Functional Imaging of Motor Recovery After Stroke: Remaining Challenges

John W. Krakauer, MD

Address
The Neurological Institute, Columbia University College of Physicians & Surgeons, 710 West 168th Street, Box 214, New York, NY 10032, USA.
E-mail: jwk18@columbia.edu

Current Neurology and Neuroscience Reports 2004, **4**:42–46
Current Science Inc. ISSN 1528–4042

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 mature brain's capacity to reorganize and restore neurologic function. Over the past decade, functional brain imaging has been a principal investigational 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 phenomenon 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 metabolites that label areas 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 deoxyhemoglobin 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) or to provide an exhaustive account of all functional imaging studies of stroke to date (see Calautti and Baron [3••] for an excellent review). Instead, it will highlight critical 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 aging-related activation changes to reorganization after stroke.

Studies of hemiparesis suggest that differences in prognosis for recovery depend on lesion location [6]. These differences seem to depend primarily on the degree of corticospinal tract involvement [7]. In addition, there is evidence to suggest that cortical and subcortical strokes have differential effects on cortical excitability in the contralesional hemisphere [8]. Specifically, whereas cortical strokes show decreased transcallosal 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 distort automated spatial normalization procedures because the lesion will be of very different intensity from the equivalent area in the template. This will lead 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 hemodynamically significant large vessel disease, especially with compromised vasomotor 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 hypoperfused hemisphere difficult. For example, unaffected regions in the ipsilesional hemisphere, supplied by the same stenosed vessel as the infarcted region, may be neuronally 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 contralesional, 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 impairment despite the presence of compensatory strategies. This is of particular importance in a functional imaging study because compensatory strategies are also likely to cause novel patterns of activation. For example, use of more proximal limb muscles to aid distal control might lead to contralesional 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 in 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 best explained 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 conjectured that 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 categoric distinction between those patients with severe 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 handgrip or finger opposition tasks. The PET environment allows for full 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 [3••], this may reflect 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. A limitation of finger tasks is the difficulty in obtaining kinematic trajectory data or studying visuomotor control. Thus, quantification of finger tasks has so far been restricted to rate and force measures.

Motor studies of stroke patients in the fMRI scanner present a number of practical problems. The first is unwanted head movements. Head motion causes misregistration of voxel locations to anatomic locations, leading to both false-positive activations when there is task-correlated 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 handgrip task or a foot flexion task in a simulated MRI 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, forearm 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 designs, choosing tasks that minimize head motion, and using head restraints.

A second practical problem encountered in patients with stroke is mirror movements. 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 compared with either hand in age-matched control subjects [21]. Although 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 contralesional motor cortex [22,23] and correlate with severity of motor deficit [21,22]. For example, in a PET study of patients who had fully recovered from hemiparesis, increased sensorimotor cortex activation in the contralesional hemisphere was always associated with mirror movements in the unaffected limb [24]. Use of electromyography or force transducers, either in the scanner or during out-of-scanner training, to confirm the absence of mirror movements increases confidence that contralesional activations relate 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 [25]. Nelles *et al.* [26] have shown that passive elbow flexion-extension movements in hemiplegic patients with subcortical stroke, when compared with healthy control subjects, activate contralesional sensorimotor cortex and bilateral parietal areas. The contralesional sensorimotor activation is interesting because similar 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], raising the possibility that these early changes may play a role in restoration of function. The second and less-used strategy to study patients with hemiplegia is 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 imaginary 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 (*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 Fugl-Meyer scale) accurately reflects the impairment (rather than just compensation), it may not relate to the more specific hand task in the scanner. Solutions to this problem include ensuring that the test that measures recovery is nearly identical to the within-scanner task or shows 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 Studies in Recovering Patients

The initial pioneering investigations of brain activation changes after stroke were PET studies of patients fully recovered from subcortical strokes [24,27,32]. More recently, emphasis has shifted to studies, often longitudinal, of still-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 good reasons, 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, Weiller *et al.* [24,27] and Chollet *et al.* [32] showed recruitment of additional areas in the ipsilesional and contralesional hemispheres in patients recovered from subcortical stroke. Similar results, showing contralesional 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 impaired motor performance when compared with age-matched control subjects. Therefore, activation differences may be attributable to this performance difference alone. If absolute performance is equated, the task may nevertheless be more difficult for the patient and require more effort. Imaging studies in healthy subjects have shown that as a task becomes more difficult, additional brain areas are recruited [35,36]. Thus, the same level of performance in a patient may lead to increased recruitment for reasons of difficulty and have nothing to do with restoration of function. Instead, if effort is equated by normalizing to the patient's own best performance on the day of scanning (an approach used recently in a longitudinal study [11•]), the problem of performance difference arises again. A further difficulty with longitudinal studies is the problem of test-retest effects that can occur when serial fMRIs are performed, with reduction in cortical activation for repetition of even overlearned tasks, perhaps due to habituation to the MRI experimental context [37–39]. This effect suggests a need to also serially scan control subjects.

