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Connectivity alterations assessed by combining fMRI and MR-compatible hand robots in chronic stroke

Dionyssios Mintzopoulos^{1,2}, Loukas G. Astrakas^{1,2}, Azadeh Khanicheh³, Angelos A. Konstas⁴, Aneesh Singhal^{2,5}, Michael A. Moskowitz^{2,6}, Bruce R. Rosen², and A. Aria Tzika^{1,2}

¹NMR Surgical Laboratory, Department of Surgery, Massachusetts General Hospital and Shriners' Burn Institute, Harvard Medical School, Boston, MA 02114, USA

²Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA

³Department of Mechanical Engineering, Northeastern University, Boston, MA 02115, USA

⁴Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

⁵Department of Neurology, Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston, MA 02114, USA

⁶Neuroscience Center, Departments of Neurology and Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA

Abstract

The aim of this study was to investigate functional reorganization of motor systems by probing connectivity between motor related areas in chronic stroke patients using functional magnetic resonance imaging (fMRI) in conjunction with a novel MR-compatible hand-induced, robotic device (MR_CHIROD). We evaluated data sets obtained from healthy volunteers and right-hand-dominant patients with first-ever left-sided stroke ≥ 6 months prior and mild to moderate hemiparesis affecting the right hand. We acquired T1-weighted echo planar and fluid attenuation inversion recovery MR images and multi-level fMRI data using parallel imaging by means of the GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) algorithm on a 3 T MR system. Participants underwent fMRI while performing a motor task with the MR_CHIROD in the MR scanner. Changes in effective connectivity among a network of primary motor cortex (M1), supplementary motor area (SMA) and cerebellum (Ce) were assessed using dynamic causal modeling. Relative to healthy controls, stroke patients exhibited decreased intrinsic neural coupling between M1 and Ce, which was consistent with a dysfunctional M1 to Ce connection. Stroke patients also showed increased SMA to M1 and SMA to cerebellum coupling, suggesting that changes in SMA and Ce connectivity may occur to compensate for a dysfunctional M1. The results demonstrate for the first time that connectivity alterations between motor areas may help counterbalance a functionally abnormal M1 in chronic stroke patients. Assessing changes in connectivity by means

Address correspondence/reprints request to: A. Aria Tzika, PhD, Director of NMR Surgical Laboratory, Department of Surgery, Massachusetts General Hospital and Shriners' Burn Institute, Harvard Medical School, 51 Blossom Street, Room 261, Boston, MA 02114, Tel: (617) 371-4871; Fax: (617) 720-3544, E-mail : E-mail: atzika@hms.harvard.edu.

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of fMRI and MR_CHIROD might be used in the future to further elucidate the neural network plasticity that underlies functional recovery in chronic stroke patients.

Keywords

Functional Magnetic Resonance Imaging (fMRI); brain; stroke

Introduction

Stroke is a major cause of morbidity and invalidity in modern society (Dobkin, 2005). In the United States alone, there are an estimated 731,000 incidents of stroke annually and 4 million stroke survivors, making stroke a major cause of long term disability (Broderick *et al.*, 1998). Patients who survive a stroke usually recover at least some of the functionality compromised by the stroke within three months, however only 25% return to the level of daily physical functioning seen in community-matched persons who have not suffered a stroke (Lai *et al.*, 2002). Thus, despite recent progress with thrombolysis (Hacke *et al.*, 2008), recovery of motor function after stroke is usually incomplete.

In the past two decades, several investigators have attempted to understand the disturbances in the complicated cortical-subcortical network that occur following stroke as well as the mechanisms of stroke recovery. Since Chollet *et al.*'s demonstration of cortical reorganization using positron emission tomography (Chollet *et al.*, 1991), subsequent studies using other imaging techniques, including integrated technologies, have extended our knowledge of the mechanisms that underlie functional and motor recovery in stroke patients (Cramer *et al.*, 2000; Cramer *et al.*, 2001; Calautti *et al.*, 2003; Rossini *et al.*, 2004; Tombari *et al.*, 2004; Calautti *et al.*, 2007; Loubinoux *et al.*, 2007; Blickenstorfer *et al.*, 2008; Dechaumont-Palacin *et al.*, 2008). Recovery of motor function after stroke is thought to depend upon many factors, including resolution of edema and survival of the ischemic penumbra (Ward, 2007). Post-stroke brain plasticity includes change of function in existing synapses, synaptogenesis, cortical reorganization, and perhaps neurogenesis, and all these changes are stimulated by activity (Dietrichs, 2007).

