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Neurofeedback and networks of depression
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Self-regulation through neurofeedback: technique and rationale

Recent advances in imaging technology and in the understanding of neural circuits relevant to emotion, motivation, and depression have boosted interest and experimental work in neuromodulation for affective disorders. Real-time functional magnetic resonance imaging (fMRI) can be used to train patients in the self-regulation of these circuits, and thus complement existing neurofeedback technologies based on electroencephalography (EEG). EEG neurofeedback for depression has mainly been based on models of altered hemispheric asymmetry. fMRI-based neurofeedback (fMRI-NF) can utilize functional localizer scans that allow the dynamic adjustment of the target areas or networks for self-regulation training to individual patterns of emotion processing. An initial application of fMRI-NF in depression has produced promising clinical results, and further clinical trials are under way. Challenges lie in the design of appropriate control conditions for rigorous clinical trials, and in the transfer of neurofeedback protocols from the laboratory to mobile devices to enhance the sustainability of any clinical benefits.

Keywords: *emotion; frontal lobe; functional magnetic resonance imaging; limbic system; mood disorder; self-regulation*

Since its invention 20 years ago, functional magnetic resonance imaging (fMRI) has become a central technique of cognitive and clinical neuroscience. The particular strengths of this noninvasive technique are its spatial resolution, fidelity, and ability to reach deep subcortical structures. Its whole-brain coverage enables the mapping of functionally connected networks and the extraction of information from distributed activation patterns. These features make fMRI particularly suitable for applications to mental disorders, where the pathology is generally assumed to reside in faulty network activity, rather than focal lesions, and where deep structures play a major role. The fMRI technique is particularly powerful in mapping correlates of mental states, another very attractive feature for psychiatry, which deals predominantly with altered states of thought, emotion, and behavior. For example, fMRI scans acquired from patients with chronic schizophrenia during the experience of auditory verbal hallucinations have revealed activation in the auditory cortex, very similar to that during stimulation with actual sounds.[1] Beyond their major contribution to the understanding of the brain correlates of psychopathology, fMRI studies have also informed our understanding of

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the effects of risk genes on cognitive and affective networks.[2] These important research contributions have led to strategies for the development of fMRI paradigms for diagnostic, prognostic, or therapeutic use in mental disorders, and are reviewed in the September 2013 issue of *Dialogues in Clinical Neuroscience (http://www.dialogues-cns.org/wp-content/themes/dcnsv2/publication.php?volume=15&issue=3).*

Whereas concerns about power and reliability[3] have dampened hopes for imminent diagnostic uses of functional imaging, there has recently been a surge of interest in a potential therapeutic application of fMRI-based neurofeedback (fMRI-NF). Imaging-based neurofeedback follows similar principles as other neuro- or biofeedback approaches. During neurofeedback training, participants receive feedback on their brain activity in real time and are instructed to change this activation. In the case of fMRI-NF, the feedback signal is computed from a real-time analysis of the time course of the blood

Real-time fMRI neurofeedback setup

MRI scanner

Feedback screen
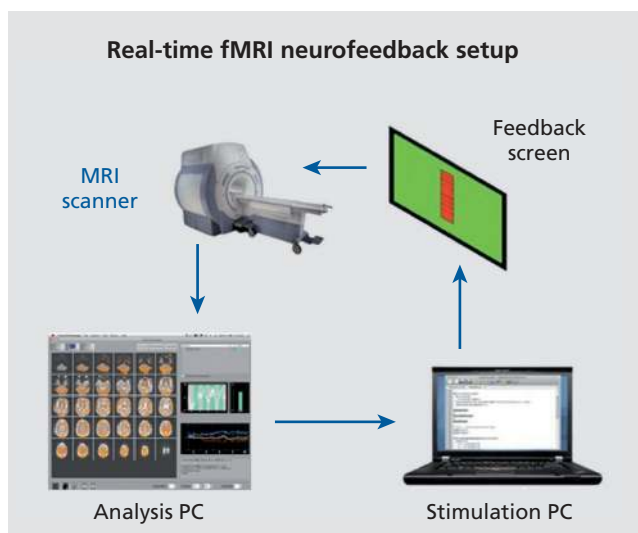
Analysis PC

Stimulation PC

Figure 1. Basic diagram of a real-time functional magnetic resonance imaging brain-computer interface for neurofeedback.
Figure courtesy of Isabelle Habes

