Stroke is a leading cause of disability in the United States and is likely to have an increasing impact on disability worldwide. In order to develop more effective rehabilitation techniques, it is critical to understand the mechanisms underlying the neural circuitry required for recovery. Over the past decade, functional brain imaging has been a principal investigative tool in elucidating mechanisms of stroke recovery. Functional imaging studies of motor performance in patients with stroke consistently demonstrate areas of brain activation not present in healthy subjects. The role of these additional areas in recovery after stroke remains uncertain. This review discusses methodologic and theoretical issues that impact on interpreting functional imaging studies of motor recovery after stroke.

Introduction

In recent years, there have been significant advances in the prevention and acute treatment of ischemic stroke. Nevertheless, stroke remains a leading cause of disability in the United States, costing approximately 30 billion dollars a year in direct costs and lost productivity [1]. Thus, there is a pressing need to characterize the mechanisms of recovery after stroke and develop methods to enhance these mechanisms with rehabilitation strategies and pharmacologic therapies. In the past 10 years, functional imaging techniques, principally positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have been at the forefront of efforts to understand the neural substrates of recovery after stroke in humans. PET and fMRI are both based on the principle that an increase in a brain region's neuronal activity is accompanied by concomitant increase in local blood flow and blood oxygenation. PET uses radioactive isotopes that label regions of increased cerebral blood flow (CBF) [2]. The fMRI blood oxygen level dependent (BOLD) signal arises from an increase in the ratio of oxy- to deoxy-hemoglobin in the draining veins of areas of increased neuronal activation [2]. The need for radiolabeled ligands in PET makes it both expensive and limits the number of times a given patient can be studied. As a result, fMRI is the imaging method of choice in most studies of stroke recovery. It is not the purpose of this review to provide any further details about PET and fMRI techniques (see Toga and Mazziotta [2] for a recent overview) to provide an exhaustive account of all functional imaging studies of stroke to date (see Cabanis and Bacon [3] for an excellent review). Instead, it will highlight methodologic and theoretical issues regarding the design, analysis, and interpretation of recent functional imaging studies of motor recovery after stroke. Although this review focuses on motor recovery, many of the issues raised are applicable to functional imaging of other forms of recovery after brain injury.

Choice of Patients and Controls

Determining general principles for recovery from stroke is a challenge because it is a heterogeneous disease with regard to patient age, lesion location, lesion size, and etiology. All these factors, unless accounted for, may affect brain activation in ways that will complicate interpretation of results as they pertain to recovery. The elderly, when compared with the young, recruit additional brain regions for even simple motor tasks [4] and show differences in BOLD signal [5]. It is therefore, essential to use age-matched control subjects in functional imaging studies of stroke in order to avoid erroneously attributing age-related activation changes to reorganization after stroke.

Studies of hemispheric suggest that differences in prognosis for recovery depend on lesion location [6]. These differences seem to depend primarily on the degree of concomitant tactile involvement [7]. In addition there is evidence to suggest that cortical and subcortical strokes have differential effects on cortical excitability in the contralateral hemisphere [8]. Specifically, whereas cortical strokes show decreased transcortical inhibition, subcortical strokes do not. Given these differences, investigators should provide explicit reasons for the decision to combine patients with either cortical or subcortical strokes in a single group analysis.

Group analysis of functional imaging data relies on successful spatial registration of homologous brain areas to an anatomic template (spatial normalization) [2]. However, focal lesions can support automated spatial normaliza-
ion procedures because the lesion will be of very different intensity from the group of patients being evaluated. This will lead to an automatic software algorithms to adjust parameters to minimize differences between the lesion and the template.

at the expense of widespread mismatches elsewhere. Brett et al. [9] have shown that masking the lesion before the normalization step reduces distortion compared with the standard affine-only normalization. This masking technique has now been used successfully in studies of stroke recovery [10,11] and should be considered for any functional imaging study of patients with focal lesions. The presence of hemodynamic significance large vessels disease, especially with compromised vascular reserve [12,13], can affect the BOLD signal by uncoupling oxygen metabolism and regional cerebral blood flow [14,15]. Theoretically, this could make interpretation of activation patterns in the hyperperfused hemisphere difficult. For example, unaffected regions in the ipsilesional hemisphere supplied by the stenosed vessel as the infarcted region, may be neurologically active and contribute to recovery but nevertheless fail to produce a BOLD signal. Rather than excluding patients with hemodynamically significant extracranial or intracranial large vessel disease from functional imaging studies, it will be necessary to design studies that specifically address this important stroke subgroup. One possible strategy would be to limit analysis to activation changes in regions that have normal perfusion or to only look at activation changes in the contralateral, hemodynamically normal hemisphere.

