Mind over chatter: plastic up-regulation of the fMRI alertness network by EEG neurofeedback

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Abstract

EEG neurofeedback (NFB) is a brain-computer interface (BCI) approach used to shape brain oscillations by means of real-time feedback from the electroencephalogram (EEG), which is known to reflect neural activity across cortical networks. Although NFB is being evaluated as a novel tool for treating brain disorders, evidence is scarce on the mechanism of its impact on brain function. In this study with 34 healthy participants, we examined whether, during the performance of an attentional auditory oddball task, the functional connectivity strength of distinct fMRI networks would be plastically altered after a 30-min NFB session of alpha-band reduction (n=17) versus a sham-feedback condition (n=17). Our results reveal that compared to sham, NFB induced a specific increase of functional connectivity within the alertness/salience network (dorsal anterior and mid cingulate), which was detectable 30 minutes after termination of training. Crucially, these effects were significantly correlated with reduced mind-wandering 'on-task' and were coupled to NFB-mediated resting state reductions in the alpha-band (8-12 Hz). No such relationships were evident for the sham condition. Although group default-mode network (DMN) connectivity was not significantly altered following NFB, we observed a positive association between modulations of resting alpha amplitude and precuneal connectivity, both correlating positively with frequency of mind-wandering. Our findings demonstrate a temporally direct, plastic impact of NFB on large-scale brain functional networks, and provide promising neurobehavioral evidence supporting its use as a noninvasive tool to modulate brain function in health and disease.

Introduction

Originally discovered more than 40 years ago (Kamiya, Callaway, and Yeager 1969), EEG neurofeedback (NFB) is a brain-computer interface (BCI) method which enables a person to gain voluntary control of their brain activity by receiving real-time feedback from their electroencephalogram (EEG). As a consequence, it holds promise for modifying neural activity in various brain disorders, such as ADHD, PTSD and epilepsy (for a review see (Heinrich, Gevensleben, and Strehl 2007)). Most NFB involves multiple sessions repeated on at least a weekly basis, whose effects generally accumulate over time, reputedly as a result of neuroplastic changes in the brain (Abarbanel 1995). However, evidence of a tangible, short-term effect of NFB remains scarce. Hence, while the lasting effects of NFB are expected after several sessions, proof of a temporally direct impact of NFB on cerebral plasticity is needed for it to be endorsed as an effective approach towards modulating brain function in a safe, accessible and cost-effective way. Recently, sustained and EEG-correlated changes in cortical excitability were detected for the first time using transcranial magnetic stimulation (TMS) in the direct aftermath of NFB (Ros et al. 2010).

We drew inspiration from this discovery by asking whether fMRI might equally capture the early physiological effects of NFB; and if so, to what extent could neuroimaging of brain functional networks be used to reveal the causal effects of NFB on EEG and behavior. To avoid confounding the experimental and sham groups with prior training effects, we considered EEG alpha rhythm desynchronization as the NFB protocol, given that we previously found that it could be learned rapidly by naïve participants (Ros et al. 2010). Elsewhere, a number of EEG-fMRI studies have linked the alpha rhythm with the activity of temporally-coherent fMRI networks (Wu, Eichele, and Calhoun 2010): with alpha power being positively correlated with 'default-mode network' (DMN) (Ben-Simon et al. 2008; Hlinka et al. 2010; Mantini et al. 2007; K. Jann et al. 2009; Kay Jann et al. 2010) as well as 'alertness network' (Sadaghiani et al. 2010) connectivity. Intriguingly, during behavioral tasks the activation of the DMN has been shown to coincide with mind-wandering (Christoff et al. 2009; Mason et al. 2007) and lapses in attention (Weissman et al. 2006), whilst alertness-network activation has been linked to successful performance of visual/auditory oddball (K. a Kiehl et al. 2005; K. A. Kiehl et al. 2001; a a Stevens et al. 2000) and auditory perception tasks (Sadaghiani, Hesselmann, and Kleinschmidt 2009; Sturm et al. 2004). In order to disentangle these seemingly contradictory functional correlates of alpha oscillations, we sought to examine to what extent NFB alpha-band 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 oddball task containing random mind-wandering probes, in order to estimate attentional level. Based on the prevailing evidence, we hypothesized that successful alpha band reduction (desynchronization) would be associated with short-term plastic alterations in DMN and alertness network connectivity after NFB, and individually correlated with "on-task" mind-wandering.

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 centre and were carefully screened for the presence of neurological or psychiatric disorders during a structured SCID-I-Interview (Spitzer et al. 1992) 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 neurofeedback session of a representative 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 participants 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 minutes 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 (mean $\pm$ SD = 24 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 next section). The task consisted of one 6 minute 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 seconds 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. 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, whilst additionally inserting a ring tone as a thought probe stimulus at a probability of 3% (approx. 1 probe every 50-70 seconds). 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 degree flip angle; 256 mm field of view [FOV]; and 2 x 2 x 2 voxel resolution (mm). Sampling consisted of 60 interleaved slices, 2mm 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 minutes. Anatomical images were obtained using a T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence: (TR / TE / TI = 2000ms / 4 ms/ 900 ms; flip angle = 9^{o}; FOV = 256mm x 256 mm; 1mm isotropic resolution; 176 slices, no gap, GRAPPA acceleration=2). Image pre-processing was performed in SPM8 (http://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 8mm. 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

Group spatial independent component analysis (GICA) was implemented using the GIFT toolbox (v1.3i, http://mialab.mrn.org/) (V D Calhoun et al. 2001) in Matlab 7.6 (Mathworks Inc., MA, USA). Here, we performed group-ICA on the pooled dataset (both experimental groups, pre and post sessions). This approach allows for unique time courses for each subject, but assumes common group maps, ensuring that independent component (IC) spatial maps match across all participants as well as conditions (Vince D Calhoun, Kiehl, and Pearlson 2008). Importantly, this particular group-ICA approach was recently shown to accurately capture inter-subject, and hence inter-group, differences in IC amplitude as well as spatial extent (Allen et al. 2011). Accordingly, we used the Infomax algorithm (McKeown et al. 1998) to extract a total of 20 independent components (ICs), based on recent methodological studies reporting good reproducibility with this number in GIFT (Schöpf et al. 2010; Rosazza et al. 2011), which was confirmed by dimension estimation using the minimum description length (MDL) criteria. For each IC, its time course corresponded to the waveform of a specific pattern of coherent brain activity, and the intensity of this pattern across voxels was expressed in the associated z-score spatial map. Hence, the z-scores reflected the degree to which a given voxel's time series was coupled to the time series of a specific component, scaled by the standard deviation of the error term. All ICs were manually inspected for the presence of obvious artifacts (e.g. edges, ventricles, white matter) and a final subset of 8 artifact-free ICs corresponding to intrinsic connectivity networks (ICNs) were identified according to the templates described previously (van den Heuvel and Hulshoff Pol 2010; Damoiseaux et al. 2006). To ensure component reliability, we ran ICA a total of 20 times with boot-strapping and random starting points (ICASSO method (Himberg, Hyvärinen, and Esposito 2004)), resulting in all identified ICNs meeting the average intra-cluster similarity > 0.9 threshold. For each group and pre-post session, the subject-specific z-score spatial maps (n=17) of each ICN were imported into SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) for a one-sample t-test, corrected for family-wise error (FWE) at $P < 0.05$. This treated each subject's session as a random effect and provided a statistical cut-off for the inclusion of voxels within each ICN. These session-specific masks were then combined manually with a Boolean OR function to give a significant group-specific map. The resultant map was then applied as an explicit mask in subsequent second-level analyses, ensuring that the same set of voxels was used for all network connectivity contrasts, both within and between groups. Here, for NFB (or SHAM) exploratory