In the longitudinal study by Ward *et al.* [11•], a negative correlation was found between a global outside-scanner measure of recovery and the number of additional brain regions activated, as compared with control subjects, when patients performed a grip task in the scanner. There were no areas of activation that showed a positive correlation with recovery. The authors concluded that optimal recovery in patients with subcortical stroke involves returning to patterns of cortical activation indistinguishable from control subjects. This is consistent with previous longitudinal studies showing a focusing of activation back to the ipsilesional hemisphere [33,34].

In summary, studies of patients with complete recovery show persistent additional activations, including 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 issue of reorganization and restorative plasticity, the longitudinal studies published to date can at best only suggest, but do 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 when cortical motor areas are damaged, additional recruitment plays a bigger role in the chronic 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 infarcted 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 infarct. 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 if 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••]. 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 most 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 [41••].

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 methodologic 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.

Acknowledgments

The author would like to thank Drs. Randolph Marshall and Pietro Mazzoni for critical reading of the manuscript. Support from this work came from NS 02138.

References and Recommended Reading

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

- • Of importance
- •• Of major importance

1. Taylor TN, Davis PH, Torner JC, *et al.*: **Lifetime cost of stroke in the United States.** *Stroke* 1996, **27**:1459–1466.
2. Toga AW, Mazziotta JC (eds): *Brain Mapping: The Methods*, edn 2. New York: Academic Press; 2002.
3. •• Calautti C, Baron JC: **Functional neuroimaging studies of motor recovery after stroke in adults.** *Stroke* 2003, **34**:1553–1566.

Excellent comprehensive review of functional imaging studies of motor recovery after stroke.

4. Calautti C, Serrati C, Baron JC: **Effects of age on brain activation during auditory-cued thumb-to-index opposition: a positron emission tomography study.** *Stroke* 2001, **32**:139–146.
5. D'Esposito M, Zarahn E, Aguirre GK, Rypma B: **The effect of normal aging on the coupling of neural activity to the bold hemodynamic response.** *Neuroimage* 1999, **10**:6–14.
6. Shelton FN, Reding MJ: **Effect of lesion location on upper limb motor recovery after stroke.** *Stroke* 2001, **32**:107–112.

7. Binkofski F, Seitz RJ, Arnold S, *et al.*: **Thalamic metabolism and corticospinal tract integrity determine motor recovery in stroke.** *Ann Neurol* 1996, 36:460–470.

8. Shimizu T, Hosaki A, Hino T, *et al.*: **Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke.** *Brain* 2002, 125:1896–1907.

9. Brett M, Leff AP, Rorden C, Ashburner J: **Spatial normalization of brain images with focal lesions using cost function masking.** *Neuroimage* 2001, 14:486–500.

10. Ward NS, Brown MM, Thompson AJ, Frackowiak RS: **Neural correlates of outcome after stroke: a cross-sectional fMRI study.** *Brain* 2003, 126:1430–1448.

11.• Ward NS, Brown MM, Thompson AJ, Frackowiak RS: **Neural correlates of motor recovery after stroke: a longitudinal fMRI study.** *Brain* 2003, 126:2476–2496.

Well-designed, recent longitudinal fMRI study of motor recovery after stroke.

12. Powers WJ: **Cerebral hemodynamics in ischemic cerebrovascular disease.** *Ann Neurol* 1991, 29:231–240.

13. Marshall RS, Rundek T, Sproule DM, *et al.*: **Monitoring of cerebral vasodilatory capacity with transcranial Doppler carbon dioxide inhalation in patients with severe carotid artery disease.** *Stroke* 2003, 34:945–949.

14. Bilecen D, Radu EW, Schulte AC, *et al.*: **fMRI of the auditory cortex in patients with unilateral carotid artery steno-occlusive disease.** *J Magn Reson Imaging* 2002, 15:621–627.

15. Rother J, Knab R, Hamzei F, *et al.*: **Negative dip in BOLD fMRI is caused by blood flow–oxygen consumption uncoupling in humans.** *Neuroimage* 2002, 15:98–102.

16. Wade DT: *Measurement in Neurological Rehabilitation. Oxford Medical Publications.* Oxford: Oxford University Press; 1994.