Defining Motor Recovery

In order to design successful functional imaging experiments investigating motor recovery, motor recovery needs to be properly defined. This is by no means trivial; a large variety of scales exist to measure motor function [16] and, depending on which scale is chosen, the patient may or may not be considered completely recovered. In addition, motor scales that assess disability rather than impairment cannot reliably distinguish between compensation and true recovery. Compensation allows a patient to achieve a task goal using an alternative strategy [eg, the patient with right hemiparesis who learns to use his or her left hand]. In contrast, complete motor recovery implies that the patient is performing the task the same way behaviorally as age-matched control subjects. Ideally performance measures should be sufficiently sensitive to detect impairments despite the presence of compensatory strategies. This is of particular importance in a functional imaging study because compensatory strategies are also likely to cause missed patterns of activation. For example, use of more proximal limb muscles to aid distal control might lead to contralateral activation, as proximal muscles have more bilateral cortical representation, but this activation would not indicate reorganization after stroke.

A final consideration is how to measure change in impairment to still recovering patients; either they can be graded on an absolute outcome scale or they can be graded as a relative change. This distinction is difficult to obtain using hypothetical examples. Using a relative change scale, a patient with hemiplegia who recovers to some degree of functioning will likely have a larger change score than someone who is only mildly affected at the time of presentation. In contrast, using an absolute outcome scale, the mildly affected patient will have a higher score than the initially hemiplegic patient. Thus, it can be difficult to interpret a change scale is likely to be more informative in moderate to severely affected patients, whereas an outcome scale is likely to be better in studies of patients with only mild hemiparesis. A categorical distinction between those patients with mild hemiparesis and those with mild impairment is supported by psychophysical studies [17,18].

The Motor Task in the Scanner

A critical component of studying motor recovery after stroke is the choice of motor task to be performed by the patients in the scanner. The majority of studies of motor recovery has used either hand grip or finger opposition tasks. The PET environment allows for all arm movements, but this is difficult in fMRI. Although it has been argued that finger movements should be the principal focus of studies of motor recovery [19], this view reflects a bias based on the difficulties of investigating any other type of movement in the MRI environment. After all, without preserved reaching the hand cannot be used. Limitations of fMRI limi- tations of fMRI as a localizer trajectory data or scanning visuomotor control. Thus, quantification of finger tasks has so far been restricted to rate and force measures.

Motor studies of stroke patients in the MRI scanner present a number of practical problems. The first is unwanted head movements. Head motion causes misregistration of voxel locations to anatomical locations, leading to both false positive activations when these are task-correlated and head motion and false-negative activations due to random motion introducing increased spatial noise in the fMRI signal [19]. In an important study, Seto et al. [20] compared head movements in young subjects, aged healthy subjects, and in patients with stroke while they performed either a hand grip task or a foot flexion task in a simulated fMRI environment. The two important findings were that patients with stroke produced more head motion than age-matched control subjects and that their head motion was significantly more task correlated. Unfortunately, head motion constraints did not effectively reduce the translational head motion. Potential solutions to the problem of head motion include training patients prior to the fMRI experiment, screening out patients with excessive motion, considering event-related design, choosing tasks that minimize head motion, and using head restraints.