within-group contrasts, paired t-tests were conducted on z-score spatial maps corresponding to pre and post sessions, at a threshold of $P < 0.05$ FWE corrected. Based on the hypothesized effects in the alertness network and DMN, we employed region-of-interest (ROI) analyses for FWE correction of the search volume. Using WFU Pickatlas, Brodmann Area (BA) 24 + 32 masks were used to select the anterior cingulate within the alertness network (Sadaghiani et al. 2010); and BA10 (frontal pole), BA31 (posterior cingulate), BA7 (precuneus), BA39 (occipitoparietal) nodes within the DMN. We were also interested in exploring whether individual pre-to-post fMRI connectivity changes were directly related to EEG neurofeedback measures and mind wandering performance. In this case, for relevant ICNs, we calculated the post-minus-pre z-score map(s) manually for each participant, which subsequently acted as the dependent variable in a multiple regression analysis, thresholded at FWE < 0.05 small volume corrected (SVC). The SVC corrected contrast (T_2 - T_1) remained unbiased given that we used an orthogonal contrast to determine the ROI centre (T_2 + T_1). Thus, the alertness network ROI we used for SVC was a sphere of 10mm-radius (dorsal ACC centre -2, 12, 38 for NFB; 8, 18, 36 for SHAM) whose z-score connectivity values were averaged across all voxels; this was similarly done for the default-mode network ROI (precuneus centre 0, -68, 34 for NFB; 2, -68, 32 for SHAM). In order to examine between-group effects, we carried out a 2 x 2 mixed ANOVA (Group x Session) derived from these same maps, setting the threshold for interaction at FWE < 0.05 one-tailed (SVC).

EEG neurofeedback paradigm

The EEG neurofeedback training session took place outside of the MRI scanner. Immediately before and after the training session, participants completed Spielberger's State Anxiety Inventory (Spielberger et al. 1983) and Thayer's Activation-Deactivation Checklist (Thayer R.E. 1986) questionnaires . All participants wore a multi-channel EEG cap which passively recorded their whole-scalp activity (see section below). In parallel, we placed an additional electrode on top of the cap, bridging with the Pz channel, which was specifically used for neurofeedback. This electrode was connected to a ProComp+ amplifier (Thought Technology, Canada) interfacing with EEGer 4.2 neurofeedback software (EEG Spectrum Systems, CA). A separate ground electrode was placed on the right earlobe, and the reference electrode on the left earlobe. Each session consisted of a 3-min baseline, followed by 30 minutes of continuous neurofeedback, and lastly a 3-min post-baseline (all in 'eyes open' condition). During (feedback-free) baseline recordings, participants were asked to relax with their eyes open and gaze at a blank wall. Sham group participants did not receive veridical feedback from their EEG activity, but were re-played EEG signal from a previously recorded session of a NFB-successful participant (their whole-scalp EEG activity was nevertheless recorded). For the purpose of online NFB training, the EEG signal was IIR (infinite impulse response) band-pass filtered to extract alpha (8-12 Hz) amplitude with an epoch size of 0.5 seconds. The protocol was set-up so that participants were rewarded upon suppression of their absolute alpha amplitude. For both NFB and SHAM participants, the amplitude threshold for reward was initially set so that their alpha amplitude would temporally occur circa 60% of the time below the initial 3-min baseline average (i.e. they received negative-feedback 40% of the time). In cases where the participant achieved disproportionately larger (> 80%) or lower (< 40%) rates of reward during feedback, this reward ratio was re-applied at the beginning of each training period based on the EEG of the preceding 30 seconds.

Visual feedback was clearly displayed on a 20" monitor via a dynamic bar graph on the centre of the screen whose height was proportional to real-time alpha fluctuations. On the same screen, participants also interacted with a "SpaceRace" game. Here, participants were told that the space-ship moved forward through space when they were “in-the-zone” of their target brain activity (i.e. alpha lower than threshold), increasing their points in the game, and which fell back to stationary when they were “out-of-the-zone” (i.e. alpha higher than threshold). The aim of the training was to use the feedback they received during the game to learn to keep the spaceship travelling through space. Participants of both groups (NFB, SHAM) were not given any explicit instructions or mental strategies by the experimenter on how to achieve control over their spaceship, but were told to be guided by the visual feedback process. Moreover, they were not informed on the type of EEG parameter or frequency that was being rewarded. The 30-min session was divided into 10 three-minute periods. Each participant had a small break (of 10 seconds) between each 3-minute period, during which their score for the preceding periods was displayed. After completing the feedback training session, NFB and SHAM participants were asked to note down what strategy, if any, in their experience was most successful for gaining points during the game.

EEG recording

Scalp voltages were recorded using a 19 Ag/AgCl electrode cap according to the 10-20 international system: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2. (Electro-cap International, Inc. http://www.electro-cap.com). The ground electrode was placed on the scalp, at a site equidistant between Fpz and Fz. Electrical signals were amplified with the Mitsar 21-channel EEG system (Mitsar-201, CE0537, Mitsar, Ltd. http://www.mitsar-medical.com) and all electrode impedances were kept under 5 kΩ. For online recording, electrodes were referenced to linked earlobes, and then the common average reference was calculated off-line before further analysis. The EEG was recorded continuously, digitized at a sampling rate of 250 Hz, and stored on hard disk for off-line analysis. EEG data were then filtered with a 0.5-40 Hz bandpass filter off-line.

EEG pre-processing

Following EEG recording, all EEG data were imported into the Matlab toolbox EEGLAB v9 (Delorme and Makeig 2004). We used ICA decomposition to first remove stereotypical artifacts, since the Infomax algorithm has previously been shown to be capable of reliably separating eye activities, such as blinking and lateral eye movement (e.g. Jung et al., 2000). Subsequent artifact rejection methods consisted of the exclusion of epochs with large amplitudes (over ±80μV), direct-current bias, physiologically irresolvable noise (Onton et al., 2006), and muscular activity of frontal and temporal muscles defined by fast activity over 20 Hz (Shackman et al., 2009).

EEG neurofeedback spectral analysis

EEG spectral amplitudes were calculated offline via Short Time Fourier Transform (STFT) in 4-second epochs (50% overlapping with Hanning time window) in each of the following bandwidths: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), low beta (12-18 Hz), and high beta (18-25Hz). We did not analyze higher frequencies (gamma >25 Hz) due to the fact that they may easily be contaminated by muscle artifact throughout the extended NFB session. We chose to capture inter-individual variability with the full alpha (8-12 Hz) bandwidth, reflective of the NFB protocol and given recent data that lower (8-10 Hz) and upper (10-12 Hz) bands provide no extra sensitivity (Shackman et al. 2010). For the alpha band, offline analysis of NFB training efficacy was defined by a training coefficient, or the Pearson correlation between the period number (0-10, baseline = 0) and the average alpha amplitude (peak-to-peak) of that period. This had a range of -1 (relative decrease) to +1 (relative increase). Hence for participants in the NFB group successful training was indicated by more negative coefficients. Additionally, for all bandwidths, the normalized training EEG change for each participant was estimated by the ratio of the average EEG amplitude during all ten training periods and the first baseline EEG, and designated as 'training EEG change'. Likewise, the normalized change in the baseline EEG amplitude was expressed by the ratio of the second divided by the first baseline, and designated as 'resting EEG change'. For NFB (or SHAM) within-group contrasts, and for each electrode, paired t-tests were conducted on absolute amplitudes corresponding to pre and post sessions, at a threshold of $P < 0.05$.

Results

Baseline differences between NFB and SHAM groups

Independent two-sample t-tests did not reveal any statistically significant ($P < 0.05$) differences between NFB and SHAM groups for age ($t = 0.5$), gender ($t = 0.7$), hours of sleep ($t = -0.4$), and time of day during testing ($t = -0.3$) In addition, independent two-sample t-tests on baseline connectivity maps disclosed no statistically-corrected ($P < 0.05$) differences between NFB and SHAM groups for either the alertness network or the default-mode network. Likewise, there were no significant baseline differences between groups in frequency of mind-wandering ($t = 0.1$), oddball stimulus reaction time ($t = -0.1$), reaction time to mind-wandering probe ($t = -0.9$); nor mean EEG alpha amplitude at frontal ($t = -0.7$), temporal ($t = -0.9$), central ($t = -0.8$), occipital ($t = -0.7$) or parietal ($t = -0.4$) electrodes.

EEG neurofeedback time-course and topography

During NFB and SHAM protocols, participants attempted to control either real-time or false (pre-recorded) alpha amplitude, respectively, which was recorded from midline parietal cortex (electrode Pz) during a 30-min feedback training session. In order to analyze the time-course, the session was subdivided into ten equal periods of 3 min each. A feedback-free, eyes-open, resting baseline was also recorded for 3 min prior to and following the end of feedback (periods 0 and 11 respectively).

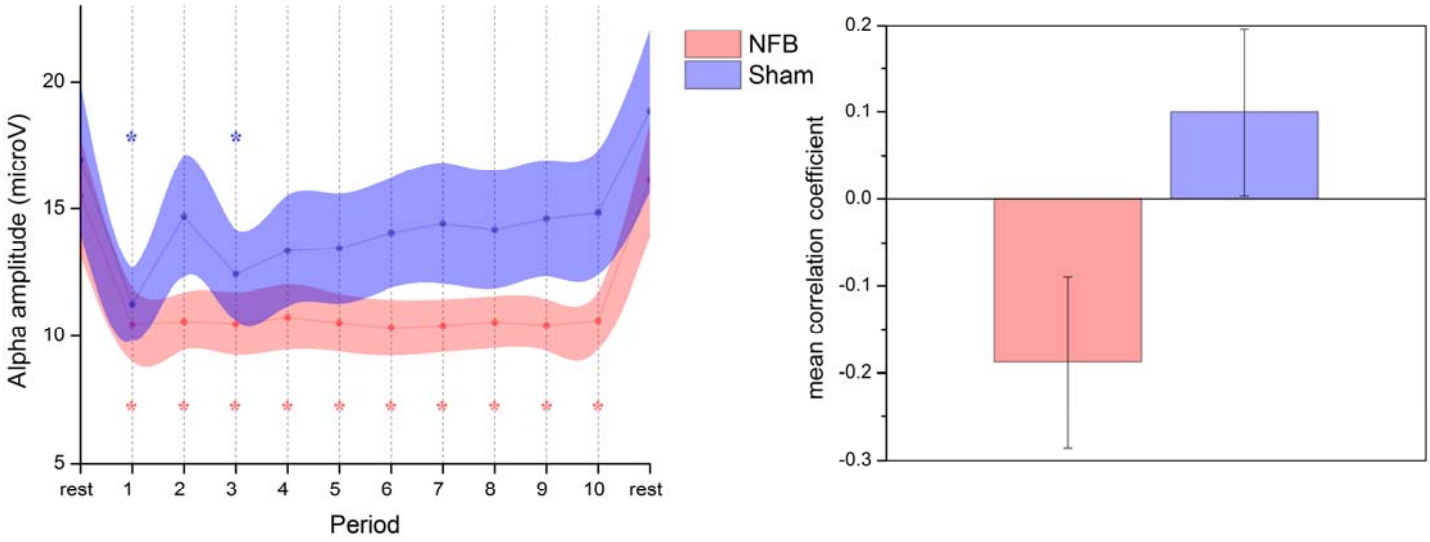

Fig 1. Left Panel: time-course of mean alpha (8-12 Hz) amplitude for NFB and SHAM groups. The session began with a 3-min resting baseline, followed by 30-min of feedback (periods 1-10) from midline parietal cortex (Pz). Periods significantly different from baseline are indicated with an asterisk ($P<0.05$). Shaded areas represent SEM. Right Panel: mean group training coefficient, or Pearson correlation of alpha amplitude vs. Periods 0-10. Error bars represent SEM.

As can be seen from Fig 1, NFB participants were successful in reducing their target alpha amplitude across all training periods. The SHAM group on the other hand, after an initial drop, experienced a recovery to near-baseline levels across time. The opening drop exhibited by the SHAM group may have reflected a focusing of attention related to the unsuccessful search for a suitable cognitive strategy. A repeated measure ANOVA (GROUP x PERIOD, 2 x 12) revealed a main effect for PERIOD ($F_{11,352} = 22.2$, $P < 0.01$) and no overall effect for GROUP ($F_{1,32} = 1.3$, n.s.). Importantly, there was a significant GROUP x PERIOD interaction ($F_{11,352} = 2.0$, $P = 0.03$), indicating a significantly different alpha amplitude time-course between groups. Post-hoc paired Dunnett's test comparisons with the first resting period revealed a significant reduction for all training periods in the NFB group ($P < 0.05$ corrected), whilst only periods 1 and 3 were significant for the SHAM group. No significant changes were detected between the two resting periods for either group. As shown in the right panel of Fig 1, the mean alpha training coefficient also distinguished NFB ($r = -0.18$, $p = 0.02$) and SHAM ($r = 0.12$, n.s.) groups. Interestingly, within-subject amplitude correlations between theta, alpha, and beta bands during NFB were consistently positive within a statistically significant range of $0.5 < r < 0.7$, suggesting a broader effect of NFB training on flanking frequency bands.

To investigate these relationships further, we constructed topographic plots representing the statistical change across the whole-scalp between the resting period and the mean amplitude of all training periods; these are depicted in Fig 2 for NFB and SHAM groups in each frequency band. In this case, a paired t-test revealed a significant global alpha amplitude reduction (collapsed across all electrodes) during NFB ($t = 2.7$, $P < 0.05$ corrected), which was absent in the SHAM group ($t = 1.9$, n.s.). Given that we primarily hypothesized alpha changes at the Pz feedback site and/or globally, the reported t-tests can be considered exploratory for all other band-widths or cortical locations ($t>|3|$, $P<0.05$ uncorrected).

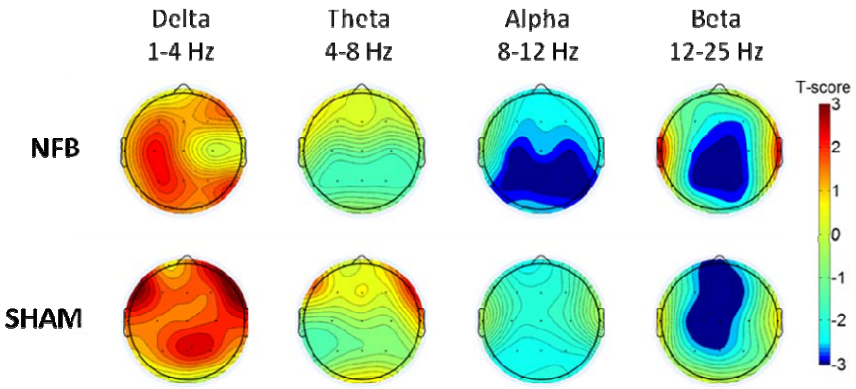

Fig 2. Topographic plots of mean EEG amplitude change during feedback (relative to rest). Upper and lower panels represent NFB and SHAM groups, with successive EEG bandwidths featuring from left to right. Dark red and dark blue colors indicate statistically significant positive and negative changes ($P < 0.05$), respectively.

