Functional Magnetic Resonance Imaging (fMRI) Neurofeedback: Implementations and Applications

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Abstract

Neurofeedback (NFB) allows subjects to learn how to volitionally influence the neuronal activation in the brain by employing real-time neural activity as feedback. NFB has already been performed with electroencephalography (EEG) since the 1970s. Functional MRI (fMRI), offering a higher spatial resolution, has further increased the spatial specificity. In this paper, we briefly outline the general principles behind NFB, the implementation of fMRI-NFB studies, the feasibility of fMRI-NFB, and the application of NFB as a supplementary therapy tool.

Keywords: fMRI, learning, neurofeedback, self-regulation

Neurofeedback Using Functional Magnetic Resonance Imaging

Neurofeedback (NFB) is a technique which allows subjects to learn how to volitionally influence the neuronal activation in the brain. The principle behind NFB training in general is that brain activity is self-modifiable through operant conditioning where the subjects are provided with feedback about ongoing neuronal activation with the goal to regulate it, and a "reward" is given should a certain level of activity be achieved. This volitional control of defined aspects of the central nervous system was successfully implemented at first using electroencephalography (EEG), whereby healthy subjects learn to control their electrical brain activity. EEG-NFB has been effectively applied to treat clinical conditions such as attention deficit hyperactivity disorder (ADHD) (1,2) and epilepsy (3,4).

The concept of 'interactive experimental paradigms' was envisioned nearly two decades ago with the advent of real-time functional magnetic resonance imaging (rt-fMRI) (5). Rt-fMRI, which allows for high spatial resolution (in the range of millimetres) and imaging of activity across the entire brain within a couple of seconds, all done non-invasively without the need of surgery or injection of contrast agents, has paved the way for a new NFB paradigm. fMRI measures the blood oxygenation level–dependent (BOLD) response, i.e., signal differences due to local changes in the concentration of deoxygenated haemoglobin in the brain tissue, which depends on neuronal metabolism and activity. Specifically, the BOLD contrast is a result of magnetic field inhomogeneity change brought about by varying levels of deoxyhaemoglobin (dHb) in the intracellular space of the red blood cells in blood vessels. dHb distorts the magnetic field around the blood vessel, enhancing the magnetic field inhomogeneity and thus, lowering the BOLD signal. Yet neural excitation increases the BOLD signal. This is due to a regional increase in cerebral blood flow (CBF) that exceeds the oxygen consumption rate, which ultimately results in an oversupply of oxygenated blood. Thus, the net effect is a drop in dHb concentration, which leads to an increase in the signal strength (as reviewed in (6,7)). The maximal change of the BOLD signal in response to neural activity is delayed by approximately 6 seconds. The relationship between the measured fMRI signal and the underlying neural activity has been thoroughly investigated, and there is solid evidence for a strong correlation between

the BOLD signal and the local field potential as a measure of the electrical brain activity (8).

Recent technical developments have made it possible to analyse the data online as they are collected (hence, the term "real-time fMRI"), so that the resulting information is immediately available and can thus be used to guide a person's attempt at self-regulation according to the experimenter's parameters (9). NFB provides a new approach in neuroscience by studying brain plasticity and functional reorganization after continuous training of volitional control of defined brain regions (10).

In this paper, we focus on general principles behind NFB, and how it can be implemented using fMRI. With evidence from our results as well as from the literature, we demonstrate the feasibility of fMRI-NFB. Finally, we highlight some possible applications of NFB as a supplementary therapy tool.

