Early Imaging Correlates of Subsequent Motor Recovery after Stroke

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Objective: To determine whether functional magnetic resonance imaging activation obtained in the first few days after stroke correlates with subsequent motor recovery.

Methods: Twenty-three patients with hemiparesis after first-time stroke were scanned at 2.0 ± 0.9 days while performing a simple motor task. We defined recovery as the change in Fugl–Meyer score from time of scan to approximately 3 months later (90 ± 8 days). We performed three different tests to assess correlations between brain activation and change in Fugl–Meyer score: (1) multivariate (most sensitive to spatially diffuse activation); (2) voxel-wise Statistical Parametric Mapping (most sensitive to focal activation), and (3) primary motor cortex region-of-interest analysis (most sensitive to average activation within this region). All tests controlled for initial stroke severity and lesion volume, as well as other established clinical variables.

Results: The multivariate test was significant [$F(595, 4{,}934) = 1.93$; $p < 0.001$]. The Statistical Parametric Mapping test detected two small clusters of focal activity located in the ipsilesional postcentral gyrus and cingulate cortex ($p < 0.05$, corrected). The region-of-interest test was not significant.

Interpretation: There is a pattern of brain activation present in the first few days after stroke, of which the postcentral gyrus and cingulate cortex are a part, that correlates with subsequent motor recovery. This result suggests that there are recovery processes engaged early after stroke that could provide a target for intervention.

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There is unexplained variability in the extent to which patients recover after stroke, particularly from the reference point of the first few days after onset. Among studies that track motor impairment and recovery, only 30 to 50% of the variance of recovery is explained by the most commonly reported predictors: lesion volume and initial stroke severity.[1,2] We hypothesized that functional imaging early after stroke could provide information over and above initial severity and lesion volume about the degree of subsequent recovery. Several prior functional imaging studies have reported altered brain activation patterns in patients at various stages of motor recovery after stroke.[3–6] These studies describe brain activation related to *concurrent* recovered performance at the time of scanning that differs to varying degrees from what is seen in age-matched control subjects. In this study, we used functional imaging to ask a specific and unique question about motor recovery after stroke: Can functional imaging in the early period after stroke detect brain activation related to *subsequent* recovered performance? Should such activation be identified, then it could serve as a physiological target for intervention (eg, noninvasive brain stimulation) in this early time period.

To investigate whether brain activation early after stroke can be correlated with subsequent recovery, we scanned patients approximately 48 hours after stroke using functional magnetic resonance imaging (fMRI) and defined recovery as the change in motor impairment from the time of scanning to a follow-up point 3 months later. We used three different statistical tests: (1) a multivariate test, which is most sensitive to spatially diffuse activation; (2) voxel-wise Statistical Parametric Mapping, which is most sensitive to focal activation; and (3) primary motor cortex (M1) region-of-interest (ROI) analysis, which is most sensitive to average activation within this region. The ROI analysis was chosen to test existing hypotheses implicating M1 and the corticospinal tract in recovery.[7–9] All tests controlled for lesion volume and initial stroke severity, as well as other established clinical variables.

Subjects and Methods

Subjects

We recruited stroke patients from a large screening database of all patients with the diagnosis of ischemic stroke admitted

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to Columbia University Medical Center between December 2004 and April 2007 (N = 993), part of Columbia's Specialized Program of Translational Research in Acute Stroke (SPOTRIAS), a National Institute of Neurological Disorders and Stroke–funded national network to investigate new pathophysiological, diagnostic, and clinical approaches in acute stroke. Thirty-three consecutive patients with first-ever ischemic stroke and hemiparesis able to undergo fMRI within 48 hours of stroke onset were recruited. Five patients were eligible but refused the fMRI scan. Three underwent fMRI but did not complete the 3-month clinical follow-up (one experienced development of dementia, one left the country, one was incarcerated). Two patients had recurrent stroke before the 3-month follow-up and were excluded from analysis. The final sample size of 23 was considered adequate for a functional imaging study of this type. Patients with aphasia or hemineglect alone were not included in this analysis. See Supplementary Table 1 for more demographic and clinical details.

