorer treatment outcome was related to lower scores on WAB comprehension subtests and larger lesions in posterior perisylvian regions. In short, patients who demonstrate larger lesions and global aphasia are less likely to benefit from the intention treatment. One hypothesis is that patients with significant impairment in comprehension from posterior lesions have lost language code that is important for leveraging re-organization of production mechanisms. Nonetheless, it should be pointed out that some profoundly impaired patients can make meaningful improvement based on treatment outcome measures and reports of family members.

Can an intention manipulation affect lateralization of word production mechanisms in the frontal lobe?

The initial studies of the intention treatment were promising and indicated that the intention manipulation was an active component of treatment. However, the findings I have discussed

to this point do not tell us whether the treatment does what it was designed to do: Does it affect lateralization of activity in the lateral frontal lobes during word production? To answer this question, my colleagues and I subjected a limited number of subjects to fMRI during word production before and after treatment. The task we used in the scanner was a category member generation task. Subjects heard the name of a category (such as “birds”) and attempted to generate a single category member in response (such as “cardinal”). This task was used for two reasons: First, we expected that if word production shifted from the left to the right frontal lobe, then this shift would generalize from the treatment task of picture naming to the task of category member generation. Second, evidence suggests that category member generation activates medial frontal mechanisms involved in intention more than naming a specific item⁵⁵. We were interested in whether medial frontal mechanisms shifted lateralization in addition to lateral frontal mechanisms. Hence, we used the word generation task. Subjects spoke aloud in the scanner. We used a selective detrending algorithm developed in our laboratory to mitigate motion-related artifacts from overt speech during BOLD contrast fMRI⁵⁶ and a second algorithm developed in our laboratory to equate pre- and post-treatment fMRI scans for sensitivity to BOLD contrast⁵⁷.

Preliminary results were published on two subjects⁵⁸. Because response latencies were variable within subject for this task, there was some question regarding whether to time analyses to stimulus presentation or to patient response (see Crosson et al.⁶ for greater details on this topic). Since we were interested in production mechanisms, my colleagues and I decided to time the analyses in this initial study to patient response. Although subjects received both the intention and attention treatments, fMRI data were only available for the intention treatment. Both patients received the intention treatment first. The first patient improved on the intention treatment but not the attention treatment, as predicted. His laterality ratio [(left – right) / (left + right)] indicated a shift toward the right frontal lobe from pre- to post-treatment fMRI scans. This shift in the ratio occurred primarily because of an increase in right lateral frontal activity during word generation. Figure 2 shows right and left frontal activity during word generation for this patient pre- and post-treatment. The increase in activity can be clearly seen in the right frontal lobe (yellow arrows). The second patient improved during both the intention and attention treatments. Her lateral frontal activity was completely lateralized to the right hemisphere prior to treatment and remained so after treatment. This right frontal activity was less extensive post- than pre-treatment, and it was confined to motor cortex post-treatment whereas it was not confined to motor cortex during pre-treatment scans. Thus, it appears that the anticipated laterality shift occurs in some patients.

We recently completed an analysis of a larger subset of patients (n = 5), including the original two⁵⁹. For this analysis we used a combination of stimulus-locked and response-locked analyses. The reason for this strategy was to be certain to capture all word retrieval processes, some of which might begin shortly after stimulus presentation. Voxels were populated with the highest statistical value (R^2 from deconvolution analysis) of the two analyses. This analysis strategy did produce greater sensitivity to lateral frontal activity in many cases than using a response-locked analysis alone. Of the five cases, four improved during treatment and one did not. One of the four patients who improved showed lateral frontal activity already completely right lateralized before treatment and continued to show complete right lateralization of lateral frontal activity after treatment. The remaining patients who improved in treatment all showed a shift of activity toward the right hemisphere; indeed, two of the three had frontal activity completely lateralized to the right hemisphere by the end of treatment. The patient who did not improve in treatment showed a leftward shift in lateral frontal activity. Thus, of the patients who improved in treatment, three showed complete dependence on right lateral frontal activity during word production by the end of treatment, and the fourth showed a rightward shift in activity. This pattern was not shown by the patient who did not improve. Data also indicated that it was not necessary for medial frontal activity to shift either for patients to improve in

treatment or for lateral frontal activity to shift rightward. Further, activity in left posterior perisylvian regions remained stable or demonstrated increases in patients who improved in treatment, suggesting that use of preserved knowledge in the posterior left hemisphere was a necessary substrate for leveraging treatment gains.

