Perceptual Plasticity Is Mediated by Connectivity Changes of the Medial Thalamic Nucleus

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Abstract: It is well known that the threshold for somatosensory perception may adapt to different inputs. Recent studies suggest the presence of a modulating effect of somatosensory inputs on the spinal dorsal horn. However, the effects of somatosensory inputs on cerebral processing and, in particular, on the functional and effective connectivity of the somatosensory brain network, are poorly understood. In this study, we investigated the longitudinal impact of somatosensory stimuli on the resting-state functional connectivity and effective connectivity of the somatosensory brain network. We performed resting-state functional magnetic resonance imaging (fMRI) in 12 healthy subjects before and after unilateral electrical median nerve stimulation. We combined this analysis with a psychophysiological examination of changes of the perception threshold. We found that the unilateral median nerve stimulation increased the perception thresholds bilaterally and increased the resting-state functional and effective connectivity between most cortical areas of the somatosensory network. The major finding, however, was a decreased resting-state functional connectivity between both secondary somatosensory cortices and the bilateral medial nuclear complex of the thalamus. This decreased connectivity was correlated with increased perception thresholds. These findings emphasize the importance of the medial thalamic nucleus for the perceptual awareness of somatosensory stimuli. *Hum Brain Mapp* 34:2343–2352, 2013. © 2012 Wiley Periodicals, Inc.

Key words: fMRI; BOLD; somatosensory cortex; functional connectivity; perception

INTRODUCTION

One of the most remarkable features of the central nervous system is its ability to adapt to new situations and to new information. This general principle applies to all sensory systems, including the perception of somatosensory stimuli. It is well known that the threshold for somatosen-

sory perception may adapt to different inputs. Repetitive stimulation at low intensities may decrease the perception threshold, thereby increasing sensitivity to such stimuli [Blankenburg et al., 2003]. In contrast, several studies have shown that strong stimulation may increase the perception threshold, causing a decrease in the sensitivity to such stimuli [Kastrup et al., 2008; Klingner et al., 2010]. These effects may outlast the stimulation period for a minimum of several hours. Based on the “gate-control” theory, this type of decreased sensitivity is often attributed to the inhibitory effects in the spinal cord [Melzack and Wall, 1965]. Spinal excitability is regulated by both local segmental and descending supraspinal mechanisms, which may originate from different brain regions (for a review, see [Heinricher et al., 2009]). However, the role of the somatosensory brain network in the regulation of this mechanism is unknown. Previous studies have found that there are persistently decreased activation amplitudes after

Contract grant sponsor: BMBF; Contract grant number: 01GZ0306.

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Received for publication 17 July 2011; Revised 1 February 2012; Accepted 13 February 2012

DOI: 10.1002/hbm.22074

Published online 25 March 2012 in Wiley Online Library (wileyonlinelibrary.com).

repetitive, strong somatosensory stimulation [Golding et al., 1986; Hoshiyama and Kakigi, 2000; Kara et al., 2010]. Although these studies have also shown that less information reaches the cortex, it remains unclear how the brain is involved in this mechanism. To this end, it would be interesting to determine if the transfer and synchronization of information that has changed within the brain occurred along with the perceptual changes. If the underlying mechanism was purely peripheral, one would expect that after the somatosensory stimulation ceased, the information transfer within the somatosensory network remains unchanged. However, if the somatosensory brain network was engaged in changing the perceptual sensitivity, one would expect sustained changes in brain structures, such as the thalamus, that are able to modulate the forwarding of information.

To address this question, we measured the functional connectivity of the somatosensory network. This parameter is defined as the temporal correlations between spatially remote neurophysiological events [Friston et al., 1993]. In addition, the strength of functional connectivity has, for example, been found to be associated with motor learning during task execution [Sun et al., 2007] and also in the resting-state [Albert et al., 2009; Barnes et al., 2009]. Correlations between the resting-state functional connectivity and individual task performance were also found for other cognitive functions, including working memory [Hampson et al., 2006], visual perceptual learning [Lewis et al., 2009] and face processing [Zhu et al., 2011]. Additionally, we performed a granger causality analysis to investigate the direction and causality of possible changes within the somatosensory brain network.

In the present study, we used a combination of functional magnetic resonance imaging (fMRI) and psychophysiological approaches to analyze the changes in resting-state functional and effective connectivity induced by repetitive electrical stimulation of the median nerve and the corresponding changes in somatosensory perception.

MATERIALS AND METHODS

Subjects

Fourteen healthy volunteers without any history of neurological or psychiatric diseases participated in this study. Two subjects fell asleep during the experiment and were excluded from further analyses, resulting in a final study group size of 12 volunteers (mean age 22.8 ± 1.9 years, five female, seven male). All of the subjects were right-handed according to the Edinburgh Handedness Inventory [Oldfield, 1971]. This study was approved by the local ethics committee, and all subjects gave their written, informed consent in accordance with the Declaration of Helsinki.

Experimental Protocol

Initially, all of the subjects underwent a resting-state fMRI scan followed by a somatosensory stimulation para-

Figure 1.

The experimental design. All subjects underwent a somatosensory stimulation paradigm. Before and after this stimulation paradigm, a resting-state scan, along with a psychophysiological examination of the current perception threshold (CPT), was conducted (fcMRI: functional connectivity MRI).

digm. After the stimulation paradigm, a second resting-state scan was completed. After each resting-state scan, a psychophysiological examination of the current perception threshold (CPT) was conducted (Fig. 1). At the end of the experiment, T1-weighted structural images were acquired.

Somatosensory Stimulation Procedures

An electrical median nerve stimulus was used to localize activation and deactivation patterns within the contralateral and ipsilateral primary somatosensory cortices (SI). The stimulus, generated by a clinical neurostimulator (Digitimer Constant Current Stimulator model DS7A), consisted of 100 Hz monophasic square-wave pulses with a duration of 200 μ s and was unilaterally applied to the right wrist. An electrode paste was applied to reduce electrical resistance at the contact between the electrode and then skin. The stimulus intensity applied during the experiment was determined individually for each subject. First, the motor threshold for thumb movement was determined. At this current intensity, no subject reported an unpleasant or painful perception. We then reduced this current by 10% to exclude any motor response and used this value as the stimulus intensity for that individual during the experiment. At this intensity, all participants self-reported a non-painful tingling in the hand (mean stimulus intensity 4.9 ± 1.1 mA). A total of 32 stimuli were pseudo-randomized and presented to subjects in a block-related regime (30 s on/30 s off). The timing of stimulus presentations was externally controlled by the MR scanner and was synchronized to image acquisition.

fMRI Recordings

Images were acquired on a 3.0 Tesla MR scanner (Trio, Siemens, Erlangen, Germany). We obtained echo-planar T2* weighted image volumes (EPI) and transaxial T1-weighted structural images. The functional resting-state data were acquired in two EPI sessions of 163 volumes each. Between both resting scans, 973 EPI images were acquired. The first three EPI volumes were discarded due to equilibration effects. A functional image volume was comprised of 40 transaxial slices obtained during the resting-state and 20 transaxial slices obtained during the stimulus paradigm.

The resting-state scans included the whole cerebrum and cerebellum, whereas the stimulus-associated scans included the upper part of the cerebrum down to secondary somatosensory cortex (SII; voxel size = 3 mm × 3 mm × 3 mm, repetition time = 2 s, TE = 35 ms). The high-resolution, T1-weighted structural images had a voxel size of 1 mm × 1 mm × 1 mm to allow for precise anatomical localization.

Data Analysis

The data analysis was performed on a workstation using MATLAB (Mathworks, Natick, MA) and SPM8 software (Wellcome Department of Cognitive Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). For each subject, all images were realigned to the first volume using a six-parameter, rigid-body transformation to correct for motion artifacts. The images were coregistered with the subject's corresponding anatomical (T1-weighted) images, resliced 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.

fMRI Analysis of the Somatosensory Paradigm

A multiple regression analysis using a general linear model was performed to obtain statistical parametric maps calculated for the somatosensory stimulation. The fMRI 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). Two contrasts of interest were examined, resulting in two t-statistic maps (i.e., stimulus > rest (1 0) and stimulus < rest (-1 0)). Individual results were projected onto their respective coregistered, high-resolution T1-weighted 3D data set. The anatomical localization of activated areas 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 (FDR; $P < 0.05$).

