OSF preregistration:

Releasing the Ghosts: Desynchronizing Alpha Default Mode Activity to Reduce Rumination in Depression Patients

(Based on Reinhart & Nguyen, 2017)

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Study Information

1. Title

Releasing the Ghosts: desynchronizing alpha default mode activity to reduce rumination in depression patients

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3. Description

This study aims to investigate whether a desynchronization of the default mode network (DMN) can lead to a reduction of rumination in major depressive disorder (MDD) patients.

Numerous studies and recent meta-analyses show that MDD is consistently associated with altered activity in the DMN. These alterations include changes in activation of regions of the DMN (Chou et al., 2023; Zhou et al., 2020), changes in functional connectivity within the DMN (Wue et al., 2011) as well as increased coherence in the alpha frequency between regions of the DMN (Khan et al., 2022).

Rumination can be defined as an internal way to cope with negative mood by self-reflection and repetitive, passive focus on one's negative emotional states (Treynor et al., 2003). In this study, rumination will be assessed using the Rumination Response Scale (RSS) (Treynor et al., 2003). Specifically, we will use the 'brooding' dimension of this scale, which has been shown to have good psychometric properties (Schoofs et al., 2010). It was also shown to be both cross-sectionally and prospectively related to depression (Burwell & Shirk, 2007).

Increased activity in the DMN might foster rumination due to its role in self-referential processing and suppression of sensory information (Zhou et al., 2020). These introspective processes are associated with increased alpha activity in core regions of the DMN, including the ventromedial prefrontal cortex (vmPFC), the posterior cingulate cortex and the precuneus (Bowman et al., 2017). Ray and colleagues (2023) found increased connectivity in the alpha band between core regions of the DMN including medial prefrontal nodes and parietal regions in patients with remitted MDD patients in comparison to healthy control subjects. A recent study investigated whether coherence between cortical nodes of the DMN can serve as a biomarker for MDD diagnosis in combination with machine learning (Khan et al., 2022). They found that MDD patients displayed stronger coherence within the DMN (Khan et al., 2022). Their approach reached an accuracy of >98% to detect MDD patients (Khan et al., 2022). Notably, this accuracy was even reached when only including a single pair of EEG electrodes, for example one electrode over the medial prefrontal cortex and one over the precuneus (Khan et al., 2022). These results further demonstrate that altered functional connectivity between core nodes of the DMN plays a crucial role in MDD.

This study aims to tackle these altered patterns of connectivity and coherence within the DMN by applying anti phase transcranial alternate current stimulation (tACS) to cortical nodes of the DMN. Anti-phase tACS induces alternate current which is phase shifted by 180 degrees. Applied to two regions, prolonged anti phase tACS leads to a relative decoupling of the targeted areas (Reinhart, 2017).

In this study, anti-phase tACS will be applied in the alpha band over the vmPFC and the precuneus. These core regions of the DMN and their synchronized activity within the alpha spectrum are expected to be involved in rumination Thus, a decoupling of these areas due to repeated stimulation is expected to reduce ruminative symptoms in MDD patients.

4. Hypotheses

H1: MDD patients show higher levels of rumination than healthy controls (HC).
Prediction: Before and after sham stimulation, MDD patients will score significantly higher on rumination measured by the RSS than the healthy control group. The group (MDD, HC) has a significant main effect on the dependent variable rumination, but not time (before, after stimulation). No interaction is expected.

H2: MDD patients display stronger phase synchronization in the alpha band between the vmPFC and the precuneus than HC subjects
Prediction: Before and after sham stimulation, vmPFC-precuneus alpha phase synchronization measured by EEG and quantified by their phase-locking value (PLV) will be significantly larger in MDD patients compared to the HC group. The group (MDD, HC) has a significant main effect on the dependent variable alpha PLV, but not time (before, after stimulation). No interaction is expected.

H3.1: Repeated anti-phase tACS in the alpha band over the vmPFC and the precuneus will reduce the alpha phase synchronization between these regions in MDD patients compared to baseline levels
Prediction: After 4 weeks of intervention, vmPFC-precuneus alpha phase synchronization measured by EEG and quantified by their phase-locking value (PLV) will be significantly decreased in the MDD intervention group compared to baseline levels.

H3.2: Repeated anti phase tACS in the alpha band through electrodes over the vmPFC and the precuneus will reduce the alpha phase synchronization between these regions in the active stimulation MDD group compared to the MDD sham control group
Prediction: After 4 weeks of intervention, vmPFC-precuneus alpha phase synchronization measured by EEG and quantified by their phase-locking value (PLV) will be significantly smaller in the MDD intervention group compared to the MDD sham control group. The interaction effect of time and group will be significant.

