Modulation of functional connectivity using neurofeedback and its effects on behaviour.

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Tübingen, den

Date Signature

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Abbreviations

MEG	Magnetoencephalography
EEG	Electroencephalography
EcoG	Electrocorticography
fMRI	Functional magnetic resonance imaging
PET	Positron emission tomography
NIRS	Near infra-red spectroscopy
FPN	Fronto-parietal networks
MSC	Magnitude squared coherence
BCI/BMI	Brain computer/machine interface
SQUID	Superconducting quantum interference device
ViBM	Visual backward masking paradigm
MCS	Method of constant stimuli
AM	Adaptive method
SDT	Signal detection theory
DBS	Deep brain stimulation
TMS	Transcranial magnetic stimulation
LFP	Local field potential
PT	Perceptual threshold
NPT	Near perceptual threshold

Abstract

The brain is composed of several functionally specialized areas. Communication between these brain regions serves as the main substrate for complex cognitive processes and behaviours that require a continuous integration of information. The kind of interaction concluding between disparate brain regions both, time-locked to, or independent of external events can be indexed by functional communication. There is abundance of literature suggesting the modulation of the underlying functional communication between different brain regions by manipulating the behaviour i.e. different variations in motor tasks and cognitive tasks. But, the outcome of all these studies only suggests the correlative nature of the task induced functional communication without suggesting the causal relation. In the presented dissertation, we have trained healthy participant to volitionally modulate their functional connectivity between the target brain regions using real-time magnetoencephalography neurofeedback (rt-MEG Neurofeedback) and assessed its effects on behavioural outcome. Together with literature reports, our result hint towards a causal relationship between changes of functional connectivity and changes in perceptual and behavioural performance.

In the first study, 30 healthy participants learned to modulate their functional connectivity between primary motor cortices using real-time neurofeedback. Effects of the training on the behavioural outcome was assessed by investigating their motor performance prior and after the training. We conclude from this study that the increase of the functional communication between the two primary motor cortices results in the deterioration of the motor performance in a bimanual finger tapping task. In the second study, 8 healthy participants learned to modulate their fronto-parietal communication using a ViBM paradigm in neurofeedback setup. Effect of the training on the perceptual threshold were assessed. We demonstrated that the modulation of the fronto-parietal communication is feasible and does influence participants' perceptual thresholds suggesting that the improvement in the fronto-parietal communication does reduce the perceptual threshold measured before (Pre-test) and after (Post-test) the neurofeedback training.

This doctoral dissertation provides evidence supporting a causal relation between the modulation of functional connectivity and behaviour and perception and thus provides

new insights in the intra-cortical communication and thus in the hierarchical organization of the human brain.

Dedicated

to

Mummy, Daddy & Alvi.

Introduction

Functional Connectivity

Brain functions are distributed across different, functionally specialized regions that communicate between each other. To sustain day-to-day life functions, the communication between brain regions is constantly modulated and adapted to current processing needs. Thus, the spatial and temporal communication between different brain regions is highly dynamic (Fries, 2005; Fries, 2015; Miltner, et al., 1999; Siegel, et al., 2012; Singer, 1999; Varela, et al., 2001). Hierarchically, brain's connectivity includes a pattern of anatomical links (anatomical connectivity), temporal statistical dependencies (functional connectivity) and causal interactions (effective connectivity) within the nervous system (Singer, 1999; Sporns, 2007). It's well known that the anatomical connections are the underlying basis of all kinds of neuronal communication (Friston, 2011). However, an existing anatomical connection does not mean that it is involved in the exchange of information in a certain situation or task. One approach to quantify the neuronal communication is to use the measure of functional connectivity and effective connectivity.

Functional connectivity estimates are based on correlation or covariance analyses of multi-channel time series recorded at different location as in electroencephalography (EEG), magnetoencephalography (MEG), EcoG and multichannel recordings (Astolfi, et al., 2007; Sakkalis, 2011; Schoffelen and Gross, 2009; Srinivasan, et al., 2007). The mainstream neuroscience predominantly focussed on the identification of functionally defined brain areas. With the development of various measures and the availability of multichannel recording systems, the estimation of the functional communication between disparate brain regions became feasible. With the shift of the focus of research towards functional connectivity it became evident, that many of the neuropathophysiological conditions are arising from disturbed or disrupted brain network communication. These studies suggest the pivotal role of communication in the normal, functioning healthy brain. In our studies, we explore the aspect of functional communication between two target brain regions. Functional communication constitutes the statistical dependencies such as correlation, coherence and transfer entropy (Gerstein and Perkel, 1969). Whereas, in an effective communication, a model with a set of assumptions is fitted, and then assessing the influence of one system on the other with or without a mediator. Following which, we always compare a model with a model on the other hand functional connectivity is not dependent on any predefined model except the null hypothesis (Aertsen, 1991).

In the here presented research we have used the squared magnitude coherence to index the measure of the functional connectivity.

$$\mathrm{C}xy(f) = \frac{[Sxy(f)]^2}{[Sxx(f)]\mathrm{x}[Syy(f)]}$$

Magnitude squared coherence (MSC) is a frequency domain cross-correlation estimate between two given signals. It allows for the quantification of the correlated activity between two target brain regions in specific frequency bands (Carter, et al., 1973; Carter, 1987; Carter, 1993; Knapp and Carter, 1976).

Neurofeedback

Neurofeedback is a subfield of biofeedback in which participants are trained to gain voluntary control on electro-magneto-physiological processes in the human brain (figure 1). Neurofeedback uses the brain activity captured by neuroimaging modalities to extract meaningful information and to visualize it to the participants. Receiving feedback about their own brain activity, participants learn to modulate it and eventually get volitional control over it. Depending upon the kind of modality being used to acquire the neurophysiological signals, neurofeedback can be categorized into two - invasive and non-invasive - types. MEG, EEG, PET, fMRI, and NIRS are the imaging modalities been used for non-invasive neurofeedback where the neurophysiological signal is recorded either by the electrodes attached on the scalp (EEG) (Birbaumer, 2006; Broetz, et al., 2010), by highly sensitive magnetic field detectors (superconducting quantum interference devices: SQUIDs) capturing the magnetic activity of the brain in MEG (Caria, et al., 2011; Mellinger, et al., 2007), by measuring the blood flow and calculating the BOLD signal (fMRI) (Sitaram, et al., 2007; Sitaram, et al., 2008; Weiskopf, et al., 2004) and by inferring the penetration and absorption of the near infra-red light at the scalp (NIRS) (Birbaumer, et al., 2008; Chaudhary, et al., 2015; Chaudhary, et al., 2016; Gallegos-Ayala, et al., 2014), and by PET (Ciernik, et al., 2003; Wolpaw, et al., 2000). Invasive neurofeedback approaches make use of electrocortical recordings (EcoG) (Deepajothi and Selvarajan, 2016; Leuthardt, et al., 2006). During neurofeedback training, subjects receive online visual or auditory feedback of his/her brain activity measured in real-time (Birbaumer, et al., 2008; Birbaumer, et al., 2013; Chaudhary, et al., 2015) in order to learn its voluntary modulation. Recently, our group demonstrated that in addition to brain activity, brain connectivity can be fed back and learnt to be modulated (Kajal, et al., 2017; Kajal, et al., 2015b). Voluntary modification of the neurophysiological signals, during neurofeedback, have been suggested as therapeutic intervention in various psychiatric and neurological disorders (Birbaumer, 2006; Birbaumer, et al., 2008). In the presented doctoral dissertation, we demonstrate the feasibility of a training in healthy participant to volitionally modulate the functional connectivity between two target brain regions. These studies are the first step towards the development of treatments of neurological and psychiatric diseases with disturbed functional connectivity's.

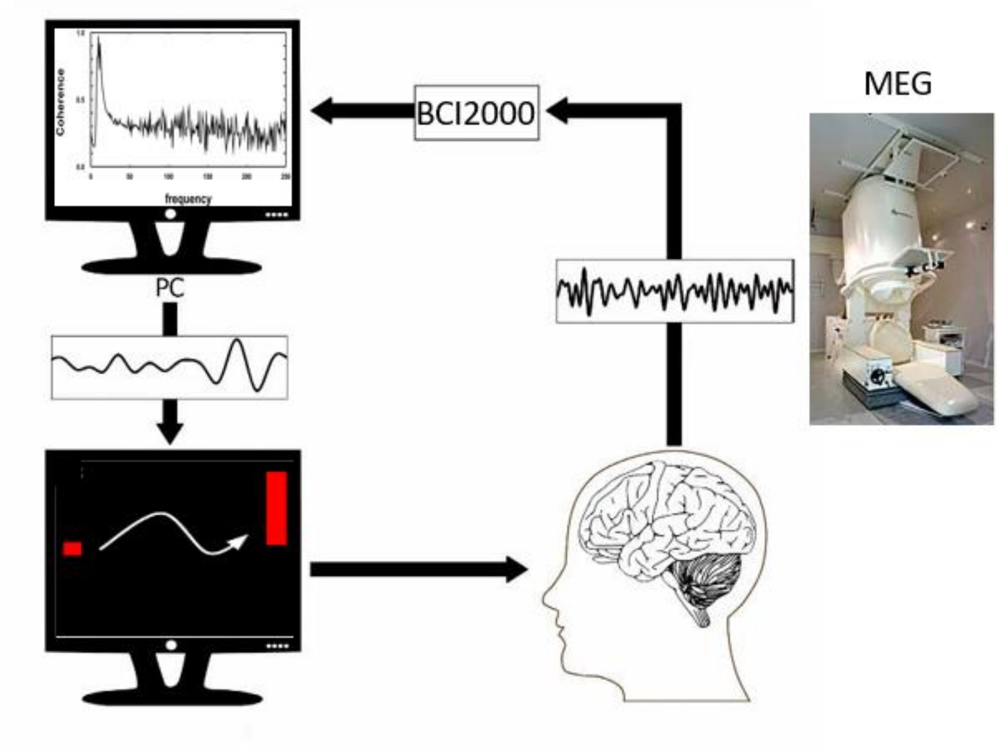

Figure 1) Plot showing the principle layout of the neurofeedback setup used in our study. The neurophysiological signals were captured non-invasively using MEG, processed online using the software BCI2000 and translated into a visual feedback signal (Mellinger, et al., 2007).

Efficient neurofeedback designs make use of operant conditioning. In operant conditioning a previous neutral discriminative stimulus is linked to a response by providing reward whenever the response follows the discriminative stimulus. After the training the appearance of the discriminative stimulus elicits the response quasi automatically. Linking the brain activation and connectivity patterns to corresponding discriminative stimuli makes the neurofeedback training more efficient. With a short training it is possible to establish a sustainable and reliable link between discriminative stimuli and the corresponding responses.

In our experiments, we have used MEG-based real-time neurofeedback based on inter-hemispheric and intra-hemispheric functional connectivity. The neurophysiological signals were processed in real-time using BCI2000 and the target feature, in our case functional connectivity, was then translated into visual feedback. Participants were asked to increase the visual feedback as much as possible. Learned successful control of the feedback stimulus reflects successfully acquired control over functional connectivity between the predefined brain regions. In the first experiment of my thesis, we have targeted the functional connectivity between left and right motor cortex to test the feasibility of our approach. With a behavioural readout that is directly related to the trained connectivity's, as in the first experiment, the chances to be able to demonstrate behavioural effects are higher than in experiments in which modulated connectivity affects behaviour only after a cascade of multiple processing steps (Kajal, et al., 2017; Kajal, et al., 2015b). In the second experiment we aimed to train the modulation of fronto-parietal functional connectivity using neurofeedback with a more therapeutic perspective. Disturbed fronto-parietal connectivity has been described for psychiatric disorders showing deficits in the processing of emotional face expressions such as schizophrenia and autism. To investigate whether neurofeedback training of fronto-parietal functional connectivity can alter the threshold for the perception of emotional stimuli we carried out a feasibility study in healthy control subjects.

Included Studies

Learned control of inter-hemispheric connectivity: Effects on bimanual motor performance.

In the first part of our study, we have explored the possibility of modulating the functional connectivity in motor cortical areas. We have taken primary motor cortex into consideration because we can expect a direct readout, behaviour. Symmetric or asymmetric bimanual movements are characterized by specific patterns of inter-hemispheric neuronal communication. Yet, studies exclusively inferred functional connectivity (dependent variable) as a function of different motor tasks (independent variable). We proposed a novel approach developed in our lab involving real-time sensor-level Magnetoencephalography (MEG)-neurofeedback by training thirty healthy individuals to volitionally control coherence between two brain areas using instrumental learning paradigms. To disentangle effects of training from effects of task repetition the group of healthy participants was evenly divided into two groups: Contingent feedback group (experimental group) and Sham feedback group (control group). Our study was divided in four main parts: pre-test session, functional localizer session, neurofeedback session and post-test session. All the sessions were performed on separate days. Pre-test and post-test sessions were used to assess the impact of the neurofeedback training on the functional connectivity and most relevantly on behaviour. In both the sessions, all the healthy participants were subjected to two types of discriminative stimuli (SD^+ and SD^-) while carrying out a bimanual finger tapping task. In the pre-test, the discriminative stimuli do not have any meaning. However, in the post-test, after a successful neurofeedback training in which SD^+ was associated to up-regulation and SD^- to down-regulation of coherence, discriminative stimuli have acquired the potential to alter brain connectivity. Pre-test and post-test were performed on the first and fifth day of the experiment. The pre-test session is subsequently followed by the functional localizer sessions scheduled for the second and third day. The functional localizer session consists of further two parts: a) Identification of the subject specific MEG sensors (day 2) and subject specific frequency (day 3). The parameters assessed in the functional localizers session (MEG sensors and subject specific frequency) were further used to decide the parameters for the neuro-feedback session (figure 2). In the neurofeedback session (day 4) healthy participant were trained to modulate the functional connectivity between left and right motor cortices. In the neurofeedback session, participants were trained to volitionally up-regulate and down-regulate the functional connectivity using MEG neurofeedback. Participants were prompted to up- and down regulate using a visual cue serving as discriminative stimuli. This approach directly modulates brain activity as an independent variable and investigates resulting changes in behavior as a dependent variable. Using this innovative approach, we investigated a hitherto unclear role of interhemispheric functional connectivity in complex, bimanual movements. Subjects who were trained with contingent feedback of ongoing neural coherence learned to both increase and decrease coherence, while those presented sham feedback failed to learn. Further, the successful group showed a differentiation in their performance in the bimanual asymmetric finger-tapping task. We found an inverse correlation between coherence increase and tapping speed, hinting towards the causal role of interhemispheric motor cortical coherence in bimanual asymmetric movements*.* We believe, our work opens up a novel approach to the correction of motor disability using neurofeedback in addition to providing new insight in the motor coordination (Kajal, et al., 2017; Kajal, et al., 2015a).

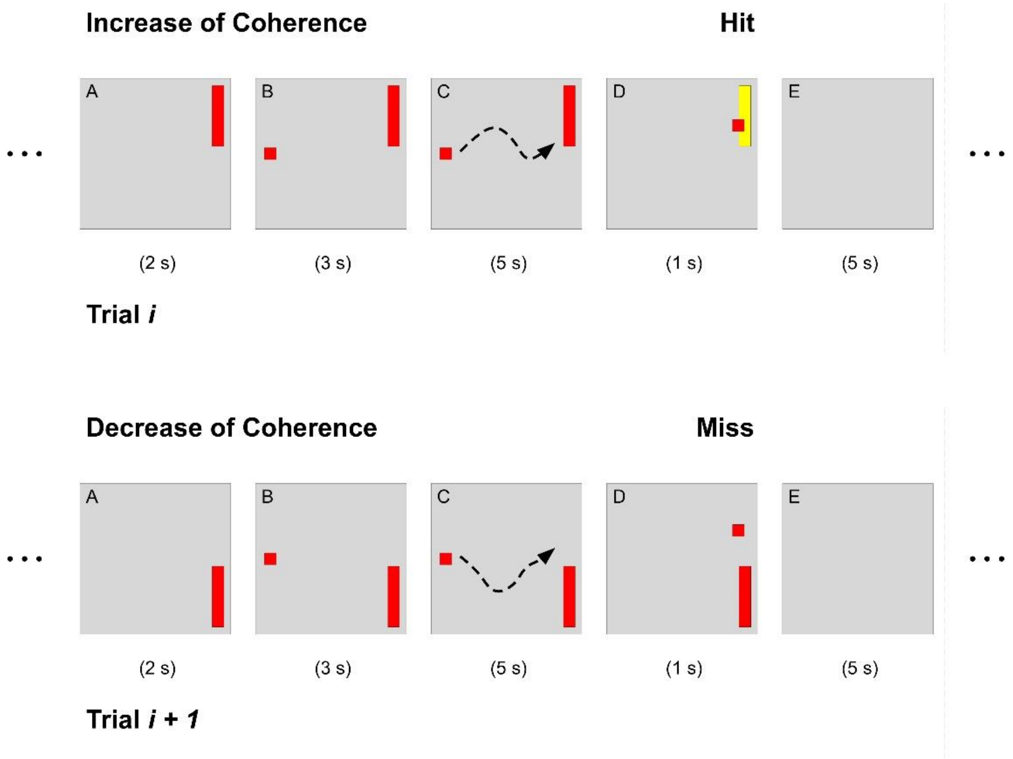

Figure 2) Schematic showing the paradigm used for the modulation of the inter-hemispheric functional connectivity between left and right primary motor cortices (Mellinger, et al., 2007). Cue Phase (A): the discriminative stimuli are presented for 2 s, suggesting whether the current trial is either up-regulation (increase of coherence) or down-regulation (decrease of coherence). B) Following, the cursor appears and remains stationary for 3 s. Then participants begin the self-regulation of the functional communication between the left and right primary motor cortices. C) Thereafter, the active phase of the neurofeedback session starts and lasts for 5 s. In this phase, the cursor moves in the x-direction at a constant velocity and in the y-direction with a speed proportionally to the functional connectivity calculated from the immediately preceding 3 s interval. D) in this phase, feedback is given. A successful trial is indicated by the target changing the colour from red to yellow for 1 s. In contrast, the target remains red in case of unsuccessful trials. E) represents the inter-trial intervals

Learned control of fronto-parietal connectivity: Effects on the perceptual threshold.

In this experiment, we have trained the healthy volunteers to volitionally modulate the fronto-parietal (FP) circuit intra-hemi spherically and studied its effects on the perceptual threshold as a behavioural outcome. Literature suggests that FPN plays an important role in the perception of emotion with a sequential interaction of top-down and bottom-up processes which are triggered with the presentation of the emotional stimuli. While bottom-up processes help in the registration of the information in the brain, it is the top-down processes that are crucial for the identification of the emotional meaning. The interaction between bottom-up and top-down processing has been very well explained using the global neuronal workspace model, suggesting that there emerge reverberant self-amplifying loops with the presentation of the visual stimuli. The information in the reverberant self-amplifying loops will reach to the level of consciousness if they are not disrupted, blocked and/or masked by another visual stimulus (Cul, et al., 2006; Dehaene and Changeux, 2003; Dehaene, et al., 2006; Dehaene and Naccache, 2001; Del Cul, et al., 2006b).

We could demonstrate that these interactions happen in the gamma frequency band when emotional stimuli were presented in a backward masking paradigm (study i. Kajal et al 2018, manuscript submitted, is under review and attached) near the PT. We have presented an emotional face either happy or sad as a prime stimulus and a neutral face stimulus of the same person as a mask stimulus. In the experiment modulating the sensor-level intra-hemispheric functional connectivity, we have used a visual backward masking (ViBM). In the ViBM (figure 3), the delay between the prime and the mask stimulus is varied across trials by selecting random delays from 10 predefined intervals. The prime stimulus will be correctly identified if the delay between the prime stimulus and the mask exceeds subjects' PT. If the delay remains below the PT level, the prime stimulus still activates bottom-up processes, but fails to initiate the subsequent top-down processes. In this case, a propagation of the emotional content of the prime stimulus to conscious processing is disrupted by the mask stimulus, and subjects are not aware of the emotion presented.

The training of FPN was done at the participants' PT. There are two well established a) Method of constant stimuli (MCS) and b) Adaptive method (AM). We have studied the difference between the estimated perceptual threshold using MCS and AM. Since the PT not only reflects the sensory capabilities but also depends on participants' bias we also investigated any contamination of the perceptual threshold estimates due to participants' bias and finally devised a novel method for its correction for the AM (study ii. Kajal et al 2018, manuscript submitted, is under review and attached). Details of all the above included studies are as follows:

Brain networks controlling the perception of the emotional valance.

Literature suggests that fronto-parietal network connections and communications plays an important role in the perception of the emotional valence of the presented visual stimuli. Lack of communication or dysfunction between the fronto-parietal network leads to the impairment of emotional valence perception. This is commonly prevalent in the patients with neuropsychiatric condition such as schizophrenia and autism.

In our experiment, to study the neural correlates of the perception of the emotional valence, a face stimulus either happy or sad looking was presented with a mask delay at the perceptual threshold such that they were correctly perceived only occasionally. These trials are then sorted and segregated according to perceived and not perceived. Finally, neural correlates for conscious perception of the emotion were extracted. This helped us to study the neural correlates/networks involved in the conscious perception of the emotional stimuli. Various top-down and bottom-up influences affecting the perception of emotional face expression could be identified. We could demonstrate a significant top-down modulation from frontal regions towards parietal regions using phase slope index in 35 Hz near the perceptual threshold. We also demonstrated inter-hemispheric lateralization between left and right hemispheres: right hemispheric fronto-parietal communication was stronger compared to the left hemisphere during perceived trials. Right FPN and right parietal regions demonstrated more interhemispheric functional communication during perceived as compared to the not-perceived trials, and furthermore, functional communication between left frontal regions and right parietal regions is higher during not-perceived as compared to perceived trials.

Adaptive procedure for the estimation of the perceptual threshold: effects of the observer's bias.

In this experiment, different threshold procedures were compared in 12 healthy participants using a ViBM paradigm. In the ViBM paradigm, an emotional visual prime stimulus was presented followed by a mask stimulus after a variable delay. Prime and mask stimuli were emotional faces and the delay was selected randomly from the predefined stimuli. We explored different avenues of the near perceptual threshold. According to the presented literature, there are two different measures to estimate the perceptual threshold. A) Method of constant stimuli, and B) Adaptive methods. The basic difference between both the methods is that in the former one predefined stimuli are presented in the pseudo-random manner and responses are recorded. Then, the near perceptual threshold is estimated by fitting a sigmoid function to the percentage of correct responses for the individual classes of predefined stimuli and by determining the class corresponding to a predefined performance level. In the latter one, the presented delay dependents on the participant's responses in previous trials. If the participant responded incorrectly in the current trial, then the level of difficulty is decreased in the subsequent trial. The delay was decreased if the participant responded correctly twice. The two correct responses did not need to occur in consecutive trials. In the adaptive method, the delay will converge to the perceptual threshold towards the end of the experiment.

We proceeded with the aim, firstly, to understand if there is any difference between MCS and AM for the estimation of NPT. Second, since bias is a main contaminating factor for the estimation of the perceptual threshold, we proposed the deduction of the bias in the MCS method using the SDT. Third, we have also proposed a novel algorithm to remove the bias contamination in the AM. We have done a simulation study for the implementation of the bias correction in the AM. With the results from this study, we were able to conclude that there is significant positive correlation for the perceptual threshold estimated using MCS and AM. We conclude from our simulation study that the bias correction needs the more trials the higher the bias. We thus suggest to preferably eliminate the contamination of the bias by designing the experiment accordingly and by altering the assignment of the response keys on trial to trial basis.

Learned modulation of fronto-parietal connectivity: Effects on perception.

Eight healthy participants were trained to volitionally up-regulate and down-regulate the fronto-parietal functional communication using a ViBM task with subject specific near the perceptual threshold with MEG. From the study it was concluded that the volitional modulation of a complex network such as the fronto-parietal network is possible and does have a significant impact of the near perceptual threshold. We have used the ViBM at presenting subject-specific near perceptual threshold stimuli. The final goal of this research is to implement the training of the FPN circuit in the patients suffering from the disconnection or disruption syndrome such as schizophrenia and autism, where the effects to be obtained on the single patient cases.

Figure 3) schematic showing the paradigm used in the ViBM task.

In this schematic showing the single trial of the neurofeedback trials using ViBM. A fixation cross was presented for 2 s, followed by the discriminative stimuli either a ‘1’ or 2’ was presented. ‘1’ requests up-regulation of the coherence and ‘2’ requests the down regulation of the coherence. Then a prime stimulus, either a happy or sad face, is presented for the duration of 16.7 ms. The delay between the prime and the mask stimulus is kept constant near the perceptual threshold. Then, a mask stimulus of 250 ms duration with a neutral emotional valence of the same individual as in prime was presented, and the thermometer appeared on the screen providing visual feedback about the match between the requested and produced fronto-parietal network connectivity. The feedback stimulus stayed for 1 s on the screen (Cul, et al., 2006; Dehaene and Changeux, 2003; Dehaene, et al., 2006; Dehaene, et al., 1998; Dehaene and Naccache, 2001).

Discussion

In the presented doctoral dissertations, I could demonstrate a convincing impact of learned modulation of functional connectivity on behavior: modulation of inter-hemispheric functional connectivity of primary motor cortex resulted in a significant effect on motor performance, and modulation of fronto-parietal functional connectivity significantly affected the perceptual threshold for detecting the emotional valence of face images. Modulating functional connectivity between target regions as independent variable and assessing its effects on behavior as independent variable further adds to our understanding about the importance of functional communication within the cortex. Going beyond the correlative nature of neuroimaging studies relating changes in neurophysiological parameters with changes in behavior, this type of approach even suggests a causal relationship between the volitional modulation of the functional connectivity and the behavioral outcome.

Study I

In the first study, we trained 30 healthy participants to volitionally modulate the functional connectivity between left and right primary motor cortices. Training induced changes in functional connectivity were related to the modulation of speed in a bimanual finger-tapping motor task assessed in a pre- and post-training-test. We have found a negative correlation between finger tapping speed in the bimanual motor task and the functional communication between left and right primary motor cortices. Our result is in line with previous findings, suggesting a decrease in interhemispheric coupling for asynchronous bimanual motor tasks (Gross, et al., 2005). Also, a decrease in the functional communication during various polyrhythmic bimanual finger-tapping tasks had been found. Studies investigating the role of phase synchronization of motor-related brain activities with respect to out-of-phase asymmetric bimanual movements, and in-phase, anti-phase and polyrhythmic movements point to the importance of flexible modulation of inter-hemispheric coupling in skilled motor performance (Houweling, et al., 2010a; Houweling, et al., 2010b; Kristeva, et al., 1991; Mayston, et al., 1999; van Wijk, et al., 2012). High levels of inter-hemispheric functional communication within motor cortices appear to reflect the controlled execution of bimanual motor tasks. Lower levels of coupling portray well-trained, “automatized” execution of motor tasks such as asynchronous bimanual movements. If increased inter-hemispheric coupling of motor cortices is an index for controlled execution and low coupling a signature of automatized motor execution or completely independent motor sequences, then the up- and down-regulation of functional communication might alter the mode of operation of motor control. Congruent with the findings of our study, up-regulation would then be associated with controlled motor execution and thus, slowed down motor performance, and down-regulation with automatized and accordingly fast motor processing.

Study II

In the second neurofeedback study, we have trained 8 healthy participants to modulate the intra-hemispheric fronto-parietal communication near the perceptual threshold for the detection of emotions in visual face stimuli. Results demonstrate the ability to train the modulation of fronto-parietal network communication at the perceptual threshold. Furthermore, we could demonstrate an inverse relation between the increase in functional communication between fronto-parietal network and the decrease in perceptual threshold. In other words, increase in functional fronto-parietal communication results in the reduction of the threshold for detecting the emotional valence of visually presented face expressions, and thus provides a conclusive role in the modulation of perception.

Our finding further complements the theory of the global workspace model (Cul, et al., 2006; Dehaene and Changeux, 2003; Dehaene, et al., 2006; Dehaene and Naccache, 2001). The global workspace theory posits that the conscious visual perception is a result of the formation of a high-level brain-scale neuronal assembly involving recurrent long-distance interactions among distributed thalamo-cortical loops, especially involving the prefrontal cortex and higher cortical association areas. A stimulus exceeding the perceptual threshold can simultaneously activate many distant areas and yield a long-lasting pattern through reverberating activity. It has been suggested that attaining such distributed pattern results in a consciously reportable state is because its active contents are broadcasted to many functionally specialized brain regions, including those for verbal or motor report. When an incoming activation fails to exceed the threshold, it can still briefly propagate through the processors but quickly vanishes, as it is not supported by recurrent self-amplifying loops (Dehaene and Changeux, 2003; Dehaene, et al., 1998; Dehaene and Naccache, 2001; Ramachandran and Cobb, 1995).

The backward masking paradigm, in which a shortly presented prime stimulus is masked by a subsequent masking stimulus has been introduced to study this model. In the backward masking paradigm, the prime stimulus does not reach the level of consciousness, unless the temporal delay between the prime and mask is above the perceptual threshold (Del Cul, et al., 2006b) due to non-generation of the reverberant and self-amplifying loops between fronto-parietal communications. The registered prime stimulus will get the emotional meaning only when these loops are not being disturbed or disrupted by the mask stimuli thus affecting the perceptual threshold (Global workspace model). Our results suggest that the modulation of the fronto-parietal communication results in differential changes in the perceptual threshold. This study, using the learned modulation of the fronto-parietal communication in conjunction with the modulation of the perceptual threshold, provides the basis for translational applications in patients with impaired fronto-parietal communication such as schizophrenia and autism patients suffering from disconnection syndrome (Bateson, et al., 1956; Breakspear, et al., 2006; Cul, et al., 2006; Deleuze and Guattari, 1988; Friston, 2002; Lynall, et al., 2010).

Functional connectivity estimates

Estimates for the functional connectivity represents temporal correlation among the activity of different neural assemblies and magnitude squared coherence estimates are used in our study as a metric of the functional coupling between different brain regions.

The computation of the coherence is based on the values of auto-spectra and cross-spectra between the two signals over the infinite length of the window.

$$S_{xy} = x\,(f)\;X\;y^{*}(f) \quad (1)$$

Where x(f) is the discrete Fourier coefficient at frequency f of the finite time series X(t), and y*(f) is the complex conjugate of the Y(t). The magnitude-squared coherence is a measure that estimates the extent to which a signal can be predicted from another using a linear time invariant system, and thus gives an estimate of the functional coupling when applied to neuromagnetic brain signals.

To provide a real-time feedback and to obtain a reliable estimate of coherence in study 1, functional coupling was quantified for the most recent 3 s interval. The interval was divided into 28 segments of 0.208 ms duration and windowed with a Welch window. In order to exploit the data most efficiently a 50% overlap between windows was chosen. Although feedback was given only at the end of a trial in study 2 the same window length as in study 1 was selected.

Stationarity of the signal is one of the important assumptions for the estimates of coherence. The stationary assumption is relaxed using the Short Time Fourier Transform (STFT), instead of the classical Fast Fourier Transform approach and coherence may be estimated around a few time instants. However, stationarity is still a required criterion within each time interval for which coherence is estimated, meaning that in practice one should decide on the optimal section length (window) over which each coherence estimate is measured. Window length and window overlap affect the frequency resolution and robustness of the estimate of the functional coupling. To which extend different aspects of connectivity are captured using different window length is however not well explored yet in neuronal coupling. Varying the window length could result in inconsistent estimates of coherence with a high degree of variability (Hutchison, et al., 2013). The reliability of the coherence estimate can be improved either by using frequency smoothing or the temporal smoothing of the spectral estimates. In the frequency smoothing the equation 1 is replaced by its convolution with the smoothing window for each frequency. In another technique, called temporal smoothing, the observation is divided into a succession of the k segments. An estimate of the spectrum is computed for every window using equation (1) and then k spectra are averaged to provide the estimate of the global window. I have used the temporal smoothing method for the neurofeedback studies using weighted overlapping segment averaging method. I have used the Welch method with the 50% overlap, which is proved to be a robust method against the bias (systemic error) incorporation and variance fluctuations (Firth, 1993; Groß, et al., 2001; Izatt, et al., 1997; Welch, 1967).

Causal inference

Consider an example of a car, the engine of the car controls the speed and generates sound. As the speed of the car is increased, there is a variation in the sound of the car. Looking at this, can we infer that the speed of the car is dependent on the variation of the sound from the car? To prove this inference, the only option is to intervene. Either we can mute the sound, manipulate the sound by adding a sound absorber or vary the supply of the engine with gas. Only the latter intervention will have an impact on the speed of the car and thus suggests a causal link between the engine and speed with sound being a mere by-product. Varying the speed of the car by pushing it does not create any sound and doesn’t consume any fuel and thus reflects a different working mode. Now replace this analogy of the speed of the car with the behavior, and measured brain activity either with the engine and the sound from the car.

In neuroscience, the relation between different brain activities and the corresponding behavior is studied by defining different conditions (motor or cognitive tasks) and assessing their effects on the measured neural activity for the target regions using various imaging modalities. The inferences made about the relation between brain activation and behavior are usually “correlative” in nature and do not provide any “causal” relation. The important question is how can we determine which of the observed brain activations are causal for behavior and which are mere by-products? Traditionally, lesion studies are most appropriate to investigate the causal link between brain function and its behaviour. Lesioning a brain region (similar to closing the fuel support line or muting the car sound) and observing accompanying changes in behaviour (similar to the changing the speed of the car) can only be explained by an effect of the lesion on behaviour, but not in the inverse direction. Similarly, brain stimulation techniques such as deep brain stimulation (DBS) or transcranial magnetic stimulation (TMS) are suitable tools to induce temporally defined, reversible ‘virtual lesions’ (Cohen, 1989; Cohen, et al., 1997; Pascual-Leone, 1997; Pascual-Leone, et al., 1994a; Pascual-Leone, et al., 1996; Pascual-Leone, et al., 1998a; Pascual-Leone, et al., 1998b; Pascual-Leone, et al., 1994b; Pascual-Leone, et al., 2000; Pascual-Leone, et al., 1991). Note, causal effects of both, lesions and brain stimulation, on behaviour do not need to be exerted via direct neural pathways.

In neurofeedback, the discriminative stimuli are associated with the control of brain activation patterns. Like brain stimulation, activation patterns can be switched on and off by presenting the corresponding discriminative stimuli. Thus, neurofeedback trained control of brain activation would then also allow for the inference of causal effects. However, this assumption is only true if the discriminative stimuli modulate the target brain region directly. In case the discriminative stimuli affect behaviour first and the target brain area only subsequently, the causality would be reversed. Without knowing the pathways through which discriminative stimuli affect the activation in the target regions, a causal interpretation is not possible. Unfortunately, brain imaging studies correlating changes in behaviour with changes in brain activation patterns do not provide any causal information of how the discriminative stimulus drives the target brain regions.

