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The impact of motor impairment on the processing of sensory information

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ABSTRACT

Sensorimotor adaptation is driven by mismatch errors between desired movements and actual movement outcomes. A mismatch error can be minimized by adjusting movements or by altering the interpretation of sensory information. While the effect of mismatch errors on the motor system has received much attention, the contribution of somatosensory feedback, particularly the sensory-motor interplay in the process of adaptation, remains poorly understood.

Our study analyzes the impact of peripheral deefferentation on the plasticity of the brain networks responsible for sensory-motor adaptation, focusing particularly on changes in the processing of somatosensory information. For this aim, task-based and resting-state functional MRI was performed on 24 patients in the acute state of a left-sided idiopathic peripheral facial nerve palsy. The functional connectivity of cortical and subcortical networks was analyzed and compared to a healthy control group.

We found a strong involvement of the somatosensory system and the thalamus in the adaptation process following an acute peripheral deefferentation. The investigated network shows the principal pattern of a reduced connectivity between cortical areas, while the connectivity to subcortical areas (the basal ganglia and the thalamus) is increased. We suggest that the increased connectivity between the subcortical and cortical structures indicates an active sensory-motor adaptation process. We further hypothesize that the decreased functional connectivity at the cortical level reflects an unsuccessful sensorimotor adaptation process due to the inability to solve the somatosensory-motor mismatch. These results extend our understanding of the somatosensory-motor interaction in response to a mismatch signal and highlight the importance of the thalamus in this process.

1. Introduction

Sensorimotor adaptation is a fundamental feature of the neural control of movements. It is driven by mismatch errors between desired movements and actual movement outcomes but is also thought to be more than a simple error cancellation process. In healthy motor learning, it is thought that the mismatch between predicted movement and actual sensory feedback mainly causes an adaptation of motor behavior. Multiple studies have demonstrated a pivotal role of the cerebral motor cortex, the basal ganglia, and the striatum, in particular, for motor adaptation due to perceptual-motor mismatch [for review see [1]].

However, a mismatch error can not only be minimized by adjusting movements but also by altering the interpretation of sensory information. Therefore, motor adaptations do not occur in isolation but are accompanied by perceptual changes [2–4]. The adaptation of somatosensory information processing becomes particularly important if a mismatch error cannot be reduced by modulating the motor behavior. For example, the inability to execute a motor signal due to a central or peripheral lesion that blocks the motor signal requires another central mechanism to handle the perceptual-motor mismatch.

While the effect of mismatch errors on the motor system has received much attention, the contribution of somatosensory feedback, particularly the sensory-motor interplay in the adaptation process, remains poorly understood. Important cerebral structures for perceptual changes are the cortical somatosensory areas and the thalamus [5–7]. The thalamus acts as the driver and modulator of somatosensory input and cortico-cortical information transfer. Additionally, there are dense connections between the thalamus and the basal ganglia, and it is assumed that basal ganglia output modulates the thalamic influence on

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motor adaptation [8]. The altered thalamic functioning due to motor adaptation includes the thalamic relay of basal ganglia output to motor areas and the thalamic relay of sensory information to both the basal ganglia and the cortex [1,9].

Currently, most of our knowledge about mismatch-based learning is derived from studies investigating visuomotor and force field adaptation tasks [10–12]. However, these studies that investigate a successful adaptation task might reveal very different mechanisms compared to an unsuccessful adaptation task. A particularly useful model to investigate the underlying mechanisms of an unsuccessful motor learning task is peripheral facial nerve palsy. The palsy is caused by a peripheral deefferentation of facial muscles, whereas the somatosensory afference of this body region is not affected. The inability to move facial muscles combined with an unaffected somatosensory afference causes a strong mismatch signal between intended and perceived movements. This disease further allows us to investigate the effects of a long-lasting mismatch (over days).

There are multiple studies currently available that demonstrate changes in activity and connectivity of the cortical motor cortex in patients suffering from this disease [13–20]. A recent study demonstrated the involvement of cortico-striatal connectivity in patients suffering from a peripheral facial palsy [19]. However, the effects on the processing of somatosensory information, particularly on thalamic functioning as well as the sensory-motor interplay at the cortical level, have not been investigated (Fig. 1).

To further elucidate the role of somatosensory information processing after peripheral deafferentation, we tested the following two primary research hypotheses:

1) Facial palsy causes altered functional connectivity of the cortical facial somatosensory network.
2) The functional connectivity of the somatosensory part of the thalamus to other parts of the cortical and subcortical facial somatosensory and the motor network is impaired.

As a secondary objective of the current study, we analyzed changes in the functional connectivity in the motor network to replicate previous findings and to elucidate the somatosensory-motor interplay.

We investigated this issue in the present study by employing functional magnetic resonance imaging (fMRI) in 24 patients in the acute stage of a left-sided idiopathic facial nerve palsy.

