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The effects of deefferentation without deafferentation on functional connectivity in patients with facial palsy

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ABSTRACT

Cerebral plasticity includes the adaptation of anatomical and functional connections between parts of the involved brain network. However, little is known about the network dynamics of these connectivity changes. This study investigates the impact of a pure deefferentation, without deafferentation or brain damage, on the functional connectivity of the brain. To investigate this issue, functional MRI was performed on 31 patients in the acute state of Bell's palsy (idiopathic peripheral facial nerve palsy). All of the patients performed a motor paradigm to identify seed regions involved in motor control. The functional connectivity of the resting state within this network of brain regions was compared to a healthy control group. We found decreased connectivity in patients, mainly in areas responsible for sensorimotor integration and supervision (SII, insula, thalamus and cerebellum). However, we did not find decreased connectivity in areas of the primary or secondary motor cortex. The decreased connectivity for the SII and the insula significantly correlated to the severity of the facial palsy. Our results indicate that a pure deefferentation leads the brain to adapt to the current compromised state during rest. The motor system did not make a major attempt to solve the sensorimotor discrepancy by modulating the motor program.

1. Introduction

Multiple studies have demonstrated that neural plasticity can change the structure and function of the central nervous system after structural brain damage and rehabilitation (Chen et al., 2010; Hosp and Luft, 2011). An important mechanism is the adaptation of the anatomical and functional connectivities between brain areas. One approach for examining connectivity between brain regions within a network involves quantifying temporal correlation in the blood oxygen level-dependent (BOLD) signal while the brain is in a resting state (Cabral et al., 2014). Multiple studies have demonstrated that resting-state functional connectivity is correlated with behavioral output in multiple domains, particularly in the motor system (Albert et al., 2009). Studies of motor impairments after stroke have demonstrated disrupted connectivity within the motor network (Golestani et al., 2013; Yin et al., 2012). The strength of this disrupted connectivity has been shown to correlate with the clinical outcomes of patients (Yin et al., 2012).

However, little is known about the network dynamics underlying these connectivity changes. The main factors responsible are the effects of structural brain damage itself (Urban et al., 2012), as well as the effects of deafferentation and deefferentation (Werhahn et al., 2002). Because most studies analyzing cortical plasticity after loss of function are conducted in patients suffering from brain damage (e.g., stroke), apportionment can be difficult. Some studies have circumvented this problem by investigating connectivity changes caused by impairment of peripheral nerves or limb amputation (Qiu et al., 2014). However, there are no peripheral pure motor nerves, and therefore, these studies have investigated the combined effect of deafferentation and deefferentation on cortical plasticity. At this time, the effects of a pure deefferentation without structural brain damage are incompletely understood.

Bell's palsy presents an opportunity to investigate a pure deefferentation. The palsy is a transient, unilateral deefferentation of facial muscles, typically of unknown cause (perhaps viral) and resolving within about 6 months. Because efferent activity to facial muscles is carried by the affected facial nerve, whereas somatosensory afference is carried by the trigeminal nerve, the palsy does not affect facial reafference. As we show, Bell's palsy brings into play central nervous system network dynamics pertaining to a pure deefferentation that may illuminate motor systems more generally. We hypothesize that the sensory-motor mismatch alone (without a structural brain lesion) is a sufficient stimulus for adaptation within the facial brain network.

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Particularly, we investigate whether such a sensory-motor mismatch is a sufficient stimulus for motor adaptation during rest or whether the brain will simply adapt to the current state of the (impaired) sensory-motor information.

We tested this hypothesis in the present study, employing functional magnetic resonance imaging (fMRI) and connectivity analyses in the acute stage of Bell's palsy.

2. Materials and methods

2.1. Subjects

The study population was comprised of 30 patients with Bell's palsy (age 40.9 ± 16.9 years ranging from 21 to 71, 17 male, 14 female, 15 right sided facial palsies), who were recruited from the Neurology and Otorhinolaryngology departments, and 31 age- and gender- matched healthy controls. Right- and left sided facial palsies were investigated in this study together in a balanced design (15 left, 15 right sided palsies) to avoid hemispheric specific effects. Only patients with idiopathic facial nerve palsies without any previous history of neurological disorder were included. The subjects underwent magnetic resonance scans between 2 and 5 days after the onset of their symptoms. Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971), which ranges from −100 for strong left-handedness to +100 for strong right-handedness. Only right-handed (>+79) patients were included. The study was approved by the local ethics committee, and all patients gave their written informed consent according to the declaration of Helsinki.

