Neurofeedback for Treating Depression: An Emerging Application of Real-Time Functional MRI

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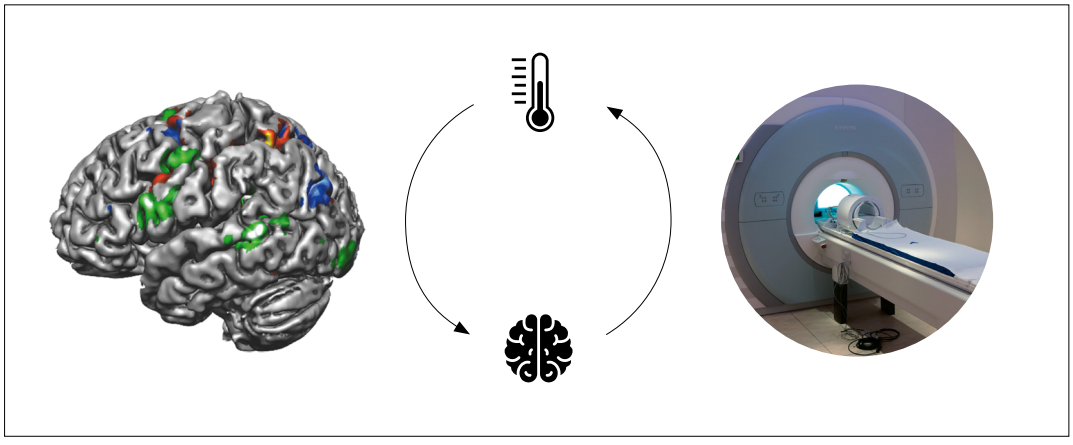
Abstract

In functional MRI (fMRI) neurofeedback, a closed-loop brain-computer interface enables participants to learn self-regulating brain activity using real-time information from their brain (Fig. 1). This method is increasingly being used in scientific and clinical settings. Several 3 Tesla studies have shown the promise of this approach as an add-on treatment for depression, helping patients improve emotion regulation and self-efficacy. Traditional neurofeedback, which uses mean activity from emotion-related areas, cannot distinguish specific emotions. It is therefore unclear whether a patient is engaging in a positive or negative emotional mental state. To address this ambiguity, a new semantic neurofeedback approach maps individual emotions onto a two-dimensional space and visualizes the current emotional state as a moving point on that map. This technique allows participants to navigate their emotional space, thereby offering clearer and potentially more effective therapy for depression. A 7-Tesla proof-of-concept study shows promise for this new real-time fMRI neurofeedback method.

Introduction to functional MRI neurofeedback

Functional magnetic resonance imaging (fMRI) has revolutionized the study of the human brain. By enabling high-resolution, non-invasive recordings of the blood oxygenation level dependent (BOLD) response, it provides indirect measures of neuronal activity [1–4]. While in many cases, the fMRI analysis is being performed quite some time after the data has been acquired, real-time fMRI (rt-fMRI) systems were developed already shortly after the inception of fMRI [5]. They process the data during scanning — i.e., as soon as it is acquired. Although the potential of rt-fMRI for quality assurance, functional localizers, intra-operative studies, and teaching has long been recognized, the uptake has been rather slow. However, the interest in rt-fMRI increased with the invention of fMRI neurofeedback about 20 years ago. One of the first neurofeedback publications [6] describes how optimized brain-imaging software (developed by this paper's co-author, Rainer Goebel) performed incremental data analysis almost as comprehensively as standard offline data



1 Real-time fMRI neurofeedback as a closed-loop system.

analysis. This included motion correction, spatial and temporal filtering, and statistical analysis of the fMRI signals from the entire brain using a recursive general linear model (for an overview of currently employed methods, see [7]). Most importantly, the software allowed to interactively select multiple brain regions, from which the neurofeedback signal was calculated and shown as visual feedback (time-course displays) to the participants in the scanner during ongoing functional scanning. The paper concluded that this novel approach meant fMRI-guided self-regulation would become feasible for healthy participants and patients.