Being able to modulate behaviour in the post-test session, i. e. bimanual motor speed in study 1 and modulation of the perceptual threshold in the study 2, raises the question of whether the acquired volitional control of brain activation patterns drives behaviour in a causal fashion. In other words: can it be ruled out that behaviour is the mediator through which brain activation patterns are changed?

To solve this issue, the temporal sequence of discriminative stimulus, activation of the target region and finally the behaviour will offer a solution. Using neuroimaging methods with high temporal resolution such as EEG or MEG can provide information about the time lag of activation of different brain regions and thus about causality. Measures such as Granger causality, phase slope value or derived metrices such as the phase lag index are capable of extracting time delays between different brain regions and thus allow for the inference of causality.

While in study 1 the causal nature of motor cortex controlling behavior has been shown in countless studies (Amassian, et al., 1989; Bejjani , et al., 1999; Bohning, et al., 1999; Cohen, 1989; Corbetta and Shulman, 2002; Fox, et al., 1997; Frank, et al., 2007; Ilmoniemi, et al., 1997; Martin and Gotts, 2005; Pascual-Leone, et al., 1994a; Pascual-Leone, et al., 1998a; Pascual-Leone, et al., 1998b; Paus, 1998; Romei, et al., 2012; Sitaram, et al., 2007; Sitaram, et al., 2008; Weiskopf, 2012; Weiskopf, et al., 2004) and thus can be taken for granted, we studied the directionality and thus the causality of fronto-parietal connections using the phase-slope index revealing an influence on right frontal brain regions on right parietal cortex.

Conclusion

Previous studies in cognitive neuroscience gave the evidence of the modulation of the behavior and assessed its effects on the modulation the functional communication between the target brain regions. In the presented dissertation, we have modulated the inter-hemispheric (primary motor cortices) (study I) and fronto-parietal (Study II) functional communication and studied its effects on behavior i.e. bimanual motor performance and perceptual threshold, respectively. Our results complement the previous studies and suggest a causal relation between modulation of the functional communication and measured behavior, furthermore, giving insight into the hierarchical nature of the brain network organization and architecture.

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List of conference proceedings/manuscripts appended

a) **Kajal, D.S., et al.**, *P113. Learning volitional control of functional connectivity: effects on behaviour.* Clinical Neurophysiology, 2015,**126**(8): p. e104.
b) **Kajal, D.S., et al.**, *Learned control of inter-hemispheric connectivity: Effects on bimanual motor performance.* Human brain mapping, 2017. **38**(9): p. 4353-4369.
c) **Kajal, D.S, et al.**, *Functional dynamics underlying near-threshold perception of facial emotions: a magnetoencephalography investigation.* ***BioRxiv 2018, 383315, Under Review in Cerebral Cortex***
d) **Kajal, D.S., et al.,** *Estimation of perceptual thresholds: Effects and correction of observer bias. Manuscript submitted in NeuroImage*
e) **Kajal, D.S, et al.**, *Learned control of fronto-parietal connectivity: Effects of perception.*

Statement of contributions

Learning volitional control of functional connectivity: effects on behaviour.

Conference Proceedings

Published in Journal of Clinical Neurophysiology (2015)

	Authors	**Contribution**
1	**Diljit Singh Kajal**	Collected and analysed the data, wrote manuscript
2	Jürgen Mellinger	Set up the experiment: BCI2000
3	Sergio Ruiz	Edited the manuscript
4	Mathew Sacchet	Edited the manuscript
5	Eberhardt Fetz	Edited the manuscript
6	Neils Birbaumer	Edited the manuscript
7	Ranganatha Sitaram	Designed the experiment, edited the manuscript
8	Christoph Braun	Designed the experiment, Statistical analysis and wrote manuscript.

reconstructive empathy (left insula and right parahippocampal gyrus) in the LE group.

doi:10.1016/j.clinph.2015.04.153

P112. The cerebellum and the Multiple Sclerosis Functional Composite Score: Voxel based morphometry identifies cerebellar regional gray matter loss correlating with walking ability, dexterity and cognitive function—M. Grothe[a], M. Lotze[b], S. Langner[b], A. Dressel[a] ([a]Ernst Moritz Arndt University, Neurology, Greifswald, Germany, [b]Ernst Moritz Arndt University, Radiology, Greifswald, Germany)

Background: The human cerebellum is involved in both motor and cognitive functions. In Multiple Sclerosis (MS), overall cerebellar gray matter (GM) volume loss has been previously described. We therefore hypothesized that regional cerebellar GM loss could be correlated with the subtests of the Multiple Sclerosis functional Composite Score (MSFC: timed 25-foot walk, 9-hole peg test, Paced Auditory Serial Addition Test).

Patients and methods: Voxel based morphometry (VBM) was used to investigate regional gray matter decline by calculating individual GM images from 45 MS patients using the VBM tool for the software statistic parametric mapping (SPM). Correlation analyses were performed on the MSFC subtests and the individual GM images.

Results: Each component of the MSFC was associated with a distinct regional cerebellar GM decrease. Impaired walking ability correlated with regional volume loss in lobule VI ($t = 5.16$; $p_{\text{unc.}} < .001$), impaired arm ability with a cluster in lobule IX ($t = 3.95$; $p_{\text{unc.}} < .001$) and cognitive impairment with volume loss in crus II ($t = 4.81$; $p_{\text{unc.}} < .001$).

Discussion: We demonstrate correlation of distinct regional cerebellar volume changes with each of the tasks out of the MSFC. Our data emphasize the importance of cerebellar gray pathophysiology in MS.

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P113. Learning volitional control of functional connectivity: Effects on behaviour—D. Singh Kajal[a,b,c], J. Mellinger[a], S. Ruiz[d,c], M. Sacchet[e,f], E. Fetz[g], N. Birbaumer[h,c], R. Sitaram[i,j,c], C. Braun[a,k] ([a]Universität Tübingen, MEG-Zentrum, Tübingen, Germany, [b]Universität Tübingen, Graduate Training Center, Tübingen, Germany, [c]Universität Tübingen, Institute of Medical Psychology, Tübingen, Germany, [d]Pontificia Universidad Catolica de Chile, Departamento de Psiquiatría, Santiago, Chile, [e]Stanford University School of Medicine, Neuroscience Program, Stanford, United States, [f]Stanford University, Department of Psychology, Stanford, United States, [g]University of Washington, Department of Physiology and Biophysics, Seattle, United States, [h]San Camillo Hospital, Scientific Institute for Research, Hospitalization and Health Care, Venice, Italy, [i]University of Florida, Department of Biomedical Engineering, Gainsville, United States, [j]Sri Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India, [k]Università degli Studi di Trento, CIMeC, Centro interdipartimentale Mente e Cervello, Trento, Italy)

Cerebral information processing involves the activation of brain regions and the exchange of information between them. As metric for intra-cortical communication, coherence, a frequency specific measure quantifying the correlation of the amplitudes across trials of two phase-locked signals, has been suggested. A value of 0 indicates that both signals are unrelated, a value of 1 that both signals are fully synchronized. It is evidenced by the plethora of findings that the functional connectivity between brain regions is modulated by brain states, mental processing and the planning and execution of actions. Thus, it might be hypothesized that volitionally modulating the functional connectivity between two interacting brain regions should have an impact either on behavior or cognition. The purpose of the study was to test whether subjects can learn to volitionally modulate brain functional connectivity between left and right motor cortices employing a neurofeedback training and whether the neurofeedback training induces specific effects on motor function.

Thirty right-handed subjects participated in the study. The subject group was partitioned into two sub-groups, namely contingent feedback group and sham feedback group, consisting of fifteen subjects. During the neurofeedback training the magnetic brain activity originating from left and right primary motor cortices was recorded using magnetoencephalography (MEG) and a feedback signal representing the coherence between the primary motor cortices of both hemispheres was presented to the subjects on a screen. Subjects receiving contingent feedback were trained to increase coherence while the discriminative stimulus S^{D+} was presented and to decrease coherence while the S^{D-} was presented. A pretest and posttest examination served to examine whether acquired control on functional connectivity evidences any behavioral effects. During pre- and posttest subjects had to perform a complex bimanual finger tapping task while the discriminative stimulus either for up- or down-training was presented.

Our findings suggest that it is possible to modulate the functional connectivity between the primary motor cortices of both hemispheres and that changes in functional connectivity do have a strong behavioral impact. Modulating the functional connectivity between brain regions can be used to study the functional role of cortico-cortical connections and will offer therapeutic interventions in brain diseases originating from impaired intra-cortical connections.

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P114. Differences in the activation of superficial brain structures by popular dance and art music: An fMRI study—C. Rusner[a], A. Todt[b], M. Knörgen[a], R.P. Spielmann[a], W. Auhagen[b] ([a]Universitätsklinikum Halle (Saale), Universitätsklinik und Poliklinik für Diagnostische Radiologie, Halle, Germany, [b]Martin-Luther-Universität Halle-Wittenberg, Institut für Musik, Abteilung Musikwissenschaft, Halle, Germany)

Background: Speculations that music might be "moving" not only in metaphorical sense date back to the 17th century. Modern measurement procedures which register activity of the brain could show that not only dancing and playing music, but also listening, and even anticipatory imagination of music may include stimulation of motor areas in the human brain. The aim of this study was to assess the activation of superficial brain structures by popular dance music and art music in young adults using functional magnetic resonance imaging.

Methods: The recruitment of volunteers for the fMRI experiment was carried out via the social network Stud.IP of the Martin-Luther-University Halle-Wittenberg (http://studip.uni-halle.de/index.php?cancel_login=1). We studied whether there is a difference in activation patterns between 10 subjects who strongly like to dance with frequent visits of music clubs and discos versus 10 subjects who are more or less indifferent towards dancing. The fMRI

Learned control of inter-hemispheric connectivity: Effects on bimanual motor performance.

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	Authors	**Contribution**
1	**Diljit Singh Kajal**	Collected and analysed the data, wrote manuscript
2	Christoph Braun	Designed the experiment, Statistical analysis and wrote manuscript
3	Jürgen Mellinger	Setup experiment: BCI2000
4	Matthew Sacchet	Edited the manuscript
5	Sergio Ruiz	Edited the manuscript
6	Eberhardt Fetz	Edited the manuscript
7	Neils Birbaumer	Edited the manuscript
8	Ranganatha Sitaram	Designed the experiment, edited the manuscript

◆ **Human Brain Mapping 38:4353–4369 (2017)** ◆

Learned Control of Inter-Hemispheric Connectivity: Effects on Bimanual Motor Performance

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Abstract: Bimanual movements involve the interactions between both primary motor cortices. These interactions are assumed to involve phase-locked oscillatory brain activity referred to as inter-hemispheric functional coupling. So far, inter-hemispheric functional coupling has been investigated as a function of motor performance. These studies report mostly a negative correlation between the performance in motor tasks and the strength of functional coupling. However, correlation might not reflect a causal relationship. To overcome this limitation, we opted for an alternative approach by manipulating the strength of inter-hemispheric functional coupling and assessing bimanual motor performance as a dependent variable. We hypothesize that an increase/decrease of functional coupling deteriorates/facilitates motor performance in an out-of-phase bimanual finger-tapping task. Healthy individuals were trained to volitionally regulate functional coupling in an operant conditioning paradigm using real-time magnetoencephalography neurofeedback. During operant conditioning, two discriminative stimuli were associated with upregulation and downregulation of functional coupling. Effects of training were assessed by comparing motor performance prior to (pre-test) and after the training (post-test). Participants receiving contingent feedback learned to upregulate and downregulate functional coupling. Comparing motor performance, as indexed by the ratio of tapping speed for upregulation versus downregulation trials, no change was found in the control group between pre- and post-test. In contrast, the group receiving contingent feedback evidenced a significant decrease of the ratio implicating lower tapping speed with stronger functional coupling. Results point toward a causal role of inter-hemispheric functional coupling for the performance in bimanual tasks. *Hum Brain Mapp 38:4353–4369, 2017.*

Key words: neurofeedback; coherence; behavior; magnetoencephalography; braincomputer interface; motor

INTRODUCTION

Humans can produce complex bimanual movements, such as typing an article on a computer keyboard or playing piano with both hands executing different tunes. In these tasks, fingers of both hands are either moved simultaneously or rather independently, yet in a coordinated fashion. Such bimanual movements require precise coordination of the timing of muscular activation in both sides of the body and close interactions between cortical areas of motor control [Cardoso de Oliveira et al., 2001].

Studies investigating the neurophysiological and neuroanatomical basis of bimanual coordination have identified various cortical and subcortical regions [Rouiller et al., 1994; Wiesendanger et al., 1994, 1996]: starting with neocortical regions, bilateral supplementary motor area (SMA: crucial role in bimanual coordination), primary motor areas (M1: motor coding), and dorsal pre-motor areas posterior parietal cortex, cingulate cortex (spatial and temporal coordination) and subcortical structures like basal ganglia and cerebellum have also been found to play a role in bimanual coordination in both, healthy individuals and patients with motor disorders such as Parkinson's and Huntington disease. The interaction between these areas for bimanual coordination is mainly indexed by functional coupling, that is, phase-locked oscillatory activity, collaborating at different frequencies [Banerjee and Jirsa, 2007; Gerloff and Andres, 2002]. As a metric of functional coupling, correlations of amplitudes, as well as parameters measuring the extent of phase-locked activity have been introduced [Akam and Kullmann, 2012; Bastos et al., 2015; Fries, 2005, 2015].

Although functional coupling occurs on various levels of the motor control system, its role in bimanual coordination might be best studied in primary motor cortices [Donchin et al., 1998, 2002] as they control the muscular activity via cortical output and thus constitutes a major easy-to-study hub for motor networks.

From behavioral as well as neurophysiological studies, two different biological models that attempt to explain the neural mechanisms involved in bimanual motor coordination have been put forward: the model of general motor programs (GMP) [Schmidt, 1975; Schmidt et al., 1979] and the model of inter-manual cross talk [Marteniuk et al., 1984; Marteniuk and MacKenzie, 1980]. The model of GMP is derived from the observation of strong spatiotemporal similarities of bimanual coordination suggesting that there is a common motor plan for both limbs. In contrast, the model of inter-manual crosstalk suggests that there are independent motor plans for each hand and that these plans interact via crosstalk between motor control signals at various levels of the motor system.

Strong support for the inter-manual crosstalk model comes from studies by Cardoso de Oliveira et al. [2001]. Using single unit recordings [Cardoso de Oliveira et al., 2001] they found that inter-hemispheric but not intra-hemispheric coupling was consistently related to the degree of bimanual coordination: symmetric bimanual movements were accompanied by significantly stronger increases of correlation than out-of-phase, asymmetric bimanual movements. However, in contrast to this study, also a decrease of inter-hemispheric functional coupling between bilateral M1 regions for symmetric bimanual movements as compared to out-of-phase bimanual tasks has been reported [Rueda-Delgado et al., 2014]. The contradicting results point to the fact that the role of functional coupling for bimanual motor control is still a matter of debate and calls for more elaborated studies.

Previous studies investigating the role of inter-hemispheric functional coupling in bimanual coordination have often varied the motor tasks as an independent variable and studied the concurrent changes of functional coupling as dependent variable. These studies deduced the role of functional coupling for bimanual movements from the correlative relation between the type of task and the degree of coupling. In our study, we follow an alternative approach that overcomes the limitations of not implying causation in correlative studies: we manipulate the degree of inter-hemispheric functional coupling between left and right primary motor cortex using a neurofeedback training and explore its effects on motor performance. In our neurofeedback approach, the dependent variable is recorded down-stream from the site of modulation and thus allows for a more causal interpretation of the relation between functional coupling and behavior.

To investigate the effects of modulating inter-hemispheric functional coupling on motor performance, the neurofeedback training should enable participants to reliably upregulate and downregulate functional coupling on request and in a motor performance task scheduled after the neurofeedback training. Given these requirements we opted for an operant conditioning paradigm for the neurofeedback training. The sole motivation for this approach comes from the dual process theory by Groves and Thompson, [Groves and Thompson, 1970] which posits that there is a fast, unconscious implicit and effortless cognitive control system for actions (System I) and a slow, conscious, explicit, effortful one, that involves deliberate reasoning and critical thinking (System II). They both activate brain areas and neuronal networks in a task-related fashion and thus eventually evoke behavior. According to Grooves and Thompson, System II is shaped by insight and observational learning and System I is modulated by classical and operant conditioning associating a reaction to a stimulus [Birbaumer et al., 2013; Chaudhary et al., 2016, 2017; Daly et al., 2012].

In our study, we trained healthy individuals using real-time magnetoencephalography neurofeedback (rt-MEG) [Kajal et al., 2015; Sacchet et al., 2012] to modulate inter-hemispheric functional coupling and to observe its effects on an asymmetric out-of-phase, bimanual finger-tapping task (AOBFT). The conditioning associated upregulation and downregulation to a discriminative stimulus S^D, with S^+ cueing the upregulation and the S^- the downregulation functional coupling. Presenting S^+/S^- in the motor performance task was supposed to elicit increased/reduced inter-hemispheric functional coupling and alter motor performance. This operant conditioning approach has been widely used to modulate brain states in neurofeedback studies [Fetz, 1969; Nowlis and Kamiya, 1970; Ramos-Murguialday and Birbaumer, 2015]. To account for unspecific effects, we trained upregulation and downregulation of functional coupling to individuals who received sham feedback (SF).

Training-induced changes in motor performance were assessed prior to (pre-test) and after (post-test) the neurofeedback training. We hypothesize that learned upregulation of inter-hemispheric functional coupling will deteriorate motor performance in the AOBFT in the presence of the S^+-stimulus. Presenting the S^--stimulus we expect an improvement of performance from pre-test to post-test sessions. Results would provide insight into the role of inter-hemispheric functional coupling for bimanual motor tasks.

MATERIAL AND METHODS

Participants

rt-MEG-neurofeedback was performed on 30 healthy participants ($M \pm SD = 26.0 \pm 3.1$ years; 20 males) with no history of neurological or psychiatric illness or head trauma. None of the participants were taking any medication. Participants were evenly and randomly assigned to one of two groups: the contingent feedback (CF) group or the SF group ($n = 15$ each). The ethics committee of the Faculty of Medicine at the University of Tubingen, Germany approved the experimental protocol. Written informed consent was acquired from all participants. Participants received financial compensation of Euro 10/hour for their participation in the study.

Experimental Procedure

The experimental protocol includes four main experimental parts that were presented across five days: (1) pre-test: execution AOBFT (day one); (2) functional localizer: participant-specific identification of the MEG sensors from which the feedback signal was computed (day two), the frequency bands of the MEG oscillatory activity from which the feedback signal was computed (day three); (3) neurofeedback training (day four); and (4) post-test: AOBFT identical to pre-test on day1 to assess the impact of the training on performance (day five).

In the following, the different sessions of the experiments are explained in the same order as they appear in the above list. Only the post-test session is explained together with the pre-test session because both setups are essentially the same.

Pre-Test and Post-Test (Day One and Five)

Examination of behavioral data from the pre-test and the post-test sessions allowed us to study how upregulation and

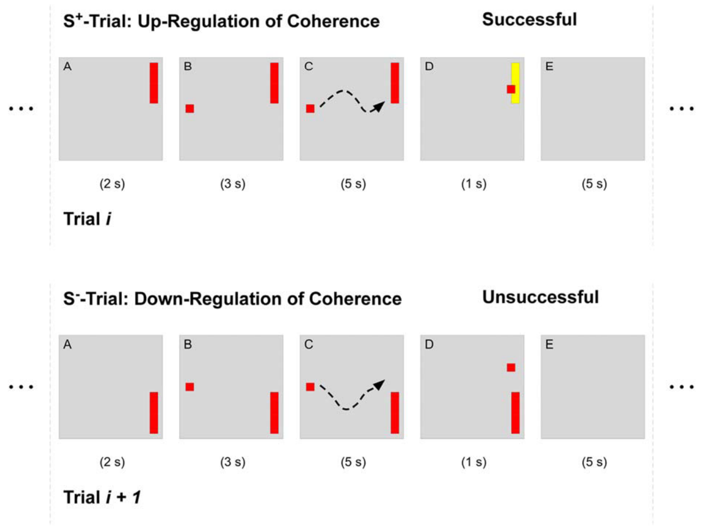

Figure 1.

Schematic of a real-time functional coupling neurofeedback trial. (A) Cue phase: the discriminative stimulus S^D appears for 2 s, indicating whether the current trial is either an S^+ or S^- trial; (B) initiation phase: cursor appears and remains stationary for 3 s while the initial real-time functional coupling is calculated and the participant begins self-regulation of functional coupling (C) active feedback phase: for 5 s the cursor moves in the *x*-direction at a constant velocity and in the *y*-direction with an amplitude relative to the functional coupling calculated from the immediately preceding 3 s interval; (D) feedback phase: a successful trial is indicated by the target changing to yellow for 1 s, and the target remains red for an unsuccessful trial; (E) inter-trial interval of 5 s. dots) indicate continuation of the next trial. [Color figure can be viewed at wileyonlinelibrary.com]

downregulation of inter-hemispheric functional coupling affects behavioral performance, and whether effects of neurofeedback training generalize to a "no feedback" condition.

Specifically, pre-test and post-test sessions used the AOBFT involving left and right hand index and middle fingers. Participants pressed four optical buttons in a self-paced, predefined sequence involving both hands (AOBFT) as follows: right hand index finger, left hand index finger, right hand middle finger and left hand middle finger. This sequence was to be completed as quickly and as accurately as possible. The AOBFT was chosen as task instead of a task that involves only one finger and its contralateral homologue, to provide sufficient room for the potential variations in tapping performance.

In both, the pre-test and post-test sessions, the two experimental conditions were indicated by the discriminative stimulus S^Ds (either S^+ or S^-) that were presented on the screen in front of the participants. In the pre-test, the S^D were meaningless since the association between the discriminative stimuli and the modulation of functional coupling had not yet been established. Only after the neurofeedback training, S^Ds were assumed to have acquired relevance such that S^+ was associated with upregulation and S^- with downregulation of functional coupling. As in the neurofeedback session, S^+ was a red bar on the right upper part, and S^- a red bar on the lower part of the screen (see Fig. 1).

Each trial started with the presentation of the S^D, which was supposed to modulate subject's functional coupling and at the same time instructed participants to start the AOBFT. All participants were requested to continue AOBFT as long as the S^D remained on the screen. Both pre-test and post-test sessions comprised 100 trials. Across trials, S^+ or S^- were presented in a pseudo-randomized manner with 50 trials per condition. Each trial lasted for 10 s. During pre-test and post-test sessions, neuro-magnetic brain activity was recorded with MEG.

Functional Localizer: Parameter Identification for Neurofeedback (Day Two and Three)

In this part of the experiment, we sought to identify participant-specific parameters of MEG signatures to be trained in the neurofeedback training. To determine the MEG channels that captured activity generated in primary motor cortex, we explored the modulation of sensorimotor rhythm

(SMR) by activity of each hemisphere (2 sensors per hemisphere). Furthermore, the individual dominant SMR frequency band in two distinct motor tasks, that produce high and low inter-hemispheric functional coupling, was determined.

For the identification of the four participant-specific MEG channels representing activity generated in primary motor cortex, participants performed self-paced hand movements, that is, hand-opening and -closing versus rest (day two). Two sensors were chosen on each hemisphere. To capture the dipolar character of motor cortex activity the two sensors showing strongest SMR activity with opposite polarity were chosen. Each session consisted of 200 trials, 100 trials each for left and right hand movements. Left and right hand movements and rest were performed in pseudo-random order. Visual cues were used to indicate which hand to move. Sequences of hand movements of 5 s were interspersed with 2 s of rest. Hand opening and closing as well as rest were different from the movement tasks in pre- and post-test sessions to avoid any interfering training effects.

To identify the frequency for which functional coupling feedback was provided (day three), participants performed the following five self-paced, continuous finger-tapping tasks: (a) tapping of the right index finger; (b) tapping of the left index finger; (c) bimanual tapping of the index fingers in a symmetric manner; (d) bimanual tapping of the index fingers in an asymmetric manner; and (e) rest. For each task, a spectrum of inter-hemispheric coupling was obtained. The pair of tasks showing the maximum difference in functional coupling was selected and the corresponding frequency was chosen to be used in the coupling feedback. Each participant completed 200 trials, that is, 40 trials for each movement type. Tasks were requested in pseudo-randomized order and participants were visually cued regarding the type of task to perform. The interval between start and stop of each trial was 5 s. The inter-trial interval, during which participants relaxed, was 2 s.

Neurofeedback Training (Day Four)

Neurofeedback training was realized in an operant conditioning setup and involved differential upregulation and downregulation of inter-hemispheric functional coupling of SMR. Coherence was estimated from the time-series of MEG signals in the four selected sensors and the frequency band identified during the functional localizer session. A real-time measure of functional coupling between the four MEG sensors over the motor cortex was used as a representation of inter-hemispheric functional coupling. Participants received real-time visual feedback of functional coupling during each trial. Indication to upregulate or downregulate inter-hemispheric functional coupling was provided by two S^Ds already introduced in the pre-test session: (a) a red bar appearing either at the right upper half of the screen (S^+) to indicate the upregulation, or (b) at the right lower half of the screen (S^-) to indicate downregulation of functional coupling. In each trial of the neurofeedback session, the goal was to direct an on-screen red cursor (Fig. 1) toward a red rectangular target (the S^D). Participants were not informed that S+ required upregulation and S- required downregulation of the coupling but only that two different brain states should be "produced" during the two S^D's.

Neurofeedback training was given in an identical manner to both groups of 15 participants each, namely: CF group which received CF and the SF group receiving SF serving as a control group. The participants in both groups and experimenters were blind regarding the type of feedback they received. Post experimental questioning indicated that the SF group did not realize the lack of contingency in the feedback, but believed that the feedback was veridical feedback as in the CF group. For the SF group, the experimental instructions provided to the participants were identical to that of the participants in the CF group. The number of blocks, trial number, and trial structure were the same as in the CF sessions.

The neurofeedback training comprised 200 trials. During half of the trials, participants performed upregulation, and in the remaining trials, participants performed downregulation of the neuro-magnetic signals. Trials of upregulation and downregulation of coupling were pseudo-randomized across trials.

A single trial started with a 2 s preparation interval during which the S^D prompted the participant to be prepared for either upregulation or downregulation (Fig. 1). At the same time, a cursor appeared on the screen remaining stationary on the screen for 3 s. During this period, the baseline for the neurofeedback was acquired. Thereafter the active feedback phase begun, lasting for 5 s. In the feedback phase, the cursor moved horizontally with a constant velocity. While for the CF group the vertical cursor movement velocity was proportional to the real-time measure of inter-hemispheric functional coupling, it was random for the SF group. The random values were modeled with a Rayleigh distribution by fitting to the histograms of the functional coupling values obtained during CF. The amount of positive and negative feedback in the SF group was identical to the CF group. The period of active feedback was followed by a 1 s interval in which the performance in the feedback task for that trial was indicated: the target either changed to yellow, indicating a successful trial, or remained red indicating an unsuccessful trial. After the feedback of the trial outcome, the S^D disappeared. Inter-trial intervals consisted of the presentation of a blank screen for 5 s. Participants were encouraged to produce as many successful trials as possible. At the end of each block they were informed about the number of generated hits.

One hour before the MEG-neurofeedback training, participants were informed and familiarized with the experimental paradigm and the tasks to be performed. During the experiment, participants sat upright in the MEG chair facing a 40 cm × 30 cm screen displaying instructions and feedback information to the participants. Participants of both the groups, CF and SF, were informed about the experiment and instructed not to perform any overt movement during the neurofeedback training session. We monitored the participants using a video camera. None of the participants performed any visible overt hand movement, although it cannot be fully excluded that subjects might have used some muscle activation escaping the observation of the experimenter. Head movements were tracked using the MEG head localization system. Participants were informed that they were free to try any cognitive strategy and to apply what worked best for them in terms of positive feedback to modulate inter-hemispheric coupling.

MEG Data Acquisition

During the experiment, participants were seated in a magnetically shielded dimly lit room (VacuumSchmelze, Hanau, Germany) at the MEG Center of the University of Tübingen with their head placed in the helmet of a whole-head MEG System (VSM Omega system MISL, Vancouver, Canada).

The MEG system comprises 275 first-order axial gradiometers with a gradiometer baseline of 5 cm. Data were sampled at a rate of 1,172 Hz, with an anti-aliasing low-pass filter set at 416 Hz. Head position was continuously monitored using localization coils affixed to the participant's head at predefined fiducial locations (nasion, and left and right preauricular points). The coils were driven using sinusoidal currents at frequencies (156.25 Hz, 125.00 Hz, and 104.16 Hz) distant from the range of brain signals of interest (< 45 Hz). The three fiducial points defined the head-centered coordinate system used in all data analyses. Using the head localization information, it was ensured that the participant's head was repositioned to the pre-test session.

Real-Time Signal Processing

The magnitude squared coherence between the two neural signals were computed as the measure of functional coupling which can be defined as follows:

$$Cxy(f)=\frac{[Sxy(f)]^2}{[Sxx(f)]\text{x}[Syy(f)]} \tag{1}$$

where S_{xy} is the cross spectral density between signal x and y and S_{xx} and S_{yy} are the auto spectral densities of x and y, respectively, at frequency f Hz. We used squared magnitude coherence for the online calculation of the feedback signal as well as during off-line data analysis. We used 19 segments of 0.208 s duration overlapping by 50% to compute a 2 s baseline coherence for each trial. As the trial proceeded, functional coupling was continuously updated using the most recent 3 s intervals for the computation.

The weighted overlapping-segment averaging (WOSA) estimator was used as a coherence estimator. This method was chosen for its advantage of minimum bias and variance in the coherence estimation [Zaveri et al., 1999]. In this method, two signals of Qs duration are divided into n segments which might overlap up to a certain percentage p and for which Fourier sample spectra are calculated. Based on the spectra, squared magnitude coherence is derived. In our experiment, functional coupling was quantified in the most recent 3 s intervals of the constantly updated input data. The interval was divided into 28 segments of 0.208 ms duration and 50% overlap.

To reduce computational cost, the WOSA neural coherence was not calculated for all frequencies. Instead, a FIR filter was used to extract signals at the participant-specific frequency of interest identified in the functional localizer session. The digital signal-processing module of the BCI2000 software performed spatial filtering and spectral analysis of the signals, which were then transformed into cursor movements.

BCI2000 software was used to provide real-time, visually presented neurofeedback of MEG functional coupling [Mellinger et al., 2007; Schalk et al., 2004]. The computer running BCI2000 was connected to the standard MEG data acquisition hardware via Ethernet interface using TCP/IP. Real-time data was accessed immediately after the CTF Acquire program had stored the raw digitized MEG data in memory. The BCI2000 computer accessed the raw data in shared memory in a constant block size of 44 samples (after digitization). The data blocks were transmitted from the MEG computer to BCI2000 software in intervals of 70.4 ms. On the computer running BCI2000, a second program acted as a relay to BCI2000 via a TCP/IP-based socket interface.

During the neurofeedback trials, the horizontal movement of the cursor (v_x) was kept constant, whereas the vertical amplitude of the cursor (v_y) changed in relation to the amount of neural coherence (NC) computed using the last 3 s of the MEG signal:

$$v_y=b^*(\text{NC} -a) \tag{2}$$

where intercept "a" and gain "b" were adapted dynamically to optimize the control over cursor movement. Specifically, the intercept "a" was dynamically adapted to facilitate the accessibility of both S^+ and S^-. At the end of each trial, "a" was recalculated as:

$$a=\frac{1}{2}(S^+-S^-) \tag{3}$$

where S^+ and S^-. are the adaptive online estimates of the mean of neural coherence (S) computed separately over the three preceding trials for S^+ and S^-, respectively. The gain parameter determined the rate at which the cursor moved vertically on the screen and was adjusted such that the rate of the cursor movement was neither too fast nor too slow. This was desirable as small gains require high visual sensitivity and do not utilize the whole screen, and large gains result in erratic cursor movement. The gain of the feedback procedure was adjusted after each trial as:

$$b \propto \frac{1}{(S^{+}-S^{-})} \tag{4}$$

Off-Line Data Analysis

Offline data analysis was conducted in MATLAB (The Mathworks, Natick, USA) using the FieldTrip toolbox [Oostenveld et al., 2011] and in-house Matlab scripts. To study the neural generators of the activity recorded at sensor level and to localize cortical sources that showed coherent activity to the sensor level motor activity (SLMA), we used the Beamformer method "Dynamic Imaging of Coherent Sources (DICS)" [Gross et al., 2001]. Potential source positions were defined using a regular 3D grid with 8 mm resolution covering the whole brain. For each potential source position, the leadfield matrix that depends on the electrical properties of the head tissues and on the geometrical relation between the sources and the sensors and describes the contribution of a pre-assumed source to the MEG sensors was calculated. In the second step, filter coefficients were estimated that define the contribution of the activity at each sensor to the source activity at that target location. Filter coefficients depend on the cross-spectral density matrix that characterizes the correlation between the activities at different sensors for a given frequency band. In general, the Beamformer is a source estimation procedure that projects and optimally focuses sensor level activity to source space.

Analysis of the Functional Localizer Data

Offline analysis of functional localizer session data included the creation of topographical maps of SMR-power changes for left and right hand movements versus rest. From each hemisphere, two MEG sensors were identified showing the highest determination coefficients (R^2-values signifying the amplitude variance of SMR for hand opening and closing versus rest) over contralateral primary motor cortex (Fig. 2). Since the two MEG channels of one hemisphere were selected such that they capture the out- and ingoing magnetic fields of the activity generated by primary motor cortex, an estimate of the time course of motor cortical activity was obtained by subtracting the activity recorded at these two channels. Using the identified SMR-MEG sensors, data from the functional localizer session were further analyzed to identify two tasks (from five total tasks) for which the difference in functional coupling was highest. The frequency at which the highest functional coupling difference occurred was chosen as frequency of coupling for which feedback was given in the training.

