Neuroimaging of Recovery of Function After Stroke: Implications for Rehabilitation

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Stroke is a leading cause of morbidity and mortality in individuals. Many patients have good functional recovery after stroke. The mechanisms of recovery remain largely unknown. Neuroimaging of patients recovering from stroke may provide important insight into the mechanisms of recovery as well as assist in the development of new rehabilitation techniques. The first part of this article reviews previous neuroimaging studies that have monitored the reorganization within the motor and language areas after stroke. In the second section, a unifying theory based on John Hughlings Jackson's "Principles of Compensation" is presented as a possible theory for recovery of function. In the final portion of the article, possible implications and future applications of neuroimaging studies for rehabilitation are presented. Key Words: Stroke—Rehabilitation—Neuroimaging—Primary motor cortex— Aphasia.
Neuroimaging Studies of Recovery of Motor Function

Previous studies have demonstrated that finger opposition gives large reproducible lateralized increases in cerebral blood flow (CBF). Motor function for the digits is predominantly represented in the contralateral primary motor cortex (PMC) in right-handed healthy subjects (17–19). Therefore, damage of the PMC due to stroke can cause contralateral hemiparesis or hemiplegia. However, after stroke, the hemiparesis is not a static phenomenon with partial or complete motor recovery being the rule rather than the exception.

A finger-tapping paradigm has been shown to lead to large reproducible increases in the CBF in the PMC and other corticospinal tract regions (20,21). A number of functional neuroimaging studies have thus used this paradigm to investigate the reorganization in adult patients who have recovered from stroke (7,22–26). In these studies, finger tapping in the hemiplegic hand was compared with finger tapping in the unaffected hand. In patients who had recovered significantly from the stroke, activation was observed within three regions: (a) the PMC ipsilateral to the hemiplegia (unaffected hemisphere), (b) the supplementary motor area (SMA) and other premotor areas, and (c) focally along the rim of the cortical infarct within the affected hemisphere.

A number of modalities including single photon emission tomography (SPECT) (27), PET (7,23,25), fMRI (22,28), and transcranial magnetic stimulation (29) have demonstrated that the PMC of the unaffected hemisphere is most commonly activated during finger-tapping movements in the hemiplegic hand of subjects who had recovered from stroke. A large quantity of evidence supports the possible restorative role for the unaffected PMC and ipsilateral corticospinal tract after stroke. In humans the corticospinal tract is highly lateralized (23). Ipsilateral projections do exist and have been anatomically identified (30,31). Most corticospinal tract fibers decussate in the medulla and form the contralateral portion of the lateral corticospinal tract. However, approximately 25% of the fibers remained uncrossed, with 15% of these fibers continuing as the ventral corticospinal tract and decussating mainly in the spinal cord to innervate the contralateral side. The remaining 10% of the fibers are uncrossed and form the ipsilateral portion of the lateral corticospinal tract (32,33). Nathan (34) has confirmed these results by demonstrating in patients with a previous cordotomy that interruption of the ipsilateral motor pathways in a second cordotomy immediately reversed any motor function recovery that had transpired after the initial cordotomy.

Animal studies have also suggested the participation of the ipsilateral PMC in the recovery of motor function after stroke. Tanji et al. (35) demonstrated that unilateral hand movements in monkeys led to bilateral activity in the PMC, the SMA, and premotor cortex. In further support, Glees and Cole (33), using lesion studies, have showed deficits in grip strength not only in the contralateral hand but also the ipsilateral hand of monkeys that had experimental lesions in the motor cortex. A monkey study by Ghosh et al. (36) also showed that motor recovery after an experimental lesion led to dendritic arborization and expansion of pyramidal cells in the unaffected PMC. Pharmacologic blockade of this arborization reduced motor recovery of the affected limb. These results suggest that neural growth within the unaffected-hemisphere PMC may be involved in recovery after stroke.

The SMA and premotor areas have also been implicated in a number of studies that have investigated recovery of motor function after stroke. Different hypotheses have been proposed to explain the involvement of these areas. Fries et al. (37) have suggested that SMA and premotor areas may become activated as tracts from these areas descend in parallel with the corticospinal tract from the PMC. Because these tracts are in close proximity, they may be intertwined such that one tract may substitute for the other functionally during recovery. Alternatively, some investigators have proposed that a hierarchic organization exists. The PMC may normally be responsible for control of limb movements with additional motor areas outside of the PMC, such as the SMA and premotor areas, involved in the planning or initiation of somatic
movements (7). In patients who have recovered from a stroke, previously simple movements may require increased task complexity and planning such that the SMA and premotor regions become activated (22,26).