A second practical problem encountered in patients with stroke is movement. These are involuntary, synchronous movements of one limb during voluntary movement of the contralateral homologous limb. There is a higher
incidence of mirror movements in the unaffected hand of patients with hemiparesis and in the contralateral hand of matched control subjects [2,21]. Among the presence of mirror movements after stroke may be the result of recovery mechanisms, their presence complicates interpretation of imaging studies of motor recovery because they are associated with activation in contralateral motor cortex [22,25] and correlate with severity of motor deficit [21,22]. For example, a PET study of patients with stroke had fully recovered from hemiparesis, increased sensorimotor cortex activation in the contralateral hemisphere was always associated with mirror movements in the unaffected limb [25]. Use of electromyography to record transcranial electrical stimulation in the scanner or during out-of-scanner training, to confirm the absence of mirror movements increases confidence that contralateral activation relates to movement of the affected limb.

A unique challenge for functional imaging of motor tasks is presented by patients with hemiplegia. Two strategies have been attempted in this group. The first is to use passive forearm and finger movements. An approach based on PET and fMRI studies in healthy subjects showing that active and passive forearm movements result in similar patterns of brain activation [26]. Nelmes et al. [26] have shown that passive elbow flexion-extension movements in hemiplegic patients with subcortical stroke, when compared with healthy control subjects, activate contralateral sensorimotor cortex and bilateral parietal areas. The contralateral sensorimotor activation has been described in several studies of active finger movements in patients with subcortical stroke who have made near or full recoveries [27,28]. However, the possibility that these early changes may play a role in remission of function. The second and less-used strategy is to study patients with hemiplegia and motor imagery. Psychophysical and functional imaging studies in healthy subjects have demonstrated strong similarities between motor imagery and motor execution [29]. These results in healthy subjects have led to analogous studies in hemiplegic patients [30,31]. A potential use of imagery movements would be to see if patterns of activation in the acute period predict future recovery. However, psychophysical studies indicating preserved motor imagery in chronic hemiplegic patients is (ie, patients who fail to recover) raise the possibility that real and imagined movements are distinct processes that do not necessarily influence each other.

A final concern with regard to the choice of motor task in the scanner is whether it can be generalized to more global measures of motor performance outside the scanner. Even if the more global measure (eg, the Fishel-Mayer scale) accurately reflects the impairment (rather than just compensation), it may not relate to the more specific hand tasks in the scanner. Solutions to this problem include ensuring that the task that measures recovery is nearly identical to the within-scanner task or that a strong correlation between the within-scanner measure and the out-of-scanner measure ideally, the latter correlation should be previously established in a separate set of patients.

Studies in Fully Recovered Patients Versus Longitudinal Datasets. In the longitudinal context, patients who have fully recovered from subcortical stroke can be considered fully recovered [25,30-34]. The initial PET imaging investigations of brain activation changes after stroke were PET studies of patients fully recovered from subcortical strokes [24-27,32]. More recently, an approach has shifted to studies after longitudinal training in recovering patients [11,33,34]. Based on the idea that recovery is a dynamic process that cannot be captured at a single time point. There are very few studies, however, to focus on fully recovered patients when attempting to elucidate the mechanisms of restorative plasticity. This is because with full recovery (absent compensation or mirror movements), any statistically significant difference in brain activation compared with control subjects is strong evidence for a true functional contribution of the unique area of activation to recovery. Using this reasoning, Neiher et al. [24,37] and Choulet et al. [32] showed recruitment of additional areas in the ipsilesional and contralateral hemisphere in patients recovered from subcortical stroke. Similar results, showing contralateral sensorimotor area and perilesional activation in patients with full or near-full recovery, have been obtained more recently using fMRI [28].

Interpretation of activation changes in studies of partially recovered patients is much more difficult. This is because partially recovered patients have imputed poorer performance compared with age-matched control subjects. Therefore, interpretation of these differences may be attributable to this performance difference. An approach based on PET and fMRI studies in healthy subjects showing that active and passive forearm movements result in similar patterns of brain activation [26]. Nelmes et al. [26] have shown that passive elbow flexion-extension movements in hemiplegic patients with subcortical stroke, when compared with healthy control subjects, activate contralateral sensorimotor cortex and bilateral parietal areas. The contralateral sensorimotor activation has been described in several studies of active finger movements in patients with subcortical stroke who have made near or full recoveries [27,28]. However, the possibility that these early changes may play a role in remission of function. The second and less-used strategy is to study patients with hemiplegia and motor imagery. Psychophysical and functional imaging studies in healthy subjects have demonstrated strong similarities between motor imagery and motor execution [29]. These results in healthy subjects have led to analogous studies in hemiplegic patients [30,31]. A potential use of imagery movements would be to see if patterns of activation in the acute period predict future recovery. However, psychophysical studies indicating preserved motor imagery in chronic hemiplegic patients is (ie, patients who fail to recover) raise the possibility that real and imagined movements are distinct processes that do not necessarily influence each other.