For the spectral analysis, continuously recorded data were segmented into 40 epochs of 5 s duration each representing the activity of an individual trial. For each epoch, the first and the last 0.5 s of data were discarded to exclude potential artifacts resulting from the initiation or termination of movements. Next, pre-processing was conducted, including demeaning, trend removal, and filtering of 50 Hz power line noise. Trials containing eyeblinks, muscular artifacts, and in which the magnetic activity exceed ± 1 pT were removed. Then, Fast Fourier Transform with multi-Hanning taper [Percival and Walden, 1993] was applied to consecutive 0.208 s intervals of the previously epoched data to estimate spectral information. Finally, magnitude squared coherence was computed.

Analysis of the Real-Time Neurofeedback Data

Neurofeedback data were segregated into upregulation (S^{+}) and downregulation (S^{-}) trials. Depending on participants' performance in controlling inter-hemispheric functional coupling in the individual trials, trials were further classified into successful (the desired increase/decrease in functional coupling was achieved) or unsuccessful trials (the desired increase/decrease of functional coupling was not achieved). The first and the last 0.5 s of each trial were discarded. Datasets were pre-processed and analyzed as for the task identification session. Trials containing eyeblinks, muscular artifacts, and in which the magnetic activity exceed ± 1 pT were removed. For all participants, a minimum of 160 artifact-free trials was obtained. To assess the time-course of training-induced changes of functional coupling, the first 160 artifact-free trials were subdivided into 8 blocks of 20 trials for each participant and the percentage of successful trials was computed. Statistical significance of changes was tested by a two-way ANOVA with the within-subject factor BLOCK (8 levels) and the between subject factor GROUP (levels: CF and SF). Post hoc tests were done by *t*-tests. To study the possible changes in the inter-hemispheric functional coupling due to differential head movements, we performed a statistical analysis of the three fiducial positions for upregulation and downregulation using a paired *t*-test for the neurofeedback session (Left, Right preauricular points and nasion).

To verify that the inter-hemispheric sensor-level coherence used in the neurofeedback trainings was a good estimate of the source level functional coupling between left and right primary motor cortices, DICS [Gross et al., 2001] was used to localize cortical sources that showed coherent activity to the SLMA of both hemispheres. Due to volume conduction, we expected strong coupling between the activity of *ipsilateral* motor cortex and the SLMA recorded from the corresponding hemisphere independently of whether individuals managed to modulate inter-hemispheric coupling. Unilateral motor cortex activity and the corresponding ipsilateral SLMA are expected to reflect identical activities either on the source or sensor level respectively. However, functional coupling between unilateral motor cortex activity on one hemisphere and *contralateral* SLMA should reflect inter-hemispheric functional coupling. Thus, we expect increased functional coupling between motor cortex activity and contralateral SLMA for trials in which S^{+} was requested and which were classified as hit $C^{S^{+}}_{\text{successful}}$. Vice versa, we expected lower inter-hemispheric functional coupling for trials in which S^{+} was

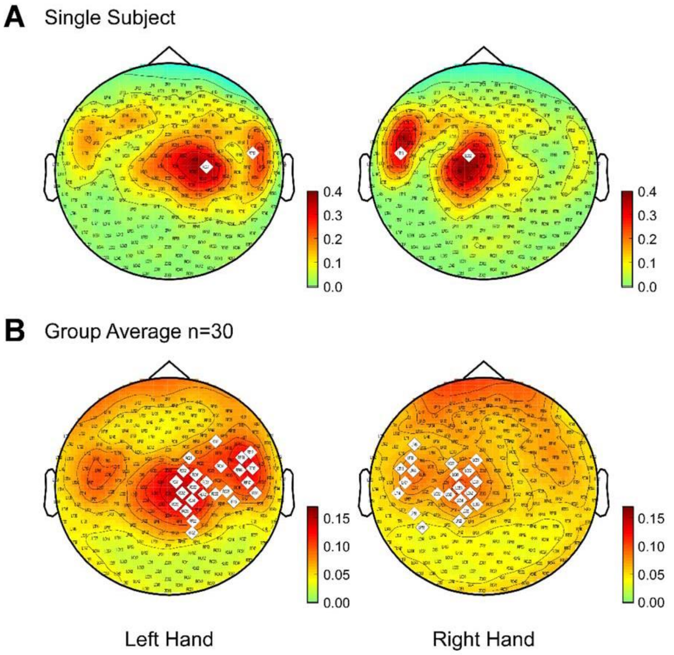

Figure 2.

Functional localizer for the identification of MEG channels to be used in the neurofeedback training. (**A**) Data from a representative participant; R^2-plots of SMR computed on data between hand closing and opening vs. rest (left panel presents results for the left hand; right panel presents results from the right hand). Patches of increased R^2-values represent maximal desynchronization and correspond to a dipolar source pattern. These sources are located approximately in the center of the hemisphere contralateral to the side of hand movement. Two channels were selected from each hemisphere from which functional coupling between left and right motor-related sensors was computed (see text). (**B**) Grand average R^2-plots of SMR for all participants of the CF group and for the SF group combined.

requested, yet not achieved according to the online feedback algorithm. Thus, subtracting the functional coupling obtained for miss (unsuccessful) trials in the S^+ condition from the corresponding hit trials $C^{S^+}_{\text{successful}} - C^{S^+}_{\text{unsuccessful}}$ should cancel the coherent activity due to volume conduction and the local spread of activity on the hemisphere ipsilateral to SLMA and reveal source level inter-hemispheric functional coupling between SLMA and the motor cortex activity contralateral to it. Similarly, subtracting functional coupling between SLMA and the source activity for trials classified as misses in the S^- condition from hit trials $C^{S}_{\text{successful}} - C^{S}_{\text{unsuccessful}}$ should yield lowest coupling values for the motor cortex contralateral to SLMA. As can be seen in the example presented in Figure 6: the double difference $(C^{S^+}_{\text{successful}} - C^{S^+}_{\text{unsuccessful}}) - (C^{S}_{\text{successful}} - C^{S}_{\text{unsuccessful}})$ of the functional coupling values reveals a pronounced patch of functional coupling between SLMA and source level activity in contralateral primary motor cortex. These results support the notion that left and right SLMA capture functional coupling to the right and left motor cortices, respectively.

Analysis of Pre-Test and Post-Test Data

To infer behavioral effects of the neurofeedback training on the AOBFT task, we compared the tapping frequency between the S^+ and S^- trials, corresponding to upregulation and downregulation trials for pre- and post-test. Tapping frequency v was defined as the inverse of the average time interval between any two-subsequent finger-taps. In case of an error in the tapping sequence, taps with erroneous sequence were discarded from the analysis until the correct sequence was reproduced again. Tapping intervals smaller than 0.1 s and longer than 2.0 s were removed prior to averaging. To reduce the inter-subject variability of finger-tapping frequency values in the AOBFT, absolute ratios r_{pre} and r_{post} of finger-tapping frequency for S^+ to S^- trials were computed for pre- and post-test: $r_{\mathrm{pre}}=\frac{v^{S^+}_{\mathrm{pre}}}{v^{S}_{\mathrm{pre}}}$ and $r_{\mathrm{post}}=\frac{v^{S^+}_{\mathrm{post}}}{v^{S}_{\mathrm{post}}}$, respectively. Since, S^+ and S^- do not have any functional relevance in the pre-test session, tapping frequencies are supposed to be similar for both conditions and thus r_{pre} should approximate 1. In the post-test session, however, r_{post} will only approach to 1 if the training has not affected the S^+ and the S^- conditions differentially. $r_{\mathrm{post}} > 1$ reflects a differential effect of the training on tapping speed, with higher speed for S^+ than for S^-. In contrast, $r_{\mathrm{post}} < 1$ reflects higher tapping speed in S^- than in S^+. To summarize the training effects on motor performance, the Motor Performance Index (MPI) was calculated as the ratio between r_{post} and r_{pre}:$\mathrm{MPI}=\frac{r_{\mathrm{post}}}{r_{\mathrm{pre}}}$. If MPI does not deviate significantly from 1, motor performance is assumed not to be affected by the feedback training. $\mathrm{MPI} > 1$ suggests a differential effect of the training on S^+ and S^- trials with higher tapping speed for S^+ than for S^- trials. In contrast, $\mathrm{MPI} < 1$ reflects a higher tapping speed for S^- than for S^+ trials.

To quantify training-induced changes in inter-hemispheric functional coupling in the post-test session as compared to the pre-test session, a functional connectivity index (FCI) was defined in analogy to MPI. First, the mean functional couplings $\gamma^{S^+}_{\mathrm{left}}$, $\gamma^{S^+}_{\mathrm{right}}$, $\gamma^{S}_{\mathrm{left}}$, and $\gamma^{S}_{\mathrm{right}}$ were calculated for left and right reference sensors across S^+ and S^- trials. Then, ratios for left and right reference sensors were averaged yielding $c_{\mathrm{pre}}=\frac{1}{2}\left(\frac{\gamma^{S^+}_{\mathrm{left,pre}}}{\gamma^{S}_{\mathrm{left,pre}}}+\frac{\gamma^{S^+}_{\mathrm{right,pre}}}{\gamma^{S}_{\mathrm{right,pre}}}\right)$ and $c_{\mathrm{post}}=\frac{1}{2}\left(\frac{\gamma^{S^+}_{\mathrm{left,post}}}{\gamma^{S}_{\mathrm{left,post}}}+\frac{\gamma^{S^+}_{\mathrm{right,post}}}{\gamma^{S}_{\mathrm{right,post}}}\right)$. In a final step, FCI was calculated as $\mathrm{FCI}=\frac{c_{\mathrm{post}}}{c_{\mathrm{pre}}}$.

A two-way ANOVA with the within factor session (levels: pre-test and post-test) and the between factor group (levels: CF and SF) was computed to test the group-specific effects of the neurofeedback training on behavior. Unpaired *t*-tests tested whether MPI and FCI differed significantly between the CF and SF group. To determine whether MPI and FCI differed significantly from one in the CF or the SF group or in both groups, one-sample *t*-tests were performed. To investigate the relation between changes in inter-hemispheric functional coupling and changes in motor performance, MPI and FCI were correlated across all 30 participants.

RESULTS

Functional Localizer: Selection of Channels

The functional localizer session identified the MEG sensors over bilateral primary motor cortices induced by event-related desynchronization (ERD) in SMR by hand opening and closing compared to rest in each participant (Figs. 2 and 3). For each participant, two channels (one for each pole of the bipolar pattern) were selected from each hemisphere for subsequent use in the neurofeedback training. Since the two poles of one hemisphere have opposite polarity, their difference was taken as a proxy for the activity of the underlying motor cortex activity of the corresponding hemisphere (SLMA). R^{2}-values (signifying the amplitude variance of SMR for hand opening and closing versus rest) for the selected sensors reached significance in all participants ($R^2 > 0.0487$, t $(98) = 2.24$, $P = 0.027$ after Bonferroni-Holm's correction for multiple comparisons [Holm, 1979]), indicating that SMLA differentiates significantly between hand movements and rest.

Parameter Selection for Neurofeedback Training

To determine the individual frequencies for training of coherence, out of the five motor tasks, functional coupling differences were computed for all pairs of tasks for each participant (Fig. 4). Frequency was selected for the range of 0 to 30 Hz. Coherence was computed at the previously identified sensors. Across participants, the frequencies exhibiting the largest functional coupling differences ranged from 5 to 23 Hz [Andres et al., 1999; Daly et al., 2012; Pfurtscheller, 1992; Pfurtscheller and Aranibar, 1979; Pfurtscheller and Da Silva, 1999; Stančák et al., 2002; Zito et al., 2014] (CF group: $M \pm SE$: 13.5 ± 6.8 Hz; SF group: $M \pm SE$: 17.1 ± 9.4 Hz).

Neurofeedback training

In this analysis, the hit rate was assessed as a measure of successful training. Analysis of block-by-block performance involving the factors GROUP (levels: CF and SF) BLOCKS (levels: block 1 to 8) revealed a significant difference in the number of hits for both S^+ and S^- between the CF and the SF groups (F (1, 28) =17.56, $P = 0.0003$) (Fig. 5). A significant main effect of BLOCKS (F (7, 196) = 3.44, $P = 0.0017$) and a significant interaction between factors GROUP × BLOCKS were also found (F (7, 196) = 8.56, $P < 0.001$). Separate posthoc analysis within groups revealed a significant effect of BLOCKS for the CF group: F (7, 98) = 13.36, $P < 0.0001$), but not for the SF group (F (7, 98) = 1.41, $P > 0.2$). The significant effect of BLOCKS in the CF group became evident as a significant positive correlation between block number and hit rate ($r = 0.96$, significance for the correlation being larger than zero: $t(6) = 8.17$, unidirectional $P < 0.0001$). As revealed by pairwise posthoc t-tests the success-rate significantly differed from chance level (50%) from the third block onwards in the CF group, (P-values $= P_{i,}$ where i = block number from one to eight: $P_1 =$ 0.46, $P_2 =$ 0.12, $P_3 =$ 0.01, $P_4 =$ 0.02, $P_5 =$ 0.003, $P_{6\text{–}8} < 0.001$). Success rate peaked in the eighth with a hit rate of 74.7 ± 2.4% (M ± SE). No significant correlation between block numbers and the number of successful trials was obtained for SF ($r = -0.55$, t $(6) = 1.62$, $P < 0.078$)

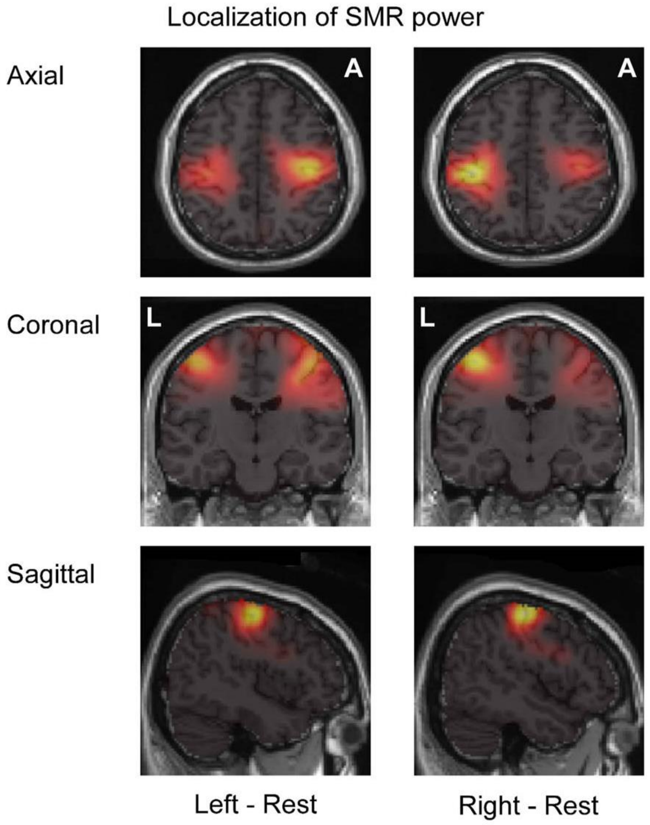

Figure 3.

Source localization of the MEG signals acquired during the functional localizer session. Source localization results are depicted for a representative participant. The left column presents source localization of Event-Related Desynchronization (ERD) of SMR, that is, the power difference between hand movement (opening and closing) versus rest and right hand was at relaxing. In general, ERD for overt, voluntary movements or motor imagery result in a decrease of SMR power over pre-motor, motor and supplementary motor cortices. ERD is more pronounced contralateral to the involved hand [Pfurtscheller and Aranibar, 1979; Pfurtscheller et al., 1979]. The right column presents sources of ERD results for the right hand. Non-overlapping windows of 0.208 s duration were used for sensor and source level analysis. Highest ERD were found for point (MNI-coordinates: −33, −19, 52) for left M1 and point (MNI-coordinates: 36, −18, 52) for right M1.

indicating that across all blocks the success rate did not deviate from the chance level in the SF group.

Since coherence values are limited between 0 and 1 and might have a skewed frequency distribution, a Kolmogorov-Smirnov test for testing normality of the sample was performed prior to the ANOVA of the coherence values. For all cells of the ANOVA, the error probability for significantly deviating from a normal distribution did not become significant ($F(1,28)$, CF ($P < 0.15$) and SF ($P < 0.55$)) and thus a parametrical analysis using ANOVA is justified.

To examine how the CF training group differed from the SF group, a three-way ANOVA of functional coupling between left and right SLMA at the training frequency with between factors GROUP (levels: CF and SF) and the within factors CONDITION (levels: S^+ and S^-) and PERFORMANCE (levels: hit and miss) was performed. No

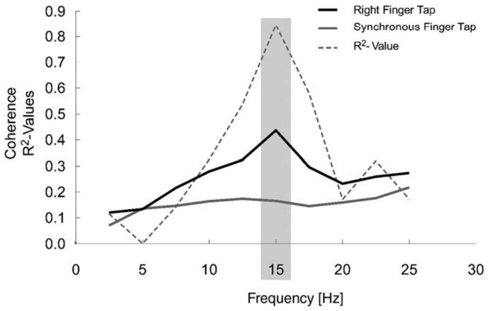

Figure 4.
Identification of participant-specific feedback frequency. Depicted is the functional coupling for right finger-tapping (black line) and symmetric finger-tapping (gray solid line) which yielded the strongest coupling differences for this participant in the functional localizer session. Right finger-tapping and symmetric finger-tapping were two out of five motor tasks for which the maximum functional coupling difference was searched for. Frequency-specific R^2–values of functional coupling are plotted. The selection of the frequency bin to be used in both, the neurofeedback training and the pre- and post-test was based on such individual plots. In this participant 15 Hz (shaded gray area) was selected as neurofeedback training frequency.

main effect for GROUP was found $F(1,28)=2{,}534$, $P = 0.1227$. Results revealed a main effect CONDITION ($F(1, 28) = 17.05$, $P = 0.0003$). Functional coupling was significantly higher for S^+ (M ± SE: 0.195 ± 0.016) than for S^- (0.168 ± 0.014). In addition, there was a significant interaction between GROUP x CONDITION x PERFORMANCE, $F(1, 28) = 11.814$, $P = 0.0019$). A post hoc pairwise t-test revealed that functional coupling differed significantly between S^+ and S^- for hit trials in the CF group ($t(14) = 7.7$, $P < 0.001$; M ± SE for S^+: 0.265 ± 0.037, and S^-: 0.178 ± 0.033), but not for the SF group ($t(14) = 1.13$, $P > 0.10$; M ± SE for S^+: 0.158 ± 0.021, and S^-: 0.145 ± 0.018). The results further indicate that the main effect of CONDITION was due to the large difference of functional coupling between S^+ and S^- found in the CF group. For missed trials, no significant difference in functional coupling between S^+ and S^- was found, neither for the CF group ($t(14) = 0.11$, $P = 0.91$) nor for the SF group ($t(14) = 0.56$, $P > 0.10$) (Fig. 7). Additionally, as revealed by a post hoc ANOVA involving the factors GROUP (levels: CF and SF) and CONDITION (levels: S^+ and S^-) for missed trials, there was neither a significant group difference ($F(1,28)=1.92$, $P = 0.1768$) nor a significant effect of CONDITION ($F(1, 28) = 0.22$, $P = 0.644$), nor any interaction GROUP x CONDITION ($F(1, 28) = 0.094$, $P = 0.761$). A post hoc test between Successful S^- and the mean between Unsuccessful S^- and S^+ for the CF group yielded a significant difference $F(1,14)=7.821$, $P = 0.0143$ (Successful S^-: (M ± SE 0.178 ± 0.033); Unsuccessful S^+ and S^-: (M ± SE: 0.205 ± 0.034).

To verify that the modulation of inter-hemispheric functional coupling is not due to the condition-specific head movements, head positions of all three fiducials were compared between upregulation and downregulation conditions. However, none of the three fiducial positions revealed a significant change in position during the neurofeedback session for upregulation and downregulation as revealed by paired t-tests (left, right preauricular points and nasion) (Left: $P = 0.17$, $t(8) = 1.47$, Right: $P = 0.35$, $t(8) = -0.97$, Nasion: $P = 0.38$, $t(8) = -0.92$).

To rule out, that the volitional modulation of the inter-hemispheric functional coupling can simply be explained by changes in the signal power, we correlated the power difference between upregulation (S^+) and downregulation (S^-) for successful and unsuccessful trials with changes of functional coupling. Spearman rank correlation was calculated across the CF and SF groups of participants. No significant correlation was found ($r = 0.22$; $t(28) = 1.19$, $P = 0.243$) suggesting no significant contribution of changes in power to the modulation of functional coupling.

Pre- and Post-Feedback Training Behavioral Tests

To infer the effects of functional coupling neurofeedback training on behavioral performance, changes of tapping frequency between the pre-test and the post-test session were studied. As evidenced by a significant interaction between the factors GROUP and SESSION for the ratio of tapping speed $r = \frac{v^{S^+}}{v^{S}}$ during S^+- and S^- -condition ($F(1,28) = 9.14$, $P = 0.005$), tapping speed differed between pre- and post-test only for the CF ($t(14)=3.41$, $P = 0.0042$; M ± SE: $r_{pre} = 100.4 \pm 0.4\%$, $r_{post} = 91.4 \pm 2.3\%$), but not for the SF (M ± SE: $r_{pre} = 99.8 \pm 0.5\%$, M ± SE: $r_{post} = 98.9 \pm 0.4\%$) group. Significant main effects GROUP ($F(1,28) = 9.58$, $P = 0.0044$) and SESSION ($F(1,28) = 13.33$, $P = 0.0011$) were not further interpreted because they were driven by the significant interaction as could be shown by posthoc tests. The

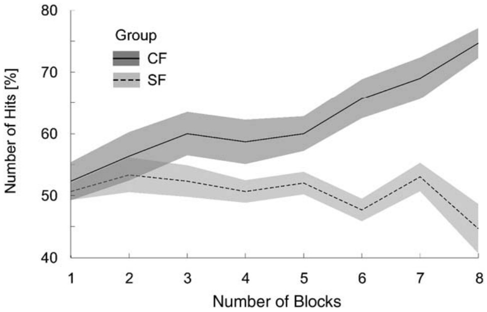

Figure 5.
Neurofeedback performance across blocks of the training for CF and SF groups. The gray shaded areas indicate standard errors of the mean.

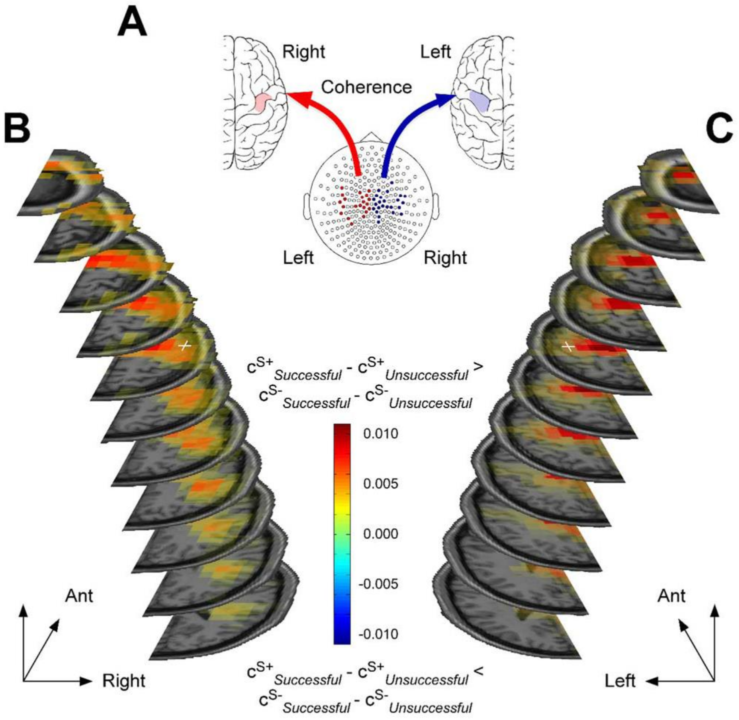

Figure 6.

(**A**) SLMA exhibits increased functional coupling between reference channels of the left (red) or right side (blue) of the head and the contralateral motor-related cortices (indicated in red and blue respectively on the sketch) during S^+ and reduced functional coupling during S^-. A template MNI brain with a resolution of 8 mm was used for source analysis. (**B** and **C**) The highest functional coupling values were found for point (–33, −19, 52) for left M1 and point (36, −18, 52) for right M1. The double difference $(c^{S^+}_{\text{successful}} - c^{S^+}_{\text{unsuccessful}}) - (c^{S}_{\text{successful}} - c^{S}_{\text{unsuccessful}})$ for the functional coupling between SLMA and the cortical source activity for S^+ and S^- and for hit and miss trials are presented here for a single participant (functional coupling differences are color coded). For this participant, functional coupling was calculated at the individual training frequency of 13.5 Hz. (B) Specifically, showing the functional coupling pattern in right hemisphere with the reference channel in the left hemisphere and (C) showing the functional coupling pattern in the left hemisphere with the reference channel in the right hemisphere.

tapping speed ratio neither differed significantly for the pretest session between groups ($t_{\text{unpaired}}(28)=0.973$, $P = 0.339$) nor for the SF group between sessions ($t_{\text{paired}}(14)=1.488$, $P = 0.159$) (Fig. 8A). Results indicate that the CF induced a slowing down of tapping speed for the S^+ conditions with respect to the S^- condition. MPI varied accordingly with a significantly lower MPI was found for CF (M ± SE: 91.2 ± 2.6%) than for SF (M ± SE: 99.2 ± 0.6; $t(28) = -3.024$, $P = 0.0053$) (Fig. 8B).

The unpaired t-test comparing FCI between CF and SF yielded a significant group difference ($t(1,28)= 2.1280$, $P < 0.0422$)). Post hoc analysis one-sample t-test comparing FCI for the CF and SF group to a value of one showed a significant effect only for the CF group ($t(1,14) = 2.155$, $P < 0.0491$, M ± SE 115.2 ± 7.00), but not for the SF group ($t(1,14) = -0.447$, $P = 0.6619$, M ± SE 98.4 ± 3.5))(Fig. 8C). Results indicate that the ratio of inter-hemispheric coupling between S^+ and S^- trials increased due to the neurofeedback training.

To study relate effects of neurofeedback training to motor performance, we correlated the percentage change in functional coupling and tapping frequency from pre-

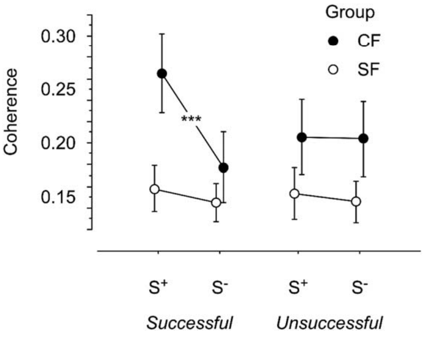

Figure 7.

Mean inter-hemispheric magnitude squared coherence across feedback sessions. The coherence is calculated between left and right SLMA for both, the CF and the SF group and successful and unsuccessful trials (*** indicates $P < 0.001$). Error bars represent the standard error of the mean.

test to post-test for both groups (Fig. 9). The presence of a significant negative Spearman rank correlation ($r = -0.389$, $t(28) = 2{,}234$, $P = 0.033$) indicated that an increase in the inter-hemispheric functional coupling was associated with a decrease in finger-tapping frequency.

DISCUSSION

In the present study, we demonstrate that the acquired modulation of inter-hemispheric functional coupling is associated with significant modifications in motor performance. Our results show that effects are stable, outlast the neurofeedback training and generalize to motor tasks. Modulating the strength of inter-hemispheric functional coupling as the independent variable and assessing its effects on motor performance complements previous approaches in which the inter-hemispheric functional coupling was studied as a function of different motor tasks. The relative decrease in tapping speed as a consequence of the learned increase of functional coupling points toward a causal role of functional coupling for the control of bimanual coordination.

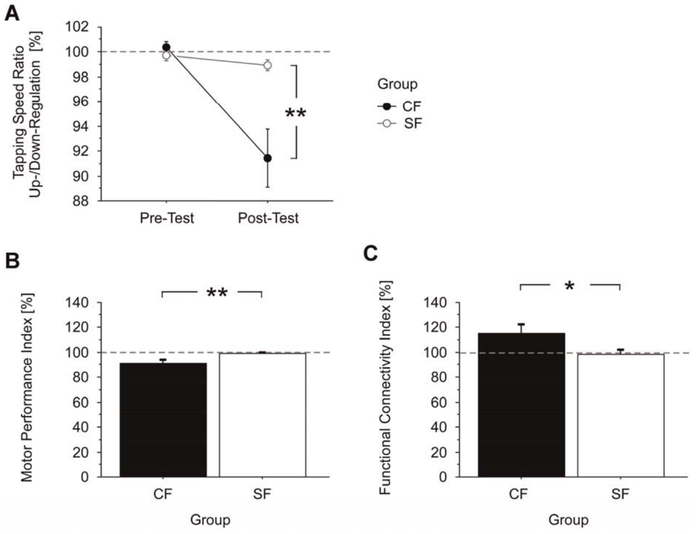

Figure 8.

(**A**) Relative tapping speed in pre- and post-test for both, the CF and the SF group. To remove interindividual variations the ration of tapping speed $r=\frac{\sqrt{S^+}}{\sqrt{S}}$ is depicted. (**B**) The MPI represents the ratio of finger-tapping speed for S^+ and S^- trials in the post session as referenced to the pre-test session for both, the CF (black filled bar) and the SF group (white filled bar). The MPIs differs significantly between the CF and the SF group (double black asterisks, $P < 0.01$). Error bars indicate the standard error of the mean across participants. (**C**) The FCI represents the ratio of coherence for S^+ and S^- trials in the post session relatively to the ratio in the pre-test session. A significant difference was found for trials for the CF (black filled bar) and SF group (white filled bar). The FCIs for the post sessions differ significantly between the CF and the SF group (black asterisk, $P < 0.05$). Error bars indicate the standard error of the mean across participants.

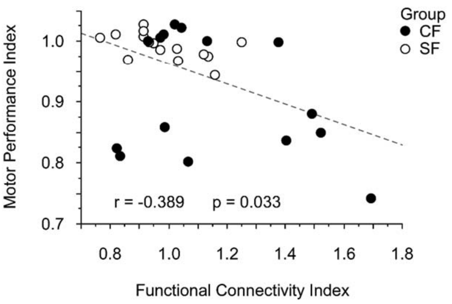

Figure 9.

Correlation between the MPI and functional coupling index at the individually trained tapping frequencies. Black dots represent CF participants, white dots SF participants. The regression line is plotted as dashed line.

Prior to speculating about the implications of our results on the organization of bimanual motor control, we will discuss possible confounding variables that might affect the interpretation of our results. The interpretation of our results with respect to bimanual motor control will consider previous research in humans and animals. The discussion will finish with an outlook suggesting future research strategies and potential applications.

Potential Confounding Variables

Effects of signal power on coherence

Squared magnitude coherence is a measure of functional coupling that depends on both, phase synchronization and amplitude correlation across time. It has been suggested that functional coupling not only reflects phase synchronization but also signal amplitude [Pikovsky et al., 1997]. Thus, it might be objected that the acquired control of inter-hemispheric functional coupling presumably reflects changes in signal amplitude rather than phase synchronization. However, in our study, the analysis of power changes for S^+ and S^- confirmed that the modulation of functional coupling cannot be explained by changes of SMR power and therefore the interpretation about the modulation of inter-hemispheric coupling as alterations of functional coupling appear to be justified.

Sensor level spreading of magnetic brain activity

The analysis of sensor level functional coupling in neuromagnetic imaging suffers from the problem of local brain activity spreading to surrounding sensors and thus generating coherent activity among them which might be erroneously interpreted as interregional functional coupling. To tackle this confounding variable, it is often suggested to use imaginary coherence that suppresses those proportion of both signals that are in phase or phase shifted by multiples of pi [Nolte et al., 2004]. However, in reciprocal symmetric connections as between left and right motor cortices, a phase difference with multiples of pi is very probable [Fries, 2005, 2015]. Using imaginary coherence, existing functional coupling might be missed and appears therefore not to be a suitable approach. Considering the difference of functional coupling between unsuccessful and successful trials and between upregulation and downregulation suppressed at least effects of apparent functional coupling due to spreading of neuromagnetic activity that is unrelated to upregulation and downregulation of functional connectivity.

Motor activity

Although we demonstrate the effects of the modulating inter-hemispheric functional coupling on motor performance, it might be objected that the modulation of inter-hemispheric functional coupling between left and right motor cortices is mediated by covert movements and differential muscle activations rather than by brain control. For example, it could be argued that participants might have learned to systematically move their heads with respect to the spatially fixed magnetic field sensors to modulate the measured neuro-magnetic coupling depending on the S^D. However, analyzing the absolute individual head positions and its variation over time, tracked with millimeter precision during the MEG recording, no differentially significant head movements for S^+ and S^- could be detected. Furthermore, video supervision of participants did not reveal any systematic gross body movements. Thus, we can exclude any direct effects of small head and gross body movements as a mediator for the modulation of inter-hemispheric functional coupling. However, task-related changes in muscle tension at any part of the body and even the execution of small movements with any limb can still be a source of modulation of the inter-hemispheric functional coupling. To control this type of confounding variable, measuring myoelectric activity is often suggested. However, even with careful recordings of many EMG electrode positions, differential myoelectric activity at different body parts, muscles and at different levels of the spinal and peripheral motor system during S^+ and S^- cannot be excluded. Only curarization or complete paralysis allows the control of subtle differential myoelectric modulations. This problem of "motor mediation" was extensively investigated in biofeedback experiments with curarized animals [Dworkin and Miller, 1977] and in paralyzed humans' neurofeedback studies [Birbaumer et al., 2013; Chaudhary et al., 2016, 2017] without conclusive results.

Even if in the present experiment differential movement-mediated modulation of inter-hemispheric functional coupling cannot be fully excluded, our results documenting a causal relationship between changes in inter-hemispheric functional coupling and motor performance are intriguing and provide strong insight into the cortical control of bimanual coordination.

Coherence in the Motor System and Bimanual Movements

The negative correlation between the strength of inter-hemispheric functional coupling and tapping speed in an AOBFT that has been found in our study complements previous work in which motor tasks have been varied and functional coupling was studied as a dependent variable. In the study by Gross et al. (2005), decreased inter-hemispheric functional coupling between primary motor cortices was shown for anti-phase bimanual movements against in-phase bimanual movements. While van Wijk et al. [2012] reported stable inter-hemispheric alpha- and beta-band coupling for iso-frequency bimanual finger-tapping, [Houweling et al., 2010a] demonstrated a reduction of functional coupling for polyrhythmic bimanual finger-tapping, that requires a more independent control of the fingers of both hands. Cardoso de Oliveira et al. [2001] measured inter-hemispheric functional coupling using single-unit recordings in awake monkey. They found that coupling is significantly decreased for out-of-phase asymmetric bimanual movements as compared to symmetric movements of both hands. In other words, as in our study, decreased inter-hemispheric functional coupling seems to be the generally preferred mode of operation in bimanual movements, in which movements of both hands are independent. On the contrary, increased functional coupling proved to be detrimental to motor performance in AOBFT, but seemed to be the preferred mode for symmetric movements in the cited studies. In conclusion, results of the different studies suggest that decreased inter-hemispheric functional coupling is beneficial for AOBFTs, while increased coupling is advantageous in symmetric finger-tapping tasks. Given the ample evidence that our motor system facilitates symmetric bimanual movements [Houweling et al., 2010a; Swinnen, 2002; van Wijk et al., 2012], one may conclude that higher inter-hemispheric functional coupling is the "default mode," and its downregulation is required for unimanual movements, and movements requiring independent control of both hands. In the framework of the GMP and the intermanual crosstalk model, one might conclude that in AOBFT primary motor cortex of each hemisphere controls the contralateral hand independently, yet according to a general motor plan. In contrast, in symmetric in-phase finger-tapping both primary motor regions are closely linked to coordinate movement execution via oscillatory activity. According to this view both models of bimanual coordination are not exclusive, and motor control might be best explained by a task-dependent activation of either processing mode.

Studies investigating the inter-hemispheric functional coupling highlight the importance of corpus callosum, which is the most dominant inter-hemispheric connection of the brain, for the coordination of activities of bimanual upper limb movements [Gerloff and Andres, 2002]. The involvement of corpus callosum in bimanual coordination has been corroborated by various studies of split-brain patients whose direct inter-hemispheric connections had been cut for medical reasons and thus abolishing inter-hemispheric functional coupling completely. Cutting the corpus callosum can be regarded as a quasi-elimination of inter-hemispheric coupling. Studies investigating split brain patients in an out-of-phase bimanual finger-tapping task revealed that patients performed better than healthy individuals [Eliassen et al., 1999], yet exhibit problems in producing symmetric bimanual movements [Geffen et al., 1994; Preilowski, 1975; Swinnen and Wenderoth, 2004]. These findings in patients suggest that functional coupling is less important in out-of-phase bilateral movements [Eliassen et al., 1999; Franz et al., 2000; Preilowski, 1972, 1975; Stephan et al., 1999].

Work in non-human primates has documented widespread functional coupling associated with periodic oscillatory activity in sensorimotor cortex [Baker et al., 1999a, 1999b; Donoghue et al., 1998; Engelhard et al., 2013; Murthy and Fetz, 1996b], including inter-hemispheric functional coupling [Murthy and Fetz, 1996a]. In the context of motor control, synchronization and crosstalk at different sites along the neural axis constitutes an important signatures for the execution of macroscopic movement [Baker et al., 1999b; Houweling et al., 2010b]. With regard to bimanual coordination, left and right motor cortices showed stronger functional coupling in the beta frequency range depending on whether monkeys performed bimanual or unimanual manipulations [Murthy and Fetz, 1996b]. Although the synchrony appeared under different experimental circumstances in these studies, a common explanation is that the modulation of the inter-hemispheric functional coupling can be modulated in a top-down fashion via operant conditioning [Fetz, 2013]. Human studies also reported stable inter-hemispheric alpha- and beta-band coupling for iso-frequency bimanual finger-tapping

With the current study, using modulation of inter-hemispheric functional coupling in conjunction with an asynchronous out-of-phase finger-tapping task for pre- and post-tests, we provided the basis for future studies investigating the role of inter-hemispheric functional coupling on bimanual motor performance. Further experiments investigating the impact of the modulation of inter-hemispheric functional coupling on different types of motor tasks in the pre- and post-test sessions will verify our interpretations of the role of inter-hemispheric coupling for bimanual coordination. In particular, studies investigating effects of upregulation and downregulation of functional coupling on in-phase, out-of-phase bimanual movements, as well as on synchronous and asynchronous finger-tapping are suggested.

Perspectives of Neurofeedback of Functional Coupling

Our results demonstrate that the learned modulation of functional coupling by means of rt-MEG neurofeedback is feasible, and is the first step toward the development tools for the better understanding of the role of functional coupling in sensory and motor processes. Further research might consider volitional modulation of inter-hemispheric functional coupling as an approach to investigate the reorganization of the brain [Fetz, 2013]. We also see a strong potential of the presented method for the treatment of diseased brains with impaired neuronal communication. However, even though volitional modulation of functional coupling was achieved in our study after a very short training of less than an hour, follow-up studies are needed that document the long-term persistence of the trained effects that is essentially needed in clinical applications.

The observed behavioral changes following the neurofeedback training of coherence suggest that functional coupling-based neurofeedback [Birbaumer et al., 2013] offers a unique opportunity to train coherent or randomly synchronized neural activities that might subsequently impact related cognitive, emotional, and behavioral processing. Despite current theories emphasizing the role of abnormal functional coupling (including long-range functional coupling/synchrony and abnormal BOLD correlations in fMRI) as the neural substrate of a variety of neurological and psychiatric disorders, such as, schizophrenia [Ruiz et al., 2013a, 2013b], epilepsy [Elshahabi et al., 2015], and Alzheimer's dementia [D'Amelio and Rossini, 2012; De Lacoste and White, 1993], only few studies have attempted to train individuals to directly modulate neural functional coupling using neurofeedback [Daly et al., 2012; Kajal et al., 2015; Koush et al., 2013; Ruiz et al., 2013b; Shibata et al., 2011]. Concluding, future studies on the modulation of functional coupling by neurofeedback should address the impact of functional coupling on different brain functions for the development of innovative non-invasive strategies, both to study normal brain function, and to examine and modify neurological and psychiatric disorders.

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Functional dynamics underlying near-threshold perception of facial emotions: a magnetoencephalography investigation.

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Functional dynamics underlying near-threshold perception of facial emotions: a magnetoencephalography investigation.

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Abstract

Conscious perception of the emotional valence of faces has been proposed to involve top-down and bottom-up information processing. Yet, it is still unclear how the cooperation of both processes is implemented and what are the underlying neuronal mechanisms. Using the visual backward masking (ViBM) paradigm, we assessed the participation of the neural networks involved in the conscious perception of the emotional stimuli near the perceptual threshold (NPT) using magnetoencephalography (MEG). Stimulating at the perceptual threshold enabled us to compare consciously perceived emotions with not correctly perceived facial expressions for physically quasi identical stimuli. Twelve healthy participants were asked to detect the emotional valence of a prime face stimulus (either happy or sad) presented for 16 ms. The prime stimulus was followed by a mask after a variable delay, showing a neutral face of the same person as of the prime. To remain at the participants' perceptual threshold, we used an adaptive method in which the delay in the current trial was decided on the outcome in the previous trial. We identified the networks for the perception of the emotional stimuli and the top-down modulation of stimulus processing using coherence analyses. We hypothesize that the networks activated during the interaction of the top-down and bottom-up processed are the key substrates responsible for the perception of the emotional valence of faces. We found a fronto-parietal network with activities oscillating in the lower gamma band and thus exerting top-down control on the processing of emotional stimuli. Moreover, we found parietal networks active in the gamma band for successfully identified emotional face expressions. For not perceiving the emotional valence of faces an enhanced coupling between left frontal and right parietal regions was found.

Introduction

Growing evidence hints towards the integration of bottom-up, sensory driven signals and top-down mediated cognitive control playing a vital role in the perception of emotional stimuli (Breitmeyer, et al., 2006; Ghazanfar and Schroeder; Green, et al., 2006; Park and Friston, 2013). Bottom-up processes that comprise various low-level processes such as visual feature extraction (color, shape, size and orientation (McCarthy and Warrington, 2013)) characterize the emotion-relevant aspects (emotion-as-stimulus-properties) of the presented stimuli (Brozoski, et al., 1979; Northoff, et al., 2006). Mapping of neural correlates of the bottom-up processes suggests the active participation of amygdala and hypothalamus in addition to the encoding of the affective properties (AP) of the presented visual emotional stimuli in the visual system (McRae, et al., 2012; Ochsner, et al., 2009). In parallel to the encoding of the AP, visual pathways via the ventral portion of the striatum, hypothalamic and brain stem nuclei also contribute to the bottom-up processing by updating any change in the information (mismatch, disruption of information flow (Adolphs, 2002; Dosenbach, et al., 2008). Thus, the function of the bottom-up processing comprises reception, registration, awareness of the visual information and eventually updating if there is any change in the registered information. Regarding the processing of the emotional stimulus content it is at that level where top-down processes come into *play* (Engel, et al., 2001; Sarter, et al., 2001). Although the emotional stimuli have been registered in the brain by the bottom up processes, the emotional meaning of the stimuli results from top-down processes. The top-down generation of the emotional response is based on the integration of AP and situational-cues (past experience, skill and memory) thus enabling an individual to comprehend the occurrence of a stimulus with a certain kind of emotional properties (Bar, et al., 2006).

The mechanisms involved in top-down processing of the registered AP, suggests the formation of recurrent long-distance interactions. These interactions involve thalamo-cortical loops, especially prefrontal cortex and higher cortical areas, which are inundated by self-amplifying reverberance of network activity. In addition to the above described mechanism, it has also been suggested attaining a consciously reportable state involves the broadcasting of the AP to many functionally specialized brain regions, including those for verbal or motor report (McRae, et al., 2012; Zanto, et al., 2011). This broadcasting follows a selective way and might adopt re-routing and/or by-passing certain networks for the information and avoiding the visual cortex network (Pessoa and Adolphs, 2010). Processing of emotional stimuli in the brain involves rapid modulations of top down processes to initiate appropriate behavioural outcomes. A plethora of studies suggest that there are two different networks enhancing the top down mediation of emotional stimulus information: fronto-parietal and cingulo-opercular networks. Fronto-parietal networks have been suggested to initiate and adjust the control of the information propagation while the cingulo-opercular networks maintain information until they are over-written or disturbed by another information whichever is before (Dosenbach, et al., 2008).

The top-down processing has been extensively studied using visual backward masking (ViBM) tasks (Dehaene, et al., 2006; Del Cul, et al., 2006b). In the ViBM paradigm, a prime stimulus is flashed and followed by a masking stimulus after a predefined temporal delay. The prime stimulus is not consciously perceived until the temporal delay between the prime and mask exceeds the perceptual threshold. When the temporal delay between prime and mask stimulus fails to exceed the perceptual threshold, information about the prime stimulus can still propagate through the bottom-up processors but will be unable to initiate the subsequent top-down processes, because the propagation of the prime stimuli to conscious processing is disturbed or disrupted by the following mask stimulus and thus not being supported by the reverberant self-amplifying loops. This defined role of the reverberant self-amplifying fronto-parietal loops are basis for the global neuronal workspace model (Dehaene and Changeux, 2003; Dehaene, et al., 1998; Dehaene and Naccache, 2001; Ramachandran and Cobb, 1995).

Any behavioral outcome of top-down and/or bottom up processes results from the coordinated activity in disparate brain regions and differently specialized networks.

This coordinated activity is assumed to be reflected in synchronized activity between disparate brain regions. Neural synchronization is studied by simultaneously measuring the activity from different and disparate locations and assessing if activities at these locations change in a correlated manner. The strength and polarity of the phase synchrony of the oscillatory activity can be interpreted as a proxy for the underlying local neural synchrony, and changes of phase differences between signals as a function of frequencies index the direction of information flow. Several human and primate studies have reported the occurrence of different brain oscillations in supporting the top-down processes (Corbetta and Shulman, 2002; Rossi, et al., 2009; Ungerleider, et al., 1989; Ungerleider, 2000; Webster, et al., 1994). (Del Cul, et al., 2006b) suggested that for visual perception of emotional stimuli in the cue-delay-target trial, parietal cortex and frontal regions work in close collaboration (Di Lollo, et al., 2000b; Enns and Di, 2000; Vorberg, et al., 2003a). Previous work has shown that fronto-parietal networks are involved in the perception of the emotion (Blonder, et al., 1991; Van Rijn, et al., 2005), but it is unclear whether the interaction is realized through neuronal oscillatory synchronization. Given that top-down processes rely on neuronal synchronization, the direction of information flow becomes relevant: does the synchronization directly reflect top-down information flow, does it rather reveal the relaying of information to frontal and prefrontal brain regions or even both. Furthermore, the direction of information flow can be elusive for the understanding of the interaction of top-down and bottom approach to study the network architecture.

In our study, we hypothesize that oscillatory synchronization of long range neural networks are the mechanisms by which the emotional content of a stimulus is consciously detected. To rule out any interference from low-level stimulus features we compared the neural synchronization at the NPT, i. e. for a temporal delay that results in both, perception and non-perception of emotional face expressions.

To study the long-range network connections involved in the perception of the emotional stimuli, in the first part, we have chosen a hierarchical approach particularly focusing on the fronto-parietal network on a rough scale by defining 4 parcels, i. e., left and right frontal and parietal cortex. In the post-hoc analysis, we have characterized the within and between parcel networks in more detail, by identifying the relevant nodes (areas) and edges (strength of functional coupling operationalized as imaginary part of the coherence) as well as the direction of information flow using phase slope index

(PSI). We demonstrated the differences in the quantitative strength of the activated brain networks during conscious and non-conscious perception of the emotion processing at NPT using graph theoretic measures.

Materials and Methods

2.1 Participants

12 healthy subjects (M±SD=25.5±3.5years: 7 females and 5 males) with normal or corrected-to-normal vision participated in the study. None of the participants had a history of neurological or psychiatric disorders. The study was approved by the local ethical committee of the faculty of medicine, University of Tübingen, Germany. A written informed consent in accordance to the Declaration of Helsinki (Carlson, et al., 2004) was obtained from all subjects prior to the experiment. All subjects received monetary compensation of 10 Euros/hour for their participation.

2.2 Design and Procedure

The experiment consists of 5 identical runs with each run containing 80 trials and lasting for 8 min, each. A ViBM paradigm was used to manipulate the detectability of the facial emotions by varying the delay between a shortly presented face stimulus and a subsequent mask. We have used the adaptive method for choosing the delay for the next trial dependent on the response of the current trial to stimulate participants at the threshold for perceiving emotional face expressions. Stimulating near the threshold provides a comparable number of trials with correctly and incorrectly perceived emotional face expressions with identical physical stimulus properties. To study the cortical networks necessary for correctly identifying emotional face expression brain oscillatory activities were recorded using a whole head magnetoencephalography (MEG).

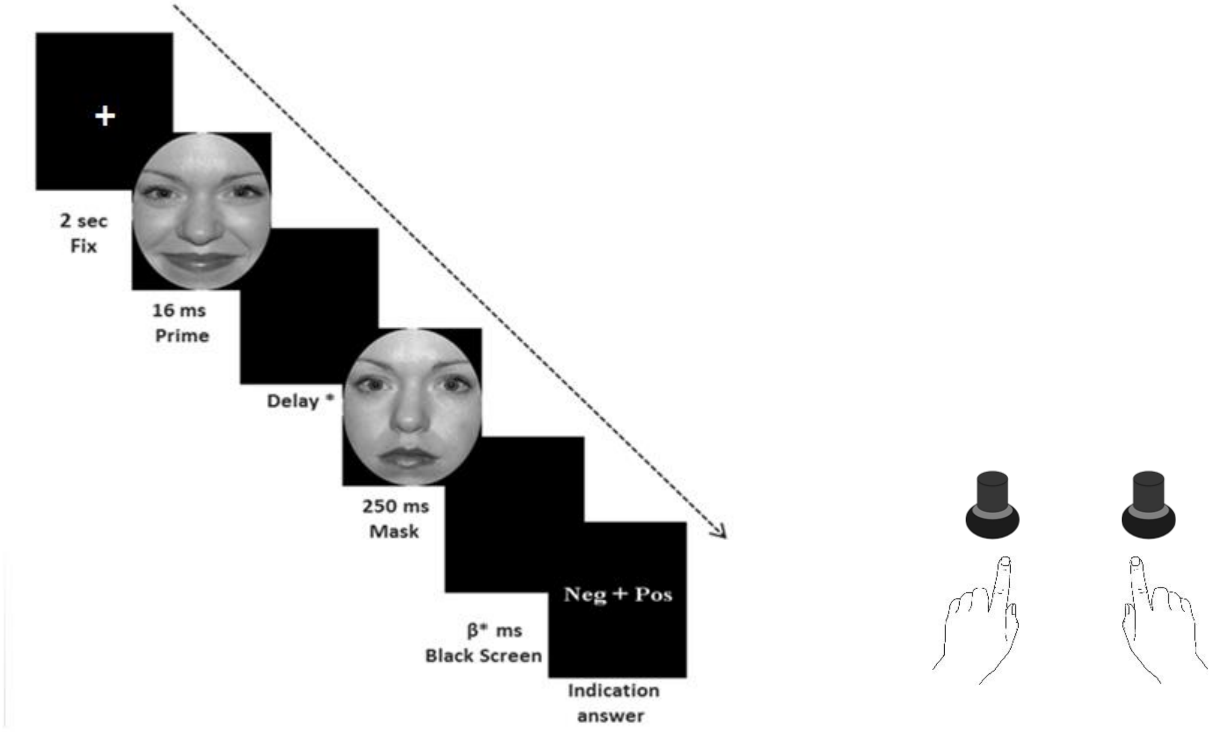


Figure 1: Experimental paradigm

In our ViBM paradigm, an emotional face either with a positive or negative emotional expression was presented shortly as prime stimulus, followed by a variable delay and an emotionally neutral mask (Fig 1). Evidently, the correct perception of the face expression becomes easier with increasing delays. Each trial started with the presentation of a fixation cross in the middle of the presentation screen. The fixation cross was flashed for 2 sec. Then the prime stimulus (either a happy or sad face) was presented for 16.7 ms (t_{prime}). The emotional faces were presented in pseudo-random manner across trials. The prime stimulus was followed by a mask stimulus after a variable delay. The delay between the prime and the mask stimuli (t_{delay}) could be either 0 ms, 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, 133.3 ms, or 150.0 ms. The mask stimulus was flashed on the screen for 250 ms (t_{mask}). It consisted of a face picture of the same individual as that of the prime, yet with an emotionally neutral expression. Colored face images of both, the emotional and the neutral faces were taken from the NimStim Face Stimulus Set (Tottenham, et al., 2009). 50% male and 50% female faces were selected. The mask is followed by a black screen. The duration of the black screen $(t_{blackscreen})$ was chosen such that the stimulation duration of all the trials was of equal length $[t_{blackscreen} = 1500\, ms -$

$(t_{prime} + t_{delay} + t_{mask})]$. Thereafter the instruction cue appeared on the screen prompting subjects to report their valence judgement for the prime stimulus. Participants were requested to report their judgements with their index finger by pressing optical buttons provided for each hand. Response options were presented on the screen as visual cues ‘’NEG+POS’’ and ‘’POS+NEG’’, with ‘+’ serving as the fixation cross. The cue “NEG+POS” instructed participants to press the left button if the facial expression of the prime stimulus was perceived as negative and the right button if it was perceived as positive. The cue “POS+NEG” indicated to press the left button for positive and the right one for negative judgements. To minimize any response bias, the two types of cues varied randomly from trial to trial. All participants were requested to respond in each trial and even guess when they were not sure about the valence of the prime face. Responses terminated a trial. The response interval during which responses were accepted lasted no longer than 2100 ms. The maximum duration of a single trial was 4.5 sec and the inter-trial interval was 5 sec.

To stimulate at the NPT, we have used an adaptive procedure (AM) (Leek, 2001; Treutwein, 1995). In the AM, the temporal delay between prime and the mask of the next trial is determined based on the stimuli and responses of previous trials. In the AM of our experiment we have implemented the ‘two-down-one-up’ rule (TDOU). The rule implies that after any two correct responses the temporal delay between prime and mask becomes shorter by one frame and thus making the task of detecting the emotional expression of the prime face stimuli more difficult. Notably, the two correct responses do not need to be in a row. When the participant responds with an incorrect answer, the temporal delay between prime and mask is immediately increased by one step and thus easing the task in the next trial. Assuming a stationary threshold, the temporal delay is expected to asymptotically reach the threshold for detecting emotional face expressions. This rule converges towards a threshold performance of 66.7% correct.

2.3 MEG Recording and Stimuli

MEG (CTF System Inc, Vancouver, Canada) data was acquired using a whole-head 275-axial gradiometer system with a baseline of 5 cm. The MEG is in a shielded room (VaccumSchmelze, Hanau Germany) at the University Clinic of Tübingen, Germany.

Brain magnetic data were sampled at the rate of 1072 Hz with an anti-aliasing lowpass filter of 208 Hz. The relative head position with respect to the magnetic field sensors was recorded continuously using three localization coils that were affixed to the left and right preauricular point and the nasion.

Emotional stimuli were presented using an in-house Pascal based program under Dos 6.2 and synchronized with the vertical refresh rate (60Hz) of a screen. The video output of the stimulation computer was send to a JVC DLA-SX21 projector to flash the stimuli via a mirror system on a screen in the magnetically shielded, dimly lit room. The screen was placed in front of participants in a viewing distance of 70 cm. Stimuli subtended a horizontal visual angle of ~2.5 ^{o}. Participants' judgements of the valence of stimuli were recorded using in-house built optical buttons. During stimulus presentation participants were advised to sit still and avoid blinking as possible.

2.4 MEG data Analysis

Neuromagnetic MEG data were analyzed using in-house MATLAB scripts (MATLAB 2017a) and using fieldtrip functions (Oostenveld, et al., 2011). Data visualization was done using BrainNet visualization toolbox (Xia, et al., 2013). The analysis comprised the following steps (figure 2):

a) *Cleaning of the data*

   Cleaning of the MEG data involved demeaning, detrending, 50 Hz line noise removal and high pass filtering (1 Hz). Magnetic brain data were then inspected visually and trials with a large variance across channel and samples ($2.5x10^{-25}$) and abnormal amplitudes were discarded from further analyses. Furthermore, trials containing muscle artifacts indicated by strong broad-band activity, squid jumps, and other non-stereotyped sources were removed. MEG channels with a noise level > 10 fT were excluded from the analysis. Eliminated trials in the MEG artifact rejection were also excluded from the analysis of the motor response. Furthermore, independent component analysis (ICA) was used to remove the contaminating ocular (eye movements, eye blinks) and cardiac artifacts. The ICA using the infomax ICA algorithm (Amari, et al., 1997; Bell and Sejnowski, 1995) decomposed the preprocessed and cleaned data into 100 components. The topography and the waveform of all components were plotted and visually inspected. The components containing eyeblink, eye-movement as well as heart beat and muscular artefacts were removed. From the remaining components, a cleaned MEG signal was reconstructed. Channels containing strong artifacts were marked as bad and excluded from further analyses.

b) *Categorization of the data: Correct and In-correct trials*

The preprocessed and cleaned data of the NPT-trials were pooled according to the participants' valence ratings into: perceived trails (trial in which participants correctly identified the prime face) and non-perceived trials (trials in which participants were not able to identify the correct emotion of the prime). The same number of perceived and non-perceived trials entered the further analysis. The number of trials was defined by the condition with the number of least trials. Trials of the same number were selected randomly for the other condition. Frequency analysis was done for the frequency range of 1 to 49 Hz using multi-tapering sliding window fast Fourier transform using discrete prolate spheroidal sequences (DPSS) tapers (Percival and Walden, 1993) in the steps of 2 Hz. Frequency analysis was done separately for the whole trial containing correctly perceived trials and incorrectly perceived trials including baseline.

c) *Condition and frequency specific spatial filter estimation using DICS*

Sources of neural oscillatory activity were localized using Dynamic Imaging of Coherent Sources (DICS) (Gross, et al., 2001), an adaptive spatial filtering method for time-frequency data. In an initial step, neural generators of the magnetic brain activity were localized in a template brain. MEG data were co-registered to an MRI template brain (specify the brain) via the three fiducials (nasion and left and right periauricular point). Discretizing the standard MRI template brain into a regular grid with 1 mm resolution a template source-model was defined reflecting potential 3000 source locations. The standard brain template was segmented, and the single shell spherical head-model was computed representing the electrical properties and the geometry of the brain. Based on the head-model for each grid point the respective leadfield was estimated. Using source- and head-model information, the leadfield reflects the projection of activity from a single source to the sensors. Based on the cross-spectral density and the leadfield matrix, frequency specific spatial filters were estimated that describes the projection of sensor-level activity to the source level. A ‘common spatial filter’ was computed for both concatenated conditions, i. e. correctly and incorrectly perceived facial expressions.

d) *Calculation of source level connectivity*

Source level activity was estimated by applying the frequency specific ‘common spatial filters’ to the sensor level activity for correctly perceived and incorrectly perceived trials. In a next step, all-to-all functional connectivity was calculated between all voxels inside the brain for each frequency bin, separately for perceived and not-perceived conditions. We have merged the voxels in an individual functional target region as defined by the Montreal neurological institute (MNI) template in one single voxel and thus we reduced the whole brain into 72 regions. Merging the voxels, we here refer to averaging all the possible connection arising from that set of voxels in the target areas and thus giving an estimate of connectivity within these target regions. To suppress the confounding problem of spatial spreading of the source activity, we have only subjected the absolute imaginary part of the coherence to further analyses.

e) Parcellation Analysis

To test our hypotheses of an involvement of fronto-parietal functional coupling in the processing of emotional face expressions and to reduce the problem of multiple testing, we further merged the brain regions into 4 parcels. Parcellation was done using the spatially normalized T1 template brain provided by the MNI (Collins, et al., 1998). Parcel I and II represent frontal and parcel III and IV parietal regions. Connectivity strength between parcel I and IV represents right intra-hemispheric fronto-parietal connections and parcel II and III represents left intra-hemispheric fronto-parietal connections, respectively.

We have segregated the all-to-all connectivity matrix of N x N (N=72) into 4 x 4 matrix for perceived and not-perceived trials by averaging the connectivity within and across areas. Within and between parcel connectivity resulted in 10 parcel combinations: (I, I), (I, II), (I, III), (I, IV), (II, II), (II, III), (II, IV), (III, III), (III, IV), and (IV, IV)). To quantify the strength of functional connectivity, we performed a cluster-based permutation test across frequency using paired t-test for the absolute part of imaginary coherence to compare the connectivity between perceived and not-perceived emotional face expressions. We looked for both positive and negative clusters, i. e. clusters where the connectivity was larger in the perceived than in the not-perceived condition and vice versa. We have performed a total of 2048 permutation tests ($2^{12}/2$: 12 subjects) by flipping the “perceived” and “not-perceived” conditions across all subjects. To determine the statistical significance of the connectivity differences between “perceived” and “not-perceived”, the experimental result was compared with the permutation based random distribution. The cumulative probability value for the positive cluster and the negative clusters is 0.025. Network visualization was done using Brain-Net Viewer (Xia, et al., 2013).

f) *Phase slope index*

To identify the direction of the information flow within and between different brain parceled areas during the processing of perceived and non-perceived emotional stimuli, we studied the phase slope index on 72x72 connectivity matrix. The phase slope index provides information on whether the signal in one brain region is leading or lagging the signal in another brain area. The polarity of the index will tell the direction of information flow. We did the post-hoc analysis and estimated the direction of the flow of information for perceived and not-perceived trials for the frequencies identified in the parcellation analysis and for the individual connections followed by sum and paired t-test (Benjamini and Hochberg, 1995).

g) *Network Analysis: Graph Theoretic Network Measures*

The main advantage of using graph theoretical measures over classical data analysis for MEG and MRI is that the network architecture of the brain is characterized as a comprehensive metric. In our case we have used this measure as post-hoc analysis for the results obtained from the cluster-based permutation across frequency for the parceled brain. The graph theoretical analysis was based on the absolute of imaginary part of coherence stored in the 72 x 72 connectivity matrix. In the network analysis, each of the 72 brain regions is treated as a node and the strength of coupling from one to another region is considered as an edge. We have used shortest path length to understand the nature of the underlying networks. We have assessed the difference in the synchronized network organization for perceived and not-perceived trials across different frequencies. (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001; Benjamini and Yekutieli, 2005).

For the statistical analysis a 72x72 all-to-all connectivity matrix for each subject is processed for the perceived and not-perceived networks. The connectivity matrix for perceived and not perceived trials were randomly mixed, vectorized and sorted in descending manner. Only the 20% shortest path length of the vectorized network areas were taken for further analysis. A t-test contrasting the two groups (perceived and not-perceived) was then computed for each pairwise association. Any association with a t -statistic exceeding 1 was admitted to the set of suprathreshold links used by the Network Based Statistics (NBS) (Zalesky, et al., 2010). The NBS was implemented with 10000 permutations to generate the null distribution of maximal component size. The NBS performs the clustering in the topological space rather that physical space. The NBS is the graph analogue of the cluster based statistical methods.

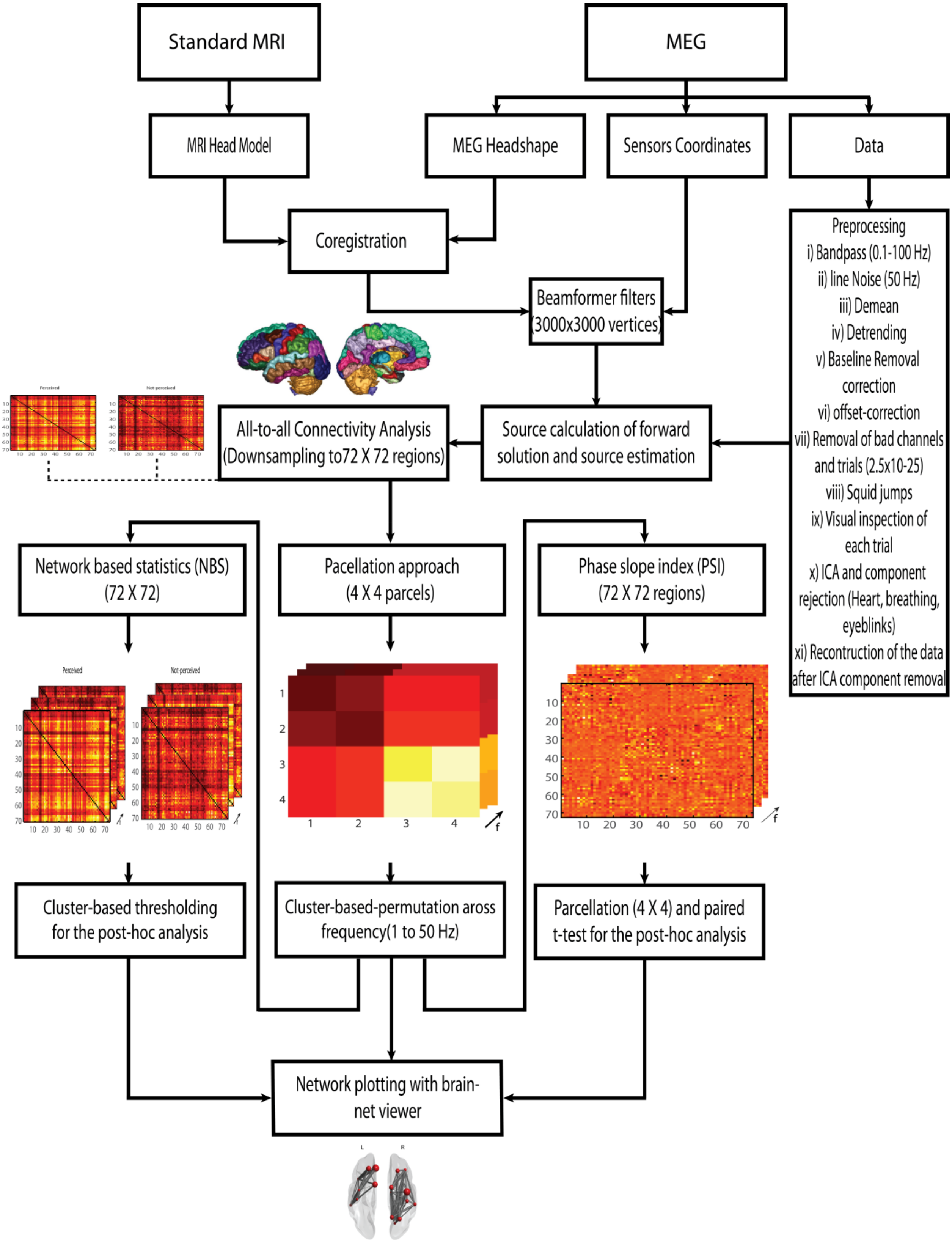


Figure 2: Represents the detail work pipeline for the analysis of the data.

Results

a) Parcellation Approach

The goal of our study is to test the hypothesis of a participation of synchronized fronto-parietal neural networks in the processing of emotional face stimuli. To this end, we studied the differential involvement of the functional connections for emotional face expression that are perceived either correctly or not. To avoid the problem of multiple comparison, we have performed the parcellation approach followed by the cluster-based-permutation across frequency. (Benjamini and Yekutieli, 2001; Benjamini and Yekutieli, 2005) for the correction of type I errors.

Cluster based permutation across frequencies revealed a significant difference between perceived and non-perceived emotional stimuli trials at 35 Hz (figure 4 A) ii), for the absolute imaginary part of the coherence (parcel I and IV: p=0.01, t=4.41, df=11). To assess the direction of the information flow in the right hemisphere, we have computed the phase slope index (PSI) for the connections crossing the frontal and parietal parcels and found a significance difference between perceived and non-perceived trials. A significant positive difference between perceived and not-perceived trials of PSI values was found for right frontal and parietal parcels (parcel I and IV: p=0.01, t=2.87, df=11) in the gamma band (35 Hz). Positive PSI values suggest the flow of information from frontal regions to parietal regions. To clarify whether the directed interaction originates from perceived or non-perceived trials, PSI was compared against zero. While the PSI for not-perceived trials (p=0.54, t= 0.63, df=11) did not differ from zero, it was significantly different (p=0.04, t= 2.25, df=11) for perceived at 35 Hz (figure 3 A). Further analysis using the parcellation approach demonstrated that the right parietal parcel revealed significantly more within-parcel connections in the perceived than in the non-perceived condition at higher beta (29 Hz) and lower gamma frequencies (31 and 33 Hz) for perceived and non-perceived trials. The right parietal cortex (parcel IV) was significantly active using the cumulative probability threshold (p=0.02, t=3.6, df=11) (figure 3 B). Furthermore, we have also investigated the contribution of interhemispheric connections for the perception of emotional stimuli. We found stronger connectivity for the non-perceived than for perceived trials between left frontal and right posterior cortex. The cumulative probability distribution value is (p=0.02, t=-3.54, df=11). This is basically demonstrated in the gamma band (37 to 41 Hz). (figure 3 C).

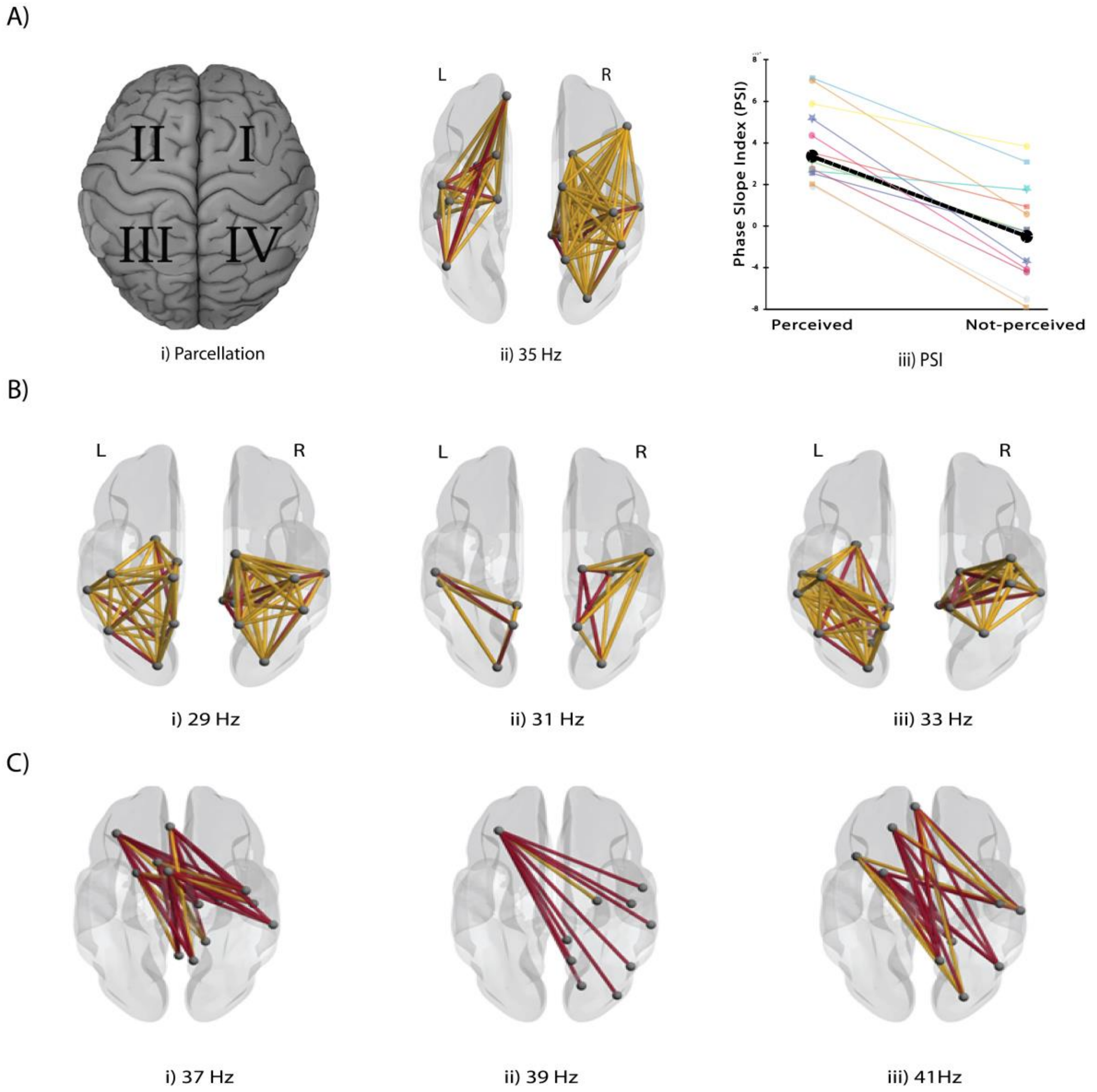
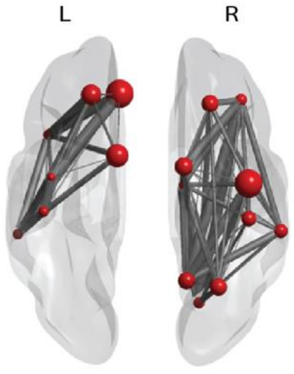


Figure 3: A: i) Division of the whole brain into four parcels. ii) Parcellation approach for the right and left hemisphere representing the positive connections of the network architecture in yellow and negative connections in red: Network organization for the difference between Perceived and not-perceived at 35 Hz. Iii) representing the PSI values for Perceived and not-perceived trials for right FPN at 35 Hz B) Shows the difference in network architecture between perceived and not perceived trial. i) high beta (29 Hz), ii) and iii) low gamma (31 and 33) in the right parietal parcel with the positive connections of the network architecture in yellow and negative connections in red. C) Shows the contribution of left frontal is contributing significantly negative toward right parietal cortex negatively. i) Representing the network organization at 37 Hz, ii) at 39 Hz and iii) at 41 Hz in early gamma from the left frontal parcel to right parietal parcel. The positive connections of the network architecture are represented in yellow and negative connections in red.

b) Graph Theoretical Measure approach: Post-hoc analysis

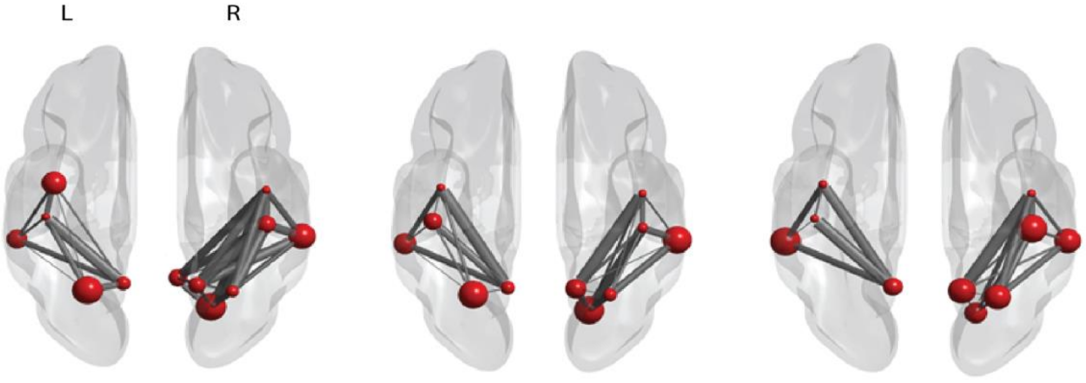
Brain networks can be mathematically interpreted as graphs consisting of a set of nodes (areas) and edges (connections between nodes). The pairwise coupling is being summarized as the network connection matrix defining the network architecture. The clustering reflects the local integration and shortest path length, or the distance reflects the level of global integration in the network. We have estimated the shortest path using the Floyd-marshal algorithm (Floyd, 1962). We studied the network organization using network-based statistics (NBS) toolbox (Zalesky, et al., 2010) for the post-hoc analysis at 35 Hz for shortest path length using the NBS with 10000 iterations (figure. Positive t-value indicate that shortest path distance is shorter in Perceived and negative t-value indicate shortest path distance in shorter in non-perceived trials (p=0.001, t=3.2, df=11). We also found the significant difference in the perceived and not-perceived trials in the right parietal hemispheres at the frequencies 29, 31 and 33 Hz. At 29 Hz, For the fourth quadrant, p=0.04 and individual t-value for each connection, at 31 Hz, for the fourth quadrant, p=0.02 and at 33 Hz, For the fourth quadrant, p=0.03 and individual t-value for each.

A)



i) 35 Hz

B)



i) 29 Hz ii) 31 Hz iii) 33 Hz

Figure 5 A i) Shows the network organization in at the 35 Hz. Right hemisphere shows the significant difference for shortest path length for perceived and not-perceived trials. B) i), ii) and iii) show the network organization are 29 Hz, 31 Hz and 33 Hz. They basically demonstrate the networks in right parietal region of the brain. Thicker line communication representing the low value for the shortest path length and vice-versa

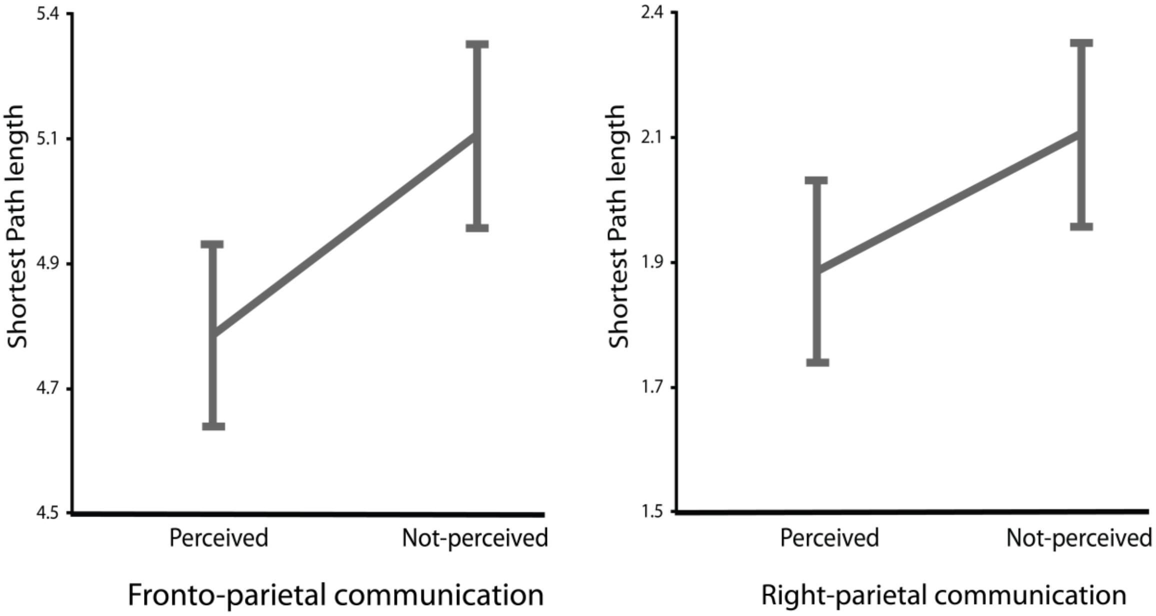


Figure 6 plot showing the regional shortest path distance for perceived and not perceived trials. a) representing for the fronto-parietal communication at 35 Hz Perceived(M±SE=4.85±0.064) and not-perceived (M±SE=5.01±0.063) and b) representing for the right parietal communication perceived (M±SE=1.88±0.05) and not-perceived ((M±SE=2.12±0.06).

Discussion

ViBM in combination with neurophysiological recordings is an established paradigm to study the neural mechanisms underlying the perception of emotional stimuli. While previous work has highlighted the activation of brain regions that are mandatory for the correct interpretation of the valence of facial expressions, here, we studied the functional connections between regions, i. e. the neural networks that are involved in the perception of emotional face stimuli. As metric of functional connectivity coherently oscillating magnetic brain activity was used. To rule out any physical differences of stimulus parameters between perceived and not-perceived emotional faces accounting for brain activation and network differences, stimuli were presented near the perceptual threshold resulting in perceived and not-perceived trials for the same masking stimulus. Neural networks characteristic for the processing of emotional face stimuli were identified by contrasting correctly perceived facial emotions to incorrectly perceived emotions. Except for correctly guessed emotional stimuli, correctly identified responses were assumed to reach a conscious level. In contrast, incorrectly perceived and correctly guessed emotions were supposed to reflect rudimentary emotional processing not reaching full awareness. Although in perceived trials correctly guessed and correctly identified emotions cannot be distinguished, there are in any case more consciously perceived emotions in the perceived than in the not-perceived condition

Based on the model that the correctly identified emotional valence relies on the well-adjusted interplay between fast bottom-up and slower top-down processes (Delorme, et al., 2004), one can conclude that stimulating with a prime-mask delay at the threshold of emotion perception provides enough time to complete the fast bottom-up processing of feature extraction and the presentation of the delayed mask and only interferes with later top-down processes. Thus, studying perception of emotions at NPT, we most likely assessed the cognitive analysis and interpretation of the presented emotional stimuli. This interpretation is supported by our findings not showing any low-level visual areas when comparing trials with perceived and not-perceived facial emotions.

In contrast, we have particularly assessed the brain networks involved in top down processing that is assumed to be maintained by reverberating long-range fronto-parietal network connections. Indeed, our results show that there is stronger fronto-parietal connectivity for correctly perceived emotional stimuli predominantly on the right hemisphere. In contrast, left hemispheric frontal control on right parietal cortex appears to be detrimental for the analysis of the emotional valence of facial stimuli.

Parcellation Approach

From the literature (Cahill, et al., 2004; Canli, et al., 1998; Silberman and Weingartner, 1986; Wager, et al., 2003), we have the understanding that sensory areas closely interact with frontal as well as with parietal areas when they are subjected to the processing of the emotional stimuli. The fronto-parietal interaction most likely involves an extended network spanning multiple regions in the prefrontal, frontal and parietal cortex rather than a point-to-point connection.

To test the participation of frontoparietal networks in the top-down processing of emotional stimuli, we have adopted a cluster-based permutation across frequency approach on source level connectivity. We demonstrated, firstly, that the fronto-parietal networks were significantly more functionally coupled in the gamma band during the perception of emotional faces in contrast to not perceived emotional faces. Secondly, using the phase-slope index we could demonstrate that in these networks the direction of information flow is from right frontal regions towards the right parietal cortex. Thirdly, within-connections of the right posterior parcel were significantly stronger in high beta and low gamma frequency bands during perceived as compared to not perceived emotional faces. Fourthly, we showed that there is higher connectivity for non-perceived stimuli than for perceived stimuli between left frontal and right parietal regions in the gamma frequency range.

Gamma Frequency Band

Fronto-parietal networks differed between perceived and not-perceived emotional stimuli mainly in the gamma band. Gamma frequency activity in emotion perception has generally been related to bottom-up sensory processing (Li and Lu, 2009; Müller, et al., 1999). Synchronized neuronal firing in the high frequency range in the human cortex has been suggested to reflect the formation of Hebbian cell assemblies (Eckhorn, et al., 1990; Pulvermüller, et al., 1995; Singer and Gray, 1995) and can be recorded with E/MEG in sensory processing. Gamma modulation has been reported to occur for the variation of features of visual stimulus (Müller, et al., 1996; Müller, et al., 1997; Tallon-Baudry, et al., 1997; Tallon, et al., 1995) and during perception (Keil, et al., 1999a; Keil, et al., 1999b; Tallon-Baudry, et al., 1996; Tallon-Baudry, et al., 1997).

Although, previous studies have investigated oscillatory brain activity in emotion perception with stimuli well above the perception threshold and thus the previously described gamma-band activity might be due to specific emotion processing, but also to low-level visual processing. In contrast, in our study we have stimulated the emotion networks near the perception threshold. By contrasting perceived and not-perceived emotions we could rule out networks involved in low-level feature extraction and highlight the fronto-parietal top-down control networks oscillating in the gamma frequency range and thus interacting with bottom-up provided information. The participation of the gamma frequency band is found to be significant in the right parietal cortex which is in line with findings attributing an important role to the right hemisphere in emotion processing (Literature). A negative contribution (stronger connectivity for non-perceived stimuli) from the left frontal cortex to parietal cortices. It seems very plausible that the functional coupling in the gamma band is a proxy for the successful perception of emotional faces in our experiment using ViBM task at the NPT (Eckhorn, et al., 1990; Pulvermüller, et al., 1995; Singer and Gray, 1995). We argue that the involvement of different networks from within and between hemispheres via gamma oscillations is the bases for the generation and propagation of reverberant self-amplifying fronto-parietal loops (Dehaene and Changeux, 2003; Dehaene, et al., 1998; Dehaene and Naccache, 2001; Del Cul, et al., 2006b) enabling the perception of emotions.

Phase Slope Index (PSI)

Using PSI, the direction of information flow from one region to another can be inferred (Nolte, et al., 2008). We have estimated the PSI values between individual areas in different parcel combinations across different frequencies identified in the cluster-based permutation parcellation analysis for perceived and not perceived trials. We found that the PSI value indicates a significantly positive contribution from right frontal cortex (parcel I) toward right parietal cortex (Parcel IV). The positive PSI value between ‘A’ and ‘B’ suggest the activities are leading at ‘A’ and ‘A’ is directing information towards ‘B’. Using this analysis, we were able to demonstrate the frontal cortex is leading and controlling the information flow towards parietal cortex. This finding supports the interpretation of fronto-parietal networks exerting frontal top-down control over parietal areas.

Except for the right fronto-parietal interaction, we were unable to demonstrate any other significant directed information flow between left frontal region and right parietal cortex or any other combination. From this result one might conclude that the communication between left frontal and right parietal cortex is bi-directional and/or may be dominated by noise. However, given the predominant involvement of the right hemisphere in top-down emotional control it might also be argued that information exchange between the other regions is less relevant.

Our finding of right directed fronto-parietal information flow in the processing of emotions are consistent with previous findings on emotion perception that suggested strong participation of the right hemisphere in the perception of emotion irrespective of the valence of the emotional stimuli (Davidson, 1984; Ehrlichman, 1987; Hirschman and Safer, 1982).

Positive and Negative emotional faces

It has been documented in the literature that left hemisphere is involved in the processing of positive emotion processing and right hemisphere is responsible for the processing of the negative emotional valence (Aftanas, et al., 1998; Müller, et al., 1999; Tucker, 1981; Tucker and Dawson, 1984). In our experiment, using a ViBM at the NPT, we did not find any significant difference in network oscillations for positive and negative faces.

Graph Theoretical Network Approach

For the past two decades, various graph theoretical measures had been extensively used to study structural and functional neural architecture of the brain. In our analysis shortest path length was differentially expressed in brain networks prevalent for perceived and not perceived emotional face expressions with shorter average path lengths for the former condition. In graph-theoretical network analysis nodes correspond to brain areas and edges correspond to the connection between nodes. The shortest path length between two nodes is the minimal number of edges to reach one node from one another. The average shortest path length for one node is the average of all shortest path lengths from this node to all other nodes. Mapping the average shortest path length for individual brain regions provides insights how well individual areas are connected to the rest of the brain. A low value of the local average path length is an index for the integration of an area in the network.

The pathlength of the network is an important predictor of the network performance (Vragović, et al., 2006). They found out that the performance of the network in basically dependent on the network average path length: *‘’The shorter the path length, the better the performance’’.* While it might be objected that in diseased brains such as schizophrenia and epilepsy, with insufficient inhibition functional all-to-all connectivity between brain areas is generally increased and thus shortest path length is decreased, performance is most likely not improved (Andreou, et al., 2015; Yan, et al., 2017). In contrast, looking at only the strongest and functionally relevant connections by selecting shortest path lengths as we did in our analysis might yield more meaningful results. In our study we demonstrated that shorter path length for the right fronto-parietal subnetwork during the successful perception of emotional face expressions supports the notion of right fronto-parietal communication mediated by oscillatory gamma band activity being crucially important for the processing of emotions.

The human brain consists of the disparate various functionally specialized regions, and the information exchange between them is always and either task dependent and/or default mode. Here, the task dependent communication requires to be very precise and efficient in the integration of the information from disparate brain regions and can be characterized be the graph-theoretical measures. A key feature of the healthy brain is to have optimum balance between segregation and integration of information being exchanged between brain regions (Tononi, et al., 1998). For example, shortest path distance, a global characteristic, is an index for the functional integration of the brain network (Achard and Bullmore, 2007) and thus suggests how easy it is to transport information or other entities within the network. Shortest path length has been demonstrated to promote the effective integration across cortical regions, implying that the longest path length might indicate the communication between connected regions but is slower, reduced strength of connectivity and less efficient (Achard and Bullmore, 2007; Bassett and Bullmore, 2006)

Our results on shortest path lengths are in line with clinical studies which have shown that tight integration of two region can be studied using shortest path length such as schizophrenia (Liu, et al., 2008; Wang, et al., 2010), autism (Barttfeld, et al., 2011), stroke. In schizophrenia, task related path length was found to be increased in the alpha, beta and gamma frequency bands (Breakspear, et al., 2006; Micheloyannis, et al., 2006; Rubinov, et al., 2009). Our study is in line with Dahaene et al (Dehaene, et al., 1998; Dehaene and Naccache, 2001) proposing the general involvement of the fronto-parietal regions in perception in masked stimuli paradigm. Adding to these findings, our results suggest a highly specific right-hemispheric fronto-parietal network for the successful processing of emotional stimuli.

Conclusion and future direction

Studies on the processing of emotional stimuli have shown that in schizophrenia, there is a significant increase in the global path length compared to the healthy participants

(Liu, et al., 2008). The perceptual threshold of the schizophrenic patient is elevated and thus affects the top-down control of emotional processing. It has been argued that the increase of the threshold for emotional processing makes these patients unable to perceive emotions correctly.

We suggest that the proposed research is highly important both in terms of answering fundamental questions about networks involved in conscious and non-conscious perception of the emotional faces and thus provide the basis for novel treatments of neurologic and psychiatric disorders. Specifically, we suggest exploring new avenues towards actively understanding the neural mechanisms underlying basic perceptual processes in syndromes as different as neglect, schizophrenia and autism.

Summary

In our study, we found that in the gamma frequency band, the right fronto-parietal networks, parietal networks and left frontal to right parietal networks are significantly coupled during the perception of the emotional stimuli at near perceptual threshold. This gives us the understanding that the perception of emotional face expression involves functional coupling between different areas and is mediated by phase-locked oscillatory activity in the gamma frequency band. In the framework of the global neuronal workspace theory, results suggest that directed fronto-parietal connections set the coordinated interplay between bottom-up with top-down processing.

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Estimation of perceptual thresholds: Effects and correction of observer bias

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4	Christoph Braun	Statistical analysis and wrote manuscript.

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Estimation of perceptual thresholds: effects and corrections of observer bias.

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Abstract

Perceptual thresholds depend on the observers’ sensory capabilities and on their expectations and preferred responses, i.e. their bias. The following paper presents results of three studies that compare different methods for the assessment of perceptual thresholds and introduces a new adaptive threshold estimation approach which incorporates bias correction.

In Study I, we investigated an adaptive method (AM) and the method of constant stimuli (MCS), which were applied in a backward masking experiment. Our results show a positive correlation between the thresholds estimated with the two methods, yet with systematic differences between both approaches.

The sensory threshold not only depend on participants’ sensitivity, but also on their bias. More precise threshold values could be obtained by eliminating this factor. In Study II, the bias-corrected threshold was estimated for the MCS using the framework of Signal Detection Theory (SDT). Subsequently, corrected and uncorrected threshold estimates were compared. Results showed that the estimates for bias-corrected thresholds were lower than the estimates for uncorrected ones.

To combine the efficiency of the AMs with the capabilities of MCS to estimate a bias-corrected threshold, we introduce and simulated a novel adaptive procedure that resorts to online bias-corrected response estimates (Study III). The results of the simulation demonstrated the advantages and limitations of the proposed method.

Keywords:

Adaptive procedure, method of constant stimuli, perception, signal detection theory, backward masking

Introduction

In psychophysics, perceptual thresholds are studied to characterize an individual´s capability to detect (or distinguish between) sensory events (Fechner, 1860; Swets, 1961). Here, we studied perceptual threshold estimation in a well-established visual backward masking paradigm (Breitmeyer and Ogmen, 2000; Di Lollo, et al., 2000a; Enns and Di Lollo, 2000; Vorberg, et al., 2003b). In the present study, we implemented this task as follows: an emotional face stimulus (*prime*), showing either a sad or a happy facial expression, was followed by a *mask* (showing the same face but with a neutral expression). Importantly, the mask was only presented after a certain *delay* (a black screen, displayed for different durations) and, the shorter the delay, the less likely the emotional expression of the prime would be perceived due to backward masking. The temporal delay at which the emotional expression of the prime can just be perceived defines the observer´s performance, i.e. her/his perceptual threshold for this task. In the present study, we estimated the perceptual threshold as the delay that resulted in 66.7% correct responses (see supplementary material [1]). Two distinct procedures are commonly used for determining perceptual thresholds:

1. Adaptive methods (AM) subsume many different approaches such as adaptive staircase procedures. These procedures try to approximate the stimulus parameters that lead to a specific response pattern (e.g. 66.7% correct) based on the relation of an observer's responses to the parameters of preceding stimuli (Treutwein, 1995; Watson and Pelli, 1983).
2. Method of constant stimuli (MCS) (McKee, et al., 1985b; Treutwein, 1995) refers to a procedure in which predefined stimuli are presented with parameters that - in an ideal case - should cover the whole perceptual range (i.e., 0% to 100% correct responses). Thresholds are then derived in a separate step, namely from a fitted psychometric function that relates stimulus parameters to a participants' response pattern. In the presented study, we applied the 'two-down one-up procedure' (TDOU) as an AM. In the TDOU approach, the delay between the prime and the mask decreases by one step (16.6 ms: 1 frame) after two correct responses and increases by one step with each incorrect response. Assuming a stationary threshold, the delay is expected to asymptotically approach the threshold, which is defined by a performance level of 66,7%, since we have

intermingled the two procedures and therefore there are not subsequent correct answer. Differently, if the correct answers are consequent, the performance level would have been of 70.7% (see supplementary material [1]). In AMs, stimulus parameters (here: delays) are more densely sampled when they are close to the individual´s threshold value (Levitt, 1971a; Levitt, 1971b). Therefore, the AM procedure was expected to provide a highly reliable threshold estimate. In contrast to the AM, the MCS approach included different predefined delays, presented across trials in a pseudo-randomized order (Leek, 2001). To determine the threshold (66.7% correct), a sigmoid psychometric function (logistic regression) was fitted to the correct responses as a function of the predefined delays. Considering that, AMs sample the delays predominantly around the threshold, whereas the MCS explores the whole range of delays, AM is regarded as being more efficient than MCS, in as-much-as a smaller number of trials are needed for threshold estimation (Watson and Fitzhugh, 1990). Furthermore, in the case of MCS, the approximate range should be known prior to the experiment. This represents a disadvantage as compared to AM. Yet, MCS has the advantage that by fitting a sigmoidal function to the total range of experimentally acquired psychophysical data, a robust estimate of the threshold can be obtained (Hesse, 1986; Taylor, 1971; Watson and Fitzhugh, 1990; Watson and Pelli, 1983). This paper compares the results obtained by the methods described above, with an additional focus on their ability to handle a participant's bias.

The bias is a systematic tendency of the observer to over- or under- estimate the presented stimulus parameters (Luce, 1963; Macmillan and Creelman, 1990; Macmillan and Creelman, 2004; Macmillan, et al., 2004). There are several types of biases that can occur at different stages of perceptual processing, e.g. at the sensory, the decision making, and the response selection level. A participant's bias can contaminate threshold estimates relevantly. It can be corrected during data analysis or reduced by an appropriate design of the threshold estimation procedure. In our paradigm, we attempted to control the response bias by pseudo-random orderly assignment of buttons to be pressed to indicate the different valences of the administered face stimuli, i.e. sad vs happy. However, sensory and decision-making biases might still be affecting the observer's perception. In situations where the observer is biased, the proportion of correct responses is not a thorough measure of the observer's perceptual sensitivity. In this context, signal detection theory (SDT) has been proposed as a framework to estimate the sensitivity (d') by modelling perception as a decision-making process (Green and Birdsall, 1978; Harvey, 1992; Macmillan and Creelman, 1990; Macmillan and Creelman, 2004; Macmillan, et al., 2004; Swets, 1961; Wickens, 2001) [for details see supplementary material 2]. While MCS allows the implementation of SDT for estimating an observer's bias, in case of AMs no generally accepted strategy exists. To combine the efficiency of the AMs with the capabilities of MCS to estimate a bias-corrected threshold, a novel adaptive procedure is introduced. In standard TDOU, each delay depends on the observer's response to the previous trial. The new method updates the estimate of an observer's bias continuously and selects a delay for the upcoming trial based on the bias-corrected response. While the observer's response is either correct or incorrect, the bias-corrected response is characterized by a certain probability for being correct. Thus, when determining the masking delay of the following trial, the (bias-corrected) TDOU-algorithm would be build on probabilistic considerations.

The paper aims to articulate the theoretical framework of the new method.

In the current paper, we compared TDOU- and MCS-based performance estimates in a backward masking paradigm comprising of visual emotional face stimuli (Study I). Subsequently, using the framework of SDT, the influence of bias correction on threshold estimates was investigated for the MCS procedure (Study II) using the data of the first experiment. The first part of the paper, including the Studies I and II, aims at introducing the problem of bias and it explains the principles of the methods to which we refer to develop a new approach for the threshold calculation (Study III). Therefore, we propose the new adaptive method which uses SDT to estimate a participant's bias-corrected responses online and which uses this probabilistic response estimate to guide the AM. Study III demonstrates the feasibility of the procedure and discusses prerequisites, advantages and possible limitations of the approach.

Method

Participants

Twelve healthy, right-handed participants (mean age: 25.5 years; 7 females and 5 male individuals) participated in the study. Participants did not have a history of psychiatric or neurological illness and had normal or corrected-to-normal vision. The experiment was approved by the local ethics committee for medical research (Faculty of Medicine, University Hospital Tübingen). Prior to the experiment, participants gave their written informed consent.

Experimental Procedure

The experimental paradigm consisted of a modified version of the visual backward masking task, developed by (Del Cul, et al., 2006a) and inspired by the work of (Di Lollo, et al., 2000a; Enns and Di Lollo, 2000; Vorberg, et al., 2003b). In the original study, Arabic numbers were used as stimuli. In the current experiment, emotional faces were used, to estimate individual perceptual thresholds.

Each experimental trial (Fig.1) started with the display of a fixation cross for 2s, followed by the prime stimulus. The latter could be either an emotionally positive (happy) or negative (sad) face, presented for 16 ms. After a given delay, the prime stimulus was masked by an emotionally neutral face of the same identity, presented for 250 ms. To determine the delay corresponding to the threshold at which the emotional expression of the prime was reliably perceived, a black blank screen was displayed between the prime and the mask stimulus. The delay corresponded to one of ten different values (0 ms, 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, 133.3 ms, 150.0 ms), according to the frame rate of 60 Hz of the projector. After the mask, another black blank screen was shown for a duration of [Tblank= 1500 ms – (Tprime + Tdelay+ Tmask)] to guarantee that the response indicator affects the processing of the prime and mask stimulus in the same way. Afterward, participants had to indicate the emotional valence of the prime by pressing a corresponding optical response button (either the one in their left or their right hand). To prevent any response bias, the assignment of the left/right response buttons to positive/negative valence judgements was counter-balanced across trials. The association was indicated by the following visual cues: “POS+NEG” and “NEG+POS”, with ‘+’ serving as fixation cross. “POS+NEG” instructed to press the left button if the participant perceived that the prime was emotionally more positive than the mask, and the right button if the prime was negative. “NEG+POS” instructed to press the left button if the participant perceived that the prime was emotionally more negative than the mask, and the right button if the prime was positive. Participants were requested to respond to each trial, and to make a guess about the emotional valence of the faces (happy or sad) when they were unsure about the right answer. The inter-trial interval was 5 sec.

The experiment consisted of 5 runs, each lasting for 15 minutes. Each run had 152 trials, including 80 trials for the AM, and 72 trials for the MCS. The MCS involved 10 different delays, including 20 trials with a delay of 0.0 ms and 150.0 ms, and 4 trials including the following delays: 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, and 133.3 ms. In each run, the trials for MCS and TDOU were presented in a pseudo-randomized order. The emotional faces of different identities were pseudo-randomly selected and consisted of 50% female and 50% male faces.

The stimuli were presented using a Pascal-based program in the Dos 6.2 operating system (developed at the MEG center of Tübingen) and were synchronized with the vertical screen refresh rate of 60 Hz. Images were presented on a screen in front of the participant using a SANYO PLC-XP41L projector. Color images of faces from the NimStim Face Stimulus Set (Tottenham, et al., 2009) were used as stimuli.

All the data analyses, including statistical tests, were performed using in-house scripts, running on MatLab version 2014.

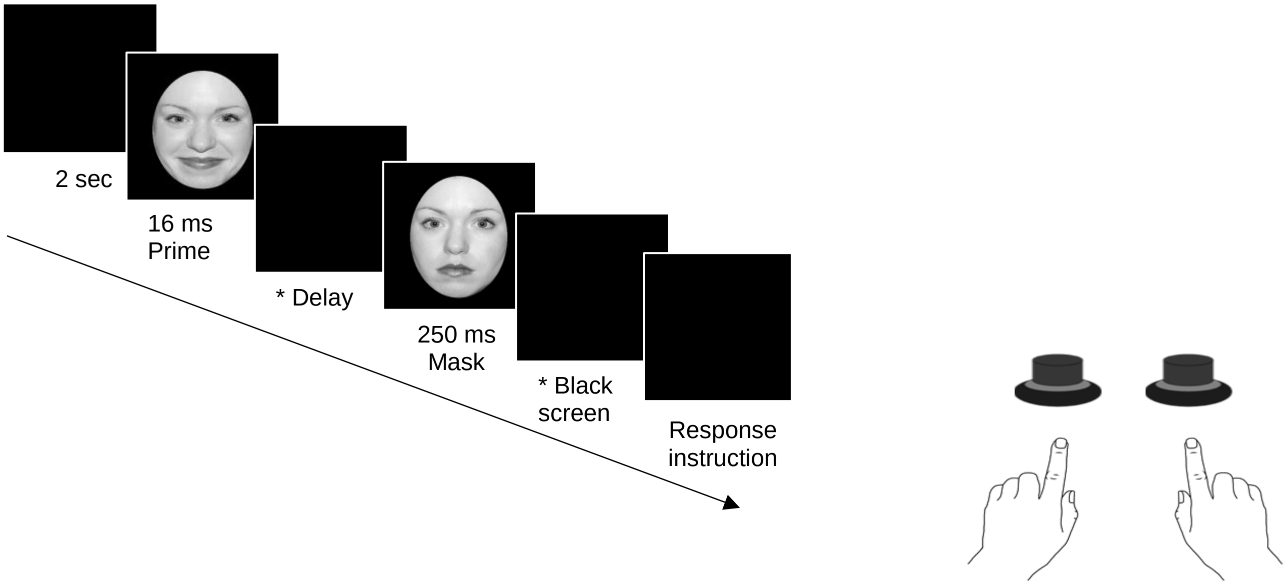

Fig.1: Threshold measurement protocol. After the presentation of a fixation cross (2 sec), the prime stimulus (an emotionally positive or negative face) was presented for 16 ms. After a variable delay (Delay *: 0.0 ms, 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, 133.3 ms, and 150. ms.), the mask (neutral face) was shown for 250 ms. The black screen, presented for duration Tblank (β *: [1500 ms – (Tprime + Tdelay+ Tmask)]), was followed by the response instructions. Participants were asked to compare the prime stimulus with the mask and to press the right- or left-hand button in order to indicate the emotional valence of the prime.