oxygenation level-dependent (BOLD) signal *(Figure 1)*. Thus, fMRI-NF can presently only be conducted while participants are in a magnetic resonance system. The signal can be based on the average time course of an individual area (such as the left primary motor cortex or the right amygdala) or even on the time course of a single voxel anywhere in the brain (although this would make it rather susceptible to noise). However, it can also be based on results of more complex computations, such as the activation difference or correlation between two areas, or the output of a multivariate pattern classification algorithm. Unlike electrophysiological neurofeedback techniques, such as EEG (electroencephalography), the fMRI technique cannot provide truly "real-time" feedback because of the "hemodynamic" delay of ≈5 seconds between the actual neural activity and the vascular response that creates the fMRI signal. However, this delay does not pose an obstacle to neurofeedback training when participants are informed of it.[4]

Compared with other neurofeedback techniques (EEG or magnetoencephalography, MEG) and to noninvasive physical stimulation techniques (transcranial direct current stimulation and transcranial magnetic stimulaiton), fMRI-NF has the advantage of higher localization accuracy and better access to deep brain structures. EEG-based neurofeedback (EEG-NF) has the advantage of being more widely available and including ambulatory settings. It is a popular procedure, especially in child and adolescent mental health settings in application to attention deficit/ hyperactivity disorder (ADHD),[5,6] although a recent meta-analysis has raised doubts about the specificity of the effects in ADHD.[7] Several studies that have also been conducted with EEG-NF in depression will be reviewed below.

Compared with deep brain stimulation (DBS),[8,9] fMRI-NF has the advantage of noninvasiveness and spatial flexibility. However, it is too early to make any direct comparisons of the clinical effects of these two techniques in psychiatry, which have so far been used for very different patient populations due to the restriction of DBS to severe and treatment-refractory cases. Neurofeedback also differs from all external stimulation techniques in that it enables the patients themselves to control their brain activity and thus to contribute to their experience of self-efficacy, which may be an important therapeutic factor.[10] This aspect will be discussed in more detail below, in the section of links between neurofeedback and social learning theory.

There are, in principle, at least two ways in which self-regulation of brain activity through neurofeedback may be beneficial for depression and other mental disorders. Self-regulation training might address a primary abnormal process, such as hyper- or hypoactivation of specific brain areas or networks. For this approach, it would be necessary to identify such abnormal activation patterns in individual patients beforehand. Although research with the fMRI technique (and metabolic imaging with positron emission tomography, PET) has yielded several potential disease-relevant targets for depression, notably imbalances between prefrontal and limbic areas,[11-14] none of these have been validated as biomarkers for use in individual patients. Similarly, although intriguing results have been obtained with EEG mapping techniques in relation to hemispheric asymmetries in depression (see EEG section below), these have not attained individual biomarker status either. At the present time, there is insufficient evidence to identify any reliably abnormal, local, or distributed brain activation patterns in individual patients with depression that could be targeted with neurofeedback (or indeed, any other neuromodulation technique, including DBS).

