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Chapter XI

Functional Imaging of Motor Recovery after Stroke

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Introduction

Stroke remains the leading cause of adult disability worldwide [1] despite significant advances in its prevention and acute treatment. Thus there is urgent need to better understand the neural mechanisms of stroke recovery in order to develop more scientific rehabilitation approaches and more effective pharmacological therapies. There has been an explosion over the past 15 years in the use of functional brain imaging to study how the mature brain reorganizes after stroke and other forms of brain injury. The purpose of this chapter is twofold: to provide a critical review of what has been learned so far about stroke recovery, specifically motor recovery, from functional imaging and to address methodological and theoretical limitations to the technique for elucidating mechanisms of brain recovery.

Selection of Patients and Controls

Determining general principles for recovery from stroke is challenge because of the heterogeneity of the condition with regard to onset and etiology, patient age, lesion location, lesion size, and severity of the behavioral deficit [1]. All these factors, unless accounted for, may lead to changes in brain activation that confound interpretation of results as they pertain to recovery. The elderly recruit additional regions compared to the young even when they perform very simple motor tasks [2] and show differences in BOLD response [3]. It is

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therefore essential to use age-matched control subjects in functional imaging studies of stroke recovery to avoid misattributing aging-related changes to reorganization after stroke. Recovery from subcortical strokes can be slower that recovery from cortical strokes, which suggests that different restorative mechanisms may be operating in the two cases. In addition, there is evidence to suggest that cortical and subcortical strokes have differential effects on cortical excitability in the contralesional hemisphere [4]. Specifically, a unilateral cortical stroke can lead to decreased transcallosal inhibition of the unaffected hemisphere while this is not seen for subcortical strokes.

Thus, it is probably better to study these two patient populations separately. Imaging studies in healthy subjects show more ipsilateral activation when movements are performed with the non-dominant left hand than with the dominant right hand [5]. Thus mixing patients with strokes in the dominant versus non-dominant hemisphere may make interpretation difficult. fMRI is the functional imaging technique of choice for most studies of brain reorganization after stroke, a technique that depends on a coupling between local cerebral blood flow and neuronal metabolism. Stroke can affect both small and large cerebral vessels and so potentially alter or uncouple this relationship. Indeed, studies have shown that the response can be reduced or absent in the hemisphere ipsilateral to a large vessel stenosis [6, 7]. This complicates interpretation of functional imaging studies of recovery because an area that is contributing to behavior may nevertheless fail to show a response. Restricting hypotheses to areas that are not supplied by the stenosed vessel, ascertained by MRA or a perfusion study, might overcome this problem but the contribution of residual areas around the lesion might be missed.

Defining Motor Recovery

In order to design a meaningful functional imaging experiment that addresses motor recovery after stroke, motor recovery needs to be properly defined i.e. how it is to be measured. This is crucial issue that is surprisingly underemphasized in studies of recovery although it should be apparent that the regions or patterns of brain activation identified will depend on the behavior in the scanner and/or the out-of-scanner behavioral measures used for modeling or correlating with activation changes. A common way to measure motor recovery is to use either an absolute or a change score using a clinical scale. It is possible, even likely, that neural correlates will differ for a change in performance versus an absolute level of performance. In a patient with only a mild deficit or full clinical recovery, a change measure will be small or zero whereas an absolute measure will be maximal. Conversely, a patient with a severe initial deficit with only partial recovery will score higher on a change measure compared to an absolute measure. 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. Psychophysical studies indicate that there may be a categorical difference in the mechanism of impairment for patients with mild versus patients with severe paresis [8, 9]. This suggests these two groups should be studied separately in functional imaging experiments. A further problem is that the term hemiparesis

encompasses both positive and negative signs that almost certainly have separable underlying mechanisms (see Krakauer 2005 for more detailed discussion [10]).

Clinical scales can either measure impairment or disability. Impairment is the neurophysiological consequence of a brain lesion whereas disability refers to the consequence of the impairment on activities of daily living (ADLs). An example of a motor impairment scale is the Fugl-Meyer (FM) assessment. This scale was specifically designed for patients with hemiparesis after stroke and sought to address the lack of a quantitative measure of stroke recovery at the level of impairment that could be used to assess the efficacy of a given rehabilitation technique [11]. The rationale behind using an impairment measure is that a disability measure is inadequate to capture the dynamic process of motor recovery and unable to distinguish between true recovery, or vicariation, of function and compensation. Compensation allows a patient to achieve an ADL using alternative strategy (e.g. the patient with a right hemiparesis who learns to use her left hand). In contrast, complete motor recovery implies that the patient is performing the task in the same way as age-matched controls. Thus a patient may be rated as fully recovered on a disability scale but only partially recovered on an impairment scale. A recovery measure needs to be sufficiently sensitive to detect impairment despite the presence of compensatory strategies. This is of particular importance in functional imaging studies 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 novel activation would not indicate reorganization after stroke. Although positing full recovery on an impairment scale serves to highlight the categorical distinction between recovery and compensation, it remains an open question whether true full recovery ever really occurs. A more sensitive quantitative measure of movement may reveal a subtle abnormality not apparent with the FM score as the FM primarily assesses movements across isolated single joints with much less emphasis on the kinematics of multi-joint movements. Thus depending on the resolution of the measurement tool, performance between patients and controls may or may not differ. This issue profoundly effects interpretation of imaging results. Any difference seen in patients might be the result of the performance difference itself rather than reorganization *per se*. The issue of performance confounds will be addressed again in the context of particular experiments later in the chapter.