Functional Connectivity Analysis

The changes in functional connectivity within the somatosensory network induced by somatosensory stimulation were investigated in the resting-state. We were particularly interested in the analysis of the bilateral SI and SII. The anatomical localization of each area was determined by referencing the standard stereotaxic atlas and was mapped using the anatomical toolbox of the SPM program [Eickhoff et al., 2005, 2006] (http://www.fz-juelich.de/ime/spm_anatomy_toolbox). The point of maximum activation strength within each area (or deactivation strength for the ipsilateral SI), along with its 26 neighboring voxel, was

selected from the group analysis of the stimulation task. The resting-state data from these identified regions of interest (ROIs) were extracted, and then cluster-specific time series were estimated by averaging the time series of all voxels within a cluster. Several sources of variance were removed from the data by linear regression, as follows: (1) six parameters obtained by rigid body correction of head motion, (2) signal from a ventricular region of interest, and (3) signal from a region centered in the white matter [Weissenbacher et al., 2009]. All signal intensity time courses were band-pass filtered ($0.01 < f < 0.1$ Hz) to reduce the effects of low-frequency drift and high-frequency noise. The Pearson correlation coefficients were computed between the bilateral SI/SII clusters and all other voxels of the brain and then converted to z-values by the Fisher r - to z-transformation, resulting in four z-maps. To test for differences between the two resting-state scans, we used paired t tests to compare the z-map of the first scan with the corresponding z-map of the scan performed after the somatosensory stimulation for each subject. The findings in the resulting group map were considered significant at $P < 0.05$ (FDR-corrected cluster threshold).

Estimation of Time-Dependent Changes in the BOLD Response

We were interested in the strength of the blood-oxygen-level-dependent (BOLD) signal responses in activated/deactivated areas of the somatosensory network during the stimulation task. We used the same ROIs (27 voxels for each area) as they were defined in the connectivity analysis (bilateral SI and SII). The time course of these voxels was extracted and then used to calculate the percent change in amplitude of the BOLD response for each of the 32 stimulation blocks. To account for baseline drifts, all of the time courses were subtracted by the last value prior to the start of each specific stimulation block. These 32 time courses were then divided into three parts, consisting of stimulus blocks 1–10, 11–22, and 23–32. For the first and the last part of the experiment, the mean amplitude was calculated across these blocks and across all subjects. To assess the time-dependent change in the BOLD amplitude, the difference between the amplitude in first and last part of the experiment was estimated. Finally, paired t tests were used to assess statistically significant differences in the BOLD amplitude between the first and the last part of the experiment.

Conditional Granger Causality Analysis

Conditional granger causality analysis (CGCA) is an approach used to explore the dynamic causal relationship between time series [Granger, 1969]. This approach has been widely used in previous fMRI studies [Goebel et al., 2003; Liao et al., 2010; Roebroeck et al., 2005; Zhou et al.,

2011]. In our current study, the CGCA was performed using the Granger causal connectivity analysis toolbox implemented by Seth [2010a]. The detailed theory behind Granger causality is described elsewhere [Granger, 1969; Seth, 2010a; Seth and Edelman, 2007]. However, a brief introduction of the Granger procedure is provided below.

The fundamental idea is that a time course X_1 causes the time course X_2 , if the knowledge of X_1 helps predict the future of X_2 . In a linear regression model of X_1 and X_2 , X_1 causes X_2 if the inclusion of past observations of X_1 reduces the prediction error of X_2 , compared to a model which includes only previous observations of X_2 . The bivariate autoregressive model can be written as

$$\begin{aligned} X_1(t) &= \sum_{j=1}^p A_{11} X_1(t-j) + \sum_{j=1}^p A_{12} X_2(t-j) + \varepsilon_1(t) \\ X_2(t) &= \sum_{j=1}^p A_{21} X_1(t-j) + \sum_{j=1}^p A_{22} X_2(t-j) + \varepsilon_2(t) \end{aligned}$$

where P is the maximum number of lagged observations included in the model. The matrix, A , contains the coefficients of the model, and ε represents the residuals. The magnitude of the interaction between X_2 and X_1 can be measured using the equation:

$$F_{1 \rightarrow 2} = \ln \frac{\text{var}(\varepsilon_2)}{\text{var}(\varepsilon_1)}$$

This model can be generalized in the context of multiple additional variables $X_3 \dots X_n$ [Seth, 2010a]; this is named “conditional granger causality.”