A number of neuroimaging studies have also observed activation in periinfarct regions after prolonged recovery from stroke. These observed periinfarct activations may reflect cortical reorganization of viable regions within the remaining region, as has been observed in motor retraining in monkeys after stroke (38). This periinfarct activation could also represent the unmasking of alternative motor representations within these sites. Cramer et al. (39) have used a finger-tapping paradigm to assess the somatotopic maps of patients after cortical infarcts. In two patients with small, well-circumscribed infarcts that were limited to the precentral gyrus, finger tapping led to activation in the postcentral gyrus. These results suggest that reorganization along the rim of the infarct may also be important for recovery of function after stroke. More recently, functional activation patterns have been shown to change in patients who had an improved recovery from stroke (40). Patients who demonstrated the greatest recovery from a motor stroke had a progressive increase in activity in the periinfarct areas of the SMA and PMC contralateral to the affected hand. This evidence suggests that multiple regions of the brain, especially the periinfarct area, may be responsible for the cortical reorganization for functional recovery after stroke (22,23,41,42).

### Neuroimaging Studies of Recovery of Language Function

The other main network that has been studied in terms of the recovery of function after stroke has been the language system. The development of language in right-handed and most left-handed subjects involves many areas of the brain including the superior temporal (Wernicke's area) and the inferior frontal (Broca's area) gyri in the left hemisphere. These results have been derived from many sources including lesion studies and Wada tests (43). However, functional neuroimaging studies have demonstrated in some individuals that both hemispheres may participate in language processing (26,44,45). For example, although activation has clearly been demonstrated to be much greater in the left hemisphere of normal subjects for language tasks, some activation has also been observed in the right hemisphere during language processing (45). Thus, in a small proportion of individuals (estimates range from 5 to 15%), language function may be represented bilaterally (46).

Aphasia commonly occurs after strokes in the left middle cerebral artery distribution. Several studies have demonstrated a significant reduction in daily activities of living in patients who have had aphasia (47-49). A greater understanding of the mechanism of recovery after stroke will allow not only better predictors of recovery but also improved rehabilitative treatments.

A long-standing controversy exists concerning the role of the nondominant hemisphere (usually the right hemisphere) in the recovery from aphasia. Some neuroimaging studies have demonstrated either increased right hemisphere and/or bihemispheric pattern of activation in patients that have successfully recovered from aphasia (6,26,43,50,51). Early SPECT and PET studies showed increased glucose metabolism in the right hemisphere of patients that recovered from stroke in the posterior temporal–inferior parietal regions (50,51). More recently, Thulborn et al. (43), by using fMRI to study two aphasic patients over 9 months, demonstrated a rapid redistribution of language function with an increase in activation in the right hemisphere occurring within days after the stroke. Within the right hemisphere, further consolidation occurred over subsequent months.

In a PET study of patients who had functionally recovered from Wernicke's aphasia, a verb-generation paradigm led to increased activation within the right superior temporal gyrus and inferior premotor and lateral prefrontal cortex, homologous area to the left hemispheric language zones. Activation was also seen in the lateral prefrontal cortex and the inferior frontal gyrus in the left hemisphere. However, no activation was seen in the left superior temporal gyrus, as destruction of Wernicke's area was used as an inclusion criterion. These authors hypothesized that the presence of other afferent pathways from Broca's area to prefrontal areas and Wernicke's area in the right hemisphere allowed recovery of language processing after stroke. The proposed mechanism(s) remain unknown but could be due to a unmasking of right hemispheric language function that had been previously suppressed during early lateralization or a gradual elaboration of new language function in the right hemisphere (6). The increased activity in lateral prefrontal areas in the right hemisphere could also be related to increased intentional mechanisms or the need for sustained attention for perception and comprehension of the stimulus (52).

These PET results studying the recovery of function after aphasia are similar to previous neuroimaging studies that have investigated recovery of the motor system after stroke. In both situations, bilateral activation was observed in the primary system, with increased activation in the nondominant hemisphere, as well as the recruitment of nonprimary areas involved in attention and intention. However, problems exist in the data analysis of
this PET study by Weiller et al. (6), as the six aphasic patients were analyzed as a single group. Such an experimental approach decreases the likelihood of detecting activation near the lesion in Wernicke's area, which was not found in this study, while increasing the likelihood of detecting right hemispheric activation, especially if patients who recovered language were from the small subpopulation (5–10%) of individuals who have bilateral representation of language (46,53).