Application in depression treatment

Despite this promising outlook, it took almost 10 years until the first psychiatric application of fMRI neurofeedback was published providing activity feedback from emotion-related brain areas in patients with depression [8]. In this 3-Tesla study, the mean activity from emotion-related areas was provided on a thermometer-like display that showed participants whether they had successfully engaged in emotional mental states during neurofeedback blocks. After only four neurofeedback practice sessions (separated by about a week), patients showed a significantly improved ability to regulate their emotions, which was accompanied in most patients by a substantial reduction of depression symptoms, as measured with the Hamilton Depression Rating Scale (HDRS). This proof-of-concept study laid the foundation for using fMRI neurofeedback to help patients self-regulate emotions in depression, and has had world-wide impact (seven active clinical trials are currently listed on clinicaltrials.gov). More generally, the increasing awareness about the high prevalence of neurological and psychological issues in society, and the limited therapeutic solutions available, has generated excitement for fMRI neurofeedback as a non-pharmacological, brain-driven, and precise treatment option. The rising interest in clinical neurofeedback has been accompanied by large-scale EU funding (e.g., the BRAINTRAIN project [9]) and an increasing number of promising clinical studies on neurofeedback applied to mental disorders such as PTSD [10] and anxiety [11], and to neurological conditions such as Parkinson's disease [12]. Because it provides direct access to (dysfunctional) brain circuits [13], neurofeedback has become a truly disease-modifying intervention, which are currently virtually absent in psychiatry and are rare in neurology.

While neurofeedback has been explored for many clinical disorders [14], depression treatment has proven to be one of its most successful applications in subsequent randomized clinical trials [15, 16]. Its clinical effect (reducing symptoms by approximately 40%) clearly surpasses that of commonly observed placebo or non-specific effects. Furthermore, it has been revealed that the reduction in depression symptoms correlates with an increase in reported self-efficacy, which is an important concept in the psychology of depression. Neurofeedback seems to positively influence two core symptoms of major depression: anhedonia and a perceived loss of control. It does this by teaching patients to engage in positive emotions and by boosting their self-efficacy, respectively. Importantly, after undergoing successful treatment sessions in the scanner, patients were able to apply the learned emotional regulation strategies also outside the scanner. This led to sustained outcome effects, as demonstrated by follow-up measurements recorded weeks or months after the intervention. Most depression neurofeedback studies have used 3-Tesla fMRI, including our studies on 3 Tesla MAGNETOM Prisma scanners in Cardiff (UK) and Maastricht (NL), but a large-scale study currently running at Stanford University is using a 7-Tesla MAGNETOM Terra.X system with impulse gradients to provide optimal feedback signals to patients [17].

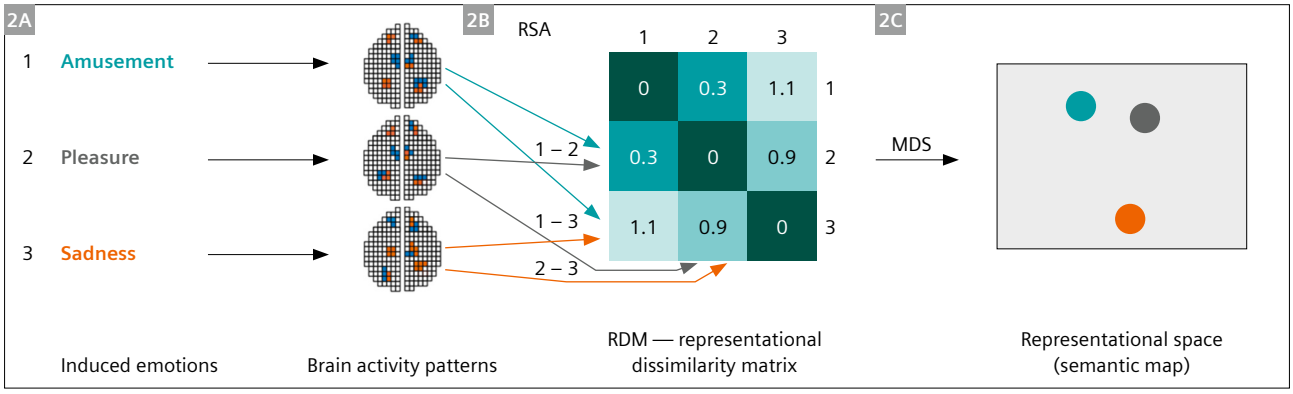
Limitations of conventional neurofeedback