However, neuromodulation can also act in a different way, by activating or suppressing circuits that are not primarily abnormal, but whose modulation may nevertheless produce clinical benefits. I have argued for the consideration of such a "functional systems" approach recently elsewhere.[15] Most biological treatments in psychiatry probably follow this path already. For example, monoamine reuptake inhibitors benefit many patients with depression by increasing serotonergic and/or noradrenergic neurotransmission, but probably not by correcting an underlying monoaminergic deficit, for which little evidence has been found.[16,17] Similarly, current lesion surgery and DBS approaches for depression or obsessive-compulsive disorder (OCD), whose targets all converge onto pathways from brain stem and basal ganglia to prefrontal cortex,[18] work through—hitherto poorly understood—effects on the function of these pathways in motivation and emotion regulation, but not necessarily because there are documented primary abnormalities in these pathways. Regarding neurofeedback, this implies that clinical benefits may be obtained from self-regulation training that activates compensatory circuits for particular cognitive processes (eg, emotion regulation) or inhibits circuits that, although normal when viewed in isolation, contribute to dysfunction in the context of the patient's primary pathology. For example, it may be beneficial to suppress canonical thought processes such as self-comparison in the context of a depressive disposition. The great progress in the understanding of the circuits of cognitive, affective, and social information processing made through the last two decades of functional imaging can thus inform the design of imaging-based clinical neurofeedback protocols, even in the absence of primarily abnormal imaging signals.

Applications in depression

Symptoms of depression can be broadly grouped into the four domains of emotion regulation, cognition, motivation, and homoeostasis *(Table I)*.[19] Although like all categorization of psychological phenomena, this classification is somewhat artificial (and some symptoms map onto more than one category), it can help the search for the biological mechanisms of depression.[20] Furthermore if the neural systems underlying some of these functional clusters prove to be modifiable (by pharmacological, psychological, or physical intervention) they may

ICD-10	DSM-IV	Domain
Depressed mood		**ER**
Loss of interest and enjoyment		**M, ER**
Increased fatiguability		**M, H**
Reduced concentration and attention		C, M
Ideas of guilt and unworthiness		C
Ideas or acts of self-harm or suicide, thoughts of death		C, ER
Sleep disturbance		H
Disturbed appetite/weight change		H
Pessimistic view of the future		C, ER
Reduced self-esteem and self-confidence		C, ER
Early-morning awakening		H
Mood worse in the morning		H, ER
Psychomotor retardation or agitation		M, H
Weight loss		H
Loss of libido		H

Table I. Symptoms of depression. Five symptoms are required over a 2-week period for an episode of major depression *(DSM-IV)*. ICD-10 defines depressive episodes by a combination of the most typical (printed in bold face) and other symptoms.[19] The number of symptoms determines the severity of the episode: 2 typical and 2 other: mild; 2 typical and 3 or 4 other: moderate; 3 typical and 4 or more other: severe. The column on the right indicates the broad domains into which the symptoms can be tentatively classified: ER, emotion regulation; C, cognition; M, motivation; H, homoeostasis.

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become viable targets for new antidepressant therapies.

New therapeutic strategies for depression are sorely needed. Depression is expected to assume the first place in the WHO's global disease burden statistic by 2020. It affects up to 15% of the population of industrialised countries. The number of prescriptions of antidepressants for England alone was almost 50 million in 2011, at a cost of £270 million, but the overall health care and socioeconomic costs of depression are much higher, at about £11 billion per year in the UK according to a recent House of Commons report.[21] The impact of depression on health and wellbeing is not confined to the patients themselves, but frequently extends to their human networks, negatively affecting social, familial, and occupational relationships.[22] Depression is presently managed with psychological, pharmacological, or physical interventions or their combination. However, all present treatment options have limitations, such as medication side effects, nonresponse (including a high proportion of treatment-refractory patients who do not respond to any therapy),[23] and frequent relapse. Even patients who have responded to antidepressant treatment are often reluctant to take medication in the long term and thus experience an increased relapse risk.[24] Together these complex challenges underscore the need for better, and more effective, treatment and relapse prevention options for depression, and for solutions that are to be designed through interaction between researchers, clinicians, and the patients themselves.

A functional imaging approach (in the broad sense, incorporating both fMRI and electrophysiological techniques) to elucidating the circuits underlying the symptom complexes of depression, but also of those involved in their remediation, can be useful in this new therapeutic endeavor in several respects. Firstly, it may allow researchers to identify correlates of individual symptoms or symptom groups, for example, altered activation of frontostriatal circuits during period of apathy and fatigue. If these imaging-based state markers can be shown to be reliable and diagnostic, they may become new targets for self-regulation training through neurofeedback (or other neuromodulatory interventions). With further refinement of functional imaging methods and higher signal-to-noise ratio obtained through higher field strengths, there may even be scope for a detailed functional mapping of brain stem nuclei that may reveal information about the underlying chemical imbalances, thus possibly giving rise to new pharmacological strategies.

