



Repetitive tactile stimulation changes resting-state functional connectivity—implications for treatment of sensorimotor decline

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Neurological disorders and physiological aging can lead to a decline of perceptual abilities. In contrast to the conventional therapeutic approach that comprises intensive training and practicing, passive repetitive sensory stimulation (RSS) has recently gained increasing attention as an alternative to counteract the sensory decline by improving perceptual abilities without the need of active participation. A particularly effective type of high-frequency RSS, utilizing Hebbian learning principles, improves perceptual acuity as well as sensorimotor functions and has been successfully applied to treat chronic stroke patients and elderly subjects. High-frequency RSS has been shown to induce plastic changes of somatosensory cortex such as representational map reorganization, but its impact on the brain's ongoing network activity and resting-state functional connectivity has not been investigated so far. Here, we applied high-frequency RSS in healthy human subjects and analyzed resting state Electroencephalography (EEG) functional connectivity patterns before and after RSS by means of imaginary coherency (ImCoh), a frequency-specific connectivity measure which is known to reduce over-estimation biases due to volume conduction and common reference. Thirty minutes of passive high-frequency RSS lead to significant ImCoh-changes of the resting state mu-rhythm in the individual upper alpha frequency band within distributed sensory and motor cortical areas. These stimulation induced distributed functional connectivity changes likely underlie the previously observed improvement in sensorimotor integration.

Keywords: EEG, resting state, functional connectivity, sensory stimulation, plasticity, sensorimotor, mu-rhythm, ongoing activity

INTRODUCTION

Pathological changes in neuronal functioning lead to a decline of perceptual and sensory abilities. The most obvious cause is a damage of sensory brain areas due to trauma or stroke (Carey et al., 1993; Feys et al., 1998; Rosamond et al., 2007), but also a variety of neurological disorders such as Parkinson's disease (Koller, 1984; Sathian et al., 1997) or dystonia (Tinazzi et al., 2003; Stamelou et al., 2011) can affect perceptual and sensory function, possibly by a dysfunction of the sensorimotor network (Silberstein et al., 2005; Tamura et al., 2009; Litvak et al., 2011). In addition, a more natural but progressive decline of perceptual and sensory capacity develops with increasing age, not only in the visual and auditory, but also in the somatosensory system (Kalisch et al., 2009). Therapeutic strategies to treat the decline of perceptual abilities, which often impacts also motor function, usually comprise intensive and repeated mass training of the respective sensory modality (Sawaki et al., 2003; Kornatz et al., 2005).

A highly efficient alternative approach consists of passive repetitive sensory stimulation (RSS), which has been shown to enhance sensory abilities in chronic stroke patients (Powell et al., 1999; Conforto et al., 2002, 2007; Sawaki et al., 2006; Smith et al., 2009). RSS is a form of repetitive stimulation, following the idea of Hebbian learning: synchronous neural activity that is instrumental to drive plastic changes, is evoked by tactile "co"-activation of the skin, or electrical co-activation of the peripheral nerves of the fingers. Several studies have shown that after such type of stimulation, tactile discrimination abilities were improved and cortical representation of the respective skin area was enlarged (Godde et al., 2000; Pleger et al., 2001, 2003; Dinse et al., 2003). Evidence for the Hebbian nature of coactivation-related learning comes in addition from the fact that, when using a modified version of the coactivation protocol consisting of a single, small stimulation site instead of one large area, no changes in perception or cortical maps occur (Pleger et al., 2003; Ragert et al., 2008). This implies that spatial summation requirements

indicative of cooperative processes need to be fulfilled to drive behavioral changes.

High-frequency RSS enhances sensory and motor abilities in post-stroke patients suffering from sensory loss (Smith et al., 2009), and counteracts age-related declines of perceptual discrimination abilities (Dinse et al., 2006) and sensorimotor performance (Kalisch et al., 2008, 2010). Several studies have related the effectiveness of RSS to an induction of neural plasticity in the somatosensory system (Pleger et al., 2001, 2003; Dinse et al., 2003). However, these findings focus predominantly on cortical representations of *evoked* sensory neuronal activity (e.g., an altered representation of the stimulated hand area in primary somatosensory cortex). Less is known about the impact of RSS on *global* connectivity features of the involved neuronal network during the *resting state*. Illuminating this relationship would be particularly helpful in order to account for the improvement of sensorimotor integration observed in chronic stroke patients (Smith et al., 2009) and elderly subjects (Kalisch et al., 2008, 2010), since changes in sensorimotor integration most likely correspond to changes of long-range interactions between sensory, motor, and association areas (Diamond et al., 2008; Aronoff et al., 2010; Mao et al., 2011).

One way to assess the functional interactions between these distant but coordinated brain areas is to analyze resting state functional connectivity, which reflects a measure of correlations between spatially distant ongoing neuronal dynamics. To investigate the impact of RSS on resting state functional connectivity was the aim of this study. We applied high-frequency RSS in healthy subjects and recorded resting state activity by means of non-invasive Electroencephalography (EEG) before and after the RSS procedure. As a measure of functional connectivity we analyzed changes in EEG imaginary coherency (ImCoh), which can be used to assess frequency-specific interactions between distinct brain areas and unlike the conventional measure of (magnitude squared) coherence has the advantage to reduce overestimation errors due to common references, volume conduction, and cross-talk (Nolte et al., 2004; Guggisberg et al., 2008). The sensorimotor system is known to exhibit dominant resting state rhythms (Salmelin and Hari, 1994b) that peak in the alpha (8–12 Hz) and beta (13–29 Hz) band, the former known as mu-rhythm or rolandic alpha rhythm (Gastaut, 1952; Kuhlman, 1978), the latter as rolandic beta rhythm (Pfurtscheller, 1981, 1992; Salmelin and Hari, 1994a). While the rolandic beta rhythm has a stronger link to the precentral motor cortex, the mu-rhythm is more tightly related to the somatosensory postcentral cortex (Salmelin et al., 1995; Ritter et al., 2009). Given the previously reported positive impact of high-frequency RSS on the sensorimotor abilities in stroke patients (Smith et al., 2009) and elderly subjects (Kalisch et al., 2008, 2010), we hypothesized that RSS might induce changes of functional connectivity within the respective sensorimotor cortical network, and therefore, focused analysis on the alpha and beta frequency bands.

