Electrodermal Recording and fMRI to Inform Sensorimotor Recovery in Stroke Patients

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Abstract

Background—Functional magnetic resonance imaging (fMRI) appears to be useful for investigating motor recovery after stroke. Some of the potential confounders of brain activation studies, however, could be mitigated through complementary physiological monitoring.

Objective—To investigate a sensorimotor fMRI battery that included simultaneous measurement of electrodermal activity in subjects with hemiparetic stroke to provide a measure related to the sense of effort during motor performance.

Methods—Bilateral hand and ankle tasks were performed by 6 patients with stroke (2 subacute, 4 chronic) during imaging with blood oxygen level-dependent (BOLD) fMRI using an event-related design. BOLD percent changes, peak activation, and laterality index values were calculated in the sensorimotor cortex. Electrodermal recordings were made concurrently and used as a regressor.

Results—Sensorimotor BOLD time series and percent change values provided evidence of an intact motor network in each of these well-recovered patients. During tasks involving the hemiparetic limb, electrodermal activity changes were variable in amplitude, and electrodermal activity time-series data showed significant correlations with fMRI in 3 of 6 patients. No such correlations were observed for control tasks involving the unaffected lower limb.

Conclusions—Electrodermal activity activation maps implicated the contralesional over the ipsilesional hemisphere, supporting the notion that stroke patients may require higher order motor processing to perform simple tasks. Electrodermal activity recordings may be useful as a physiological marker of differences in effort required during movements of a subject's hemiparetic compared with the unaffected limb during fMRI studies.

Keywords

BOLD fMRI; Electrodermal activity; Stroke recovery; Ankle dorsiflexion; Grip; Hemiparesis

The application of blood oxygenation level-dependent (BOLD) contrast functional magnetic resonance imaging (fMRI) as a tool to investigate stroke has improved our theoretical understanding of the processes of motor recovery,^{1–3} providing insight that has the potential to influence clinical decision making. The present study focuses on 2 areas of research that would help to refine theories of motor recovery. The first involves going beyond fMRI motor paradigms that have concentrated on hand function to observe activations induced by lower-extremity movements. The second aims to acquire greater insight into fMRI patterns of activation by employing combinatorial and complementary physiological measurements.

Using fMRI to probe lower limb and gait-related stroke deficits is an important and natural extension to the literature, as lower limb disorders are the most common after stroke. Thirty-five percent of stroke survivors with lower limb motor impairment show no functional improvement.⁴ Jorgensen and colleagues⁵ found that a prognosis regarding walking can be made within 6 weeks because improvement, under the conditions of no focused rehabilitation for locomotor recovery, tends not to occur beyond 11 weeks after stroke. Only a small body of neuroimaging literature has been directed at the lower limb in relation to motor recovery.^{6–10}

Stroke recovery fMRI studies that include complementary measurements are also an important research direction.^{11,12} Combining fMRI with transcranial magnetic stimulation (TMS) or with an electroencephalogram (EEG) can provide additional insight regarding the role of interhemispheric communication or neurovascular coupling during recovery, although both are challenging from the logistical standpoint. However, neuroimaging with simultaneous recording of electrodermal activity (EDA), a physiological measurement of autonomic tone, is feasible. A typical EDA measurement is relatively innocuous to the participant and entails fastening electrodes containing conductive paste to the palmar surface of any 2 fingers. The EDA signal reflects changes in the secretions from the sweat glands, which are measured as a change in the electrical conductivity of the skin. The EDA signal has been shown to vary over time scales that are comparable to the BOLD hemodynamic signal in response to tasks that involve attention, cognitive effort, or emotion arousal and even during a challenging motor task in healthy individuals. A fruitful application of EDA is to incorporate the autonomic signal as a physiological covariate in fMRI studies to investigate brain and behavior relationships.^{13,14}

The present pilot study incorporates an fMRI-compatible EDA system in a small group of subacute and chronic stroke patients to provide a physiological marker of the sense of effort during tasks with the affected limb. It is hypothesized that EDA can be incorporated into fMRI analysis to provide interpretation of activation patterns that is complementary to typical task-related analyses. Examples of the utility of EDA measurements are provided in a sensorimotor battery that employs an event-related design during fMRI activation. Compared with a block design, event-related fMRI is better suited for stroke recovery because it is less affected by the potential confound of a compromised vascular system.^{15–17}

Furthermore, event-related design is less sensitive to head motion that may be correlated with the task.¹⁸ Finally, EDA signals that are correlated with fMRI data are likely to isolate the sense of effort in hemiparetic subjects associated with performing brief movements in an event-related design and less likely to be related to fatigue due to repetitive movements that may occur in a block design.

METHODS

Patients

This study involved 2 subacute stroke patients (2 men with left hemisphere lesions) and 4 chronic stroke patients (3 men and 1 woman, 2 right, 2 left hemisphere lesions) with paresis of the upper and/or lower extremities (see Table 1). Patients were recruited if they had some motor function and met the following inclusion criteria: no impairment in visual perception, neglect, or brainstem stroke. Figure 1 shows the lesion location for all 6 patients. Patient 5 had a small lesion in the right lentiform nucleus from a previous stroke. Participants provided informed consent, and the study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre.

MRI Acquisition

Imaging data were collected using a 3.0 T whole-body MRI scanner (General Electric Healthcare, Waukesha, Wisconsin). Axial anatomical images were acquired using a 3-dimensional T₁-weighted spoiled gradient recall echo sequence with the following parameters: TI/TR/TE/FA = 300 ms/7.0 ms/3.1 ms/15°, with voxel dimensions of 0.86 mm × 0.86 mm × 1.4 mm and 220 mm × 165 mm field-of-view (FOV) in-plane. Additional anatomical (FLAIR, PD/T2 FSE) and diffusion sequences (DTI) were performed, time permitting, but are not reported here for brevity. Patients underwent whole-brain, axial multislice fMRI scans with voxel dimensions of 3.1 mm × 3.1 mm × 5 mm, 200 mm × 200 mm FOV in-plane and TR/TE/FA = 2000 ms/30 ms/70°. For fMRI, T₂*-weighted BOLD signal contrast was acquired during single-shot spiral-in and then spiral-out k-space trajectories (spiral IO). As is described elsewhere,¹⁹ spiral IO data with signal-weighted averaging increase the signal-to-noise ratio significantly compared with conventional spiral-out sequences, without sacrificing temporal resolution. The first 5 data points in all fMRI time series were ignored to ensure that subsequent magnetization had reached steady state. The total imaging time varied across patients, depending on tolerance levels, lasting 1.5 hours or less.

Sensorimotor Battery

The overall goal was for each patient to perform the entire sensorimotor battery. However, this was not possible in practice. Depending on logistics and the spectrum of deficits, patients participated in as few as 2 and as many as 4 motor tasks consisting of brief, isolated, repeated movements involving the hand, fingers, or ankles (Table 1). In the lower limb tasks, patients performed a 2-second ankle dorsiflexion of the unaffected limb (1. ankle—unaffected) or affected limb (2. ankle—affected) followed by 18 seconds of rest, repeated 15 times (310-second duration). In the upper limb tasks, patients performed 1 to 4 different task conditions: (3) gripping—affected, (4) gripping—unaffected, (5) finger (easy)—affected,

and (6) finger (hard)—affected. During gripping tasks, patients used digits 1, 2, and 3 to grip a rubber bulb (2-second duration) and to move a horizontal bar to a predetermined target that was less than 50% of the patient's maximum voluntary contraction. This brief visual biofeedback, which was introduced to control for inter- and intraindividual variations in motor behavior, was followed by 12 to 18 seconds of rest. Ten repetitions were performed involving the affected hand or the unaffected hand (162- to 210-second duration, respectively). Grip force was displayed in real time to the patient using an fMRI-compatible force-sensing resistor apparatus. For “easy” finger movements, patients performed a 3-second fractionated finger movement involving the simultaneous abduction of all 5 digits, followed by 12 seconds of rest, with 24 repetitions (372-second duration). When possible, a more difficult (hard) finger task was performed that involved a single flexion followed by extension of digit 2 over 4 seconds, followed by 16 seconds of rest, for 10 repetitions (210-second duration).