What Hypotheses about Recovery Are Best Addressed by Functional Imaging?

The increased access to MR scanners in hospitals, the user-friendliness of imaging analysis software packages, and the sheer seductiveness of the images themselves has led to a susceptibility to lose sight of the assumptions underlying functional imaging in general, and issues of restoration of function in particular. Investigators should have explicit hypotheses that are optimally suited to testing with functional imaging. As in other areas of scientific investigation, fishing expeditions are not desirable.

Functional imaging is a correlative technique and at best can prove necessity to but not sufficiency of a brain area to behavior. Identification of a novel area of activation does not in itself tell the investigator what the area is doing computationally. An implicit computational assumption, common in the literature, is that if novel areas are involved in recovery then they must be contributing to motor execution. Alternatively, inferring the computational function based on what that area is known to do from other data, risks circularity. Ideally activation in the identified brain area should correlate with a behavioral measure rather than just rely on a simple contrast. Interpretation is also complicated by the possibility that activation is related to factors that are hard to define or measure such as attention, task difficulty or effort rather than execution of the behavior *per se*.

Recovery of function may occur through a number of distinct mechanisms. Utall [12] has provided a list of possible hypotheses regarding the mechanism of recovery of function (Table 1). A well-conducted imaging study should be able to identify or distinguish between these possible mechanisms. We will address these mechanisms again below when we cover cross-sectional and longitudinal study designs.

Hemiparesis, as clinically defined, can result from lesions in a variety of cortical and subcortical locations. Ideally, group analysis would be reserved for studies in which the patients are homogenous with respect to lesion location and other factors. Unfortunately, this is difficult in practice and so far the best that has been managed is to separate cortical and subcortical strokes and subacute and chronic hemiparesis. Group analysis on a heterogenous patient population implicitly assumes that general patterns of recovery-related activation can be identified despite individual differences in lesion location, stroke onset and severity of paresis. This is an empirical question but it could also be that each patient recovers in their own way and that it is the inter-individual variability that is informative rather than average activation across subjects. It is also conceivable to have inter-intervidual variability due to differential expression of a common recovery network. A multivariate approach would be required to demonstrate this.

Measurement of Motor Behavior in and Outside the Scanner

The functional imaging environment limits motor behavior. Although proximal arm movements can be studied with PET, MR studies are restricted to distal movements of the wrist and fingers or flexion/extension at the elbow. The majority of studies of motor recovery after stroke have used fMRI and almost exclusively employed finger tasks. A limitation of finger movement studies is that they are hard to quantify, being limited to measures of pinch force and tapping rate. Precise quantification is important because, as mentioned above, performance differences can lead to activation differences that might confound interpretation, although it is unlikely that large activation differences are caused by small differences in motor execution. Kinematic trajectory data are rarely obtained and more complex visuomotor control is infrequently studied [13]. Another option is to make the within-scanner task simple but correlate activation changes with more complex measurements obtained at another time outside the scanner. This approach is predicated on the notion that there are general patterns of activation for a range of motor behaviors.

Patients with stroke present a number of additional challenges in the scanning environment compared to age-matched healthy controls. First, patients have reduced stamina and so tire easily. Scans that last more than an hour are likely to yield diminishing returns. Second, there is a higher incidence of mirror movements, involuntary synchronous movements of limbs on the opposite side to the voluntarily moving limb, in the unaffected hand of patients with hemiparesis compared with either hand in age-matched controls [14]. Clearly the presence of mirror movements makes any conclusion about the contribution of ipsilateral motor areas to recovery invalid. This problem was encountered in the original pioneering PET studies of motor recovery after stroke [15-17]. Potential solutions to the mirror-movement problem include EMG measurements from the ipsilateral hand either during the scan or, more conveniently, obtaining arm and leg EMG measurements during pre-scan training in the supine position outside the scanner. Of course, the latter approach assumes that patients will behave in a similar manner once in the scanner. Third, it has been shown that patients with stroke make more unwanted head movements in the scanner when they move either their hand or foot [18]. Head motion causes misregistration of voxel locations to anatomical locations, leading to false-positive activations when the head motion is task-correlated and false-negative results because random motion decreases signal to noise. Unfortunately, patients make more random and more task correlated movements compared to age-matched controls and thus limit who and what can be studied in the scanner.

Cross-Sectional Studies

The following three criteria, taken from Rickard (2000) [19], have been suggested for the ideal cross-sectional fMRI study of plasticity: (i) There must be clear evidence of complete behavioral recovery of function in the patient; (ii) the computational steps executed by the patient and the controls in the service of the task should be equivalent or differences readily identifiable and quantifiable. (iii) There must be statistically significant activation in a novel area not seen in controls.