While a causal link between cerebral reorganization and functional recovery has yet to be firmly established, brain imaging studies in chronic stroke patients have shown plastic changes, including enhanced bilateral activation of the sensorimotor cortex, increased activity in secondary or higher order sensorimotor areas, and recruitment of additional cortical areas during performance of a hand sensorimotor task (Weiller, 1998). Functional magnetic resonance imaging (fMRI) in particular has been described as a reliable method for assessing stroke patients (Kimberley *et al.*, 2008). Nevertheless, the chronic stroke literature lacks functional integration studies examining functional reorganization of motor systems through assessment of altered connectivity between motor related areas.

Dynamic causal modeling (DCM) of fMRI data has been introduced as an approach to modeling the task-dependent influences that one area exerts over another, in order to infer connectivity strengths between activated areas within a distributed network (Friston *et al.*, 1993; Friston *et al.*, 2003). DCM, in contrast to other connectivity analysis methods such as structural equation modeling (SEM), accommodates the nonlinear and dynamic aspects of neuronal interactions by modeling neuronal activity explicitly using Buxton *et al.*'s balloon model (Buxton *et al.*, 1998; Buxton *et al.*, 2004). FMRI experiments have demonstrated strong temporal connections between spatially distinct but functionally related regions during rest in healthy brains (Biswal *et al.*, 1995). Connectivity has also been described in patients with psychiatric disease (Schlosser *et al.*, 2003; Schlosser *et al.*, 2008). A recent DCM study 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 (Grefkes *et al.*, 2008). However, similar analysis has yet to be reported in patients with chronic stroke.

Here, we report an investigation of motor systems functional reorganization in which connectivity between motor related areas in chronic stroke patients was examined by combining fMRI with a novel MR-compatible hand-induced, robotic device (MR_CHIROD). We present findings suggesting that in chronic stroke the effective connectivity is altered due to neuroplasticity in the acute and subacute phases. Our findings are discussed in the contexts of compensation for a dysfunctional motor system and potential facilitation of rehabilitation using MR_CHIROD.

Methods

Study design and procedure

Twelve healthy volunteers and five chronic stroke patients provided written informed consent to participate in this cross-sectional study. All experiments were approved by the institutional review board at Massachusetts General Hospital and performed at the Athinoula A. Martinos Center for Biomedical Imaging. All participants used the MR_CHIROD during fMRI at approximately 45% of their maximum strength. Each subject's maximum strength was determined *a priori* based on a dynamometer measurement of each participant's maximum hand-grip strength. The fMRI protocol and data analysis methods employed are described below. The brain maps and connectivity strengths of stroke patients were compared to those of control subjects.

Patients

Patients (≥ 6 months after stroke) who agreed to be contacted for stroke recovery and rehabilitation studies were recruited through registries of stroke survivors maintained at Massachusetts General Hospital. Briefly, the inclusion criteria were first-ever left-sided ischemic subcortical middle cerebral artery (MCA) stroke confirmed by computed tomography (CT) or MRI ≥ 6 months prior; mild to moderate contralateral hemiparesis affecting the right hand; premorbid right hand dominance; ability to give written consent; and age 40–70 years. Exclusion criteria were defined by the NIH stroke scale questions (www.ninds.nih.gov/doctors/NIH_Stroke_Scale_Booklet.pdf) for decreased level of consciousness (questions 1a, 1b, 1c; each >0), aphasia (question 9; score >2), and neglect (question 11; score >2). No patient exhibited evidence of spasticity or joint stiffness while performing the motor task. Sensory modalities such as proprioception and ability to detect a pinprick and light touch were confirmed to be intact in the patients. No patient presented signs or history of somatosensory deficits of the right hand or other neurological or psychiatric disease, deafness and/or blindness, prior cerebrovascular disease, brainstem stroke, or multiple cerebral lesions.