How neurofeedback can influence brain functions

Self-regulation of neural activity

Numerous studies have proved that subjects can learn how to influence their brain activity. The growing interest is reflected in the increasing rate of publications on rt-fMRI from ca. one paper per year to about seven papers per year following the first publications on fMRI-NFB in 2002/2003 (11). Over the course of several NFB training sessions, subjects have successfully come up with a strategy or optimised an already existing one to elicit the desired level of activation. The importance of feedback from the ongoing activation as a predictor of success is undeniable and can be elucidated by various controls used in NFB experiments. The first control for the specificity of the NFB training effect is the transfer experiment, which is the comparison between pre- and post-training measurements, during which subjects try to regulate their own brain activity while not provided feedback. This comparison would tell us whether the subjects' ability to regulate their brain activity has improved. On a higher level, behavioural tests may prove whether the training effects generalise to produce any behavioural changes. The transfer experiments and the behavioural tests by themselves, only prove that the investigation had an effect on the targeted brain function (specificity in brain function). On the next level, control subjects who do not undergo NFB training can prove that the effect occurred due to the NFB training and not by chance (specificity in time). However, only subjects exposed to non-specific stimuli can prove that the effect is very specific to the NFB setup and not to non-specific elements of the training such as physical rest, scanner noise, concentration on the task, and observing a variable signal. These non-specific elements can be controlled with no-feedback training, sham feedback (feedback from a different region) or yoke feedback (feedback from another participant). Carefully designed studies must include one or more controls. A recent review by a group of prominent authors in the field of fMRI-NFB highlighted the importance of positive controls for future research (12), which would allow comparisons of NFB results to other means that efficiently achieve the desired effect.

The implications of learned self-regulation of a brain area are two-fold. The first implication of NFB would be to complement conventional neuroimaging methods in making inferences about brain function. Conventional neuroimaging experiments measure brain activity as the dependent variable which changes due to sensory stimulation or performing a behavioural task, while NFB allows investigating the effects of changing the BOLD signal (independent variable) on behaviour (dependent variable). Therefore, while conventional neuroimaging studies provide correlational information, fMRI-NFB complements these methods by additionally allowing researchers to investigate questions of causality (12). The potential impact would be substantial as corresponding capabilities are currently limited to interventional techniques such as transcranial magnetic stimulation, deep brain stimulation, and focal lesions. The second implication of the causal link between brain activity and behaviour is the possibility to modulate behaviour by influencing brain activity. One may argue against the success of NFB by saying that it merely trains the regulation of blood flow instead of the neuronal activity, particularly because biofeedback itself has been employed for modulating blood pressure (13). The modulation of the behaviour as a result of self-regulation of the corresponding neural activity is a proof against this argument.

Change in brain function and structure

In a study of London taxi drivers' brains structure, a correlation between the changes in volume of the right posterior hippocampus — a structure that stores spatial representations of the environment — and the time spent as a taxi driver has been reported, suggesting a plastic change in healthy adult brains in response to environmental demands (14). A follow-up study

detected no correlation of *de novo* navigational skills with brain structure; thus, providing further evidence that the structural changes observed in the taxi drivers were acquired and not merely due to innately good navigation skills (15). Recently, similar experience-dependent structural changes have been demonstrated in white matter, as well: a localised increase in fractional anisotropy, a measure of microstructure, has been detected in white matter underlying the intraparietal sulcus — an area involved in visually guided movements of the eye, hand, and visuo-motor coordinate transformation — following training of a complex visuo-motor skill (16). All these results provide evidence that not only the function but also the structure of our brain can be altered by regular mental training even in adulthood.

These promising results allow us to hypothesise that NFB, by its nature of subjecting participants to self-regulation training for a certain duration, may also induce structural brain changes. So far, studies have focused mainly on the feasibility of fMRI-NFB in healthy subjects or a clinical population, i.e. whether one can learn how to influence their own brain activity. Changes in the brain due to NFB training have been investigated only recently. Modulation of the relevant functional connectivity has been demonstrated after NFB training of the anterior insula (17,18), the left amygdala (19), auditory attention-related brain areas (20) and the somatomotor cortex (21,22). Modulation of functional connectivity has also been demonstrated in our study where four weeks of NFB training of the somatomotor cortex (i.e. target brain area) induced an increase in functional connectivity (23) between the target brain area and the anterior mid-cingulate cortex as a result of the increased cognitive control over the target brain area. Structural connectivity changes, however, proved to be ambiguous (24).