H4.1: Repeated anti-phase tACS in the alpha band through electrodes over the vmPFC and the precuneus will reduce rumination in MDD patients compared to baseline levels

Prediction: After 4 weeks of intervention, rumination as measured by the RSS will be significantly decreased in the MDD intervention group compared to baseline levels.

H4.2: Repeated anti-phase tACS in the alpha band through electrodes over the vmPFC and the precuneus will reduce rumination in the active stimulation MDD group compared to the MDD sham control group
Prediction: After 4 weeks of intervention, rumination as measured by the RSS will be significantly smaller in the MDD intervention group compared to the MDD sham control group. The interaction effect of time and group will be significant.

Design Plan

5. **Study type**

Experiment - A researcher randomly assigns treatments to study subjects; this includes field or lab experiments. This is also known as an intervention experiment and includes randomized controlled trials.

6. **Blinding**

The subjects will not know the treatment group to which they have been assigned.

Personnel who collect and analyze the data from the study are not aware of the treatment applied to any given group.

7. **Is there any additional blinding in this study?**

Participants are not aware of the hypotheses surrounding the measurements and manipulations. After completion of the measurements, participants will be debriefed. If the results confirm our hypotheses, MDD participants form the sham condition will be invited to a follow up study in which they will receive active stimulation.

8. **Study design**

This experiment will have a mixed design with three groups. One group is the treatment group, which consists of MDD patients, and which receives active stimulation. A second group also consists of MDD patients but receives sham stimulation only. A third group consists of healthy control (HC) subjects and receives sham stimulation only. The stimulation period will last 4 weeks. Each week, every participant will receive stimulation on two days which are at least two days apart from each other.

9. **Randomization**

MDD patients will be randomly assigned to one of two groups (active stimulation and sham control group). Randomization will be done in R.

Sampling Plan

10. Data collection procedures (required)

MDD participants will be recruited through advertisements at the department of psychology, advertisements at local social services and psychiatric hospitals and through a social media campaign. All MDD participants must have been previously diagnosed with major depressive disorder and score higher than 25 points on the Beck Depression Inventory BDI-II during a first screening day. Healthy control subjects will be recruited through advertisements at the department of psychology and through social media. Participants will receive 140 SEK for each begun hour of participation. All participants must at least be 20 years old but younger than 60 years. Participants will be excluded if they meet at least one of the following criteria: metal implants in head, implanted electronic devices, head injuries, skin sensitivity, claustrophobia, pregnancy, dementia, and other neuropsychiatric comorbidities such as schizophrenia or ADHD.

11. Sample size

Each group will consist of 100 participants, resulting in a total of n = 300 participants.

12. Sample size rationale

We used the software program G*Power 2 to conduct a power analysis. Our goal was to obtain 80% power to detect a medium effect size of $d = 0.4$ at the standard .05 alpha error probability in an independent two-tailed t-test.

Variables

13. Manipulated variables

The primary manipulated variable will be the active vs. sham tACS stimulation. The sham stimulation will consist of no active stimulation, whereas the active stimulation consists of an anti-phase alpha frequency stimulation.

We will use a high definition tACS device (M x N nine channel) from Soterix medical. The 12mm electrodes will be implemented in a BrainCap and filled with conductive gel. The active stimulation will be performed over the vmPFC and the precuneus, with a peak-to-peak intensity of 2 mA. The specific alpha frequency used form stimulation will be tuned to each

subject specifically. To determine the subject specific frequency, we will run a short (25 minute) EEG session on the screening day of each subject. This data will be analyzed for alpha vmPFC-precuneus PLV for all frequencies from 8 to 13 Hz in increments of 0.1 Hz. The calculation of PLV is described below. For each subject, the frequency that displayed the highest PLV will be chosen for stimulation. The placement of the electrodes will be guided by current-flow modelling, for which we will perform a small pilot study with n=10 subjects. We aim to optimize the placement of the electrodes to effectively stimulate the vmPFC and the precuneus.

The stimulation in all conditions will be performed over a span of 4 weeks. Each week, every participant will receive stimulation on two days, with at least 2 days between dates. On each day, the stimulation will be performed for 60 minutes with eyes closed, while participants listen through speakers to an audiobook of their choice.

14. Measured variables

Rumination

Rumination will be assessed with the Rumination Response Scale (RSS) by Treynor and colleagues (2003). Specifically, we will focus on six out of the 22 items, that were identified by Burwell and Shirk (2007) as the 'brooding' subscale.

Of these six items, a composite score will be computed by calculating the mean of these items for each subject. For all groups at each measurement time-point, group means and standard deviations will be calculated.

