A randomized controlled trial into the efficacy of neurofeedback for treatment of major depressive disorder

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON41680

Source
ToetsingOnline

Brief title
Neurofeedback for depression

Condition

- Mood disorders and disturbances NEC

Synonym
depression, major depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: depression, neurofeedback, treatment

Outcome measures

Primary outcome

Main outcome measures are the Quick Inventory of Depressive Symptoms (QIDS-SR), the Hamilton Depression Rating Scale (HDRS), the Remission from Depression Questionnaire (RDQ) and change in AA between frontal cortical regions.

• The QIDS-SR is a 16-item self-rating scale to assess symptom severity of MDD and will be administered prior to each NF session (3 times a week).

• The HDRS is a 17-item clinician-rated scale for estimating severity of depression during the past week. It will be administered once a week by a trained research assistant during the 6-week study period.

• The RDQ is a 41-item self-rating scale that measures symptomatic and functional remission from depression. It will be administrated once a week during the 6-week study period.

• AA in frontal regions (F3-F4) will be calculated as described in the intervention paragraph above. Based on results from our studies in healthy volunteers and depressed participants, no changes in AA in the sham-condition can be expected as opposed to significant decreases in AA in the active condition.

Secondary outcome

• The State and Trait Anxiety Inventory (STAI). This instrument measures state and trait anxiety symptomatology.

• RAND-36. Based on 36 items, this instrument measures the general health on

several dimensions.

• Age, gender, duration of current depressed episode, marital status,

educational level.

Study description

Background summary

Evidence-based treatments for major depressive disorder (MDD) possess moderate efficacy. However, applicability, availability and acceptability of these treatments are limited. Antidepressant treatment is not acceptable for a vast number of patients with MDD, resulting in high rates of non-compliance. Short-term psychotherapy is not effective in the majority of these patients and not routinely available. Moreover, It is estimated that at least 10-20% of all patients do not respond at all to these treatments even when applied simultaneously and in residential contexts. Therefore, new, acceptable, and efficacious treatments for MDD will help to fill the therapeutic gap that is left by current evidence-based treatments.
There is a growing interest in neurofeedback (NF) as a treatment for psychiatric disorders including MDD. It is thought that this technique, within an operant conditioning framework, helps individuals to regulate cortical elektroencephalographic (EEG) activity while receiving feedback from a visual or acoustic signal. The resulting change in EEG activity is presumed to be associated with a change in underlying cortical activation, and subsequently to result in a reduction of associated psychiatric symptoms. NF is an outstanding example of a non-invasive brain-computer interface which may be particularly appealing to younger patients. Despite widespread claims of efficacy of NF in MDD, the scientific literature consists only of some case-reports and 1 case-control study.
Nevertheless, NF may be an efficacious treatment for MDD. Results from fundamental research indicate that MDD appears to be characterized by relatively more left than right resting (alpha, 8-13 Hz) activity in prefrontal regions, although some inconclusive studies exist . This finding has become known as alpha-asymmetry (AA) in MDD. AA is considered as a representation of reduced approach-related behaviours and reduced sensitivity to rewards in MDD.

Study objective

In this study, we have the following research objectives:
1. To examine if NF, by applying the above mentioned AA-protocol, is an efficacious treatment for major depressive disorder. We will conduct a RCT in which active NF will be compared to sham-NF. We expect an equivalent efficacy

in comparison to existing treatments.
2. To examine the associations between changes in elektrophysiological cortical activity and clinical outcome.
3. To address the specificity of the intervention on the target cortical locations (F3-F4) and the target brain-waves (alpha activity) in the real and sham condition. Changes in other frequencies and locations are expected to be minimal.
4. To examine underlying changes in elektrophysiological cortical activity in both real as well as sham-NF. We expect that some participants in the sham-condition will improve due to non-specific factors like activation (coming to the lab on a regular basis), and the attention by the research team. The current project provides a unique opportunity to study temporal changes in brain-activity as a result of a placebo-intervention. Earlier research used brain-imaging techniques that only provided pre-post cross-sectional data.
5. To examine enduring therapeutic effects at 3 months follow-up.

Study design

RCT with 50 participants of which 25 will receive active neurofeedback treatment and 25 will receive sham-neurofeedback. Both participants and all members of the research team will be blind to the condition applied to each participant.

Intervention

After signing informed consent, participants will be invited to the neurofeedback laboratory of the school for Mental Health and Neuroscience (MheNS). This laboratory is a facility that meets the requirements as outlined in NEN 60601 by the Nederlands Normalisatie-instituut. The intervention will take place while participants sit behind a table and look at a monitor on top of this table. The monitor displays a visual feedback signal (thermometer) based on real-time analysis of their elektrophysiologidal data. The participants are instructed to raise the bar of the thermometer (which is indicative of a decrease in AA). During the NF sessions, while being in the laboratory, participants are in constant contact with the research assistant through an audio-channel, additionally there is constant video-surveillance. Prior to the NF session, depression-severity will be assessed (see outcome measurements)
EEG-elektrodes will be attached following the international 10-20 system at F3, F4, C3, C4, P3 en P4. EEG will be referenced by 2 elektrodes attached to the earlobes. Under and above the left eye an elektrode will be placed to measure EOG. The elektrode will be applied after cleaning the skin with scrubgel. The impedance on all locations will be kept lower than 5 K*.
Each 0.512 second, the power within the alpha frequency band (7.8 Hz - 13.1 Hz) of both F3 and F4 is calculated. AA at F3-F4 will computed as the difference of the natural log-transformed F3 and F4-alpha power. Based on this calculation,

subjects will receive AA visual feedback on a flatscreen. Goal in each session is to decrease the asymmetry in comparison to the asymmetry as assessed at baseline prior to each session.
The sham-NF will be delivered with the same data acquisition protocol, but the AA will be randomly multiplied by +1 or -1, which reduces the correlation between measured brain activity and the visual feedback signal to almost zero.
Prior to the start of the study, an independent, non-involved technician will generate the randomization sequence (using the sequence generator on www.random.org) and pre-program the NF equipment accordingly in a random sequence of real and sham NF treatments for consecutive participants. A research assistant will only have to activate the NF procedure without knowing whether a real or sham treatment is applied. In this fashion, each participants will be double blind assigned to either a real of a sham NF-treatment.