The order of the tasks was randomized, except that the 2 lower limb tasks always preceded the upper limb tasks due to experimental practicalities. Tasks 1 (dorsiflexion—unaffected) and 4 (gripping—unaffected) were considered “control” tasks, with the expectation that observed brain activity and motor behavior would be very similar to that displayed by healthy age-matched individuals. Given the logistics of the study, preference was given to task 3 over task 4 because the unaffected upper limb was affixed with electrodes, and limb motion could potentially confound EDA results. The EDA measurements were made using a custom-made fMRI-compatible system with electrodes (TSD 203, Electrodermal Response Electrode Set, BIOPAC Systems, Inc, Goleta, California) fastened to digits 4 and 5 of the unaffected hand. With the exception of the task 4, patients were instructed to keep their unaffected arm still throughout the entire experiment, which was confirmed by visual inspection. The EDA measurements were filtered (2-Hz low-pass cutoff frequency) and sampled at 100 Hz using LabVIEW software developed in the laboratory (National Instruments, Austin, Texas).

Data Analysis

Image processing was performed using AFNI software (Cox 1996). Retrospective coregistration was performed and revealed that runs from some patients showed excessive head motion. Experimental runs were excluded based on a head motion >1 cm in translation or clear sign of a head motion artifact in the general linear model (GLM) activation maps because conventional coregistration methods are unlikely to recover image corruption when head motion exceeds voxel size.²⁰ Images were smoothed temporally using a 3-point median filter and spatially using a Gaussian filter with full-width half maximum of 4 mm. Maps of brain activity were generated using a univariate GLM with 2 different model waveforms: (1) the binary task waveform convolved with a hemodynamic response function, denoted “HEMO” (Cox 1996), and (2) the normalized, filtered electrodermal time series for each individual participant, denoted EDA. Activation maps were inspected for each patient after converting to Z scores, setting a threshold of Z score >3.1 ($P < .001$), and correcting for multiple comparisons using a Monte Carlo simulation of activated voxel cluster size²¹ with the cluster size set at 1500 μL .

Activation maps were subsequently transformed to Talairach space for recording the location of significantly active brain regions. The BOLD percent signal change, the Z score, and the coordinates of peak activation within the sensorimotor cortex (SMC) were determined for each patient. Laterality indices were calculated using an anatomically derived mask circumscribing the pre- and postcentral gyri (ie, the range from inferior to superior was $Z = [14-68 \text{ mm}]$). Within the mask, the number of suprathreshold voxels in the left and right hemispheres was compared using a metric often quoted in the literature ($LI = [R - L]/[R + L]$).² A fixed effects analysis of variance (ANOVA) was performed on both HEMO and EDA maps. One patient (P1) had to be excluded because of excessive head motion and corrupted EDA data. Significant voxels were reported after clustering and thresholding the mean effect z statistic ($Z > 3.1$, uncorrected $P < .001$).

RESULTS

All 6 patients were clinically stable at the time of fMRI. Table 1 shows the age (mean age, 36 ± 13 years; range, 18–52 years), gender, National Institute of Health Stroke Scale (NIHSS), and the time poststroke that fMRI was performed (range, 25 days to 5 years). Table 1 also lists the sensorimotor tasks that each patient performed. Of the 20 runs undertaken across all 6 patients, only 3 were excluded due to excessive head motion. Event-related BOLD hemodynamic responses showed characteristic stimulus-locked cycling with robust peak percent BOLD signal changes.

For the 4 patients who performed the ankle dorsiflexion tasks, activation foci in the SMC were generated. Although group statistics were not performed, Table 2 shows that the location of peak SMC activation across patients was found to be more variable in X and Y and consistent in Z: $X_{\text{affec}} = 0.5 \pm 5 \text{ mm}$, $X_{\text{unaffec}} = -6 \pm 0.5 \text{ mm}$, $Y_{\text{affec}} = -24 \pm 16 \text{ mm}$, $Y_{\text{unaffec}} = -22 \pm 8 \text{ mm}$, and Z_{affec} and $Z_{\text{unaffec}} = 64 \pm 4 \text{ mm}$ (x-coordinates for patients with right hemiparesis were flipped). Mean and standard deviation BOLD percent change values for voxels in the SMC were calculated and found to be nonsignificant between affected $1.24\% \pm 0.42\%$ and unaffected dorsiflexion $1.06\% \pm 0.38\%$ ($P < .28$).

Activation foci in the SMC were generated for 4 of the 6 patients who performed upper limb tasks without deleterious head motion artifact. Table 3 shows the location of the peak activation in Talairach coordinate space, Z scores, and computed laterality index (LI) values. The location of peak SMC activation across patients was found to be $X_{\text{affec}} = -39 \pm 4 \text{ mm}$, $Y_{\text{affec}} = -21 \pm 3 \text{ mm}$, and $Z_{\text{affec}} = 51 \pm 4 \text{ mm}$. Mean and standard deviation BOLD percent change values for voxels in the SMC were calculated to be $1.1\% \pm 0.33\%$ for the affected hand.

For patient 3 (right arm/leg affected, subacute), comparison of the HEMO activation maps for movement of the affected and unaffected limbs reveals mirror symmetry about the midline, an observation that would be expected in a healthy participant (Figure 2A). The EDA activation map for the affected dorsiflexion (right ankle) shows significant increased activation compared with the rest condition in the contralesional (left) insula, secondary somatosensory cortex (SII), SMC, and ipsilesional SMC and cingulate (Figure 2B). Greater activation was found for the rest condition versus the task condition in the ipsilesional

middle temporal lobe. For dorsiflexion of the unaffected ankle, the EDA time series was unremarkable for this patient; consequently, the EDA GLM analysis produced no activation. A similar trend was observed in patient 6 during dorsiflexion of the affected limb, with significant regions found exclusively in the contralesional hemisphere: premotor, insula, SMC, and SII. These data show that even simple movements involving the affected limb produce task-correlated changes in EDA for certain patients. Conversely, dorsiflexion of the unaffected limb did not produce EDA changes in any of the patients tested.

A second individual patient result is shown in Figure 3A for patient 2 (chronic) performing a gripping task with biofeedback involving the affected hand. Unfortunately, due to time constraints, this patient did not perform gripping with the unaffected hand as a control task. The HEMO map illustrates predominant activation in the ipsilesional SMC, as well as ipsilesional SII and bilateral SMA, an activation that is consistent with good recovery. In contrast, EDA GLM analysis produced activation in the contralesional middle frontal gyrus, premotor cortex, inferior parietal lobe and SII, and ipsilesional middle frontal gyrus and cerebellum activation. The EDA time series shown in Figure 3B shows phasic changes that are correlated with the task pattern.

Finally, mean effect group HEMO and EDA maps are overlaid on an average brain in Talairach coordinate space ($Z > 3.1$, $P < .001$, uncorrected; Figure 4). As expected, the HEMO map produced activation in the sensorimotor network bilaterally. Of interest, however, were the small but significant regions identified in the group EDA map—namely, the cingulate cortex and the contralesional SII. A subsequent regions-of-interest (ROI) analysis of the cingulate showed a trend between BOLD percent change and the EDA signal change, expressed as a ratio (EDA task vs rest), but this was not significant ($r = 0.52$, $P = .14$).

DISCUSSION

The present study demonstrates that investigating motor impairments using fMRI in stroke patients can be improved through the use of simultaneous measurement of EDA signals. The EDA signal provides a physiological probe of autonomic function and is thought to reflect the level of arousal, which in the case of motor tasks can be thought of as sense of effort. In 3 of the 6 patients investigated, EDA time-series data during tasks involving the affected limbs were found to correlate significantly with numerous brain regions that were not accounted for in the hemodynamic model. In addition, group analysis of fMRI data highlighted brain regions that showed statistically significant correlations with EDA. In the subsequent discussion, emphasis is placed on the implication of both the individual activation maps and the group findings, given the high quality of the fMRI and EDA data and that the patients under study exhibited heterogeneity in time poststroke, lesion size and location, and motor impairment. A group analysis would yield averaged results that can obscure important differences among patients. Incorporating a measure such as EDA enables more comprehensive interpretation of individual fMRI findings. The analogous argument has been made recently relating to use of electromyography (EMG) to control for interindividual differences in motor performance in patients with movement disorders.²² The present work suggests that EDA signals potentially could be used as part of motor recovery

group fMRI statistics to control for the variation in sense of effort across patients or time poststroke.

Almost exclusively, the patients exhibiting task-correlated EDA when moving the affected limb showed activity in brain regions involving the contralesional hemisphere. Simultaneous measurement of fMRI and EDA provides the means to test the theory that poststroke patients with greater deficits are likely to engage attention-related networks.²³ The EDA maps revealed activity in the insula and contralesional SII at a group level, regions that are known to be modulated by attention demands in healthy participants.²⁴ These findings are corroborated by recent studies in well-recovered patients in whom the contralesional hemisphere was found to play a role in higher order motor processing.²⁵ This is also consistent with the view that tasks involving the affected limbs recruit the contralesional hemisphere in proportion to the sense of effort.

Regarding the brain activity observed in this case study, the ankle dorsiflexion data were consistent with a study of unilateral knee movements in chronic stroke patients.⁸ Patient focal SMC activations were found to be in close proximity to those found for previous work involving healthy participants.^{7,18} Similarly, activation foci due to grip and hand tasks were comparable to a recent study involving young healthy participants performing a complex fractionated finger movement task.¹³

Due to the small sample size, it was not possible to assess the variability in autonomic tone or its effect on the fMRI signal when patients moved the affected versus unaffected limbs. However, given that the fMRI-compatible EDA system is relatively easy to use, is cost-effective, and requires immobilization of 2 digits only (ie, digits 4 and 5 of the unaffected hand), EDA measurements can be incorporated into future studies. In principle, EDA recordings can be made at the foot or possibly the face, although this strategy was not explored here. In much the same way that motion artifact affects electromyography and electroencephalography, EDA measurements are also susceptible to motion artifact. To avoid this problem, stroke fMRI and EDA data presented in the present study predominantly focused on motor tasks where the site of the EDA measurement was kept still (ie, unaffected hand). However, fMRI runs involving the unaffected hand were conducted in 2 of 6 patients, and these EDA measurements were adequate and showed unremarkable temporal features in the time series.

The present study used a battery of event-related tasks, producing robust percent BOLD signal changes and providing the means to interpret BOLD responses to brief, isolated movements. The low NIHSS scores and the robust BOLD signals from SMC revealed that the patients investigated were well recovered and with relatively intact motor pathways for the upper or lower limb. One of the advantages of the event-related design is that it is relatively independent of fatigue and may be less sensitive to hemodynamic confounds,^{13,26} such as cerebrovascular stenosis or compromised cerebrovascular reactivity.

The task-correlated changes in EDA were comparable in latency and amplitude to those that have been previously reported.¹³ One implicit assumption in the present study is that the patients under investigation had intact autonomic systems, and conduction time from the

brain to the sweat gland was not changed appreciably after stroke. Given that the patients did not exhibit any brainstem lesions, this assumption appears reasonable but may not be the case in all circumstances.

Despite the accepted methodology of performing group analyses of fMRI data acquired from cohorts of stroke patients, there is a need to refine and improve the methodology as well as the interpretation of results. Efforts to make fMRI more robust, reproducible, and less sensitive to confound or patient motion continue to be important areas of research, leaving many avenues for future work. The present study observed task-correlated changes in EDA that, at least for the small sample of patients investigated, were found to be independent of the time poststroke. This is an expected result, given that both subacute and chronic stroke patients can perceive even simple motor tasks as difficult. Further work is needed to characterize this observation better and to determine the variation that exists across patients and time poststroke. One natural extension of the present study is to measure EDA longitudinally, such as throughout physiotherapy, to help quantify how the sense of effort varies as a function of the movement type and time during recovery, as well as to probe the interplay between sense of effort and brain reorganization by fMRI and TMS.²⁷

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Figure 1.
T₁-weighted magnetic resonance images for the stroke patients. The arrow indicates the primary lesion locations.

Figure 2.

(A) Functional magnetic resonance imaging (fMRI) activation maps for patient 3 during ankle dorsiflexion. Hemodynamic modeling of the fMRI data (HEMO) produced activation maps shown in the top panel (movement of left unaffected side) and middle panel (movement of right affected side). Electrodermal activity (EDA) modeling of the fMRI data (EDA map) produced significant activation in the contralesional hemisphere. (B) EDA time course during affected (aff) and unaffected (unaff) ankle dorsiflexion (top), along with the task waveform (bottom). Phasic changes in skin conductance appear to habituate after the first few trials during unaffected ankle dorsiflexion (unaff) task, whereas larger amplitude changes persist throughout the affected ankle task.