A Typical fMRI Neurofeedback Experiment

Data acquisition in rt-fMRI

Recent advances have rendered real-time analyses possible, so image reconstruction, transfer, and analysis can be accomplished within the time frame necessary for the acquisition of a single volumetric dataset (repetition time: TR) — typically within 2 seconds. Most scanners are equipped with a BOLD echo-planar-imaging (EPI) sequence enabling fMRI, but acquired volumes are usually available only in one package after finishing the whole measurement. Because

built-in solutions for fMRI analysis are usually inadequate due to a lack of processing options, access to the volumes by an auxiliary tool which performs online fMRI analysis is also essential. Most companies provide option for real-time export of the acquired data which reconstructs each volume one-by-one right after its acquisition (i.e. online), therefore allowing parallel analysis with the acquisition. At the time of writing, some companies' solutions (e.g. Philips') work out-of-the-box, while others (e.g. Siemens') require additional adjustments to ensure maximal temporal consistency (25).

Apart from the real-time access to the data, a separate computer dedicated to real-time analysis is also necessary. The computational burden of the real-time analysis is higher than that of any other NFB component, therefore this computer should be powerful enough to perform all the necessary processing. In other words, a computer with high processing power would allow a higher number of more complex processing steps. The results of the analysis need to be presented to the subject in parallel with the acquisition, which requires a stimulus-generating computer presenting the feedback to the subject through a beamer or LCD-goggles in the case of a visual feedback, or through headphones in the case of auditory feedback. A connection between the scanner and the stimulus-generating computer may be also useful (but not essential) to compensate for the temporal variability of the analysis and to synchronise feedback presentation with the acquisition via a trigger pulse from the scanner (Figure 1). Because this variability is usually well below the TR that is generally used, simply presenting the results of the analysis as soon as they are available can be also a viable solution.

Visual feedback is the most commonly used feedback modality because vision is the most dominant human sense, and visual feedback has been shown to surpass auditory feedback (26). The graphical representation of visual feedback varies from a continuously updated graph (27), smiling avatars (28) to fluctuating levels of a thermometer (29) or fire (30). The subjects are usually informed of the feedback presentation delay, which depends on the image acquisition and processing time, and the inherent delay of the BOLD signal, which takes 6 seconds to peak. This does not allow "immediate" feedback and control of the NFB signal like EEG-NFB does, thus leading to reduced contingency, which in some cases could render the NFB training with fMRI more difficult.

Data analysis

There are a tremendous number of pre-processing techniques (motion correction to ensure spatial consistency in time; correction of the distortion due to magnetic field inhomogeneity; slice timing to ensure temporal consistency across slices acquired at slightly different time points; spatial normalisation to ensure spatial consistency across subjects; spatial filtering to improve signal-to-noise ratio at the expense of effective spatial resolution) and evaluation methods (univariate and multivariate; model-based and model-free approaches) at hand, and all of them are applicable in real time as well. The main challenge is how to increase speed while maintaining quality at the same time. Motion correction is the most important step, because it ensures the spatial consistency over time. It is also the most time-consuming; therefore, its optimisation usually means finding the trade-off between time and quality (31,32). Distortion correction and spatial filtering may further improve the data quality (33).

The other essential step is to find the spatial correspondence between the volumes and the target region(s) of interest (ROI) selected for feedback. These ROIs can be selected on a functional or anatomical basis, or based on an atlas. Using a functional localiser only requires a within-subject (i.e. rigid-body) registration, which can be easily combined with the motion correction: we only have to specify the first scan of the functional localiser measurement as a reference scan for the motion correction. Using the anatomical scan of the given subject or an atlas additionally requires affine registration and involves spatial filtering. The former is more computationally intensive, while the latter decreases effective spatial resolution. A more preferable approach could be to map the ROI obtained from the anatomy or an atlas to the functional volume of the actual measurement (34), which is fast and preserves the original functional data.