Each of these three criteria merit further comment. Evidence for complete behavioral recovery implies that convincing measurements of impairment were obtained in the patient in the subacute period after their stroke. This is important because a return to normal behavior in the subacute period could just be a return to pre-morbid patterns of activation after resolution of transient metabolic abnormalities or edema. Thus, any seemingly novel pattern of activation might reflect how subjects accomplished the task before injury. To claim that patients have made a true recovery requires that their movements are kinematically equivalent, e.g. move at the same average speed and achieve similar accuracy for the within-scanner task, to movements with their unaffected hand, or preferably, to movements made by age-matched controls. Showing a result that is statistically significant at the population level implies, despite heterogeneity in lesion location and severity of the initial deficit, that there are patterns of activation common to all patients who recover from hemiparesis and assumes that these play a role in recovery although it is possible that idiosyncratic individual and lesion-specific mechanisms are equally important.

The initial pioneering PET investigations of motor recovery after subcortical stroke essentially followed the reasoning of the three criteria outlined above. The first study was of 6 patients, two months or more out from first hemiplegic stroke and with good to complete recovery [15]. Patients were required to make sequential finger-to-thumb opposition movements, three every two seconds, with the rate set by a metronome. Patients served as their own controls by performing with their good hand as well as recovered hand. Group analysis showed that finger movement with the good hand primarily activated the contralateral primary sensorimotor cortex and ipsilateral cerebellum. In contrast, finger movements with the recovered hand activated both ipsi- and contra-lateral primary sensorimotor cortex and both cerebellar hemispheres. In addition, they also showed bilateral insula, premotor and inferior parietal activations. The authors concluded that ipsilateral motor pathways may contribute to motor recovery after stroke. However, this interpretation is complicated by a number of limitations, which indicate that the criteria outlined at the beginning of this section were not met by this study. First, no quantification of the extent of the initial paretic deficit is provided. Second, the authors state that testing of power at the wrist and hand showed no deficit but do not quantify their testing nor describe how it was done. Third, finger opposition is not a power task and so strength testing may not be apposite as it is a well-known clinical observation that patients with hemiparesis can recover power before finger individuation. Fourth, there was no detailed measurement of the finger-opposition task itself and so it is possible that there may have been subtle differences in performance, the authors themselves mention the possibility of mirror movements and overflow activity from axial muscles. Thus, the statistically significant additional activations seen with the 'recovered" hand may not represent recovery-related reorganization. The same group performed a follow-up study in 10 patients with recovery from striatocapsular infarction [16]. At least four of the patients made mirror movements. The results were very similar to the first study, with patients showing bilateral primary sensorimotor and cerebellar activation, along with bilateral insula and inferior parieatal activation. However, other than using age-matched controls instead of the unaffected hand, the same limitations stated above apply to this second study. The main concern is that mirror movements may have been responsible for the ipsilateral activations observed. The authors make the valid point that mirror movements themselves might be part of the recovery process but this does not answer the question whether the additional ipsilateral activations are necessary for movement of the recovered fingers rather than just the unaffected ones. This question was addressed by a third PET study perfomed by this group in which they compared activation in individual patients to a group of age-matched controls [17]. Notably, ipsilateral primary sensorimotor activation was only seen in those patients who made mirror movements. However, all patients showed increased ipsilateral premotor and contralateral cerebellar activation compared to controls, suggesting that ipsilateral activations may also relate to movements of the recovered hand. Overall, it is apparent that these three studies, although groundbreaking both in terms of question and approach, were confounded by mirror movements and potentially confounded by inadequate quantification of the initial deficit, of the degree of recovery and of the motor task in the scanner.