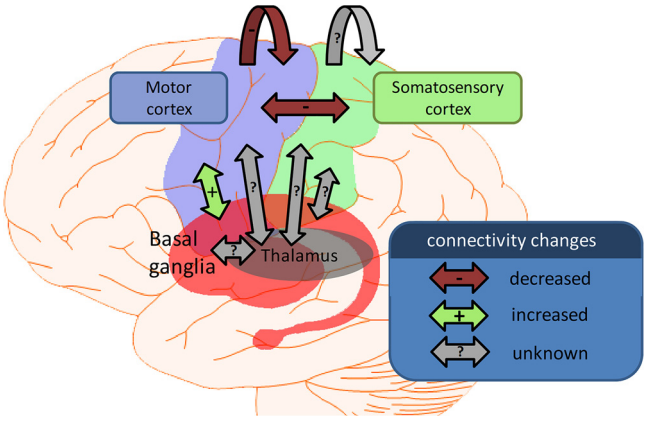

Fig. 1. Schematic outline of the currently known and unknown effects of facial palsy on the brain network responsible for facial adaptation and motor learning. This study investigated the whole network, aiming to characterize changes in the functional connectivity between all of the engaged parts of the involved brain network.

2. Materials and methods

2.1. Subjects

The study population comprised 24 patients suffering from a left-sided facial palsy (age 42.1 ± 18.5 years, ranging from 20 to 78 years old; 12 males and 12 females) who were recruited from the Neurology and Otorhinolaryngology departments and 24 age- and gender-matched healthy controls. Only patients with idiopathic facial nerve palsies without any previous history of neurological disorder were included. All subjects underwent fMRI scans between 2 and 5 days after the onset of their symptoms. Handedness was assessed by the Edinburgh Inventory [21], 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 per the Declaration of Helsinki.

2.2. Clinical assessment of facial function

For the clinical assessment of the severity of peripheral facial nerve palsies, we used the Stennert grading system, which is one of the most widely applied scales [22]. 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 during movement (second value). The grading was developed by expert viewing and otorhinolaryngological assessment.

2.3. MRI experimental design

2.3.1. Motor paradigm

Patients were instructed to move the left and right mouth angle up, and then relax their facial muscles to regain the starting position. The motor task was performed with a frequency of 1 Hz for 30.6 s, followed by a 30.6-s rest (10 blocks). 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. All subjects were trained in this paradigm prior to MRI scanning.

2.3.2. Somatosensory stimulation paradigm

Tactile stimuli were delivered to the bilateral face by balloon diaphragms driven by compressed air (Fig. 2). Each stimulus lasted for 200 ms (40 ms rise time, 100 ms plateau, 60 ms return to baseline pressure). These stimuli were presented in a block design with the same configuration as the motor task. No subject reported any perception of pain.

2.3.3. 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. Each subject was instructed to lie down with his/her eyes closed, to think of nothing in particular, and to 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 mm × 3 mm × 3 mm, repetition time = 2.52 s, TE 35 ms). The task-related fMRI sessions were performed after the resting state scan, during which 385 images (voxel size = 3 mm × 3 mm × 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 mm × 1 mm × 1 mm) were acquired.

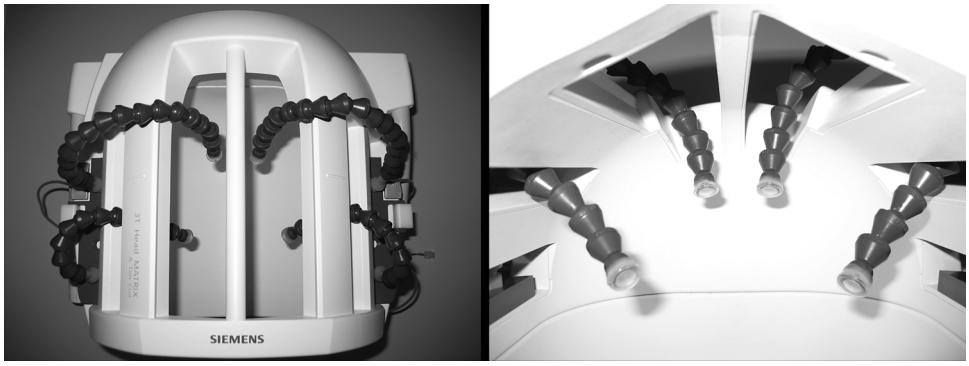

Fig. 2. Somatosensory stimulation device used in the current study. Tactile stimuli were delivered to the bilateral face by balloon diaphragms driven by compressed air. The left image shows a view from the top of the head coil, while the right image shows the view into the head coil.

2.4. Preprocessing of functional data (resting state and functional paradigms)

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 [23] to report MNI coordinates, and smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel.