All patients except for four underwent a single session of fMRI scanning at our target of 24 to 48 hours after stroke onset (the remaining four patients had their scans between 49 and 96 hours because of scheduling delays; mean time to scan, 47.8 ± 21.6 hours; median, 46 hours). Exclusion criteria also included seizure at stroke onset, moderate-to-severe aphasia or other cognitive impairment that precluded training on the fMRI task, or any contraindication to MRI. None of the patients had neglect or apraxia on examination. Patients did not smoke on the day of scanning (they were inpatients); caffeine intake was not recorded. The strict eligibility criteria permitted us to control for unwanted variables whereas preserving the wide spectrum of initial motor severity that would contribute to the correlation analysis. Total lesion volumes were estimated by summing the volumes of the diffusion-weighted imaging lesion in each slice (length by width by slice thickness measured with the measurement tool in the picture archiving and communication system (PACS) system software) in which the diffusion-weighted imaging was positive.

Recovery Measure

Motor impairment was measured with the upper-limb Fugl–Meyer assessment *(FM),*[11] which has a maximum score of 66, and is valid and highly reliable over a wide spectrum of severities.[12–16] FM was assessed on the day of scanning (FM_{initial}) and again at 3 months ($FM_{3\ \text{months}}$). Recovery (ΔFM) was defined as follows: $\Delta FM = FM_{3\ \text{months}} - FM_{\text{initial}}$. Our decision to use a change score as our measure of recovery was based on the idea that the degree of change, rather than the final level achieved, would better reflect a biological recovery process.[17]

In addition to the FM, we also measured hand dynamometry at baseline on the day of scanning (DYN_{initial}). The reason for doing so was that hand dynamometry score should presumably correlate with the degree of difficulty subjects would have to perform the fMRI hand closure task. DYN_{initial} was taken as an average of three measurements of maximal grip force.

Functional Magnetic Resonance Imaging Data Acquisition

Patients underwent gradient-echo echo planar fMRI (GE 1.5 Tesla General Electric, Fairfield, CT; 64 × 64 matrix; field of view = 19cm; 21 slices; slice thickness/skip = 4.5/0mm; TR = 4,000 milliseconds; TE = 52 milliseconds; flip angle = 60 degrees) while performing the repetitive hand closure task described later. One session (40 volumes) was performed per hand. The order in which the hands (affected/unaffected) were tested was counterbalanced across patients except for those with complete plegia (see later).

Motor Task Used during Functional Magnetic Resonance Imaging

The task was a simple repetitive hand closure in synchrony with a 1Hz metronome click, following a block design: 20-second rest epochs alternating with 20-second task epochs (4 cycles total per hand). The instruction was: "Close your hand gently in rhythm with the click you hear. Start and stop when you hear the instructions through the headphones." The metronome click was played continuously via MRI-compatible headphones in the scanner. No other instructions were given about a particular level of grip force. Auditory "Start" and "Stop" commands were given via the headphones at the beginning and end of each 20-second task block. Separate runs were performed for the affected hand and unaffected hand. For patients with plegia, defined as maximum grip force of less than 1kg on dynamometry, the unaffected had was tested first to demonstrate correct understanding of the task in the scanner. For these patients, instructions were given to "do exactly what you did with your good hand." Differences in in-scanner performance were controlled for by including FM_{initial} and DYN_{initial} in the regression model (see statistical analysis method later). Although in-scanner performance clearly could differ across patients, this approach allowed us to include in our analysis patients with a wide spectrum of initial severity. Patients were pretrained on the task outside of the scanner, lying supine with the metronome tone until they could perform the task without difficulty. Qualitative, direct visual assessment of mirror movements was made by an investigator during scanning (only rare, intermittent movements of the opposite hand or foot were seen). No other quantitative behavioral data were acquired during pretraining or during the scanning itself.