MATERIALS AND METHODS

SUBJECTS AND EXPERIMENTAL SCHEDULE

Thirty-three healthy, right-handed subjects (three male, 26.1 ± 4.0 years) participated in the study. The study was performed

in compliance with the relevant laws and institutional guidelines and approved by the ethics committee of the Charité University Medicine Berlin. In the *pre-session*, 15 min of resting state EEG was recorded using a 64-channel EEG system (BrainAmp, Brain Products, 0.1–250 Hz hardware bandpass filter, 59 scalp channels arranged according to the International 10–20 System, two ECG channel, and one vertical EOG channel, all referenced against FCz, impedances <5 k Ω , sampling rate 5 kHz). During the whole session subjects were sitting in a quiet and dimly lit room and were instructed to stay awake and watch a silent animal documentary on a distant computer screen, which allowed maintaining a high state of vigilance while still minimizing eye movements. During the *RSS-session* high-frequency somatosensory stimuli were delivered for 30 min to the right index finger (IF) of the subject (see section “*High-frequency RSS*” for details of the stimulation protocol). EEG was continuously recorded during RSS and was used to identify EEG somatosensory signal components (see section “*EEG pre-processing*”). In the *post-session*, 30 min after RSS terminated, another 15 min of resting state EEG was recorded, with all settings identical to the *pre-session*.

HIGH-FREQUENCY RSS

Two types of previously reported somatosensory RSS stimuli were used (electrical or vibrotactile). In 21 subjects, two disposable surface electrodes with an area of 15×20 mm were attached to the palmar skin of the right IF, with the positive electrode applied to the distal and the negative electrode applied to the proximal phalanges (Smith et al., 2009; Kalisch et al., 2010). In 12 subjects, a small loudspeaker diaphragm with a diameter of ~ 8 mm was mounted to the tip of the right IF and was used to transmit the tactile stimuli to the skin (Godde et al., 2000; Pleger et al., 2001; Dinse et al., 2003). Stimulation trains consisted of 20 single pulses within 1 s (i.e., a repetition rate of 20 Hz) with an inter-train interval of 5 s. Duration of the RSS protocol was 30 min, resulting in a total number of 6000 pulses. RSS stimuli were applied at 50% above perception threshold.

PSYCHOPHYSICAL MEASUREMENTS

Behavioral impact of RSS was assessed by testing tactile discrimination performance via a two-alternative forced-choice simultaneous spatial two-point-discrimination (2PD) paradigm. This data was in fact acquired in the context of another study and not used for any further analysis, but is reported here for the sake of completeness. In every subject, 2PD was performed before and after RSS, for the right stimulated and left control IF. For details of the 2PD procedure please refer to previous studies using the identical protocol (Godde et al., 2000; Pleger et al., 2001; Dinse et al., 2003).

EEG—PRE-PROCESSING

All EEG data analysis was carried out using MATLAB v7.6.0 and the EEGLAB toolbox (Delorme and Makeig, 2004). EEG was down-sampled to 100 Hz and filtered (1–40 Hz) to remove slow drifts and line-noise and to improve the frequency specificity of subsequent post-processing techniques. EEG data were visually inspected and segments containing gross artifacts (due to movements or bad electrode impedances) were excluded. In all datasets

such segments constituted less than 2% of the data, indicating an overall sufficient data quality. For each subject, EEG datasets of all three sessions (*Pre*, *RSS*, *Post*) were merged and submitted to an independent component analysis (ICA). ICA linearly unmixes the original EEG channel data into a sum of maximally temporally independent and spatially fixed components (Bell and Sejnowski, 1995; Makeig et al., 1996). Characteristics of the resulting independent components (ICs) were obtained by the following analyses: for *pre*- and *post*-sessions, we calculated resting state power spectra using Welch's methods, where the time series is divided into overlapping, Hamming-windowed segments, the squared magnitude of the discrete Fourier transform is computed for all segments and then averaged. Segments had 50% overlap and a window length of two seconds (i.e., twice the number of data points sampled every second), resulting in a frequency resolution of 0.5 Hz. For the *RSS* session, we calculated two types of activity: stimulus-locked activity, i.e., the somatosensory-evoked potentials (SEP), reflecting evoked activity, and the event-related spectral perturbation (ERSP), reflecting frequency-resolved induced oscillatory activity [please refer to (Delorme and Makeig, 2004) for a detailed description of ERSP calculation]. ICA was used for further identification of artifacts. Time-courses, spectra, and topographic distributions of all ICs were inspected to identify components that reflected eye movement, scalp muscle artifacts and movement artifacts. These ICs were removed from the data. Furthermore, in each subject an IC was identified that represents activity related to sensorimotor activity and in particular to the somatosensory processing of the high-frequency *RSS* stimulus (further termed somato-IC). The somato-IC was identified by four criteria: (1) a somatosensory topography of the component map, (2) an alpha (8–12 Hz) frequency peak in the component spectrum (a beta peak is usually expected, but was not obligatory), (3) a significant SEP, and (4) a significant event-related desynchronization in the alpha frequency band of the ERSP images. If more than one somato-IC was identified in one subject, the first in order (explaining the most variance) was chosen.