Study I: Comparison of AM (TDOU) and MCS

In the first study, we compared the thresholds estimated through AM and MCS, both at a level of 66.67% correct responses. The trials were intermingled between the two methods, reducing the potential influence of further external factors on the procedure and the results.

Methods

For the estimation of the thresholds, trials belonging to AM and MCS were separated. Since the delay is assumed to converge towards a performance level of 66.67%, with an increasing number of trials, in case of the TDOU rule (see supplementary material [1]), the threshold can be determined by averaging the delays across a certain number of trials. In the present study, the average of the last 20 trials of each run was used. We assume that the varying delays have reached an asymptotic level after 60 trials, and averaging the delays of the last 20 trials, should result in a stable final value. Finally, the mean of the thresholds estimated for each run was calculated. In the MCS, the psychometric function was estimated by analyzing the frequency of correct responses for the ten different delays. Considering Fechner's law of logarithmic relation between perceived and physical magnitudes of sensory input (Dehaene, 2003), the logarithm of all delays was calculated. The logarithm involves the possibility to obtain a minus infinity for a delay of zero, to avoid this problem, 1 ms was added to all delays prior to the transformation. Afterwards, a Weibull psychometric function was fitted to the frequencies of correctly identified emotional face expressions:

$$f(x) = 1 - (1 - g)e^{-\left(\frac{kx}{t}\right)^{b}} \qquad (1)$$

$$k = -\log\left(\frac{1-a}{1-g}\right)^{\frac{1}{b}} \qquad (2)$$

x = logarithmic transformation of delays

g = performance at chance level: in our example set to 0.5

t = threshold

a = performance level defined as threshold (0.667)

b = slope of the psychometric function

The Weibull function asymptotically converges towards 50% for a delay of 0.0 ms and towards 100% for increasing delays. The Weibull function fitted to the psychophysical data resulted in a threshold estimate t, i.e. a delay for which a performance level of a was reached. Furthermore, a value for the slope of the psychometric function, reflecting contrast sensitivity, was obtained. However, this parameter is not discussed any further here. The MCS threshold was defined as 66.67% correct, which is well above chance level, and corresponds to the threshold level of the AM.

Results

In a first step, the perceptual thresholds for the AM and the MCS were estimated and subsequently compared. Two participants were discarded from the experiment, as it was not possible to fit a sigmoid Weibull function to their MCS data. Fig.2a shows the perceptual threshold calculated using AM for a typical participant. The graph contains the participant's correct and incorrect responses for 5 runs. In contrast to our expectation, the threshold is only asymptotically reached in a few runs. Fig.2b shows the procedure to estimate the threshold using MCS for the same participant as in Fig.2a. The percentage of correct answers is represented for each delay. Across all participants, no significant difference (t(9)= 0.9, p = 0.39) between the threshold estimates for AM (M ± SE: 43.47 ± 3.79) and MCS (M ± SE: 38.28 ± 7.00) were found. Moreover, Fig.2c illustrates a significant correlation between participants' AM and MCS estimates (r = 0.579, t(8) =2.008, p = 0.04 (one sided)).

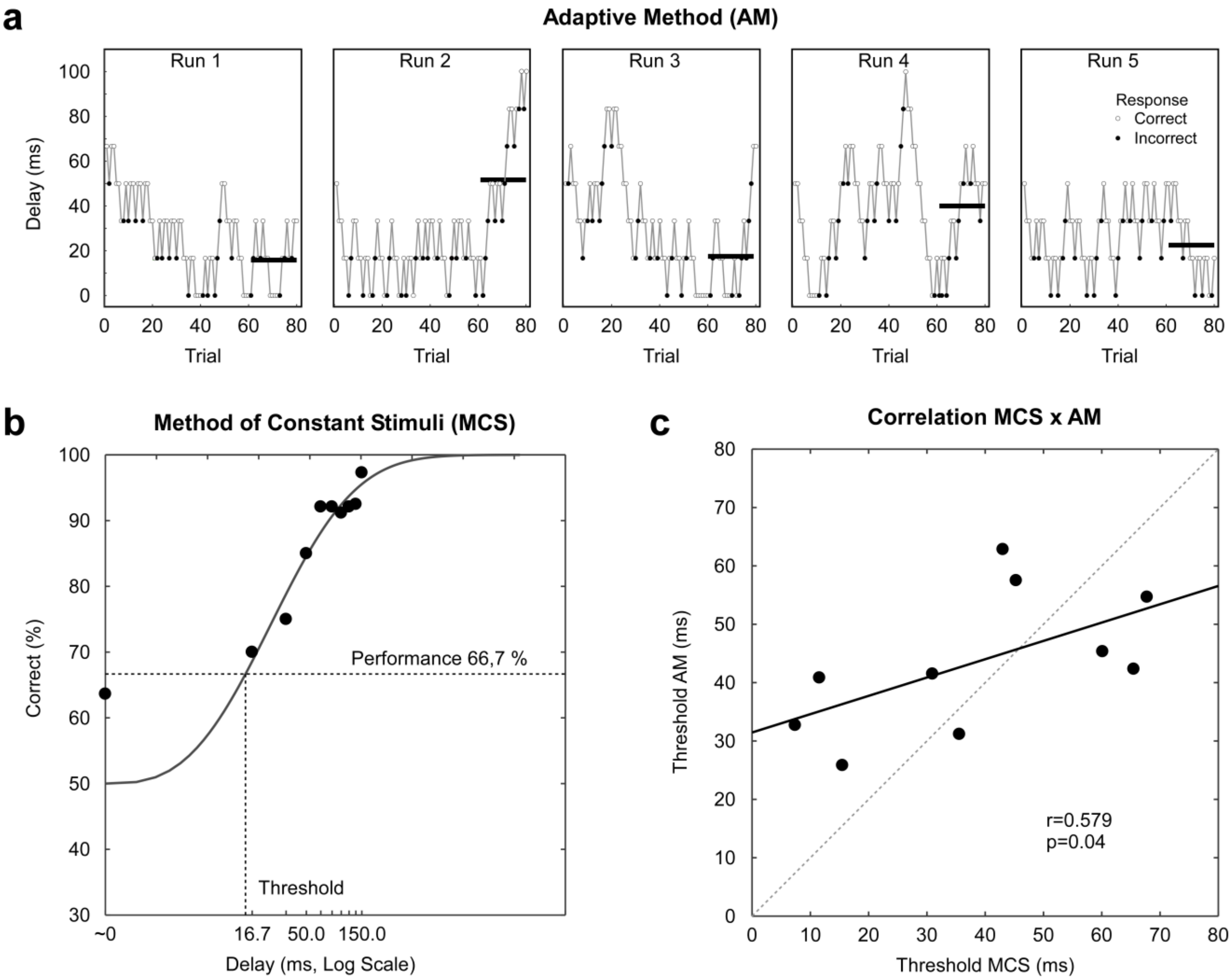

Fig.2 a-c: a) Plot showing the AM method for threshold estimation in a single participant using the TDOU rule. White dots indicate correct responses and black dots represent incorrect answers. The x-axis represents the number of trials and the y-axis the delay. b) Threshold estimation of the same participant, using MCS. The x-axis shows mask delays on a logarithmic scale and the y-axis indicates the percentage of correct responses. The threshold is defined as 66.67% of correct answers. c) Correlation between participants' threshold estimates using AM and MCS. r = 0.579 and p = 0.04 across 10 participants.

Discussion

The described experiment investigated the comparability between two perceptual threshold estimation techniques (AM and MCS), using a backward masking paradigm. Although thresholds were determined quasi simultaneously for both methods, only a rather moderate correlation was obtained.

Previous investigations, assessing the similarity of threshold estimations with MCS and AMs, have produced heterogeneous results (Hesse, 1986; Kollmeier, et al., 1988; Shelton and Scarrow, 1984; Shelton, et al., 1982; Stillman, 1989). Several simulation studies have shown a certain consistency between threshold estimation, using MCS and AMs. Our present experiment confirmed these results. The study reveals that the AM threshold is lower than the MCS threshold for MCS thresholds that are higher than 40 ms. In contrast, when participants had MCS thresholds lower than 40 ms, thresholds obtained for the AM were higher than that of the MCS. A possible explanation for the systematic inconsistency between AM and MCS is that, if in AM the adaptive procedure reaches lowest (0.0 ms) or highest delays (150 ms), the next delay might not be chosen according to the TDOU procedure because of floor and ceiling effects (in our case, floor effect correspond to 1.9% ± 0.4% and the ceiling effect to the 0.0%).

As previously described, the AM is expected to sample the performance near the threshold and thus should result in a rather reliable threshold estimate. Even if the AM starts from a delay that is far away from the ultimate threshold delay, the latter will be reached in a comparatively small number of trials depending on track length and step-size. In the MCS, on the other hand, the psychometric function is fitted to the observer's data for the whole range of delays. Therefore, in MCS the threshold estimate depends on the type of psychometric function, the transformation of the delay data, and is possibly also affected by data points that are further away from the threshold of interest, and thus the MCS estimates might differ from the ones obtained using AM.

Study II: Bias and MCS

When assessing a participant's perceptual threshold, bias has an impact on the threshold estimate. In an ideal bias-free scenario, the lowest individual thresholds would be obtained. The introduced bias will lead to either an increase or decrease of the estimated threshold value. In case of the MCS, bias correction has been implemented using Signal Detection Theory (SDT) (Clark, 1966). In the following experiment, using the data of the Study I, the uncorrected and bias-corrected MCS threshold estimates are compared. In addition to demonstrating how threshold estimates are affected by bias and its correction, the study also serves as an introduction to the bias correction procedure implemented in the new adaptive method presented in Study III.

Methods

In SDT, the representation of the intensity of a sensory stimulus is assumed to follow a probabilistic function, usually modeled as a normal distribution. In case of two distinct stimuli and two respective response alternatives (stimulus A, for instance 'happy face', vs. stimulus B, 'sad face'), the perceptual decision outcome depends on whether or not the intensity of the sensory representations exceeds a decision criterion (Kingdom and Prins, 2010; Prins, 2016). The criterion for sensory decisions can vary according to previous information and decision biases. Hence, the decision criterion (supplementary material [2]) directly reflects the observer's bias (Fig.2a).

In our experiment, each stimulus would be characterized by its own probability density function. Overlapping probability functions for happy and sad face images will be found for two stimuli that can only be discriminated at chance level. The higher the separation between the probability density functions of two stimuli, the better they can be discriminated. The separation between the probability density functions is a measure of the sensitivity d' (pronounced as 'd prime') of a detector.

SDT allows the estimation of both sensitivity d' and criterion g (and thus bias) based on participants' response behavior, i.e. the number of hits (the percentage of correctly identified happy faces), correct rejections (the percentage of correctly identified sad faces), misses (incorrectly perceiving the happy face as sad) and false alarms (incorrectly perceiving the sad face as happy) (Table S1). Accordingly, we determined the probability of correctly detecting a happy face ($p_{CH}(t)$), the probability of correctly detecting a sad face ($p_{CS}(t)$), the probability of incorrectly detecting a sad face (happy faces erroneously perceived as sad: $p_{IH}(t)$), and the probability of incorrectly detecting a happy face (sad faces erroneously perceived as happy: $p_{IS}(t)$) for each delay. Afterwards, d', the distance between the probability density function for HF (happy face) and SF (sad face) was separately estimated for each delay, namely as the difference between the Z-transforms, with the following formula:

$$d' = Z\left(p_{CH}(t)\right) - Z\left(p_{IS}(t)\right). \qquad (3)$$

The criterion g was estimated as follows:

$$g=-\frac{1}{2}\left(Z\left(p_{CH}\left(t\right)\right)+Z\left(p_{IS}\left(t\right)\right)\right). \tag{4}$$

Subsequently, based on d', the probabilities $p_{CH}\left(t\right)$, $p_{CS}\left(t\right)$, $p_{IH}\left(t\right)$, and $p_{IS}\left(t\right)$ were computed for an assumed bias of zero, and the bias-corrected percentage of correct answers for each delay was estimated with the following formula:

$$p_{corr}\left(t\right)=\frac{p_{CH}\left(t\right)+p_{CS}\left(t\right)}{p_{CH}\left(t\right)+p_{CS}\left(t\right)+p_{IH}\left(t\right)+p_{IS}\left(t\right)}. \tag{5}$$

The standard correction was applied when any response probability $p\left(t\right)$ had a value of 1 or 0 because the Z-transform is not defined in such cases. While in case $p\left(t\right)$ was 1, it was replaced by 1-1/2N (where N is the total number of trials with a particular delay). In case $p\left(t\right)$ was 0, the probability was replaced by the following formula: 0+1/2N. Fitting a Weibull function to the bias-corrected percentage of correct responses for all delays $p_{corr}\left(t\right)$ allowed us to estimate a bias-corrected threshold. Bias-uncorrected and -corrected thresholds were compared by means of correlation analyses. The corrected, unbiased psychometric function is represented by the criterion of 0.

Results

Fig.3a illustrates the impact of a non-zero bias for each delay in a single participant. The percentage of correct responses $p_{corr}\left(t\right)$ is lower when the criterion g deviates from 0 compared to the situation $g=0$, despite the same d'. The percentage of correct responses $\tilde{p}_{corr}\left(\tau\right)$ is maximum, when the criterion value is 0. In other words, the performance of the observer improves when there is no bias. In conclusion, the bias value affects the psychometric function as well as the estimated thresholds (Fig. 3c). In the framework of SDT, the observer’s bias for different delays can be represented by the receiver operating characteristic (ROC) curve (Egan, 1975; Metz, 1978) (Fig.3b). In the plot, each iso-sensitivity curve represents the perceptual performance for individual delays with varying biases (see supplementary materials [2]). A filled circle marks the observed bias for each delay. The bias-corrected sensitivities located on the diagonal with slope -1 are marked with black diamonds.

Fig.3c contains the percentage of correct identification of happy and sad faces for each delay in a single participant. The uncorrected performance is represented by grey, and the bias-corrected performance by black dots. After fitting psychometric Weibull functions to the uncorrected (grey) and corrected performance (black), the respective individual thresholds were determined. In case of the presented participant, a reduced threshold for the bias-corrected performance is evident (Fig.3c).

When comparing bias-corrected and uncorrected thresholds of the participants, a strong correlation was found ($r = 0.99$; $p \leq 0.0001$) (Fig.3d). The slope of the linear regression has a value lower than 1.0 (namely 0.9453), indicating that the average thresholds are lower for bias-corrected performance than for uncorrected performance.

Discussion

In the second study, we estimated the participants' perceptual thresholds, using MCS and applied bias correction using the SDT framework. Across all participants, bias-corrected thresholds were lower than uncorrected thresholds. Obviously, the observer's bias affects the threshold estimates and can lead to an underestimation of the observer's performance.

According to the SDT framework, we would expect participants' decisions to be based on a fixed criterion that does not vary with delays. However, in contrast to our expectation, the bias in the experimental data varied unsystematically for different delays (e.g. compare Fig.3a). In other words, participants might change their decision strategies for the differential identification of happy and sad faces depending on the level of the delays. For short delays, it is possible that observers focus on easily detectable features, which are not necessarily very reliable. In case of longer delays, more complex aspects might come into play, leading to a shift of the detection criterion. Considering this, bias correction is an important procedure to obtain valid sensory thresholds. Moreover, at least in case of our experimental paradigm, there is need for more systematic studies, in which the application of different strategies for solving the task can be disentangled.

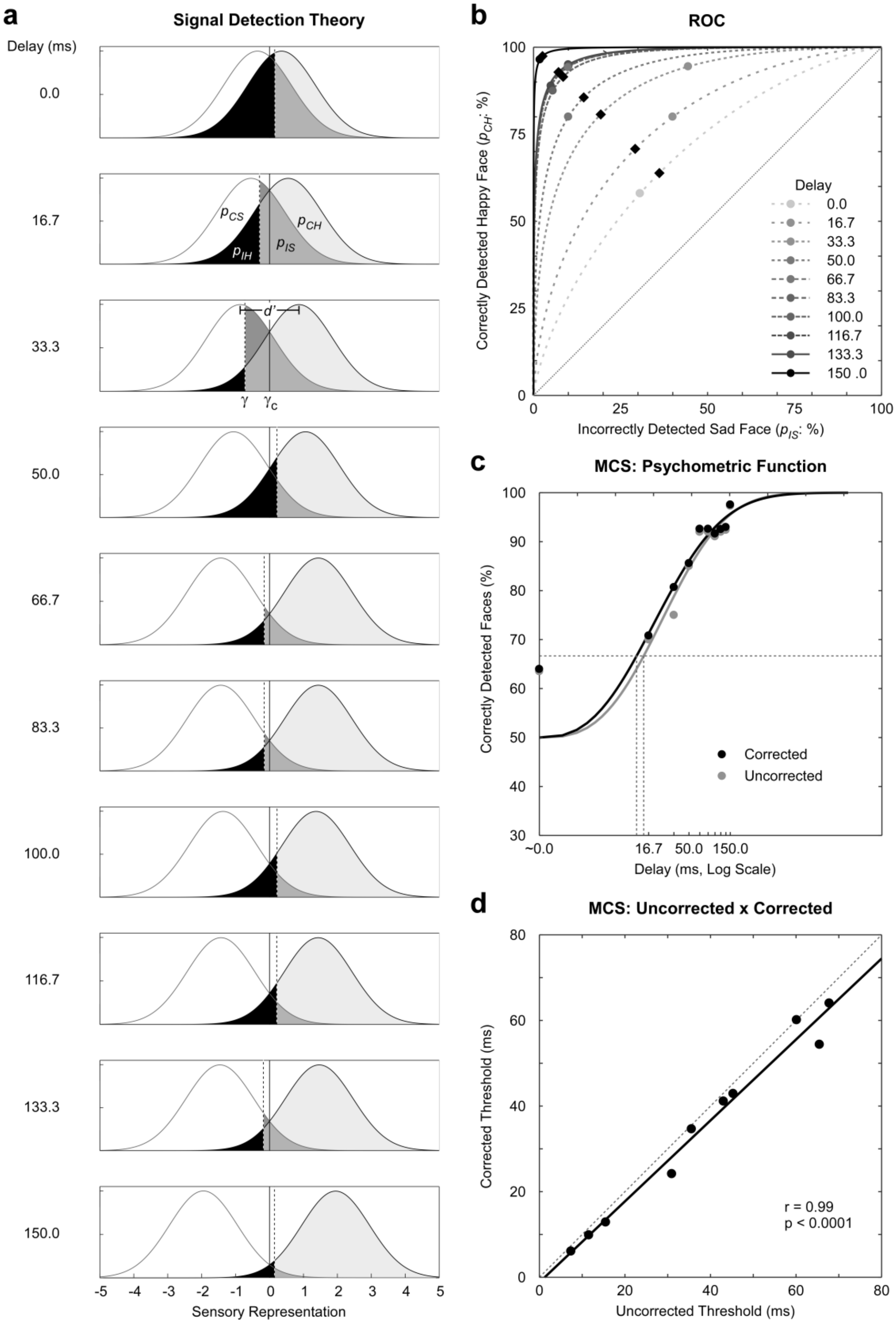
a
Signal Detection Theory
Delay (ms)
0.0
16.7
33.3
50.0
66.7
83.3
100.0
116.7
133.3
150.0
p_{CS}
p_{CH}
p_{IH}
p_{IS}
d'
γ
γ_c
-5 -4 -3 -2 -1 0 1 2 3 4 5
Sensory Representation
b
ROC
Correctly Detected Happy Face (p_{CH}: %)
Incorrectly Detected Sad Face (p_{IS}: %)
0 25 50 75 100
Delay
0.0
16.7
33.3
50.0
66.7
83.3
100.0
116.7
133.3
150 .0
c
MCS: Psychometric Function
Correctly Detected Faces (%)
30 40 50 60 70 80 90 100
~0.0
16.7
50.0
150.0
Delay (ms, Log Scale)
Corrected
Uncorrected
d
MCS: Uncorrected x Corrected
Corrected Threshold (ms)
Uncorrected Threshold (ms)
0 20 40 60 80
r = 0.99
p < 0.0001

Fig.3 a-d: a) shows the sensory representation of a single participant for 10 different delays. p_{CH} (probability of correctly detecting a happy face), p_{CS} (probability of correctly detecting a sad face), p_{IH}(probability of incorrectly detecting a happy face), and p_{IS} (probability of incorrectly detecting a sad face) are represented in different grey levels. d' is represented by the distance between the two probability density functions. The participant's decision criterion g for each delay is indicated by a vertical dashed black line. The bias-corrected criterion g_c is represented by a vertical solid line. b) represents the data derived from the same participant in a ROC curve. Each iso-sensitivity curve shows the relation between p_{CH} rate and the probability of incorrectly detecting a happy face for a specific delay, corresponding to one sensitivity level d'(all delays are represented). Besides the original bias (grey dots), the bias values of 0 (black diamond) are represented. The higher the d', the darker and the more solid the lines of the iso-sensitivity curves c) The difference between the uncorrected and corrected threshold derived from the psychometric function for a single participant. The grey curve with grey markers represents the uncorrected performance and the solid black line with black dots indicates the bias-corrected performance values and the corresponding psychometric function. d) shows the correlation between the uncorrected threshold and the corrected threshold for all participants. If the corrected and uncorrected were the same, the regression line (solid line) would follow the dashed line (1st diagonal). The calculated R-value of the correlation is 0.99 and is highly significant ($p<0.0001$).

Study III: Bias Correction for AM

In the third study, a new adaptive threshold detection method is proposed and simulated. The AM procedure estimates the threshold using the TDOU rule. In addition, the procedure considers an initial estimate of the observer's bias. Along with the adaptive procedure, the bias estimate will be continuously updated during each trial and subsequently used to determine an observer's bias-corrected response. The bias-corrected response in combination with the TDOU rule will be applied to select stimulation parameters, i.e. here the mask delay, for the following trial. Using simulations, we demonstrate the feasibility of the approach and its efficiency in handling biases of varying size.

Methods

The rules of this approach are summarized in a flowchart and were tested through a simulation. A virtual observer's performance for different numbers of trials and several levels of bias was simulated to estimate the thresholds (with and without bias correction), for both AM and MCS. As a final step, the results are summarized, and potential advantages and disadvantages of the new method are illustrated.

Figure 4 depicts the four different conditions that need to be considered in the approach.

a) Assuming that in a certain trial a 'happy face' (HF) is presented and the observer's criterion to classify the stimulus as 'happy' or 'sad' is at a level of $\gamma < 0$ *(this situation describes the case of a bias towards happy faces)* (Fig.4a), the probability to choose 'sad face' as a response corresponds to the rate of $p_{IS}(t)$. In contrast, the probability to select HF as a response is referred to as $p_{CH}(t)$. The probability $p_{CH}(t)$ can be thought of as being composed of $p_{CH} = p_{CHa} + p_{CHb}$, where $p_{CHa} = \int_{x=\gamma_c}^{x=+\infty} P(x)\,dx$ is the cumulative probability for $x > \gamma_c$, and $p_{CHb} = \int_{x=\gamma}^{x=\gamma_c} P(x)\,dx$ is the probability for $\gamma < x \leq \gamma_c$. $\gamma < 0$ represents participant's perception criterion and $\gamma_c = 0$ the bias-free perception criterion. $P(x)$ is assumed to be normally distributed. In the proposed method, the selection of the next stimulus is based on a participant's bias-corrected response. In case the virtual observer (VO) responded with 'sad face' (SF), the response was wrong, regardless of any potential bias. However, given the response bias towards HF, whenever VO answers HF, only a proportion $\frac{p_{CHa}}{p_{CHa}+p_{CHb}}$ of these responses can be accepted as HF. In case of the remaining trials, the response will be converted to SF. In an individual trial, depending on the estimated proportion, the response will be kept or changed, based on random selection. In detail, a random number r will be drawn from a uniform distribution between 0 and 1. If $r > \frac{p_{CHa}}{p_{CHa}+p_{CHb}}$, the observer's response will be changed from HF to SF, i.e., from correct to incorrect.

b) Likewise, for HF stimuli, a HF response will remain unchanged when the criterion is set at a level of $g > 0$ *(this situation describes the case of a bias towards sad faces)* (Fig.4b). The probability of incorrectly perceiving a happy face $p_{IH}(t)$, i.e. responding with SF to the HF stimulus, can be split into a proportion depending on the bias-free criterion p_{IHa} and a proportion that corresponds to the observer's bias p_{IHb}. If the random variable $r > \frac{p_{IHa}}{p_{IHa}+p_{IHb}}$ the SF response will be changed to HF.

c) For SF stimuli, a SF response will remain unchanged when the criterion is set at a level of $g < 0$ *(this situation describes the case of a bias towards happy faces in the presence of a SF stimulus)* (Fig.4c). The probability of p_{IS} (responding with HF to the SF stimulus), can be split into a proportion depending on the bias-free criterion p_{ISa} and a proportion corresponding to the observer's bias p_{ISb}. In case $r > \frac{p_{ISa}}{p_{ISa}+p_{ISb}}$ the HF response will be changed to SF.

d) Finally, for SF stimuli a HF response will remain unchanged when the criterion is set at a level of $g > 0$ *(describing a bias towards sad faces)* (Fig.4d). The probability of correctly perceiving a sad face p_{CS}, i.e. responding with SF to the

SF stimulus, can be split into a component depending on the bias-free criterion p_{CSa} and a proportion that corresponds to the observer's bias p_{CSb}. If the random variable $r > \frac{p_{CSa}}{p_{CSa} + p_{CSb}}$, the SF response will be changed to HF. In all four cases the bias-corrected response is used for the selection of the next stimulus according to the TDOU rule in the subsequent step of the algorithm.

In the simulation, corrections of the responses were carried out only after acquiring a robust estimate of the bias for the individual delays. A minimum of 25 trials, and a minimum of at least 3 trials in each of the SDT response categories for the current delay t $(p_{CH}(t), p_{CS}(t), p_{IH}(t), p_{IS}(t))$ was requested prior to application of the correction procedure. The bias correction was not applied in the same time for each delay since the same delay does not occur consecutively.

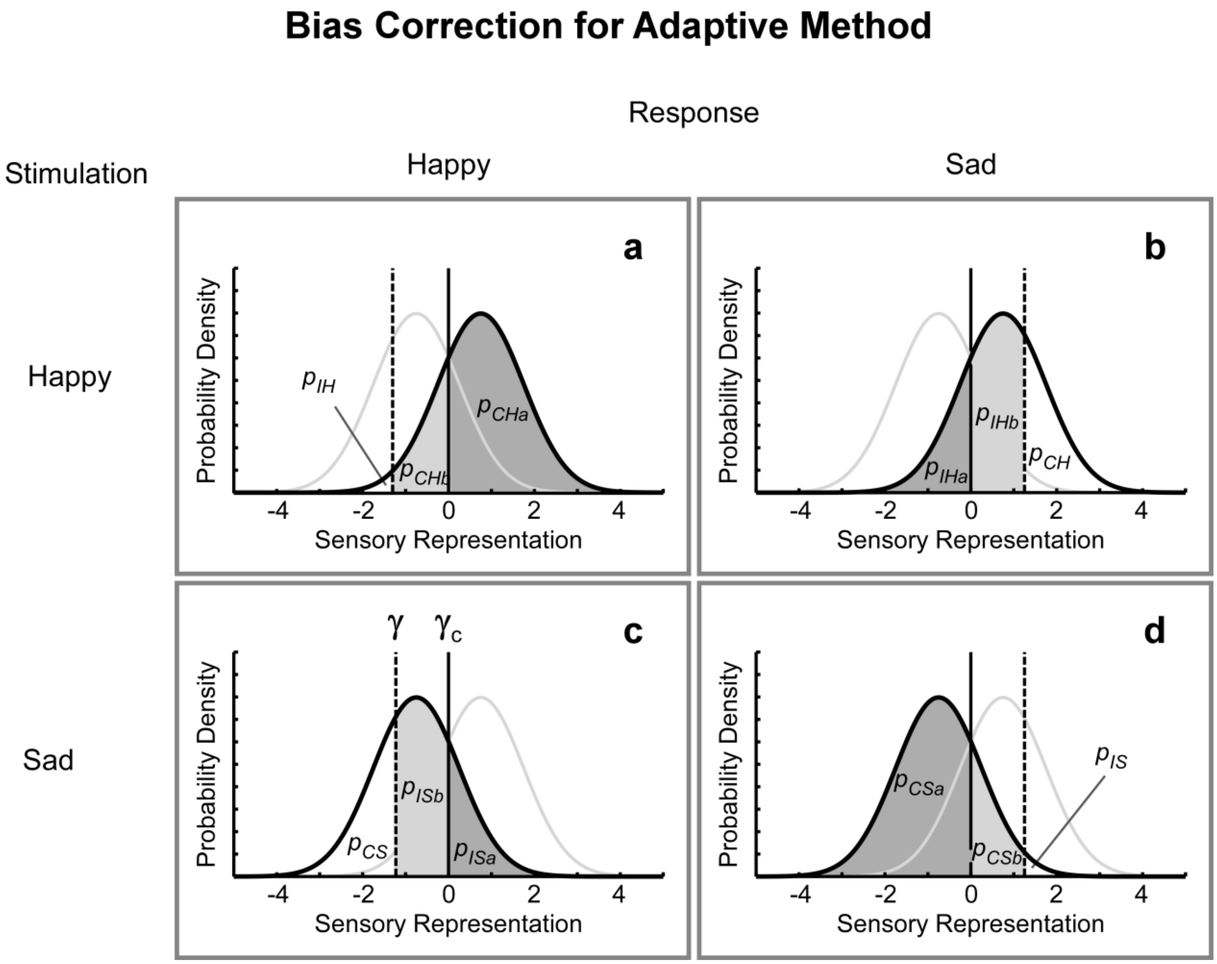

Fig.4: In the AM with bias correction, the observer's bias is estimated and the stimulus will be chosen depending on the TDOU rule and the bias-corrected response. Since in a single trial it is unknown whether the decision was based on a bias, a probabilistic correction will be carried out. For this purpose, probabilities for ($p_{CH}(t), p_{CS}(t)$, $p_{IH}(t), p_{IS}(t)$) will be split into a component that describes the probability for the unbiased criterion $g_c = 0$ (solid vertical line) and the proportion due to the bias-dependent criterion g (dashed vertical line). The unbiased proportion of the probabilities refers to $p_{\cdot a}$ and the component that is due to the response bias to $p_{\cdot b}$. In a) and b) HF stimuli and in c) and d) SF stimuli are presented. In a) and c) the correction needs to be considered for the response HF, while in b) and d) it needs to be considered for the response SF.

The flowchart below displays rules for the selection of a delay for the next trial, implemented through an algorithm that is based on corrected responses.

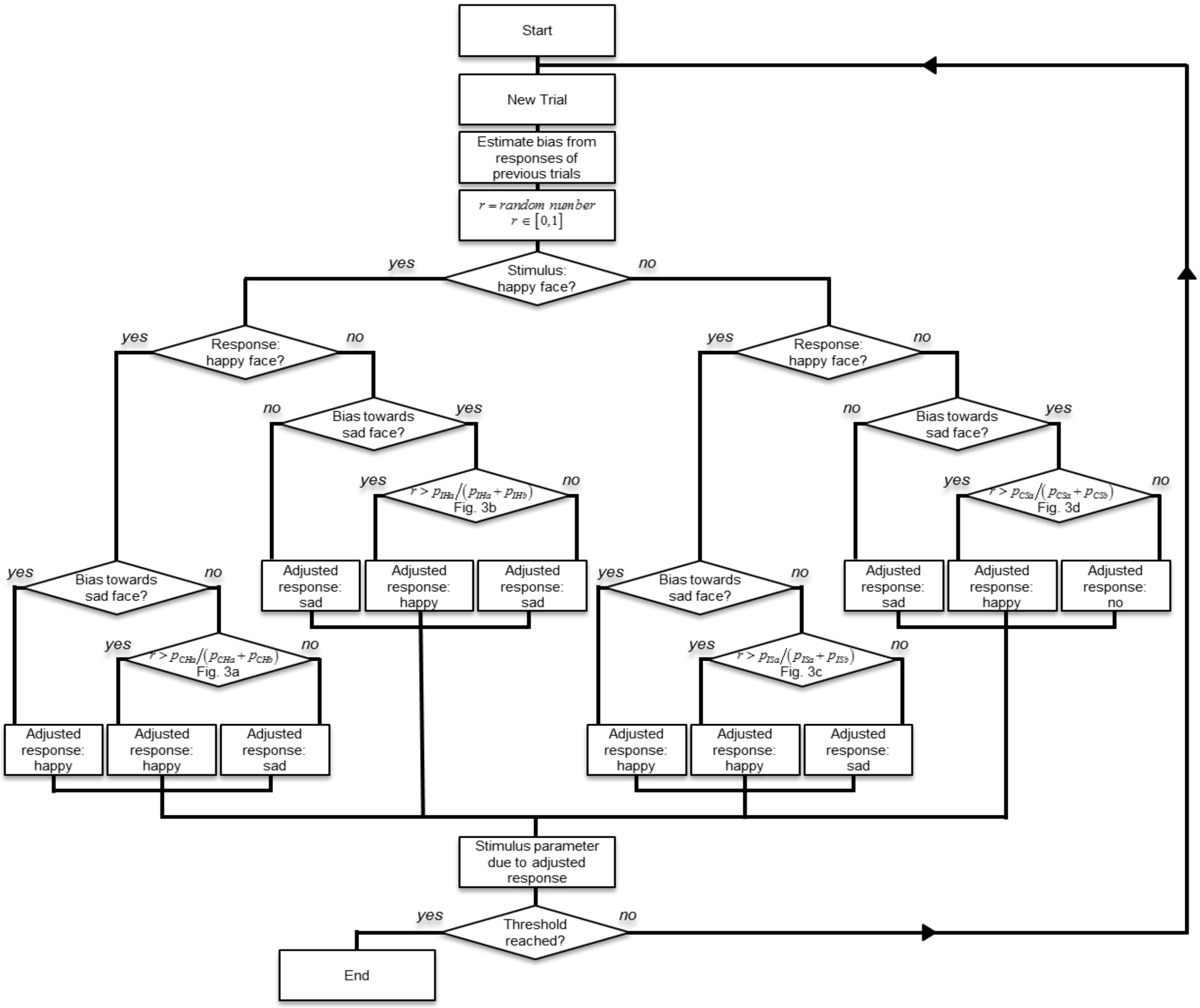

Fig.5: The flowchart describes the algorithm presented in the suggested approach.