Functional Magnetic Resonance Imaging Preprocessing

All image preprocessing was implemented using the Statistical Parametric Mapping 5 (SPM5) program (Wellcome Department of Imaging Neuroscience, London, United Kingdom). The following steps were performed per patient: All functional images were realigned to the first volume of the first session. The first functional image was then used to determine parameters (7 × 8 × 7 nonlinear basis functions) for transformation into a Talairach standard space[18] defined by the Montreal Neurological Institute gradient-echo echo planar template brain supplied with SPM5. This transformation was then applied to all the functional volumes, which were resliced using sinc-interpolation to 2 × 2 × 2mm. Using knowledge of the infarct location, we oriented all images

such that the right side of the brain corresponded to the ipsilesional hemisphere.

Image Processing and Statistical Analysis

The general statistical approach applied to the fMRI data comprised in turn: (1) a within-subject, voxel-wise regression of the fMRI time series to estimate task-related brain activation (ie, standard SPM first-level[19]); (2) an across-subject, voxel-wise regression of the first-level regression coefficients on a set of predictors including ΔFM, yielding second-level regression coefficient at each voxel (ie, standard SPM second level[19]); and (3) the application of 3 different statistical tests applied to the relation between the second-level regression coefficients and ΔFM: (i) a multivariate test, which assesses effects of interest in all voxels in the brain with a single, global test statistic; (ii) an SPM test of cluster-wise significance (height thresholded at $p < 0.001$ uncorrected, and with cluster size threshold = 163 voxels; this cluster size threshold was chosen because it provided a map-wise corrected cluster-wise false-positive rate of 0.05 given the chosen height threshold); and (iii) a t test on the spatially averaged signal within an ROI. The purpose of using three different tests for the same relation was that they have different relative sensitivities for different types of spatial signals: the multivariate test is relatively more sensitive to low-amplitude, spatially diffuse signals; the SPM cluster-wise test is relatively more sensitive to intense, spatially focal signals (though there is also some dependence on spatial extent); and the ROI test has the best sensitivity for the average effect in a given ROI.

For the first-level analysis, fMRI time series from each subject were regressed voxel-wise on a square wave convolved with the default hemodynamic response function in SPM5 (high-pass filter cutoff = 0.01875Hz). The resulting regression coefficient at each voxel (for each subject) was divided by the corresponding time series mean to yield values proportional to percentage fMRI signal change. These images were then spatially smoothed (isotropic Gaussian kernel, full-width at half-maximum = 8mm). The resulting images were then entered into a second-level, across-subject, random-effects regression model that included ΔFM as a covariate. Additional covariates included variables that were both significant in a previous regression analysis to predict ΔFM (initial stroke severity [$FM_{initial}$], subcortical lesion volume, and age), as well as others that were not significant but were included because of a plausible biological relation to ΔFM: baseline grip force ($DYN_{initial}$), cortical lesion volume, and cortical and subcortical lesion location. The point of including all these variables besides ΔFM was to ensure that any correlation detected between task-related brain activation and ΔFM reflects a linear relation over and above that between these other variables and ΔFM.

Tests for statistical significance were then applied. It should be noted that the null hypothesis for both the multivariate test and the SPM cluster-wise test was the same, namely, that there are no second-level effects of interest (ie, correlations between task-related fMRI activation and ΔFM) at any voxel. The tests differ in their results, however. Rejecting the null hypothesis with the cluster-wise test allows formal localization of effects in suprathreshold clusters, whereas rejecting the null hypothesis with the multivariate test only provides evidence for the existence of effects somewhere in the brain without the ability to infer effects at the individual voxel level. This is because the multivariate statistical test involves assessing the significance of all the voxels in the search volume in ensemble, not separately. The process can be heuristically understood as an averaging across voxels of the F-statistics associated with the effects of interest and then comparing this single value with an appropriate null hypothesis F distribution. (More details are provided in the supplementary materials; for full details, see Worsley and colleagues'[20] article.)