Even if this combination of advanced functional (and structural) neuroimaging and a symptom cluster–based approach to depression does not produce clear, individually targetable state markers, the knowledge of the functional systems involved can still inform new treatment approaches, notably in neuromodulation. I have argued[15] that the biological correlates of the mechanisms that help to overcome a mental illness, such as emotion regulation or fear extinction,[25] may be more consistent than those of the original illness. Thus, if we can apply functional imaging to reveal the neural correlates of successful treatment[26-29] (see also the article by Beauregard in this issue, p xx), we can subsequently apply neuromodulation techniques to target these neural networks directly. This was the rationale behind the target selection for the first DBS protocol to depression, which targeted the subgenual cingulate cortex based on the observation that activation in this area was reduced after successful pharmacotherapy of depression[11,30] (see also the article by Holtzheimer in this issue, p xx). This idea of mimicking the neural correlates of successful treatments through direct brain intervention can now be implemented even more flexibly through self-regulation training with neurofeedback, which can even track moving targets (unlike psychiatric surgery, which is normally confined by a specific lesion or stimulation site), because functional localizers can be adjusted flexibly over treatment sessions.

EEG neurofeedback in depression

EEG-NF studies of depression were originally based on Davidson's approach/withdrawal model of emotion,[31] which posited that appetitive and aversive emotional behaviors are subserved by the left and right frontal cortex respectively,[32] and that hypoactivity of left frontal areas would be associated with depression.[33,34] Because alpha activity of the EEG is commonly linked with lower metabolic activation, this relative left hypoactivity would be associated with relatively higher right than left frontal alpha power. The logical consequence in neurofeedback terms would be to train patients to decrease left-hemispheric alpha activity, increase right-hemispheric alpha activity, or shift an asymmetry index toward the right in order to rebalance activation levels in favor of the left hemisphere. This asymmetry model received initial support from the stroke literature because depression seemed to occur more frequently after damage to the left than the right hemisphere. However, current neuropsy-

chiatric evidence suggests that there is no such preferred association between depression and left-hemispheric damage.[35] The EEG literature has also been inconsistent in that not all authors found higher left-hemispheric alpha activity in patients with depression compared with healthy controls,[36] although a recent meta-analysis supported the asymmetry model based on resting EEG data.[37] The considerable interindividual variability of EEG asymmetry limits its usefulness as a neurofeedback target.[38] The main asymmetry-based EEG-NF protocol has used an asymmetry index of alpha power as feedback signal and trained patients to increase the right-to-left ratio, essentially rebalancing a putative hypoactivation of the left hemisphere. This asymmetry index is computed as $A=100 \times (R-L)/R+L$), where R and L are the square root of power of alpha activity (obtained by Fast Fourier Transformation) measured at a right and left frontal electrode respectively.[39]

Compared with earlier research, which did not incorporate control groups, a recent placebo-controlled randomized (but not blinded) study has implemented several design improvements.[40] This study (again with the alpha asymmetry training protocol) included 24 patients with depression who were assigned to a 5-week EEG-NF or a psychotherapy control group. Patients in the active group showed an improvement of over seven points on the 17-item Hamilton Depression Rating Scale (HDRS; from 11.33 to 4.08). Conversely, the psychotherapy group only showed minimal improvement (12.36 to 11.08). However, the scope of this study is limited by the relatively low depression levels before treatment (a mean HDRS score of 12 indicates mild depression and is below the conventional cutoffs for treatment trials). Furthermore, the choice of control group does not exclude the impact of nonspecific effects of neurofeedback training, for example, the gaming component, which may make the training more interesting and engaging than conventional psychotherapy.