Use of MR_CHIROD for MR neuroimaging

The design and testing of the first generation MR_CHIROD have been described in detail previously (Khanicheh *et al.*, 2005; Khanicheh *et al.*, 2006; Tzika *et al.*, 2006), and the design of the second generation MR_CHIROD, was published recently (Khanicheh *et al.*, 2008). Designs for two forms of the second-generation prototype were generated, one with rotary brakes and the other with linear brakes. The linear brake version was chosen for fabrication because of its relative simplicity and lower cost (Khanicheh *et al.*, 2007). The assembled MR_CHIROD is shown in (Khanicheh *et al.*, 2008). The MR_CHIROD consists of three major subsystems: a) an electro-rheological fluid (ERF) resistive element, b) handles, and c) two

sensors, one of which is an optical encoder to measure patient-induced motion and the other of which is a force sensor. Each subsystem includes several components of varying complexity. All of the components were optimally designed with durability, safety, and MR-compatibility in mind and for the ability to withstand regular and high-stress testing.

The MR_CHIROD provides 200 N of resistive force and is controlled in real time (Khanicheh *et al.*, 2008). It was empirically found that the maximum force of squeezing a dynamometer with fixed handles (Baseline® Hydraulic Hand Dynamometer, 200 lb, Best Priced Products, Inc.) is greater than the maximum force of dynamically squeezing the handles of the MR_CHIROD. Henceforth, maximum force of active squeezing has been estimated using the MR_CHIROD itself. Specifically, the MR_CHIROD was set at high values of resistive force and subjects were asked to squeeze. Maximum force was defined as the force at which subjects could barely complete one to three strokes of the MR_CHIROD. Patients' maximum active squeezing force was $128 \text{ N} \pm 13 \text{ N}$ ($N = 5$, male). For each patient, percent levels of applied force were calculated in Newtons using the patient's own maximum force as a reference (100% of effort).

The MR_CHIROD was configured to securely attach to the scanner table next to the participant, who thus feels no weight. During testing, the MR_CHIROD's power supply (Trek 609-C, $\pm 4 \text{ kV} / 20 \text{ mA}$) activating the ERF fluid (Fluidicon) and the DAQ unit (NI 6062-E) and laptop with control software (NI Labview) were located outside the RF-shielded MRI scanner room. The cables connecting the power supply and the sensors to MR_CHIROD were of appropriate length and impedance and properly shielded. The damper consisted of two electrodes and contained the ERF fluid. The piston (piston shaft drawn) moves through the ERF fluid with a controlled force of contraction provided by the voltage-controlled variable viscosity of the ERF fluid. A Faraday cage enclosed the device's core, with an opening to allow unobstructed movement of the piston shaft. The negative electrode of the damper (connecting to the negative terminal of the power supply) and the Faraday cage were grounded to the penetration panel of the MR room. A low-pass filter (LPF) was attached to the penetration panel. Sensor readings (force, position) were transmitted through the penetration panel through grounded DSub-9 connectors. The sensor wires were coaxially shielded and all were properly grounded to the penetration panel. The sensor readings enabled real-time, closed-loop control of the ERF resistive element. The output from the control-loop regulated the voltage output of the power supply, in turn ensuring control of the ERF resistive element and force of contraction.

MR neuroimaging examination protocol

All studies were performed on a state-of-the-art 3-T MR system in order to obtain a high signal-to-noise ratio (SNR). We used a systematic approach to optimize our protocol with respect to SNR by varying the number of echoes, the echo time, the repetition time, the GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) acceleration factor, the field of view (FOV), and the number of excitations (NEX). These factors were set such that the protocol could be completed in 30–45 min and a 12-channel Siemens Tim coil was used.