The spatial distribution of the multivariate correlation, which can be referred to as the "recovery pattern," is simply the standard statistical parametric map [SPM(t)] of the second-level regression. Once the recovery pattern (correlation) was identified by applying the multivariate test, we could then compute for each subject a "pattern expression" (degree of expression of the recovery pattern) by taking the inner product of the recovery pattern with each second-level–dependent image after having adjusted the latter for effects of the additional predictors. This would allow us to represent graphically the value of the fMRI signal correlation for each individual plotted against their ΔFM.

The M1 ROI was defined as the BA4 ROI from WFU Pickatlas (version 2.4).[21] The same second-level regression model as described earlier was applied to the spatially averaged first-level regression coefficient within this ROI, and a t test was performed on the resulting second-level coefficient corresponding to ΔFM.

Results

Patient Data

Of the 23 patients who were analyzed in the study, average age was 59.0 ± 10.5 years, 16 were men, and 22 were right-handed. All lesions involved some part of the corticospinal tract. Twelve had strokes in the right hemisphere, 16 were subcortical only (7 brainstem, 9 striatocapsular/corona radiata), 3 were cortical only (2 frontal/insula, 1 frontal/occipital), and 4 were combined (2 insula/coronal radiata, 1 occipital/frontal/insula/corona radiata, 1 occipital/pons). A single patient had bilateral strokes (Patient 17), although the left hemisphere lesion was a small cortical occipital infarct (see Supplementary Table 1). Eleven of the patients received physiotherapy after stroke (total number of hours per week of therapy is listed in Supplementary Table 1).

Behavioral Results

Each subject's $FM_{initial}$, ΔFM, and hand dynamometry at time of scanning are listed in Supplementary Table 1. $FM_{initial}$ ranged from 6 to 63 (mean, 36.3 ± 22.9). Dynamometry scores at the time of scanning ranged from 0 to 40kg. ΔFM ranged from 0 to 40 (mean, 16.5 ± 14.5). All patients performed the in-scanner hand closure task without difficulty with the unaffected hand.

Main Effect of Task

We first tested for brain activation associated with the main effect of the motor task (ie, the across-subject average of the motor task-versus-rest regression coefficient) to establish that fMRI as implemented in this study would yield patterns of task-related activity consistent with previous reports. Although theoretical concerns existed whether altered vasoreactivity early after stroke[22] could have altered our results, a replication of patterns reported in the subacute and chronic periods confirmed the validity of our protocol tested in the early stroke setting. Using SPM cluster-wise testing ($p < 0.05$, corrected), we found that with use of the unaffected hand there were significant clusters in contralateral M1 and S1, supplementary motor area, and ipsilateral cerebellum, consistent with previous studies in healthy subjects[23–25] (Fig 1, blue). With use of the affected hand, there were activations not only in areas homologous to those just mentioned, but also extra activations in ipsilateral M1, ipsilateral premotor cortex, bilateral prefrontal cortex, and contralateral cerebellum, as has been described previously[26–28] (see Fig 1, red). The Table lists coordinates of the maxima of the significant clusters.

Recovery-Related Functional Magnetic Resonance Imaging Results

We next tested for correlations between brain activation early after stroke and Δ*FM* while controlling for the clinical variables described in Subjects and Methods. The multivariate test was significant for use of the affected [$F(595,4934) = 1.93$; $p < 0.001$] but not the unaffected [$F(595,4934) = 0.91$; $p = 0.99$] hand. Because the multivariate test cannot be used to infer anatomical information at the voxel level, the recovery-related activation pattern identified with this test is not illustrated in a figure. Applying the SPM cluster-wise test to the correlation between fMRI signal and Δ*FM* ($p < 0.05$, corrected), we found significant clusters in the right (ipsilesional) postcentral gyrus and posterior cingulate gyrus for affected hand activity (see Fig 1, green; see the Table for maxima coordinates), and none for the unaffected hand. It is important to understand that areas other than those identified in the cluster-wise analysis could have activation truly correlated with Δ*FM,* because sensitivity of the SPM test is poor for sufficiently low voxel-wise statistical effect sizes. However, such weak voxel-wise effects, taken in ensemble over the entire brain, could lead to an appreciable multivariate statistical effect size, which was the reasoning behind our use of the multivariate test. As it turned out, both multivariate and SPM test results were positive, but we are careful not to conclude that the suprathreshold SPM clusters were the sole contributors to the multivariate test result. We also note the distinction between the clusters of activation associated with Δ*FM* and those atypical clusters of "extra" activation associated with the main effect of task when using the affected hand. The fact that these extra activations did not show significant correlation with Δ*FM* suggests that they are not predominantly related to subsequent recovery.