Using the Akaike information criterion, we found that two was the optimum number of time-lags (P) to be included in the analysis. We used six time courses of six different ROIs into the analysis, including the four time courses used for the estimation of the functional connectivity and the two time courses from ROIs in the medial part of the thalamus (see the results for their spatial location). The influence that one of the selected brain regions can exert over another was estimated for both resting-state scans and then analyzed for significant differences using a paired t test. Additionally, the autonomy of each selected brain area was estimated and was compared between both scans. The autonomy of a variable describes the extent that its own past helps predict its future and that these predictions are not accounted for by external variables [Seth, 2010a]. The autonomy is also considered to be the degree of self-determination of self-causation [Bertschinger et al., 2008; Seth, 2010a,b]. Findings were considered significant at $P < 0.05$ (FDR-corrected).

Psychophysiological Experiments During fMRI Experiments

To observe quantitative changes in somatosensory perception induced by electrical stimulation of the right me-

dian nerve, we used CPT, which is the minimum amount of transcutaneously applied current that an individual consistently perceives as an evoking sensation. This approach has recently been proposed as a suitable method for investigating sensory function [Blankenburg et al., 2003; Davey et al., 2001; Kastrup et al., 2008; Klingner et al., 2010; Yamashita et al., 2002].

Monophasic, square wave current pulses (100 Hz) were delivered via ring electrodes to the tip of the left index finger (anode-cathode separation ~ 1 cm). At the beginning of each CPT measurement, the current intensity was slowly increased until the subject reported feeling a sensation and then the current pulses were turned off. This assessment of CPT was performed ten times after each resting-state scan. A one-way analysis of variance for correlated samples was used to determine if there were differences in CPT values between measurements. Findings were considered significant at $P < 0.05$.

RESULTS

The Observations of Positive and Negative BOLD Responses

The electrical stimulation of the right median nerve evoked highly significant activations ($P < 0.05$, FDR-corrected) in the random effect group analysis (Fig. 2). These activations occurred in the following areas: contralateral (left) SI/MI ($x,y,z = -48, -21, 57$; $t = 9.3$), contralateral SII ($x,y,z = -42, -21, 18$; $t = 7.9$), and ipsilateral SII ($x,y,z = 54, -24, 21$; $t = 5.9$). We did not find significant activation within the ipsilateral SI in the group analysis; however, the most caudal part of the SI (Area 2), as well as Area 5, showed significant activation in 6 out of 12 subjects in the single-subject analysis. Significant ($P < 0.05$, FDR-corrected) negative BOLD responses were found in the ipsilateral SI ($x,y,z = 36, -24, 57$; $t = 6.1$).

Functional Connectivity

The functional connectivity for all resting-state data was investigated using a correlation analysis based on four ROIs positioned in the bilateral SI and SII. The spatial locations of these ROIs were individually determined according to the clusters activated by median nerve stimulation in the single-subject fMRI analysis. These maps were used to perform a paired t test (before and after median nerve stimulation) for the entire group to investigate increases and decreases in functional connectivity. Multiple cortical brain areas revealed a significantly increased connectivity to our seed regions in the second resting-state scan (after median nerve stimulation) when compared with the first scan obtained before median nerve stimulation (Table I, Fig. 3). These areas of increased connectivity to our ROIs were found within the somatosensory cortex, but also in areas of other sensory modalities (visual

Figure 2.

The random effect group analysis ($n = 12$) of BOLD responses. Activations and deactivations ($P < 0.05$, FDR-corrected) in response to a blocked (30 s) right median nerve stimulation are shown superimposed on an inflated brain. The yellow-red color positive BOLD signals, whereas blue encodes negative BOLD signals.

cortex, primary acoustic cortex). Moreover, we found increased connections to the motor network (MI, SMA) and to the anterior cingulate cortex.