fMRI neurofeedback in depression

One of the limitations of EEG-NF is its low spatial precision, which is owed to the effects of volume conductance and the attenuation of electrical signals on their way from the source to the scalp, and the ill-posed nature of the source localization problem.[41] Although the fMRI technique provides only indirect measures of neural activity (obtained through neurovascular cou-

pling) and has a much lower temporal resolution than the electrophysiological techniques (in the second range compared with the millisecond precision of EEG and MEG), its spatial resolution and access to deeper brain structure make it an attractive tool for network mapping in psychiatric disorders and neurofeedback.[42] Our research group has designed an fMRI-NF protocol for patients with depression *(Figure 2)*.

Rather than using anatomically fixed target regions (as conventionally used in psychiatric surgery), the fMRI-NF approach gave us the opportunity to identify the relevant target areas in each training session using a functional localizer. Localizer scans with emotionally charged pictures can identify areas involved in the processing of positive or negative affective stimuli, and we initially showed that healthy participants can attain control over the activation levels in these areas.[44,45] The "positive emotion" areas were then used as the target for fMRI-NF in a pilot study with patients with mild-to-moderate levels of depression.[46]

We tested eight patients, all with a longstanding history of depression. They were informed that the areas they trained to upregulate had been associated with positive emotional pictures, but no specific strategy was suggested to them. Most patients started their attempts to upregulate the target areas that, although varied in local-
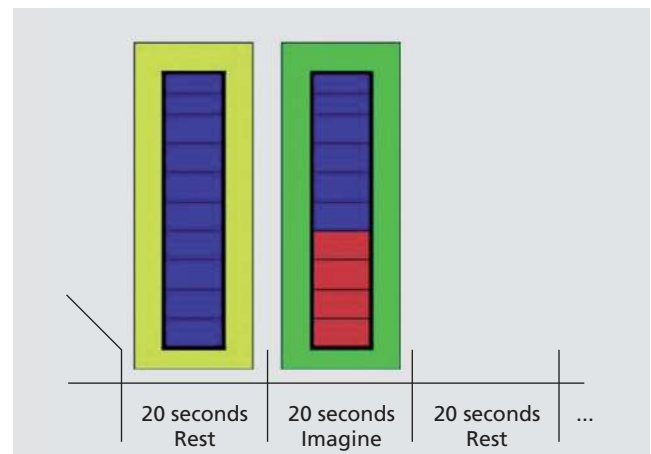

Figure 2. Display screen of visual neurofeedback with an outline of the protocol. The patients trained to increase activity in functionally localized areas during 20-second periods, alternating with 20 second periods of rest. Overall, they did this for 20 minutes each in four weekly sessions.
Adapted from ref 43: Subramanian L, Hindle JV, Johnston S, et al. Real-time functional magnetic resonance imaging neurofeedback for treatment of Parkinson's disease. *J Neurosci.* 2011;31:16309-16317. Copyright © Society for Neuroscience 2011

ization, mostly included areas in the ventral prefrontal cortex and limbic system, by imagining the pictures, which included serene landscapes and uplifting sporting scenes. However, most of them reported at debriefing that it worked better to try and evoke positive images that related to themselves, for example, memories of happy events. In a psychotherapeutic sense, the neurofeedback training may have helped them engage with positive aspects of their own lives. The clinical effects of the pilot study were also promising.[46] The patients in the neurofeedback group improved by about 30% on their symptom score over the 1-month trial (about four points on the 17-item HDRS), whereas a control group, which performed emotional imagery for the same duration outside the scanner, did not improve at all.