EEG resting state activity

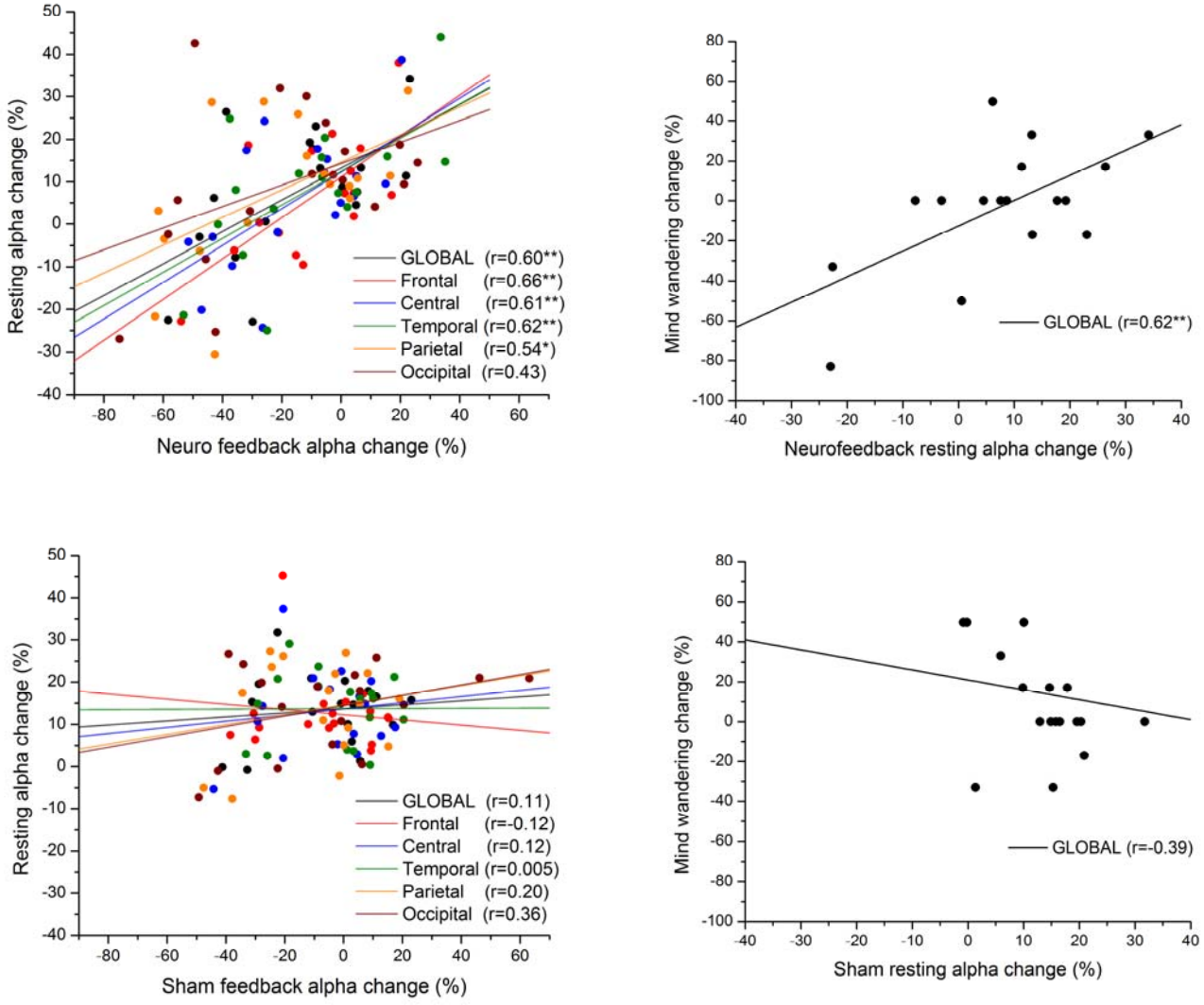

Fig 3. Scatter-plot of mean alpha amplitude change across electrodes during feedback vs. resting (post-feedback), for NFB (upper-left panel) and SHAM (lower-left panel) groups. The anatomical location of each subgroup of electrodes is represented by a different colour (see legend). Correlation of global alpha change with mind-wandering change is shown in the right panels, respectively. Linear regression lines pertaining to each subgroup are in their respective colours. * P < 0.05, **P <0.01.

Our previously published results (Ros et al. 2010) had pointed to a causal influence of dynamic EEG changes during neurofeedback training on subsequent EEG resting state activity. We interrogated this effect in the current dataset, which benefited from a sham-feedback control group. For both groups, we correlated the mean amplitude change during feedback and the respective change in resting state amplitude after feedback. We utilized % signal change (relative to the first resting period) in order to normalize alpha amplitude change between participants. As can be seen in Fig 3, resting state changes were predicted by and were positively correlated with changes during NFB; yet this effect was wholly absent during sham-feedback.

This outcome is consistent with Hebbian forms of neural plasticity whereby sustained (de)synchronization of synaptic activities (directly reflected by the EEG) may shift the population dynamic to an increasingly more (de)synchronized state (Tass and Hauptmann 2007). Interestingly, for the NFB group this dependency was robust across the majority of anatomical locations, suggesting a global modulation of cortical alpha oscillations. Given the homogeneity of this effect, we concentrated on global alpha changes in further analyses.

For the NFB group, we identified a significant positive correlation between global resting alpha change and mind-wandering change ($r = 0.62$, $p < 0.01$), which was nonsignificant ($r = -0.39$, n.s.) for the SHAM group. An analogous effect was seen for alpha at the feedback-electrode Pz (NFB: $r = 0.61$; SHAM: $r = -0.41$). Exploratory analyses on flanking bandwidths revealed a significant univariate correlation between resting theta change and mind-wandering change for the NFB group ($r = 0.52$, $P = 0.03$) but not for the SHAM group ($r = -0.15$, n.s.). This appears consistent with a recent study investigating EEG changes associated with mind-wandering during meditation (Braboszcz and Delorme 2011). The relationship between mind-wandering and the delta or beta bands was nonsignificant for both groups. To investigate the shared variance (multicollinearity) between multiple EEG bands and mind-wandering change, we conducted a multivariate regression with all band-widths as independent variables: this yielded the NFB group resting alpha-band change as the only significant regressor ($r = 0.62$, $p < 0.01$).

fMRI network connectivity

Pooling the NFB and SHAM data, and from the total of 20 components extracted by the ICA decomposition, we were able to reliably identify 8 anatomically-circumscribed, intrinsic connectivity networks (ICNs) compatible with current literature (van den Heuvel and Hulshoff Pol 2010; Damoiseaux et al. 2006): *default-mode* (C7), *cingulate* (C11), *motor* (C5), *visual* (C2), *auditory* (C17), *rostral PFC* (C9), right and left *fronto-parietal* (C15, C16) networks. Prior to further statistical analyses, masks were created corresponding to each ICN using a one-sample t-test ($P < 0.01$ FWE). The principal goal of subsequent analyses was to examine whether, pre-to-post neurofeedback, any reliable fMRI connectivity changes could be detected within circumscribed ICNs, and how these changes were related to differences in EEG and mind-wandering measures. Our primary hypotheses were derived from previous reports linking alpha-band power with i) the alertness/salience network (Sadaghiani et al. 2010), and ii) the default-mode network (K. Jann et al. 2009; Hlinka et al. 2010).