After the bias estimation, it is possible to correct a participant's response by taking the initial bias value (criterion in the original position) into account and using a new bias-free decision criterion set to 0.

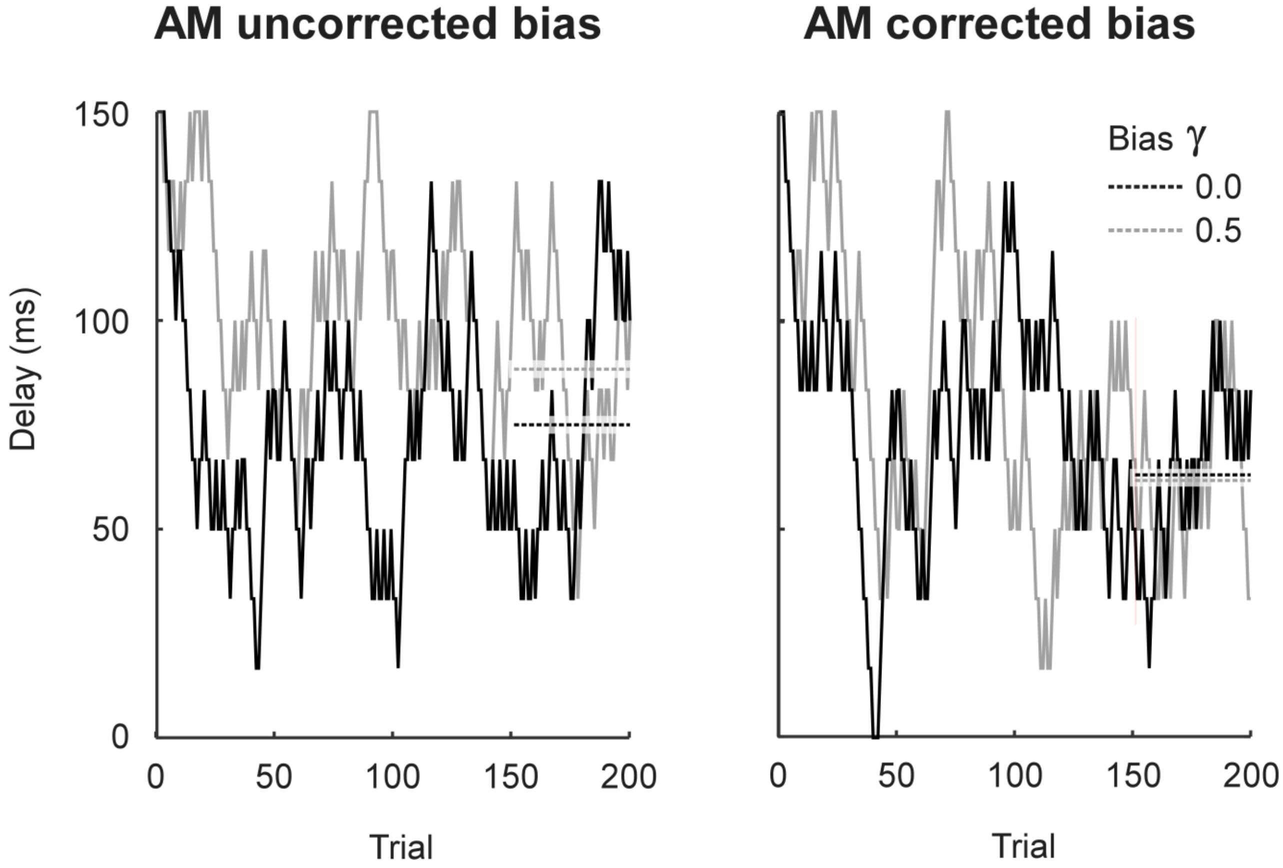

Fig.6: Simulation of AM with or without correction for biases of $g=0$ and $g=0.5$. As threshold estimates, the average of mask delays across the last 50 trials was taken. Averages are represented as horizontal lines extending from trial 150 to 200.

To verify the suitability of our approach for the on-line bias correction, a simulation was performed. We simulated the threshold's procedure for AM and MCS both with and without bias correction. A virtual observer's detection skills were defined for ten delays. Each delay was assigned to different d' according to: d'=12Δt. Since the d' of 0.861 corresponds to a percentage of correct answer of 66.7%, the preset threshold is 72 ms. Furthermore, different observer's biases were considered (0.0, 0.2, 0.5) (Fig.6).
The same delays used in the experimental paradigm were adopted to the simulation i.e, 0.0 ms, 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, 133.3 ms,

150.0 ms. Once the virtual observer's detection skills were defined, their performance for four different numbers of trials (100, 200, 500, and 1000 trials) was simulated.

During the simulation, HF and SF were presented in pseudo-random order. The probabilistic decisions of how HF and SF were perceived, were modeled in the framework of SDT and were based on Gaussian normal distributions centered at $\pm d'/2$ and with standard deviations of 1. The VO's performance depending on the mask delay was expressed as d' and increased linearly with increasing delays: $d' = 12\Delta t$ (see above). To simulate the VO's decision, a random number r_S was chosen from the normal distribution with standard deviation of 1 and $\mu = d'/2$ for HF and $\mu = -d'/2$ for SF. Depending on whether r_S exceeded the predefined decision criterion γ: $r_S \geq \gamma$, the virtual observer's response was HF. Conversely, in case of $r_S < \gamma$, the response was SF.

The results of the simulation for each set of parameters (level of biases and number of trials) were iterated for 1000 times and the corresponding thresholds were inferred. Note that the observer's responses are based on a probabilistic selection of responses. Therefore, the simulated thresholds vary for the same stimulus conditions.

Results

In table 1, the mean and standard deviations values across the 1000 repetitions for corrected and uncorrected thresholds and different bias values and different trial numbers are presented. Table 2 summarizes the estimated biases values that were inferred from the VO's response as a function of trials.

The simulation revealed that in the case of a low number of trials (≤ 200), both for corrected and uncorrected thresholds, the MCS fails to fit the Weibull function, while the AM is not affected by this problem. Furthermore, in the uncorrected AM procedure, the estimated thresholds are independent from the number of trials. Conversely, in the corrected AM, the estimated threshold values approach the threshold which has been preset in the simulation. In general, the results show that the threshold values are consistently lower in MCS than in AM. The reliability of the threshold, indicated by the standard deviation, is independent from number of trials in both, bias uncorrected and bias corrected AM. Moreover, reliability is lower for AM as compared to MCS (Table 1).

Table (1): threshold estimates of AM and MCS with and without bias correction for a bias of 0.0, 0.2 and 0.5 and for trial numbers of 100, 200, 500, 1000. For each condition, mean and standard deviations across 1000 simulations are presented. ‘Inf’ indicates that the simulation failed in fitting a sigmoid Weibull function and thus the threshold could not be estimated.

Threshold	Trials	**γ = 0.0**		**γ = 0.2**		**γ = 0.5**	
Method		AM	MCS	AM	MCS	AM	MCS
uncorrected	100	74.6± 22.02	Inf	76.5± 22.73	Inf	82.0± 22.16	Inf
	200	73.7± 22.77	Inf	76.7± 22.28	Inf	81.1± 23.00	Inf
	500	73.7± 22.62	69.7± 14.16	75.2± 22.13	71.0± 14.08	80.2± 22.90	79.0± 14.33
	1000	74.2± 22.15	70.6± 9.64	73.1± 22.05	71.0± 9.59	80.2± 22.25	79.5± 9.49
corrected	100	75.2± 22.05	Inf	75.6± 22.25	Inf	81.7± 23.51	Inf
	200	73.6± 23.42	Inf	75.4± 23.36	65.3±2 26.12	81.8± 22.61	Inf
	500	73.6± 22.40	68.5± 14.26	73.6± 22.01	68.1± 14.29	77.3± 23.63	67.2± 15.14
	1000	72.7± 22.98	69.9± 9.67	72.9± 22.25	69.0± 9.71	74.3± 22.43	69.1± 10.04

Bias correction is based on the estimation of the bias, derived from the participant’s previous responses. In Table 2, the estimated biases are presented for different trial numbers and at different simulated bias levels. The accuracy of the bias, deviation from the simulated preset bias value, and their precision, reflected by the standard deviation (the lower the standard deviation, the higher is the precision) became higher with an increasing trial numbers. The performance of the bias estimates is comparable for both AM and MCS, however with smaller errors for AM (Table 2).

Simulated Bias γ	**= γ 0.0**		γ **=0.2**		γ **= 0.5**	
Trials	AM	MCS	AM	MCS	AM	MCS
100	-0.0210± 0.1677	-0.0006± 0.3364	0.0839± 0.1671	0.1335± 0.3371	0.2250± 0.1715	0.3316± 0.3179
200	-0.0027± 0.1334	-0.0029± 0.2947	0.1406± 0.1335	0.1837± 0.2908	0.3335± 0.1471	0.4636± 0.2896
500	-0.0006± 0.0608	0.0007± 0.1972	0.1897± 0.0653	0.2091± 0.1966	0.4748± 0.0690	0.5117± 0.1998
1000	0.0007± 0.0432	-0.0010± 0.1368	0.2004± 0.0428	0.2057± 0.1369	0.5016± 0.0472	0.5145± 0.1458

Table (2) shows the estimated biases values determined by AM and MCS with bias correction. Mean bias estimates $\tilde{\gamma}$ and standard deviations $\sigma_{\tilde{\gamma}}$ across 1000 simulations are presented for simulated decision criteria $g$of 0.0, 0.2 and 0.5 and for trial numbers of 100, 200, 500 and 1000.

Discussion

In Study III, a new approach for the bias correction of adaptive threshold procedures (AM) was proposed.

In case of low trial numbers (100-200), the MCS suffers from an inability to reliably fit a sigmoid psychometric function to the experimentally acquired data while the AM still allowed a threshold to be acquired. In a real experiment the failure of fitting the psychophysical curve is equivalent to the loss of the corresponding participant. The relevance of this issue is evidence from the experimental data presented here, in which two participants had to be excluded. In conclusion, the higher the number of trials, the better the signal-to-noise ratio and the fitting of the sigmoid psychometric function. This leads to an improvement of the reliability of estimates produced by MCS.

Results of the bias uncorrected AM show that the threshold estimate does not change with the number of trials. Assuming that the delays used for stimulation in AM converge towards the threshold rather quickly, and using the averaged delay of the last 50 trials in each run, threshold delays should be independent from trial number especially for trial numbers larger than hundred. Since there were only 10 steps of delays, the lowest delay (0.0 ms) could be reached within 20 trials using the TDOU rule even if the procedure starts at the maximum delay (150 ms). With increasing number of trials, the bias corrected AM yielded threshold estimates approaching the value preset in the stimulation. Depending on the strength of the bias, the needed number of trials increases considerably.

We observed that the thresholds are consistently lower in MCS as compared to AM. As previously discussed, the floor effect (Study I) in selecting the delays, for low thresholds in AM, could result in an overestimate of the threshold value. Nevertheless, considering the standard deviations of the thresholds for AM and MCS, the ranges of the estimated thresholds are largely overlapping and thus are not distinguishable.

Considering reliability, the standard deviation of threshold estimates in the AM is constant, independently of the number of trials and bias-levels. However, in contrast to MCS, the standard deviation of threshold levels is rather high rendering the AM method less reliable. With the TDOU rule applied here, only a few trials determine the variation of the stimulus delay in the upcoming trials making the approach sensitive to random variations due to noise. Using an alternative rule that considers the response of more trials will most likely reduce the effects of noise and will enable the estimation of threshold levels for performance levels higher than 66.7%.

To estimate a bias-corrected threshold, the proposed AM method relies on bias-corrected responses of the observer to determine the stimulus delay for the next trial according to the TDOU rule. For this purpose, a first estimate of the bias is generated during the initial trials. Afterwards, when the bias estimate is available, the algorithm used for bias correction becomes effective. Along with the threshold procedure, the bias estimate is constantly updated and thus becomes increasingly more reliable. This strategy, however, implies that a sufficiently high number of trials has been sampled to get a reliable estimate of the bias. Our simulations show that it takes around 200-500 trials in MCS and AM respectively.

The need for high number of trials becomes especially relevant for strong biases because the tails of the probability density functions defined in the SDT framework become smaller and thus increasingly difficult to estimate. The results of the simulation demonstrate that bias-uncorrected threshold estimates for AM and MCS lead to more corrupted threshold estimates the stronger the bias. In both methods, bias correction improves threshold accuracy, in particular for high biases. However, an effective bias correction requires a large number of trials, insofar as a bias reduces the areas of probability density function that need to be determined (see: S1a-b). Since for stronger biases the required trial numbers to obtain a stable estimate is high for both methods the advantage of AM over MCS with only a few trials is lost.

General Discussion

In this paper, we investigated different methods to calculate perceptual threshold estimates in a backward masking paradigm, namely an adaptive method (AM) and the method of constant stimuli (MCS).

Despite similarities between data obtained with AM and MCS, our results show that there can be some discrepancy between both methods. This difference seems partly due to floor and ceiling effects that introduce a violation of the rule determining the delay in the next trial. This problem can be avoided adapting the step size for increasing trials numbers in the AM procedure (i.e.: bigger step size at the beginning and smaller at the end). In our experiment, however, determining the threshold delay for a visual mask stimulus, the step size could not be altered because of the fixed frame rate of the stimulus projector.

Study II highlights the need of bias-correction to reliably estimate perceptual thresholds. We applied a SDT-based bias-correction to participants' responses retrieved during study I with the MCS procedure and show that thresholds are consistently underestimated without such correction.

The estimation of an observer's bias allows distinguishing if there are true differences in perceptual thresholds, such as under different experimental conditions or in patients as compared to healthy participants. SDT enables to distinguish between the observer's sensitivity and the bias that can vary independently from each other. In case of patients with depression, for example, the suggested method could be applied to differentiate between the altered sensory performance and a disease-related, predominantly negative evaluation of the valence of visual stimuli (i.e. a systematic bias).

Although signal Detection Theory (SDT) is a powerful framework for the correction of perceptual biases during the estimation of sensory thresholds, there was a debate about its validity. As described above, the foundation of SDT is represented by the criterion and the sensitivity. The assumptions related to the criterion were criticized by various authors (Balakrishnan, 1998a; Balakrishnan, 1998b; Balakrishnan, 1999; Balakrishnan and Macdonald, 2002). In an attempt to verify the basic assumptions of SDT, Balakrishnan applied new nonparametric measures to experimental data. The author came to the conclusion that those assumptions are not supported and that SDT does not reliably represent/account for the full range of perceptual and decision processes. Note, however, that Balakrishnan's conclusions have been challenged by Treisman (Treisman, 2002) who argues that the underlying principles of SDT are still valid and who provided an alternative interpretation of Balakrishnan's results. In the meantime, several authors have continued to study the possible applications of SDT (Mueller and Weidemann, 2008; Pastore, et al., 2003). Being aware of the ongoing debate on this issue, we are confident that the SDT fits the purpose of the study presented here.

Finally, a new method was presented in Study III, which now also allows for efficient bias-correction in AM procedures. In this study, bias correction based on SDT was applied in a simulation, both, for the MCS and AM in a novel approach. When it comes to the bias correction many trials were needed in any case. In particular in case of strong biases the problem of a sufficient trial number becomes very strong. Therefore, it is important to reduce the bias by choosing an appropriate experimental design.

The more reliable results for the MCS that is indicated by the lower standard deviations speaks in favor of the MCS at least for higher trial numbers. In contrast, combining AM with bias correction is certainly beneficial when there is a need for keeping trial numbers low. AM with bias correction becomes the method of choice if during an experiment stimulation should constantly be applied at the threshold. In an experiment in which sensory performance is trained, adapting the stimulation parameters to the threshold allows for keeping the challenge. The framework presented here combining AM with the SDT-based bias correction doubtlessly leaves space for further improvements that particularly aim at increasing the reliability of the AM procedure. Moreover, the conducted studies revealed new characteristic and the relation with bias of the classical methods to calculate the threshold, contributing with new insights to the better understanding of the threshold estimation.

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Modulation of Perception using functional connectivity-based neuro-feedback.

(Manuscript attached)

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1	**Diljit Singh Kajal**	Collected and analysed the data, wrote manuscript
2	Sergio Ruiz	Edited the manuscript
3	Ranganatha Sitaram	Designed the experiment and edited the manuscript
4	Christoph Braun	Designed the experiment, statistical analysis and edited the manuscript.

Modulation of Perception using functional connectivity-based neuro-feedback

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Abstract

Perception of the emotion concludes with the active communication between fronto-parietal networks (FPN), and literature suggests that this communication is either disrupted or disturbed in the neuropsychiatric conditions such as schizophrenia and autism. In the current study, we trained healthy participants to volitionally modulate the functional connectivity between FPN using real-time neurofeedback magnetoencephalography (rtMEG). Participants in our experiment were presented with masked stimuli of emotional face expression at near the perceptual threshold (NPT). During the processing of the emotional stimuli, functional connectivity in the FPN was estimated in real-time and were presented as feedback stimulus at the end of the trial.

Subjects were instructed to modulate their connectivity, for up-regulation and down-regulation trials respectively. We have assessed the effects of training on the FPN and the threshold by comparing pre-test and post-test performance. A significant difference in the functional connectivity for up-regulation and down regulation trials of the neurofeedback session was found, suggesting that participants successfully achieved the modulation of FPN. Furthermore, we also found a significant reduction in the perceptual threshold in post-test compare to pretest. Our finding demonstrates that healthy participants can be trained to modulate the functional connectivity in the FPN using MEG-neurofeedback and suggest gamma band activity to be critically involved in the control of FPN.

Introduction

Perception of emotions is a crucial ability for smooth and appropriate social interaction in day-to-day life. This ability is diminished in patients suffering from neuropsychiatric conditions like schizophrenia and autism (Andreasen, et al., 2012; Bateson, et al., 1956; Deleuze and Guattari, 1988; Endicott and Spitzer, 1978; Kay, et al., 1987). A plethora of literature both in humans and experimental animals suggests that these neuropsychiatric conditions are basically the outcome of a disrupted or disturbed communication of fronto-parietal communication (Andreasen, et al., 1999; Friston; Friston, 2002; Hoffman and McGlashan, 2001; Stephan, et al.; Stephan, et al., 2009).

The decisive role of FPN in the perception of emotions suggests, neurofeedback as a suitable and side-effect free means to restore or support the functional communication in the FPN in patients suffering from impaired processing of emotional stimuli. Neurofeedback making use of non-invasive brain computer/machine interfaces (BC/MI) has proven to be a promising tool to selectively modulate brain activation and communication with the help of feedback (Birbaumer, et al., 2008; Birbaumer, et al., 2013; Sitaram, et al., 2017; Sulzer, et al., 2013; Weiskopf, et al., 2004; Wyckoff and Birbaumer, 2014). Previous neurofeedback studies using magneto-electrophysiological signals functional magnetic resonance imaging (fMRI): (Birbaumer, et al., 2013; Caria, et al., 2012; Shibata, et al., 2011; Sitaram, et al., 2017; Sitaram, et al., 2008; Sulzer, et al., 2013;

Weiskopf, 2012; Weiskopf, et al., 2004), magneto/electro-encephalography (MEEG): (Buch, et al., 2008; Mellinger, et al., 2007; Schalk, et al., 2004; Schalk and Mellinger, 2010) and near infrared spectroscopy (NIRS): (Chaudhary, et al., 2017; Sitaram, et al., 2009) have mainly demonstrated the training of the localized brain activity within the region of interest. However, although various neuroimaging experiments have firmly established functional specialization as a principle of brain organization, almost all cognitive abilities and neuropsychiatric conditions are associated with functional integration of interconnected networks (Bullmore, 2012; Lynall, et al., 2010). Assessing the integration between disparate brain regions has been made possible with the development of various data analysis methods (Fries, 2005; Fries, 2015).

Yet, there are a very few studies showing the modulation of interregional coupling. One of the pioneering work from our laboratory demonstrated the training of healthy individuals to modulate their interhemispheric functional connectivity of bilateral primary motor cortices (Kajal, et al., 2017; Kajal, et al., 2015b) and assessed effects of the modulation of the functional inter-hemispheric communication of the motor behaviour.

FPN networks plays a very important role in the perception of emotion with a conclusive interaction of various top-down and bottom-up processes which are triggered with presentation of the emotional stimuli. We could demonstrate that these interactions happen in the gamma frequency band when emotional stimuli were presented in a backward masking paradigm (Kajal et al 2018, article in preparation) at NPT. In the visual backward masking paradigm (ViBM), a delay between the prime and the mask stimulus is varied as predefined, resulting in a conscious perception of the prime stimulus if the delay exceeds subjects' NPT. In our current experiment, we have presented an emotional face either happy or sad as a prime stimulus and a neutral face stimulus of the same person as a mask stimulus. If the delay remains below the NPT level, the prime stimulus still activates bottom-up processes, but fails to initiate the subsequent top-down processes. In this case, a propagation of the emotional content of the prime stimulus to conscious processing is disrupted by the mask stimulus, and subjects are not aware of the emotion presented. In contrast, the meaning to the unconsciously processing emotion is provided by top-down processes (i.e., emotional meaning). The interaction between bottom-up and top-down processing has been very well explained using the global neuronal workspace model, suggesting that there is generation of reverberant self-amplifying loops with the presentation of the visual stimuli. These reverberant self-amplifying loops will reach to the level of consciousness if they are not disrupted, blocked and/or masked by another visual stimulus, before the certain duration defined as the near perceptual threshold (NPT) (Cul, et al., 2006; Dehaene, et al., 1998; Dehaene and Naccache, 2001; Del Cul, et al., 2006b).

In the current study, we strived to study, if it is possible to train healthy participants to volitionally modulate the FPN circuit responsible for top-down modulation of the processing of emotional stimuli. We expected that the successful modulation of the FPN would result in changes of participants' threshold. The answers to the above questions will add to our understanding of the neural networks involved in the conscious perception and thus can provide specific treatment of neurological and psychiatric disorders.

We trained eight healthy individuals using real-time magnetoencephalography neurofeedback (rt-MEG) instrumental conditioning to modulate their intra-hemispheric FPN. Up-regulation and down-regulation was linked to the visual discriminative stimulus, with '1' indicating up-regulation and '2' cueing down-regulation of FPN. Depending on the success of modulating functional connectivity feedback was given. Assuming successful instrumental condition, the originally neutral discriminative stimuli not eliciting any specific change in functional connectivity will be linked to up- and down-regulation of FPN. The effect of the training on the threshold for perceiving emotional stimuli was assessed by comparing the differential thresholds for up- and down-regulation cues between the pre- and the post-training sessions.

We hypothesize that neurofeedback training enables the control of FPN coupling and thus to alter the threshold of emotional face stimuli. To infer changes in perception, individual's threshold was assessed prior to (pretest) and after (posttest) the neurofeedback training and compared. We hypothesized that learned up-regulation of FPN elicited by the discriminative stimulus '1' will decrease the perceptual threshold, and presentation of '2' will down-regulation the fronto-parietal network leading to an increase of the perceptual threshold.

Material & Methods

Participants

The connectivity-based neurofeedback study was performed on 8 healthy participants (M±SD= 26±4.3 years, 5 males) with no history of neurological or psychiatric illness. All participants had normal or corrected-to-normal vision. None of the participants was under any medication. The study was approved by the local ethical committee of the faculty of medicine, University of Tübingen, Germany. A written informed consent in accordance to the Declaration of Helsinki was obtained from all subjects prior to the experiment (Carlson, et al., 2004). They gave written informed consent to participate in the experiment and received a financial compensation of 10 Euro / hour for their participation in the experiment.

Experimental Procedure

The experimental procedure includes three main experimental parts that were presented across three days: (1) the pre-test session served to get an estimate of the perceptual threshold (PT) for detecting emotion valance using a ViBM paradigm. Different delays ranging from 0 to 150 ms were presented and PT was determined using the method of constant stimuli (MCS). Furthermore, MEG sensors were identified from which the feedback signal was to be calculated (day one); (2) neurofeedback training session: subjects were trained to control FPN functional connectivity using ViBM task (day two); (3) post-test session: which was identical to the pretest and assessed the effects of neurofeedback training on FPN functional connectivity and the PT (day three).

In the following, all the different sessions of the experiment are explained in detail. Pre- and post-test sessions are explained together as their setup is essentially the same.

Pre-test and Post-test session (Day one and three)

Pre-test and post-test session used a ViBM paradigm to assess subject specific PT. In the ViBM paradigm, an emotional face (either with positive or negative emotion valence) is masked by the neutral face after a predefined delay. Color images of faces from the NimStim Face Stimulus Set were used as visual stimuli (Tottenham, et al., 2009). The predefined delay has been chosen in a pseudo-random fashion from the following delays: 0.0 ms, 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, 133.3 ms, 150.0 ms. By fitting a Weibull function to the percentage of correctly identified emotions of face expressions the delay corresponding to a performance of 67.7 % percent correct was chosen (Rinne, 2008). Chance level corresponded to a performance of 50 %. The pre-test experimental procedure consists of 10 runs and each run consists of 80 trials. Each pre-defined delay was presented for eight trials.

In both pre-test and post-test session, each trial (figure 1) started with a presentation of the fixation cross on the screen for 2 secs, followed by the cue stimulus. The cue stimulus served as discriminative stimulus and was presented for 1 sec. The cue stimulus could either be ‘1’ or ‘2’. Across trials, the presentation of the cue occurred in pseudo-random order. In the pretest, the cue stimulus does not have any meaning. After the neurofeedback training, the cue stimulus is expected to have assumed the ability to modulate FPN connectivity. In the post-test session, cue ‘1’ denotes up-regulation of the functional connectivity and cue ‘2’ denotes the down-regulation of the functional connectivity. After the discriminative cue stimulus, the prime stimulus, a face with either positive or negative emotional valance, was presented on the screen for 16.7 ms (T_{prime}). After the prime stimulus, a black screen was presented which served as a variable delay between the prime and mask stimuli. Matching the vertical refresh rate of the projector, the variable delay (T_{delay}) could take any of ten different values (0.0 ms, 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, 133.3 ms, 150.0 ms) and was selected pseudo-randomly for each trial. After the delay, a mask stimulus – the face of the same individual shown as prime stimulus yet with a neutral expression, was presented on the screen for a duration of 250 ms (T_{mask}). After the mask, another black screen was shown for a duration of [T_{blank}= 1500 ms – (T_{prime} + T_{delay}+ T_{mask})]. Following the second black screen lasting for 500 ms, a response instruction screen was presented. The response signaled either “POS+NEG” or “NEG+POS” and was pseudo-randomized across the trials. The instructions were presented in the center of the screen, with the ‘+’ symbol serving a fixation point. The duration of the instruction screen presentation was 1 sec. The instruction “POS+NEG’’ instructed participants to press the right button if they had perceived the prime face as a negative face or the left button if they had perceived a positive face presented as a prime. Participants responded pressing one of the two in-house optical response buttons and were instructed to respond in each trial even if they were uncertain about the valence of the prime stimulus. The trial was terminated after participant’s response, or after a maximum time duration of 2000 ms. Each of the pre-test and post-test session lasted a maximum of the 1.5-hour duration.

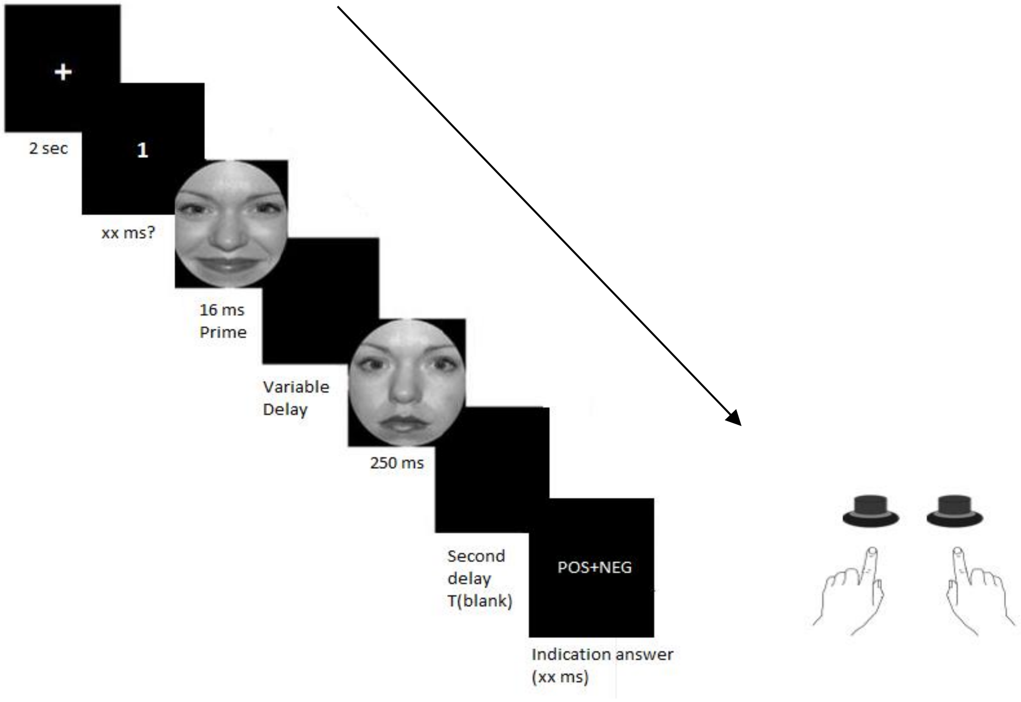

Figure 1: Example of a single pretest and posttest trial. Fixation cross was presented for 2 seconds, followed be cue; either ‘1’ or ‘2’ for 1 sec and then followed by a 16.7 ms long prime stimulus (either positive or negative emotion). Delay was then presented for a variable amount of time (0 ms, 16.7 ms, 33.3 ms, 50.0 ms, 66.7 ms, 83.3 ms, 100.0 ms, 116.7 ms, 133.3 ms, 150.0 ms), and was followed by the mask stimulus (neutral face) which lasted for 250 ms. The black screen was presented again, now for the duration of

T_{blank} (β *: 1500 ms – (T_{prime} + T_{delay}+ T_{mask})) and was followed by the response instruction screen (i.e. “POS+NEG”). A trial ends as soon as the participant has entered his/her response or the maximum trial duration of 2000 ms had elapsed. From subject’s responses the threshold delays were computed separately for up- and down-regulation trials.

Neurofeedback session (Day two)

In the neurofeedback session healthy participants were trained to up- and down-regulate FPN connectivity. Coherence was used as an index to measure the strength of functional coupling. Coherence was estimated from the MEG neuromagnetic time-series in-between the sensors selected during the pre-test session.

The sequence of stimuli was identical to the pre- and posttest session except for the feedback. Each trial starts with a presentation of a fixation cross for the duration of 2 sec. This is followed by a cue stimulus either ‘1’ or ‘2’. Cue stimulus ‘1’ denotes the up- and ‘2’ denotes the down-regulation of the FPN connectivity. After the presentation of the cue stimulus, a prime stimulus (stimulus face could either be a positive or negative face) is presented for 16.7 ms duration followed by a black screen for a fixed mask delay. The fixed mask delay is the subject specific PT obtained in the pre-test session. After the fixed mask delay, the mask stimulus (face with neutral emotion) was presented for the duration of 250 ms. After a black screen presented for the duration of 500 ms, the reward bar (thermometer), except for the trial belonging to baseline estimation, is presented as visual feedback. The reward bar was presented for the duration of 1 sec. The length of the bar indicated how well participants managed to match the requested connectivity in the ongoing trial. The feedback reward is always calculated against a baseline estimated at the beginning of the current run. A trial ends after 2 sec. All participants were instructed to try to increase the length of the bar using different strategies for cue ‘1’ and ‘2’. ViBM task in neurofeedback was identical to the one used in pretest and posttest phase and is described in Fig.2. But in the neurofeedback session, a fixed delay between the prime and mask stimulus was used (instead of variable delays in the pre- and post-test session) and no response was given after the presentation of the mask stimulus (remember the indication answer screen seen in Fig.1).

A neurofeedback session consisted of ten runs, each run containing eighty trials (figure 2). In each run, the first eight trials were used as the baseline estimation. All trials were presented with a constant delay at NPT between prime and mask. Real-time functional connectivity is estimated between predefined sensors for FPN in right and left hemispheres at 35 Hz, respectively. The feedback for each trial is calculated from the sensors identified for left and right hemispheres for FPN in the pretest session. The feedback is always calculated from the difference between functional connectivity estimates of the baseline, i. e. the initial trial in each run, and the current trial. The feedback value is estimated by taking the absolute value of the difference between the mean of the real time functional connectivity estimate of left and right hemispheres and the baseline estimate of the current run. This feedback value is then scaled by the factor of 10 to translated it into the visual feedback signal.

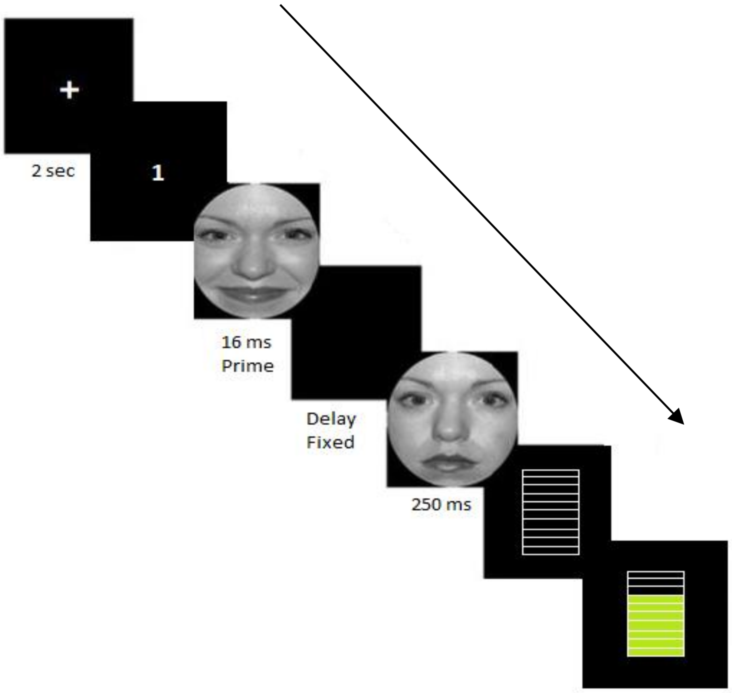

Figure .2: Example of a feedback trial. A fixation cross was presented for 2 seconds, followed by the cue either ‘1’ or 2’. Then a prime stimulus is presented for the duration of 16.7 ms. The delay between the prime and the mask stimulus is kept constant near the PT. Then, a mask stimulus of 250 ms duration, and the thermometer appeared on the screen providing visual feedback about the match between the requested and produced FPN connectivity. The feedback stimulus stayed for 1 s on the screen.