For each subject, the individual alpha peak frequency of the rolandic rhythm was determined (further termed αf) as the frequency in the power spectrum of the somato-IC showing the maximum value within the broad alpha (8–12 Hz) band (Klimesch, 1996; Klimesch et al., 2006). We defined three sub-bands with reference to αf : peak ($\alpha f - 0.5 \text{ Hz} - \alpha f + 0.5 \text{ Hz}$), lower ($\alpha f - 1.5 \text{ Hz} - \alpha f$), and upper ($\alpha f - \alpha f + 1.5 \text{ Hz}$) alpha frequency band. This subdivision was motivated by previous studies showing that the broad alpha band can be divided into a lower and an upper sub-band, which exhibit different functional properties (Klimesch et al., 1994, 1997, 2006; Rohm et al., 2001; Doppelmayr et al., 2002). Additionally the beta band was defined as 13–29 Hz (since a beta peak was not identifiable in every subject, no individual beta peak frequency was calculated). Our approach to identify components extracted by the ICA related to somatosensory processing had the primary goal of ensuring that the *RSS* was conducted correctly. However, we performed all subsequent analyses in channel space and not in component space because we did not want to bias our analysis a priori only to ongoing activity related to the somatosensory system. A considerable

fraction of rhythmic brain activity relevant to our hypothesis might be hidden in other components that were not categorized as somato-ICs.

EEG—IMAGINARY COHERENCY

Functional connectivity was assessed by means of ImCoh. Introduced by Nolte et al., this connectivity estimate is known to reduce overestimation biases inherent in many other measures of EEG functional connectivity, such as absolute coherence, phase locking, or synchronization likelihood (Nolte et al., 2004; Guggisberg et al., 2008). In these measures, spurious interactions with zero time lag arise due to common references, cross-talk, and volume conduction. In contrast, ImCoh only captures “true” interactions that occur with a certain time lag, omitting all spurious zero time lag interactions. ImCoh is defined as the imaginary part of coherency $C_{ij}(f)$, which is a complex measure of the linear relationship between two time series $\hat{x}_i(t)$ and $\hat{x}_j(t)$ at a certain frequency f . $C_{ij}(f)$ is defined as the normalized cross-spectrum between the two signals (which in our case are the time series of two EEG channels i and j):

$$C_{ij}(f) = \frac{S_{ij}(f)}{(S_{ii}(f)S_{jj}(f))^{1/2}},$$

where $S_{ij}(f) \equiv \langle x_i(f)x_j^*(f) \rangle$ is the cross-spectrum, $*$ is the complex conjugate, $\langle \rangle$ is the expectation value, and $x_i(f)$, $x_j(f)$ are the complex Fourier transforms of $\hat{x}_i(t)$, $\hat{x}_j(t)$.

With $n = 59$ scalp channels available, there are $\frac{n(n-1)}{2} = 1711$ possible ImCoh values, since C is antisymmetric with vanishing diagonal. ImCoh was calculated separately for each subject, recording session, and channel pair combination. The 15 min EEG time series was partitioned into overlapping (50%) segments with a window length of 2 s, which resulted in a frequency resolution of 0.5 Hz. ImCoh values for each of the four frequency bands (three alpha sub-bands and beta band) were calculated by averaging the ImCoh of the respective frequencies. For each channel pair, changes of ImCoh between *pre*- and *post*-session were tested for significance using Student's t -tests. In order to allow appropriate use of a parametric statistical test, Fisher's Z -transformation was used to normalize the distribution of ImCoh data (see Nolte et al., 2004 for details on the transformation of complex coherency). After transformation normality of the distribution was confirmed by an Anderson–Darling test.

CORRECTION FOR MULTIPLE COMPARISONS

The large number of tested channel pairs increases the probability that one or more null hypotheses are mistakenly rejected, also known as the family-wise error rate (FWER). Thus, a correction for multiple comparisons is needed before a statement with respect to statistical significance can be made. Due to the possible redundancy between neighboring channels, a classical Bonferroni correction is a too conservative approach. An established alternative is the false discovery rate (FDR), which is a less conservative and more powerful method for controlling the FWER (Benjamini and Hochberg, 1995).

FDR calculates the expected proportion of false positives (type I error) among all significant hypotheses $H_1 \dots H_m$.

Their corresponding P -values $P_1 \dots P_m$ are sorted in increasing order and for a given threshold α the largest $P(i)$ such that $P(i) \leq \frac{i}{m}\alpha$, is identified. Then all hypotheses $H_1 \dots H_i$ are rejected. Here, we used the generalized Benjamini–Hochberg–Yekutieli procedure which controls the FDR under arbitrary dependence assumptions by using $P(i) \leq \frac{i}{m \sum_{j=1}^m 1/j} \alpha$ and thus is guaranteed to be accurate for any test dependency structure, i.e., even if the tests are positively or negatively correlated (Benjamini and Yekutieli, 2001).

