Trends in Cognitive Sciences

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Review

Advances in fMRI Real-Time Neurofeedback

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Functional magnetic resonance imaging (fMRI) neurofeedback is a type of biofeedback in which real-time online fMRI signals are used to self-regulate brain function. Since its advent in 2003 significant progress has been made in fMRI neurofeedback techniques. Specifically, the use of implicit protocols, external rewards, multivariate analysis, and connectivity analysis has allowed neuroscientists to explore a possible causal involvement of modified brain activity in modified behavior. These techniques have also been integrated into groundbreaking new neurofeedback technologies, specifically decoded neurofeedback (DecNef) and functional connectivity-based neurofeedback (FCNef). By modulating neural activity and behavior, DecNef and FCNef have substantially advanced both basic and clinical research.

Trends

Advanced fMRI neurofeedback can be conducted without participant awareness of what is manipulated.

Advanced fMRI neurofeedback techniques use multivariate analysis of a particular brain region to induce a specific activation pattern in the targeted region, rather than simply increasing or decreasing the mean activation level throughout the region.

Advanced neurofeedback fMRI techniques can modify connectivity between different brain regions and could lead to amelioration of aberrant connectivity in clinical populations.

DecNef integrates aspects such as implicitness, reinforcement schedule with external reward, and multivariate analyses.

FCNef integrates aspects such as implicitness, reinforcement schedule with external reward, and connectivity analyses.

Recent Advances in fMRI Neurofeedback

Functional magnetic resonance imaging (**fMRI**; see Glossary) **neurofeedback** is a type of biofeedback in which real-time online fMRI signals are used to self-regulate brain function [1–9]. Studies using fMRI neurofeedback have shown improvements or changes in specific brain functions and/or behavior associated with changes in the activity of localized brain areas [10–20]. For example, fMRI neurofeedback changed the activation of the visual cortex and improved performance on a visual task [20].

Since its initial development in 2003 [9] fMRI neurofeedback research has grown rapidly in popularity. This is demonstrated through the accelerated number of publications on fMRI neurofeedback over the past decades (Figure 1).

Such an increase in attention has been accompanied by significant progress in fMRI neurofeedback techniques. We focus on four of these advances. First, the use of implicit protocols allows the participants to be kept unaware of the purpose of neurofeedback training [10–12,15,19–21] or even the fact that they are being trained [22]. Second, the use of external rewards, such as money, has been reported to facilitate neurofeedback learning [20,23]. Third, the development of multivariate analysis techniques, which allows more sensitive neurofeedback [24–28], has been incorporated into neurofeedback [13,20,29]. Fourth, changes of connectivity in a targeted brain network [30,31], which could be a cause of mental abnormalities [32–34], have been incorporated into neurofeedback techniques. Combined, the use of these techniques has provided insights into a causal relationship between the modified neural change and modified behavior.

Recently, these four fMRI neurofeedback technique advances have been further integrated into new technological developments, specifically **decoded neurofeedback** (DecNef), which is usually applied to specific brain regions, and **functional connectivity-based neurofeedback** (FCNef), which is applied to connectivity strength between different brain regions. Both

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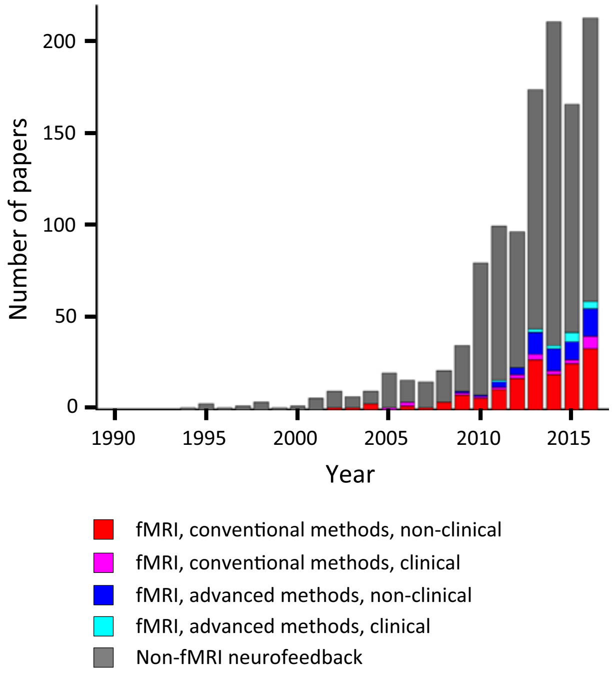

Figure 1. The Number of Publications of Neurofeedback Studies in the Past Three Decades (1990–2016). Each color represents the number of publications searched with a different set of words on PubMed. Red and magenta: studies with the terms 'neurofeedback AND fMRI'; non-clinical populations are shown in red and clinical populations in magenta. Blue and cyan: studies with the terms 'neurofeedback AND fMRI AND (multi-voxel OR decoding OR connectivity)'; non-clinical populations are in blue, and clinical populations in cyan. Grey: studies with the term 'neurofeedback' in which studies using fMRI were excluded, without overlapping with other color bars.

DecNef and FCNef are recent developments in fMRI neurofeedback techniques with unique features (see below). These technologies have helped uncover the relationships between basic brain functions and behavior, and have successfully been applied in clinical settings (Table 1). Although the results of individual studies using DecNef and FCNef have been promising [10–12,19–21,35–37], several fundamental questions about these technologies have been left unanswered.

In this review, after briefly discussing each of the four aspects of the recent advances of fMRI neurofeedback, we address the following four questions about recent neurofeedback technologies, specifically DecNef and FCNef. First, how have the four advances (implicitness, reward, multivariate analysis, and connectivity) been integrated into DecNef and FCNef? Second, how do these new technologies control fMRI **voxel patterns** resulting in specific activity changes at the neuronal level? Third, how is a specific fMRI voxel pattern determined from a huge number of possible combinations of fMRI voxel patterns in a brain region? Fourth, how have these new technologies advanced basic and clinical research?

Note that this paper does not aim to comprehensively survey fMRI neurofeedback studies or discuss general models of fMRI neurofeedback. Readers interested in a more comprehensive review of neurofeedback work are encouraged to read other recently published reviews [1,38,39].

Four Significant Aspects of Progress of fMRI Neurofeedback

We discuss here the characteristics as well as representative basic and clinical studies of each of the above-mentioned four aspects. We indicate how each of these characteristics has an

Glossary

Correlation-based neurofeedback: one of the most frequently used types of connectivity-based neurofeedback. Feedback scores reflect temporal correlations between fMRI signals in two brain regions.

Curse of dimensionality: this refers to a problem that is caused by an exponential increase in volume in association with adding extra dimensions to Euclidean space [76]. The curse of dimensionality can occur wherever a high-dimensional dataset is handled. For instance, MRI datasets are considered to be high-dimensional. One MR image contains many voxels (see below). If one MR image contains 100 voxels, and each voxel has one of two values (0 or 1), the number of possible voxel patterns (see below) in the MR image should be 2^{100}, which exceeds one nonillion. One effective method to circumvent the curse of dimensionality is to reduce the number of dimensions.

Decoded neurofeedback (DecNef): DecNef was introduced in 2011 [20]. This advanced neurofeedback technique has been developed by the integration of recent technological advances including implicit protocols, external rewards, and multivariate analysis (main text for details). The integration of these aspects enables DecNef to induce a specific pattern (see below) of fMRI signals in the targeted brain region without the participants being aware of the meaning of the neurofeedback provided to them.

Dynamic causal modeling (DCM): this method infers causality between different brain regions, or mutual influences of different regions in a network. In a DCM-based connectivity neurofeedback, the degrees of fitness of two or more competing models to neuroimaging data are calculated. The model with the largest degree of fitness is selected as the right model.

Functional magnetic resonance imaging (fMRI): fMRI measures blood oxygen level-dependent (BOLD) signals, which are thought to reflect neuronal activation. fMRI is an MRI technique that employs high magnetic field strengths.

Functional connectivity-based neurofeedback (FCNef): a neurofeedback technique that was advantage over earlier fMRI neurofeedback studies. Finally, we point out controversies and unclear characteristics of each of these aspects.

Implicit Neurofeedback

In conventional fMRI neurofeedback methods, participants are informed of the purpose of training, what the neurofeedback signal represents, what brain function is to be trained by neurofeedback, and/or what behavioral changes are expected to occur [4,14,18]. However, recent studies have demonstrated that neurofeedback training can be highly effective even when participants do not know what behavior is being trained, or indeed that they are being trained at all [10–12,15,19–22]. We have termed this type of fMRI neurofeedback **implicit neurofeedback**.

For example, participants might be presented with a disk that represents their feedback score, and asked to try to make the disk as large as possible without being informed of any additional information. Unknown to the participants, the size of the disk actually reflects the degree of 'similarity' of an fMRI voxel pattern in a specific brain region measured on a real-time basis to the fMRI voxel pattern based on a predetermined targeted neural activity pattern. After repetitive trials with this procedure, participants learn to significantly enhance the degree of the similarity [10–12,15,19–21]. In other words, they learn to induce neural activity patterns similar to the targeted predetermined activity pattern. Importantly, results of post-experiment questionnaires showed that participants are indeed unaware of what brain functions were being trained [10–12,15,19–21].

Implicit neurofeedback has several advantages and/or novel features compared to traditional neurofeedback. First, implicit neurofeedback reduces or eliminates the possibility that the changes in brain function or behavior associated with neurofeedback training are due to neural pattern changes involved in the specific intention of the participants to improve the function. This is because, using implicit proposals, participants are aware of the presence of feedback scores, but they are unaware of what the feedback scores represent. Thus, the modified behavior can be more confidently attributed to the brain region that was targeted by the neurofeedback. Second, implicit neurofeedback decreases the possibility of the so-called experimenter effect in which participants consciously or unconsciously learn how to produce results that they think would meet the expectations of the experimenter [40] (Box 1). Third, implicit neurofeedback may be applied to clinical interventions where conventional methods do not effectively work. For example, in conventional methodology for extinguishing fear responses to traumatic memories, a participant is repeatedly presented with an aversive stimulus associated with fear [41]. The repeated presentation of the aversive stimulus can cause overwhelming distress in the participant, and can therefore lead to a high dropout rate from the extinction therapy [42]. However, the implicitness of neurofeedback could eliminate or greatly reduce the possibility of patients developing such distress during training. Another advantage of implicit feedback in clinical interventions is that it can be used for patients whose cognitive ability does not allow them to understand complicated training instructions. Fourth, if implicit neurofeedback successfully improves a brain function or behavior without the awareness of the participant, this suggests that conscious processing is not greatly involved in the improved function or behavior.

Although studies that use implicit neurofeedback have demonstrated very robust effects [10–12,15,19–21], it remains unclear whether implicit or explicit neurofeedback is more effective. One study did demonstrate a case in which implicit neurofeedback was more effective than explicit neurofeedback in changing fMRI activity in the supplementary motor area [23], but this study did not investigate resultant behavioral measures. Systematic investigations of comparisons between effectiveness between implicit and explicit

first introduced in 2015 [35]. FCNef integrates correlation-based neurofeedback with the recent technological advances including implicit protocols and external rewards (main text for details). FCNef changes the temporal correlation of fMRI signals between two brain regions in a network without the participants being aware of the meaning of neurofeedback given to them.

Implicit neurofeedback: a type of neurofeedback in which participants are not aware of the meaning of the feedback provided to them or of the purpose of the neurofeedback training in which they participate. Implicit neurofeedback is opposed to explicit neurofeedback in which participants are informed of the meaning of feedback, what brain area(s) are intended to be changed, and/or the purpose of the neurofeedback training.

Neurofeedback: a generic term for methods to provide participants with information that reflects their own physiological state (e.g., brain activation or blood pressure) as a feedback signal for possible self-regulation.

One-to-many relationship: the relationship between two entities (A and B) in which an element in A is linked to multiple elements in B, while an element in B is linked to only one element in A.

Resting-state functional connectivity: this is characterized as temporal correlations between fMRI signals in multiple brain regions. fMRI signals are measured during a resting state in which participants merely fixate on a blank visual display without performing any other task.

Voxel pattern: a pattern of multiple voxel values. A voxel refers to a 3D volumetric unit in an MR image. A voxel is analogous to a pixel in a 2D picture or computer screen, although a voxel is 3D. In fMRI measurements, one voxel is typically cubic of a few millimeters in size (e.g., $3 \times 3 \times 3$ mm^3). One voxel consists of one BOLD signal located at one point in the gradation of intensity between black and white.

Table 1. Development and Applications of DecNef and FCNef in Chronological Order

Year	Refs	Population	Method	Target brain area/connectivity	Purpose of neurofeedback training	Increase in neurofeedback scores? (effect size of major results)	Behavioral change? (effect size of major results)	Correlation between neural and behavioral changes?
2011	Shibata *et al.* [20]	Normal	DecNef	Early visual cortex	To test if inductions of activations in the early visual cortex lead to visual perceptual learning of an orientation	Yes (1.06)	Perceptual learning of an orientation occurred (1.77)	Significant (r = 0.87)
2015	Megumi *et al.* [35]	Normal	FCNef	Parietal and motor cortices	To test if FCNef is capable of inducing a long-term increase in target connectivity	Yes (0.74)	N/A[a]	N/A
2016	Amano *et al.* [10]	Normal	DecNef	Early visual cortex	To test if the early visual cortex is capable of associative learning of an orientation and color	Yes (1.88)	Associative learning of an orientation and red color occurred (0.87)	N/A
2016	Shibata *et al.* [19]	Normal	DecNef	Cingulate cortex	To test if induction activations in the cingulate cortex increase and decrease preferences for faces	Yes for increase (1.17) and decrease (0.70) groups	Preferences for faces increased (1.38) and decreased (0.96)	Significant (r = 0.78)
2016	Koizumi *et al.* [15]	Normal	DecNef	Early visual cortex	To test if pairings of monetary reward and activations of the early visual cortex lead to counter-conditioning of fear memory	Yes (0.53)	Skin conductance response to a fear-associated stimuli decreased (0.46)	N/A
2016	Cortese *et al.*[b] [11]	Normal	DecNef	Parietal and frontal cortices	To test if inductions of activations in the parietal and frontal cortices increase and decrease perceptual confidence	Yes for increase (2.40) and decrease (2.65) groups	Confidence in a visual task increased (1.60) and decreased (0.37)	Significant (r = 0.68)
2017	Taschereau-Dumouchel *et al.* [21]	Phobia	DecNef	Ventrotemporal cortex	To test if pairing of monetary reward and activation of the ventrotemporal cortex reduces fear to a specific object category	Yes (0.62)	Skin conductance response to a fearful category decreased (0.57)	N/A
2017	Yamada *et al.* [36]	Major depression	FCNef	Middle frontal gyrus and precuneus	To test if FCNef on abnormal connectivity for patients with major depression reduced the severity of depression	Yes (1.85)	Hamilton depression rating scale improved (1.83)	Significant (r = 0.87)
2017	Yamashita *et al.* [37]	Normal	FCNef	Parietal and motor cortices	To test if changes in target connectivity lead to changes in reaction times in a visual task	Yes (0.22)	Changes in reaction times in a color/word Stroop task (0.38)	Significant (adjusted R^2 = 0.22)

[a]N/A, not available.
[b]The authors published another paper [12] using a different method of data analysis with a different purpose.

neurofeedback will be necessary to clarify this issue. One possibility is that implicit feedback is more effective on passive types of learning, such as exposure-based learning [43] and classical conditioning [44], which do not require much conscious effort for learning acquisition.