Testing specifically for fMRI Δ*FM* correlations in primary motor cortex with the ROI test, we found no statistically significant result in either contralateral [$t(15) = 1.58$, two-tailed, $p = 0.14$] or ipsilateral [$t(15) = 1.40$, two-tailed, $p = 0.18$] M1 ROIs. The correlations were also not significant in either the con-

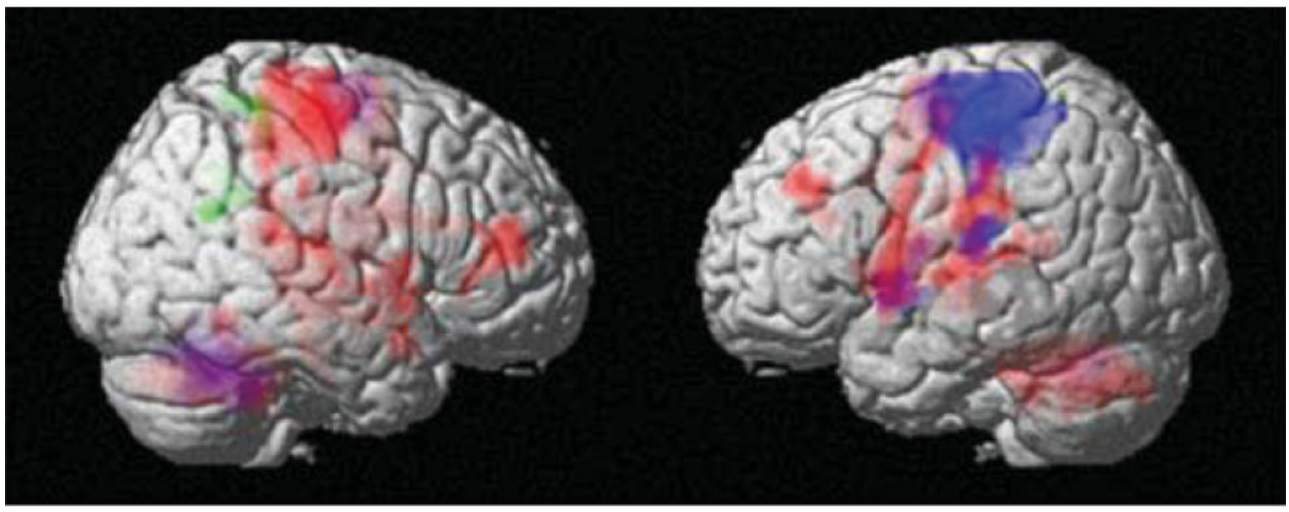

Fig 1. Functional magnetic resonance imaging activation for 23 hemiparetic stroke patients. Activation pattern related to hand closure task using the nonparetic hand is shown in blue; activation related to hand closure task using the paretic hand is shown in red; activation pattern derived from hand closure task of the paretic hand that correlated with subsequent motor recovery is shown in green. All effects were height-thresholded and corrected for cluster size to yield a false-positive rate of $p < 0.05$.

tralateral [$t(15) = -0.31$, two-tailed, $p = 0.76$] or ipsilateral [$t(15) = 0.59$, two-tailed, $p = 0.56$] M1 ROIs when using the unaffected hand.