EEG: Recording & Preprocessing

We will perform EEG recordings of all subjects on the first and last day of the intervention. Each EEG recording will last 30 minutes, while participants are asked to sit with closed eyes and rest calmly in a sound-proof chamber. The recorded EEG signal will be high-pass filtered at 0.1 Hz and low-pass filtered at 170 Hz. The EEG signal will then be split into segments of 10 seconds. Visual inspection will be performed to remove any muscle artifacts. An independent component analysis will be performed to detect and remove any blink and noise artifacts.

The EEG signal will then be projected into source space. We will use the software CURRY 7.0 to create a head model with white and gray matter, compact and spongy bone, CSF and skin as layers. The source grid will consist of voxels in a 1cm spacing, resulting in a grid of 3294 voxels. The subject specific electrode positions will be detected using CapTrak. Then, we will use a linearly constrained minimum variance (LCMV) beamformer to project the EEG data into source space.

EEG: Source-level phase-locking value (PLV)

To quantify phase synchronization, the PLV of the alpha frequencies localized in source space in the vmPFC and the precuneus will be calculated. This will be done for each pair of voxels that is associated with each area. The PLV will be calculated for alpha frequencies between 8

Hz and 13 Hz (in incremental steps of 0.5 Hz) and finally averaged over these frequencies. To calculate PLV, the following formula will be used:

$$\mathrm{PLV} = \frac{1}{N}\left|\sum_{n=1}^{N} e^{i(\theta_1(n)-\theta_2(n))}\right|$$

where N is the number of sampled time points and θ_1 and θ_2 are the instantaneous phase values at time point n (Reinhart & Nguyen, 2019).

Analysis Plan

15. Statistical models

H1: Mixed measures ANOVA with time (baseline, after sham stimulation) as within-subject factor and group (MDD, HC) as between-subject factor. The dependent variable is rumination as measured by the RSS. We will perform F-tests for the main effects of time, group, and the interaction effect.

H2: Mixed measures ANOVA with time (baseline, after sham stimulation) as within-subject factor and group (MDD, HC) as between-subject factor. The dependent variable is the alpha PLV between vmPFC and precuneus. We will perform F-tests for the main effects of time, group, and the interaction effect.

H3.1: Dependent-sample two tailed t-test between two time points (baseline, after stimulation) within the active stimulation MDD group. The variable on which the time points are compared is alpha band PLV between the vmPFC and precuneus.

H3.2: To test for group differences (MDD sham vs. MDD stimulation) in alpha band PLV between the vmPFC and precuneus after intervention, an independent samples two-tailed ttest will be used. To test for an interaction effect, we will use a mixed measures ANOVA with time (baseline, after sham stimulation) as within-subject factor and group (MDD, HC) as between-subject factor. The dependent variable is the alpha PLV between vmPFC and precuneus. We will an perform F-tests for the interaction effect.

H4.1: Dependent-sample two-tailed t-test between two time points (baseline, after stimulation) within the active stimulation MDD group. The variable on which the time points are compared is rumination measured by the RSS.

H4.2: To test for the group differences (MDD sham vs. MDD stimulation) in rumination as measured by the RSS after stimulation, an independent samples two-tailed t-test will be used. To test for an interaction effect, we will use a mixed measures ANOVA with time (baseline, after sham stimulation) as within-subject factor and group (MDD, HC) as between-subject

factor. The dependent variable is ruminations as measured by the RSS. We will perform a Ftests for the interaction effect.

16. Inference criteria

Statistical significance: For all statistical tests we will use the standard alpha level of $p < .05$ to determine the significance of the effect.

Effect sizes: For t-tests, Cohen's d will be reported. For ANOVAs, partial and generalized eta squared will be reported.

17. Data exclusion

EEG: Data with massive artifacts will be removed before analysis, based on visual inspection.

Outliers: Participants who deviate more than 2.5 standard deviations in rumination or mean alpha PLV from their group mean will be treated as outliers and excluded from the analysis.

Awareness check: To check for the efficiency of the blinding, we will ask all participants after the intervention whether they were aware of the experimental design and whether they can determine with confidence, which group they belonged to. Subjects who have been aware of their group allocation will be excluded from the analysis.

18. Exploratory analysis

After the confirmatory analysis described above we will use all 22 items of the RSS to explore whether the factor structure reported in previous literature (Treynor et al., 2003; Burwell & Shirk, 2007) is replicated in our sample. We will use an exploratory factor analysis to extract the factors found in our sample to repeat the abovementioned analyses with each extracted factors of the scale to report whether the results differ between subtypes of rumination.

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