



# NEUROPLASTICITY: EVIDENCE FROM APHASIA

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## INTRODUCTION

Grafman, in this issue, discusses four forms of neuroplasticity that may account for development and recovery of functional neural networks in the human brain. These include homologous area adaptation, cross-modal reassignment, map extension, and compensatory masquerade. The following discussion focuses on these forms of neuroplasticity as they pertain to recovery of language function in aphasia. The first part of the paper presents data showing that two of the four forms, homologous area adaptation and map extension, are relevant to recovery from aphasia. The second part of the paper discusses factors related to neuroplastic activity during language recovery, including neurophysiological, subject, and environmental, that is, treatment variables. Data from animal studies as well as recent data from aphasia treatment studies will provide a basis for this discussion.

## HOMOLOGOUS AREA ADAPTATION AND MAP EXTENSION

There is substantial evidence indicating that individuals with aphasia show recovery of language function despite sustained damage to left hemisphere language areas (Holland, Fromm, & DeRuyter, 1996). Converging evidence from clinical studies of aphasic patients, neural imaging studies, and other data suggest that the primary candidates for recovery include homologous right hemisphere areas (also referred to as *right hemisphere compensation* or *laterality shift*), undamaged portions of the language network in the left hemisphere, or both. Clinical evidence supporting the theory of homologous area adaptation came as early as 1893 when Gowers observed that recovered language function after initial left hemisphere injury deteriorates when a new right hemisphere infarct occurs. Clinical evidence such as this as well as observations that language re-

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covers to some degree even in individuals with large left hemisphere lesions are common (Basso, Gardelli, Grassi, & Mariotti, 1989, Willmes & Poeck, 1993). Studies of language development and restitution in left-hemispherectomized individuals also provide compelling evidence that the right hemisphere has the capacity to subserve language (Dennis & Whitaker, 1976; Wilson, 1970). The notion that recovery of function involves expanded cortical language regions in the left hemisphere, that is, map extension, is another widely accepted concept (Kertesz, 1988, 1989) also supported by clinical evidence. For example, individuals with aphasia often show further language decline after a second stroke in the left hemisphere (Basso, Gardelli, Grassi, & Mariotti, 1989), suggesting that cortical regions in the left hemisphere that are perhaps dedicated to another function in preinfarction states are recruited into the language network when brain damage occurs.

Neuroimaging studies also have provided insight into mechanisms underlying recovery of language in aphasia. Studies using single photon emission computed tomography (SPECT) or positron emission tomography (PET) show increased glucose metabolism or regional cerebral blood flow (rCBF) in the right hemisphere as well as in undamaged portions of the language network in the left hemisphere in aphasic individuals (Demeurisse & Capon, 1987; Cappa, Perani, Grassi, et al., 1997; Heiss, Kessler, Karbe, et al., 1993; Heiss, Kessler, Thiel, et al., 1999; Knopman, Rubens, Selnes, et al., 1984; Weiller, Isensee, Rijntjes, et al., 1995). Weiller, Isensee, Rijntjes, et al. (1995), for example, examined rCBF in six healthy persons and six individuals who had putatively recovered from Wernicke's aphasia. Participants repeated pseudowords in one condition and in another they generated as many verbs as possible when presented with nouns. Results showed rCBF primarily in the left hemisphere under both conditions in the healthy participants (although some right hemisphere activity also was noted), whereas those with aphasia showed increased rCBF in the right hemisphere in areas homologous to both Wernicke's and Broca's areas, that is, in the superior temporal gyrus and the inferior premotor and lateral prefrontal cortices. Individuals with aphasia also showed greater activation of undamaged areas of the left hemisphere, such as frontal areas in and around Broca's area, extending to the prefrontal cortex, than did the healthy participants.