There are (at least) two ways of designing clinical protocols for fMRI neurofeedback. On the one hand, one could directly target pathological hyper- or hypoactivation with down- or upregulation. For this approach, stable patterns of abnormal fMRI activity that can be detected and modulated in single trials (without pooling data over longer timeframes) would need to be identified in patients, which is often not possible. On the other hand, one could use the real-time fMRI signal to reinforce particular (desirable) mental states, such as those from positive emotional imagery or memories [8, 15, 16]. This is the approach that most studies on depression have taken so far. However, these clinical studies on fMRI neurofeedback were based on mean activity in a target area or on functional connectivity between brain areas or networks (for example, partial correlation coefficients). In previous studies on neurofeedback for emotion regulation in depression treatment, this conventional approach was "blind" to the type of emotion, since it does not distinguish between specific emotions. Since both positive and negative emotions can lead to an increase in the mean activity in the emotion network, it is thus not automatically known whether a patient is engaging in a positive or negative emotional mental state, despite specific instructions. This lack of specificity presents a challenge for further optimizing therapeutic outcomes, because the feedback should ideally be specific to the targeted emotion. We can now move beyond such low-dimensional feedback signals and harness brain activity patterns that reflect semantic representations in the brain, especially on ultra-high-field (7-Tesla) MRI scanners [16, 18].

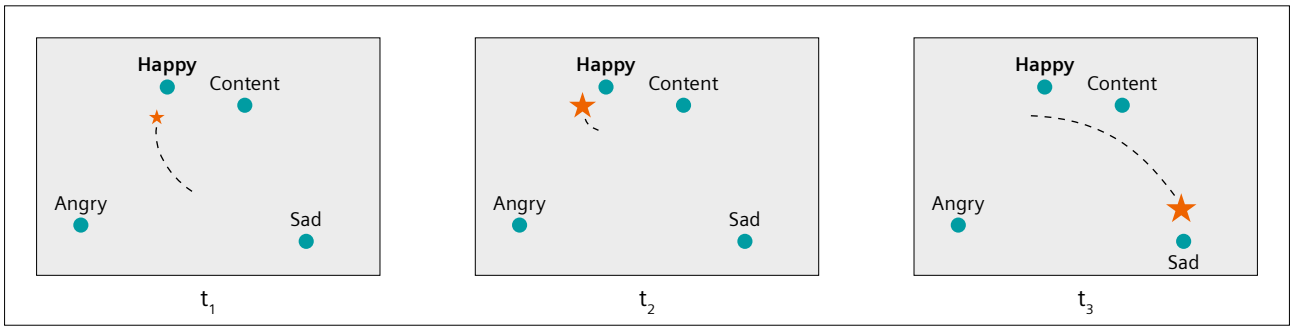
Semantic neurofeedback of emotions

To overcome the limitations of conventional neurofeedback for depression, a novel approach termed "semantic neurofeedback of emotions" has been recently proposed [20]. This method leverages multivariate brain activity patterns using representational similarity analysis (RSA) and multi-dimensional scaling (MDS) to capture the semantic structure of emotional representations in the brain (Fig. 2). The experimental protocol begins with an individualized mapping session, in which participants recall autobiographical memories associated with a range of emotions. Brain activation patterns in an emotion-related network are extracted and used to construct a personalized two-dimensional emotion map. In subsequent neurofeedback sessions, a participant's current emotional brain state is visualized as a moving point on the map. Patients are instructed to navigate their mental state toward a target emotion in a series of neurofeedback periods that are interspersed with rest periods. The distance between the current mental state and the other emotions on the map reflects pattern similarity; the size of the visual marker represents the intensity of the evoked emotion brain pattern (Fig. 3).

This semantic ("unblinded") continuous feedback allows participants to consciously explore and regulate their emotional states. It also trains engagement with negative emotions when therapeutically appropriate, particularly to help participants learn how to shift brain activity patterns from negative states toward desired positive emotions.