2.5. fMRI analysis of the functional paradigms

A multiple regression analysis using a general linear model was performed to obtain statistical parametric maps calculated for motor tasks and sensory stimulation. Functional MRI signal time courses were high-pass filtered (128 s) and modeled as an experimental stimulus onset function, convolved with 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 a standard stereotaxic atlas and by visual inspection of the individual T1-weighted structural data. Family-wise error rate (FWE; $p < 0.05$) served as the threshold for the resulting statistical maps.

2.6. Connectivity analysis of resting state data

Functional connectivity is a measurement of the temporal correlations of low-frequency (< 0.1 Hz) blood oxygenation level dependent (BOLD) fMRI signal fluctuations between distinct brain areas [24,25]. Most studies examine functional connectivity in the resting state, where these BOLD fluctuations are presumed to relate to "spontaneous" neural activity and reflect information transfer and collaboration between brain areas [24,26]. Changes in functional connectivity within the facial motor network were investigated in the resting state. To identify relevant areas of the facial motor network, 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 ($0.01 < f < 0.1$ Hz) to reduce the effect of low-frequency drift and high-frequency noise.

We estimated the functional connectedness using correlation analysis between different ROIs. The spatial locations of these ROIs were determined using the clusters activated during the motor task and the somatosensory stimulation paradigm in the random effect fMRI analysis. Regions of the basal ganglia and the motor and somatosensory subregions of the thalamus were extracted using probabilistic atlases [27,28]. Due to the multitude of thalamic subregions, the associated multiple comparison problems and to stay in line with our research

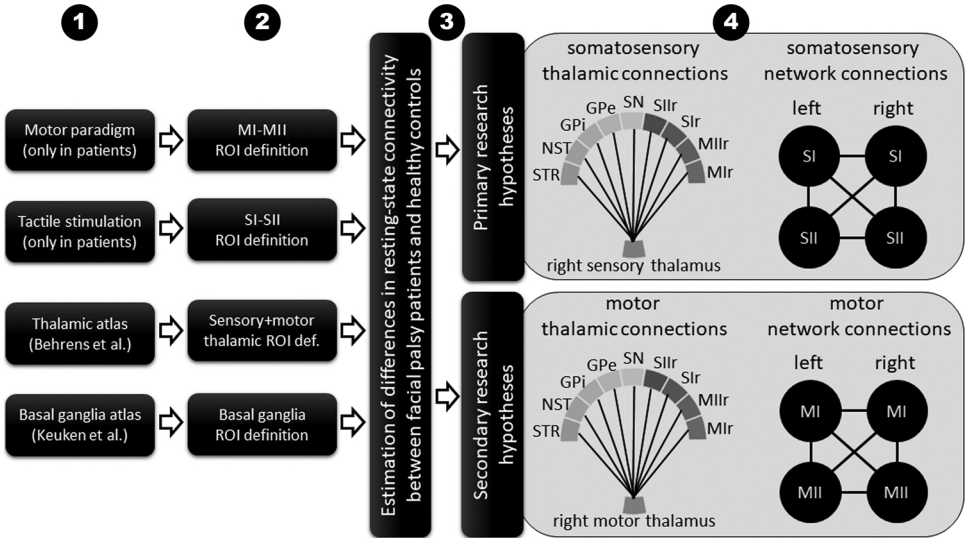

Fig. 3. Schematic of ROI definitions and their contributions to the primary and secondary research hypotheses. The first column (column 1, left) provides information about the origin of the different ROI definitions that are shown in the second column. This spatial information was then used for the estimation of the functional connectivity that was then tested for differences between the group of facial palsy patients and healthy controls to test our primary and secondary research hypothesis (column 3). The right part of the figure (column 4) shows an outline of the constructed networks that were tested.

hypotheses, we decided to use only the somatosensory and the motor subregion of the thalamus-atlas as ROIs (see Fig. 3 for a schematic of the ROI definitions and their contribution to our research hypotheses). In general, Pearson's correlation coefficient was computed between different ROIs for each subject. The resulting coefficients were transformed to z-scores by Fisher's r-to-z transformation. The z-scores were analyzed by two-sample t-tests to determine whether the two groups (healthy vs. facial palsy) showed a significantly different functional connectivity.

To answer our first primary research hypothesis, we tested for group differences in the functional connectivity of the whole facial cortical somatosensory network. That means that we first estimated the global connectivity of the somatosensory network by averaging the Pearson's correlation coefficients across all connections between areas of the facial cortical somatosensory network for each subject (bilateral SI and bilateral SII (see Fig. 3)). These global network connectivity values were then tested for differences between groups. In addition to this network connectivity value, we tested for differences between individual connections.

To test our second research hypothesis of an altered connectivity of the somatosensory part of the thalamus, we tested for group differences of the somatosensory thalamic connections to the cortical somatosensory areas (SI and SII), to the cortical motor areas (bilateral MI and MII) and to five areas of the basal-ganglia (see Fig. 3 for details). According to our hypothesis we restricted the analysis of thalamic connectivity to the right hemisphere (contralateral to facial palsy).