There are two main groups of evaluation approaches to analyse fMRI data in real time. The growing-window or incremental approach (35) simply uses all available data; therefore, its statistical power increases with more acquired data. On the other hand, it rather provides information about the mean activation over time. The sliding-window or constant approach uses only a temporal subset of data, thus keeping the
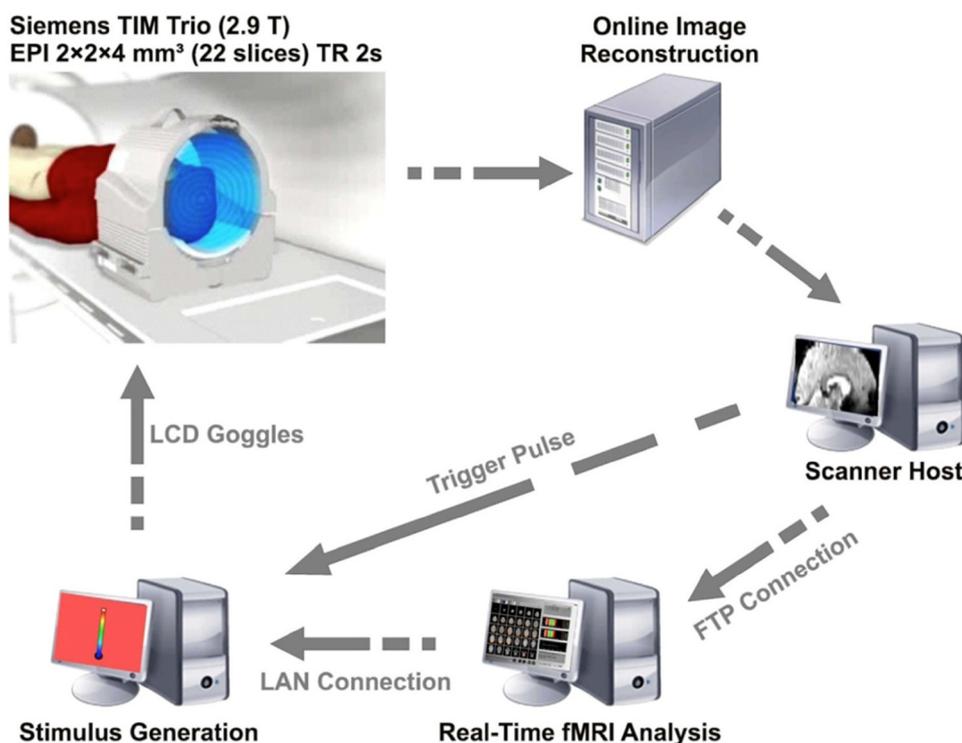

Figure 1: Real-time fMRI neurofeedback setup. The real-time fMRI neurofeedback system set up is a closed loop. The subject tries to self-regulate their brain activity while getting feedback of their own brain activity from the stimulus-generating computer through a beamer or LCD-goggles.

statistical power fixed and reduced compared with the maximum achievable with the growing-window approach. The sliding-window approach (36) reflects the current activation state better, and the smaller the window's width, the better the temporal resolution. For both approaches, all the statistical evaluation techniques developed for conventional fMRI are available, such as t tests (37), correlation analysis (38), (multiple) regression (39), and independent component analysis (40). The scan-to-scan approach can be considered as a sliding-window approach with a window width of one single scan; therefore it provides maximum temporal resolution. However, this approach suffers the most from the signal fluctuations resulting from both technical and physiological noise. The loss of temporal information about the noise can be partially compensated for in the spatial domain; namely by accumulating even weak information available in more voxels. The most straightforward and the most widely employed approach is to average the signal of a subset of voxels (ROI-based analysis). In this case, a "background" ROI taken from a non-involved area should also be used to correct for the global changes during the measurement due to changes in the general arousal state or in the breathing rate. The introduction of "control" phases during the measurement allows taking the last several time points of the previous control period as reference, thus correcting for the signal drift:

$$NS_t = (S_t / S_{previous\_control} - 1) \times 100$$

where NS_t and S_t correspond to the normalised and raw signal intensity at time point t, respectively, while $S_{previous\_control}$ refers to the mean signal intensity during the previous control period. To increase the robustness and minimise the sensitivity of the normalised signal to signal fluctuations around zero, a double logistic-like function (f) for calculating the feedback signal (FS) with the following characteristics can be implemented: a relatively flat centre between -0.5 and 0.5 NS ensures that small changes in NS will have limited effect on FS, while plateaus at -2 NS and 2 NS control saturation (Figure 2). These values may be adjusted for the actual experiment:

$$FS = f(NS_t)$$

A more sophisticated approach for combining signals from more voxels is employing a pattern recognition technique, which offers good sensitivity even if the signals in each voxel of the ROI do not change identically (41). Its real-time implementation has the ability to provide feedback based on intuitive translations of "brain state" rather than localised fluctuations (42).

Outline of a neurofeedback training

NFB training enables the self-regulation of the activity of a defined brain region. In the case of fMRI-NFB, a region or network of interest may be selected from which the signal is then acquired. The selection of an ROI can be done structurally as well as functionally. In structural localisation, ROIs are generally defined based on macroanatomy, such as gyral anatomy. It is best to define such ROIs for each individual based on their own anatomy, since there can be substantial inter-subject variability. In functional localisation, a separate 'localiser' measurement is used to identify voxels in a particular anatomical region that show a particular response (e.g. voxels in the fusiform gyrus that are more responsive to faces than to other objects); these voxels are then explored to examine their response to NFB (43).

Then subjects undergo several training sessions in which they are instructed to come up with their own mental strategy and optimise it in order to enhance self-regulation of their brain activity. The mental strategy is achieved by mental imagery, where the subjects need to imagine situations or feelings without overtly experiencing them. Concurrently, subjects also view feedback originating from their own brain activity, which guides them towards selecting the most efficient strategy. It is hoped that during successful NFB training, the subjects' ability to
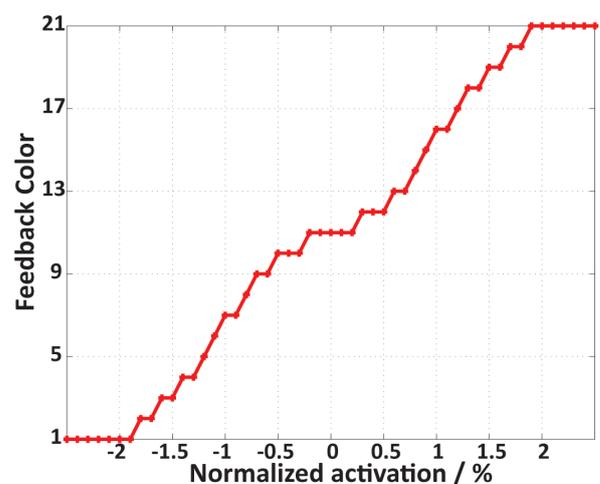

Figure 2: Double logistic-like function used to calculate feedback signal (FS).

influence their brain activity would gradually increase, and training effects would be manifested when subjects find a strategy that reliably elicits the desired brain activation(s) even without the help of feedback. Therefore, the ultimate test of the NFB training effect is the transfer condition, which is the comparison between pre- and post-training measurements, during which subjects try to regulate their own brain activity while not provided feedback. This comparison would tell us how much the subjects' ability to regulate their brain activity has improved. In addition, behavioural tests may also be performed pre- and post-NFB training to investigate whether the training effects generalise to produce any behavioural changes.

Neurofeedback Training in Various Brain Regions

Ever since fMRI-NFB has been shown to be feasible, it has paved the way for researchers to experiment with fMRI-NFB training in various areas of the brain. Researchers have trained subjects to volitionally control specific cortical and subcortical areas such as the primary motor cortex (22), the supplementary motor area (SMA) (27), the anterior cingulate cortex (ACC) (27,30), the amygdala (19,44), and the insula (45). Here, we attempt to briefly summarise major studies of fMRI-NFB training in these areas.

Somatomotion: Training the somatomotor cortex

The somatomotor cortex (SMC) is responsible for planning, control, and execution of voluntary movements. The SMC is easily accessible and produces a robust signal; moreover, it is a "natural" target for a brain-computer interface, an approach attempting to establish mind control over machines such as computers, robots, and prosthetics. Therefore, the SMC was one of the first (46) and perhaps the most often targeted areas when investigating the feasibility of fMRI-NFB.

In a pioneering study, subjects were shown to be able to increase their BOLD signal activity in the hand area of the SMC more significantly than the controls who did not receive valid feedback (21). This also held true when two weeks of NFB training included only daily self-practice (without scanning) of motor-hand imagery established during an initial fMRI-NFB session (22). This group also showed that the NFB training resulted in the recruitment of additional neural circuitries implicated in motor skill learning such as the

hippocampus and the limbo-thalamo-cortical pathway.

