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# Improving emotion regulation in depression using real-time fMRI-based neurofeedback

**Submission date**
28/10/2022

**Recruitment status**
No longer recruiting

**Registration date**
01/11/2022

**Overall study status**
Completed

**Last Edited**
29/12/2023

**Condition category**
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

## Plain English summary of protocol

Background and study aims
Major depressive disorders (MDD), commonly known as depression, have a high prevalence worldwide. Patients suffering from depression have deficits in emotion-processing brain regions and networks. This highlights emotional biases in depression patients, as patients show selective or enhanced brain reactions to negative emotions, while the processing of positive emotions is reduced. Modern neuroimaging methods such as real-time fMRI-based neurofeedback can help patients self-regulate their dysfunctional brain regions by presenting them with feedback on their own brain activity. By modulating brain responses through appropriate cognitive strategies, patients can improve their emotion regulation skills.
The researchers' goal was to use these findings to address positive and negative emotional biases in depression. In this experimental MRI-based intervention, patients are shown faces with different emotions ranging from fearful to happy. They are asked to make neutral faces more happy by actively using positive strategies while decreasing facial fearfulness to reduce anxiety symptoms. This approach serves as a therapeutic measure by allowing patients to learn to control their dysfunctional brain activity. It is non-invasive and has no major side effects, hence it is safe. Most importantly, it focuses on a fundamental human trait, our ability to learn. This study aims to evaluate the effectiveness of such an innovative neurofeedback modality in improving the symptoms associated with depression.

Who can participate?
Right-handed adults (18-65 years of age) diagnosed with unipolar depression and on stable antidepressants, who do not have MRI contraindications such as metal implants, brain tumors, pregnancy and other neurological comorbidities like epilepsy or stroke.

What does the study involve? (for participants)
Participants learn to up- and down-regulate their brain (amygdala) activity by using emotion regulation strategies in response to dynamic facial stimuli which also act as a feedback signal. They learn to control their emotional responses simply by changing the facial expression of the naturalistic stimuli. Participants complete two sessions (four training runs/session) of neurofeedback training and MRI-based cognitive tasks with a psychometric assessment before and after neurofeedback training.

What are the possible benefits and risks of participating?
The fMRI neurofeedback is a non-invasive brain-based procedure that is safe with no major risks. There are no direct benefits to the patients for participating in the study. However, patients may learn to establish brain responses by developing regulation strategies to overcome depressive symptoms.

Where is the study run from?
Psychiatric University Hospital, Zurich (Switzerland)

When is the study starting and how long is it expected to run for?
June 2017 to November 2022

Who is funding the study?
University of Zurich (Switzerland)

Who is the main contact?
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# Contact information

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## Additional identifiers

### Clinical Trials Information System (CTIS)
Nil known

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
Nil known

## Study information

### Scientific Title
Real-time fMRI-based adaptive amygdala neurofeedback using dynamic human facial stimuli to target affective biases in depression

### Study objectives
Real-time fMRI-based adaptive amygdala neurofeedback reduces depression-associated negative and positive affective biases.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approved 01/10/2017, Cantonal Ethics Commission of Zürich (Stampfenbachstrasse 121, 8090 Zürich, Switzerland; +41 (0)432597970; admin.kek@kek.zh.ch), ref: BASEC ID. 2017-01306

## Study design
Single-center interventional single-blinded randomized placebo controlled within subject proof-of-concept trial

## Primary study design
Interventional

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Patients diagnosed with mild to moderate unipolar depression (major depressive disorder, MDD)

## Interventions
The researchers employed a pseudo-randomization method in which patients were alternately assigned to the two experimental groups.

The study involves five visits. Visit 1 (day 0): pre-training clinical and MRI assessment; Visit 2 (day 1): neurofeedback training session 1; Visit 3 (day 2): neurofeedback training session 2; Visit 4 (day 3): post-training clinical and MRI assessment and Visit 5 (day 56): follow- up assessments similar as the fourth visit.
MDD patients perform eight neurofeedback runs spread across two training sessions (four runs /session) on two consecutive days (Visits 2 and 3). Patients are briefed about the amygdala feedback and asked to try to change the emotional expression of the dynamically changing facial stimuli. The change in the valence of the emotional face is linked to the patient's ongoing amygdala activity. Each training run consisted of the two alternatively arranged happy-up and fear-down regulation blocks.

