Recovery of Cerebral Hemodynamics Induces Normalization of Atypical Ipsilateral Motor Activity on fMRI

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Objective
To determine if correction of unilateral hemodynamic failure will reverse the atypical (ipsilateral) motor-related functional magnetic resonance imaging (fMRI) activity that was induced as a consequence of the hypoperfusion.

Background
fMRI studies of stroke recovery report atypical ipsilateral motor activation associated with movement of the hemiparetic hand. The ipsilateral activity generally disappears as motor recovery occurs. Stroke-free patients suffering unilateral critical large-vessel disease can have cognitive impairments suggestive of injury to that hemisphere that are not attributable to focal lesions. We showed previously that even in the absence of stroke, uni-hemispheral impairment in cerebral hemodynamics due to large-vessel stenosis/occlusion can also induce atypical ipsilateral motor-related brain activity in the opposite hemisphere.[1,2] We hypothesized that reversal of the hypoperfusion would result in reduced ipsilateral motor activation.

Figure1a. Interaction of the two patients over time

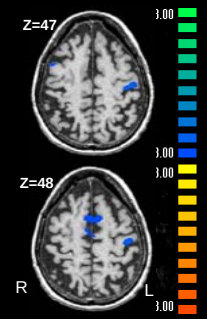


Figure1b. Interaction of controls and patients over time.

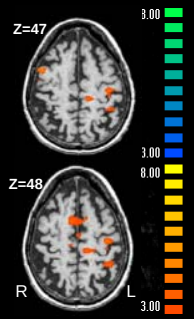


Figure 2a

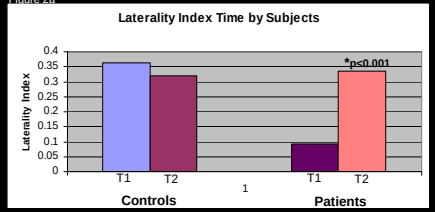
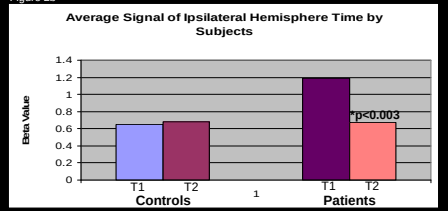


Figure 2b



Methods: Two patients were included in this study. A 53 year old right handed patient with right middle cerebral artery (MCA) high grade stenosis and impaired vasomotor reactivity (VMR), as measured by transcranial Doppler with 5% CO_2 inhalation, had spontaneous normalization of VMR 18 months later. A second patient, a 78 year old right handed man with right internal carotid high grade stenosis and impaired VMR, underwent a carotid artery stenting that resulted in normalization of VMR as measured by TCD on 3rd post-operative day. Normalization of VMR was confirmed 2 months later when the patient underwent a follow-up fMRI scan. We compared the change in fMRI motor activation pattern of the two patients to 7 healthy controls scanned twice at an interval of 3 months using voxel-wise statistical map (Brainvoyager QX1.7). During fMRI subjects performed a repetitive hand closure task in synchrony with 1Hz metronome tone in three 20- second blocks alternating with rest. Imaging was performed on a GE 1.5T magnet, imaged at 128x128 matrix, 19cm2FOV, slice thickness=4.5mm/0skip, TR=4000, TE=60, flip=60, 25 slices, functional voxel dimensions 1.5 x 1.5 x 4.5mm. Image volumes were co-registered, motion and slice timing-corrected, subjected to high pass filter, normalized to Talairach template, and smoothed with a 6mm Gaussian kernel. The first 3 volumes of each run were excluded for signal stabilization. For all patients motion correction (3 transposition planes, 3 directions of rotation) was well within the functional voxel dimensions.

METHODS cont'd.

A fixed-effects group analysis compared the blood oxygen level dependent (BOLD) activity in the 2 patients at Time 1 (baseline) and Time 2 (after normalization of VMR) with the controls' BOLD activity at Time 1 and Time 2, evaluating for a condition-by-time interaction. The interaction contrast was therefore represented as (P1-P2) – (C1-C2) whereby P1 and P2 represented the patients at Time 1 and Time 2, and C1 and C2 represented the controls at Time 1 and Time 2. All contrasts were assessed at a threshold of t=3.0, corresponding to p=.0027 uncorrected.

ROI Analysis:
To quantitatively test our hypothesis that the atypical activation in the ipsilateral motor cortical areas decreased as a result of VMR normalization, we performed an independent region of interest (ROI) analysis among all subjects over 2 time points by computing average BOLD signal intensity (beta value) in the primary motor cortex (M1), lateral premotor cortex, and Supplementary motor area (SMA). We drew the ROIs using a Talairach template and criteria described by Fink and colleagues.[3]

The average beta value of the 3 ROIs in each hemisphere at each time point was represented by a single number, then entered into a repeated-measures ANOVA to look for interaction between patient group (stroke patients vs. controls) and time. Two computations were performed – the laterality index (Betacontra – Betaipsi) / (Betacontra + Betaipsi) and absolute Beta value of the ipsilateral hemisphere alone.)

Results: Figure 1a shows that over time the 2 patients had a reduction in ipsilateral motor region activity (blue color) In **figure 1b**, the group analysis shows that relative to the hypoperfused state and compared with normal controls over time, normalization of VMR in our patients in the previously hypoperfused hemisphere was associated with reduced atypical activation in the opposite hemisphere in the ipsilateral M1, premotor and SMA cortex ($p<0.0027$ uncorrected). Post-hoc analysis demonstrated a significant increase in laterality index following VMR normalization as compared to controls, indicating a shift of activity towards the contralateral hemisphere (**Figure 2a**). Further confirmation by ROI analysis showed significant decrease in BOLD intensity in patients as compared to controls in the ipsilateral hemisphere after VMR normalization indicating that the increase in laterality index was predominantly driven by a decrease in ipsilateral activation rather than an increase in contralateral activation as might be expected following restitution of hemodynamic failure (**Figure 2b**).

Conclusion/Relevance: Our results suggest that hemodynamic impairment induces a functional reorganization to the opposite hemisphere that is reversible when physiological blood flow is restored to the previously hypoperfused hemisphere. This extends our previous findings that impaired cerebral hemodynamics may be an independent variable in altering motor activity pattern.
These results have important implications for determining both the consequence of hemodynamic failure and the role of the ipsilateral hemisphere in motor behavior. The recruitment of alternative brain regions to share neuronal burden of the task during conditions of chronic ischemia can permit maintenance of normal neurological function. Our findings suggest that the brain is capable of dynamic and reversible reorganization in responding to physiological stressors such as hemispheral hypoperfusion.

References:.

1) Marshall RS, Krakauer JW, Matejovsky T, Zarahn E, Barnes A, Lazar RM, Hirsch J (2006) Hypoperfusion without Stroke Alters Motor Activation in the Opposite Hemisphere
2) Krakauer JW, Radoeva PD, Zarahn E, Wydra J, Lazar RM, Hirsch J, Marshall RS (2004) Hypoperfusion without stroke alters motor activation in the opposite hemisphere. Ann Neurol 56:796–802
3)Fink GR, Frackowiak RS, Pietrzyk U, Passingham RE (1997) Multiple nonprimary motor areas in the human cortex. J Neurophysiol 77:2164–74

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