Figure 3.

(A) HEMO and electrodermal activity (EDA) activation maps for patient 2 performing unilateral gripping with the affected hand. (B) Phasic changes in EDA are evident during 10 repetitions of gripping (top), with the task waveform plotted for reference (bottom).

Figure 4.

Activation maps showing the results of fixed effects analysis of variance from HEMO (red to yellow) and electrodermal activity (EDA; blue to cyan) maps across 5 of 6 patients ($Z > 3.1$, $P < .001$, uncorrected). HEMO map produced significantly more voxels than the EDA map, but the cingulate and secondary somatosensory cortex emerged from the EDA group map.

Patient Demographics Showing That 4 Patients Were in the Chronic Stage of Recovery and 4 Had Right-Side Hemiparesis

Table 1

Patient	Age, y	Gender	Poststroke, d	Hemiparesis	NIH Stroke Scale	Tasks
1	49	M	2045	L	1	1, 2, 3 ^a
2	18	M	670	R	1	1, 2, 3, 6
3	37	M	25	R	1	1, 2, 3, 5
4	25	M	88	R	0	3, 4, 5 ^a
5	52	F	2022	R	0	3, 5
6	37	M	1567	L	0	1, 2, 3, 4

Sensorimotor tasks include (1) ankle—affected, (2) ankle—unaffected, (3) gripping—affected, (4) gripping—unaffected, (5) finger (easy)—affected, and (6) finger (hard)—affected. NIH = National Institutes of Health.

^aIndicates runs where functional magnetic resonance imaging data were rejected due to head motion.

Table 2

Coordinates for Activation in the SMC for Patients Performing Ankle Dorsiflexion With Affected and Unaffected Legs Individually

Ankle Dorsiflexion								
Patients	X	Y	Z	Side	Task	Z Score (SEM)	LI	BOLD % Change (SD)
1 ^a	-6.0	-2.0	70.0	L	1	3.02 (0.016)	-1.00	1.62 (1.08)
	-6.0	-21.0	68.0	R	2	3.26 (0.011)	-1.00	0.79 (0.37)
2	6.0	-32.0	68.0	L	2	4.62 (0.018)	1.00	0.74 (0.12)
	-4.0	-39.0	60.0	R	1	4.45 (0.011)	-0.51	1.06 (0.20)
3	6.0	-14.0	59.0	L	2	4.59 (0.010)	0.53	1.14 (0.36)
	-4.0	-22.0	64.0	R	1	4.21 (0.007)	-0.70	0.72 (0.26)
6	6.0	-33.0	60.0	L	1	4.89 (0.005)	0.03	1.54 (0.72)
	-5.0	-20.0	60.0	R	2	3.88 (0.012)	-0.33	1.56 (0.87)

Laterality index (LI) values were calculated using a mask that spanned the pre- and postcentral gyri (positive LI: R SMC > L SMC). BOLD percent change values are calculated from 5 voxels in the SMC (with standard deviation [SD] values). SMC = sensorimotor cortex; BOLD = blood oxygen level dependent.

^aIndicates Z score > 2.6, $P < .01$.

Table 3

Coordinates for Activation in the SMC for Patients Performing a Task With the Affected Hand

Patients	Affected Hand: Finger or Grip Tasks					
	X	Y	Z	Side	Task	Z Score (SEM)
2	-37.0	-22.0	45.0	R	6	3.79 (0.001)
3	-45.0	-17.0	52.0	R	5	4.24 (0.017)
4 ^a	-37.0	-25.0	52.0	R	3	6.11 (0.014)
5	-38.0	-21.0	53.0	R	5	5.93 (0.010)

Laterality index (LI) values were calculated using a mask that spanned the pre- and postcentral gyri (positive LI: R SMC > L SMC). BOLD percent change values are calculated from 5 voxels in the SMC (with standard deviation [SD] values). SMC = sensorimotor cortex; BOLD = blood oxygen level dependent.

^aIndicates Z score > 4.9, $P < 10^{-6}$.