2.2. Clinical assessment of facial function

Although a variety of scoring systems for the clinical assessment of the severity of peripheral facial nerve palsy are available, the Stennert grading system, which is one of the most widely applied, was selected for use in this study (Stennert et al., 1977). The scale assesses the severity of facial palsy at rest and during voluntary facial movements. This score ranges from 0/0, representing normal facial function, to 4/6, which represents gross facial asymmetry at rest (first value) and complete paralysis (second value).

2.3. MRI experimental design

Subjects were instructed to move the left or right mouth angle up, then relax their facial muscles to regain the starting position. These motor tasks were performed with a frequency of 1 Hz for 30.6 s, followed by a 30.6 s rest. The pace was set visually. The movement effort should be equal on both sides of the face, even if it elicited marginal or no movement on the paretic side. Every subject was trained in this paradigm prior to the MRI scanning. The paradigm during the MRI measurement consisted of 10 blocks (five times the motor task of the left and five times of the right corner of the mouth) in a pseudo-randomized order, which were visually directed.

2.4. MRI recordings

All examinations were performed on the same 3.0 Tesla MR scanner (Trio, Siemens, Erlangen, Germany) to obtain echo-planar T2*-weighted image volumes (EPI) and transaxial T1-weighted structural images. Functional resting state data were acquired in one EPI session of 203 volumes. The patient was instructed to lie down with the eyes closed, to think of nothing in particular, and not fall asleep. The first 3 volumes were subsequently discarded due to equilibration effects. A functional image volume was composed of 44 transaxial slices, including the whole cerebrum and cerebellum (voxel size = 3 × 3 × 3 mm, repetition time = 2.52 s, TE 35 ms). The motor task was performed after the resting state scan, during which 255 images (voxel size = 3 × 3 × 3 mm, repetition time = 2.52 s, TE 35 ms) were acquired. The first 3 volumes were subsequently discarded due to equilibration effects. After functional measurement, high-resolution T1-weighted structural images (voxel size = 1 × 1 × 1 mm) were acquired.

2.5. Preprocessing of functional data (resting state and motor paradigm)

To make patients with right-sided palsy and their age and gender matched healthy control subject comparable to left-sided ones, all their images were flipped along the y-axis prior to analysis.

For each subject, all images were realigned to the first volume using a six-parameter rigid-body transformation that corrected for motion artifacts. The images were co-registered with the subject's corresponding anatomical (T1-weighted) images, re-sliced to correct for acquisition delays, normalized to the Montreal Neurological Institute (MNI) standard brain (Evans et al., 1993) to report MNI coordinates, and smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel.

2.6. fMRI analysis of the motor task

A multiple regression analysis using a general linear model was performed to obtain statistical parametric maps calculated for all three conditions (tongue and right/left sided facial movement). Functional MRI signal time courses were high-pass filtered (128 s) and modeled as an experimental stimulus onset function, convolved by the canonical hemodynamic response function (low-pass filter). Individual results were projected onto the co-registered individual high-resolution T1-weighted 3-D data set. The anatomical localization of activations was analyzed with reference to the standard stereotaxic atlas and by visual inspection of the individual T1-weighted structural data. The resulting statistical maps were thresholded by the family-wise error (FWE; $P < 0.05$).

2.7. Connectivity analysis of resting state data

In the present study, functional connectivity is examined in the resting state, where temporal correlations of low frequency (<0.1 Hz) blood oxygenation level dependent (BOLD) fMRI signal fluctuations (Biswal et al., 1995; Friston et al., 1993) are presumed to relate to neural activity and reflect information transfer and collaboration between brain areas (Biswal et al., 1995; Greicius et al., 2003). While most studies analyzed the functional connectivity during rest in this frequency range there are also methods to investigate the connectedness between brain areas in other frequency ranges. Particularly, the estimation of the causal influence that one brain area exerts over another (effective connectivity) requires higher frequencies and is usually estimated during a task or the modulation of a task.

Changes in functional connectivity within the facial motor network were investigated in the resting state.

To identify relevant areas of the facial motor network relevant for connectivity analysis, we used the activation maps obtained from the motor task. The point of maximum activation strength, along with its 26 neighbors, was selected from each activated region, and these were further used as regions of interest (ROIs). The resting state data from these identified ROIs were extracted, and cluster-specific time series were estimated by averaging the time series of all voxels within a cluster. Several sources of variance were then removed from the data by linear regression as follows: (1) six parameters obtained by rigid body correction of head motion, (2) the signal from a ventricular ROI and (3) the signal from a region centered in the white matter. All signal intensity time courses were bandpass filtered ($0.01 < f < 0.1$) to reduce the effect of low-frequency drift and high-frequency noise.

We estimated the functional connectedness using a correlation analysis between different ROIs. The spatial locations of these ROIs were determined using the clusters activated during the motor task in the random effect fMRI analysis. The Pearson's correlation coefficient was