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Running head: Mid-frontal theta detects training manipulation

**Mid-frontal theta oscillations discriminate between sham-control and
neurofeedback training manipulations: a signal detection analysis**

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Abstract

Neurofeedback training allows people to control their brain wave oscillations, which has been reported to be beneficial in alleviating symptoms associated with clinical conditions and enhancing cognitive ability in healthy individuals. However, to provide scientific evidence to this effect, placebo-controlled studies are needed that control for the influence of practice, motivation, and the passage of time. One widely used design feature is the use of a sham-control condition, in which the participant is deceived into thinking that a true training procedure is being implemented. During post-study debriefing, participants typically report not knowing whether they were in the control or training condition and thus the sham-control design is regarded as being successful. We present results that cast doubt on the person's inability to detect group membership. Sixty participants were randomly allocated to an EEG neurofeedback training group for upregulating mid-frontal (Fz) alpha band (8 - 12 Hz) power or a sham-control group. We observed that participants were at chance in identifying their group membership during post-study debriefing. However, the relative power in the theta band (4 - 7 Hz) decreased over training blocks in the neurofeedback group, but remained constant in the sham-control group. The slope of the change in relative theta power was shown to be a reliable classifier of group membership as demonstrated using signal-detection analysis (AUC = .73). These results call into doubt the praise for sham-control conditions, and we recommend that researchers assess the brain's ability to detect group membership in addition to post-study verbal reports.

Keywords: EEG neurofeedback; sham-controlled; theta oscillation; unconscious detection

Introduction

During neurofeedback training, the trainee receives information about their brain signals and using feedback given by a brain-computer interface tries to wilfully change the brain signal towards a target goal, such as increasing or decreasing the brain activity. Electroencephalography (EEG) has been the most-often used brain signal due to its history in the discovery of neurofeedback and its portability. EEG neurofeedback has been used in the clinical field to alleviate symptoms associated with such diverse conditions as developmental disorders (e.g, ADHD, autism), epilepsy, substance abuse, and PTSD [1-6]. The versatility of the method in addressing these conditions has attracted much skepticism from the scientific community [7,8] decelerating progress in the field. A healthy dose of skepticism is certainly necessary and several publications have appeared arguing for the use of controlled research designs [9-11]. However, as we will report in this paper, the brain cannot be so easily fooled. We report on a preliminary analysis of a EEG neurofeedback study that includes a sham-control condition. The main results of the study will be reported elsewhere, but here we focus exclusively on the neural signature that identifies the training condition.

Identifying brain states involves metacognitive processes and the neuroscientific basis of these processes has been widely researched (see for reviews [12,13]). For example, Molenberghs et al. [14] presented participants a video of a person's face, exhibiting an emotional or non-emotional expression. They were then asked to answer a multiple-choice question about the video and rate their confidence in their response accuracy. Molenberghs et al. found that activation in the medial-frontal

region was correlated with participants' subjective confidence and mainly signalled low confidence, whereas the striatal areas signalled high confidence. The medial-frontal region is known to be the neural generator of theta oscillations [15] and therefore the expectation is that mid-frontal theta power relates to metacognitive ability. This was indeed observed in a recent study in which participants were asked to complete a complex categorisation task and then indicate the quality of their decision [16]. Using signal-detection analyses, mid-frontal theta oscillations were specifically associated with metacognitive adequacy.

Given this backdrop, we anticipated that mid-frontal theta oscillations would be related to the detection of training versus placebo condition in placebo-controlled designs. However, the spirit of the placebo-controlled design is that the brain does not discriminate between the actual and placebo conditions. The neural profile of a training block would reflect the experience of the person in that block. Therefore, in the event that a neural signal was to distinguish the two conditions, we expected that the relevant theta-related metric would be the change in theta power across blocks. However, *a priori* it was unclear whether theta power could be used to detect veridical training blocks, sham-control blocks or both.

There are different ways of constructing placebo-controlled designs for neurofeedback research. First, the wait-list design in which one group of participants will not undergo any training for the same duration during which participants in the training group are being trained. Both groups will undergo a pre- and post-training session with cognitive and/or neural assessments to address transfer effects, which controls for practice effects. This design is financially attractive, as participants do

not get paid for the time that they are not in the lab and researchers can train more actual trainees. However, it comes with the caveat that the wait-list group is not engaged with the neurofeedback interface and laboratory environment. This difference might lead to differences in motivation, which could lead to underperformance of the wait-list group on post-"training" assessments. Thus, positive evidence in favour of neurofeedback training might actually be related to the underperformance of the wait-list group. Demonstrating that the wait-list group is not underperforming is key to data interpretation.