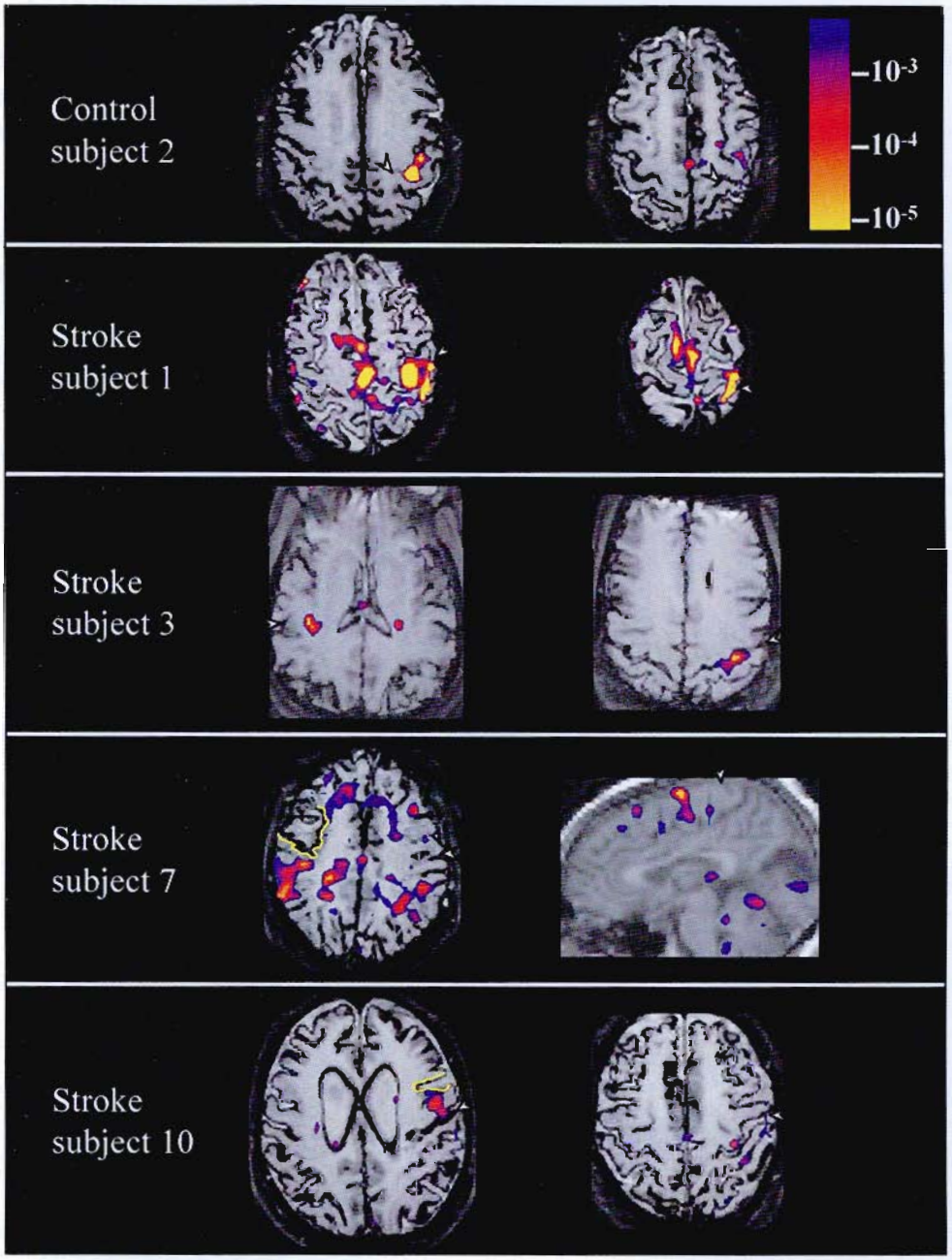

Figure 1. (Taken from Cramer et al. (1997), with permission). Axial fMRI activation images for a control subject and four patients recovered from hemiparesis, obtained by comparing rest with tapping of the right index finger. Increased activation in patients with stroke was identified by comparing the number of activated voxels within pre-chosen ROIs for each patient against a distribution generated from all control subjects' activations for the same task. Row 1, fMRI activation images for a control subject. The patients in rows 2 and 3 had left subcortical infarcts, located ventral to the images shown. In both patients there was significantly increased activation in the right (contralesional)sensorimotor cortex and in the SMA compared to controls. The patients in rows 4 and 5 had cortical infarcts (outlined in yellow). Two types of additional activation are apparent: increased activation in bilateral sensrimotor cortex and peri-infarct activation.

A similar rationale and approach to the aforementioned PET studies has been used in recent fMRI studies. In one such study [20], recovery was, like in the PET studies, defined on the basis of fairly crude strength criteria. The investigators used an index finger tapping rather than a finger-opposition task, applied a region-of-interest (ROI) analysis to compute a laterality index, and included patients with cortical strokes. Findings were very similar to the earlier PET studies with increased ipsilateral primary sensorimotor and premotor activation, and contralateral cerebellar activation, compared to controls (Figure 1). Importantly, only one patient was observed to make mirror movements in the scanner, suggesting that ipsilateral activation in primary sensorimotor cortex may not just be due to mirror movements but to recovery itself. These findings were confirmed in more recent prospective study [21], for which 8 patients were recruited with hemiparetic stroke from cortical or subcortical stroke within one month of the first motor measurement and who underwent 6 weeks of rehabilitation before undergoing functional imaging. The advantages of this study were that time after stroke was more uniform, motor performance was assessed before and after recovery, and EMG was obtained within the scanner to detect mirror movements. All the patients were deemed to have made excellent recoveries on the basis of grip force measurements and a functional battery called the Jebsen hand test. The main finding was that the patients, when they performed a 1 Hz finger opposition task, activated bilateral primary and premotor cortices even in the absence of EMG activity in the unaffected hand. In contrast, healthy subjects showed strictly contralateral activation of motor areas. Thus both PET and fMRI studies in patients with good clinical recovery indicate that additional contralesional brain regions are activated compared to controls despite similar motor performance and absent mirror movements.

As outlined above, studying patients with complete or near-complete recovery controls for performance confounds and thus allows comparison of activation patterns in patients and controls. However, this approach excludes the large number of patients who only make partial clinical recovery. To address this problem, cross-sectional studies have also been attempted in patients with only partial recovery or variable degrees of recovery.