Figure 2 shows a scatterplot of ΔFM for each of the 23 patients plotted against their recovery pattern expression derived from the multivariate test: those with lower expression of the recovery pattern had lower ΔFMs, and those with higher expressions had higher ΔFMs. Notable is the wide distribution of locations on the plot among patients with severe paresis ($FM_{initial} < 20$) at onset (data points in black). Even though these patients were always severely affected at onset, those with little subsequent recovery had low expression of the pattern in the early period after stroke, and those with greater subsequent recovery expressed the pattern to a much greater extent. This dissociation could be expected because we controlled for severity at onset in the regression model, and it supports the finding that there may be subpopulations of patients, perhaps most striking among those with severe motor deficits, who recover either proportionally to their initial deficits or poorly,[17] and that their relative expression of the recovery pattern may be reflecting a biological difference between them.

Discussion

We identified a correlation between task-related fMRI activity in the first few days after stroke and subsequent motor recovery. This study is the first to demonstrate an association between fMRI activation early after stroke and a later measure of recovery. Previous studies, including our own, have shown atypical task-related activations days to weeks after stroke before or while recovery is ongoing.[27–31] The functional significance of any such activity, however, cannot be determined in the absence of a quantitative relation between the fMRI signal and a later behavioral measure of recovery, and without simultaneously controlling for stroke severity at the time of scanning, lesion volume, and other clinical variables. The fMRI task used to determine the correlation with ΔFM was a distal hand movement task, whereas the behavioral measure *(FM)* assesses both distal and proximal movements. This meant that information about overall motor recovery can be derived by engaging the motor system in a simple motor task in the scanner. Our findings provide evidence for a functional relevance of early brain activity over and above clinical predictors.

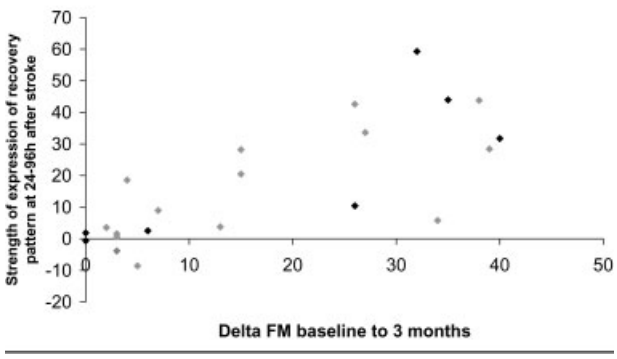

Fig 2. Scatterplot of motor recovery defined as the change in Fugl–Meyer assessment (FM) from baseline to 3 months versus degree of expression of the functional magnetic resonance imaging (fMRI) motor recovery pattern obtained 24 to 96 hours after stroke for the 23 stroke patients. Patients with severe motor dysfunction at baseline are designated by black diamonds. *Note that the fMRI pattern expression is shown as the* y*-axis because mathematically it was treated as the dependent variable for the purposes of the multivariate analysis, even though conceptually the fMRI pattern is the predictor.*

There were several variables that were not in our model, including sex, lesion location, stroke cause, and cognition. Whereas these variables have been shown to affect recovery when disability scales and functional scores are used as outcome measures,[32–34] some, such as sex, do not appear to predict recovery when motor impairment is used as an outcome as we did in this study.[17,35,36] Stroke causative factors (cardioembolic, atherothrombotic, lacunar) were not included because this variable's salient physiological effects were subsumed under existing variables: lesion volume, cortical versus subcortical lesion location, and stroke severity. Most of our patients had relatively small strokes. Although controlling for lesion volume in the model allows us to generalize our results, future work with a larger cohort could assess the correlations specifically in patients with larger strokes.