T1-weighted MR images—A high-resolution 3-dimensional T1-weighted, MP-RAGE (magnetization-prepared rapid gradient echo) image was acquired for anatomical reference and optimal gray-white matter contrast. Images were collected in a sagittal orientation at a 7° flip angle with the following parameters: TE = 4.73 ms; TR = 2530 ms; TI = 1100 ms; slice thickness = 1.00 mm; and matrix = $352 \times 352 \times 192$.

Fluid attenuation inversion recovery (FLAIR) MR images—A FLAIR image was acquired for each subject to provide anatomical localization of hyperintense regions and stroke lesions. FLAIR images were acquired with the following parameters: GRAPPA factor 2, 0.6

mm $\times$ 0.8 mm in plane resolution / 288 $\times$ 384 matrix, 5 mm slice thickness, and TR/TE/TI = 10000 ms / 71 ms / 2500 ms.

Multilevel fMRI—A high-resolution GRAPPA EPI sequence was used for whole-brain BOLD fMRI near optimal spatial resolution for BOLD detection. Typical parameters were used: 96 $\times$ 96 matrix (2 mm $\times$ 2 mm in-plane resolution), 50 slices / 3 mm slice thickness, GRAPPA factor 3, 85 auto-calibration lines, BW/px = 1.3KHz/px, TR/TE = 3000 ms / 30 ms. Sixty volumes (180 s) were used in fMRI processing.

Motor hand paradigm

As the study participant squeezed the device, we monitored the changing levels of force and compared precise measures of compression force with features of brain activation.

Compression, because of its potential as a marker of motor function in stroke patients and because it can be performed by patients with motor deficits (Brunnstrom, 1970), has been used in several clinical brain-mapping studies (Honda *et al.*, 1997; Schlosser *et al.*, 1997; Lee *et al.*, 1998; Cramer *et al.*, 2001). Our experimental paradigm consisted of alternating action and rest periods, of 30 s each. During the action period, the participant compressed the robotic device and released continuously at a rate of 0.5 Hz. The palm of the participant's right hand rested on the stationary handle of the device and his or her four fingers on the moving handle. The squeezing motion was performed by flexing the four fingers; the thumb was kept in a natural rest position such that it was not flexed to form a fist nor used to push against the handle.

All participants selected were right-handed and used only the paretic hand. The participant's squeezing rate was guided by a visual 'metronome' cue circle oscillating radially at 0.5 Hz frequency, projected on a neutral-background screen. A fixation cross was projected during the rest periods. The stimulus was implemented using the PsychoPhysics Toolbox (www.psychtoolbox.org/). Previous experience has shown that head movement increases at rates above 1.5 Hz. Meanwhile movement below 1.5 Hz is generally associated with less fatigue, but also with decreased signal. A squeezing rate of 0.5 Hz was a well-justified compromise, especially given that the study was performed at 3 T which provides a high SNR. Moreover, It was confirmed empirically that this rate allows all subjects to complete full squeezing strokes of the device at all force levels.

The paradigm trial lasted 180 s, consisting of 3 action and 3 rest periods. The force of the paradigm was set at 45% of each individual subject's maximum force to ensure that all subjects could perform the required motor task. It has been our consistent experience that patients can perform the protocol at this portion of their own maximum force. The use of percent levels compensates for performance confounds by constraining between-subjects performance to be approximately the same (Poldrack, 2000). Training took participants approximately 15 min and was performed before scanning. Patients performed the paradigm at each force level with the paretic hand. Motion artifacts were minimized by placing foam rubber pads and straps across the forehead and the arms. Participants' arms were kept extended at their sides and extra foam padding was placed at the elbow to dampen vibratory couplings between the magnet bore wall and the participant's arm as well as between the participant's arm and body. The pads also served to minimize elbow flexion and additional reflexive motion, and to minimize translational and rotational head motion (typical translational head motion is well under 1 mm, typically ranging from 0.1 to 0.4 mm for most subjects). Care was taken to restrain inadvertent movement or squeezing of the non-task-performing hand.

FMRI data analysis

A standard processing stream was employed, using SPM (www.fil.ion.ucl.ac.uk/spm). Images were corrected for timing (time-slicing correction), aligned and normalized to MNI152 space.