One study used an event-related design and a near-isometric wrist extension task in 3 patients with chronic (> 6 months) hemiparesis and only partial clinical recovery [22]. The combination of a simple movement requirement and an event-related design, which permits elimination of poorly executed trials from image analysis, allows approximate matching of performance between patients and controls. Patients showed, as in studies of patients with excellent clinical recovery, increased activation in ipsilateral motor cortex despite the absence of detectable force production in the unaffected hand. A larger cross-sectional study recruited 20 patients with variable degrees of recovery after cortical and subcortical stroke [23]. One novel aspect to the study was to control for performance *within* the scanner but then correlate activation changes with performance variation on a composite *out-of-scanner* measure obtained on the same day as the fMRI. The within scanner task was a paced dynamic isometric handgrip task with a force requirement normalized to each patient's own maximum voluntary contraction. This was done in order to control for effort and relative performance. A second novel aspect to the study was to perform a principal components analysis on the whole data set of outcome measures to obtain a single representative outcome score, the first principal component, with which activation patterns across the patient group were correlated.

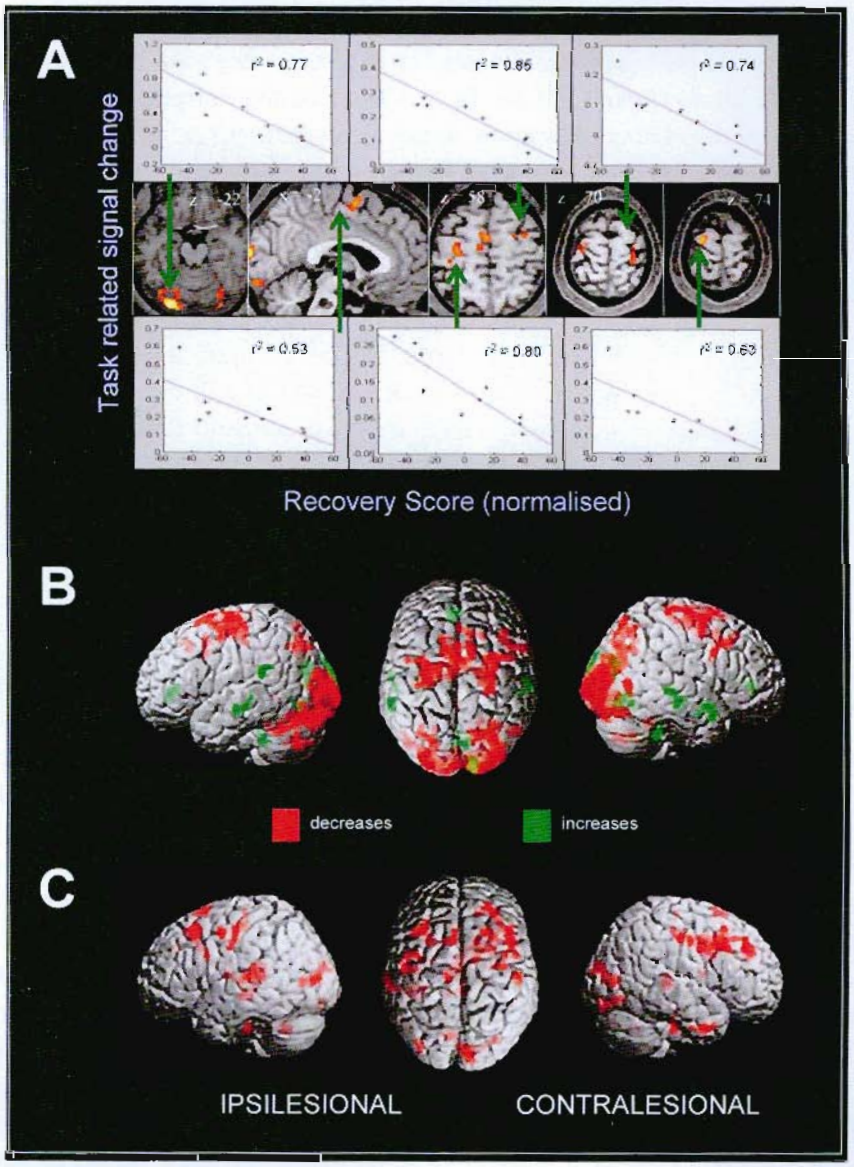

Figure 2. (Taken from Ward et al. (2003), with permission). A. Results of a single patient longitudinal analysis examining linear changes in task-related brain activations over sessions as a function of recovery. The patient had a left-pontine infarct resulting in right hemiparesis. Results are displayed on the patient's own normalized T1-weighted anatomical images (voxels significant at $p < 0.05$, corrected for multiple comparisons, with corresponding plots of size of effect against a normalized recovery score. The correlations coefficients were significant for all six of the selected brain regions. B. Results surface rendered, in three projections, on a canonical brain; red areas represent recovery-related decreases in task-related activation across sessions, and green areas represent task-related activation increases. C. Group 'recovery map' rendered on a canonical brain: brain regions in which linear reductions in task-related activation across sessions as a function of recovery were consistently detected for the whole group of patients. Random effects analysis, all clusters significant at $p < 0.05$, corrected for multiple comparisons). Images for patients with left-sided lesions were flipped about the mid-sagittal plane so that all patients were assumed to have a right-sided lesion. (left hemisphere is on the left, CL = contralesional; IL = ipsilesional).