In another PET study, Heiss, Kessler, Thiel, Ghaemi, and Karbe (1999) found rCBF patterns similar to those derived by Weiller et al. (1995). Patients with aphasia ( $n = 7$  with posterior lesions and  $n = 7$  with anterior lesions) underwent PET scanning involving a word repetition task. All participants were scanned at 2 and 8 weeks after stroke to examine changes in patterns of blood flow in early stages of recovery (i.e., during spontaneous recovery). Patients with posterior lesions showed increased rCBF in the right hemisphere in both anterior and posterior areas grossly homologous to Broca's and Wernicke's areas at 8 weeks after stroke. Healthy participants in the study also showed

right hemisphere activation, but only in posterior brain sites. In addition, the posteriorly lesioned patients showed increased activity in the left anterior area at 8 weeks as compared with 2 weeks after stroke. Individuals with lesions in the frontal area showed similar patterns, although both right and left hemisphere activation was constrained to posterior sites at the 8-week scan.

The findings derived from Weiller et al. (1995) and from Heiss et al. (1999) are suggestive of both homologous area adaptation and map extension. It is important to emphasize, however, that the healthy participants in both studies also showed activity in the right hemisphere. Therefore, observations of right hemisphere activation in aphasia may reflect part of the large-scale neural network that subserves language in at least some healthy individuals. This also holds true for map extension. That is, it is possible, and likely, that some healthy persons recruit cortical sites that extend beyond traditional left hemisphere sites when processing language. Because PET studies require averaging of data across several persons, individual patterns of language processing cannot be gleaned from such studies. Clearly, the extent to which right hemisphere activation, extended left hemisphere activation, or both in persons with aphasia is evidence of adaptation or map extension, respectively, cannot be resolved without further study of normal language processing as well as studies of pre- versus postrecovery activation patterns in aphasic individuals.

Another set of imaging studies that shed light on recovery of language in aphasia are concerned with brain mechanisms involved in sentence processing. Investigating the postulate that Broca's area is required for complex syntactic operations, several researchers have undertaken both PET and functional magnetic resonance imaging (fMRI) studies examining brain sites engaged during complex as compared with simple sentence processing in healthy volunteers (Caplan, Alpert, & Waters, 1998, 1999; Just, Carpenter, & Keller, et al., 1996; Stromswold, Caplan, Alpert, & Rauch, 1996; Thompson, LaBar, Fix, et al., 1998; Thompson, Fix, Gitelman, et al., 2000a). For example, in a recent fMRI study, Thompson et al. (2000a) asked participants to listen to complex object cleft sentences such as *It was the student who the biker lifted* and simpler subject cleft sentences such as *It was the biker who lifted the student* and to respond by pressing a button when these sentences matched pictures presented. Results showed that in all but one study (i.e., Just et al., 1996), activation during complex sentence processing was constrained to the left hemisphere: Broca's area was shown to be active in all studies, and in two of the five studies (both fMRI studies), Wernicke's area activity was noted as well.

Thompson, Fix, Gitelman, et al. (2000b) recently studied activation patterns under fMRI sentence processing conditions in four individuals with aphasia and compared them with our healthy volunteers' data. All participants had experienced a single, left hemisphere stroke in the distribution of the middle cerebral artery, and at least 1 year had passed since the stroke at the time of the study. All were right-handed, monolingual, English speakers with years of

education ranging from 14 to 16 years. Extensive language and neuropsychological testing showed patterns of performance consistent with a diagnosis of nonfluent, Broca's aphasia. Using the same paradigm used with our healthy volunteers, we found that three of the four participants recruited right hemisphere brain sites. Interestingly, none of these participants showed activation in right anterior brain sites (a finding consistent with Heiss et al., 1999); instead, all showed posterior activation in areas homologous to Wernicke's area. The fourth participant showed significant activation in the left hemisphere BA 37, with no recruitment of the right hemisphere. These data once again show evidence of homologous area adaptation as well as map extension, albeit the same caveats expressed above are relevant to these findings.