Conclusions

Previous research data suggest that both the left and right hemispheres participate in language recovery and treatment gains in aphasia. In patients with small lesions and good recoveries, left-hemisphere activity seems to be primarily responsible for recovery. However, in cases of large lesions and poorer recovery, right-hemisphere activity is prominent. The fact that recovery in these cases is poor does not indicate that the right hemisphere is not useful for or necessarily interferes with language processes. Rather, it suggests that right-hemisphere structures are most active when left-hemisphere structures are so damaged that they are not adequate for the task. It is possible that activity in both hemispheres of aphasia patients interferes with language processes, depending on the patient, the size of the lesion, and the severity of aphasia. Evidence suggests that silencing such extraneous activity in either hemisphere will have a positive impact on treatment.

Previous findings suggest that lateralization of brain processes related to language is not entirely a passive process, but can be influenced by manipulation of attention. Initial findings indicate that pairing an intention manipulation (complex left-hand movement) with picture naming during treatment has a positive impact on outcome and shifts lateral frontal activity toward the right hemisphere. However, these data, especially the fMRI data, should be considered preliminary at this point in time. Much work has to be done before the full impact of this manipulation on treatment can be assessed. For example, it is unknown how much the complex left-hand movement contributes to treatment outcome and re-lateralization of lateral frontal activity to the right hemisphere. My colleagues and I are currently conducting a study to address these questions. Another question that should be addressed is whether the intention manipulation can enhance the effects of other treatment manipulations. Hence, there is much work to be done before we completely understand the potential contributions of the intention component to treatment outcome.

To return to our opening comments, it is important to place this work in a broader context. At the beginning of this paper, I noted that two simple, related assumptions regarding the development of new treatments for aphasia. The first was that aphasia researchers and clinicians can develop treatments to engage specific neural substrates in the service of aphasia rehabilitation. Implementing this conceptually driven method requires that we learn a great deal more than we currently know about the neural substrates of treatment and recovery of function in aphasia. Doing so will require increasing investment in functional imaging studies. The second, related assumption was that aphasia researchers can use functional brain imaging to ascertain whether treatments developed in this fashion actually engage the targeted substrates. The findings regarding our novel intention treatment are promising in this regard. This treatment was developed to help patients with nonfluent aphasia focus word production mechanisms in the right lateral frontal lobe. To date, functional imaging data suggest that we have been successful in accomplishing this goal. More importantly, the data suggest that fMRI and other functional imaging modalities can be a powerful tool in developing conceptually driven treatments for aphasia that target specific neuroplastic substrates. Findings from functional imaging can be used to verify the conceptual basis of the treatment and to guide further development.

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Figure 1.

For each treatment phase, change in percent correct responses to probe items from baseline is shown. A significant treatment by phase interaction indicates that patients relearned words more quickly in the intention treatment (red) than the attention treatment (blue). From Crosson, Fabrizio, et al. (2007), *Journal of the International Neuropsychological Society*, reprinted by permission.

Figure 2.

Significant activity for the first patient described in the text is overlaid onto whole brain images divided into three slabs to facilitate viewing of activity. Pre-treatment images are on the left side of the figure; post-treatment images are on the right side of the figure. Since the brains are facing the viewer, the right side of the brain is on the left side of the image. The yellow arrows point to the areas in which activity increased from pre- to post-treatment scans.