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In summary, studies of patients with complete recovery show preserved functional activity in the contralesional hemisphere, not seen in age-matched control subjects. In contrast, studies in still-recovering patients show that recovery is associated with a return, over weeks to months, to more normal patterns of activation. A number of important issues are raised by this apparent contradiction. First, the longitudinal studies only show a correlation between improved performance and a return to patterns of activation seen in age-matched control subjects. As outlined previously, all this demonstrates is that the more patients perform like normal subjects, the more normal is their pattern of activation. Such a finding, however, is a negative result with regard to reorganization. In order to demonstrate reorganization related to restoration of function in a longitudinal study, it is necessary to show a positive correlation between a novel area of activation that is not present in healthy subjects and improvement in performance. Thus, on the basis of reorganization and restoration plasticity, the longitudinal studies published to date can at best only suggest, but not demonstrate, that early recruitment of additional areas may play a role in the transition to more normal patterns of activation. Second, there has not yet been a longitudinal study of motor recovery after cortical stroke. It is possible that in those cases where cortical motor areas are damaged, additional recruitment plays a bigger role in the chonic state. Third, a contribution of ipsilesional and contralesional motor areas to motor recovery is strongly suggested by recent animal and human studies. For example, in a recent microelectrode stimulation study in squirrel monkeys, Frost et al. [40] showed that there was increased hand representation in ipsilesional ventral premotor cortex in direct proportion to the decrease in representation in contralesional primary motor cortex. This is an important result because it indicates that the degree of additional recruitment is a function of the severity of the deficit. This is consistent with recent imaging studies and provides an explanation for why studies have shown an inverse relationship between recovery and degree of additional recruitment. The critical point is that motor impairment might be even worse if additional recruitment does not occur, even though the optimal solution is to return to normal patterns of recruitment. This point is supported by a recent study using transcranial magnetic stimulation (TMS) [41,42]. In this study, the investigators demonstrated that single-pulse TMS applied early (100 ms after a reaction time cue) to contralesional dorsal premotor cortex impaired finger movement reaction time on the affected side and did so in proportion to the degree of contralesional activation seen with fMRI. Specifically, there was a near-significant positive correlation between the degree of contralesional activation and the degree of hand paresis. The authors concluded that greater impairment produces a greater restorative response in contralesional areas, with contralesional dorsal premotor cortex activation mediating partial recovery in the most impaired patients.

Conclusions

Functional imaging studies of motor recovery in patients with hemiparesis have consistently shown recruitment of additional areas. The significance of these recruitment patterns to motor performance remains an open question. The majority of recent functional imaging studies indicate that optimal recovery is best accomplished by returning to patterns of activation seen in healthy control subjects. These studies, however, do not directly address the possible role of alternative brain regions in restoration of motor function nor are their conclusions incompatible with such a possibility, as the study by Johansen-Berg et al. suggests [43].

The functional imaging literature reveals a series of dichotomies regarding the potential for motor recovery after stroke that need to be resolved: cortical versus subcortical strokes, the presence versus absence of hemodynamic flow failure, fully recovered versus partially recovered patients, cross-sectional versus longitudinal studies, and ipsilesional versus contralesional activations. In addition, there are significant methodological issues that can confound interpretation of functional imaging results. These include motor recovery measurement, task difficulty, test-retest reliability, and the independent effect of motor performance differences on brain recruitment patterns. Solutions to these problems, apart from careful study design with larger numbers of well-selected patients, will require a convergence of information from reversible inactivation studies with TMS, detailed psychophysical characterization of motor deficits, and parallel studies in animal models.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

1. Of importance
2. Of major importance


21. Important study of the effects of noise on head motion during motor tasks in the MRI scanner.


First TSMS study to show functional importance of a contralateral area, identified by fMRI, for motor recovery after stroke.