### **FACTORS RELATED TO NEUROPLASTIC PROCESSES**

There are several factors that may influence the course of language recovery in aphasia and concomitant neural correlates. One set of factors relates to neurophysiological processes that are at work during spontaneous recovery and thereafter. These organism-internal factors include processes occurring at the neural level such as regeneration and sprouting, changes in neurotransmitter release, return to premorbid blood flow levels, and so forth. Another set of factors are subject variables, that is, organism-specific factors. These include variables such as site and extent of lesion, age, education, gender, as well as motivation and other related factors. The precise influence of these factors on recovery is unclear, particularly with regard to how, or if, they influence neural tissue that will be recruited to support language as it recovers, that is, whether individuals will recruit homologous brain sites or will map language processes onto spared areas close to existing, but damaged, areas previously involved in language.

One factor related to recruitment of homologous brain sites discussed by Grafman (this issue) concerns the site and extent of brain damage. Grafman conjectured that when lesions completely destroy cortical regions that serve a particular function, homologous area adaptation is most likely to occur. Transfer of function is less likely to occur when damage is incomplete because homologous sites are inhibited under normal conditions by connections from contralateral regions. When damage is incomplete, inhibitory input is retained, thereby precluding transfer of function. Our data (Thompson et al., 2000b) and those of Heiss et al. (1999) do not completely support this postulate in that individuals in both studies with lesions only in left frontal regions showed recruitment of Wernicke's area on the right. Further study of recovery patterns in aphasia with careful attention to lesion site and extent will help to clarify this issue.

The third set of variables can be considered organism-external, including environmental factors such as the type and amount of language treatment provided. More specifically, the issue here is the extent to which treatment influ-

ences reorganization of the language system. Does treatment influence recovery or does language reorganize in a certain biologically predisposed manner, considering site and extent of lesion and other variables? Given the results of animal studies as well as recovery studies of aphasia, it is highly likely that treatment plays a strong role. Indeed, animal studies have shown that motor learning and motorically enriched environments, tactile stimulation, and auditory stimulation strongly influence neural organization of the primary motor, somatosensory, and auditory cortex, respectively (Black, Isaacs, Anderson, et al., 1990; Greenough, Larson, & Withers, 1985; Jenkins, Merzenich, Ochs, et al., 1990; Nudo, Milliken, Jenkins, & Meraenich, 1996; Recanzone, Jenkins, Hradek, & Merzenich, 1992; Recanzone, Schreiner, & Merzenich, 1993; Van Praag, Kempermann, & Gage, 1999). For example, Nudo, Milliken, Jenkins, and Merzenich (1996) found plastic changes in the functional topography of the primary motor cortex of adult squirrel monkeys after motor learning tasks, and Jenkins, Merzenich, Ochs, Allard, and Guic-Robles (1990) reported enlargements of somatosensory areas associated with controlled tactile stimulation in adult owl monkeys.

Studies also have shown that rehabilitative training after injury results in enhancement of representational plasticity (Nudo et al., 1996; Xerri, Merzenich, Peterson, & Jenkins, 1998). For example, Nudo et al. (1996) trained monkeys to retrieve pellets from small wells, an activity that requires skilled digital use. After training, lesions in the motor cortex were induced, after which the monkeys were once again trained to perform the task. Comparison of intracortical microstimulation maps of the motor cortex derived before and after lesion (and subsequent treatment) revealed substantial rearrangement of representations. Areas of cortical digital representation were expanded, while wrist and forearm representations were contracted. These findings indicate that experience directly shapes physiological reorganization after brain damage. Thus it is likely that treatment provided for aphasia influences the extent and manner of reorganizational processes.

Research aimed at examining the physiological bases of treatment-induced recovery from aphasia, however, is limited. The first investigation of short-term recovery on brain activation was recently reported by Musso, Weiller, Kiebel, et al. (1999). Four patients with Wernicke's aphasia secondary to lesions in the left temporoparietal area underwent a series of 12 consecutive PET scans. During each scan, participants were required to follow commands either to "point to" or "take" certain objects. Between each of the 12 scans (12-minute intervals), patients' comprehension was tested using a shortened form of the Token test (the sTT, part of the Aachen Aphasia Bedside Test) and treatment focused on language comprehension was provided. Group results showed activation in two brain sites correlating with improved performance on the shortened form of the Token test. These included the right hemisphere homologue of Wernicke's area, that is, the posterior part of the superior temporal gyrus, and the posterior part of the precuneus in the left hemisphere.