To investigate our secondary research hypothesis regarding the involvement of the motor network all above analyses were additionally performed for the motor network (MI and MII) and for the motor part of the thalamus (see Fig. 3). Given the resulting number of statistical tests, a correction for multiple tests was necessary, and accordingly, all results were corrected by the Bonferroni correction and considered significant at $p < 0.05$.

3. Results

3.1. Clinical assessment of facial function

During the acute state of Bell's palsy, all patients showed a left-sided loss of facial function, with Stennert grades ranging between 0 and 4 (mean 1.6 ± 1.3) and activity indices ranging between 1 and 6 (mean 3.8 ± 1.9). All patients reported normal taste and hearing.

3.1.1. fMRI

All patients performed a facial motor task and received bilateral tactile stimulation of the face. The tactile stimulation evoked highly significant activations in the random effect analysis ($p < 0.05$, FWE corrected, Fig. 4). At this significance level, the bilateral SI and bilateral SII were found to be activated. The bilateral motor task also evoked highly significant activations ($p < 0.05$, FWE corrected) in all patients. The random effect group analysis revealed significant activations in the bilateral MI, bilateral LPMCv (MII), bilateral ACC, bilateral SMA, and bilateral putamen (Fig. 4). The t-values and MNI coordinates with standard deviations for the random effect analyses of the motor task and the sensory stimulation paradigm are summarized in Tables 1 and 2, respectively. The spatial locations of activated clusters were further used in the following connectivity analysis.

3.2. Functional connectivity

We estimated the functional connectivity in the resting state between cortical brain regions that were activated during the somatosensory and motor tasks, as well as the subcortical regions of the basal ganglia and thalamus, for which spatial locations were derived from open available atlases [28,29]. The functional connectivity was estimated for all subjects and compared between both groups (patients with facial palsy and healthy control subjects) by a two-sample t-test.

3.3. Cortico-cortical functional connectivity

First, we tested whether there was an overall disturbed connectivity in patients compared with healthy controls in the motor and somatosensory network. Both networks showed a significantly decreased functional connectivity in facial palsy patients compared with controls (motor network $p = 0.0013$, somatosensory network $p = 0.0071$, Fig. 5). The strength of the connectedness in the motor network showed a significant correlation with the strength of the connectedness in the somatosensory network in the patient group ($r = 0.59$, $p = 0.0026$) but not in healthy subjects ($r = 0.013$, $p = 0.95$, Fig. 6).

We further investigated differences between groups of the individual connections in both networks. To reduce the number of tests and to be in line with our primary research aim, we limited the connection analysis to between the primary and secondary motor and somatosensory areas (MI, MII, SI, and SII, respectively). In both networks, we found multiple connections that showed a significantly reduced (Bonferroni corrected) connectivity (Fig. 7). We further investigated the inter-network connectivity between the motor and the somatosensory networks. We found a reduced connectedness in patients compared to healthy subjects between the right SI and each motor area (Fig. 7).

3.4. Thalamic connectivity

According to our hypothesis, we restricted the analysis of thalamic connectivity to the right hemisphere (contralateral to facial palsy). We estimated the functional connectivity between the two thalamic subregions and five subareas of the basal ganglia (the substantia nigra, globus pallidus externus, globus pallidus internus, nucleus subthalamicus, and striatum), as well as between the thalamus and the primary and secondary somatosensory motor and somatosensory areas. After correction for multiple comparisons, we found a significantly ($p < 0.05$) increased connectivity in patients compared to healthy controls between the motor thalamus and the globus pallidus externus, striatum, as well as to the secondary motor area. The somatosensory thalamus showed significantly increased connectivity to the striatum and the secondary somatosensory area ($p < .05$, corrected for multiple comparisons). Additionally, both thalamic subregions showed significantly decreased connectivity to the contralateral (left) cerebellum.

3.5. Clinical correlation

Logistic regression was performed to examine the association of clinical severity of symptoms and the strength of the connectedness in the somatosensory and motor networks, as well as the thalamic connectivity. The age of the patient was also entered into this model. To use a binomial regression model, we divided the patients into two groups of similar numbers (less affected and stronger affected, Stennert activity score > 4). We found a significant association between the clinical severity of the facial palsy and decreased connectedness of the motor system ($p < 0.05$). The parameters of age ($p = 0.97$), somatosensory connectivity ($p = 0.41$) and thalamo-cortical connectivity ($p = 0.17$) failed to show significant associations with the clinical severity of symptoms.

4. Discussion

The current study demonstrates that a peripheral deefferentation affects not only the motor system but also the somatosensory system at the cortical and subcortical level. Particularly, we found a reduced functional connectivity in the somatosensory cortical system, while the thalamo-cortical connectivity was increased.