RESULTS

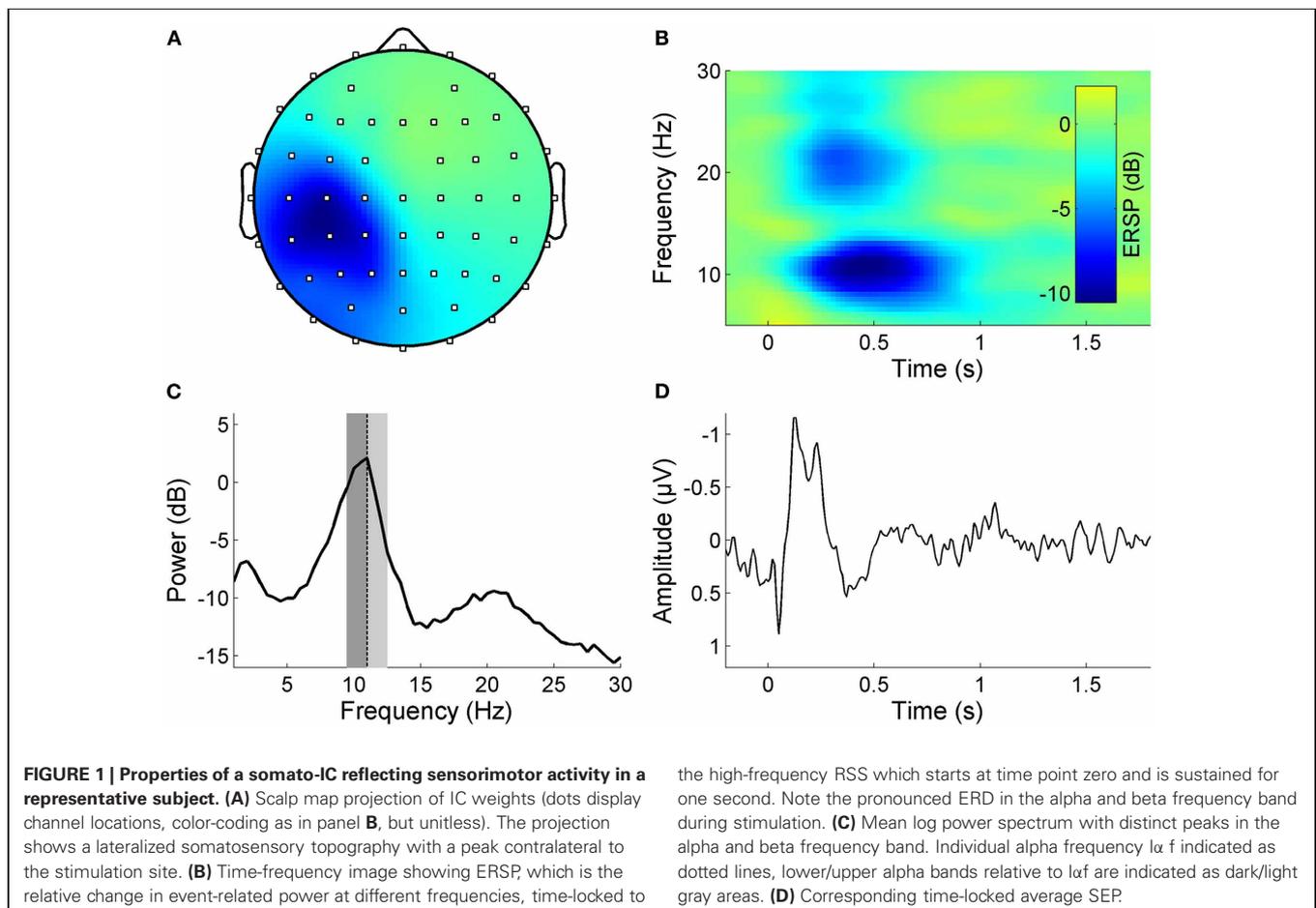
EEG—IDENTIFICATION OF SENSORIMOTOR COMPONENTS

We aimed to investigate the impact of high-frequency RSS on resting state functional connectivity in the sensorimotor system. As a first step we used ICA to identify EEG components in each subject that reflect sensorimotor activity (somato-ICs), including the response to the RSS (for definition of criteria see Materials and Methods section “EEG—pre-processing”). **Figure 1** shows the properties of a somato-IC in a representative subject. The distribution of the component’s weights shows a clear sensorimotor topography (**Figure 1A**). Its resting state frequency spectrum exhibits distinct peaks in the alpha and beta frequency bands, which reflect the ongoing rolandic rhythms (**Figure 1C**).

The component shows both an evoked and an induced response to the RSS (**Figures 1B and D**).

In seven subjects we could not identify any somato-IC. Neither did they show any somatosensory features (SEP, ERD, spectral alpha peak) in channel space. In fact all subjects that showed an EEG response to the RSS in channel space yielded at least one somato-IC. There might be several reasons why these subjects did not respond to stimulation, at least in terms of a measurable EEG response. The stimulation amplitude was set to 50% above perception threshold, which was determined in an iterative manner via the subjects’ feedback. It is conceivable that in some cases, the amplitude of the stimulation might have been too low to induce any EEG response (and also any perceptual learning). Another possibility is a malfunction of the stimulation device. Since we could not exclude technical failure or a bad setting of the stimulation amplitude we excluded these subjects. Importantly the exclusion was based on the absence of their EEG response, not on the basis of their behavioral results. Nevertheless, these subjects did not show any behavioral improvement (mean \pm SD two-point-discrimination threshold changes of the right stimulated IF were $-1.03 \pm 7.27\%$, $p < 0.8125$, Wilcoxon-Signed Rank test).