Alertness/Salience Network

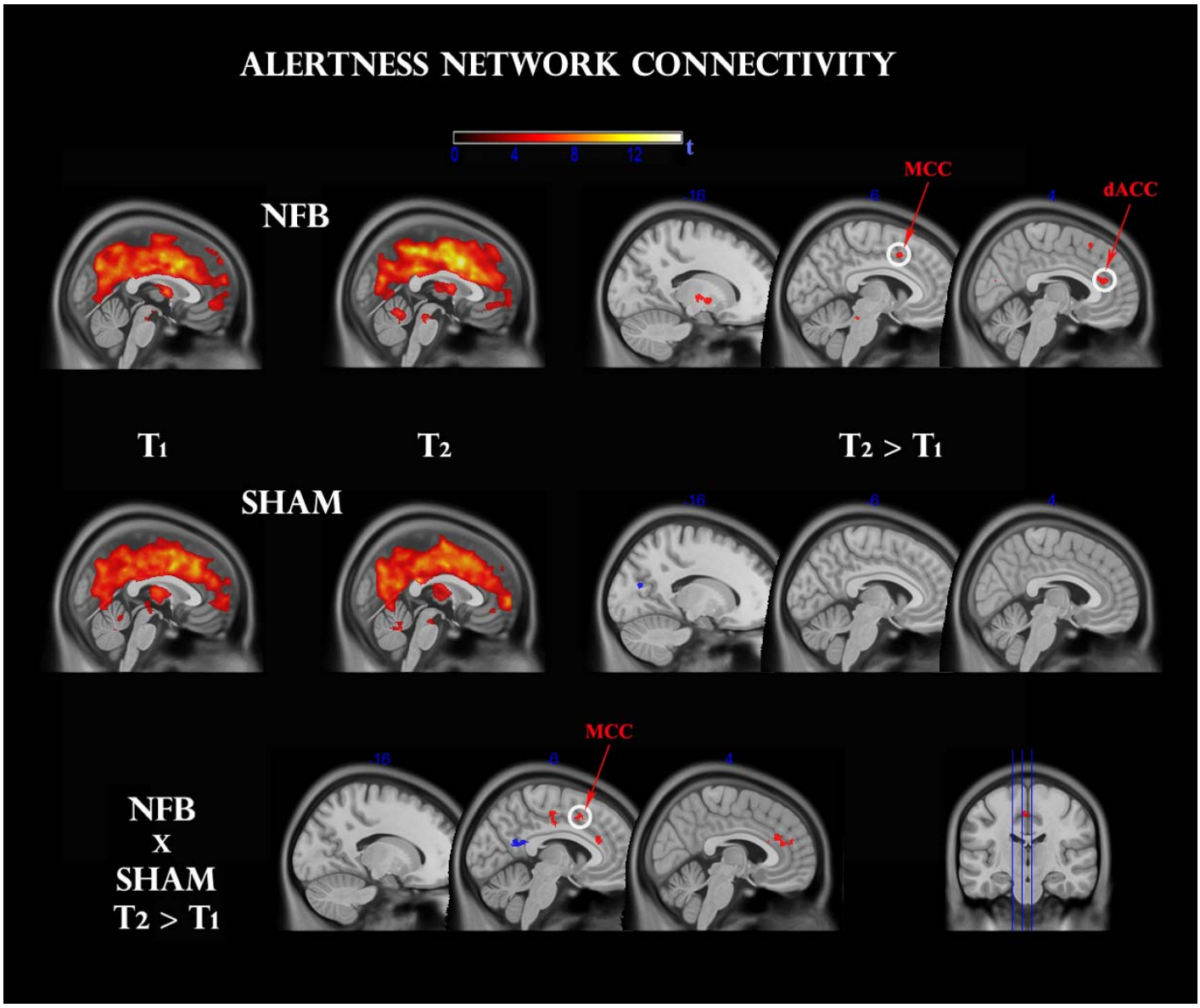

Fig 4. Functional connectivity change within the alertness/salience network, before (T1) and after (T2) feedback, for NFB (top panel) and SHAM (middle panel) groups. Clusters surviving the family-wise error (FWE < 0.05) correction are circled in white. Other clusters were thresholded at $p < 0.001$ uncorrected. A TIME x GROUP interaction (bottom panel) reveals a significant modulation in comparable regions. dACC: dorsal anterior cingulate cortex; MCC: mid-cingulate cortex.

A one-sample t-test within pre (T_1) and post (T_2) sessions of each group revealed a coherent cingulo-opercular network of activation during the oddball task, with maximal connectivity at dorsal anterior (dACC), middle (MCC) and posterior cingulate cortex (PCC), as well as bilateral insular, thalamic, basal ganglia, cerebellar and ponto-mesencephalic regions (see Fig 4, top panel). This is consistent with areas previously reported to be responsible for salience detection (Seeley et al. 2007) and intrinsic alertness (Clemens et al. 2011).

For the NFB group, a paired t-test indicated significantly increased functional connectivity after neurofeedback in the dACC (t = 6.0, 55 voxels) and MCC (t = 5.27, 15 voxels) clusters at FWE > 0.05, as seen in Fig 4. Exploratory analyses (P < 0.001 uncorrected) additionally revealed up-regulation of left thalamus (t = 4.5, 20 voxels), left medial globus pallidus (t = 5.6, 20 voxels), and (most likely) left locus coeruleus (t = 4.0, 15 voxels). No significant effects were detected for the SHAM group at this statistical and cluster-extent threshold. In order to contrast these effects with the SHAM group directly, we additionally conducted a mixed repeated-measures ANOVA, and observed a significant GROUP x TIME interaction (P < 0.05, voxels □ 15): NFB group changes were more positive once again for the ACC (t = 2.0, 25 voxels), MCC (t = 2.5, 25 voxels) and globus pallidus (t = 3.0, 50 voxels); of which the MCC cluster survived a small-volume correction (FWE < 0.05 one tailed).

Default-Mode Network

No statistically significant group effects (FWE P < 0.05) were found within the default-mode network after feedback, for either NFB or SHAM groups.

fMRI vs mind-wandering vs EEG

Alertness/Salience Network

In this analysis we separately regressed global resting-alpha change, as well as mind wandering change, against individual z-score connectivity change maps in the alertness network. In order to explore their intersection we searched for common voxels which passed the P < 0.001 uncorrected threshold with both regressors. As can be seen in Fig 5 for the NFB group, both mind-wandering and alpha change correlated negatively with connectivity in large clusters (k > 50) of the dorsal ACC (t = -4.4 and t = -4.0 respectively) and MCC (t = -6.0, t = -4.1 respectively), with the latter cluster passing the small-volume corrected threshold (FWE < 0.05) for both mind wandering and alpha change. Hence, individual *reductions* in alpha as well as mind-wandering were associated with increased connectivity in the alertness network. Interestingly for the SHAM group, and opposite to the relationship seen with the NFB group, a positive correlation was observed between resting alpha change and functional connectivity within a proximal cluster within the MCC (t = 4.2, 40 voxels) at p < 0.001 uncorrected. On the other hand, negatively correlated clusters with changes in mind-wandering were located predominantly in white matter areas, with exploratory p < 0.001 clusters in posterior cingulate (t = -4.2) and subgenual cingulate (t = -4.5) regions. Positive correlations were found in the medial orbital gyrus (t = 5.4) and right brainstem (t = 5.3). However, none of these clusters coincided with regions that were significantly correlated with resting EEG changes.