We also investigated areas of decreased functional connectivity to our seed regions by comparing the second

resting-state scan with the first). We found a decreased connectivity of the contralateral SII to the bilateral thalamus. The ipsilateral SII also revealed a decreased connectivity to the bilateral thalamus (Table I, Fig. 4). The areas of decreased connectivity in the thalamus were located

TABLE I. Changes in functional connectivity after median nerve stimulation

Seed-region: SII c					Seed-region: SII i				
Brain region	x	y	z	t value	Brain region	x	y	z	t value
SI c	-48	-21	45	7.76	SIc	-42	-27	51	5.94
SI i	54	-18	48	5.58	SI i	54	-36	54	4.91
ACC i	9	-9	48	4.72	ACC i	9	-3	51	4.69
VPC c	-45	39	0	5.40	ACC c	-9	-3	45	5.85
VPC i	48	45	-6	6.46	PAC c	-48	-33	21	6.95
VC c	-18	-93	-3	5.21	SII/PAC i	51	-30	27	5.70
					VC i	45	-81	-6	4.75
fACC c	-6	54	6	5.84					
Thalamus c	-9	-24	6	6.63	Thalamus c	-9	-24	6	6.31
Thalamus i	6	-21	3	6.03	Thalamus i	6	-21	3	5.32
Cerebellum i	6	-57	-45	6.16					
Seed-region: SI c					Seed-region: SI i				
Brain region	x	y	z	t value	Brain region	x	y	z	t value
SI c	-33	-24	57	7.54	PCC c/i	-3	-18	51	8.18
SI i	42	-18	63	5.07					
MI c	-45	-15	54	7.23					
MI i	48	-12	57	5.64					
PCC c	-9	-18	39	4.58					
SMA c/i	-3	-18	57	5.95					
PAC c	-54	-33	12	4.98					
PAC i	66	-30	12	6.96					
VC c	-33	-90	-6	5.07					
VC i	18	-102	-3	5.88					

MNI coordinates of brain areas with significantly altered functional connectivity are shown with corresponding t values for right-sided median nerve stimulation. Decreases in functional connectivity are highlighted in grey. (SI: primary somatosensory cortex, SII: secondary somatosensory cortex, PCC: posterior cingulate cortex, ACC: anterior cingulate cortex, PAC: primary auditory cortex, VC: visual cortex, c: contralateral, i: ipsilateral).

Figure 3.

The random effect group analysis ($n = 12$) of connectivity increases. Each row shows areas of increased functional connectivity ($P < 0.05$, FDR-corrected) after somatosensory stimulation. The glass brains are shown from the right side (left image), from behind (middle image), and from above (right image).

mainly in the medial nuclear complex. Moreover, the SII contralateral to the median nerve stimulus showed a decreased connectivity to the frontal part of the anterior cingulate cortex and to the ipsilateral cerebellum (Table I, Fig. 4).

Estimation of Time-Dependent Changes in the BOLD Response

The time courses of the BOLD responses during the stimulation paradigm were divided into stimulation blocks 1–10, 11–22, and 23–32. The mean amplitude of the BOLD response for the first and the last portion of the paradigm was estimated for the four ROIs (bilateral SI and SII) and analyzed for significant differences. With the exception of the ipsilateral SI, all areas showed a significant reduction

in the BOLD amplitude between the first (stimulus blocks 1–10) and last (stimulus blocks 23–32) sections of the experiment (SIc $21.2\% \pm 32.6\%$; SIi $14.7\% \pm 24.9\%$; SIIc $32.6\% \pm 39.1\%$; SIIi $58.0\% \pm 46.1\%$; Fig. 5).

CGCA

We found multiple connections that displayed an increased conditional granger causality in the second scan when compared with the first scan. The SI and SII showed

Figure 4.

The random effect group analysis ($n = 12$) of connectivity decreases. The activation maps shows clusters of significantly ($P < 0.05$, FDR-corrected) decreased functional connectivity with the contralateral SII (upper half of the image) and the ipsilateral SII (lower half of the image). The glass brains are shown from the right side (upper left), from behind (upper right) and from above (lower left). Additionally, the activation map is superimposed on the axial slice of an individual T1-weighted image.

Figure 5.