The final subject group was still large enough to perform proper group analyses and statistics (26 subjects, 3 male,



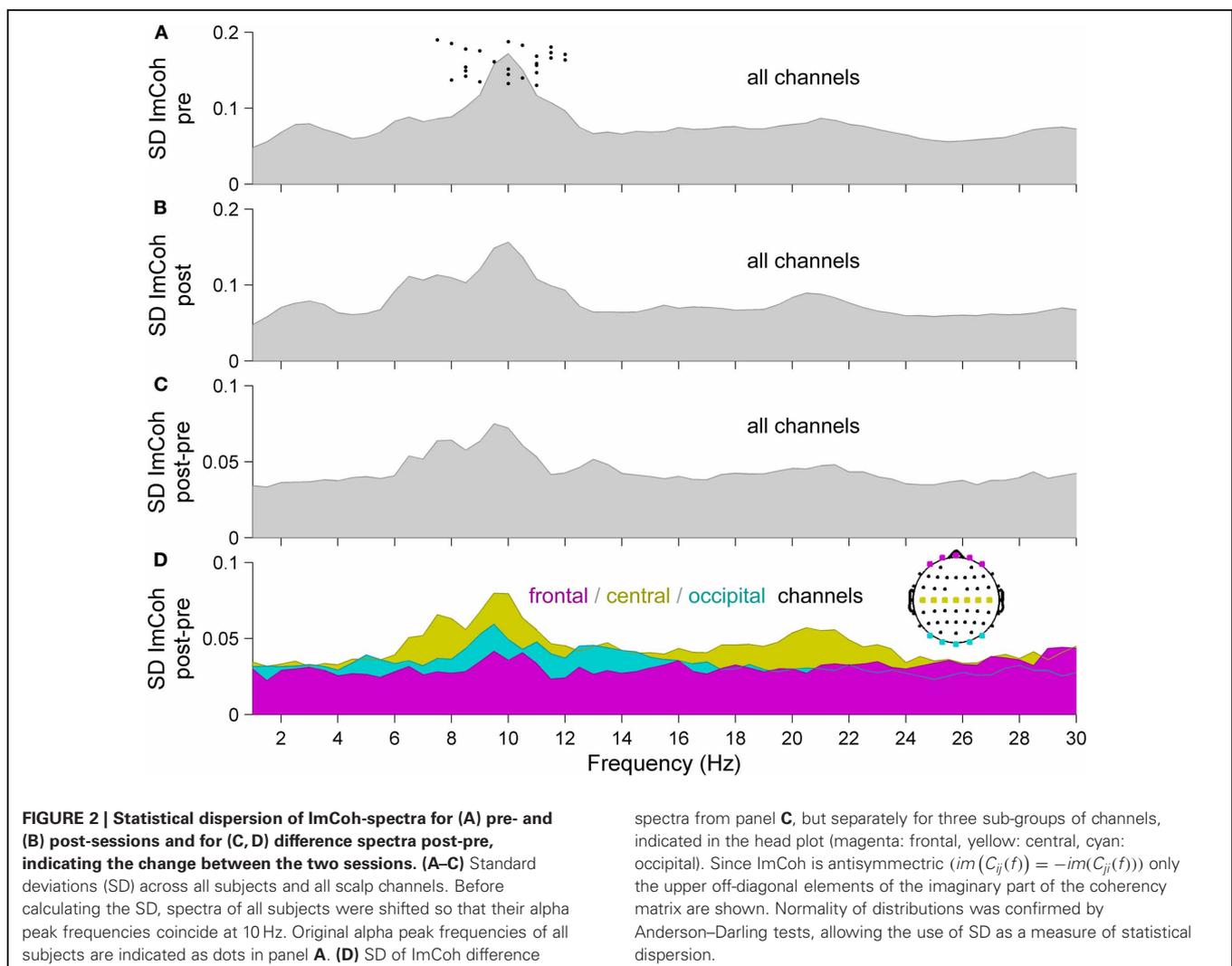
26.1 ± 4.0 years). All remaining subjects exhibited a clear alpha peak in the resting state spectrum of their primary somato-IC. The group mean (±SD) peak frequency in the alpha band was 9.9 ± 1.35 Hz.

Prior to further analysis, ICs representing eye movement, scalp muscle artifacts, and movement artifacts were removed from the data. The mean ± SD number of ICs removed from data was 2.19 ± 0.89, which corresponds to 3.7 ± 1.5% of the total 59 ICs per subject. Although the total number of discarded ICs limits the maximum number of independent coherencies, the removal of these non-physiological and non-neuronal ICs increases the overall sensitivity for coherencies based on neuronal processes.

EEG—FUNCTIONAL CONNECTIVITY CHANGES

To assess the impact of RSS on resting state functional connectivity, we analyzed ImCoh before and after the RSS procedure. **Figure 2** shows an overview of the frequency-resolved (1–40 Hz, resolution 0.5 Hz) statistical dispersion of ImCoh-spectra. Depicted are the standard deviations (SD) across all subjects and all channel pairs for *pre*- and *post*-sessions and for