Another common control condition is the active control design, in which the group is doing a different neurofeedback training protocol. This is an effective design, as both groups are involved in training and therefore experience the brain-computer interface. However, the success of this design relies on the differential impact of each training protocol on the outcome measures. For example, protocol 1 should enhance performance on task A, whereas protocol 2 has no effect on task A or even decreases performance. If both training protocols change the outcome measures in the same direction then the study is more likely to become underpowered, leading to the incorrect conclusion that each protocol had no impact on the outcome measure.

A third control design (the focus of this paper), is the sham-control condition, in which the control group attends the same number of times as the training group, receives the same instructions and brain-computer interface, but the feedback is not veridical. The feedback might be a playback of a previous recording or a computer-generated sequence of feedback signals. This control condition is usually touted as the best placebo-controlled design, as it avoids the problem of motivation that

plagues the wait-list control design and is theorised to have no impact on the outcome measures (other than practice effects). However, the Achilles heel of this design is that the participant must be unaware of the condition, information easily obtained by the researcher during post-study debriefing. As participants have 50% chance of guessing correctly, the approach is to check whether at the group level, participants were able to identify their group membership. Signal detection theoretical measures, such as d-prime or area under the curve (AUC) are used to demonstrate (the lack of) awareness of group membership. Although lack of awareness is critical to the argument that participants in the control group were not differently engaged with the sham-training than participants in the training group, this is not to say that the brain's ability to detect group membership is of no impact. Given that mid-frontal theta oscillations have been associated with metacognitive processing, we evaluated the possibility that mid-frontal theta can be used to identify group membership in a sham-controlled study.

The current study is part of a larger project involving the influence of congruent versus incongruent instructions on neurofeedback learning. We focus here only on the sham versus training group membership and therefore collapse the method and results across the instruction manipulation. The training protocol was focused on alpha upregulation in order to separate the theta-related processes from the training frequency.

Methods

Participants

A total of 60 participants (33 female) were tested in exchange for £10. Participants in the sham-control group were slightly older ($M = 36.7$ years, $SD = 13.0$ years) than the training group ($M = 32.9$ years, $SD = 10.5$ years), but this was not significantly different ($p > .2$).

Design

This study conforms to a two-groups design where allocation of group membership was randomised. The study was approved by the Local Ethics Committee and was conducted in accordance with the Helsinki Declaration for ethical human research.

Procedure

Prior to the test session, participants self-reported their quality of the previous night's sleep on a 10-point scale. Participants sat in front of the computer screen and completed five blocks of EEG recordings. In the first (baseline) block, participants sat quietly for three minutes with their eyes open. Before each subsequent block, instructions were read aloud to the participants containing guidance on strategies to use during the block. After the final block, a questionnaire debriefed participants and asked about whether they thought they were in the neurofeedback or sham-control group.

Each participant received auditory and visual feedback of the EEG recordings using a Procomp 2 EEG neurofeedback system (sampling rate = 256 Hz). For the neurofeedback group, the absolute frontal alpha power produced an auditory signal every time it was above a threshold for 0.25 seconds. The threshold for the four training blocks was set at 70% of the mean baseline measurement. When artefacts

(e.g., eye blinks) occurred, the system provided a visual signal. The rationale for splitting the veridical EEG feedback and the artefact information over modalities was to enhance the feeling of veracity in the sham-control group. Over the four training blocks, the sham-control group received a pre-recorded stream of auditory feedback signals, while the visual feedback on artefacts was valid and occurred in real time. This enhanced the experience that the participants were receiving real-time audio feedback. This design allowed us to record the EEG activity of all participants for off-line analyses, regardless of the experimental condition.

Data analysis

The raw EEG data was first bandpass filtered between 1 and 40 Hz using a second-order Butterworth filter. The filtered signal was then epoched using Hamming windows of 4 seconds with 50% overlap. Using fast Fourier transformation, the relative frequency spectrum of each window was obtained from which the theta band (4 - 7 Hz) was extracted. The median theta values of the windows were used for further analyses. For each individual, the baseline value was subtracted from the relative power values and the slope of the best-fitting regression line was computed for each person in order to compare the two groups. The sign of the instruction was taken into account.