In the acute stage of a facial palsy, patients are limited in their ability to move one side of the face due to a lesion of the peripheral

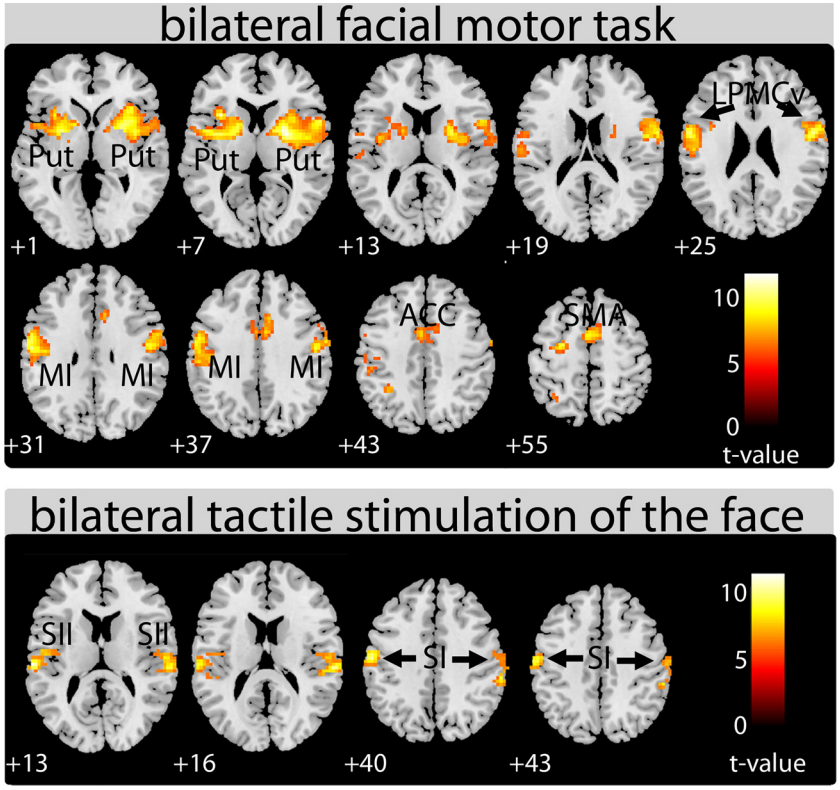

Fig. 4. Random effects group analysis of facial sensory and motor activity of patients suffering from a facial nerve palsy. The upper part of the image shows significant activations ($p < 0.05$, FWE corrected) in response to blocked (30 s) movement of both sides of the face (see also Table 1 for spatial location and t-values). The lower part of the image shows activations ($p < 0.05$, FWE corrected) in response to a tactile stimulation of both sides of the face (MI: primary motor cortex; LPMCv: ventral lateral premotor cortex (MII); SMA: supplementary motor area; ACC: anterior cingulate cortex; r: right; l: left).

Table 1
MNI coordinates of activation maxima with corresponding t-value and standard deviation for the bilateral facial motor task (MI primary motor cortex, LPMCv ventral lateral premotor cortex, SMA supplementary motor area, ACC anterior cingulate cortex, r right, l left).

	bilateral motor task			
	x	y	z	t-value
MI r	51 ± 4.1	−10 ± 4.2	34 ± 3.3	10.8
MI l	−57 ± 4.2	−10 ± 4.5	31 ± 3.5	9.7
LPMCv r	57 ± 4.6	5 ± 4.2	22 ± 4.4	9.0
LPMCv l	−57 ± 4.8	5 ± 4.1	25 ± 5.3	8.1
SMA r	6 ± 2.6	2 ± 3.9	55 ± 4.1	8.4
SMA l	−3 ± 2.4	2 ± 3.2	55 ± 3.3	9.3
ACC r	6 ± 2.3	5 ± 4.2	37 ± 3.5	8.8
ACC l	−3 ± 2.5	5 ± 4.1	40 ± 3.6	8.6
Putamen r	−27 ± 3.0	2 ± 3.1	1 ± 2.8	10.1
Putamen l	27 ± 2.5	5 ± 3.4	4 ± 3.5	11.7

MNI coordinates of activation maxima with corresponding t-value and standard deviation for the bilateral facial motor task (MI primary motor cortex, LPMCv ventral lateral premotor cortex (MII), SMA supplementary motor area, ACC anterior cingulate cortex, r right, l left).

Table 2
MNI coordinates of activation maxima with corresponding t-value and standard deviation in response to bilateral tactile stimulation of the face (SI primary somatosenosry area, SII secondary somatosensory cortex, r right, l left).