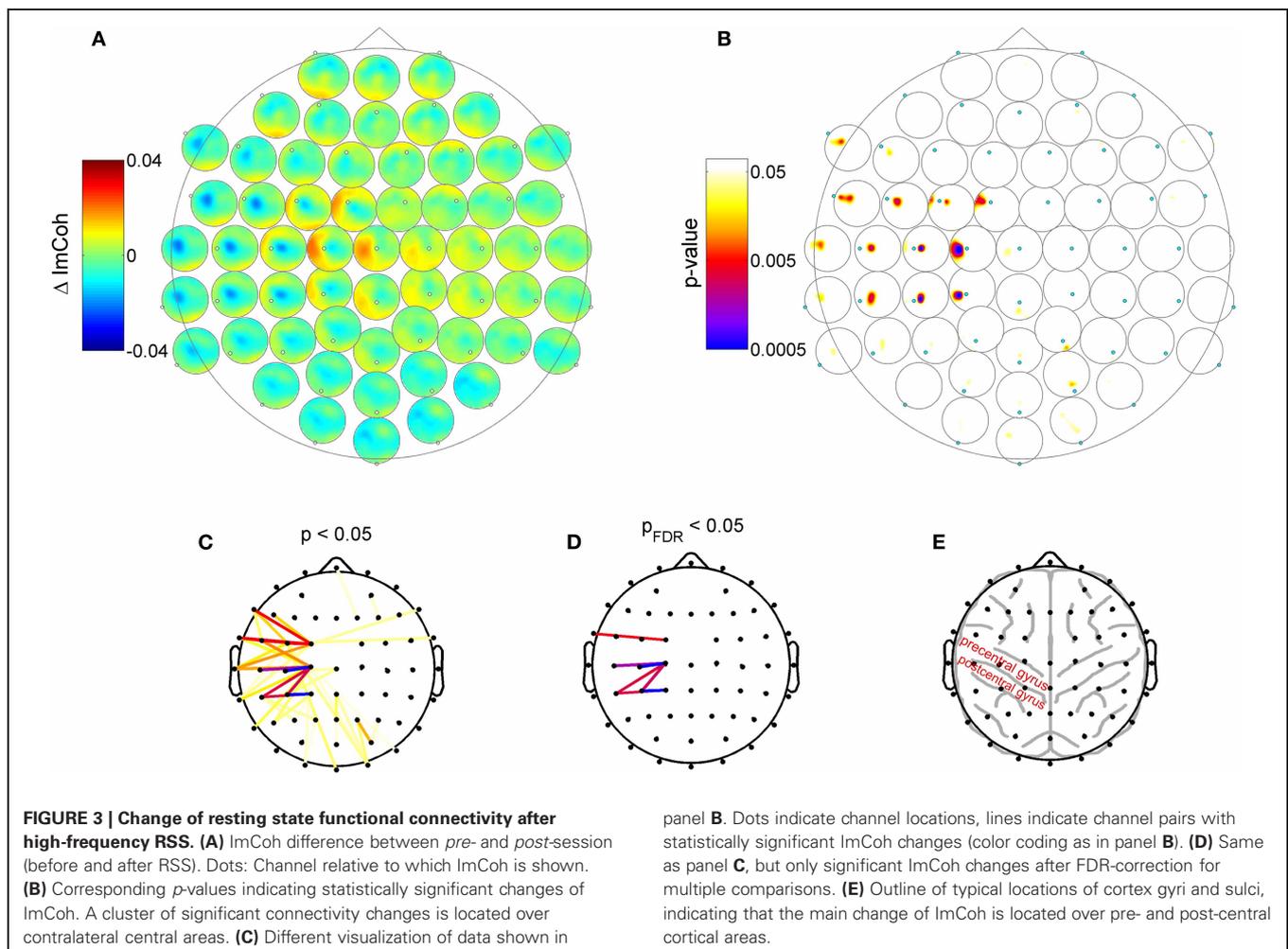
the difference spectra *post-pre* indicating the change between the two sessions. Before calculating the SD, spectra of all subjects were shifted so that their alpha peak frequencies coincide at 10 Hz (e.g., if a subject exhibits an alpha peak frequency of 11.5 Hz, the spectrum is shifted 1.5 Hz to the left). This visualization corresponds to the band-specific analyses, which we performed based on individual peak frequencies (Klimesch, 1996; Klimesch et al., 2006). The original alpha peak frequencies of all subjects are indicated in **Figure 2A** as black dots. The most pronounced change of ImCoh is clearly visible in the alpha frequency band (8–12 Hz). A first hint to the location of the alpha ImCoh change is given when looking at the SD of ImCoh spectra of channel pairs in specific regions-of-interest (ROIs). A separate display for frontal, central, and occipital channels, with maximal changes in the alpha and beta frequency bands (**Figure 2D**). This fits to the sensory modality of the RSS stimulation, since the sensorimotor system is known to exhibit oscillatory activity in these bands (Kuhlman, 1978; Pfurtscheller, 1981, 2006).



Please note that **Figure 2** is purely illustrative and does not allow for any statistical interpretation. Therefore next, we analyzed which of the changes of ImCoh between *pre*- and *post*-sessions were statistically significant. Given the sensory modality of the applied RSS, we focused on the ongoing oscillatory activity in the alpha (8–12 Hz) and beta (13–29 Hz) frequency bands. Also, given the known distinct functional roles of different alpha sub-bands (Klimesch and Doppelmayr, 1997; Pfurtscheller et al., 2000; Klimesch et al., 2003; Sadaghiani et al., 2010), we additionally defined three alpha sub-bands (peak, lower and upper band), which were determined in each subject according to their individual peak frequencies (see Materials and Methods section for details). Of all analyzed frequency bands, we found the maximum connectivity change in the upper alpha frequency band. **Figure 3** shows the group results for this band. A pronounced change of ImCoh can be seen over central cortical areas contralateral to the somatosensory stimulation. This change is highly significant (**Figures 3B and C**). **Figure 3D** shows significant channel pairs after FDR-correction for multiple comparisons, which were: C1–C3, C1–C5, C1–CP5, CP1–CP3, CP1–CP5, CP3–C1, FC1–FT7. In the other analyzed alpha and beta frequency bands, we also found significant changes of ImCoh, but they were

only marginal and after FDR-correction for multiple comparisons confined to isolated single channel pairs (lower alpha band: no significant changes, peak alpha band: C1–C3, beta band: FC3–TP7).

