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Changes in the location of cortico-muscular coherence following stroke

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ABSTRACT

Stroke results in reorganization of residual brain networks. The functional role of brain regions within these networks remains unclear, particularly those in the contralesional hemisphere. We studied 25 stroke patients with a range of motor impairment and 23 healthy age-matched controls using magnetoencephalography (MEG) and electromyography (EMG) to measure oscillatory signals from the brain and affected muscles simultaneously during a simple isometric hand grip, from which cortico-muscular coherence (CMC) was calculated. Peaks of cortico-muscular coherence in both the beta and gamma bands were found in the contralateral sensorimotor cortex in all healthy controls, but were more widespread in stroke patients, including some peaks found in the contralesional hemisphere (7 patients for beta coherence and 5 for gamma coherence). Neither the coherence value nor the distance of the coherence peak from the mean of controls correlated with impairment. Peak CMC in the contralesional hemisphere was found not only in some highly impaired patients, but also in some patients with good functional recovery. Our results provide evidence that a wide range of cortical brain regions, including some in the contralesional hemisphere, may have influence over EMG activity in the affected muscles after stroke thereby supporting functional recovery.

1. Introduction

After stroke, both functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) studies have demonstrated alterations in brain activity during movement of the affected hand, particularly in the contralesional hemisphere (Ward et al., 2003; Serrien et al., 2004; Gerloff et al., 2006a; Cramer, 2008). However, the most widespread changes are seen in those patients with more impairment and it is still unclear whether new task related brain activity, particularly within the contralesional hemisphere, is supporting or hindering recovered motor function. Evidence of the former is provided by studies in which single pulse transcranial magnetic stimulation (TMS) to dorsal premotor cortices in either hemisphere disrupted motor performance in chronic stroke patients but not in control subjects (Johansen-Berg et al., 2002; Fridman et al., 2004; Lotze et al., 2006). Evidence of the latter comes from the finding that contralesional primary motor cortex (M1) in chronic stroke patients maintains an inhibitory influence over ipsilesional M1 during both movement preparation and execution (Murase et al., 2004). This finding in particular has led to small clinical studies using cortical stimulation to suppress activity in the contralesional hemisphere in order to enhance training effects on upper limb function, via interhemispheric effects on ipsilesional M1 (Stagg et al., 2012; Liepert et al., 2007; Talelli et al., 2012; Seniów et al., 2012). The results have been mixed, raising the possibility that contralesional cortical motor regions actually contribute to motor recovery in some but not all stroke patients.

One way of addressing this question directly is to determine which cortical regions have the most direct influence over muscles in the affected limb. Oscillatory signals from the brain and affected muscles can be measured simultaneously during task performance using magnetoencephalography (MEG) and electromyography (EMG) respectively, and coherence between the two can be calculated (Conway et al., 1995; Halliday et al., 1998). Cortico-muscular coherence (CMC) is detected most prominently in beta (15–30 Hz) and gamma (30–80 Hz) frequency bands. Beta band coherence is highest in tasks requiring maintenance of a posture (Kilner et al., 2000; Baker et al., 1997) whereas gamma band coherence increases with increasing muscle contraction strength and dynamic movements (Brown et al., 1998; Omlor et al., 2007). Beta band CMC has previously been found to reflect efferent drive from

Abbreviations: CMC, cortico-muscular coherence; MEG, magnetoencephalography; EMG, electromyography; fMRI, functional magnetic resonance imaging; TMS, transcranial magnetic stimulation; M1, primary motor cortex; PCA, principal component analysis; MVC, maximum voluntary contraction; DICS, dynamic imaging of coherent sources.

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contralateral M1 to the muscle (Gerloff et al., 2006b; Braun et al., 2007). CMC therefore provides a non-invasive means of assessing the brain areas which are interacting with the muscle. Furthermore, MEG provides a method of assessing post-stroke brain activity which is not influenced by potential disturbances in neurovascular coupling that can affect blood oxygen level dependent signal used by fMRI.

Here, we performed simultaneous MEG–EMG recordings during a simple isometric hand grip to address the hypothesis that locations of peak coherence in both the beta and gamma bands would be more widely distributed in stroke patients than in healthy controls. In particular, we were interested to see whether the peak coherence would be present in the contralesional hemisphere and whether the location of this CMC was related to the level of impairment in patients.

2. Materials and methods

2.1. Subjects

Twenty-five stroke patients (mean age 52 ± 14 years, range 19–81 years; 19 male, 3 left-handed, 13 dominant hand affected) and twenty-three healthy controls (mean age 50 ± 20 years, range 23–77 years; 11 male, 2 left-handed) participated. All patients suffered from first-ever stroke and weakness of at least wrist and finger extensors and hand interossei and were not suffering from any other neurological disorder. A full written consent was obtained from all subjects in accordance with the Declaration of Helsinki. The study was approved by the Joint Ethics Committee of the Institute of Neurology, UCL and National Hospital for Neurology and Neurosurgery, UCL Hospitals NHS Foundation Trust, London.