In the SMC, the success of NFB training possibly depends on the length and/or the distribution of training. Recent studies have shown that short training periods (1–4 runs within one day) (47,48) could be inadequate to achieve self-regulation of an ROI. Our own results have shown that in an intensive 48-run NFB training period that spanned four weeks, subjects who underwent NFB training of the SMC showed a distinct increase of the BOLD signal in the SMC (49). In addition, successful NFB training of the SMC not only resulted in enhanced fMRI activation during transfer (i.e. without feedback) but also during overt finger movements (23). The latter also implies functional plasticity changes in the SMC in an overt movement condition involving activation of the trained neuronal substrate. We could also prove that training efficiency (i.e. how subjects were performing during the training) was highly correlated to the overall training success (pre- to post-training transfer), which helps us to predict the effect of training on the fly (50).

Emotion: Training a single ROI and a whole network

Emotions shape human beings' interaction with the world. Ever since the scientific community developed interest in understanding the neural basis of emotion and its relationship to cognitive function and behaviour, fMRI has been used as a tool to achieve this goal. As neuroimaging technology advanced, neuroscientists began to wonder if emotions can be self-regulated via NFB. One of the early fMRI-NFB studies in the domain of emotion was on the amygdala (51).

Since then, researchers have embarked on investigating the feasibility of fMRI-NFB in the emotional domain. Self-regulation has been investigated in the subgenual ACC (sACC) — a region involved in the generation of affective states and implicated in psychopathology (52,53). In that study, subjects had to come up with one strategy for increasing positive mood (hence decreasing the sACC activity) during the NFB training. Subjects who had received feedback were able to decrease their sACC activity, in contrast to subjects who received sham feedback. Similarly, self-regulation of the amygdala using positive autobiographical memory retrieval was successful in subjects who received feedback but unsuccessful in the sham control group (19).

Training of areas involved in emotional regulation could be beneficial for patients who suffer from emotion impairment, which manifests

in depression, bipolar disorder, and obsessive-compulsive disorder, among others. The aim of doing NFB training in these areas is to the reduce emotional symptoms of a particular disorder.

NFB using fMRI can be applied to train not only a single ROI but also a whole network. Training the emotion network in the brain, which includes the amygdala and the insula, has shown that subjects were able to modulate the activity of that network (29,44). Training also generalised to a behavioural measure in which participants' sensitivity to aversive pictures had increased with learned regulation of the insula (29). Consequently, promising results in this domain have steered researchers towards using actual patients in NFB studies.

Training the cognitive engine— Anterior Mid-Cingulate Cortex

In addition to training the motor and limbic cortical areas that directly control action and emotion respectively, training the anterior mid-cingulate cortex (aMCC), the cognitive engine that drives both domains, has also been in the focus since the beginning (54). The aMCC is best described as a limbic premotor cortex with regard to its functions in general (55). New data gathered from meta-analysis suggest integration of three domains in the cingulate cortex: negative affect, pain, and cognitive control (56). This has shown that all three of these domains activate a common region within the aMCC. Since the aMCC might implement a domain-general process (56), we may hypothesise that self-regulation of the aMCC activity could be beneficial to any of those three domains. The feasibility of fMRI NFB in the aMCC was shown first by Weiskopf et al. (54) and later applied in the chronic pain domain (30).

Application of Neurofeedback as a Supplementary Therapy Tool

Neuroimaging already contributes to the treatment of mental disorders by providing information about the pathophysiological sources that may become the targets for physical (TMS, deep brain stimulation) or NFB intervention (57). NFB treatment can also be incorporated into a comprehensive biopsychosocial intervention package. However, we need to be aware that some neuropsychiatric diseases are heterogeneous; for example, depression may be brought about by focal lesions in the brain but can also occur as a result of a range of other mental disorders. Nevertheless, if a causal link is shown between mental illness and dysfunctional activity in specific areas or networks in the brain, the ability to self-regulate these areas may potentially have a favourable effect on a patient's mental health (57).

