Connectivity alterations in motor-related areas suggest neuroplasticity in chronic stroke

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Introduction–Brain imaging studies in chronic stroke patients have shown evidence for plastic changes co-localization of areas showing structural and functional plasticity after a stroke [1]. Here, we present results combining motor fMRI with a novel MR-compatible hand-induced robotic device (MR_CHIROD) [5-8] to investigate functional reorganization of motor systems by probing connectivity alterations between motor related areas. . We are thus attempting to fill the current gap in stroke recovery knowledge using dynamic causal modeling (DCM) of functional magnetic resonance imaging data of chronic stroke patients and controls. Friston et al., [2] introduced this approach of modeling task-dependent influences that one area exerts over the activity of another, using DCM in order to infer connectivity strengths between activated areas within a distributed network. DCM models, in contrast to other connectivity analysis methods such as structural equation modeling (SEM), accommodate the nonlinear and dynamic aspects of neuronal interactions by modeling the neuronal activity explicitly using Buxton et al.'s balloon model [3]. The strength of functional connectivity in healthy brains has been examined using fMRI whereby strong temporal connections between spatially distinct but functionally related regions have been identified during rest [5]. A recent DCM study examining effective connectivity in 12 patients with subacute stroke [4] indicated that hand motor disability following subacute stroke was associated with dysfunctional connectivity between ipsilesional and contralesional primary motor area (M1), and between ipsilesional supplementary motor area (SMA) and contralesional M1. Such analysis has not been reported in patients with chronic stroke. More importantly, it is not known whether connectivity might be influenced by training in chronic stroke patients.

Materials and Methods– Patients had first-ever left-sided ischemic subcortical middle cerebral artery (MCA) stroke ≥ 6 months prior, with no spasticity or joint stiffness. Patients trained at home and underwent serial MR evaluation at baseline (before training), and after 8 weeks of training. Training at home consisted of squeezing a gel exercise ball with the paretic hand at approximately 75% of maximum strength for 1 hour/day, 3 days/week. For each patient, reference (100%) was own maximum force, defined as the force at which subjects could just completely squeeze the MR_CHIROD [group max force: 128 N ± 13 N (n = 5, male)]. All studies were performed on a Siemens Tim Trio (3T). BOLD fMRI was performed using GRAPPA gradient-echo EPI (TR/TE=3000ms/30ms, 1.56 mm×1.56 mm×3 mm). T1-MPRAGE and FLAIR served as anatomical reference and to localize hyperintense regions and stroke lesions. A block design paradigm was used for fMRI. During the action period, subjects squeezed the MR_CHIROD and released continuously. Squeezing rate was guided by a visual 'metronome' cue circle oscillating radially at 0.5 Hz. A fixation cross was projected during rest. Each volunteer performed the paradigm at 45%, 60%, and 75% of their maximum grip strength and could fully squeeze the device at all levels. The percent levels compensate for performance confounds. Care was taken to minimize elbow flexion and/or reflexive motion, and head motion (typically 0.1 to 0.4 mm). The DCM model was constructed using brain regions that were activated in all subjects (Figure 1A) and comprised three regions: M1, SMA, and cerebellum (Cer). Volumes of interest were defined in these regions using a sphere centered at the maximum activation from the second-level analysis and with a radius of two voxels. The cognitive input encoding the motor task (Mot) was represented by a step function. We allowed all possible connections between the brain areas to account for plasticity changes in the stroke group. We also allowed Mot to connect to the SMA, which is the only region in the model responsible for motor planning. Connectivity strengths and posterior probabilities were calculated using the DCM utility in SPM5. The fMRI analysis revealed activations in M1, SMA, premotor cortex and Cer in both stroke patients and controls (Figure 1B). Greater connection strength translated into a greater absolute value of the parameter shown, and thus a more prominent effect of one area on another. Connectivity strengths of healthy subjects are shown in Figure 15A and percent changes in connectivity strengths after training relative to baseline are shown in Figure 1C.

Results– The DCM analysis produced the following results: a) In healthy subjects during a simple motor task, there is minimum effective connectivity from Cer to M1 (Figure 1A). This result has been reproduced by an independent electromyographic study [6] that validates our analysis; b) Motor planning in SMA is coupled to the cognitive input Mot and is stronger in stroke patients after training (Figure 15C). c) We observed significantly increased coupling between M1 and SMA with training, suggesting the induction of SMA recruitment (Figure 1C). This possibility has been suggested by earlier fMRI studies in healthy volunteers [7]; and d) Cer coupling to M1, especially SMA coupling to Cer, was induced by training (Figure 1C). Cer hyperactivity has been documented in Parkinson disease patients, where it was suggested to represent a compensatory mechanism for defective basal ganglia [8]. Here it most likely reflects efforts by stroke patients to improve motor control and function.

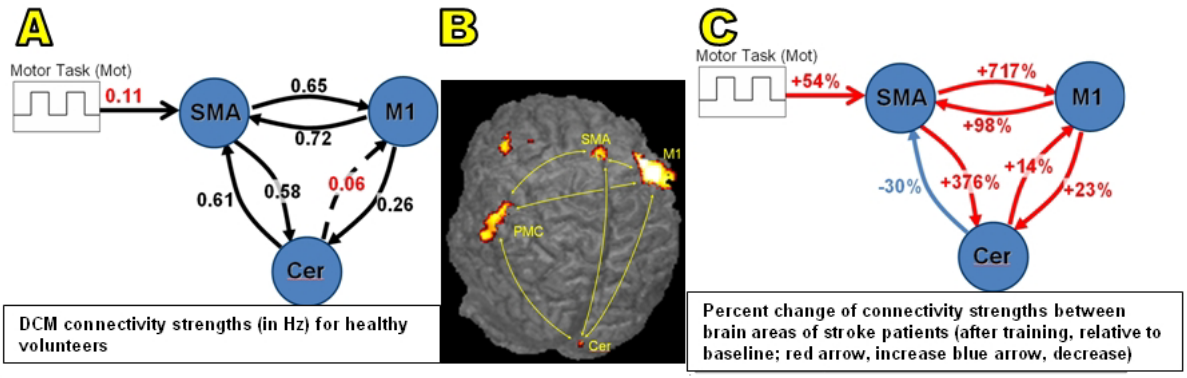

Figure 1. DCM Model and Results

Discussion– These findings are consistent with a recently published study on subacute stroke suggesting dysfunction between M1 and SMA [5]. These preliminary data demonstrate for the first time that an enhanced connectivity between M1 and SMA and between SMA and Cer underlies hand motor recovery following chronic stroke that can be enhanced by training. Positive change in connectivity strengths between M1 and Cer is probably compensatory and may help counterbalance a functionally abnormal M1, which in turn is more tightly coupled to SMA. Enhancement of SMA activity, (i.e., by high-frequency transcranial magnetic or direct current stimulation) has been suggested as a potential means for ameliorating M1 dysfunction after stroke [9]. Our findings suggest that rehabilitative exercise training can induce a similar effect. Thus, investigating changes in connectivity caused by rehabilitative training will assist in monitoring and elucidating neuroplasticity.

References

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