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Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback

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ABSTRACT

Neurofeedback (NFB) involves a brain–computer interface that allows users to learn to voluntarily control their cortical oscillations, reflected in the electroencephalogram (EEG). Although NFB is being pioneered as a noninvasive tool for treating brain disorders, there is insufficient evidence on the mechanism of its impact on brain function. Furthermore, the dominant rhythm of the human brain is the alpha oscillation (8–12 Hz), yet its behavioral significance remains multifaceted and largely correlative. In this study with 34 healthy participants, we examined whether during the performance of an attentional task, the functional connectivity of distinct fMRI networks would be plastically altered after a 30-min session of voluntary reduction of alpha rhythm (n = 17) versus a sham-feedback condition (n = 17). We reveal that compared to sham-feedback, NFB induced an increase of connectivity within regions of the salience network involved in intrinsic alertness (dorsal anterior cingulate), which was detectable 30 min after termination of training. The increase in salience network (default-mode network) connectivity was negatively (positively) correlated with changes in 'on task' mind-wandering as well as resting state alpha rhythm. Crucially, we observed a causal dependence between alpha rhythm synchronization during NFB and its subsequent change at resting state, not exhibited by the SHAM group. Our findings provide neurobehavioral evidence for the brain's exquisite functional plasticity, and for a temporally direct impact of NFB on a key cognitive control network, suggesting a promising basis for its use to treat cognitive disorders under physiological conditions.

Introduction

EEG neurofeedback (NFB) is a brain–computer interface (BCI) method that enables users to gain voluntary control of their cortical oscillations by receiving moment-to-moment feedback from their electroencephalogram (EEG) (Kamiya et al., 1969). As such, it holds promise for modifying abnormal brain oscillations in various disorders, such as ADHD and epilepsy (Heinrich et al., 2007). Most NFB involves multiple sessions repeated on at least a weekly basis, whose effects generally accumulate over time, reputedly as a result of long-term changes in the brain (Sterman et al., 1970). However, evidence of a temporally direct impact of NFB on brain plasticity remains crucial for it to be recognized as a ground-breaking approach that is veritably safe, inexpensive, and accessible.

Recently, lasting changes in cortical plasticity were detected for the first time in the direct aftermath of NFB, using transcranial magnetic stimulation (TMS) (Ros et al., 2010). Inspired by this discovery we asked whether fMRI would be able to capture the early neuromodulatory effects of NFB, while harnessing its high spatial-resolution in order to expose the causal effects of NFB on brain functional networks and behavior. For NFB we considered voluntary control of the alpha (8–12 Hz) rhythm, based on its prevalence in the human EEG and our previous finding that its amplitude can be readily attenuated (desynchronized) by naïve participants (Ros et al., 2010). Alpha rhythm synchronization or desynchronization, respectively, generally reflects the inhibition or excitation of sensory cortex (Romei et al., 2008; Haegens et al., 2011) which frequently appears during internally versus externally-directed attention (Cooper et al., 2003). Recent simultaneous EEG–fMRI studies have attempted to correlate the alpha rhythm with the activity of temporally-coherent fMRI networks: revealing alpha synchronization to be positively associated with both the task-negative 'default-mode network' (DMN) (Hlinka et al., 2010; Mantini et al., 2007; Jann et al.,

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2009) and task-positive 'salience network' (Sadaghiani et al., 2010) connectivity. Behaviorally, the activation of the DMN has been shown to coincide with mind-wandering plus lapses in sensory attention (Christoff et al., 2009; Mason et al., 2007; Weissman et al., 2006); while in contrast, salience-network activation has been linked to the successful performance of sensory attention tasks (Kiehl et al., 2005; Sadaghiani et al., 2009; Langner et al., 2012). In order to disentangle these seemingly conflicting functional correlates of alpha rhythm, we sought to examine via NFB to what extent alpha desynchronization would modulate the connectivity of these networks, together with attentional function. To do so, we undertook separate fMRI recordings of participants immediately before and after NFB, during the performance of an auditory attention task containing random mind-wandering probes. Based on the prevailing evidence, we hypothesized that successful alpha desynchronization would lead to greater plastic alterations in DMN and/or salience network, which would individually correlate with reduced mind-wandering behavior.

Methods

Participants and experimental design

After approval of the study by the Research Ethics Board of University of Western Ontario, Canada, a total of 34 right-handed participants (mean age: 32.6, SD: 10.7, 24 women, 10 men) were recruited in the study. All participants were recruited from the neighborhood of the university scanning center and were carefully screened for the presence of neurological or psychiatric disorders during a structured SCID-I-Interview at the Psychiatry Department. Prior to the study, written informed consent was obtained from each participant. Upon arrival to the examination facility, participants were randomized to one of two experimental groups: EEG-neurofeedback (NFB, $n=17$) or sham-neurofeedback (SHAM, $n=17$). Experimental procedures were identical in every way for the two groups, except that SHAM group participants did not receive veridical feedback from their EEG activity, but rather were re-played EEG signal from a previously recorded session of a NFB-successful participant (their real EEG activity was nevertheless recorded for offline analysis). The overall experimental protocol of 3 sequential parts that occurred within the same daytime visit: MRI scan before neurofeedback (~30 min), EEG neurofeedback (~30 min), and MRI scan after neurofeedback (~30 min). No adverse effects were reported by any participant either before or after NFB or SHAM.