Additionally, a mask of each patient's stroke lesion was drawn and incorporated into the normalization step for that patient (Brett *et al.*, 2001). Images were then smoothed with a $4 \times$ (voxel dimensions) anisotropic Gaussian kernel. The $4 \times$ kernel was chosen to maximize sensitivity through use of large smoothing kernels (Friston *et al.*, 1996) while retaining ample spatial specificity of the original functional images. A temporal 4-s FWHM Gaussian filter was applied to account for temporal autocorrelations in the time series. The fMRI time-series were corrected for confounds such as the global mean and low-frequency components. The voxel-wise activation threshold was set at $P < 0.05$, corrected for multiple comparisons. The force trace of the MR_CHIROD was used as a covariate and provided accurate timing information for the onset and duration of the squeezing blocks, correcting for possible timing errors in subject performance.

Our bilateral areas of interest were the primary motor cortex (M1), the supplementary motor area (SMA), and the cerebellum (Ce). SMA was defined as the medial wall of the hemisphere from the top of the brain to the depth of the cingulate sulcus, with the posterior boundary considered to be halfway between the extension of the central and precentral sulci onto the medial surface and the anterior boundary considered to be the vertical line through the anterior commissure (Dassonville *et al.*, 1998). The location of activation in stroke patients was checked in normalized space using the Wake Forest University Pickatlas tool (Lancaster *et al.*, 2000; Maldjian *et al.*, 2003) and the Montreal Neurological Institute (MNI) Space Utility (MSU; www.fil.ion.ucl.ac.uk/spm/ext/) in SPM.

Since our simple motor task has been analyzed in many occasions in the past and the motor areas revealed here are well known, we conducted random effects analysis (2nd-level fMRI analysis) to pinpoint the exact location of these areas (M1, SMA, and Ce) in our groups in order to use them as building blocks of our DCM network. Our subsequent statistical comparison was performed not voxel-wise but for ROI-based results for which the two groups (control, patient) are sufficient.

Connectivity analysis

DCM (Friston *et al.*, 2003; Mechelli *et al.*, 2003), as implemented in the SPM2 software package, was employed. The aim of DCM is to estimate, and make inferences about the influence that one neural system exerts over another and how this is affected by the experimental context. For a combined hemodynamic and neuronal model, different priors are implemented to enable Bayesian parameter estimation. The estimated underlying neuronal activity is then used for the state equation (Friston *et al.*, 2003).

The DCM model employed here included M1 and SMA contralateral to the affected hand and Ce ipsilateral to the affected hand (Figure 1). These regions were chosen because they have been reported to be activated during visually guided movements (Ellermann *et al.*, 1998), and because they are considered important for rehabilitation therapy of patients after stroke to improve their motor abilities (Blickenstorfer *et al.*, 2008). As expected, all three of these regions were activated in all subjects in this study.

Activated cortical areas were identified by examining the coordinates of the activated clusters in the MNI152 space (Montreal Neurological Institute MNI152 template, based on the stereotactic coordinate system of Talairach and (Lancaster *et al.*, 2000) against published coordinates (Hanakawa *et al.*, 2002; Solodkin *et al.*, 2004), and was further aided by overlaying labeled masks of Brodmann Areas, according to the WFU Pickatlas tool (<http://www.fmri.wfubmc.edu/>; Lancaster *et al.*, 2000; Maldjian *et al.*, 2003; Maldjian *et al.*, 2004) on the functional data. The SMA was identified at (-2, -4, 60) to (-4, -4, 60) in the vicinity of Brodmann area 6 (medial). The M1 was identified at (-38, -16, 56) to (-44, -10, 66) in Brodmann area 4 at the level of the Precentral Gyrus, by inspecting the activated cluster in the

M1 area and the coordinates of the most activated voxels as reported by SPM2 and the boundaries of Precentral Gyrus and Brodmann Area 4 according to WFU Pickatlas. Peak voxels in the Ce were identified from (-22, -52, -18) to (-26, -62, -20).