	Bilateral tactile stimulation of the face			
	x	y	z	t-value
SI r	57 ± 4.1	−16 ± 4.6	40 ± 3.4	10.6
SI l	−57 ± 4.2	−13 ± 4.0	43 ± 3.4	7.8
SII r	60 ± 2.5	−25 ± 3.6	16 ± 2.8	10.4
SII l	−63 ± 3.4	−22 ± 4.5	13 ± 2.7	11.4

MNI coordinates of activation maxima with corresponding t-value and standard deviation in response to bilateral tactile stimulation of the face (SI primary somatosenosry area, SII secondary somatosensory cortex, r right, l left).

motor nerve. When considering the possible implications for the brain, it is important to note that the brain is unable to “detect” whether the reduced somatosensory feedback (due to the minor facial movements) is caused by disturbances of the efferent or the afferent signal. The brain only detects a divergence between motor "command" and sensory feedback but is blinded to the source of this mismatch. In this context, a peripheral deafferentation due to facial nerve palsy can be regarded as a general example of how the brain reacts to a sensory-motor divergence. Previous studies demonstrate that this divergence causes altered motor activation patterns [17,18,20] and reduced functional connectivity in the motor network, as well as in areas with higher integrative roles [14–16]. The current study replicates these findings and extends them by demonstrating that the functional connectivity is also reduced in the cortical somatosensory system. These results are in line with previous studies demonstrating that the size and connectivity of the primary somatosensory hand area is affected by a facial palsy [13,30]. A more recent study has demonstrated a decreased intrinsic connectivity in a cortical area that comprises the somatosensory and motor representation (SI/MI) of facial function contralateral to a facial palsy [19]. These findings suggest that not only the processing of motor information but also the processing of somatosensory information is affected in the acute stage of facial palsy. Moreover, analysis of the inter-network connectivity shows that communication between these systems is also affected. The decreased connectivity is focused on connections between the contralateral SI and the primary and secondary motor areas. However, the decreased connectivity in the motor network was bound to the connectivity decrease of the somatosensory network in patients but not in healthy controls. These results indicate that the information transfer between the somatosensory and motor cortices is already affected at a very early stage in the somatosensory processing hierarchy. If we interpret the reduced connectivity as correlate for a reorganization process [31], these results also indicate that the amount of reorganization in the motor system is tightly bound to the amount of

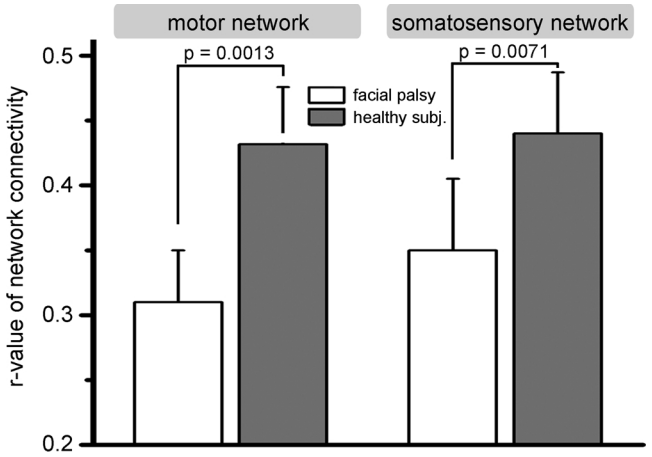

Fig. 5. Functional connectivity of the motor network (left) and somatosensory network (right). The R-values of the functional connectivity (Pearson correlation) between all areas within a network were averaged in each subject. These network-specific averaged connectivity values were then tested for differences between patients (white columns) and healthy controls (gray columns) by a two-sample t-test. Both networks showed a significant lower connectivity value in patients compared to the healthy controls (motor network p = 0.0013, somatosensory network p = 0.0071).

reorganization in the somatosensory system. One possible explanation for this observation is that the adaptation processes are driven by the somatosensory-motor mismatch that originated from the comparison between expected (motor) and perceived (somatosensory) information. The resulting mismatch error has validity for both systems, and it therefore seems plausible that the strength of the reorganization process is coupled between both systems. However, as an alternative explanation, it is well conceivable that maladaptive motor plasticity causes an altered somatosensory functioning that is correlated by the dense interconnections between the primary motor and primary somatosensory cortex.

Considering the thalamus, we found an altered connectivity to the basal ganglia, to the cerebellum as well as to the secondary somatosensory and motor areas. From the increased thalamic connectivity alone, one would expect an increased amount of information transfer and processing. The finding that the thalamo-cortical connectivity is mainly altered to secondary areas further suggests an active role of the thalamus as driver of somatosensory adaptation at a higher processing level, which is in line with previous results of altered cortico-cortical connectivity to higher brain areas in facial palsy [14,16]. The increased connectivity between the basal ganglia and thalamus should be interpreted with respect to the critical role of the basal ganglia in learning new motor behaviors [32,33]. A previous study has shown an increased connectivity between the basal ganglia and the motor cortex in facial palsy [34], which was discussed as a correlate to an ongoing motor adaptation to solve the sensory-motor mismatch problem. The current results suggest, in analogy to the motor system, a role of the thalamus as the driver for a changed interpretation of somatosensory signals and that the process of adaptation is coupled between the motor and somatosensory systems by connections between the basal ganglia and the thalamus.