Results

Both groups self-reported comparable quality of sleep (sham group: 6.92, sd = 1.7; training group: mean = 7.2, sd = 1.85; $t(58) = 0.611$, $p = .54$). Importantly, individuals in both groups were at chance at guessing whether they were in the neurofeedback

training group (sham group: 16/30, neurofeedback group: 14/30). Typically, this is where the researcher would conclude that the sham-control design was a success.

< INSERT FIGURE 1 ABOUT HERE >

Figure 1 presents the relative time frequency spectrum of the neurofeedback and sham-control groups with the positive instructions. Whereas the profile does not change across the four training blocks in the sham-condition, the relative theta power seems to decrease as training continues for the neurofeedback group. Data from one participant in the sham-control group was excluded due to extreme values. The qualitative profiles of significance did not change when this person was included. Figure 2 shows the average slopes of the relative theta power across the training blocks for each group. The slope of the neurofeedback group is significantly different from zero [$t(29) = 2.88, p < .01$] and from the slope of the sham-group [$t(57) = 3.50, p < .001$], which did not differ from zero [$t(28) = 2.03, p > .05$]. No difference in slopes was found when comparing groups defined by guessed group membership (all $ps > .2$).

< INSERT FIGURE 2 ABOUT HERE >

The significant group difference in the change in relative theta power suggests that this measure could be used to correctly identify the participant's group membership. Figure 3 (left panels) shows the frequency distributions of the slopes for actual and "guessed" group membership together with a fitted normal distribution. Figure 3 (right

panel) shows the receiver operating characteristic (ROC) curves for actual and “guessed” group membership. The area under the curve is .73 and .44, respectively, which was only significantly different from chance for the former (two-tailed bootstrapped $p = .0017$, using 100,000 bootstrap samples).

< INSERT FIGURE 3 ABOUT HERE >

Discussion

In this study, we set out to investigate whether people are aware of their group membership in a placebo-controlled neurofeedback design with a specific control group: sham-control. We hypothesised that detection would require metacognitive processes that are supported by frontal cortical regions, which are the generator of theta-band brain oscillations. We observed that although participants did not seem to have conscious awareness of the experimental manipulation, as indicated during the post-study debrief session, the change in relative theta band power showed superior classification accuracy. In other words, even though the person could not detect group membership, their brain could.

This is the first study to address detectability of placebo-controlled designs using neural measures. The findings are relevant to studies and topics outside the realm of neurofeedback and it should be noted that studies like these require many participants to investigate the actual experimental design. There are a number of limitations that future work could resolve. First of all, the neural measure was recorded during the very time period of the experimental manipulation, whereas the

participants were asked about group membership after the electrodes were taken off and their heads were cleaned. These intervening actions could constitute a novelty-induced change in episodic context [17], which has been shown to lead to memory forgetting [18,19]. Thus, it is possible that if participants were asked about group membership as soon as the final block ended or in the middle of a sequence of blocks, their guesses might be more accurate. If so, then it would damage the reputation of the use of sham-control designs. If not, then simply asking a person whether they can guess their group membership is not the most sensitive way to test whether the sham-control methodology was successful. Second, the signal was found to predict whether the person was in the training condition. This means that the very act of neurofeedback training might have produced the change in relative theta power. We speculate below about why this might be. It does mean that the sham-control as a condition “in which nothing happens” is still valid, at least within the current study. An auxiliary analysis revealed that the slope of the relative theta power (a non-target training frequency) correlated with the slope of the relative alpha power (the target training frequency) ($r = -.58, p < .001$), which holds true for both groups (sham-control: $r = -.68, p < .001$; training group: $r = -.47, p < .05$). Thus, it is not the case that the variability in relative power is due to undergoing veridical training. If anything, the association is slightly stronger in the sham-control condition than in the training group. It implies that the slope of the change in theta power carries additional information, which is orthogonal to the association with alpha band activity. Finally, as we had a training and a sham-control group, there was only the option of a two-groups comparison. Ideally, both groups would be compared against a reference group. However, by making the sham-control condition an actual manipulation, we lost our reference and as such a third group would be needed. This

third group would require the same brain-computer interface during the training blocks and an active control condition would be appropriate. The caveat would be that any differences between the active control group and the target training group would be explained by the differences in training protocol, leading to all three groups differing from each other for different reasons. This methodological conundrum would need to be addressed in order to truly test the validity of the chosen placebo-controlled design.