Although our data allows only limited claims regarding the exact cortical source of the change in resting state functional connectivity, they indicate that the main change is possibly related to activity in the sensorimotor cortex. First, the peak of change is located over central electrodes contralateral to the somatosensory stimulation site, indicating that the change in functional connectivity is produced by the repetitive somatosensory stimulation. Secondly, the main change in functional connectivity is reflected in a change of ImCoh in the alpha band, which, due to the location, most certainly corresponds to mu-rhythm activity, which is the dominant resting state rhythm of the sensorimotor system. The observed connectivity changes exhibited a predominant medio-lateral orientation and are distributed over frontoparietal sensorimotor cortex (**Figure 3E**). According to Koessler et al. (2009), who estimated the cranio-cerebral correlations between surface EEG channel positions and the underlying cortical fissures, our main effect reflects connectivity changes between precentral gyrus and postcentral/inferior parietal gyrus (channel C1



to channels C3, C5, Cp1), and within postcentral/inferior parietal gyrus (channel CP1 to CP3, CP5).

INCREASED TACTILE ACUITY AFTER RSS

RSS led to a significant reduction of the 2PD threshold (*post-hoc* difference post-pre = -0.24 mm, $p < 4.67 \times 10^{-6}$, paired Student's *t*-test) for the stimulated right IF, while threshold of the left control IF remained unchanged (difference post-pre = -0.0058 mm, $p < 0.906$). These results are closely in line with earlier studies using the identical stimulation protocol as used in our current study (Godde et al., 2000; Pleger et al., 2001; Dinse et al., 2003). While 2PD data was measured here to ensure stimulation efficacy and for further analysis in the context of another study, we do not believe it is an effective test for changes in functional connectivity between distant brain regions, and hence did not further analyze behavioral data in the scope of this study. We plan to follow up on the link between functional connectivity changes and behavior by testing e.g., sensorimotor integration by means of motor tasks (Smith et al., 2009).

DISCUSSION

We investigated the impact of a specific form of intermittent high-frequency RSS on the network characteristics of the brain. In particular, we analyzed resting-state functional connectivity and found effects within sensorimotor areas which are known to be relevant for sensorimotor processing and integration (Diamond et al., 2008; Aronoff et al., 2010; Mao et al., 2011). The here-used RSS paradigm is known to evoke Hebbian-like learning processes and as a consequence causes both an improvement in tactile acuity (Godde et al., 2000) and a cortical reorganization of the somatosensory representational maps (Pleger et al., 2001, 2003; Dinse et al., 2003).

Similar improvements in tactile discrimination as well as in cortical representation can be induced by repetitive transcranial magnetic stimulation (rTMS). The approaches of RSS and of rTMS share a common conceptual idea: to adapt stimulation protocols typically used in studies of synaptic plasticity at a cellular level in order to alter perception and behavior in human individuals. Crucial to this approach is the observation that changes induced in this way are bidirectional depending on stimulation frequency. Both low frequency repetitive stimulation as well as low frequency rTMS have been shown to reduce cortical excitability in parallel to impairment of behavior. In contrast, high-frequency, intermittent stimulation enhances excitability, which is associated with improvement of performance (Siebner and Rothwell, 2003; Ragert et al., 2004; Tegenthoff et al., 2005; Reis et al., 2008; Dinse, 2011). What makes exposure-based learning different to rTMS is the fact that in contrast to rTMS, the use of sensory stimuli employs the natural sensory pathway to reach a particular cortical area, and that this allows application of highly specific stimulus features such as orientation or luminance, which has been shown to induce specific learning effects for those features (Beste et al., 2011), an option not possible for rTMS.

Please note that we referred to the effects of passive stimulation as “learning processes.” The rationale for this is based on previous studies showing that the effects of repetitive stimulation

depend on NMDA-receptor activation (Dinse et al., 2003), thus demonstrating that the effects of passive stimulation are mediated by very basic mechanisms underlying synaptic plasticity, and on empirical findings showing facilitation of intracortical excitability (Hoffken et al., 2007). We therefore argue that the effects of passive stimulation are based on modifications of synaptic efficacy and transmission, both fundamental principles underlying “learning.” In a more general view, learning is defined as the acquisition of new knowledge, behaviors, skills, values, preferences or understanding, and may involve synthesizing different types of information. Apparently, the term “learning” is rather broadly defined. Given such a broad definition, in our view the outcome of persistent improvement observed following passive stimulation qualifies as learning.

High-frequency RSS was previously proposed as therapeutic approach to treat the decline and loss of sensory abilities (Kalisch et al., 2008, 2010; Smith et al., 2009). Additionally, high frequency RSS has been shown to improve sensorimotor abilities such as haptic and fine motor performance in elderly subjects (Kalisch et al., 2008, 2010). It has, therefore, successfully been applied in stroke patients to improve motor test results and to stabilize motor training effects over a longer time course (Smith et al., 2009). These data implicate that a purely passive sensory repetitive stimulation protocol has a pronounced impact on the network characteristics of the sensorimotor system, and point to the importance of sensory input and sensorimotor integration for the outcome of motor-training rehabilitation paradigms. Here, we provide neurophysiological evidence supporting these recent behavioral results. We show that high-frequency RSS not only changes sensory function and evoked activity in somatosensory areas (Pleger et al., 2001, 2003; Dinse et al., 2003), but also significantly affects resting-state functional connectivity between brain areas engaged in sensorimotor integration processes.