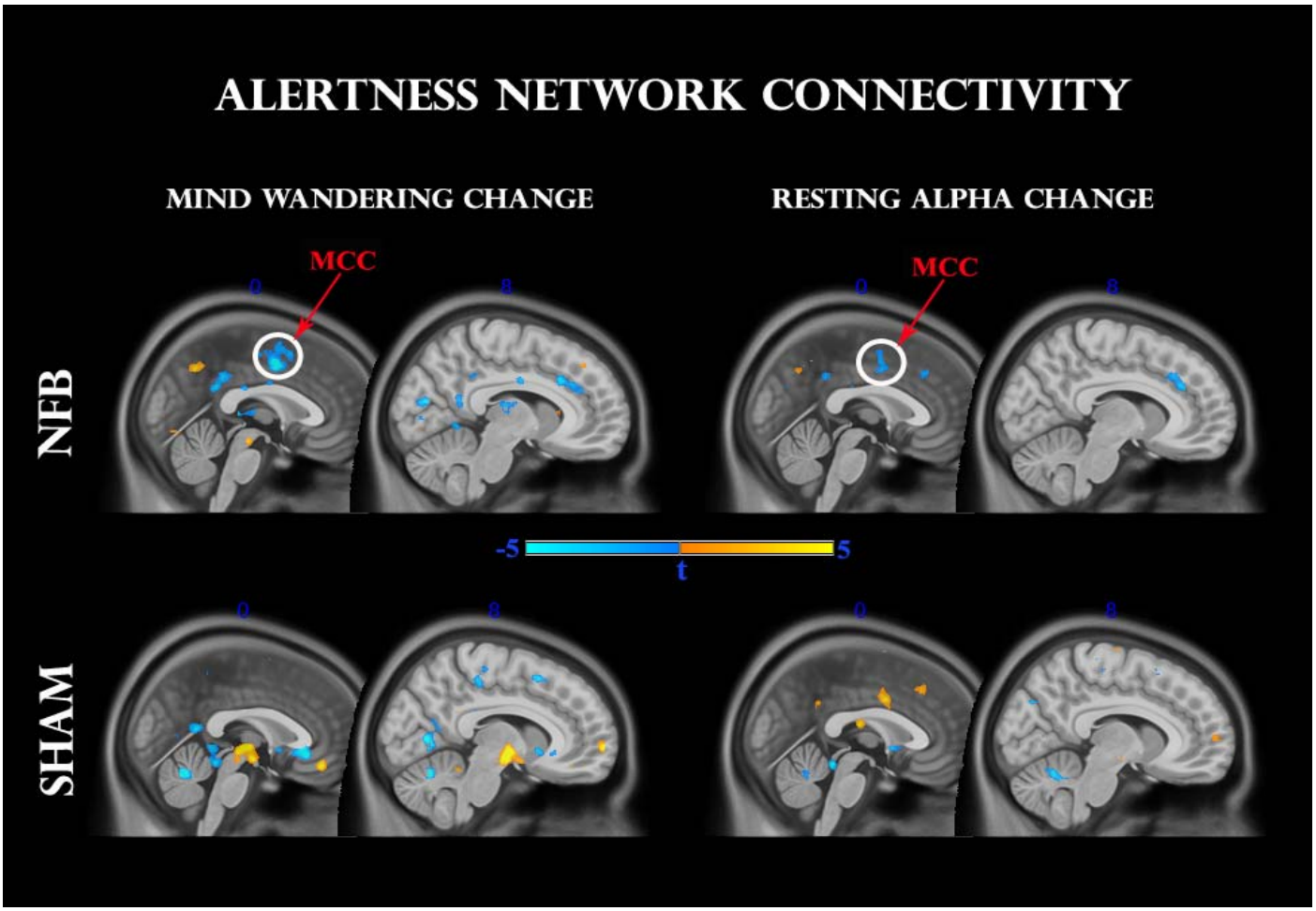

Fig 5. Regression analysis between pre-to-post changes in alertness network functional connectivity and mind-wandering change (left panel), as well as resting alpha change (right panel). Upper and lower panels indicate NFB and SHAM groups, respectively. Clusters surviving the family-wise error (FWE < 0.05) correction are circled in white. MCC: mid-cingulate cortex

Default-Mode Network

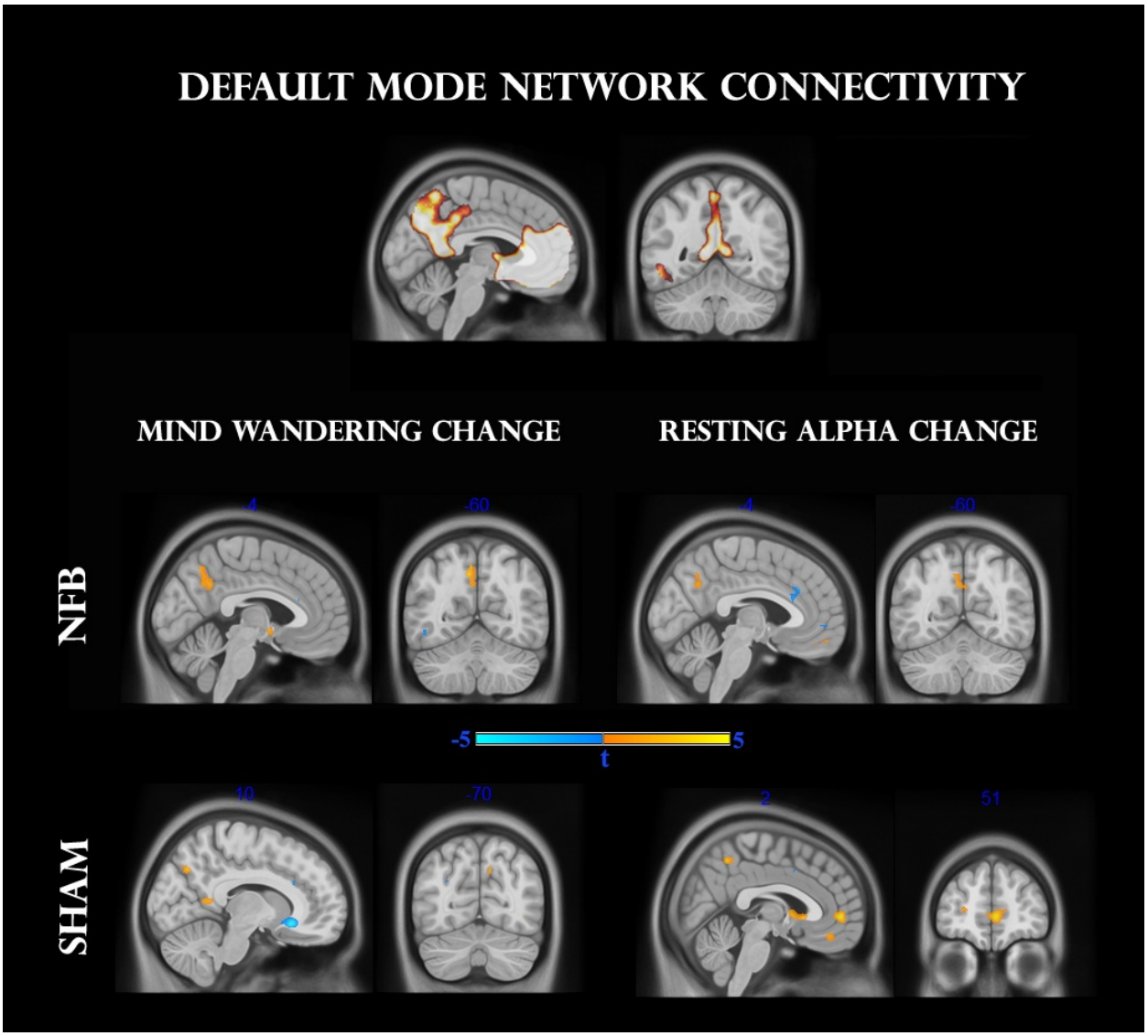

Fig 6. Regression analysis between pre-to-post changes in default-mode network (DMN) functional connectivity and mind-wandering change (left panel), as well as resting alpha change (right panel). The upper panel designates the DMN mask used for analysis. Middle and lower panels indicate NFB and SHAM groups, respectively. Clusters surviving the family-wise error (FWE < 0.05) correction are circled in white. Pcn: precuneus; mPFC: medial prefrontal cortex

As for the alertness network, we identified clusters of DMN connectivity that mutually correlated with changes in resting state alpha amplitude and frequency of mind-wandering. As shown in Fig 6 for the NFB group, both mind-wandering and alpha change correlated *positively* with connectivity in sizeable clusters ($k > 25$) of the precuneus ($t = 3.7$ and $t = 3.6$, respectively), passing the small-volume corrected threshold (FWE < 0.05). This positive relationship was mirrored by the SHAM group, albeit by smaller clusters ($k > 10$) within the precuneus ($t = 4.1$ and $t = 3.8$, respectively). Moreover for the SHAM group only, exploratory analyses ($P < 0.001$) identified a more extensive positive correlation with resting state alpha change in a region of the medial prefrontal cortex ($t = 5.0$). Hence, both NFB and SHAM groups

remained consistent with numerous reports of a positive association between alpha power and DMN connectivity (Ben-Simon et al. 2008; Hlinka et al. 2010; Mantini et al. 2007; K. Jann et al. 2009; Kay Jann et al. 2010).