A further crucial structure involved in processing and adaptation of sensorimotor mismatch errors is the cerebellum [40,41,43,12]. The cerebellum is thought to be important for the formation of internal models of motor actions [42] and for monitoring motor errors [44]. Accordingly, there are studies available demonstrating the involvement of the cerebellum in sensory-motor mismatch adaptation during the course of facial palsy [15,16,34,19,45]. These studies demonstrated decreased cerebellar connectedness to the dorsal caudate nucleus [34,19], and to the default mode network [16]. Other studies demonstrated increased cerebellar activity during facial motor practice with the impaired side in the acute stage [15] and after recovery of motor symptoms [45]. In the current study, we extend this knowledge by demonstrating a decreased connectivity between the cerebellum ipsilateral to the facial palsy and the contralateral motor and somatosensory parts of the thalamus. Interestingly, we did not find an altered connectivity between the cerebellum and the investigated basal ganglia regions. Although, the strong involvement of the cerebellum in monitoring and adapting to sensorimotor mismatch errors might suggest an altered information transfer between the striatum and the cerebellum, this was not found in the current study. However, the same result of an unaltered striato-cerebellar connectivity was also found by a previous study [34,19]. Taken together, the finding of an altered thalamo-cerebellar but unaltered basal ganglia-cerebellar connectivity also supports the hypothesis that in the acute stage of facial palsy, the inability to solve the sensory-motor mismatch by adaptation motor actions (due to the peripheral palsy) leads to a pronounced adaptation of the interpretation of somatosensory signals.

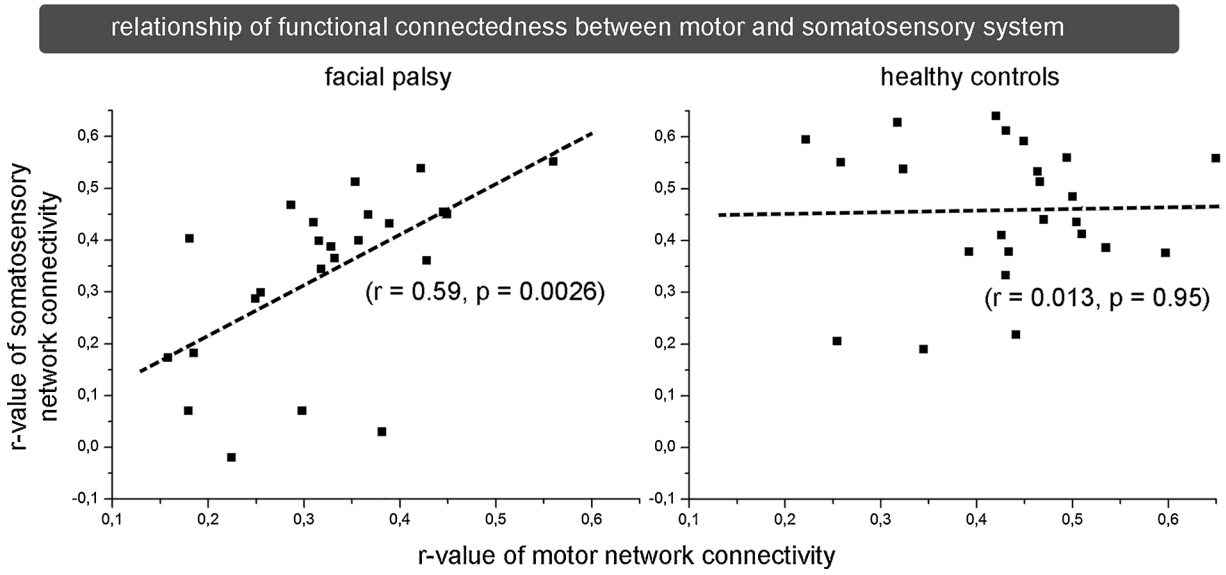

Fig. 6. Correlation between functional connectivity of the motor and somatosensory systems. In patients suffering from facial palsy, the motor and somatosensory connectivity was significantly correlated (r = 0.59, p = 0.0026), while in healthy subjects, no significant correlation was found (r = 0.013, p = 0.95).