We found that changes in relative theta power were indicative of the veridical training condition. Why the direction should be negative (decrease in slope) is unclear. We could speculate that this is due to the role of the anterior cingulate, the mid-frontal theta generator, in conflict monitoring. The reasoning would be as follows. In each condition, there are two pieces of information: the external feedback and the internal neural signals. In the sham-control condition (but not in an active control condition), these signals are not synchronised and thus are in conflict, leading to increased activation in the anterior cingulate. In essence, the anterior cingulate signals the prediction error [20-22] of not receiving the anticipated external feedback based on current interoception. This signalling of prediction error increases the theta power [23,24]. In the veridical training condition, initially there is conflict, but as the participants learn, they also learn the association between the external feedback and the interoceptive neural processing. Over learning blocks, the conflict decreases concomitantly with the theta power. In effect, the results interpreted this way suggest that our sham-control condition was a success in having a constant level of theta power across blocks. However, change in conflict signal is rewarding and theta oscillations have been associated with reward-based processing [25] and the link

between dopamine-(D1)-receptors in the medial-frontal cortex and theta power [26], thus introducing prediction-based reward processing as an unanticipated confounding factor in the sham-controlled design. It is yet unknown whether the same pattern appears irrespective of the feedback training protocol, but a recent meta-analysis of fMRI neurofeedback studies [27] and theoretical work [28] implicate the basal ganglia as an important neural substrate of the regulatory process underlying neurofeedback learning. In clear terms, sham-controlled neurofeedback designs do not control for the intrinsic level of motivation due to congruent feedback-interoception contingency present in the veridical training group.

To conclude, we observed that even though participants cannot accurately guess whether they were in the sham-control or veridical training condition, the brain is able to make this distinction. This finding suggests that sham-controlled designs may be inappropriate for neurofeedback studies where the same object under investigation (i.e., the brain) is also detecting the experimental manipulation. Alternative control designs should be utilised, such as active control or wait-list control designs. Nevertheless, all designs would need to address whether the neural detection of the veridical training condition influences the learning within that training condition.

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Figure captions

Figure 1. Time-frequency plots for the sham-control and neurofeedback training groups over the testing session. The redder the colour, the higher the relative power in that frequency. Note the decrease in relative theta band power (4-7 Hz) for the neurofeedback group.

Figure 2. Average slopes of relative theta power across training blocks for the sham and neurofeedback group. Error bars represent standard error of the mean.

Figure 3. Left panels: Frequency distributions of the slopes for sham-control (in blue) and neurofeedback training (in red) groups. The slopes are inverted in order to have the neurofeedback group on the right side of the panels. Right panel: ROC curves based on the frequency distributions, where a “hit” reflects accurately detecting the neurofeedback group classification.