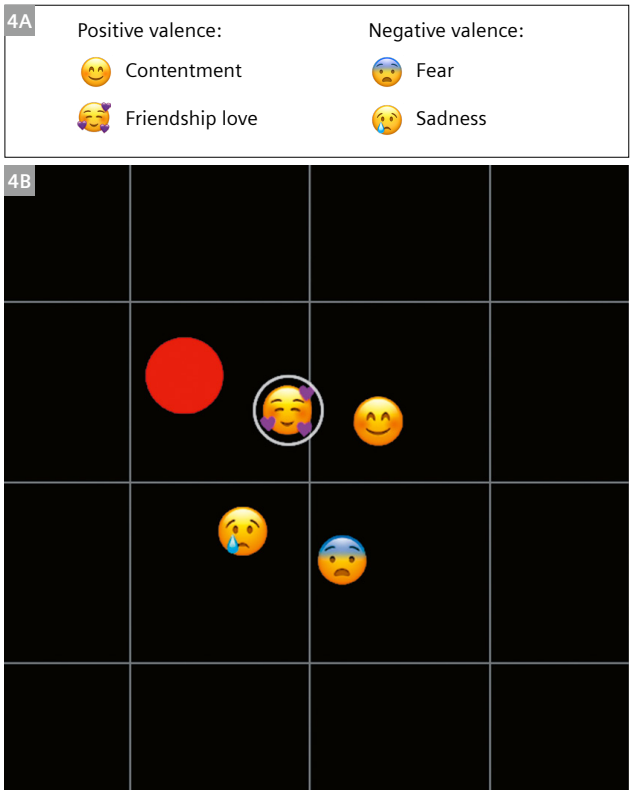
2 Illustration of representational (dis)similarity analysis (RSA) and semantic map creation with N = 3 conditions of induced emotions. **(2A)** Presented stimuli (e.g., pictures or recalled emotional autobiographical memories) evoke distributed activity patterns (N = 3). For voxels in a selected region of interest, the N patterns are compared pairwise (e.g., by calculating a linear correlation value). **(2B)** Similarity (e.g., correlation) values are converted into dissimilarity values d (e.g., d = 1 – correlation, ranging from perfect correlation (d = 0) over no correlation (d = 1) to perfect anticorrelation (d = 2)); pairwise dissimilarity values are placed in respective cells of the representational dissimilarity matrix (RDM) and are often color-coded (here: dark petrol for low dissimilarity, light petrol for high dissimilarity). **(2C)** Using multi-dimensional scaling (MDS), the high-dimensional similarity information in the RDM is projected onto a two-dimensional representational space or semantic map (adapted from [20]).



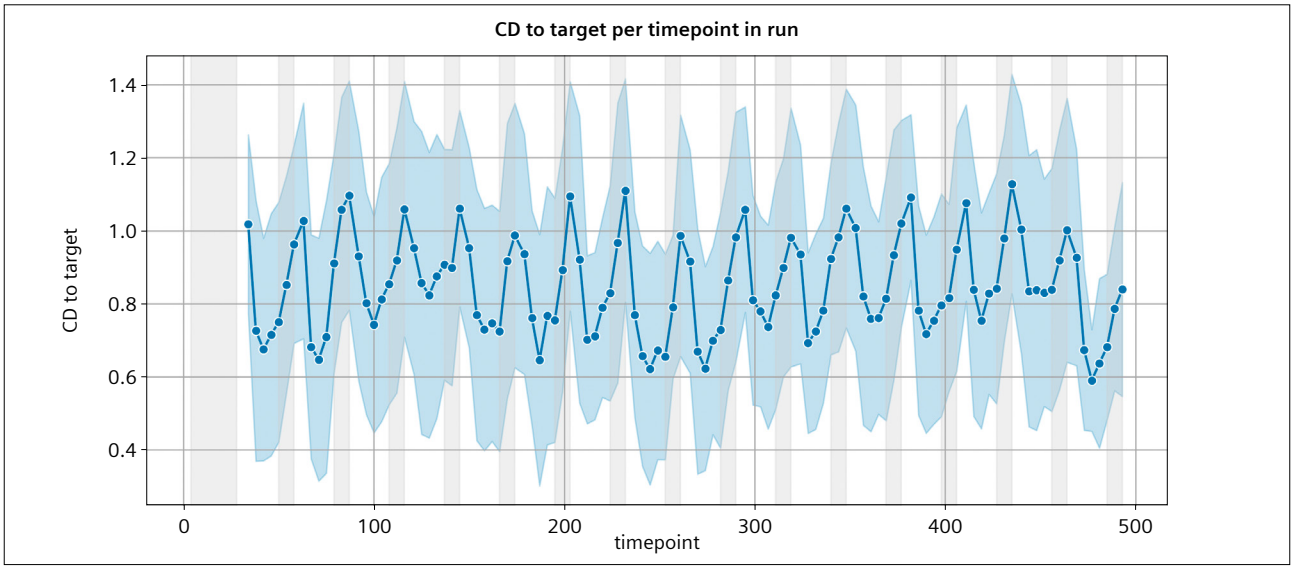
3 Schematic illustration showing semantic neurofeedback of emotions for depression treatment. After a localizer session, the (individual) semantic map contains the four mapped emotions 'happy', 'content', 'angry', and 'sad' as anchor points. After receiving the instruction "navigate to 'happy'", the participant engages in a happy emotional autobiographical memory. The red star, which represents the current mental state, moves from a relatively neutral emotional state (start of dashed line) toward the 'happy' emotion in the semantic map (t_1). By staying close to the target emotion, the participant increases the strength of the 'happy' emotion pattern, as indicated by the larger size of the red star (t_2). After subsequently receiving the instruction "navigate to 'sad'", the participant engages in a sad emotional state, and the current mental state star moves toward the 'sad' emotion in the semantic map (t_3) (adapted from [20]).

