The right place at the right time?

Language functions that are disrupted by focal lesions in the left hemisphere often recover substantially over time. It has long been hypothesized that the right hemisphere gradually assumes language functions that have been impaired by left hemisphere lesions. This hypothesis has received support from a variety of sources. Individuals who recover from aphasia after stroke often become aphasic again after right hemisphere lesions (Nielson, 1946; Levine and Mohr, 1979) or after sodium amytal injection in the right carotid artery (Kinsbourne, 1971), consistent with the hypothesis that language had ‘crossed’ to the right hemisphere. Likewise, functional neuroimaging studies have often revealed more activation in the right hemisphere during language tasks in recovered aphasic patients compared to healthy controls (Weiller et al., 1995; Ohyama et al., 1996; Cappa et al., 1997; Musso et al., 1999; Thulborn et al., 1999; Thompson et al., 2000; Leff et al., 2002; Crinon and Price, 2005).

However, other functional imaging studies have revealed increased perilesional activation in the left hemisphere during language tasks compared to normal controls (Karbe et al., 1995; Heiss et al., 1999; Warburton et al., 1999; Thiel et al., 2001). Furthermore, several PET and fMRI studies have demonstrated that the degree of activation in right hemisphere areas (or perilesional left hemisphere areas) does not correlate with the degree of recovery (Heiss et al., 1999; Cardebat et al., 2003). A brief review of the literature on functional imaging studies of recovery of any function after stroke reveals that some studies show increased activation with improved function (e.g. Kessler et al., 2000; Thompson et al., 2000), while others, including that by Saur et al. published in this issue of Brain, show decreased activation with improved function, or first increased then decreased activation with recovery. Reduced activation with improved function is consistent with evidence from an overwhelming number of functional imaging studies in normal subjects indicating that activation decreases with increased expertise (e.g. Raichle et al., 1994).

Note that the apparently conflicting results from various functional imaging studies of aphasia recovery may not lead to mutually exclusive conclusions. These studies have investigated different language functions, or the same language function but using different tasks or paradigms. It is plausible that some language functions (e.g. word meanings) can be assumed by the right hemisphere, while other language functions (e.g. converting orthography to phonology) may not, but might be undertaken by perilesional regions of the left hemisphere (Coltheart, 2000; Hillis, 2002). There may also be increased activation (possibly related to active inhibition of some regions) with increased expertise in certain functions, but reduced activation with increased expertise in others.

The article by Saur and colleagues reports yet another variable that dramatically influences results of functional imaging studies of aphasia recovery—timing of the study in the course of recovery. The authors longitudinally studied 14 aphasic patients at three time points after left hemisphere stroke, in an event-related fMRI design using sentence comprehension (detection of semantic violations in spoken sentences). The patients, who demonstrated considerable recovery of language comprehension, showed distinct patterns of activation at each time point. In the acute phase of stroke recovery (mean 1.8 days after stroke), when their comprehension was most impaired, there was relatively scant activation (compared to that of normal subjects) that correlated with listening to intelligible sentences, primarily in perilesional regions of the left hemisphere. In the subacute stage (mean 12.1 days after stroke), when language comprehension had improved to some degree, there was greater activation in bilateral regions relative to controls, particularly in the right posterior inferior frontal cortex—the right hemisphere homologue of Broca’s area. This increase was largest in patients who showed early relative improvement in language. Finally, at mean of 321 days after stroke, when comprehension had largely recovered, there was a return to the normal pattern of activation, with greatest activation in the left hemisphere, particularly Wernicke’s area. This pattern of increased right hemisphere activation, followed by ‘re-shifting’ of increased activation to the left hemisphere has been previously reported in aphasia recovery (Heiss et al., 2003; Fernandez et al., 2004). In addition, patients exhibiting the best recovery are those who show this shift of language function back to the left hemisphere (Rosen et al., 2000). However, this finding may be at least partly explained by the fact that patients with the best recovery have smaller strokes, so that more of the left hemisphere is capable of showing activation.