Mind-wandering and oddball task

For the NFB group, pre-to-post RT change to mind-wandering probes was positively correlated with change in mind-wandering frequency ($r = 0.58$, $p = 0.1$), while no reliable relationship was evident for the SHAM group ($r = -0.24$, n.s.). Correlations between RT change to mind-wandering probes and oddball-targets were not significant for either NFB ($r = -0.28$, n.s) or SHAM ($r = -0.15$, n.s.). Paired t-tests revealed there were no significant pre-to-post differences in mind-wandering frequency for NFB ($t = 0.4$, n.s.) or SHAM ($t = -1.4$, n.s.). Likewise, no significant differences were evident in pre-to-post RT to mind-wandering probes for NFB ($t = -1.5$, n.s.) or for SHAM ($t = 0.5$, n.s.); nor RT to oddball-targets for NFB ($t = -0.8$, n.s.) or for SHAM ($t = 0.3$, n.s.).

Anxiety vs resting state alpha

There was no significant correlation between changes in global resting alpha amplitude and state anxiety following NFB ($r = 0.3$, n.s.) or SHAM ($r = 0.3$, n.s.), demonstrating that alpha reduction was not significantly related to changes in anxiety.

Discussion

Our principal aim was to examine whether a single session of EEG neurofeedback (NFB) could modify brain dynamics beyond the immediate time frame of the training session. Indeed, our results indicate that at around 30 minutes after training, NFB induced a statistically significant up-regulation of functional connectivity within the dACC/MCC of the alertness network in the experimental but not in the sham group. Hence utilizing fMRI and a placebo-control group we extend the findings of Ros et al. (Ros et al. 2010) demonstrating that the adult cortex is sufficiently plastic that a mere half-hour of targeted volitional activity (i.e. NFB) is capable of intrinsically reconfiguring the brain's functional activity to last above and beyond - and at least as long as- the time period of training itself. Recent real-time fMRI studies have reported functional connectivity changes during NFB proper (Rota et al., 2011, Hamilton et al 2011), with the exception of Hampson et al. who found altered brain dynamics in the 5-min resting period across multiple NFB sessions (Hampson et al. 2011). However, this relatively brief elapsed time following NFB remains insufficient to substantiate LTP-like (long-term potentiation) brain plasticity effects, which last beyond approx. 20 min (Schulz and Fitzgibbons 1997). Hence, our observations provide a temporally direct association between NFB and plastic modulation of brain functional networks, forming an important link with emerging evidence of longer-term (> 1 week) functional connectivity changes following multiple sessions of NFB training, either via EEG (Coben and Padolsky 2007) or fMRI (Yoo et al. 2007; Ruiz et al. 2011).

The main result of our study is crucially strengthened by the finding that the mean increase of connectivity within alertness network regions-of-interest (ROIs) coincided with a major cluster that individually correlated with decreases in resting-state EEG alpha-band amplitude; the latter measure was in turn predicted by individual degrees of alpha reduction during NFB, directly echoing the NFB protocol (alpha desynchronization). This overall concordance was absent from the sham group, where resting EEG amplitude change was not predicted by the degree of individual EEG control during NFB; neither did we observe a significant GROUP x TIME cluster overlap with ROIs derived from EEG alpha-band regression analyses, as was the case with the NFB group.

Furthermore, NFB effects were found to be tightly coupled to individual changes in internal task-unrelated thoughts (i.e. mind-wandering). There was firstly a significant correlation, absent from the sham group, between resting-state alpha change and frequency of self-reported mind-wandering. Moreover, greater resting state alpha reductions were associated with lower reaction times to the mind-wandering probe. Secondly, fMRI connectivity change in dACC/MCC correlated with reductions in mind-wandering, consistent with a previous report of enhanced alertness network activity during meditative awareness of mind-wandering (Hasenkamp et al. 2011) Importantly, the same region coincided with a large cluster separately associated with negative resting alpha changes. The sham group did not exhibit this overall congruence between EEG, fMRI connectivity and mind-wandering change, as individually there was no significant correlation between EEG resting state (in any band) and mind-wandering change. Nevertheless, we found a *positive* correlation between resting alpha change and a comparable region of the MCC. Hence, for the NFB group, our result of a negative correlation between global resting alpha and alertness network connectivity confirms the same anatomical location but is of opposite sign to the relationship observed by Sadaghiani et al. Of note, a couple of participants in the Sadaghiani et al study exhibited a negative coupling (Sadaghiani et al., 2010, supplementary data). However, there are several caveats to bear in mind while comparing our findings to those by Sadaghiani et al. Firstly, our fMRI recordings were made during an active auditory task with eyes open, whereas Sadaghiani et al. used a resting condition with eyes closed. There is preliminary evidence that EEG-BOLD coupling may vary between different behavioral states (Schölvinck et al. 2010). Another caveat is that we did not perform online EEG-fMRI, our regressors being based on offline, spontaneous EEG. Thus, our design cannot exclude the possibility that greater *tonic* alpha desynchronization at rest resulted in stronger *phasic* synchronization during the oddball task. However, this interpretation would contradict several lines of evidence indicating pronounced alpha desynchronization during effective detection of auditory stimuli (Mazaheri and Picton 2005; Weisz et al. 2011). From a different perspective, the positive correlation observed within the sham group may be seen to corroborate the Sadaghiani et al. findings, giving rise to an intriguing account that NFB may have induced a qualitatively different brain state, manifested by an altered EEG-fMRI coupling. Interestingly, one of the earliest online EEG-fMRI studies revealed a robust negative correlation between alpha power and anterior cingulate activity (Goldman et al. 2002).

In accordance with previous work, we found a positive relationship between changes in alpha synchronization and functional connectivity/activity in the default-mode network (DMN) (Ben-Simon et al. 2008; Hlinka et al. 2010; Mantini et al. 2007; K. Jann et al. 2009; Kay Jann et al. 2010). Here, NFB and sham group participants displayed the strongest positive correlations with precuneal and mPFC functional connectivity, respectively. Moreover, in both groups, positive precuneal connectivity change was associated with higher frequency of mind-wandering, consistent with previous real-time thought-sampling investigations (Christoff et al. 2009; Mason et al. 2007; Stawarczyk et al. 2011; Hasenkamp et al. 2011).

NFB possesses a notable advantage over basic correlational designs in that it is able to directly test for 'cause and effect'. However, behavioral interventions are usually faced with the problem of dissociating stimulus-dependent (extrinsic) vs. stimulus-independent (intrinsic) effects, yet our NFB paradigm ensured that all participants were exposed to the same sensory stimuli and frequencies of reward. Hence participants' entrained neuronal (EEG) differences could be considered as resulting minimally from external factors, and may instead be regarded as being driven by the modulation of internal, stimulus-independent brain states (Poulet and Petersen 2008). We would thus like to propose the existence of mechanisms that modulate the brain's 'intrinsic plasticity', operating independently of - and not driven by- external factors, in view of our finding of a significant three-way correspondence between individual NFB changes in EEG network oscillations, fMRI network connectivity, and mind-wandering behavior. Furthermore, while visual stimuli were used for feedback and posterior alpha rhythms have been implicated in visual processing (Ergenoglu et al. 2004; Romei et al. 2008), our attention task involved auditory perception. Hence, the fact that no exploratory functional connectivity alterations were observed in either visual or auditory networks once again points to a potential cross-modal and/or sensory-independent role of global alpha rhythms in regulating alertness (Schürmann et al. 2000). As a result, our data indicate for the first time that the intrinsic, stimulus-independent effect of tonic alpha desynchronization is reflected in amplified dACC/MCC connectivity specifically within the alertness network. The alertness network has previously been implicated in a variety of functions, including salience detection (Seeley et al. 2007), cognitive control (Sridharan, Levitin, and Menon 2008) maintenance of task-sets (Dosenbach et al. 2006), and fluid reasoning (Yuan et al. 2012) while the dACC/MCC has been found to activate during selective attention (Weissman et al. 2005), stimulus anticipation (Aarts, Roelofs, and van Turennout 2008), error monitoring (Pourtois et al. 2010), autonomic processing (Medford and Critchley 2010), and emotional arousal (McRae et al. 2008).