Figure 1

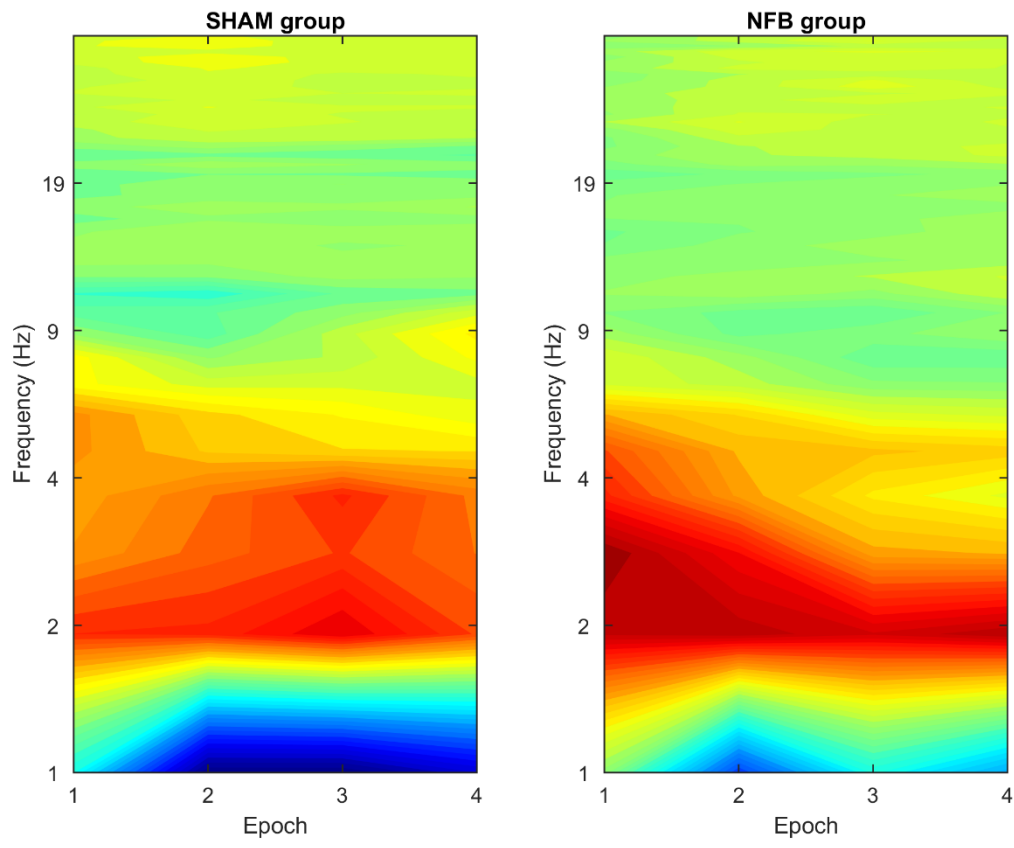


Figure 2

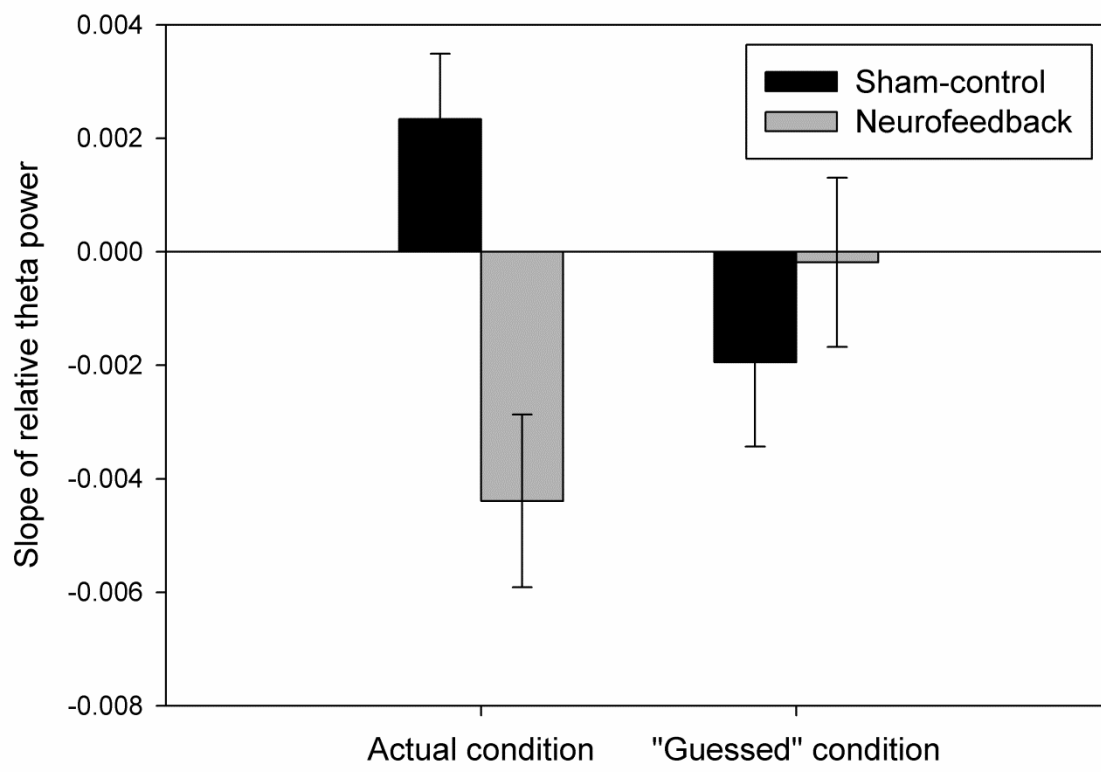


Figure 3