We also recently undertook an fMRI study to determine neural patterns associated with recovery. The aim in this study was to examine the effects of intense treatment focused on syntactic processing. The participant was a well-educated, 52-year-old, right-handed gentleman who had experienced onset of a left middle cerebral artery stroke resulting in aphasia 10 years previously. The patient had received a small amount of treatment for his aphasia soon after its onset. Extensive language testing at the time of the study showed residual agrammatic aphasia. Sentence length and grammaticality was compromised, and he produced more open-class than close-class words, and more nouns than verbs. Language comprehension was largely intact, although he showed the characteristic pattern of asyntactic comprehension, whereby only comprehension of complex, noncanonical sentences was compromised.

Before treatment, the patient was tested in the scanner using the protocol used with both healthy and aphasic individuals in our previous studies. He listened to sentences, both simple and complex, presented one at a time and viewed pictures. When a sentence matched a picture presented, he pressed a button. Thirty-two contiguous 4-mm axial slices were obtained relative to the AC-PC line using whole-brain echo-planar imaging. Before treatment, sentence processing as compared with a single-word control condition, resulted in significant activation in the right hemisphere in BA 22 (right homologue of Wernicke's area) and BA 46 (dorsolateral prefrontal cortex). After a 32-week course of linguistic-specific treatment (Thompson, Shapiro, Ballard, et al., 1997) focused explicitly on comprehension and production of verbs, verb argument structure, and movement operations involved in forming noncanonical sentences, increased activation was noted in right hemisphere homologous areas in and around Wernicke's area (activation now encompassed BA 22, 21, and 37) and in Broca's area (BA 44 and 45). These changes were associated with marked improvement in scanner task performance and behavioral testing.

These findings are indeed exciting and indicate that improvements in language processing ability, induced by treatment, can be mapped onto the brain. Importantly, it also appears that the areas of the brain recruited to support recovery differ depending on the type of treatment provided. Musso et al. trained patients to improve language comprehension, and concomitant improvement was noted in right hemisphere homologues of Wernicke's area; our treatment, focused on syntactic processing (both comprehension and production), resulted in marked changes in activation in right hemisphere homologues of Broca's area as well as Wernicke's area. Further research examining the neural correlates of treatment, of course, is needed to corroborate patterns demonstrated by the patient in our study and by those in the Musso et al. study. Further study examining the influence of the type of treatment on reorganizational processes also is needed. Because of the relation between behavioral change and brain reorganization that has been noted in the animal literature and now preliminarily in humans, it is likely that different treatments,

resulting in differential behavioral outcomes, are supported by different neural mechanisms.

## CONCLUSIONS

In conclusion, there is evidence for both homologous area adaptation and map extension in aphasia language recovery. Portions of the right hemisphere, extended left brain sites, or both have been shown to be recruited to perform language functions after brain damage. However, the extent to which such observations reflect processes of neuroplasticity is not entirely clear. It may be the case that such observations instead reflect large-scale neural networks that serve language even under normal conditions at least in some individuals. Indeed, further research charting normal patterns of language processing as well as work with brain-damaged individuals examining the neural basis of recovery throughout its course will help to clarify this debate.

The factors related to what parts of the brain are recruited to perform language functions after brain damage include a number of potential variables, although the precise influence of these variables remains unclear. Recent evidence from the animal literature appears, however, to extend to humans in that there is evidence that treatment influences language recovery and that the physiological bases of this recovery can be charted. Further work detailing recovery patterns and their physiological correlates will lead to a better understanding of neuroplasticity in aphasia recovery.

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