Role of External Reward

In most conventional fMRI neurofeedback studies, feedback scores are provided to participants in the form of a visual or auditory stimulus without external reward [4,9,13,14,17]. Feedback scores basically reflect how close the brain activation is to the predetermined targeted measure. If the brain activation becomes closer to the predetermined target, a larger

Box 1. Artifact Possibilities

In fMRI neurofeedback there are two possible sources of contamination: (i) experimenter effects, and (ii) explicit consciousness strategy.

(i) Experimenter effects refer to an experimental artifact in which participants consciously or unconsciously aim to produce the results to meet what they think of as the expectation of the experimenter [40]. In conventional neurofeedback methods participants are given an explicit instruction, which may increase the possibility of contamination with experimenter effects because participants are aware of what is expected. By contrast, in DecNef and FCNef it is difficult for participants to guess what is expected because they do not know what the feedback represents. Some might think that participants in implicit neurofeedback also learn to induce voxel patterns similar to the predetermined targeted voxel pattern by trying to learn what is expected by the experimenters. However, this possibility has been ruled out by DecNef training with a double-blind method [21], an extension of [15], and by DecNef training in a totally automated and modern monkey experimental system [77], which replicated the human study [19].

(ii) Explicit consciousness strategy refers to various voluntary and active efforts of the participants to improve feedback scores. It has been assumed that DecNef is accomplished without the participants being aware of what neurofeedback signals represent, and therefore no explicit consciousness strategy is used. However, one may raise the possibility that, to obtain higher feedback scores during neurofeedback training, participants intentionally generate and hold an image related to the trained feature as an explicit consciousness strategy. For example, DecNef led to higher sensitivity to the trained orientation [20]. This sensitivity enhancement could have occurred because subjects intentionally caused a visual image of the trained orientation. However, this possibility is highly unlikely. After a DecNef experiment was over, participants were asked to report what they were doing during training. If subjects had intentionally used an explicit conscious strategy, such as having an image of the trained feature, and thereby obtained higher scores, subjects should have a vivid memory of the strategy and/or the image they had during the training. However, none of the participants reported anything close to the strategy or image.

feedback score is provided to participants. In this case, feedback scores may work as a reinforcement signal, which provides (i) cues to making activations closer to the targeted activation measure as a supervising signal, and also gives (ii) an internal sense of achievement or internal reward [45].

In addition to feedback scores, some recent fMRI neurofeedback studies provide participants with external reward such as money [10–12,15,19–21,35,37], an approach inspired by human and animal reward studies [46–48]. These experiments have robustly shown that external rewards enhance learning. Indeed, a combination of feedback scores and external rewards enhanced neurofeedback effects to a greater degree than feedback scores or external reward alone. A previous study [23] recently reported that feedback scores combined with monetary reward are more effective on fMRI self-regulation in the supplementary motor area (SMA) than feedback scores alone. Conversely, at least in simple human instrumental conditioning, external reward alone without feedback scores did not seem to produce a large effect [49]. Although feedback scores play both roles in inducing goal-directed neural activity and in providing participants with internal sense of achievement, which reinforces neural activity induction, it is possible that external reward merely acts as an additional reinforcing factor.

One interesting question concerns how the timing of the presentation of external rewards and feedback scores affects neurofeedback training. In general, feedback scores are presented in two different ways during the fMRI neurofeedback training; continuously and intermittently [50–52]. Continuous feedback refers to feedback that is presented continuously during neurofeedback training, and the feedback score changes every time brain activation is measured by fMRI, for instance, every 2 s. Intermittent feedback is defined as feedback that is not provided continuously, and is provided only intermittently, for instance at the end of a block that spans 40 s. The intermittent feedback score is based on the brain activation averaged across the block, which includes several fMRI measurements [50,51]. Which type of feedback is more effective remains controversial. A recent computational study [52] has indicated that, for successful fMRI neurofeedback learning, the temporal characteristics of the fMRI signal need to be considered because the fMRI signal is delayed and blurred in time relative to underlying neural activities because hemodynamics is slower than neuronal firing. These characteristics form a temporal credit assignment problem [53] in which participants need to associate their neural activities at a particular timepoint with a feedback score that reflects the delayed and blurred fMRI signals. The results of this study [52] suggest that continuous feedback is more effective when participants are provided with explicit knowledge of how the feedback is calculated because this knowledge helps participants to solve the temporal credit assignment problem. On the other hand, intermittent feedback may lead to better neurofeedback learning without such knowledge (i.e., implicit neurofeedback training) because intermittent feedback largely reduces the temporal credit assignment problem. It is yet to be revealed how often feedback scores and external reward should be given to achieve maximum neurofeedback training.