The next step in the development of fMRI-NF into a potential therapeutic tool will be the investigation of its short- and long-term benefits and mechanisms in rigorous trials. Essentially the same standards apply as those required before the introduction of a new drug. We can be relatively certain that neurofeedback has no major direct side effects,[47] but cannot rule out that some patients may experience parts of the procedure as stressful. Furthermore, researchers in the field will have to show that the clinical benefits are not merely placebo effects induced by patients' expectations, but genuinely superior to other interventions. The design of appropriate control conditions for clinical trials is a challenge. The current standards of randomized controlled trials were developed with drug studies in mind, where the aim is to distinguish the chemical effects of a drug from the associated expectations. One of the principles of these trials is that they are conducted in a "double-blind" fashion. Yet when treatments require the active collaboration of the patients, which is the case in neurofeedback (and also in all forms of psychotherapy), these patients cannot be completely "blind." Furthermore, the experience of gaining control over the brain, the increased "self-efficacy" and heightened awareness of one's own mental states may all be nonspecific components of neurofeedback that contribute to improvement across disorders. Although we can control them with sophisticated experimental designs, this may miss the point, as these psychological mechanisms may actually be valuable drivers of change for the patients, rather than mere components of a placebo effect. An ongoing randomized controlled trial of neurofeedback for depression conducted by the author's group at Cardiff

University (clinicaltrials.gov: NCT01544205) pits upregulation of emotion networks against upregulation of a higher visual area, a rather conservative active control condition that also involves mental imagery and the rewarding experience of brain self-control. This trial will also provide some initial information about any sustained benefits of fMRI-NF by including a follow-up assessment 1 month after the completion of the 2-month intervention. So far no published information is available about any longer-term benefits of fMRI-NF in depression or in any other mental or neurological disorder.

Neurofeedback and social learning theory

Isolating the generic effects of the experience of self-control from any region- or network-specific effects, is particularly relevant because neurofeedback may have nonspecific positive effects on self-efficacy. If this was shown to be the main factor in any treatment effects, this information would considerably influence the development of neurofeedback protocols. According to Bandura, " People have to live with a psychic environment that is largely of their own making. Many human distresses result from failures to control disturbing, ruminative thoughts. Control of one's thought processes is therefore a key factor in self-regulation of emotional states."[48]

If neurofeedback is to benefit patients by helping them attain control of their own thought processes and consequently their emotional states, this will probably require fine tuning of self-regulation protocols to the appropriate neural networks. However, social learning theory also posits that depression can be caused by a general low sense of agency and loss of experience of control of the environment. For these patients the "imposed environment," in Bandura's terms, would take precedence over the "constructed environment." Successful control over one's own brain activity (and in this scenario the exact region would probably matter less) could then give patients a sense of agency and particularly the experience that their own brain activity is constructed (rather than merely imposed).

Neuromodulation might receive a further, presently speculative, interesting inspiration from social learning theory. Already in 1999 Bandura pointed out that, "Electronic technologies greatly extend human capabilities to test the likely outcomes of given decisions and

courses of action through the use of computerized enactments in simulated realities without having to carry out the activities."[48]