Feasibility and benefits of semantic neurofeedback

The feasibility of semantic neurofeedback of emotions has recently been demonstrated in a first proof-of-concept study with five participants [21]. The study consisted of two sessions per participant, conducted at 7 Tesla on a MAGNETOM 7T Plus scanner in Maastricht, the Netherlands. The first session was used to identify the patterns evoked by different emotions. In the second session, the participants practiced navigating to emotions using semantic neurofeedback. Out of nine emotions (contentment, gratitude, friendship love, enthusiasm, surprise, sadness, anger, disgust, and fear), four were selected for each participant to best reflect different valence and arousal categories. In the localizer runs, participants engaged in autobiographical memories matching the selected emotions. An individual mask was created by combining activation from each emotion within the emotional network [22]. Activation patterns were then extracted for the four emotions inside the mask and used to calculate the representational dissimilarity matrix, from which the individual two-dimensional map was created (Fig. 2). During the second session, this map was used to provide the participants with feedback on how their current emotional state was related to the emotion patterns from the first session. The calculated similarity was displayed by a moving red dot, the size of which represented the intensity of pattern activation (Fig. 4). The pilot results demonstrated that participants managed to regulate their brain activation and navigate closely to the emotional target (Fig. 5). These findings indicate the general feasibility of the approach, as high accuracy and



4 Snapshot of real-time fMRI semantic neurofeedback of emotion. **(4A)** Legend showing the four emotions that were selected for the participant and displayed as emojis in the semantic map. **(4B)** Snapshot of the display shown to a participant after they successfully navigated to the cued emotion (white circle) of 'friendship love'. The large size of the red dot indicates that the participant experienced a strong feeling of friendship love.



5 These results of semantic neurofeedback of emotion (average of five participants) show that the participants were able to navigate toward the target emotion in individual trials. The distance from the current mental state to the target emotion (y axis) is the correlation distance (CD), which corresponds well with the Euclidean distance (ED) shown on the semantic map. The CD decreases in the white sections (neurofeedback blocks) and rises in the gray sections (rest periods).

engagement were achieved even with non-optimized protocols and methods, suggesting substantial potential for future improvements.

We have not yet systematically compared semantic neurofeedback of emotions at 3-Tesla fMRI versus 7-Tesla fMRI. However, robustly discriminating between different emotion patterns to create a semantic map of emotions is challenging and will likely benefit from the enhanced signal-to-noise ratio or higher spatial resolution at 7 Tesla.

Overall, we believe that this new, transparent technique of navigating one's own emotional space has the potential to enable more specific training for future clinical studies on depression and, more generally, mood disorders.

While fMRI has revolutionized brain research in humans, clinical applications of fMRI are rare. Real-time fMRI neurofeedback for depression has the potential to become a routine application of fMRI in the future, benefitting patients who are not sufficiently responding to conventional interventions.

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