Multivariate Methods

A new trend in fMRI neurofeedback [20,29] is to employ multivariate analyses or decoded fMRI signals [24–28,54]. Conventional fMRI neurofeedback methods increase or decrease the 1D amplitude of fMRI signals averaged across a region of interest (ROI) in the brain. However, neurofeedback based on multivariate analysis can change fMRI voxel patterns in the ROI rather than the mean amplitude of fMRI signals of the ROI. Figure 2 (Key Figure) and Box 2 show a typical procedure with a decoding technique. For example, first a decoder is constructed to classify an fMRI voxel pattern into one of different states for a participant (different tasks, exposure to different stimuli) in advance. Second, one of these states is selected as the target state for neurofeedback training. Third, in each training trial (i) the fMRI voxel pattern in the ROI of the participant is measured on a real-time basis, and (ii) the fMRI voxel pattern is input into the decoder, which then computes the likelihood of the targeted state. (iii) A feedback score is given to the participant, which is proportional to the likelihood of the targeted state [20]. A new sequence then starts for a new trial.

One advantage of using a multivariate analysis for neurofeedback over a general linear model (GLM)-based method is that feedback based on multivariate analysis reflects increased and more spatially sensitive information from the fMRI signal patterns than does feedback based on the GLM method. Neurofeedback from the multivariate analysis is based on an fMRI voxel pattern, whereas GLM neurofeedback is based on the averaged amplitude of fMRI voxels in an ROI.

Connectivity-Based Neurofeedback

Previous neurofeedback approaches have focused on modifying brain activity within a targeted ROI [4,9,10,13,15,17,19,20]. However, important brain functions are also formed through a network of interacting brain regions that are highly correlated with each other [55–57]. Recent technological developments, known as connectivity-based neurofeedback [31], have enabled us to modify the connectivity of a targeted network.

There are two main methods for connectivity-based neurofeedback. One is based on **dynamic causal modeling** (DCM) [30,31]. In DCM-based connectivity neurofeedback, participants are asked to try to increase feedback scores that are based on the comparison between two or more predefined alternative models to a targeted model. That is, positive feedback is given to a participant when connectivity strength estimated from measured activity fits better with the targeted model than with an alternative model, while negative feedback is given when connectivity strength fits better with the alternative model than with the targeted model [30,31]. This DCM-based connectivity approach can strengthen unidirectional connectivity where the direction of information flow is hypothesized.

The other method is **correlation-based neurofeedback** in which the feedback score is based on Pearson's correlation coefficients of activity time-courses between two ROIs

Key Figure

A Typical Procedure of One Cycle (Trial) of Decoded Neurofeedback (DecNef) Training

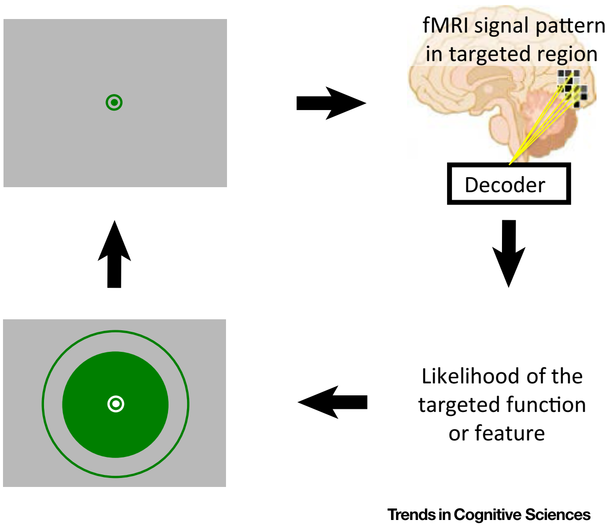

Figure 2. First, while in the scanner, the participant is presented with a fixation mark on which (s)he is asked to maintain his/her gaze (top left). Second, an fMRI voxel pattern in a targeted brain region is measured and input to the decoder that has been constructed before DecNef training (top right). Third, based on the measured fMRI pattern and decoder, the likelihood of the targeted function or feature is computed (bottom right). Finally, the participant is presented with a disk whose size is proportional to the likelihood (bottom left). This cycle is then repeated (Box 2 for more details).

[35,37,58]. No model of connectivity is presumed in this method. Unlike the DCM-based approach, the correlation-based approach is not capable of manipulating the direction of connectivity. However, the correlation-based approach has taken advantage of the development of biomarkers of psychiatric disorders (see below) based on fMRI **resting-state functional connectivity** (rs-fc).

Connectivity-based feedback has been developed to change the degree of interactions between different brain areas. DCM-based neurofeedback is based on predefined models, whereas correlation-based neurofeedback does not assume a model. Because a feedback

Box 2. Typical Procedure of DecNef Experiments

A typical DecNef procedure is described here. First, the function or feature that is to be trained by DecNef is determined. We call this the predetermined targeted function or feature. We also term the underlying fMRI and neural activity patterns associated with the targeted function or feature as the predetermined targeted voxel and neural activity patterns, respectively. The targeted brain region in which neural activity processing of the predetermined function or feature that is to be trained by DecNef is also predetermined. Second, fMRI voxel patterns that correspond to the targeted function or feature in the targeted brain region are measured. Third, using a multivariate analysis based on the measured fMRI signal patterns, a decoder is constructed to decode the targeted function or feature from the fMRI voxel patterns. A decoder may be based on various techniques. For DecNef, sparse logistic regression [20] or sparse linear regression [19] is used, and a support vector machine algorithm is employed in most cases [29]. Fourth, a few days of DecNef training are conducted as illustrated in Figure 2 in main text. Participants in an MRI scanner are presented with a fixation mark where they are asked to somehow regulate their brain activity (Figure 2, top left). They are told that they will be given an amount of bonus money, provided as the external reward, in proportion to the size of the disk which is presented several seconds later (Figure 2, bottom left). No further information is divulged to the participants. Fifth, participant fMRI voxel patterns in the targeted brain regions are measured on a real-time basis and are input into the decoder (Figure 2, top right). The decoder provides the likelihood of the predetermined targeted function or feature together with the likelihood of irrelevant functions or features (Figure 2, bottom right). Sixth, the size of the disk displayed to participants is changed according to the likelihood of the predetermined targeted function or feature provided by the decoder (Figure 2, bottom left). Seventh, this cycle of 20 s (regulation of brain activity → fMRI measurement → calculation of the likelihood of the targeted function or feature → presentation of the disk) is repeated for about 1 h per day.