2.2. Behavioural testing

All patients were scored on the following outcome measures; 1) action research arm test, 2) grip strength, 3) nine hole peg test, and 4) box and block timed test. A principal component analysis (PCA) was performed on these scores to take account of floor and ceiling effects and the first component was used as a single impairment score per patient.

2.3. Motor task/experimental paradigm

The subjects performed visually cued isometric hand grips with a manipulandum during MEG recording. Prior to scanning, maximum voluntary contraction (MVC) was recorded for each subject. Patients used their affected hand and controls were scanned using each hand in separate blocks. For each hand, 2 × 8 min blocks of 60 trials were performed. The cue to perform a hand grip was the appearance of a 'force thermometer' on the screen which provided continuous visual feedback about the force exerted. The target force was set between 15 and 30% of their MVC and displayed visually. Each grip was sustained for 3 s with an interstimulus interval between 3 and 7 s. A manipulandum was placed in the inactive hand to check for mirror movements.

2.4. MEG recording

MEG signals were measured continuously at 600 Hz during the task using a whole-head CTF Omega 275 MEG system (CTF, Vancouver, Canada). Head localization was monitored continuously during the recordings in order to check for excessive movement. The MEG data were pre-processed offline using SPM8 (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm) (Litvak et al., 2011). Data were down-sampled to 300 Hz and were filtered from 5–100 Hz. Data were epoched from −3 to +3 s where time 0 indicated onset of the visual cue. Data with large eye blinks or other artifacts were excluded.

2.5. EMG recording

Bipolar surface electrodes were used to record EMG from flexors and extensors of the forearm involved in grip during the task. EMG was recorded as part of the MEG dataset and so had the same pre-processing parameters. The EMG channel was rectified (Myers et al., 2003). The force output from the two manipulandi was also recorded as part of the MEG dataset in order to check that the task was being performed accurately.

2.6. Structural MRI recording

A 3T Siemens Trio scanner (Siemens, Erlangen, Germany) was used to acquire high resolution T1-weighted anatomical images (1.3 × 1.3 × 1.3 mm voxels); 176 partitions, (FoV = 256 × 240, TE = 2.48 ms, TR = 7.92 ms, FA = 16°). Structural MRIs could not be obtained in one of the patients and three of the controls due to MRI contraindications.

2.7. Data processing and analysis

For control subjects, we used data acquired during either left or right hand grip in order to match the patient group for both age and dominance of the hand used to perform the task. For further analysis, scans acquired during right hand use were flipped about the sagittal plane, so that the right hemisphere was therefore contralateral to the moving hand in all subjects. In the case of the patient group, the right hemisphere was always the ipsilesional side and all affected hands were on the left side. This enabled comparisons across subjects.

Lead fields were computed using a single-shell head model (Nolte, 2003) based on an inner skull mesh derived by inverse-normalizing a canonical mesh to the subject's individual MRI image (Mattout et al., 2007). For subjects without individual MRI the canonical mesh was affine-transformed to fit their MEG fiducials. Coregistration between the MRI and MEG coordinate systems used three fiducial points: nasion, left and right pre-auricular. While acquiring the structural MRI, fiducial points were marked with vitamin-E capsules in order to coregister with the MEG fiducials.

The beamforming method is based on the linear projection of sensor data using a spatial filter computed from the lead field of the source of interest and either the data covariance (time domain) (Van Veen et al., 1997) or cross-spectral density matrix (frequency domain) (Gross et al., 2001). Dynamic imaging of coherent source (DICS) analysis was used to calculate the coherence between the MEG sensors and EMG signal in both beta (15–30 Hz) and gamma (30–80 Hz) frequency bands in the time window 0.5 s to 3 s after the visual cue. The location of peak coherence was determined after the source localization results were thresholded to one standard deviation (computed across voxels) above the mean.

The coherence values were computed on a 3D grid in Montreal Neurological Institute space with spacing of 5 mm bounded by the inner skull surface (regularization = 1%). Values at the grid points were then linearly interpolated to produce volumetric images with 2 mm resolution.

The primary interest was the location of peak CMC in stroke patients compared to controls. To investigate this, we performed Hotelling's T-squared test (Hotelling, 1931) to examine (multivariate) differences in peak location between patient and control groups. We used the same test to identify individual patients whose peak location significantly differed from that of the control group. In addition, the distance of each patient's coherence peak from the mean control group coordinate was calculated.

The source signal was extracted from the peak beta and gamma coherence coordinates using Linearly Constrained Maximal Variance (LCMV) beamformer (Van Veen et al., 1997). The source orientation was in the direction yielding maximal signal variance. A coherence plot was generated between the MEG source signal and EMG channel