Regions of interest (ROIs) were defined around these coordinates, including all voxels within a 6 mm radius. The DCM model was set up on these ROIs according to standard SPM specification. We allowed all possible connections between the brain areas (i.e. bi-directional coupling between SMA and Ce; between M1 and Ce; and between SMA and M1.) to account for plasticity changes in the stroke group. We also allowed the Mot to connect to the SMA, which is the only region in the model responsible for motor planning. The cognitive input encoding the motor task (Mot) was represented by a step function (Figure 1). The DCM analysis was then run on these ROIs and connectivity strengths and posterior probabilities were calculated (Buchel *et al.*, 1997; Fletcher *et al.*, 1999; Schlosser *et al.*, 2003).

Statistical analysis

Normality of variances in activated voxels was tested using the Shapiro-Wilks test in R software (R 2.5.1), ($P = 0.94$). Comparisons between the control group and the patient group were carried out with an ANOVA design with group (patient or control) and connectivity pathway as fixed factors and patient or control identity as random factors. The design was run in the SPSS mixed program. Post-hoc comparisons between patients and controls for each connectivity pathway were carried out using a Bonferroni test with correction for multiple comparisons. A P value of 0.05 was used as the criterion for statistical significance for all comparisons.

Results

Healthy control subjects and stroke patients underwent online brain mapping with fMRI using our novel MR_CHIROD prototype. We used a simple model (Figure 1) that includes activation of brain regions seen both in healthy controls and stroke patients (Figures 2 and 3).

The areas that were included in the DCM model specification were activated in both controls and patients when the subjects performed the task (Figure 2) and voxel-wise comparison (2-sample t-test) at the second (group) level did not show significant differences. Therefore, there is no potential problem in our analysis since the included of areas are activated in all subjects. DCM, while based on the fMRI analysis, is an intrinsically different analysis revealing different information, namely subtle effects relating to the coupling strength between activated areas. Therefore it is possible to see DCM differences even when voxel-wise comparison (2-sample t-test) at the second (group) level does not show differences between the activation patterns.

The DCM analysis of the specific impact of unimanual hand movement on the motor network is summarized in Table 1. These results show intrinsic neural coupling strengths for healthy controls and chronic stroke patients for our selected intrinsic model. Relative to controls, stroke patients exhibited reduced coupling between the cognitive input for the task, referred to as Mot, and motor planning in the SMA. M1 to SMA coupling was decreased in stroke patients, whereas SMA to M1 coupling was significantly increased ($P = 0.09$). Coupling of SMA to Ce was increased after stroke, while Ce to SMA coupling was significantly decreased ($P = 0.04$). Finally, both Ce to M1 and M1 to Ce coupling were decreased ($P = 0.003$ and 0.001 , respectively).

Our DCM results are presented graphically in Figure 4. Note that all neural couplings between M1, SMA and Ce were affected by stroke. Of all the connection, the coupling between M1 and Ce was affected to a greater extent.

Discussion

The present study demonstrates that fMRI using a novel hand device, MR_CHIROD, can detect functional connectivity disturbances in patients who have suffered a stroke, even when the stroke occurred six months or more prior. The study introduces a novel method of monitoring functional connectivity and confirms prior studies suggesting that recovery of function after stroke may be a consequence of central nervous system (CNS) reorganization and plasticity (Dietrichs, 2007). This method may be used to map functionally relevant adaptive changes in the human brain following CNS damage. It can thus lead to a greater understanding of how these changes are related to the recovery process, facilitate the development of novel therapeutic techniques designed to minimize CNS impairment, and assist in targeting these treatments to individual patients.