One hour before the MEG-neurofeedback training, participants were informed and familiarized with the experimental paradigm and the tasks to be performed. During the experiment, participants sat upright in the MEG chair facing a 40 cm X 30 cm screen displaying instructions and feedback. We have monitored all the participants using a video camera during the whole experiment to avoid participants from sleeping and making unwanted movements during the experiment. Head movements were monitored continuously using the MEG head localization system. Participants were informed to freely choose and try any cognitive strategy to modulate their FPN connectivity and to use what works best for them

Selection of the near perceptual threshold and the frame rate at which the stimulation was provided.

The near perceptual threshold was estimated by fitting a sigmoid psychometric function (logistic regression) was fitted to the correct responses as the function of the predefined delays. The correct responses considered here were irrespective of the presented happy or sad face. The delay corresponding to the 66.7 % correct responses was the subject specific perceptual threshold. Here we would like to highlight the point that the NPT presented was rounded to match the refreshing frame rate of the projector. We have used the projector with the refresh rate of 60 Hz with frame rate of 16.66 ms.

Feedback Setup

The real-time neurofeedback training was implemented using the BCI2000 program (Mellinger, et al., 2007; Schalk, et al., 2004) and Pascal based program under Dos 6.2.

MEG data acquisition hardware was connected to the PC running Linux operating system, and data acquisition was done through the Acquire software (Acquire, CTF Inc.). To access the data in real time a CTFs Acquire program wrote 44 samples of raw digitalized data into a shared memory in regular time intervals (70.4 ms). A second program was connected as a relay to the BCI2000 with a TCP/IP-based socket interface. Frequencies and sensors identified in pretest session are used as parameters in BCI2000 program. Visual stimuli and feedback was presented using Pascal based program under Dos 6.2. This program was communicating with the BCI2000 computer through USB 2.0 connection. The BCI2000 program is only used to calculate the reward value and this value is sent to the pascal-based program for the presentation as a reward to the participant.

MEG data acquisition and Stimuli presentation

MEG (CTF System Inc, Vancouver, Canada) data was acquired using a whole-head 275-axial gradiometer system. The MEG is in a shielded room (VaccumSchmelze, Hanau Germany) at the MEG Centre, University Clinic of Tübingen, Germany. Neuromagnetic data was sampled at the rate of 1172 Hz using an anti-aliasing lowpass filter of 390 Hz. The relative head position with respect to the sensors of the MEG was recorded continuously during the scan using three fiducial coils which were affixed to the nasion and left and right preauricular points. Using the head localization information, it was ensured that the participant’s head was exactly repositioned to the pre-test session across the following sessions.

Visual stimuli were presented using a Pascal based program under Dos 6.2 and were synchronized with the vertical refresh rate (60Hz) of the screen. The video output of the stimulation computer was send to a JVC DLA-SX21 projector, which then flashed the visual stimuli via a mirror system on a screen in front of the participants in the magnetically shielded room. The rate of th frame loss during the presentation of the delay was less than 1%. Participant’s responses were recorded using two in-house built optical buttons. Emotional stimuli for the experiment are chosen from the colour images of faces contains 50% of female and 50% of male faces.

Coherence: Index for the functional connectivity

Coherence is used as the measure of the functional coupling between two disparate brain regions. In our experiment coherence is analyzed as a magnitude squared coherence between two signals, both in the online (neurofeedback) and offline (pretest and posttest) analysis. Coherence between two signals x and y is defined as:

$$\mathrm{C_{xy}} = \frac{\left[\mathrm{S_{xy}(f)}\right]^2}{\left[\mathrm{S_{xx}(f)}\right] * \left[\mathrm{S_{yy}(f)}\right]} \tag{1}$$

Where, S_{xy} denotes the cross-spectral density between signals x and y, and S_{xx} and S_{yy} are auto-spectral densities of signals x, and y (respectively), at some frequency (f).

Offline Data Analysis

The offline analysis was done using the in-house MATLAB scripts and using fieldtrip toolbox.

Signal Processing

The offline analysis of the pretest, posttest and neurofeedback session included demeaning, detrending, low pass filtering 100 Hz, high-pass filtering 1 Hz, and power line noise removal (50 Hz). The whole dataset was visually inspected trial-by-trial. Trials containing a large variance across channels (2.5×10^{-25}) and abnormal amplitudes were discarded from further analysis. Furthermore, trials containing muscle artifacts, squid jumps, showing broad band activity were also eliminated. Independent component analysis (ICA) using the infomax ICA algorithm was applied to remove the contamination followed by ocular (eye movement and eye blinks) and cardiac artefacts (Amari, et al., 1997; Bell and Sejnowski, 1995). To this end the preprocessed and cleaned signal recorded from 272 sensors was decomposed into 100 components. The topography and the waveform of all the components were plotted and visually inspected. All the component containing the eye blinks, eye movement, heart beat and muscular artefacts were removed. From the remaining components an artifact-cleaned dataset was reconstructed.

Offline analysis of Pretest and Posttest

a) Threshold estimation

We have adopted the method of constant stimuli (MCS) (McKee, et al., 1985a) for the estimation of the PT for pretest and posttest sessions. In the offline analysis, to estimate the subject specific PT, a sigmoid psychometric function (logistic regression) was fitted to the percent correct responses as the function of the predefined delays. The correct responses considered here were irrespective of the presented happy or sad face. The delay corresponding to the 66.7 % correct responses, was further used as the NPT for the neurofeedback session and for identification of the sensors in the offline analysis of the pretest.

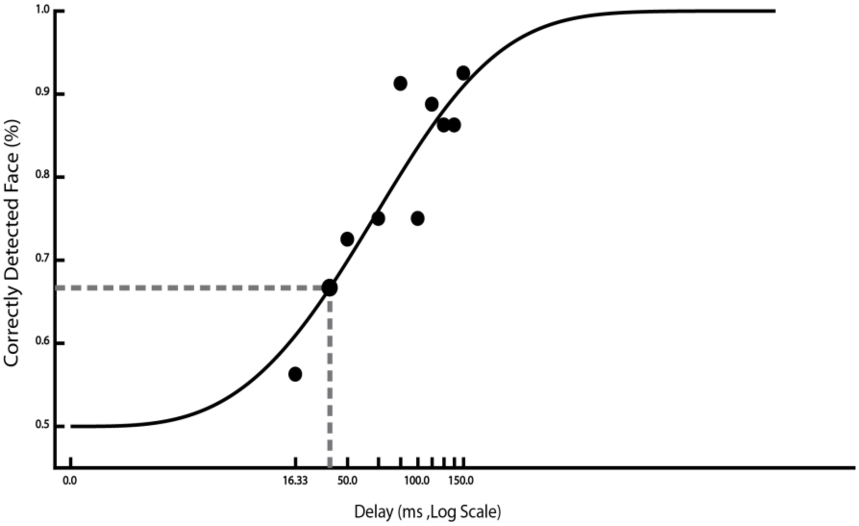

Figure 3: Above plot shows the fitting of the psychometric function to the correct responses to the participants.

b) Identification of the Channels to be used in the neurofeedback session

The preprocessed and cleaned data was further segregated into two: perceived (trials in which the participants reported the emotional valance of the presented prime face correctly) and not-perceived trials (trials in which the participants reported the emotional valence of the presented prime face incorrectly). Frequency analysis was done separately for perceived and not-perceived trials at 35 Hz using a multi-tapering sliding window fast Fourier transform with discrete prolate spheroid sequences (DPSS) tapers (Percival and Walden, 1993). Same number of trials for both perceived and not-perceived trials were selected for further analysis. Sensor-level all-to-all squared magnitude coherence was estimated separately for the perceived and not-perceived trials. Paired t-test was performed for all sensors across trials and t-statistic topoplots were plotted with the reference sensors from left and right frontal areas. MEG sensors corresponding close to frontal and parietal regions and showing the strongest difference in t-statistic for squared magnitude coherence for perceived and not-perceived trials were selected and used for providing the real-time feedback. A minimum of 6 sensors from each hemisphere were selected to be used in the following neurofeedback session.

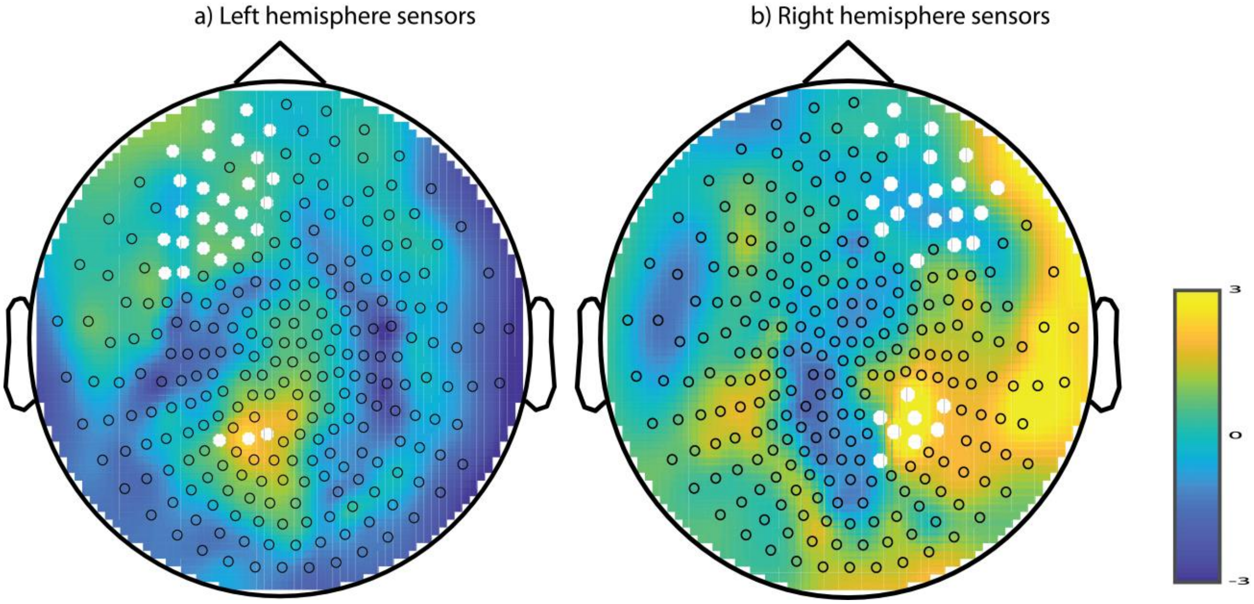

Figure 4) Topoplots showing the t-statistic for the difference between perceived and not-perceived trials for a single subject. A) plot showing the t-statistic difference with left frontal sensors as a reference sensor. B) plot showing the t-statistic difference with right frontal sensors as a reference sensor.

Offline analysis for the neurofeedback session

The preprocessed and cleaned data from the neurofeedback session was further segregated into two: up-regulation and down regulation trials. For the neurofeedback session, each of the trials belonging either of the up- and down-regulation was further analyzed for the estimation of the squared magnitude coherence and power. The coherence spectra and power spectra were estimated from the Fourier spectra at 35 Hz for the preselected sensors used in the online neurofeedback session for the feedback calculation. Statistical analysis was done using paired t-test(s) for the coherence and power estimated for the up- and down-regulation. To study the possible contribution of the head movement in the modulation of the functional connectivity, we have done the paired t-test for on the fiducial movements for up and down regulation of the functional connectivity. Statistical analysis was done using SPSS and in-house scripts using statistical toolbox of the MatLab

Results

Neurofeedback session

Differential modulation of the functional connectivity between the selected channels for requested up- and down-regulation of gamma band activity was assessed as a measure of the success of the neurofeedback training. The paired t-test comparing average functional connectivity for runs belonging to up-regulation and down-regulation between frontal and parietal channels at the training frequency of 35 Hz, suggests a significant difference between up- and down-regulation (figure 5) during the neurofeedback session (p=0.04, t=2.3 df=7; up-regulation (M±SE = 0.04±0.03); down-regulation (M±SE = 0.02±0.03))

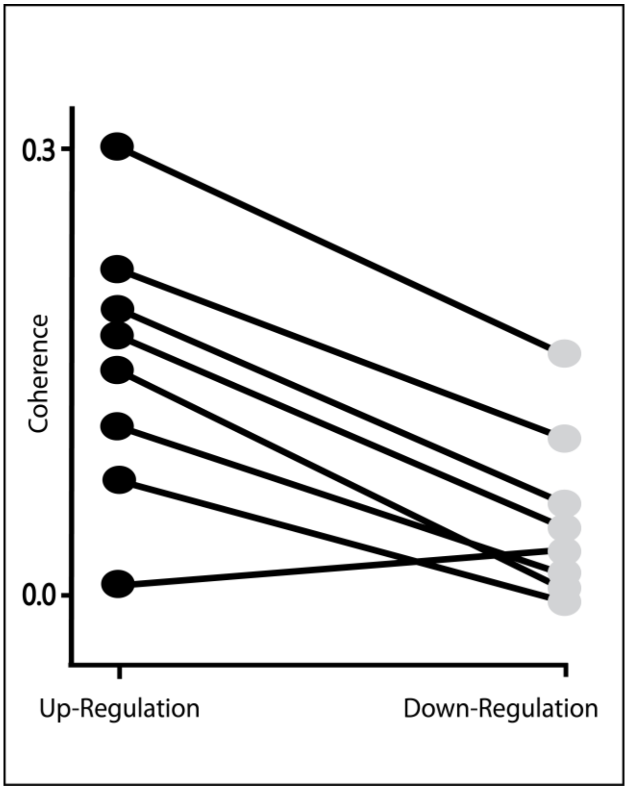

Figure 5) Plot showing the difference in the functional connectivity modulation between up and down regulation. The metric of the functional connectivity used is the squared magnitude coherence.

To rule out the possibility of the modulation of the functional connectivity merely by the power modulation, we did the paired t-test on the power estimates for the up-regulation and down-regulation trials of the neurofeedback session (figure 6). We did not find any significant difference for the power modulation between up and down regulation (p=0.68, t=-0.429, df=7, up-regulation (M±SE = 0.01±0.009), down-regulation (M±SE = 0.02±0.01). Furthermore, to assess participation of the power modulation towards the modulation of the functional connectivity, we correlated power and functional connectivity for up-regulation (p=0.23, r=0.47, df=8), and for the down-regulation (p=0.55, r=0.24, df=8) and thus suggest a non-significant participation.

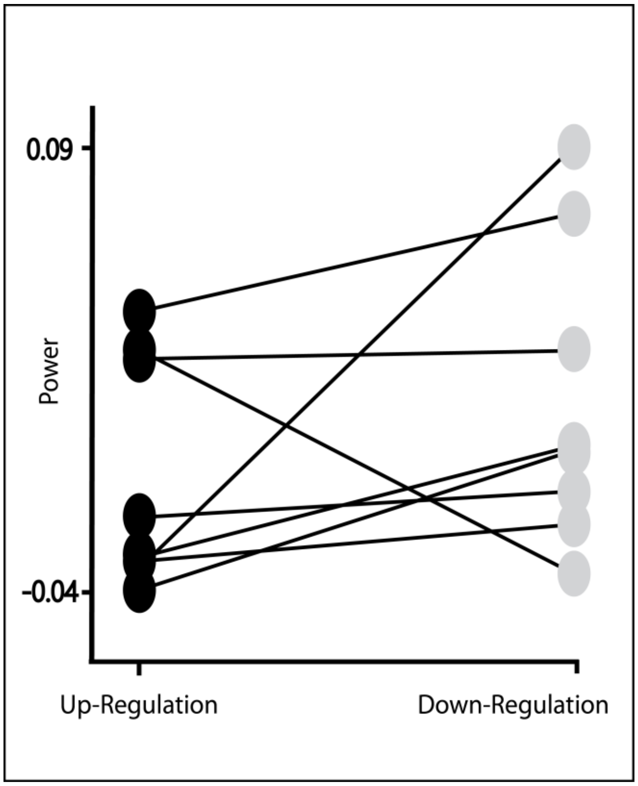

Figure 6: Plot showing the difference in the power modulation between up and down regulation.

Furthermore, to rule out the possibility of the modulation of the functional connectivity merely by participants' systematic head movements, we studied the differential movement of the participants head in the MEG scanner for up and down regulation from the three fiducials. We performed a paired t-test for differential head movement between mean movement of the three fiducials for up-regulation and down-regulation, respectively. We did not find any significant head movement in the scanner across runs for left auricular (p=0.7, t =0.4, df=5), right auricular (p=0.82, t=-0.23, df=5) and nasion (p=0.74, t=0.34, df=5). This finding suggests that the differential head movement across trials did not modulate the estimate of the neuromagnetic functional connectivity

Pre-test and Post-test session

To assess the effects of the neurofeedback training on the PT, we performed the 2-way ANOVA with within factor SESSION (Pre- and Post-test) x within factor TRAINING (Up- and Down-regulation) for the NPT estimates. We found a significant difference in the SESSION (p=0.03, t=2.694, f (1,7) =7.25; Pre-test (M±SE = 54.81±2.16), Post-test (M±SE = 50.97±2.66)). We did not find any significant difference in the TRAINING. Our results suggest that the NPT have decrease significantly from pre-test to post-test (figure 7).

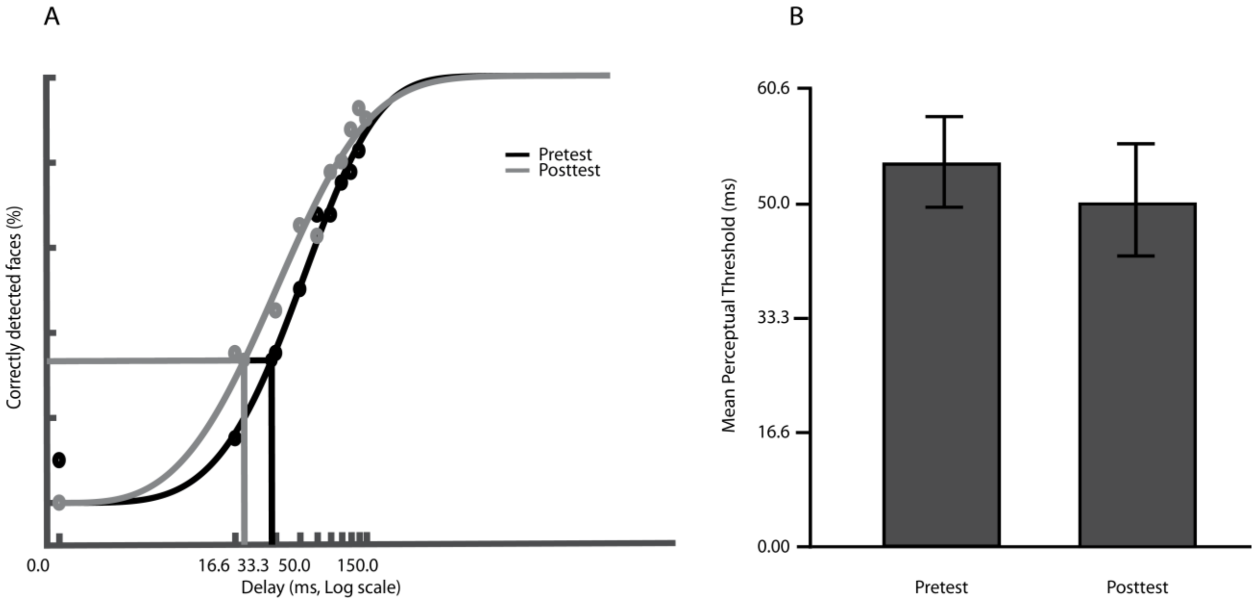

Figure 7: Plot showing the significant difference between PT for pre-test and post-test. a) plot representing the sigmoid function for a single subject b). plot representing the group level analysis for the pre- and post-test

To study the possible effects of the neurofeedback training on functional coupling between the FPN at NPT, we have performed a 2-way ANOVA with within factor SESSION (Pre- and Post-test Session) x within factor TRAINING (Up and Down regulation) on the functional connectivity estimates for the preselected feedback channels. We found a significant difference in the connectivity measures between pre-test and post-test SESSION (p=0.04, f (1,7) =6.04), Interaction of SESSION x TRAINING (p=0.04, f (1,7) =6.04). Our results suggest that prior to the neurofeedback training, there was no significant difference between up and down regulation for the functional connectivity as shown in the pre-test session but after the neurofeedback training session, it is clearly evident as a significant difference between up and down regulation session as shown dominantly in the post-test session (figure 8). To study the transfer effects of the volitional modulation of the functional connectivity between FPN on the NPT, we did the Spearman rank correlation analysis between the difference in the functional connectivity for up and down regulation in the neurofeedback session with difference between up and down regulation trials for pre-test and post-test session. We find a significant negative correlation between the FPN functional connectivity and the NPT suggesting that the NPT is inversely dependent on the FPN communication. These results further strengthen our results suggesting that the near perceptual threshold is being modulated with the volition modulation of the functional connectivity (Figure 9).

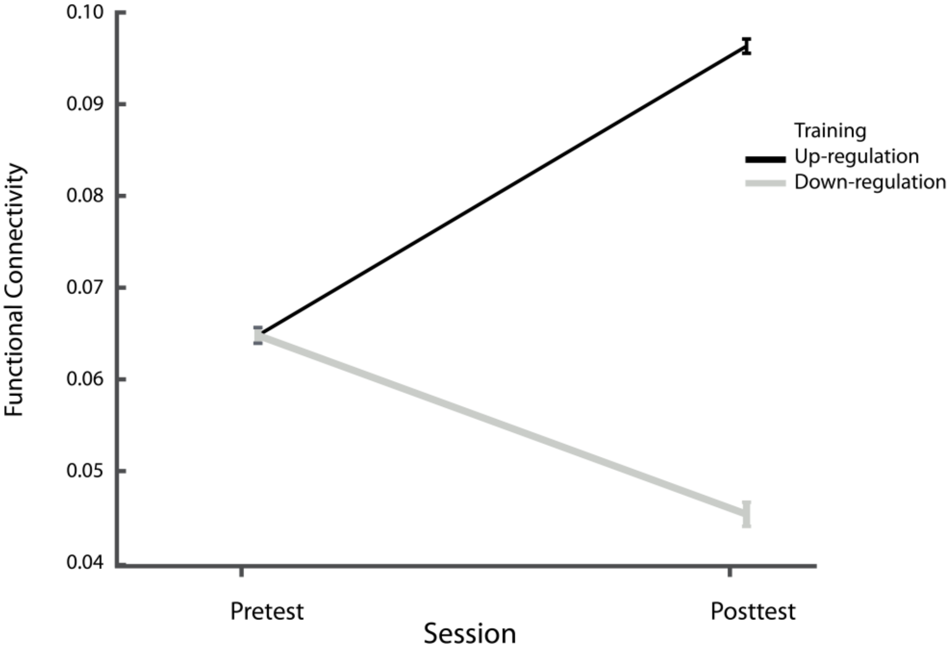

Figure 8: Plot Showing the interaction from pre and post-test connectivity

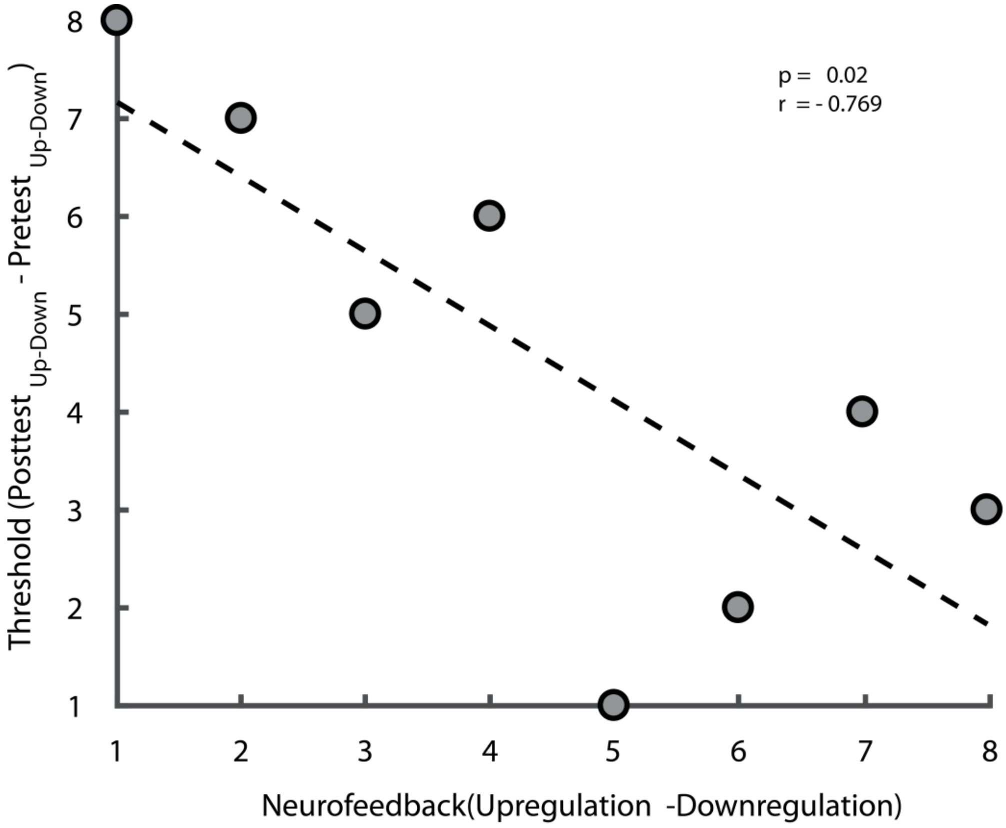

Figure 9) Rank correlation between the difference of upregulation and downregulation for Neurofeedback and NPT for difference between Posttest $_{\text{upregulation – downregulation}}$ and Pretest $_{\text{upregulation -downregulation}}$.

Furthermore, for the post-hoc analysis, we segregated the preselected feedback channels into two: a) MEG sensors belonging to left hemisphere and MEG sensors belonging to the right hemisphere. We performed the 2-way ANOVA on the functional coupling with within factor SESSION (Pre- and Post-test Session) x within factor TRAINING (Up and Down Regulation) for the left and right hemisphere, separately. For right hemisphere, we found a significant difference in the connectivity measures between pre-test and post-test SESSION (p=0.04, f (1,7) =5.64, df=7), TRAINING (p=0.04, f (1,7) =5.84) and interaction of SESSION x TRAINING (p=0.04, f (1,7) =5.84, df=7). This post-hoc analysis suggests that right hemisphere is contributing significantly in the modulation of the FPN in the perception in emotional face stimuli. Furthermore, Post-hoc analysis suggested that functional connectivity in the down-regulation for the right hemisphere sensors in the post-test is significantly correlated with the perceptual threshold estimates in the post-test for the down-regulation (Figure 10).

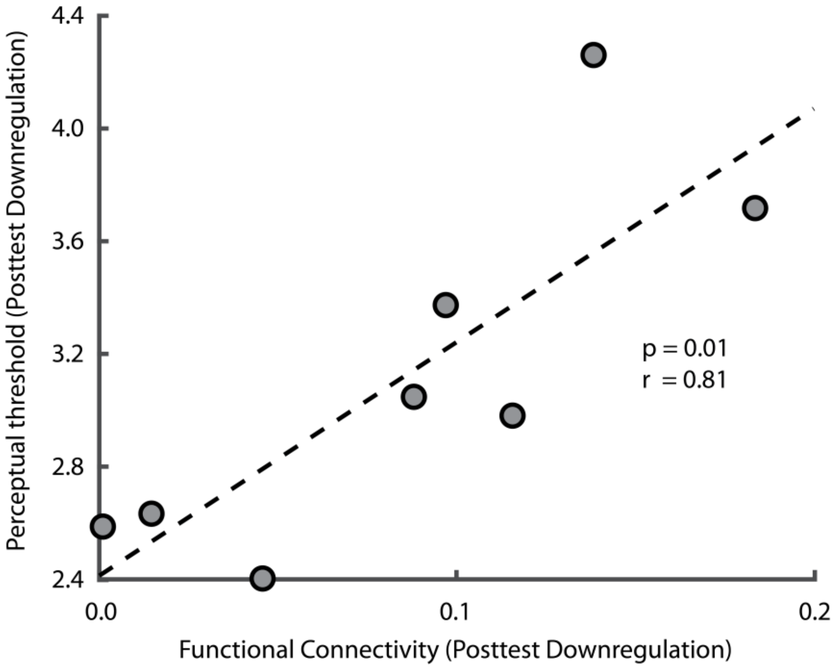

Figure 10) Plot showing the correlation between Functional connectivity in the Posttest session during the downregulation trials and Perceptual threshold during the downregulation trials in Posttest session.

Discussion

In the current experiment, we have trained 8 healthy subjects to acquire volitional control over their FPN functional connectivity using masked delay paradigm at NPT at 35 Hz using neurofeedback. We have demonstrated that the modulation of the FPN has a significant effect on the PT, as the PT is significantly reduced from pretest to posttest. One might argue that this significant decrease in the NPT from pretest to posttest is merely an effect of repeatedly training the perceptual task. We would like to add to this information that reduction in NPT is not just the training effect, but it also includes the contribution from the neurofeedback training. To back up this conclusion, we have studied the correlation between up and down regulation of functional connectivity in the neurofeedback session with the PT estimates in pre-test and posttest. A significant negative correlation suggests that the resulting reduction in the NPT is inversely associated with the neurofeedback training of the functional connectivity.

Potential confounding variable

Effect of power on the coherence modulation

It is well known from the literature that the measure of coherence between the two signals cannot be singled out without the potential influence for the power (Pikovsky, et al., 1997). In our study, we also studied the influential effect of amplitude modulation separately for up and down regulation runs in the neurofeedback session. Non-significant difference for the amplitude modulation between up and down regulation trials further gave us the confidence of the modulation of the functional connectivity as the measure of the phase rather than by the amplitude modulation furthermore, the power estimate in the downregulation trials are relatively higher than upregulation. This non-significant power difference for up and down regulation further strengthened our results that we have demonstrated the modulation of functional connectivity between FPN without any significant contribution from the power modulation is plausible. We have also demonstrated the non-significant correlation between power estimates and functional connectivity estimates for upregulation and downregulation trials, further suggesting the non-significant contribution of the power in the functional connectivity modulation.

Volume Conduction

Volume conduction is often a significant problem in mostly all the neuro-electromagnetic studies. Volume conduction includes smearing of the neuronal activity to all the nearby sensors, and thus making the very probable for the synchronized activity. It is often suggested that the problem of volume conduction can be significantly avoided by using the imaginary part of the coherence. But using the imaginary part of coherence also comes with disadvantage as the connectivity estimates between long range connectivity already have the phase shift concluded with shifted pi (Nolte, et al., 2004). And thus in our study, studying the connectivity only with the imaginary part of the coherence, could lead to missing out the communication which are the multiples of pi (Fries, 2005; Fries, 2015) .Considering the fact that, in our study we are modulating the long range connectivity between FPN, using only the imaginary part of the coherence can lead us to missing the important information. Thus, we have used the squared magnitude coherence as the feedback signal (Carter, et al., 1973; Carter, 1972).

Significance of the modulation of the functional connectivity on fronto-parietal communication

We have demonstrated in the current study that the volitional modulation of the functional communication between FPN plays an inverse role on the part of the near perceptual threshold. With this finding we conclude that an improvement in the FPN communication can lead to the reduction in the PT and thus plays a conclusive role in the modulation of the perception.

Global workspace model suggests that in the masked visual paradigm, the prime stimulus will reach the level of consciousness only when the temporal delay between the prime and mask is above the perceptual threshold of the participants. This is where, various top-down and bottom-up process comes into play. According to this model, with the presentation of the prime stimulus, there is generation of reverberant and self-amplifying loops running between fronto-parietal networks. The registered prime stimulus will get the emotional meaning only when these loops are not mask, disturbed or disrupt by the subsequent stimuli. The threshold to reach the level of consciousness serves as the perceptual threshold. Our study is also in line and supporting the global workspace model and suggests that the modulation of the functional communication between FPN is resulting in the differential changes in the perceptual threshold. In our study we have demonstrated that with the improvement in the FPN communication, there is the negative correlation towards the estimated perceptual threshold suggesting that the improvement in FPN is result in the reduction in the perceptual threshold.

It is well known fact the left and right hemisphere are not identical in terms of function and plethora of studies has also shown the lateralization of the left and right hemisphere in the perception of the emotion (Demaree, et al., 2005; Reuter-Lorenz and Davidson, 1981;

Silberman and Weingartner, 1986; Wager, et al., 2003). A variety of studies in both unimpaired and lesioned subjects have suggested that the right hemisphere is very much specialized in the processing of the emotional aspect of the presented information (Reuter-Lorenz and Davidson, 1981). Continuing in the same lineage, we would also like to highlight that we have trained the two hemispheres, left and right, differentially, supported by the results in our post-hoc analysis. We have found that the right hemisphere is participating significantly in the modulation of the perception leaving out the left hemisphere and playing the role in modulation of the behavior. This modulation can also be interpreted as based on the literature suggesting dominant role of the right hemi sphere in the emotion perception. Furthermore, we have found a significant correlation between perceptual threshold and functional connectivity estimates only in the right hemisphere. Which also provides a strong evidence and is in-line with our previous study emphasizing the importance of the right hemisphere in the emotion perception.

Future Directives and it potential effect in helping the patients with schizophrenia and autism

With our current study, we have provided the evidence that it is possible to volitionally modulate the fronto-parietal functional connectivity using masked emotional stimuli. Patients suffering from neuropsychiatric disorders such as schizophrenia and autism are deficient in the perception of the emotional stimuli. Studies have shown that in these patients fronto-parietal communication is disturbed which leave them devoid of the perception of the emotional stimuli. Our finding of the volitional modulation of the fronto-parietal communication and thus restoring the gapped communication could prove to be a very important tool for treating these patients.

Acknowledgement

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