Recently a number of studies have suggested that perilesion areas remaining within the left hemisphere may provide an indicator of possible recovery from aphasia (54–60). Naessar et al. (58–60) have performed computed tomography (CT) scan on patients 2 or 3 months after stroke onset to assess potential long-term recovery of speech and comprehension. These studies demonstrated that language recovery may be linked primarily to functional recovery in the dominant hemisphere with increased perfusion to areas adjacent to the lesion crucial for recovery (58–60). Similar results have also been observed by Heiss et al. (61). The amount of residual perilesion area in the superior temporal lobe of the dominant hemisphere correlated with the degree of functional language recovery from stroke. During a word-repetition task, immediately after a stroke, patients activated the right inferior frontal (contralateral to Broca) and right temporal areas (planum temporale and posterior superior temporal gyrus). Those patients who maintained language improvements had pattern shifts in their activation. Activation in the right temporal areas persisted, whereas activation in the right inferior frontal areas disappeared, and left temporal area was reactivated (61). A satisfactory functional recovery was observed only in those patients who had preserved enough of their left superior temporal gyrus and the left planum temporale so that they could be successfully reintegrated into the perisylvian circuitry of the dominant hemisphere. In those patients with complete or almost complete destruction of the posterior superior temporal lobe, functional recovery was markedly reduced (61). These results are in accord with a previous finding that prognosis after a stroke can be predicted by the relation between the flow and metabolism in and around the infarct (62).

Hughlings Jackson's “Principles of Compensation” May Provide a Unifying Theory for Explaining Recovery of Function After Stroke

John Hughlings Jackson (1835–1911) developed the "Principles of Compensation" to explain the mechanisms of recovery of function after stroke (31,63). According to the Hughlings Jackson organizational scheme, the nervous system is hierarchic with each evolutionary level containing a complete representation of the next lower level. However, within each level, a particular element is uniquely weighted for a specific body function. This ordinal representation ensures that each level is ordered by inclusion. At the lowest level of this hierarchic system, an element represents a particular function. In the middle levels of this system, an element is rerepresented. However, in this middle level, one element is more heavily weighted for a certain body function. Similarly, the highest level contains a complete representation of the middle level with each element rerepresented (31,63,64).

If the nervous system were organized according to this theory, then focal destruction of certain nervous tissue could lead to dynamic changes in undamaged areas. Those areas that are spared will be recruited in proportion to their initial weighting for the affected area. Damage to lower levels would produce more severe symptoms compared with higher levels as lower levels do not contain complex and interconnected representations of the damaged areas.

Hughlings Jackson's "Principles of Compensation" may provide a good initial model for understanding recovery of function after stroke if (a) an ordinal hierarchic system was observed; (b) "remote effects" due to hierarchic links were seen; and (c) a rerepresentation occurred after stroke. Figure 1 represents the changes in activation that would be expected for a fingertapping paradigm before, during, and after recovery from stroke. Before stroke, an ordinal hierarchic system is observed, with finger movements leading to increased activity within the corresponding contralateral finger area representations in the lowest level (PMC) as well as areas that represent finger movements in middle (SMA) and higher (premotor areas) levels (Fig. 1A). As seen in Fig. 1B, a stroke in the contralateral PMC leads to hemiplegia of the digits. Recovery from the stroke will lead to increased activity within a number of regions. An increase in activity in perilesion areas within the same lower level could occur. In addition, other lower levels, such as the unaffected ipsilateral PMC, also may become activated. An increase in activation could also be present in middle levels such as the SMA and higher levels such as premotor areas. As demonstrated previously in many of the neuroimaging studies, an increase in activation has been observed in all of these regions after recovery from stroke (22,23,41,42). These results of increased activity within undamaged levels both at the same level as well as at higher levels suggest that a hierarchic ordinal system of recruitment may occur during functional recovery from stroke (31).
NEUROIMAGING OF RECOVERY OF FUNCTION AFTER STROKE