The importance and pervasiveness of such virtual simulations has increased even further in the past 14 years and started to enter the field of mental health, for
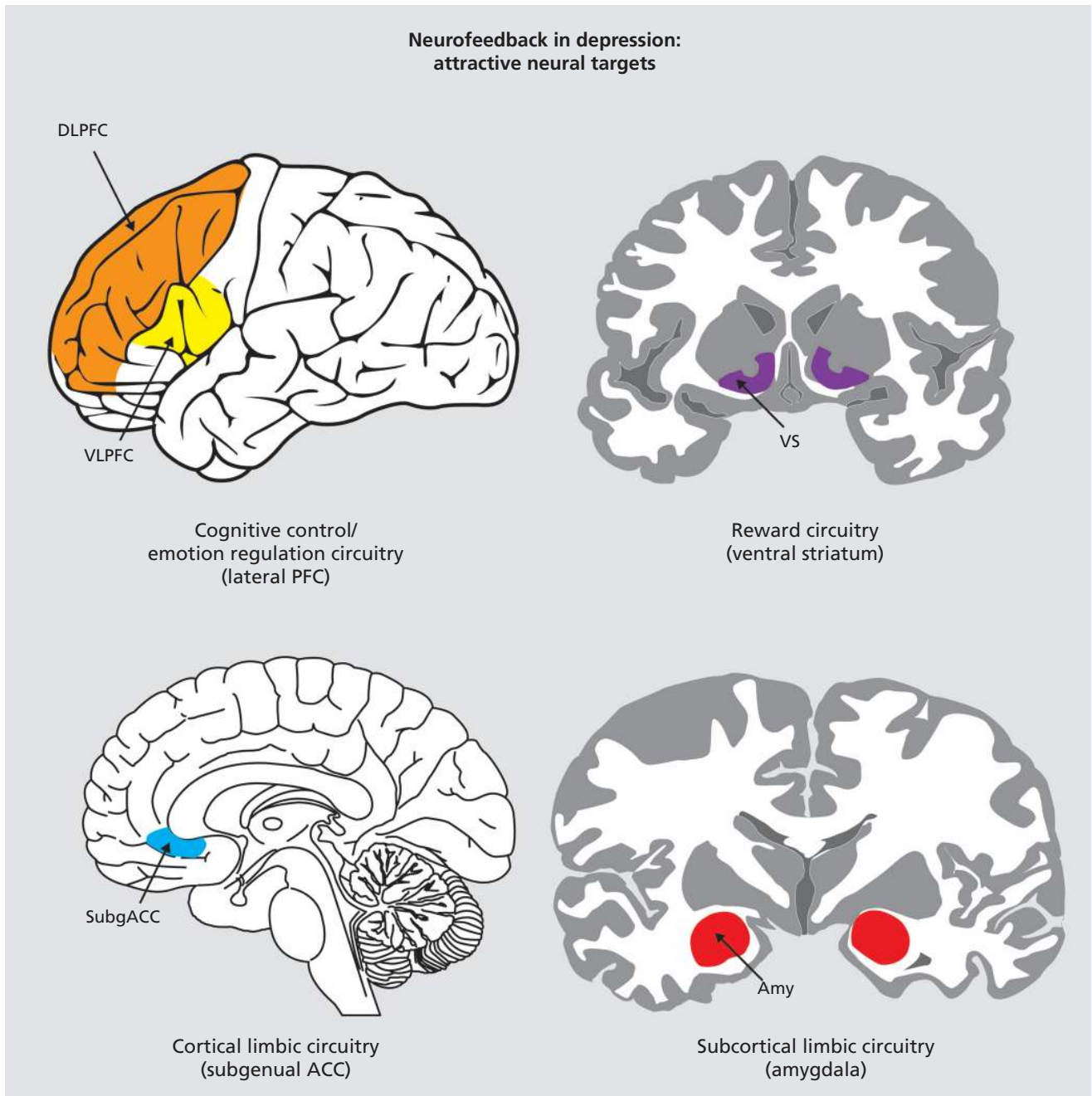

Figure 3. Cognitive-affective brain systems that could become targets for neuromodulation in depression. DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; ACC, anterior cingulate cortex; Amy, amygdala
Adapted from ref 38: Esmail S, Linden D. *Cogn Sci*. 2011;6. Copyright © Nova Science Publishers, Inc.

example in the treatment of post-traumatic stress disorder.[49] Neurofeedback may now provide an avenue toward simulation, not just of environments and mental processes, but of the relevant brain processes themselves (although the term "simulation" here is an incomplete analogy, because even with neurofeedback the neural changes would be real rather than virtual). One potential application might be the simulation of the effects of DBS, which could guide the later placement of permanent neuromodulation devices based on the behavioral, cognitive, or clinical effects of transient brain activation changes during neurofeedback.