NFB using fMRI has recently been used to treat Parkinson's Disease (PD) (58). PD patients who underwent NFB training learned how to increase activity in the SMA using motor imagery and subsequently improved their motor speed of finger tapping, an overt movement. The transfer also generalised to their clinical ratings of motor symptoms, which improved after the NFB training. PD patients who did not receive feedback of their SMA activity did not gain control of SMA activation and consequently showed no motor improvement. This study has shown that self-regulation of motor circuits in PD patients through fMRI-NFB is achievable and may be clinically beneficial. In a proof-of-concept study of NFB in depression, depressed patients who underwent NFB using a positive emotion strategy not only learned to self-regulate emotion networks but also reduced their clinical symptoms (59). These studies are certainly promising, but randomised clinical trials would be needed to assess the clinical efficacy of NFB as supplementary therapy tool for these psychiatric diseases.

The use of NFB in clinical applications as a supplementary treatment is not limited to psychiatric diseases but could also be applied to lifestyle diseases such as obesity. The ability to intervene directly in the brain by voluntary regulation of eating-related regions could be used as a tool to increase the control of such brain regions and consequently influence eating-related behaviour. Exploratory work has been done recently where fMRI-NFB training of the anterior insula — a brain region involved in gustatory function — was investigated in lean and obese men (60). The study found out that obese men were able to upregulate the anterior insula more significantly compared to lean men. This may suggest that obese men are more sensitive to gustatory learning; hence, future studies could be aimed at trying to downregulate activity in brain networks or areas involved in gustation and reward processing.

In the domain of chronic pain, an influential study has shown that healthy subjects were able to learn to control activation in the rostral ACC (rACC) — a region involved in pain perception and regulation (30). When subjects increased or decreased rACC activation, there was a significant change in the subjects' perception of pain caused by an externally applied noxious thermal stimulus. Moreover, pain perception was correlated with the level of rACC activation. This

study has revealed that voluntary control over rACC activation mediated by fMRI-NFB leads to control over pain perception. The brain system that mediates pain perception is a highly relevant target for NFB training in a clinical setting. Chronic pain is an important clinical problem and is treated mainly with drugs which target neurons based on their selective expression of drug receptors. However, a drug may act on other receptors on other cells, which may bring about unwanted side effects. NFB using fMRI could be a promising supplementary, if not main, treatment, as it has not produced any detectable side effects, is less invasive, and most importantly, targets the "source" of a disease anatomically.

Despite numerous studies confirming the feasibility of fMRI-NFB and its clear advantages over EEG-NFB in many aspects such as higher spatial resolution, and better specificity, it is still rather mainly a research tool, while EEG still dominates in routine therapy due to its lower cost and higher availability. The lower temporal resolution of fMRI and the sluggish nature of the BOLD signal strongly reduce the contingency between the behavioural change (i.e. switching between strategies) and the feedback signal; therefore, NFB requires longer and probably more conscious training with fMRI than with EEG, which may also pose a limitation to the former in clinical applications. On the other hand, fMRI can be used to study brain areas hardly accessible via EEG (e.g. basal ganglia, hippocampus), and its indirect yet single measure (i.e. the BOLD signal) provides a lower degree of freedom in parameter selection (i.e. a more straightforward link to the brain functions) than the more direct but multiple measures (e.g. frequency bands, power, amplitude) of EEG. The issue of multiplicity can be well demonstrated by the abundance of EEG-NFB protocols determining which measure(s) should be trained and how (61,62). Moreover, despite the longer history of EEG-NFB, the field has largely proceeded without validation until recently (63), methodologically satisfactory studies on its efficacy were lacking (64), and treatment effect is sometimes hard to distinguish from placebo effect (65). On the other hand, fMRI-NFB emerged from methodological research, and studies have usually been performed with careful controls as demonstrated in deCharms' study (30). We believe that these two techniques are complementary to each other, and while EEG-NFB may benefit from the more carefully controlled specificity of fMRI-NFB, the latter may benefit from the vast clinical experience of the former.

Conclusion

In this review, we have outlined the implementation of fMRI-NFB and highlighted that NFB is a promising tool that has both scientific and clinical applications. The feasibility of NFB training has been demonstrated in several domains of the brain, namely somatomotion, emotion and cognitive control. Studies of NFB on patient populations are starting to gain momentum. Nevertheless, there are still many open questions in various aspects of NFB and it would certainly be interesting to follow closely the developments of the field.

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Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for the important intellectual content, final approval of the article, provision of study materials or patient, statistical expertise, obtaining of funding, administrative, technical or logistic support and collection and assembly of data: WID, TA

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