There was no evidence for mirror movements by EMG when subjects performed the same isometric task outside the scanner. The main result of this study was that across the whole patient group and across stroke subtypes, there was a *negative* correlation between outcome and the degree of task-related activation in novel primary motor, premotor, parietal and cerebellar areas (Figure 2). There was no difference in task-related activation compared to the normal population in six patients with the best outcome. This study appears to contradict previous cross-sectional studies but can perhaps be reconciled with them by positing that in those studies, patients deemed fully-recovered would have been found to have a residual motor deficit with the more detailed outcome measure of the later study. A possible overall conclusion from the cross-sectional studies would be that activation of novel brain areas may represent functional reorganization but these areas are unable to mediate complete recovery. A problem with this interpretation, however, is that the additional activations could instead be due to the performance differences across patients rather than reorganization *per se*. An indirect answer to this issue of a performance confound came from an interesting cross-sectional study, which compared patients with chronic hemiparesis from cortical versus subcortical strokes [24]. The important finding was that despite comparable motor impairment, i.e. performance, in the cortical and subcortical groups, they showed significantly different patterns of brain activation when they moved the paretic limb. Specifically, whereas patients with subcortical stroke recruited canonical corticocerebellar regions along with ipsilateral post-central gyrus, patients with cortical stroke only showed activation around the stroke cavity, in mesial frontal areas and ipsilateral post-central gyrus. As performance did not differ across the two groups, these results suggest that novel patterns of brain activation represent post-stroke reorganization.

In general it is safer to infer that novel activation is related to restoration of function if there is a well-documented initial deficit followed by a recovered state at the time of imaging. This is especially true for studies of studies of higher cognitive functions, such as language, where a novel pattern of activation may reflect a pre-morbid pattern rather than reorganization. The functional anatomy of the motor system is more consistent across subjects, however, and makes it possible to ask the question whether the absence of a motor deficit in the presence of a lesion is because the brain has reorganized to maintain normal motor performance. This argument has had more traction with slow progressive disease than in stroke. For example, patients with multiple sclerosis without focal deficit or with only a single episode of optic neuritis show increased ipsilateral fMRI motor activation that correlates with lesion burden [25]. A conclusion from this result is that the additional ipsilateral activation maintains normal motor function despite the presence of lesions expected to cause a motor deficit. A similar result has been obtained recently in patients with critical carotid or middle cerebral artery stenosis or occlusion causing unilateral hemispheric hypoperfusion without infarction [26]. Patients showed increased motor activation in the normally perfused hemisphere despite the absence of any motor deficit on examination (Figure 3). An analogous result was obtained in a recent functional imaging study of movements of the ipsilesional arm in patients with right MCA infarction. The main finding was that although there were no observable behavioral differences in the left arm of patients and controls, patients showed significantly more bi-hemispheric activation [27]. Taken together, the results in the contralateral arm of patients with hemispheric hypoperfusion and

in the ipsilesional arm of patients with unilateral stroke show that altered patterns of brain activation occur in the absence of an observable neurological deficit.

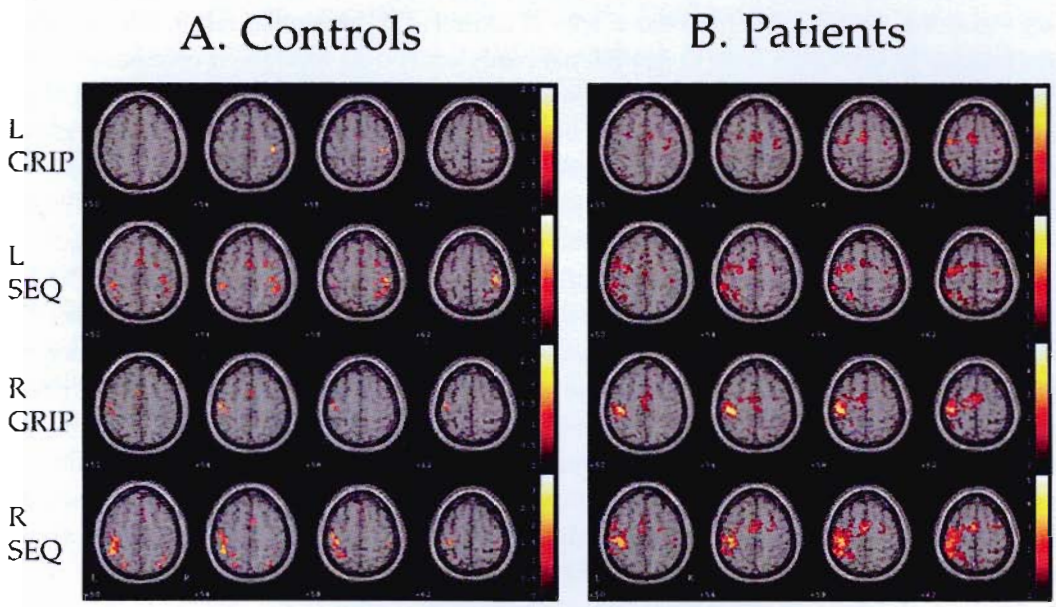

Figure 3. (Taken from Krakauer et al (2004).Group analyses on controls and patients with unilateral hemispheric hypoperfusion without stroke. Axial activation maps using a fixed-effects model with conjunction analysis ($p < 0.001$, uncorrected). Patients using the "affected" left hand predominantly activated left (ipsilateral) areas, whereas controls predominantly activated right (contralateral) areas. Both patients and controls activated contralaterally when using the "unaffected" right hand. Color bars to the right of each condition indicate the range of activation t – values.