At the start of each NF session, the baseline EEG is being measures without NF to assess baseline AA which serves as a starting point for feedback. Measuring baseline prior to each session is necessary as can be expected that, at least in the active arm, AA decreases over time. Data collection will be channeled through an acquisition PC with a BrainAmp DC EEG amplifier (Brain Products) using a 1000 Hz sample frequency. Online calculations are done by a filter written for BrainVision RecView. The data will be epoched online into 2.048-s epochs that overlap by 75% and then transformed by a fast Fourier transform (FFT) to the frequency domain (frequency resolution 0.488 Hz). Every 0.512 second, the power within the alpha frequency band (7.8 Hz - 13.1 Hz) of both F3 and F4 will be calculated. AA is computed as the difference of the natural log-transformed F3 and F4-alpha power: Ln(F3-alpha) - Ln(F4-Alpha). Current asymmetry is subsequently compared to the personal mean baseline asymmetry. The result of the calculation will be sent to a stimulus PC running Presentation stimulus delivery software (Neurobehavioral Systems) with an 8-bit parallel port (LPT-port) to control a paradigm showing a visual representation of the asymmetry. In the Presentation paradigm, the last 20 values of the asymmetry are used in a moving average to prevent *jitter* in the feedback. Participants receive feedback with visual feedback; they are instructed to increase the level of a thermometer that is shown on a flatscreen. Additionally, a numerical score below the thermometer indicates their actual total performance. This score is adjusted (i.e. increased) continuously by a number ranging from 0 and 128, depending on the level of the thermometer. In this way a good actual performance (a shift in asymmetry in the desired direction) results in an increasing total score. A big shift in the desired direction results in a rapidly increasing total score, whereas a small shift in the desired direction results in a slow increasing total score. A shift in the undesired direction produced no change in total score. The purpose of this total performance score is to give participants feedback on the differential effect of the sessions.

After informed consent is obtained, the NF intervention will consist of 18 sessions, each lasting 3 x 6 minutes divided by 2 breaks of 4 minutes. Prior to

and after each session, baseline EEG alpha-activity will be measured at right- and left frontal regions. Sessions will be done 3 times a week. Based on our pilotdata in which clinical response emerged between 15-20 NF sessions, the total intervention will consist of 18 sessions during 6 weeks to minimize burden on participants. If no clinical response occurs, participants will be offered an evidence-based treatment at the unit for treatment of mood disorders at the RIAGG Maastricht. Additionally, the NF treatment will be stopped in cases of severe suicidality (HDRS item # 3 with a score >2) or severe depression symptomatology (HDRS score > 25). In these cases, the research assistant will contact the principal investigators who will responsible for referral for standard depression treatment.

Study burden and risks

Participants will be receive written and verbal information about the procedure and have the right to discontinue participation at any moment. Partcipants wil receive either an experimental or sham experimental treatment for their depressive disorder. To minimize burden resulting from participation in the study, the duration of the study is kept to a maximum of 6 weeks. This duration is based on data from our pilot-study and is totally comparable to the duration of RCT*s that examine novel antidepressants with the use of placebo. Given the extensive waiting-lists for regular evidence-based treatments for depression (3-4 months), participation in the study does not lead to additional delay in the start of standard therapy. Thus, those participants that wish to receive standard antidepressant treatment after participation in the study, will receive such treatment within a normal time-frame.
As mentioned earlier, no side-effects of NF are reported in the literature. Moreover, in our pilot-study in depressed participants, we did not observe any side-effects.
There will be an independent physician available to address all questions and concerns of potential participants. All participants will provide written informed consent. Their data will be collected in a anonymized in a central database in our laboratory. Participants can withdraw consent at any moment without any restrictions. If requested, all participants can be informed of the final results after completion of the study.
As already indicated, we carried out a pilot-study in depressed participants with application of the same NF intervention as described in the current proposal. No complications occurred during this study. The MEC approved this study, correspondence can be found under reference number MEC 08-2-115.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Primary axis-1 disorder of Major Depressive Disorder fulfilling DSM-IV-TR criteria.
• Written informed consent.

Exclusion criteria

• History of brain trauma (commotio or contusio cerebra) or CVA
• Current use of antipsychotics, moodstabilizers or benzodiazepines. Current use of antidepressants is permitted if this medication is not changed within a period of 6 weeks prior to participation in the study. Additionally, no changes in antidepressant medication are allowed during active participation in the study.
• Chronic depression (> two years duration).
• Dysthymia as a primary axis-1 diagnosis
• Bipolar disorder or schizophrenia as a primary axis-1 diagnosis
• Severe suicidality (HDRS item # 3 with a score >2) or severe depression symptomatology (HDRS score > 25).
• Pregnancy.
• Age < 18 years.

• Daily alcoholintake of >7 units.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2014
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	12-08-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-09-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL44637.068.13