Potential concerns about our result include those related to the effects of rehabilitation, medical comorbidities, and mirror movements. Specifically, these could affect the relation between brain activation and ΔFM. For example, differences in rehabilitation dosage could attenuate correlations with early brain activation. However, this concern is moot because we found a significant correlation between ΔFM and brain activation. Another potential rehabilitation-related concern is that the recovery pattern was simply a surrogate for a relation between rehabilitation dose and ΔFM; this would mean that brain activation, which was measured before any therapy was delivered or any decisions about therapy were made, would need to correlate with the amount of therapy subsequently delivered, which would appear implausible. The same problem with temporal causality would apply to medical comorbidity or the use of sedative medications. Finally, although subtle mirror movements could not be ruled out, for this variable to alter our main finding, one would have to postulate that mirror movements correlated positively with recovery, when, in fact, the opposite has been reported.[37]

The fMRI recovery pattern was identified using a

multivariate statistical method. Because multivariate tests assess effects across all voxels simultaneously, correction for multiple comparisons is not required. For the same reason, however, the method cannot be used to infer regional anatomical information at the individual voxel level.[38] To assess focal effects, we used SPM cluster-wise testing. The SPM results were negative except for two clusters (right postcentral gyrus, cingulate cortex). It is necessary to recognize that statistical significance in a multivariate test does not require that the effects at any single voxel exceed the SPM threshold to make sense of the paucity of suprathreshold clusters in the face of a statistically significant multivariate result. Rather, a spatially diffuse pattern of activity with many regions contributing to the overall effect may produce this type of result. We consider it most likely that a widely distributed pattern of brain activity (of which the postcentral gyrus and cingulate are only a small part) is the true correlate of motor recovery in our study.

The correlations between ΔFM and brain activation averaged within contralateral and ipsilateral M1 ROIs were not significant. This result suggests that early recovery processes per se do not involve activation in M1. However, this is not to say that residual corticospinal tract (CST) integrity is not important to allow subsequent behavioral expression of these recovery processes.[39] Indeed, this dissociation between activation related to future recovery versus activation related to performance at the time of scanning at any time point over the course of recovery is the central idea of this article. The former reflects processes required to achieve subsequent recovery; the latter reflects the outcome of these processes. We would suggest that a major contributor to interindividual differences in motor recovery is the degree to which other brain regions, whose existence is implied by our multivariate result, can recruit and facilitate the ipsilesional residual CST and other descending pathways.

We have established the presence of a correlation between an acute brain imaging pattern and degree of subsequent motor recovery, which we hypothesize represents capacity to monitor and evaluate motor performance, and drive adaptive changes that lead to recovery, similar to changes that have been reported to occur with motor learning in healthy subjects.[40–42] In such studies, several areas that are not directly connected to the corticospinal tract contribute to the acquisition of motor skills, which are then expressed through corticospinal tract output. Animal studies also support the idea that cortical reorganization remote from the site of the injury mediates recovery. For example, it has recently been shown that a lesion in the primary motor cortex of squirrel monkeys leads to major anatomical reorganization in cortical areas distant from the injury.[43] In humans, a longitudinal study that used transcranial magnetic stimulation to assess corticospinal tract integrity and corticocortical excitability in a group of patients with stroke-related hemiparesis showed that motor performance at 3 months correlated only weakly with a measure of corticospinal tract integrity but strongly with a measure of the degree of corticocortical excitability,[7] suggesting that variables other than how well the corticospinal tract is working at a given time determine how well it is able to work later. Indeed, the fact that we included measures of impairment at the time of scanning ($FM_{initial}$ and $DYN_{initial}$) as predictors in the regression model means that the detected multivariate correlation between task-related fMRI activation and ΔFM is not explainable simply as a relation between $FM_{initial}$ or $DYN_{initial}$ and ΔFM.

Our findings suggest that there are determinants of the recovery process that are present early after stroke. The presence of significant recovery-related activation in this time period justifies the investigation of interventions designed to enhance the recovery process. Further study will be needed to assess the ability of early brain activation to prospectively predict recovery, to elucidate the anatomical basis of the recovery pattern, and to investigate whether analogous recovery patterns exist in patients with other stroke deficits such as aphasia or hemineglect.

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