Longitudinal Studies

Longitudinal studies of motor recovery after stroke image patients serially over the time course of recovery. The advantages of a longitudinal approach are that it allows study of patients who have not fully recovered and better captures a process that is known to change over time. A longitudinal study is a potentially powerful way to show reorganization if a *positive* correlation can be shown between an area of activation not seen in controls and longitudinal recovery on a behavioral measure. Such a result would be compelling because impaired motor performance would be expected to show the opposite correlation, i.e. negative, with the time course of recovery.

The first longitudinal functional imaging study of motor recovery after stroke scanned 8 patients with subcortical infarcts within 48 hours of their stroke and then again 3-6 months later [28]. Activation was compared between patients and controls and at the two time points by computing a laterality index using primary sensorimotor, medial and lateral premotor ROIs. The main findings were that patients showed more contralesional motor area activation than controls and that the laterality index increased, i.e. the ratio of ipsilesional to contralesional motor area activation, from the acute to the chronic timepoint, in parallel with

observed increased ipsilateral cerebellar activation may reflect a learning process, which contributes to recovery. In addition to the interesting positive result, this study emphasizes the fact that increased activation cannot be assumed to be relevant to recovery unless correlation is found with good behavioral measures. The activation might instead relate temporally to the evolution of other variables such as hemodynamics or diaschisis or represent a general response to hemiparesis or injury that is not relevant to recovery.

A more recent study [36] tested the hypothesis, based on results in non-human primates [37], that a stroke limited to a portion of primary motor cortex is associated with reorganization within the surrounding motor cortex and that this leads to reacquisition of a motor skill. Four right-handed patients with ischemic strokes limited to M1 were imaged longitudinally over three sessions: <20 days, 4 months, and 2 years after stroke. Four age-matched controls were imaged at the same intervals. The basic finding was that skilled motor recovery was associated with a transition from contralesional activation to ipsilesional activation in a location in M1, which was more dorsal compared to controls. The observed dorso-medial shift is consistent with AN adjacent cortical reorganization mechanism as has been seem in non-human primates.

Functional Imaging Correlates of Stroke Rehabilitation

The cross-sectional and longitudinal studies described above were conducted in patients with both acute and chronic stroke. The studies did not control for the modality of or time spent in rehabilitation and therefore results may reflect a combination of spontaneous recovery and responses to therapeutic intervention. There have, however, been a few small studies that have used functional imaging to assess responses to specific forms of rehabilitation. All these studies attempted to control for performance confounds and obtained scans before and after treatment. One small study recruited four patients who had a chronic stroke, either left or right, cortical or subcortical, and suffered loss of finger individuation [38]. The motor task was 4-finger flexion-extension movements at 0.5 hz. Subjects received two weeks of constraint-induced therapy (CIT) [39-41]. ROIs were drawn for primary motor cortex, premotor cortex and SMA. The extent of activation was determined by counting the number of activated voxels and then a laterality index was calculated. Patients showed an improvement on the Fugl-Meyer stroke scale and on the Wolf-Motor function test. In association with this motor improvement there was a decrease in the laterality index, i.e. a shift towards contralesional activation. This result is interesting in so much that it contradicts most of the longitudinal studies described in the previous section, which showed an increase in the laterality index as recovery proceeded. It is important to note, however, that this was very small study with a heterogeneous mix of patients and not much can be concluded from it. Indeed, three other studies have shown that activation increases in motor areas on the ipsilesional side in response to task-oriented training [42] and CIT [43, 44]. In the most careful of these studies [44] , a group analysis of 7 patients with chronic hemiparesis showed that therapy-related improvements in hand-function correlated with increases in fMRI activity in the premotor and secondary somatosensory cortex on the ipsilesional side and bilateral

superior cerebellum. Again, infarct location and side was heterogeneous, although the authors state that the hand region of the pre-central gyrus was not involved. The task was a paced 4-finger flexion/extension task and performance did not appreciably differ across scans.

At best, with the assumption that performance in the scanner did not change before and after therapy, the aforementioned studies suggest that motor representation changes in response to therapy. Not much more can be said because of the low patient number and the heterogeneity of lesion locations. The question whether reorganization in patients with chronic stroke in response to therapy is qualitatively different from spontaneous reorganization in the acute and sub-acute post-stroke period, as seen in the longitudinal studies described in the previous section, will require further investigation.