As a means of assessing functional connectivity, we examined coherency changes of ongoing oscillatory activity in human EEG. Although the approach of using ImCoh as a measure of functional connectivity is fairly new (Nolte et al., 2004), it has been applied in a wide variety of studies of different clinical and neuroscientific context (Guggisberg et al., 2008; Cole et al., 2010; Hinkley et al., 2010, 2011; Gonzalez et al., 2011; Martino et al., 2011; Nicolas et al., 2011; Sander et al., 2011).

Our results show that a brief application of RSS alters functional connectivity of the sensorimotor system. Connectivity changes had a mainly medio-lateral orientation, which principally is in line with earlier findings indicating a change of the center of gravity of somatosensory-evoked activity in medio-lateral direction in EEG and fMRI data (Pleger et al., 2001, 2003). In contrast to those previous results, however, the here-reported changes of functional connectivity were present during the resting state, i.e., in the absence of any explicit sensorimotor stimuli and are distributed over EEG channels which are located over pre- and post-central cortex (Koessler et al., 2009)—suggesting an involvement of not only sensory but also motor areas.

Hence, the here reported connectivity changes might be related to the findings by Smith et al. (2009) and Kalisch et al. (2008, 2010), who observed enhanced sensorimotor integration,

enhanced information transfer, and enhanced learning after RSS. Furthermore, our findings might not only be related to these studies on stroke rehabilitation and physiological aging, but possibly apply to a variety of pathologies associated with sensory loss and motor function impairment.

The observed effect is based on changes in oscillatory coupling of ongoing EEG rhythms, with the main finding being in the upper alpha band (~10–12 Hz). The alpha rhythm is one of the most prominent oscillatory hallmarks of the resting human brain. The amplitude of alpha-band oscillations exhibits temporal correlations and spatial coherency, over long-range distances (Nunez et al., 2001; Freyer et al., 2009a, 2011), which makes them eligible for the investigation of the brain's network characteristics. The most prominent alpha rhythm is related to the visual system and plays a strong functional role in the processing of visual stimuli (Makeig et al., 2002; Kirschfeld, 2005; Hanslmayr et al., 2007; Becker et al., 2008, 2011; Ritter and Becker, 2009; Scheeringa et al., 2011). However, the changes in functional connectivity in the present study relates to alpha activity that is distinct from the “classic” occipital alpha rhythm, which dominates the EEG when the subject is at rest with eyes closed. In the present case, the subjects had their eyes open, which leads to a strong attenuation of the occipital alpha rhythm. As can be seen in **Figure 2D**, alpha band ImCoh changes in occipital electrodes were much less pronounced than in central electrodes. In fact, the change in the alpha band is not stronger than in any other of the investigated frequencies indicating that it does not exceed noise level. Given the clear peak in central channels and the modality of the stimulus, the present finding most likely reflects the alpha band activity of the sensorimotor system, i.e., the mu-rhythm (Gastaut, 1952; Kuhlman, 1978).

Evidence for a functional role of the mu-rhythm is plenty. For example, intermediate amplitudes of the rhythm facilitate somatosensory stimulus perception in near-threshold stimulation conditions (Linkenkaer-Hansen et al., 2004). Pre-stimulus mu-rhythm amplitude predicts detection of a target stimulus against stronger masking stimuli (Schubert et al., 2009). The rhythm is also involved in higher cognitive processes, as indicated by studies showing a modulation of the mu-rhythm by attention (Jones et al., 2010; Anderson and Ding, 2011) and by the numerous application of mu-rhythm-based brain computer interfaces (Blankertz et al., 2007; Muller et al., 2008; Yuan and He, 2009; Pfurtscheller et al., 2010; Boulay et al., 2011). Combined EEG-fMRI studies have shown the mu-rhythm to be negatively correlated to the BOLD signal in primary somatosensory

and motor cortex (Ritter et al., 2009), indicating less net neuronal activity, which is well in line with the recently proposed theory that alpha band rhythms serve a “gating-by-inhibition” (Klimesch et al., 2007; Jensen and Mazaheri, 2010). Finally, mu-rhythm has been shown to exhibit a functional connection to stimulus-induced brain signals in remote brain areas, thus providing evidence for long-range connectivity (Reinacher et al., 2009). But what might be the role of this rhythm in sensorimotor integration? Here, we speculate that the observed RSS-induced change in oscillatory coupling between distant sensorimotor areas reflects enhanced effectiveness of neuronal information transfer and sensorimotor integration, possibly via a modified feedback loop between motor and sensory areas, which in turn lead to the observed improvement of behavioral sensorimotor abilities. In order to provide a more detailed account of the mechanisms that link changes in oscillatory resting-state dynamics, altered connectivity, and improved somatosensory capabilities, comprehensive approaches combining advanced multimodal empirical data acquisition capable to also monitor ultrahigh frequency activity (Ritter et al., 2008; Freyer et al., 2009b), spatiotemporal nesting analysis (Schultze-Kraft et al., 2011), multivariate approaches (McIntosh et al., 1996; Boonstra et al., 2007; Krishnan et al., 2011), and computational modeling will be employed in the future.

CONCLUSIONS

Here we provide evidence for the impact of passive sensory stimulation on the resting state functional connectivity in the human brain. We show that 30 min of RSS leads to significant coherency changes of the ongoing mu-rhythm, the dominant resting state rhythm of the sensorimotor system. These changes might constitute a neurophysiological substrate for the previously observed improvements in sensorimotor training in response to RSS (Kalisch et al., 2008, 2010; Smith et al., 2009). Functional connectivity measures provide tools for assessing network interactions in the human brain, and may thus be used to study efficacy of different sensory and motor training paradigms.

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