The relative decay of the BOLD amplitude. The mean BOLD amplitude during median nerve stimulation was estimated for the first and the last portions of the experiment (stimulus blocks 1–10 vs. 23–32). The error bars represent the inter-subject standard deviation. Paired *t* tests were used to assess statistically significant decreases in the BOLD amplitude between the first and the last stimulus blocks (*P < 0.05; **P < 0.005).

an increased influence on each other in both hemispheres. Between hemispheres, only SII showed an increased influence on the SII of the opposite hemisphere. The medial thalamus, contralateral to the stimulation side, revealed an increased influence on the contralateral SI (Fig. 6). We did not find significant decreases in the conditional granger causality in the second scan when compared with the first scan. Analysis revealed an increased autonomy of the contralateral medial thalamus (*P* = 0.006), while the ipsilateral medial thalamus did not show significant differences (*P* = 0.088).

Psychophysiological Results During fMRI Experiments

Quantitative measures of somatosensory function were obtained directly after the acquisition of resting state images by determining the perception threshold for electrical stimulation of the left and right index finger (CPT). The CPT values for both hands significantly increased after median nerve stimulation was conducted, as compared with the first CPT measurement taken before median nerve stimulation (right hand: *P* < 0.005, mean increase 0.49 mA ± 0.27; left hand: *P* < 0.005, mean increase 0.36 mA ± 0.21). The increase in CPT showed a strong positive correlation with the individual decreases in resting-state functional connectivity between the SII and thalamus (Fig. 7). We found no significant correlations with both other areas of decreased functional connectivity [cerebellum (*r* = 0.034, *P* = 0.918) and anterior cingulate cortex (*r* = 0.24, *P* = 0.448)].

DISCUSSION

In our present study, we investigated the sustained effects of repetitive, unilateral stimulation of the median nerve on the somatosensory network. We combined the behavioral testing of somatosensory function with measures of functional and effective connectivity.

Electrical median nerve stimulation, as used in this experiment, produces robust activation in the contralateral SI and bilateral SII. This is in line with previous fMRI, positron emission tomography, and magnetoencephalography studies [Deuchert et al., 2002; Kampe et al., 2000; Karhu and Tesche, 1999; Nihashi et al., 2005; Ruben et al., 2006]. In addition, this activation is characterized by a positive BOLD response. Aside from areas of positive BOLD response, we found a negative BOLD response in the ipsilateral SI, also in line with recent reports [Hlushchuk and Hari, 2006; Kastrup et al., 2008; Klingner et al., 2011a,b]. These four areas were used as seed regions for a voxel-wise analysis of resting-state functional connectivity before and after repetitive stimulation of the median nerve.

As expected, repetitive somatosensory stimulation caused increases in the functional connectivity between areas in the somatosensory network. It is thought that increases in resting-state functional connectivity reflect increased synchronization of neuronal activity and

Figure 6.

Increased conditional granger causality was observed after median nerve stimulation. The conditional granger causality analysis was performed for both resting-state scans. The results were compared between each scan. We found multiple connections of increased conditional granger causality in the second scan when compared with the first scan (indicated by arrows). We did not find any significant decreases of the conditional granger causality in the second scan when compared with the first. The findings were considered significant at *P* < 0.05 (FDR-corrected; *P < 0.05; **P < 0.005; c/i: contralateral/ipsilateral to median nerve stimulation; SI: primary somatosensory cortex; SII: secondary somatosensory cortex; T: Thalamus).

Figure 7.

The correlation of decreased functional connectivity (x-axis) with the change in current perception thresholds (y-axis). On the left side of the figure, the correlation between the CPT of the right hand and the change in connectivity between the left thalamus and the bilateral SII is shown. On the right side of the figure, the correlation between the CPT of the left hand and the change in connectivity between the right thalamus and the bilateral SII is shown.

increased information transfer and collaboration between brain areas. Multiple studies have demonstrated a tight correlation between task performance and the strength of resting-state functional connectivity in the corresponding cortical network [Albert et al., 2009; Hampson et al., 2006; Lewis et al., 2009; Zhu et al., 2011]. Our additional analysis of the granger causality showed that the connectivity increases were mostly bidirectional, indicating an increased information flow along the known processing hierarchy (SI → SII), but also an increased feedback from higher somatosensory brain areas.