Experiments That Complement Functional Imaging Studies

Functional imaging can only show that an area of activation correlates with motor behavior but not that it is necessary for recovery. If an area of novel activation mediates recovery then there should be re-emergence of the original deficit when the area is inactivated. This test has been applied in animal models with ablation or muscimol infusion and in humans with transcranial magnetic stimulation (TMS). A lesion of the hand representation in primary sensorimotor cortex in adult macaques resulted in complete loss of dexterity in the hand for 1-2 months. At around 3-4 months, there was a return to about 30% of pre-lesion dexterity. This improvement was reversed with muscimol infusion into the ipsilesional dorsal and ventral premotor areas but not with muscimol infusion into perilesional cortex or contralesional M1 [45]. More recently, it was shown that an ischemic lesion in the forelimb region of M1 in squirrel monkeys led to expansion of the hand representation in ipsilesional ventral premotor cortex (PMv) [46]. Interestingly, the degree of map reorganization in PMv was proportional to the amount of hand representation destroyed in M1. This result in monkeys provides a clue as to why novel functional activation patterns are seen most in patients with the greatest deficit. Similar results have been obtained using TMS in patients with chronic stroke and good recovery [47]. Four patients with capsular infarcts and good recovery from moderate to severe hemiparesis underwent single pulse TMS to the ipsilesional dorsal premotor cortex (PMd), which caused a delay in reaction time for the contralateral hand in patients but not in controls. In these well-recovered patients, TMS applied to contralesional M1 or PMd had no effect on reaction time. The same approach was used in a group of patients with more variable degrees of recovery [48]. TMS applied to contralesional PMd led to an increase in reaction time in the patients but not in controls. Importantly, the magnitude of the effect of TMS on contralesional PMd was correlated with the degree of hand impairment, consistent with the studies in monkeys described above. Thus reorganization can occur in cortex adjacent to the infarct, in premotor regions in the ipsilesional hemisphere and in motor regions in the contralesional hemisphere. Recruitment of more remote regions may depend both on the extent and location of the infarct and on stroke severity. This conclusion is supported by a recent study in rats [49], which showed that

recruitment of the undamaged hemisphere depended on the degree of functional integrity of the remaining ipsilesional sensorimotor system.

The idea that contralesional motor recruitment is a function of degree of damage to motor areas on the ipsilesional side is attractive and explains several results in animals and humans. However, it is clear that this is not the whole story. We have already encountered situations above in which additional activation is seen in patients with good recovery and even in patients with no symptoms but with hemodynamic or structural lesions. A further example of the likely ability of remote regions to contribute to good recovery comes from reports of re-emergence of stroke deficits in patients who suffer a second stroke on the opposite side. C. Miller-Fisher [50] described two patients with pure motor hemiparesis with substantial recovery who then had subsequent mirror lesions (proven at autopsy) on the opposite side, the capsule in one patient and the medulla in the other patient, and presented with quadraparesis. A similar case has been reported more recently [51]. Thus, the contradiction seen between cross-sectional and longitudinal functional imaging studies in humans is also to some extent seen in animal experiments and clinical observations. With the current state of knowledge, all that can be said is that additional brain regions might be contributing to behavior in a number of different ways, only some of which have been effectively probed.

Conclusions

Functional imaging seeks to correlate areas and patterns of brain activation with behavior. Even in healthy subjects, the technique is faced by considerable technical, anatomical and conceptual difficulties. These difficulties are compounded in studies of neurological patients, especially in the acute and subacute phases of a disease, because of the lack of stable baseline as brain systems are likely to be dynamically changing. Stroke is a particularly challenging disease to study because it is heterogeneous with respect to lesion location, initial severity and individual idiosyncrasies in the time-course of recovery. The complexities of using functional imaging to study brain reorganization after stroke are exemplified by the apparent contradictory findings between cross-sectional and longitudinal studies of stroke recovery. Cross-sectional studies often show altered brain activation patterns in patients with good recovery whereas longitudinal studies suggest that altered activation patterns are associated with the worst recovery. Part of the explanation for such conflicting results is that different types of stroke patient were selected for the two types of study. For example, in the initial PET studies of stroke recovery, patients with alleged full recovery may in fact have had deficits that were not adequately measured. Future studies will need to select larger and more homogeneous groups of patients with respect to lesion side and location and make great efforts to quantitatively measure performance and control for performance confounds. A change in conceptual approach that emphasizes interactions between brain regions rather than correlations between behavior and mean activations in single regions will likely prove more promising.

The use of functional imaging to assess responses to pharmacological and rehabilitation is also fraught with difficulties. Showing activation changes as patients respond to treatment is trivial unless performance can be kept constant across time points. This seems counter-

intuitive because the hope is that the patients will show substantial improvements with therapy. As in all science, it is necessary to have a hypothesis before embarking on a study using functional imaging techniques. It is useful to ask what question will be answered by functional imaging that otherwise could not be answered. The demonstration of changes in the brain in the absence of an either/or hypothesis is not very interesting. True insights into brain mechanisms of recovery from stroke will only come from complementing functional imaging studies with other types of experimental investigation in human and non-human animals.

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