score is computed more rapidly based on the correlation-based approach, this may be a more practical choice for connectivity-based neurofeedback in clinical populations than DCM-based neurofeedback (see below).

New Neurofeedback Techniques Resulting from the Integration of Multiple New Aspects

Thus far we have reviewed the four key aspects of recent progress in fMRI neurofeedback: implicit neurofeedback, external reward, multivariate methods, and connectivity-based neurofeedback. Recently these aspects have been integrated into DecNef and FCNef for further improvements. In this section we mainly discuss these two new fMRI neurofeedback techniques. The goal of DecNef is for participants to learn to induce a specific activity pattern within a target brain region. To achieve this goal, implicit neurofeedback, external reward, and multivariate analysis are introduced into DecNef training. The goal of FCNef is to change specific functional connectivity between two brain regions. For this goal, FCNef consists of implicit and correlation-based neurofeedback which is accompanied with external reward.

We first outline DecNef and FCNef and indicate their conceptual advantages as neuroscientific and clinical tools. We then discuss how DecNef and FCNef circumvent potential problems. Finally, we discuss clinical applications of DecNef and FCNef.

Conceptual Advantages of DecNef and FCNef

A long-term goal of neuroscience is to establish a causal relationship between specific neural activity and specific behavior. To attain this goal, it is necessary to develop a method by which neural processing, including spatiotemporal brain activity patterns and network-level functional connectivity, are solely and precisely manipulated. We believe that DecNef and FCNef have come closer to this goal than have previous neurofeedback technologies. This is largely because both techniques have incorporated some of the four new aspects discussed above. Specifically, during neurofeedback training both DecNef and FCNef utilize implicit protocols as well as external reward, but DecNef utilizes multivariate analysis whereas FCNef utilizes correlation-based connectivity.

The combination of multivariate analysis and implicitness in DecNef may change brain processing in a more specific manner than other neurofeedback methods. This is because multivariate analysis is sensitive to patterns of activation instead of averaged signals within a brain area. This sensitivity can allow neurofeedback signals to carry more detailed and finer-grained information, and can cause activity patterns that are more specific and closer to the targeted pattern in the targeted brain area. Furthermore, implicitness in DecNef may eliminate or reduce the possibility of contamination from verbal instruction, participant's knowledge of what brain function is being trained, and the use of explicit cognitive strategies to achieve the purpose of training. Contamination by these factors may prevent neurofeedback from precisely producing targeted neural processing, and therefore may produce uncontrolled neural processing. Thus, implicitness in neurofeedback may also better specify the targeted patterns and brain area(s).

Several reports suggest that DecNef causes participants to induce specific activation patterns in the targeted brain region as well as targeted behavioral changes [10–12,15,19–21] (Table 1). For example, DecNef successfully increased the rating of the facial preferences of the participants by presumably repeatedly inducing a specific brain activation pattern within the cingulate cortex and also decreased the rating by inducing another brain activation pattern within the same brain area [19]. In this study, analyses of brain activity during neurofeedback training indicated that the area modulated by DecNef was largely confined to the cingulate cortex, the predetermined target area. Preference changes occurred in the two groups of participants whose preference was set to be changed in either the positive or negative direction. These results suggest that DecNef changed activity patterns in a specific way (preference in the positive or negative direction) within the same targeted area [19]. Such specification in changed activity patterns in the specific brain area resulting from multivariate analysis and implicitness in DecNef could narrow down the possible causes of changing behaviors in a particular manner, and therefore better explore the causal relationship than neurofeedback without multivariate analysis and implicitness. Similarly, implicitness in FCNef can also narrow down the number of connectivity patterns that are affected by FCNef training. The recent finding that neurofeedback is effective even when participants do not know that they are being trained [22] could allow implicit neurofeedback to even more greatly narrow down the effective areas.

Potential Problems and Solutions of DecNef and FCNef

Although DecNef and FCNef have the potential to narrow down the possible causal neural activity and resultant behavioral changes, they face two potential problems. The first problem involves the **one-to-many relationship** from a voxel pattern to neuronal patterns (Figure 3). Many different neural activity patterns can cause the same targeted fMRI voxel pattern in the ROI. If everything is randomly determined, and if participants successfully induce the predetermined voxel pattern the likelihood of the targeted neural activity could be the same as the likelihood of other neural activity patterns. Whether and how DecNef solves this indeterminacy in mapping from a voxel pattern to a neuronal activity pattern is an outstanding question.

We propose here a model of how DecNef handles this problem. The indeterminacy in mapping a voxel pattern to neural activity patterns should occur in a system in which other information processing is randomly determined. However, we suggest that, owing to the regularity of brain processing and the logistic regression analysis used in DecNef, the number of possible neural activity patterns that cause a targeted fMRI voxel pattern may be reduced to one. First, several studies have shown that spontaneous activities in a sensory cortex of animals are not random but are constrained by responses to stimuli that frequently occur in natural scenes, and also by neural circuits that are well organized [59–64]. Such regularities in spontaneous activities largely limit the number of possible neural activity patterns that underlie a function or feature. Second, because the logistic regression analysis used in DecNef can achieve much higher multivariate resolution than voxel size [27,28], DecNef should generate correspondingly hyper-resolution signals, which could make mapping an fMRI voxel level pattern to a neural activity level a one-to-one correspondence or at least mapping an fMRI voxel level pattern to a constrained small number of neuronal activity patterns as in Figure 3. Finally, neurofeedback with external reward may strongly reinforce the component in spontaneous activity, which is stochastically equal to the predetermined neural activity pattern.

The second problem involves the **curse of dimensionality**. In DecNef training the goal for the participant is to learn to induce the targeted voxel pattern in a ROI. The curse of dimensionality in DecNef is the problem that dimensional space of potential voxel activity patterns in a ROI is too large for the brain to discover an efficient solution within as few as hundreds of trials because the search space is excessively high-dimensional [65]. However, there are two reasons that the curse of dimensionality should not apply to DecNef. First, the curse of dimensionality would arise if each voxel pattern is randomly searched in a standard reinforcement learning paradigm. However, this may not be the case [66]. Because numerous neurons are connected to many other neurons, and these connections are not random, the number of neural activity patterns should be limited. Therefore, the number of possible voxel patterns should also be limited [66]. Second, functions used for decoders in DecNef are either pseudolinear [28] or linear [54] and monotonically increasing functions. In this case, reinforcement learning may become almost equal to supervised learning with stochastic gradient ascent [67]. Therefore, the curse of dimensionality should not apply to DecNef.

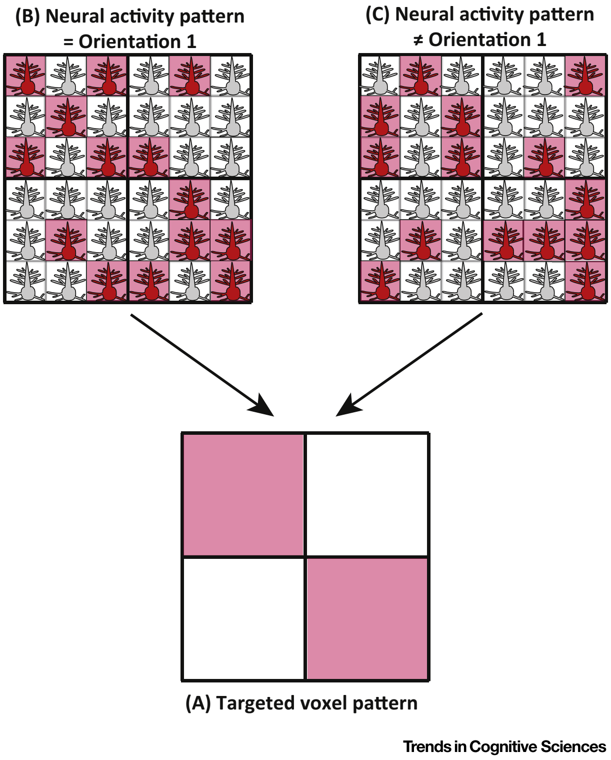

Figure 3. Schematic Illustration to Explain Indeterminacy in Mapping a Voxel Pattern to a Neuronal Pattern (One-to-Many Problem). Red cells and neurons represent activation and grey/white cells no activation. (A) The targeted predetermined voxel pattern. If the majority of the nine neurons in a neural activity pattern are activated, the voxel that receives activity from the nine neurons in a neural activity pattern is excited. (B) Neural activity pattern caused by the presentation of orientation 1 and that leads to the targeted voxel pattern as in (A). (C) Neural activity pattern which is irrelevant to orientation 1 but still leads to the same targeted voxel pattern as in (A).

FCNef may have the same mathematical problems of the one-to-many relationship and the curse of dimensionality as DecNef, although the level at which problems occur could be different because DecNef concerns voxel patterns while FCNef concerns connectivity. However, we suggest that similar solutions and principles for DecNef also apply to FCNef.

In summary, there appear to be two potential problems that might prevent DecNef and FCNef from narrowing down the possible causal neural activity and resultant behavioral changes. One potential problem is that one voxel activity reflects so many neural activities that inducing the targeted voxel activity pattern does not guarantee that the targeted neural activity pattern has occurred. The other problem is the curse of dimensionality, where the dimensional space of potential voxel activity patterns is too large for the brain to discover an efficient solution within hundreds of trials. These problems are serious when a system consists of random processing. However, regularity in brain processing and logistic regression analysis in DecNef may work as powerful constraints to significantly reduce the number of possible neural activity patterns.