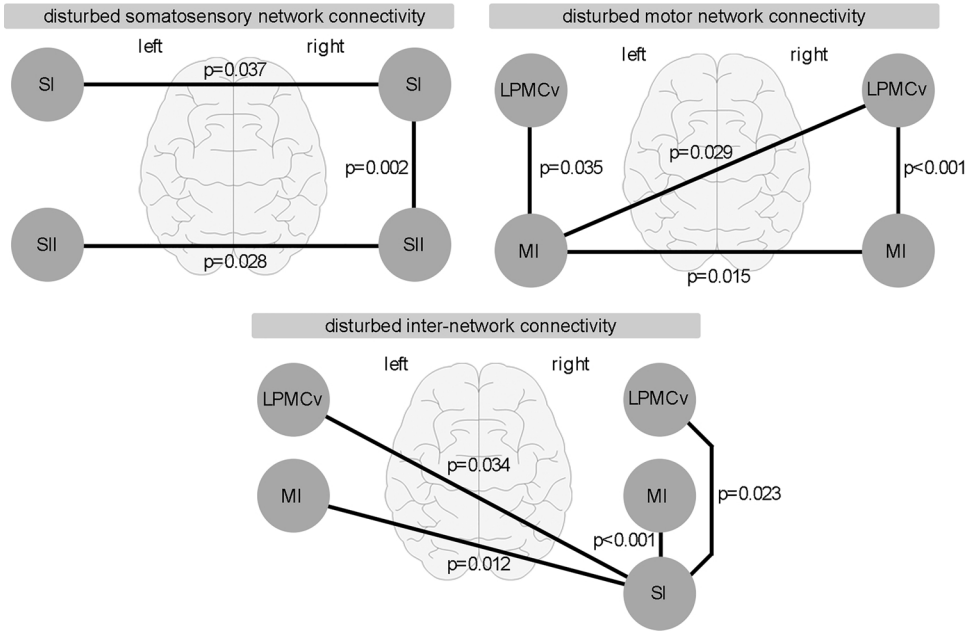

Fig. 7. Functional connectivity was measured in the motor and somatosensory networks between each combination of areas. These values were analyzed for group differences by two-sample t-tests. The black lines mark connections between areas that showed a significantly ($p < 0.05$, Bonferroni corrected) reduced functional connectivity in patients compared with healthy controls. The lower part of the image shows the same analysis for internetwork connections (each area of the somatosensory network with each area of the motor network). The black lines mark connections between areas that showed a significantly ($p < 0.05$, Bonferroni corrected) reduced functional connectivity in patients compared with healthy controls.

A further interesting finding that should be discussed is the divergence between decreased cortico-cortical connectivity and increased subcortical-cortical connectivity. Previous studies have shown that the strength of functional connectivity changes with behavioral performance. In most cases, it is increased during healthy motor learning, while it is decreased after stroke, particularly after a stroke-associated loss of function [35]. At first glance, it seems obvious that functional connectivity should be reduced in the affected systems of facial palsy patients corresponding to reduced behavioral function. However, the sensory-motor mismatch signal during facial palsy can also theoretically be regarded as a learning paradigm of a healthy brain in the case of a mismatch signal. This point of view encourages discussion of the question regarding the difference between a learning paradigm with an artificially generated somatosensory-motor mismatch [e.g., a force field-induced mismatch [36–38]] and the adaptation process following an acute facial deefferentation. In the former case, an increased functional connectedness is found within the somatosensory-motor network [38,39], while facial palsy causes a reduced connectedness. The difference between them is that in the force field adaptation paradigm, there is a positive learning process (the mismatch error reduces during adaptation), while in the case of a facial palsy, the mismatch error cannot be easily reduced by motor adaptation and remains mainly unaltered. Therefore, we speculate that the increased connectivity at the subcortical level indicates the presence of an ongoing adaptation process, while the decreased connectivity found in the cortical sensory-motor system corresponds to an unsuccessful adaptation process. This further suggests that increased functional connectivity, at least at the cortical level, is not simply an equivalent for an increased information transfer during "trying to learn" but is bound to an effective feedback-loop and the reduction of mismatch errors.

4.1. Limitations and strengths of the current study

One main limitation of the current study is the testing of a high number of hypotheses, and with this comes the necessity of corrections for multiple comparisons. These corrections have reduced the sensitivity of our analyses. However, this is partly compensated by the high number of subjects. Moreover, this is the first study that used motor and somatosensory tasks for the exact localization of the involved brain areas. It is also the first study investigating this disease by using only subjects with only left-sided palsies. All previous studies have used left- and right-sided facial palsies. The avoidance of flipping the data from half of the subjects in the current study has possibly increased the sensitivity of the current results. A further limitation is that the motor- and somatosensory stimulation paradigm was performed only in patients and not in healthy controls. Therefore, it cannot be excluded that the spatial location of activation maxima might have moved due to the facial palsy.

5. Conclusion

In conclusion, we demonstrate the involvement of the somatosensory system and the thalamus in the adaptation process following an acute peripheral deefferentation. The investigated network shows the principal pattern of a reduced connectivity between cortical areas, while the connectivity to subcortical areas (basal ganglia and the thalamus) is increased. We suggest that the increased connectivity between the basal ganglia, thalamus and cortex indicates an active sensory-motor adaptation process. We further hypothesize that the decreased functional connectivity at the cortical level reflects an unsuccessful sensorimotor adaptation process due to the inability to solve the somatosensory-motor mismatch. These results extend our understanding of the somatosensory-motor interaction in response to a mismatch signal and underline the importance of the thalamus in this process.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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