In the 'Happy-up' condition, patients are asked to make the presented neutral facial stimulus happier through amygdala upregulation by using mental strategies of their choice.

In the 'Fear-down' condition, they are instructed to reduce the fearfulness of the facial stimulus to neutral by downregulating amygdala activity using relevant mental strategies.

To control for non-specific training effects, each training run has alternative experimental and sham conditions. In the experimental condition, the continuously updated feedback as changing intensity of the facial expression reflects the patient's ongoing amygdala activity. In the sham condition, the feedback is generated based on the patient's performance in the preceding experimental condition.

Arm 1: Happy-up Group
Patients receive real/experimental feedback in the happy-up condition and a sham feedback in the fear-down condition.

Arm 2: Fear-down Group
Patients receive experimental feedback in the fear-down condition and a sham feedback in the happy-up condition.

## Intervention Type
Behavioural

### Primary outcome(s)
Depressive symptoms measured using clinician administered 21-item Hamilton Depression Rating Scale (HAMD-21) and the Montgomery-Asberg Depression Rating Scale (MADRS) at pre-training (visit 1), post-training (visit 4) and follow-up (visit 5).

### Key secondary outcome(s))
1. Positive and negative affectivity measured using the self-rated Snaith-Hamilton Pleasure Scale for Depression (SHAPS-D) and State and Trait Anxiety Inventory (STAI), respectively, at pre-, post-training and follow-up.
2. Self-control and self-efficacy assessment performed using the self-rated Competence and Control Beliefs Questionnaire (FKK) at pre-, post-training and follow-up.
3. Mood states measured using the Multidimensional Mood State Questionnaire (MDBF) at pre-, post-training and follow-up.
4. Valence and arousal ratings of happy, fearful and neutral facial stimuli measured by the face rating task at pre-, post-training and follow-up.
5. Patients' amygdala activity measured in response to the happy, fearful, and neutral facial stimuli in the pre- and post-training transfer tasks.
6. Patients' amygdala activity measured in response to the happy, fearful, and neutral facial stimuli using dynamic emotion matching task at pre-, post-training and follow-up.
7. Resting-state functional connectivity measured at pre-, post-training and follow-up.

### Completion date
30/11/2022

## Eligibility

### Key inclusion criteria
1. Right-handed adults (18 - 65 years of age) with normal vision.
2. Primary diagnosis of unipolar depression based on DSM-IV.
3. Currently in a depressive episode with/without stable SSRI antidepressant medication or oral contraceptives and with/without co-morbid anxiety.
4. Fluent in German without any intellectual deficits (basic education completed).

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
18 years

### Upper age limit
65 years

### Sex
All

### Key exclusion criteria
1. Relevant Axis-1disorders: F0 (organic disorders), F1 (alcohol, opioids, etc), F2 (psychotic disorders), bipolar disorder, prominent F4 disorders (i.e., PTSD, Panic disorder), main diagnosis F6 (particularly emotionally unstable personality disorder), known F7 disorder.
2. Neurological comorbidities such as epilepsy, stroke, brain tumor, and traumatic brain injury based on the MINI Neuropsychiatric assessment.
3. Patients on antipsychotics, benzodiazepines, medications such as Temesta (>1-2 mg/day), Methadon or Haloperidol except for SSRI antidepressants.
4. Alcohol, nicotine, or other substance dependence per DSM-IV criteria.
5. MRI contraindications such as pregnancy, lactation, brain surgery, or metallic implants.

### Date of first enrolment
19/08/2021

### Date of final enrolment
29/09/2022

## Locations

### Countries of recruitment
Switzerland

### Study participating centre
**Psychiatric University Hospital, Zürich**
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## Sponsor information

### Organisation
University of Zurich

### ROR
https://ror.org/02crff812

## Funder(s)

### Funder type
University/education

### Funder Name
Universität Zürich

### Alternative Name(s)
University of Zurich, Switzerland, University of Zurich, UZH

### Funding Body Type
Government organisation

### Funding Body Subtype
Universities (academic only)

### Location
Switzerland

## Results and Publications

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository (Open Science Framework, OSF). The anonymized datasets include brain imaging data and clinical test scores. Experimental and data analysis scripts will be shared upon completion of the study. Informed consent in accordance with the Declaration of Helsinki has been obtained from the participants.

### IPD sharing plan summary
Stored in publicly available repository

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | | 18/12/2023 | 29/12/2023 | Yes | No |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |