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Parietofrontal network upregulation after motor stroke

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ABSTRACT

Objective: Motor recovery after stroke shows a high inter-subject variability. The brain's potential to form new connections determines individual levels of recovery of motor function. Most of our daily activities require visuomotor integration, which engages parietal areas. Compared to the frontal motor system, less is known about the parietal motor system's reconfiguration related to stroke recovery. Here, we tested if functional connectivity among parietal and frontal motor areas undergoes plastic changes after stroke and assessed the behavioral relevance for motor function after stroke.

Methods: We investigated stroke lesion-induced changes in functional connectivity by measuring high-density electroencephalography (EEG) and assessing task-related changes in coherence during a visually guided grip task with the paretic hand in 30 chronic stroke patients with variable motor deficits and 19 healthy control subjects. Quantitative changes in task-related coherence in sensorimotor rhythms were compared to the residual motor deficit.

Results: Parietofrontal coupling was significantly stronger in patients compared to controls. Whereas motor network coupling generally increased during the task in both groups, the task-related coherence between the parietal and primary motor cortex in the stroke lesioned hemisphere showed increased connectivity across a broad range of sensorimotor rhythms. Particularly the parietofrontal task-induced coupling pattern was significantly and positively related to residual impairment in the Nine-Hole Peg Test performance and grip force.

Interpretation: These results demonstrate that parietofrontal motor system integration during visually guided movements is stronger in the stroke-lesioned brain. The correlation with the residual motor deficit could either indicate an unspecific marker of motor network damage or it might indicate that upregulated parietofrontal connectivity has some impact on post-stroke motor function.

1. Introduction

The basis of spontaneous recovery from a motor stroke in humans is unclear. Given a window of heightened microstructural plasticity (Rossini et al., 2003; Ward, 2017) and evidence for dynamic reconfiguration of cortical areas engaged in motor activity after stroke (Grefkes and Fink, 2011), it is conceivable that interaction patterns between cortical areas reorganize after a lesion. Unravelling common patterns of neuroplastic processes that lead to regain of motor function is a major challenge of neurorehabilitative medicine and a prerequisite for a mechanistic approach of interventional therapies.

During physiologic motor activity, the primary and secondary motor areas engage in balanced facilitatory and inhibitory interactions (Bonstrup et al., 2016; Grefkes et al., 2008a). After a motor stroke, in the acute phase, the facilitatory coupling among the frontal motor areas, i.e. ventral premotor cortex (PMv), the supplementary motor area (SMA) and the primary motor cortex (M1) in the contralateral (ipsilesional) hemisphere appears to be disrupted; and to normalize along with recovery (Rehme et al., 2011b). Most of our daily activities require precise interaction between visual perception and the motor system. For higher order movements, that require visuomotor and sensorimotor integration (Vingerhoets, 2014) as well as for reaching and grasping (Bernier et al., 2017; Corbetta and Shulman, 2002; Grefkes et al., 2004; Konen et al., 2013), parietal motor areas are

Abbreviations: aIPS, anterior intraparietal sulcus; cIPS, caudal intraparietal sulcus; CTC, communication through coherence; DCM, dynamic causal modelling; UEFM, Fugl–Meyer score upper extremity subsection; LCMV, linear constrained minimum variance; LME, linear mixed effects; MVC, maximum voluntary contraction; NHP, Nine-Hole Peg Test performance; M1, primary motor cortex; SMA, supplementary motor area; TR-Coh, task-related coherence; TR-Pow, task-related spectral power; PMv, ventral premotor

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specifically engaged. However, their relative role in motor system reconfiguration after stroke is less well understood compared to the frontal brain. Conceivably, parietofrontal pathways are of high importance for post-stroke rehabilitation (Wu et al., 2014). Recently, it was shown that lesion-induced network plasticity involves parietofrontal motor pathways connecting PMv with the anterior intraparietal sulcus (aIPS) (Schulz et al., 2015). And in functional magnetic resonance imaging (fMRI), it was demonstrated that reciprocal facilitatory connectivity between the aIPS and M1 in the ipsilesional hemisphere is enhanced in well-recovered chronic stroke survivors compared with healthy participants during a visually guided grip task (Schulz et al., 2016). However, the functional relevance of parietofrontal network upregulation for motor function has not been characterized yet. Whether the abnormally increased parietofrontal connectivity in stroke survivors is systematically varying with the degree of paresis, is a highly intriguing question not only for deeper pathophysiologic understanding, but also to substantiate the validity and importance of this connection as a tentative target for non-invasive brain stimulation protocols.

We recorded high-density EEG during a visually guided grip task with the paretic hand in 30 chronic stroke patients (we use the term chronic in agreement with previous definitions and use (Di Pino et al., 2014; Ward et al., 2003)) and 19 healthy control subjects.

We first set out to reproduce the previous finding of enhanced facilitatory coupling between the parietal and motor cortex in a larger patient cohort and with a different method to detect brain connectivity: Across perceptual, cognitive and motor systems, synchronization of oscillations has been detected as a key mechanism of how transient coalitions of neural populations at small- and large spatial scales commit to a common task (communication through coherence concept) (Bonnefond et al., 2017; Siegel et al., 2012). We hypothesized that parietal and frontal motor areas would show higher coherence during the task for patients than for control participants. Secondly, we hypothesized that higher coherence parameters are found in patients with a stronger residual motor deficit.

2. Participants and methods

2.1. Participants

30 patients (19 male, 1 left-handed, aged 65 ± 13 years, mean ± std) were included three months (104 ± 17 days) after first-ever ischemic stroke causing a motor deficit involving hand function (five subcortical, 25 cortical/cortico-subcortical). 14 patients had lesions to the dominant hemisphere. Initial and residual motor impairment was determined by means of grip force, the Nine-Hole Peg Test performance (NHP), and the Fugl–Meyer score for the upper extremity (UEFM) 3–5 days after stroke and 3 months after stroke. For the grip force and the NHP, behavioral scores were calculated as proportional values (affected/unaffected hand), whereas in case of the NHP, prior to normalization the score for each hand was expressed as pegs/s to give a performance value. Individual motor recovery values were obtained by calculating the difference between initial and residual behavioral scores. A group similar in age and gender (n = 19, 10 males, one left-handed, aged 64.8 ± 11.1 years) served as controls. The study design was approved by the local ethical committee. All participants gave their written informed consent according to the ethical declaration of Helsinki.

2.2. Motor task

Participants underwent EEG during a simple motor task which required them to perform isometric visually guided whole hand grips with the paretic hand using a grip-force device (Grip Force Bimanual, Current Designs, Inc., Philadelphia, USA). The control participants were randomly assigned to use the left or right hand in a distribution matching the lesion-side of the patient group (nine right hand). Participants were seated comfortably in an armchair with the right and left arm relaxed positioned in their lap, each holding one of the bimanual grip-force devices. We compared two conditions of varying target grip force, one keeping the force constant across the group (constant output of 5 kg) and the other keeping the task effort constant across the group (constant effort of 20% MVC). Each condition was recorded with 20 repetitions of a 9 s constant grip hold phase. The begin of each grip as well as continuous feedback about the applied force were provided visually by the appearance and vertical level of a horizontal bar on a screen. The participants were instructed to lift the bar into the target zone (paralleling the target force of either 5 kg (= constant-output) or 20% of maximal force (= constant-effort)) and hold it constant until it disappeared (after 9 s, Supplementary Fig. 1). Participants were instructed to avoid eye movements and fixate the bar, whose level was within a small visual angle of ± 5°, thus not requiring large amplitude eye movements during the force build-up. During the inter-trial interval of 12 ± 2 s, participants were instructed to fixate a cross in the center of the screen and relax. To assess bilateral movements, the force applied with the (unaffected) non-active hand was continuously monitored throughout the hand grip as the patient held a grip force device in both hands. If necessary, breaks were introduced depending on the participant's needs. The task was described in the previous report on functional MRI (fMRI) derived effective coupling (Schulz et al., 2016) and in (Bonstrup et al., 2015).

2.3. Data acquisition

2.3.1. Electroencephalography

The EEG was recorded from 63 cephalic active surface electrodes, referenced to a nose-tip or Cz-electrode during recording (interim replacement of recording setup). One electrode was mounted below the left eye for electrooculogram recording. Before and after each experimental session, a resting state was recorded for 3–4 min with eyes fixed on a cross in the center of the screen. See Supplementary material section 1.1 for details on the recording setup.

2.4. Data analysis

2.4.1. EEG data preprocessing

The continuous EEG was offline down sampled to 125 Hz, detrended and subjected to an independent component analysis (logistic infomax ICA; (Makeig et al., 1996)) to remove eye-blink artifacts. The 20 trials of each grip condition were segmented in epochs of 1 s duration covering the hold phase, starting 1 s after the beginning of each trial until the end (20 × 8 s). The resting state condition was likewise segmented into epochs of 1 s. Trials were then visually inspected to reject remaining artifacts (number of 1 s long trials after artifact rejection (mean ± std): task 119 ± 14, rest 235 ± 29). See Supplementary material section 1.2 for details on the preprocessing.

2.4.2. Source reconstruction and spectral power and coherence analysis

We reconstructed source space activity and connectivity in the parietofrontal motor network using spatial filtering. The network consisted of five ipsilesional regions of interest (ROIs) contralateral to the (affected) active hand, consisting of M1, PMv, SMA, and the aIPS and caudal part of the intraparietal sulcus (cIPS). Coordinates were predefined as reported previously ((Schulz et al., 2016), Suppl. Table 2). For each location, a linear constrained minimum variance (LCMV) beamforming filter was computed based on an individual forward model and a covariance matrix of sensor space time series. The choice of a beamforming approach for spatial filtering was based on previous publications in the field of motor stroke research using EEG or magnetoencephalography (MEG). Cross-spectra between each pair of sensors were calculated at frequency bands of interest using the continuous wavelet transformation with a width of 5 cycles. The cross-spectra were