Figure 1. Graphic depiction of Hughlings Jackson's "Theory of Compensation" for describing recovery of function after stroke (modified from York and Steinberg, 1995). A: Hierarchic ordinal system with weighting according to Hughlings Jackson's model in a normal subject. F, face; H, hand; L, leg. Weighting in the middle and highest levels are depicted in bold. B: Acute stroke occurring in the lowest levels (the primary motor cortex). Ipsi refers to the cortex ipsilateral to the hemiplegic hand and contra refers to the cortex contralateral to the hemiplegic hand. C: Recovery after stroke in the primary motor cortex. Reweighting is depicted by changes in size of the elements. Recovery occurs in four regions: (a) area surrounding the cortical infarct, (b) the primary motor cortex ipsilateral to the hemiplegic hand, (c) a reweighting in the supplementary motor area of the cortex contralateral to the hemiplegic hand, and (d) a reweighting in the premotor cortex contralateral to the hemiplegic hand.

According to the Hughlings Jackson theory, decreased CBF should be observed in areas damaged by the stroke as well as in more distant areas (middle and higher levels according to Jackson classification). This diaschisis or "remote effect" has been observed in PET studies, in which hypometabolism and hyperperfusion areas were seen in areas distant from the visible infarct that had not been infarcted (15,65). These remote effects may be due to structural disconnections by means of wallerian or retrograde degeneration (6). In addition, the patterns of activation in patients that had recovered from stroke are different from those in normal subjects. An increase in bilateral activation, as well as increased activation in middle and higher levels, supports the idea of a possible reweighting during recovery, with recruitment of areas that originally contained a representation of the damaged area.

However, for many patients, small cortical strokes can lead to permanent hemiplegia or muteness, with the patient never recovering. These patients would seem to demonstrate a possible unifocal representation of a particular function rather than the Hughlings Jackson weighted representation. A system of dynamic weighting that is specific for each individual may account for the observed differences in recovery among patients. Just as some areas may be strongly weighted for a given function within an individual, there may exist intersubject differences in the weighting of a function (26,31). In some individuals, the representation for a particular function may be so heavily weighted within a small area, that if this region is destroyed, then the residual representations may not be able to compensate (66). Alternatively, a regulatory center for reweighting of representation may be damaged such that recovery cannot occur. This dynamic weighting hypothesis may explain the different recovery results observed for aphasic patients (67,68). Recovery is severely limited in those patients, with complete destruction of the posterior superior temporal lobe as access to the dominant hemisphere network is no longer possible. Instead, recovery of language function could be mediated, although in a more limited capacity, by nondominant hemispheric structures. However, if some of the temporal eloquent cortical areas are preserved and are reintegrated within the functional network, then satisfactory recovery of language can occur (61).
Limitations of The Neuroimaging Studies of Recovery of Function

Although neuroimaging studies have provided many insights into the recovery of function, several limitations exist with the current techniques. First, a major assumption of neuroimaging studies is that regions that are activated for a particular task are causally involved in that process. In reality, this may not always be true, because of the observational and correlative nature of neuroimaging (69–72). In some cases the subject may unwittingly engage in additional processes other than the one being tested or may fail to engage in the process at all. Thus, it is impossible to know if the observed cerebral blood flow (CBF) changes associated with an increased neuronal activity are due to the process of interest that is being tested or if the increased neuronal activity is unintended. Additional studies of these patients with transcranial magnetic stimulation may be required to determine the necessity of these particular regions after functional recovery.

Second, most neuroimaging techniques use either metabolic activity (PET) or changes in CBF (fMRI) as markers of neuronal activity. These measurements may not be adequate measures of neuronal activity if CBF is a nonlinear transformation of neural activity (73). Moreover, significant vascular changes may occur after stroke. These changes may alter the patterns of activity observed with PET or fMRI. More direct measurements of neural activity such as magnetic encephalogram and electroencephalogram are required in conjunction with the neuroimaging techniques (74,75).

Third, often the original representation of the lesioned area is not known before the stroke. Penfield (76) initially demonstrated that there exists a wide variability in the somatotopy of individuals. Somatotopic differences not only exist between individuals, but also between hemispheres in an individual (8). An understanding of those areas activated before stroke would allow determination of the areas that had become functionally recruited after stroke.

Fourth, the site and extent of the lesion cannot be controlled, as every human stroke is different. This is particularly an issue with some PET studies in which subjects were combined for data analysis. With fMRI, this issue does not occur, as within-subject studies can be easily performed.