Clinical Applications of FCNef and DecNef

A growing body of evidence has indicated that fMRI neurofeedback is a promising tool to ameliorate brain dysfunctions [18,39]. While it is argued that placebo-controlled and double-blind trials on fMRI neurofeedback are necessary to confirm clinical effects [68], recent studies have started to document significant clinical effects of neurofeedback with exactly these types of study design [21,69].

FCNef is characterized as (i) implicitness and external-reward driven and as (ii) rs-fcMRI-based. The combination of these characteristics makes FCNef a powerful tool. Implicitness narrows down targeted networks and connectivity pairs. Changes of the targeted network and connectivity are reinforced by external reward in FCNef. Such strong reinforcement may render FCNef training long-lasting with a relatively short training time. For example, one study [35] applied FCNef to targeted functional connectivity with a 4 day training period, and found that the modified state of connectivity lasted for more than 2 months.

FCNef has two advantages because it is rs-fc-based. One is that it can be directly applied to rs-fc-based abnormal connectivity, or to a biomarker, in networks [32–34]. For clinical purposes, connectivity-based neurofeedback techniques including FCNef need to be combined with biomarkers that characterize psychiatric disorders based on rs-fcMRI. Therefore, success in clinical applications of connectivity-based neurofeedback largely depends on the development of biomarkers. Regrettably, early studies of biomarkers suffered from overfitting of machine-learning algorithms and did not exhibit generalization to completely independent validation cohorts [70–74]. However, the recent development of sophisticated machine-learning algorithms has overcome these technical problems and has led to the production of rs-fcMRI-based biomarkers which are capable of distinguishing patients from controls with high accuracy, and can be generalized to completely independent cohorts [32–34,75]. Development of these robust rs-fcMRI-based biomarkers have allowed FCNef, which is also rs-fcMRI-based, to directly modify them. The second advantage of rs-fc in FCNef is computational efficiency. That is, rs-fc can be estimated easily and quickly during a single-trial period lasting for tens of seconds to 1 minute of an fMRI session without any sensory stimuli presentation, movement, or performance of cognitive tasks [55,56].

Considering these advantages, FCNef has produced preliminary but encouraging therapeutic results in patients with depression as well as in adults with high-functioning autism spectrum disorder (ASD) [34,36,75]. With regards to depression, abnormally more positive functional connectivity between the left dorsolateral prefrontal cortex and left precuneus/posterior cingulate cortex was found to play the most crucial role in patients with high depression scores and melancholic depression [32]. This suggests the possibility that this abnormality may be one of the causes of the depression. Thus, this network was identified as a target of FCNef. FCNef was then applied only to this network to change the connectivity in the negative direction [36]. Both subclinical and patient groups successfully changed the connectivity towards more-negative and normal connectivity after 4 days of FCNef training. The subclinical group showed a significant correlation between the amount of decrease of the connection by FCNef and the degree of improvement in the Beck depression inventory, a self-report inventory that is one of the most widely used psychometric tests for measuring the severity of depression. For the patient group, FCNef training was associated with significant improvement in scores on the Hamilton depression rating scale, the most widely adopted clinician-administered depression assessment scale [36]. This not only indicates the clinical effectiveness of this method but also supports the idea that network connectivity can be a cause of mental disorder because the strength of connectivity of the specific network predicts the severity of depression.

In contrast to the above depression study [36] in which FCNef was applied to only one connectivity, in a study exploring the application of FCNef to ASD patients all 16 functional connections that had been detected as abnormal by the rs-fcMRI biomarker of ASD [34] were selected as FCNef targets [36]. Because there were multiple targeted connections, the weighted linear summation of ASD biomarkers was used as the FCNef neurofeedback score. Intriguingly, several adults with high-functioning ASD successfully changed their neurofeedback scores to a typically-developed level, and retained the typically-developed-like connectivity on a long-term basis [36]. These results indicate that FCNef can be successfully applied to abnormal connectivities that have been identified as biomarkers of depression or ASD.

Although DecNef is less extensively used in clinical applications than FCNef, it can be also a strong tool to change activity patterns that underlie mental disorders or abnormalities, for example phobia [21].

Concluding Remarks

Implicitness, external reward, multivariate analysis, and connectivity in fMRI neurofeedback have recently been integrated to produce ground-breaking methods such as DecNef and FCNef. These methods have the unique ability to explore causal relationships between targeted brain functions and resultant behavioral changes, particularly via implicit protocols. DecNef and FCNef have great potential for interventions in psychiatric disorders which may be caused by abnormal brain functions and/or connectivity. However, the basic principles of fMRI neurofeedback including DecNef and FCNef have yet to be completely clarified (see Outstanding Questions). It is vital to strive to understand these basic principles and address these outstanding issues.

Outstanding Questions

Is fMRI neurofeedback with implicit protocols more effective than neurofeedback with explicit protocols?

How effective is fMRI neurofeedback in treating mental disorders if combined with conventional medication?

How can 1D neural feedback such as disk size change a high-dimensional voxel pattern to the targeted pattern?

A neural activity pattern has many-to-one relationship to a voxel pattern. Given this, how can DecNef induce a targeted neural activity pattern by neurofeedback based on a voxel pattern?

What is the underlying neural mechanism of DecNef and FCNef?

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