The authors discuss a number of explanations for the relative paucity of activation in the acute stage of stroke, including diaschisis, persistent hypoperfusion of perilesional areas and impaired autoregulation that interferes with the blood oxygen level-dependent (BOLD) effect in fMRI. It is also possible that some patients were not really doing the task, but just guessing when to respond.
The more interesting result is the change in pattern from the subacute to more chronic stage of recovery, discussed as a 'shift' to the right hemisphere, followed by a shift back to the left hemisphere. But it remains unclear what (if anything) shifted places. Is it plausible that the right hemisphere 'took over' the task of sentence comprehension, or one or more of the cognitive processes required for detecting semantic violations in sentences? If this occurred, why did the right hemisphere later 'give up' these functions? If it became adept at processing sentence meaning, what advantage would there be to the shift back to the left hemisphere? Another possible explanation is that nothing really shifted hemispheres. Instead, the aphasic patients may have simply relied more on normal right hemisphere functions to carry out the task. The normal subjects did show activation of posterior inferior frontal gyrus during the sentence comprehension task, just not as much activation as seen in the second scans after stroke. This activation might reflect some rather general 'cognitive control' process as the authors suggest, such as an aspect of working memory, attention or response selection that engages bilateral posterior frontal cortex. Alternatively, or additionally, the activation might reflect cognitive processes involved in sentence comprehension for which the right hemisphere is specialized, such as perception of the prosody or integration of word meanings with contextual cues. It seems plausible that when left hemisphere cognitive mechanisms underlying semantic and syntactic processing of sentences are compromised, patients rely more on normal right hemisphere cognitive mechanisms to understand sentences. If so, the apparent shifts from left to right described in this study may reflect reorganization of cognitive processes that support sentence comprehension more than reorganization of structure/function relationships in the brain.

Further recovery was associated with re-emergence of the normal left-predominant activation, underscoring that left hemisphere cognitive processes are best attuned to sentence comprehension. This return to the normal pattern might be due to further reorganization of brain/language relationships (re-shifting of language, as the authors describe it). Equally likely, it might be due to resolution of diaschisis, allowing the normal left hemisphere language areas, and the semantic and syntactic processes that rely on these areas, to again support sentence comprehension (see Seitz et al., 1999; Price et al., 2001 for discussion of imaging changes in diaschisis). In other words, while there is clear evidence from neurophysiological studies that reorganization of structure/function relationships can occur after focal lesions, presumably through synaptic plasticity, changes in patterns of activation on functional imaging may not always arise from such plasticity. Other accounts of the results should always be considered.

There is undoubtedly much to be learned from functional imaging of language recovery after stroke. The article by Saur and colleagues illustrates the important influence of timing, best captured in longitudinal studies. Future longitudinal studies of patients who fail to recover language, compared to those with similar lesions who show good recovery, would provide additional useful information toward uncovering the mechanisms of recovery. It will be essential to investigate not only the changes in activation on scans, but also potential adjustments in cognitive processes that are used to carry out the tasks. It will also be valuable to compare changes associated with recovery to changes in normal subjects over time, since normal subjects can show alterations in patterns of activation with as little as 15 min practice of a task (Raichle et al., 1994). The study by Saur and colleagues provides a springboard for subsequent investigations, revealing the dynamic nature of language processing by the brain in response to focal injury.

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References
The NCLs encompass a group of lysosomal storage diseases and neurological consequences as seen in the human NCLs. Another disorder finds its gene, as exemplified by mutations in the CTSD gene. This gene encodes CTSD, which plays a critical role in the degradation of cellular proteins. Mutations in CTSD can lead to a variety of neurological disorders, including one form of lipidosis. The identification of the CTSD gene has provided insights into the genetic basis of these diseases and has opened avenues for further research into treatment strategies.

### Table 1: The Neuronal Cereoid Lipofuscinoses. Clinical classification, gene affected, and protein designation.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosome location</th>
<th>Gene affected</th>
<th>Protein designation/function</th>
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<tr>
<td>CNCL</td>
<td>11p15.5</td>
<td>CTSD</td>
<td>Cathepsin D</td>
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### Further Reading


### Additional Notes

- The identification of the CTSD gene has significant implications for the understanding of neurological disorders, particularly those associated with lysosomal storage diseases. Further research is needed to explore the full spectrum of diseases caused by mutations in CTSD and to develop effective treatments for these conditions.