fMRI paradigm

Participants underwent a total of 2 identical, pre-and-post MRI sessions: the first session directly preceded neurofeedback, and the second scan directly followed it. More specifically, given the time required for setup of EEG recording, neurofeedback started ~30 min after completion of the first fMRI scan. Since we were particularly interested in the plasticity of neurofeedback effects, we made note of the elapsed time between the end of neurofeedback and the beginning of the second fMRI scan for every participant ($\text{mean} \pm \text{SD} = 24 \text{ min} \pm 2$). Participants were instructed to keep their eyes open, remain motionless as much as possible and not to think of anything in particular. Following a localizer and anatomical scan (~10 min), participants completed an auditory oddball fMRI task (details of MRI data acquisition in the next section). The task consisted of one 6 min run of 181 auditory stimuli presented with a computer presentation system (E-Prime 2.0, Psychology Software Tools Inc., USA), by means of sound attenuating MRI-compatible headphones (Serene Sound System, Resonance Technology Inc., CA, USA). Participants had to identify the pseudo-random occurrence of 1000 and 2000 Hz long-tone sine stimuli (500 ms, target) within a sequence of short-tone sine stimuli (200 ms, non-target): pressing Button 1 for the former and no response for the latter. The interstimulus interval (ISI) was 2 s and the probability of long-tone vs. short-tone stimulus occurrence was 20% vs. 80%. The traditional approach for assessing levels of mind-wandering (Mason et al., 2007; Christoff et al., 2009) is to engage the participant with a low-attention task, during which "thought" probes occurring at random intervals interrogate the participant whether they were "on-task" (attentive) or "off-task" (mind-wandering). For example, Christoff et al. (2009) used a visual task where participants had to identify a target number within a sequence of random digits while a thought-probe question was presented during 5% of the trials. We adapted the protocol by Christoff et al. for the present experiment by implementing an auditory oddball as the low-attention task, while additionally inserting a ring tone as a thought probe stimulus at a probability of 3% (approx. 1 probe every 50–70 s). Upon hearing the telephone ring, participants were instructed to ask themselves the question "Was your mind wandering at the time of the ring?", and reply "Yes" or "No" via the keypad. Mind-wandering was described to each participant as "having any thoughts that are not related to the task". Lastly, we recorded the trial-by-trial reaction time (RT) to oddball target stimuli as well as mind-wandering probes during the task.

fMRI acquisition

All MRI data were acquired using a Magnetom Verio 3.0 Tesla scanner (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel phase array head coil. Whole-brain BOLD functional images were obtained with gradient echo (EPI) sequence, with 3000 ms repetition time [TR]; 20 ms time of echo [TE]; 90° flip angle; 256 mm field of view [FOV]; and $2 \times 2 \times 2$ voxel resolution (mm). Sampling consisted of 60 interleaved slices, 2 mm thick, no gap, parallel to the anterior–posterior commissure (AC–PC) line. The first four (extra) images in each run were automatically discarded by the scanner to allow the magnetization to reach equilibrium. The functional time-series consisted of 120 consecutive image volumes obtained over 6 min. Anatomical images were obtained using a T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence: ($\text{TR/TE/TI} = 2000 \text{ ms}/4 \text{ ms}/900 \text{ ms}$; flip angle = 9°; $\text{FOV} = 256 \text{ mm} \times 256 \text{ mm}$; 1 mm isotropic resolution; 176 slices, no gap, GRAPPA acceleration = 2). Image pre-processing was performed in SPM8 (www.fil.ion.ucl.ac.uk/spm/), and included slice-timing correction, motion correction, spatial normalization and smoothing using a FWHM (full-width half-maximum) Gaussian filter of 8 mm. Motion correction was performed by aligning (within-subject) each time-series to the first image volume using a least-squares minimization and a 6-parameter (rigid body) spatial transformation. Data were normalized using the unified segmentation on T1 image pipeline (Ashburner and Friston, 2005) which can improve the accuracy of spatial normalization and thus inter-subject comparisons. This involves four steps: coregistering the functional volumes to their respective anatomical images using 12 parameter affine alignment, segmenting the anatomical images into gray and white matter, normalizing the anatomical volumes to the T1 gray-matter template, and applying the same transformation to the functional volumes. During the latter, process images were resliced to 3 mm isotropic resolution in Montreal Neurological Institute (MNI) space.

fMRI connectivity analysis

The overall connectivity dynamics of fMRI behavioral experiments are difficult to study due to a lack of well-understood brain-activation models plus inter-subject variability (Allen et al., 2012). A strength of independent component analysis (ICA) is that it is model-free and thus makes no underlying assumptions about the spatiotemporal time-course of individual fMRI activations. Previous work has also revealed a correspondence of temporally-coherent networks across behavioral tasks and resting-state conditions (Calhoun et al., 2008). Hence, group spatial independent component