Our ability to control the resistivity and operability of ERF-controlled devices (Khanicheh *et al.*, 2005; Khanicheh *et al.*, 2006; Tzika *et al.*, 2006; Khanicheh *et al.*, 2007) may enable MR_CHIROD to assist in providing more sensitive, specific, and accurate brain mapping. Its MR-compatibility allows online brain function monitoring, which is an essential aspect of monitoring neurological disabilities associated with stroke recovery as well as recovery after brain tumor surgery, and monitoring of other CNS disorders including neurodegenerative disorders (e.g., Parkinson's). Apart from patient monitoring, theoretically, it can also be used for monitoring muscle enhancement and augmentation in healthy individuals. The novelty of our device relies on its unconventional type of actuation, via electrorheological fluids (ERF), which change their viscosity in response to varying electric fields. This ERF-based device is unlike previously described devices (Siekierka *et al.*, 2007; Tsekos *et al.*, 2007) in that has been demonstrated to function in conjunction with fMRI for online brain mapping in chronic stroke patients. Furthermore, the MR_CHIROD readout provides information about the timing of the task (onset and duration of each squeezing cycle), as well as information about the amplitudes of each squeezing cycle, which enables MR_CHIROD information (force traces) to be used as covariates, resulting in much improved output (voxel-count) statistics at the group level. Finally, MR_CHIROD should also be a suitable form of robot-assisted rehabilitation for patients (Johnson *et al.*, 2007).

Our parallel MRI (pMRI) approach to neuroimaging using GRAPPA is also novel (Pruessmann *et al.*, 1999; Griswold *et al.*, 2002; Heidemann *et al.*, 2003). This method is not hindered by artifacts and is advantageous in high magnetic field conditions (Little *et al.*, 2004; Pruessmann, 2004; Heidemann *et al.*, 2006; Moeller *et al.*, 2006) and we believe that our use of phased array coils further increased spatial and/or temporal resolution (Wald *et al.*, 1995; Frederick *et al.*, 1999; Mintzopoulos *et al.*, 2007). Our results are in agreement with prior studies describing brain activation during visually guided movements (Deiber *et al.*, 1991; Grafton *et al.*, 1992; Clower *et al.*, 1996; Kertzman *et al.*, 1997; Ellermann *et al.*, 1998). We demonstrate for the first time that an enhanced connectivity between M1 and SMA, and between SMA and Ce, underlies hand motor recovery following chronic stroke and this can be probably further enhanced by training. A dysfunctional coupling between M1 and Ce is a novel finding and is consistent with a prior study reporting decrease of bilateral cerebellar activation in recovering and clinically stable stroke patients (Tombari *et al.*, 2004). On the other hand, cerebellar hyperactivity has been documented in Parkinson's disease patients, where it was suggested to represent a compensatory mechanism for defective basal ganglia (Yu *et al.*, 2007). Here, SMA seemed to recruit Ce, as indicated by an increased SMA to Ce coupling. This recruitment may compensate for reduced M1 to Ce coupling, which has a prominent role in visually guided movements (Glickstein *et al.*, 1980; Stein *et al.*, 1992; Ebner *et al.*, 1997). Indeed, this may only be possible in patients with a preserved corticospinal system following a subcortical stroke (Ward *et al.*, 2007). Furthermore, the adaptive activity within M1 and Ce over the course of task-specific therapy has been shown previously and supports our findings (Dong *et al.*,

2007; Luft *et al.*, 2008). Moreover, we have observed strengthened SMA to M1 and SMA to Ce couplings in chronic stroke patients following rehabilitation (unpublished observations). Hence it is our view that the strengthening of these couplings may help compensate for a dysfunctional M1.

Our findings extend a previous report on subacute stroke in which a dysfunctional M1 to SMA coupling was reported (Grefkes *et al.*, 2008). Here in chronic stroke, an increased SMA to M1 coupling indicates recruitment of SMA to assist the M1 affected by stroke. This finding is in agreement with the hypothesis that there is reorganization within the SMA (Tombari *et al.*, 2004). The SMA has been shown to be plastic under different circumstances. For example, SMA reorganization has been reported in healthy subjects trained with increasing force (Cramer *et al.*, 2002) and in stroke patients asked to perform index-finger tapping (Cramer *et al.*, 1997; Cramer *et al.*, 2001). Indeed, 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 (Hummel *et al.*, 2005a; Hummel *et al.*, 2005b). Our findings suggest that spontaneous plasticity and rehabilitation after stroke in patients with minor corticospinal system damage can induce a similar effect, which might be enhanced by continuing rehabilitation in chronic stroke patients. Our study suggests that Ce may also be a target of rehabilitation since it is disconnected from M1. Strengthening the connectivity to SMA and/or M1 would be expected to benefit stroke patients. Of course this would require a preserved capacity for plasticity in chronic stroke patients.