In support of our findings, a growing body of evidence has linked alertness, attention, and/or arousal, on the one hand, and alpha reduction (desynchronization) on the other. Trial-by-trial variations in visual/sensorimotor detection (Ergenoglu et al. 2004; Haegens and Luna 2011) and subjective attentional state (Macdonald, Mathan, and Yeung 2011) are found to be negatively associated with peri-stimulus EEG alpha power, while the excitability (Romei et al. 2008; Sauseng et al. 2009) and neuronal spike rate (Haegens and Luna 2011) of sensory cortices is heightened during low alpha power. Secondly, concurrent reduction of theta, alpha, and beta amplitudes (comparable to the broader attenuation observed during our NFB protocol) appears to be a distinctive signature of the alerting response (Fan et al. 2007) as well as during selective attention (Fries et al. 2001).

Alpha rhythm has been shown to globally attenuate upon eyes opening whilst correlating negatively with skin conductance, a classic measure of sympathetic arousal (Barry et al. 2007). Moreover, administration of caffeine, an often used stimulant to boost alertness, induces global reductions in alpha power and increased galvanic skin response (Barry et al. 2005). Conversely, momentary cognitive lapses during a sustained-attention tasks (such as simulated driving) are found to be associated with increases in alpha power (Huang et al. 2008). In sum, evidence suggests that higher alpha synchronization reflects inhibition of sensory cortical areas (Jensen and Mazaheri 2010; Wolfgang Klimesch, Sauseng, and Hanslmayr 2007), acting as a functional correlate of internally versus externally-directed attention (Cooper et al. 2003). Hence, given its impact on the alertness network and mind-wandering, the alpha desynchronizing NFB protocol could be seen as facilitating external or bottom-up attentional drive, characterized by suppressed internally-generated activity and cortical fluctuations typical of vigilant brain states (Harris and Thiele 2011; Schroeder and Lakatos 2009). Indeed, self-report data suggest that the overwhelming strategy reported by NFB participants was that of focused visual attention (12/17 or >70%), while the SHAM group presented no predominant strategy. Within this framework, our findings draw interesting parallels with the effects of attention-based meditation training, which include the strengthening of dACC connectivity after focused attention (Manna et al. 2010) and during mindfulness (Kilpatrick et al. 2011).

It is fascinating to speculate what neuronal mechanisms could be responsible for the functional reconfiguration observed in the alertness network. Conceivably, NFB regulation of the EEG, which comprises of summed post-synaptic potentials (Nunez 2000), may act to directly modulate gross synaptic activity (Crochet et al. 2006) plus internal brain states (Poulet and Petersen 2008; Steriade and Timofeev 2003). Brain state changes could result from the activity-dependent release of various neuromodulators acting along diffuse pathways (Castro-Alamancos and Calcagnotto 2001). In an earlier TMS investigation of cortical alpha desynchronization (Ros et al. 2010), we noted that the post-NFB pattern of enhanced motor-evoked potential and reduced short-intracortical inhibition (SICI) mirrored the effects of noradrenergic (NA) agonists (Ziemann 2004). Analogous alpha rhythms in animals have been reported to be distinctly affected by the lesion and pharmacological blockade of NA pathways (Rougeul-Buser and Buser 1997). Interestingly, a new study has indicated that NA mechanisms are also implicated in the up-regulation of alertness network connectivity (Hermans et al. 2011). Moreover, the NA agonist methylphenidate has been demonstrated to increase dACC activation (Schneider et al. 2011) as well as decrease SICI (Schneider et al. 2011) in proportion to the clinical response of adults with attentional-deficits. Irrespective of the neurochemical mechanisms that subserve its effects, the present NFB protocol may have a significant therapeutic prospect in brain disorders exhibiting blunted dACC or alertness network function. The pervasive role of this large-scale network and its dACC node have been linked to a wide range of pathophysiologies (Menon 2011), with reports of altered function in ADHD (Bush 2011), addiction disorders (Goldstein et al. 2010), major depression (Pizzagalli 2011), schizophrenia (White et al. 2010), fronto-temporal dementia (Zhou et al. 2010) and PTSD (R A Lanius et al. 2001; Daniels et al. 2010). Of note, a therapeutic study that observed improvements in ADHD symptoms reported normalization of dACC activation following multiple NFB sessions (Lévesque, Beauregard, and Mensour 2006). Hence, our findings provide direct, sham-controlled support for EEG-based NFB as a promising method to modulate the critical anatomical regions implicated in ADHD. The

evident strength of the current NFB protocol is that it may be rapidly learned by naive participants, inducing tangible changes within one session; data from our recently completed study with PTSD patients favour this view (Kluetsch et al., in preparation).

There are several limitations related to our study. Firstly, although we detected group changes in alertness network coupling, we did not find an overall difference in post-NFB behavior measures, such as frequency of mind-wandering or reaction-time. This could be related to the high baseline performance of participants and/or the relative ease of the oddball task. Inspection of our data actually indicates that more than a third of experimental participants (NFB n=6, SHAM n=6) performed at ceiling during the initial baseline session (with 100% absence of mind-wandering). Thus in a significant proportion of participants, our task turned out to be insensitive to the improvements we hypothesized. Secondly, since we did not perform simultaneous EEG-fMRI, we could not ascertain the relationship between task-evoked EEG and BOLD changes, and did so only with the resting EEG. Thirdly, it is evident from exploratory analyses that the NFB protocol did not alter alpha amplitude selectively (we observed relative reductions in flanking bands). However, the alpha band was the most robustly suppressed and correlated most significantly with reduction in mind-wandering and negatively with alertness network coupling. Naturally, our results do not preclude other spectral patterns from being associated with increased mind-wandering, such as low alpha-high theta (Braboszcz and Delorme 2011), which frequently corresponds to early states of drowsiness. From a different perspective, changes in alertness network connectivity could be argued to be due to a self-regulation effect that potentially discriminated the NFB and sham groups. Here, self-report data indicate that the majority (>80%) of the sham participants *did* attempt to self-regulate during the session and were uncertain as to whether they were part of the sham group. Furthermore, taking into consideration the tight correlations with mind-wandering and the previously observed association between alpha and the alertness network (Sadaghiani et al. 2010), self-regulation alone does not seem to be a plausible account for the observed outcome. Finally, it would have been fascinating to explore whether the current short-term effects may have generalized to longer time-scales (> 1 week) following the repeated application of the NFB protocol; we look forward to future studies investigating this relationship.

To conclude, we have provided the first neuroimaging evidence that an EEG-based NFB protocol can directly induce a plastic reinforcement of dACC connectivity within the alertness network, which individually correlates with decreases in mind-wandering. Functional coupling within this network appears to be critical for cognitive control while its dysfunction has been implicated in a range of brain disorders. Hence, our sham-controlled study offers promising neurobehavioral support for the use of EEG-based NFB as a noninvasive tool for modulating brain function in health and disease.

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