17. Cirstea MC, Levin MF: **Compensatory strategies for reaching in stroke.** *Brain* 2000, 123(pt 5):940–953.

18. Reinkensmeyer DJ, McKenna CA, Kahn LE, Kamper DG: **Directional control of reaching is preserved following mild/moderate stroke and stochastically constrained following severe stroke.** *Exp Brain Res* 2002, 143:525–530.

19. Jezzard P, Matthews PM, Smith SM (eds): *Functional MRI: An Introduction to Methods*, edn 1. London: International Institute for Strategic Studies; 2001.

20.• Seto E, Sela G, McIlroy WE, *et al.*: **Quantifying head motion associated with motor tasks used in fMRI.** *Neuroimage* 2001, 14:284–297.

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

21. Nelles G, Cramer SC, Schaechter JD, *et al.*: **Quantitative assessment of mirror movements after stroke.** *Stroke* 1998, 29:1182–1187.

22. Kim YH, Jang SH, Chang Y, *et al.*: **Bilateral primary sensori-motor cortex activation of post-stroke mirror movements: an fMRI study.** *Neuroreport* 2003, 14:1329–1332.

23. Wittenberg GF, Bastian AJ, Dromerick AW, *et al.*: **Mirror movements complicate interpretation of cerebral activation changes during recovery from subcortical infarction.** *Neurorehabil Neural Repair* 2000, 14:213–221.

24. Weiller C, Ramsay SC, Wise RJ, *et al.*: **Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction.** *Ann Neurol* 1993, 33:181–189.

25. Weiller C, Juptner M, Fellows S, *et al.*: **Brain representation of active and passive movements.** *Neuroimage* 1996, 4:105–110.

26. Nelles G, Spiekermann G, Jueptner M, *et al.*: **Reorganization of sensory and motor systems in hemiplegic stroke patients. A positron emission tomography study.** *Stroke* 1999, 30:1510–1516.

27. Weiller C, Chollet F, Friston KJ, *et al.*: **Functional reorganization of the brain in recovery from striatocapsular infarction in man.** *Ann Neurol* 1992, 31:463–472.

28. Cramer SC, Nelles G, Benson RR, *et al.*: **A functional MRI study of subjects recovered from hemiparetic stroke.** *Stroke* 1997, 28:2518–2527.

29. Gerardin E, Sirigu A, Lehericy S, *et al.*: **Partially overlapping neural networks for real and imagined hand movements.** *Cereb Cortex* 2000, 10:1093–1104.

30. Johnson SH: **Imagining the impossible: intact motor representations in hemiplegics.** *Neuroreport* 2000, 11:729–732.

31. Johnson SH, Sprehn G, Saykin AJ: **Intact motor imagery in chronic upper limb hemiplegics: evidence for activity-independent action representations.** *J Cogn Neurosci* 2002, 14:841–852.

32. Chollet F, DiPiero V, Wise RJ, *et al.*: **The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography.** *Ann Neurol* 1991, 29:63–71.

33. Marshall RS, Perera GM, Lazar RM, *et al.*: **Evolution of cortical activation during recovery from corticospinal tract infarction.** *Stroke* 2000, 31:656–661.

34. Feydy A, Carlier R, Roby-Brami A, *et al.*: **Longitudinal study of motor recovery after stroke: recruitment and focusing of brain activation.** *Stroke* 2002, 33:1610–1617.

35. Bullmore E, Suckling J, Zelaya F, *et al.*: **Practice and difficulty evoke anatomically and pharmacologically dissociable brain activation dynamics.** *Cerebral Cortex* 2003, 13:144–154.

36. Hummel F, Kirsammer R, Gerloff C: **Ipsilateral cortical activation during finger sequences of increasing complexity: representation of movement difficulty or memory load?** *Clin Neurophysiol* 2003, 114:605–613.

37. Loubinoux I, Carel C, Alary F, *et al.*: **Within-session and between-session reproducibility of cerebral sensorimotor activation: a test-retest effect evidenced with functional magnetic resonance imaging.** *J Cereb Blood Flow Metab* 2001, 21:592–607.

38. Jantzen KJ, Steinberg FL, Kelso JA: **Practice-dependent modulation of neural activity during human sensorimotor coordination: a functional magnetic resonance imaging study.** *Neurosci Lett* 2002, 332:205–209.

39. Henson RN, Rugg MD: **Neural response suppression, haemodynamic repetition effects, and behavioural priming.** *Neuropsychologia* 2003, 41:263–270.

40. Frost SB, Barbay S, Friel KM, *et al.*: **Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery.** *J Neurophysiol* 2003, 89:3205–3214.

41.•• Johansen-Berg H, Rushworth MF, Bogdanovic MD, *et al.*: **The role of ipsilateral premotor cortex in hand movement after stroke.** *Proc Natl Acad Sci U S A* 2002, 99:14518–14523.

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