Fifth, most of these neuroimaging studies that have been performed have selected a small group of chronic patients who have almost completely recovered from stroke (77,78). Studies of the recovery of motor function have been performed on adult chronic patients that have regained sufficient motor control to voluntarily perform simple movements, such as index finger tapping (22,39,42) or sequential finger opposition (7,19). Only recently has a neuroimaging study with PET investigated the early functional organization of motor and sensory systems in hemiplegic stroke patients before motor-recovery therapy. Passive movements in hemiplegic stroke patients before clinical recovery elicited similar patterns of activation (ipsilateral PMC and SMA and premotor areas) compared with patients with substantial motor recovery that performed similar tasks (77). These results suggest that recovery may occur rapidly and may have important implications for developing rehabilitation programs early in recovery.

Implications for Future Rehabilitation Techniques

Debate still surrounds the importance of rehabilitation after stroke. Early reviews of the efficacy of rehabilitation after stroke asserted that “convincing evidence concerning the therapeutic usefulness of stroke rehabilitation does not exist” (79). However, more recent animal models of rehabilitation have demonstrated an important role for rehabilitation in the recovery of function after stroke. Experimental studies in squirrel monkeys have demonstrated that retraining of hand skills 5 days after stroke prevented the loss of the hand representation around the lesion that was normally observed after stroke (38). Other experimental studies of rehabilitation in monkeys have demonstrated that cortical reshaping after stroke depends on the nature of the practice rather than just simply its presence. In adult squirrel monkeys that had experienced small ischemic lesions in the hand area, goal-directed training led to better outcomes in both performance and neuroanatomic reorganization compared with no training or simple motor movements (16). More recently a number of human studies have reached similar conclusions. Early extensive rehabilitation can lead to an increase in recovery of function (80–82). Recent meta-analysis studies have demonstrated a small but statistically significant improvement in activities of daily living with increasing intensity of rehabilitation after stroke (83,84). However, a fine balance may have to be achieved, because experimental evidence from rats has demonstrated that overuse of the affected limb during the first week after the lesion can increase the volume of the lesion (85).

Recently the rehabilitative technique of constraint-induced (CI) movement therapy has shown great promise. CI consists of two components: (a) constraining the movement of the healthy upper extremity, and (b) intensive training of the paretic arm (86,87). This therapy
has been demonstrated in both animal models and humans to lead to enhanced neuronal excitability in the damaged hemisphere of the target muscles. A small effort in studying the pharmacologic effects on the recovery in patients with chronic stroke has also led to some promising results. A previous animal model of stroke demonstrated short-term decreases in catecholamine concentrations in the cortex and brainstem of rats that experienced a small lesion. In particular, a decrease in the concentrations of norepinephrine (NE) and dopamine (DA) were present chronically after a stroke in rats (88). Intravenous administration of dextroamphetamine, haloperidol, and phenoxybenzamine in combination with training led to significant improvements in rats that had experienced strokes (89). Similar results have been also observed in humans. Patients that received D-amphet­amine in conjunction with behavioral and physical therapy had a significant improvement in recovery from stroke compared with controls (90).

No studies have been performed using neuroimaging techniques to monitor the changes in recovery that occur with rehabilitation. These studies may have important implications for the future development of rehabilitation techniques. Recent studies of recovering aphasic patients have demonstrated that preservation of perilesional tissue in the dominant hemisphere may be a good predictor of successful recovery of function (61). These future studies may also be important, as one report that investigated aphasic patients undergoing melodic-intonation therapy demonstrated that patients who had improved speech performance had decreased right hemisphere activation and increased left hemisphere activation (91). This result may be interpreted as suggesting that at least in some patients, increased right hemispheric activation may correlate with a persistence of an aphasic deficit rather than maximal recovery. An increase in activation of the right hemisphere may also suggest a maladaptation that could decrease as recovery progresses (40). Imaging of patients at different time points during rehabilitation may also provide insight into the mechanisms involved in the recovery of neurologic function (92). Investigating the changes in activation within certain regions of interest during recovery may help differentiate among possible mechanisms of recovery such as (a) subcortical reorganization by means of tissue repair caused by denervation, (b) axonal sprouting and synaptogenesis, (c) activation of temporarily deactivated intact brain regions that are remote from but anatomically connected to the area of primary injury (deactivation by diaschisis), and (d) reinforcement of ipsilateral pathways (93). With the development of improved imaging techniques, new rehabilitation strategies for the recovery of function after stroke may appear in the near future.

References