Future developments

In addition to the rigorous testing of existing fMRI-NF protocols it will also be attractive to develop new protocols based on different ways of extracting information from brain activation data, eg, multivoxel pattern analysis,[50-52] or on different brain networks. The choice of potential target areas can be informed both by the experience of other neuromodulation techniques, particularly lesion surgery and DBS, and by the symptom clusters discussed above. The fMRI-NF approach to depression has so far focused on emotion regulation, and thus the overlap between the cognitive and affective domains. The target areas for this approach are mainly in the frontal lobe *(Figure 3)*.[38] Another approach starts from the observation that many patients with depression are impaired in their ability to react to rewards or generally to have positive experiences (lack of enjoyment: "anhedonia"). It has been well established through functional imaging in humans and a long tradition of animal experiments that areas in the midbrain, striatum, and frontal cortex, linked anatomically through the medial forebrain bundle and chemically through the neurotransmitter dopamine, support the ability to experience and learn from rewards. These "reward circuits" would therefore be another potentially suitable target for fMRI-NF, as they are for DBS.

Another area for development in clinical research into fMRI-NF is the identification of suitable patient populations and predictive markers. For example the cognitive and motivational factors that underlie successful neurofeedback training are largely unknown. One option would be to include metacognitive scales such as the Thought Control Questionnaire (TCQ),[53] the Thought Control Ability Questionnaire (TCAQ),[54] and the behavioral inhibition system and behavioral activation system (BIS/BAS) scale[55] in order to enable predictions of feasibility of neurofeedback and clinical effects. Another recommendation would be to assess the short-term changes associated with individual neurofeedback sessions on patients' mood and perceived self-regulation ability in order to evaluate whether these immediate effects are associated with the longer-term clinical response. At the moment it is envisaged that neurofeedback, like DBS, will be a procedure that is added to existing treatments, rather than one that replaces it. With these caveats the prospect of neurofeedback as a treatment for depression sound far more prosaic, but still the potential is considerable. ❏

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Retroalimentación neural y redes de la depresión

Los recientes avances en la imaginología y en la comprensión de los circuitos neurales relacionados con la emoción, la motivación y la depresión han impulsado el interés y el trabajo experimental en la neuromodulación en los trastornos afectivos. La resonancia magnética funcional en tiempo real (RNMf) se puede emplear para entrenar a pacientes en la autorregulación de estos circuitos y así complementar las tecnologías existentes de retroalimentación neural basadas en la electroencefalografía (EEG). La retroalimentación neural EEG para la depresión se ha basado principalmente en modelos de alteración en la asimetría hemisférica. La retroalimentación neural basada en la RNMf (RN-RNMf) puede emplear exploraciones de localizaciones funcionales que permiten el ajuste dinámico de las áreas o redes blanco para el entrenamiento en autorregulación para patrones individuales del procesamiento de las emociones. Una aplicación inicial de la RN-RNMf en la depresión ha producido resultados clínicos promisorios y también ensayos clínicos que están en desarrollo. Los desafíos están en el diseño de condiciones control apropiadas para ensayos clínicos rigurosos y en la transferencia de protocolos de retroalimentación neural desde el laboratorio a los dispositivos móviles para reforzar la sostenibilidad de cualquier beneficio clínico.

Neurofeedback *et réseaux de la dépression*

Des avancées récentes dans la technologie de l'imagerie et dans la compréhension des circuits neuronaux liés à l'émotion, à la motivation et à la dépression ont stimulé l'intérêt et le travail expérimental en neuromodulation dans les troubles affectifs. L'imagerie par résonance magnétique fonctionnelle en temps réel (IRMf) est utilisée pour entraîner les patients à l'autorégulation de ces circuits et vient donc compléter les techniques de neurofeedback basées sur l'électroencéphalographie (EEG) principalement fondée, dans le cadre de la dépression, sur des modèles de changements d'asymétrie des hémisphères. Le neurofeedback basé sur l'IRMf, (IRMf-NF), utilise des images de localisation fonctionnelle qui permettent l'ajustement dynamique des zones ou réseaux cibles pour l'entraînement par autorégulation des processus émotionnels individuels. Les premiers résultats de l'IRMf-NF dans la dépression sont prometteurs et d'autres études cliniques sont en cours. Les difficultés résident dans la création de bonnes conditions de contrôle pour des études cliniques rigoureuses et dans le transfert des protocoles de neurofeedback *du laboratoire à des dispositifs mobiles pour améliorer le maintien des bénéfices cliniques.*

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