Evidence of preserved capacity for plasticity in chronic stroke patients indicates that regional connectivity should be capable of modification and adjustment (Fasoli *et al.*, 2003; Fasoli *et al.*, 2004). Indeed, neuroimaging data in humans and corroborative neurophysiology studies in animals have shown considerable plasticity of M1 representations and cell properties related to motor skill learning and cognitive motor performance following pathological or traumatic changes (Sanes *et al.*, 2000). The present findings support the notion of a plastic functional reorganization of SMA and M1 in adult mammals, which apparently results from broad connections and the capacity for activity-driven changes in synaptic strength (Sanes *et al.*, 2000).

Conclusion

We propose that assessing effective connectivity by means of fMRI and DCM is useful for the evaluation of sensorimotor brain networks. Furthermore, investigating changes in connectivity caused by both brain injury and rehabilitative training will assist in monitoring and elucidating the physiology of functional recovery and neuroplasticity in patients who have suffered strokes. It is our view that brain fMRI using novel hand devices provides accurate monitoring and can be used in rehabilitation. We purport that this possibility is clinically relevant since it will allow caregivers to select the most appropriate rehabilitation approach for each patient and to fine-tune it based on brain maps obtained before and after a short trial of therapy.

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Figure 1.

DCM used in this study. The model for intrinsic connections has links between primary motor area (M1), supplementary motor area (SMA), and cerebellum (Ce). All possible connections between these areas were allowed to account for plasticity changes in the stroke group.

Figure 2.

Activated brain regions in representative healthy controls and chronic stroke patients using MR_CHIROD during fMRI, and regions (volumes) of interest used for DCM definition. The primary motor area (M1, green color), supplementary motor area (SMA, red color), and cerebellum (Ce, blue color) were identified and the coordinates of activated clusters verified by extracting the cluster coordinates. L and R denote left and right respectively.

Figure 3.

Group activations of brain regions in healthy controls and chronic stroke patients using MR_CHIROD during fMRI. Activation maps of healthy controls (Figure 3A) and chronic stroke patients (Figure 3B) are superimposed on T1-weighted anatomical image (group level, random effects analysis, activation threshold $P < 0.01$, uncorrected). The bar at the right bottom corner shows the t-score scale. Primary motor area (M1), supplementary motor area (SMA), cerebellum (Ce), visual areas (V2/V5). Note that M1 and Ce are less activated in stroke patients. The premotor cortex was not easily separated from M1 thus it is not labeled here.

Figure 4. Overview of pathways in which intrinsic neural coupling strengths in chronic stroke patients differed from those in healthy controls. Red arrows indicate an increase while blue arrows indicate a decrease.

Table 1

Intrinsic neural coupling strengths in healthy controls and chronic stroke patients for the selected intrinsic model.

Pathway	Controls (<i>N</i> = 11)	Patients (<i>N</i> = 5)	% change from controls ^{<i>b</i>}
Mot → SMA	0.18 ± 0.03 ^{<i>a</i>}	0.14 ± 0.01	-22
M1 → SMA	0.64 ± 0.02	0.63 ± 0.08	-2
SMA → M1	0.17 ± 0.03	0.27 ± 0.07	+59*
SMA → Ce	0.12 ± 0.02	0.16 ± 0.02	+33*
Ce → SMA	0.41 ± 0.02	0.29 ± 0.05	-29*
Ce → M1	0.40 ± 0.04	0.23 ± 0.02	-43*
M1 → Ce	0.55 ± 0.04	0.35 ± 0.06	-36*

^{*a*} values are means ± SE in Hz

^{*b*} values are percent (%) difference between patients and controls, while asterisks indicate statistical significance