From these increased connections alone, one would expect an improved processing of somatosensory information and a decreased perception threshold. However, a decreased perception threshold was not observed in the psychophysiological data, and the stimulus-induced amplitudes decreased during the time of somatosensory stimulation. Our results, along with other reports of decreased activation amplitudes in the brain after repetitive electrical nerve stimulation [Golding et al., 1986; He et al., 2007; Hoshiyama and Kakigi, 2000; Kara et al., 2010], suggest

that input to the somatosensory cortical network is reduced. Therefore, we were particularly interested in decreases in resting-state functional connectivity that reflect decreased information transfer. Such decreases in resting-state functional connectivity were demonstrated to correlate with functional deficits [Carter et al., 2010; van Meer et al., 2010].

Many aspects of somatosensory information are conveyed to the somatosensory cortical network via the ventroposterior nucleus of the thalamus. No alterations of connectivity to this nucleus were found following repetitive stimulation. We did, however, find a decreased connectivity between the SII and the medial thalamic nuclei. It is well known that the left SII and right SII are strongly interconnected. In agreement with this, connectivity between the SII and the medial thalamic nuclei was decreased bilaterally after a unilateral stimulation of the median nerve. This is in agreement with the observation that a bilateral increase of the somatosensory perception threshold follows a unilateral stimulation of the median nerve.

Our results indicate that the medial thalamus is partially blocked from somatosensory information (increased autonomy after repetitive median nerve stimulation) while it exerts a stronger influence on the information processing completed by the primary somatosensory cortex (increased granger causality). This suggests that the correlation between reduced functional connectivity (SII-thalamus) and perceptual awareness is not only a side effect of a reduced forwarding of somatosensory information, but that the medial thalamus influences a portion of the somatosensory processing. However, it remains unclear whether this influence is exerted by a direct connection between the medial thalamus and the SI or if this influence is relayed by other brain regions. The current results are also compatible with an inhibitory influence of the medial thalamus on the ventroposterior nucleus of the thalamus, or even earlier stages of somatosensory processing, which could lead to a reduced forwarding of somatosensory information. A recent study provides evidence that psychological factors can influence nociceptive processing in the dorsal horn of the spinal cord in humans [Eippert et al., 2009]. This suggests the existence of an unknown descending pathway for cortical control of spinal excitability. The medial thalamic nucleus receives somatosensory inputs and is strongly connected to the periaqueductal gray, a brain region known to modulate spinal excitability (reviewed by [Heinricher et al., 2009]). This type of modulating effect of the medial thalamus would explain the inhibition of dorsal horn nociceptor cell activity by repetitive somatosensory stimuli [Garrison and Foreman, 1994, 1996, 1997; Sluka and Walsh, 2003].

Following repetitive median nerve stimulation, the functional connectivity from the somatosensory network was decreased not only to the bilateral median thalamus but also to the contralateral anterior cingulate cortex. This area has been described as an important entry point for the affective interpretation of perceptions [Price and Dubner, 1977; Vogt and Sikes, 2000]. One might therefore speculate that this decoupling contributes to reduced pain perception following median nerve stimulation. However, this hypothesis requires further experimental investigation.

Another interesting finding concerns the connectivity changes of somatosensory brain areas with areas of other sensory modalities, such as the acoustic cortex and the visual cortex. Although the visual cortex receives reduced information (eyes were closed during the measurement) and the acoustic cortex receives a high level of scanner noise, we found an increased synchronization of the somatosensory cortex to both areas. It might be expected that the forwarding of acoustic information is reduced in a similar way as for somatosensory information while the forwarding of visual information might be increased. However, this was not seen in the current data. A possible explanation might be that the reduced input of somatosensory information leads to a relative shift of the quantity of processed information within the somatosensory cortex toward cross modal information. This might explain the

resulting increased synchronization with other sensory modalities.

CONCLUSION

In summary, we have shown that changes in cortical functional connectivity in the somatosensory system correlates with perceptual plasticity. Specifically, strong unilateral somatosensory stimulation decouples both secondary somatosensory cortices from the medial thalamic nuclei, which could explain the observed bilateral change in perception threshold. These findings emphasize the importance of the medial thalamic nucleus for the perceptual awareness of somatosensory stimuli.

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