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Real-Time fMRI in the Treatment of Mental Health Disorders

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Abstract

Multiple mental disorders have been associated with dysregulations of precise brain processes. However, few therapeutic approaches are currently available in order to correct such specific patterns of brain activity. Since the late 60s and early 70s, many have hoped that this feat could be achieved by closed-loop brain imaging approaches, such as neurofeedback, that aim at modulating brain activity directly. However, neurofeedback never acquired mainstream acceptance in mental health, in part due to methodological considerations. Here, we argue that, when contemporary methodological guidelines are followed, neurofeedback is one of the few intervention methods in psychology that can be assessed in double-blind placebo-controlled trials. Furthermore, using new advances in machine learning and statistics, it is now possible to target very precise patterns of brain activity for therapeutic purposes. We review the recent literature in functional magnetic resonance imaging (fMRI) neurofeedback and discuss current and future applications to mental health.

Keywords: Real-time brain imaging, machine learning, neurofeedback, decoded neurofeedback, functional magnetic resonance imaging.

Introduction

The treatment of mental illnesses still represents one of the greatest contemporary challenges. During the 20th century, considerable scientific efforts were devoted to developing new intervention methods in mental health. However, many treatment strategies turned out to be less successful than expected (Hyman, 2012; Griebel and Holmes, 2013). For instance, after years of research, pharmaceutical companies are now reducing their efforts to develop new treatments for many mental disorders (Miller, 2010; Hyman, 2012; Greenberg, 2013). This state of affairs urges researchers and clinicians to rethink classical intervention methods through the lens of new concepts and modern technologies.

In recent years, modern machine learning algorithms achieved remarkable successes in the field of pattern recognition and computer vision (LeCun, Bengio and Hinton, 2015; Goodfellow *et al.*, 2016). Such algorithms (sometimes called decoders) have notably been applied to recognize patterns of brain activity associated with specific psychological states (Haxby *et al.*, 2001; Haxby, Connolly and Guntupalli, 2014; Cohen *et al.*, 2017). For instance, such brain decoders have been used to predict the subjective experience of fear (Taschereau-Dumouchel, Kawato and Lau, 2020; Zhou *et al.*, 2020) or pain (Wager *et al.*, 2013; Woo *et al.*, 2017). Thanks to the increasing power of computation hardware and the sophistication of modern neuroimaging tools, it is now possible to conduct such brain decoding in real time. This new reality opens up interesting avenues for the purpose of clinical intervention (Keynan *et al.*, 2016, 2019; Ramot *et al.*, 2017; Taschereau-Dumouchel, Liu and Lau, 2018). For instance, this technology can be used to devise various clinical interventions aiming at modulating brain activity. This can notably be achieved by providing participants with visual or auditory feedback representing their decoded brain activity (i.e., neurofeedback intervention). Such interventions can be designed in order to facilitate the reinforcement of brain activity directly and unconsciously in the human brain (Taschereau-Dumouchel, Liu and Lau,

2018). Importantly, as we will see, the efficacy of such closed-loop interventions can be rigorously assessed in double-blind placebo-controlled experiments.

As numerous reviews of the fMRI neurofeedback literature have been written in recent years (Weiskopf, 2012; Sulzer *et al.*, 2013; Sitaram *et al.*, 2017; Watanabe *et al.*, 2017; Thibault *et al.*, 2018; Pindi *et al.*, 2021), our goal is not to provide an extensive review of current literature. Rather, here we try to present an integrated historical overview of the field, with a particular focus on the road ahead. Specifically, we aim to discuss how modern statistical and experimental approaches are currently revitalizing the field of real-time brain imaging.

A brief history of neurofeedback

a. Early closed-loop experiments

Non-invasive brain imaging methods are correlational in nature. Using these approaches, we can observe an association between a given brain activity and an outcome. However, we usually do not know if a direct manipulation of the brain activity would also change the outcome. In the late 1960s-early 1970s, researchers devised some of the first closed-loop systems (Fig. 1) precisely to investigate the causality of brain activity. One such early experiment was conducted in 1969 by Eberhard Fetz. Fetz was interested in studying how precentral neurons generate muscle contractions in macaque monkeys. He showed that, by providing a food pellet contingent on the firing rate of precentral neurons, it was possible to increase the firing rate of these neurons by 50 to 500 percent (Fetz, 1969). Later on, Fetz and Finocchio used a similar approach in order to study the causal link between precentral neurons and peripheral muscle contractions. They showed that precentral neurons could be conditioned with or without simultaneously triggering peripheral contractions (Fetz and Finocchio, 1971). Taken together these early findings represented one of the first demonstrations that neural activity could be directly regulated in the brain, possibly through reinforcement learning.

Furthermore, these findings called into question the direct causal influence of individual precentral neurons in muscle contraction and were taken as an early indicator of distributed coding in the brain.

Around the same time, other researchers were experimenting with electroencephalography (EEG). Here again, some early closed-loop experiments were designed in order to investigate the causality of specific brain signals. For instance, Joseph Kamiya was interested in studying the link between subjective experience and the alpha rhythm recorded in EEG signals (Kamiya, 1968, 2011). In a series of experiments, he reported that, when prompted by a bell, participants could learn to correctly guess if an alpha burst was occurring in their brain. While conducting such experiments, Kamiya noticed that participants could also learn to produce alpha bursts at will (Kamiya, 1962). This serendipitous finding prompted a follow-up experiment revealing that participants could indeed be trained to modulate their own alpha activity (Kamiya, 1966). Motivated by such early demonstrations, multiple new experiments were conducted and showed similar modulation of various brain signals (Serman, Howe and Macdonald, 1970; Beatty *et al.*, 1974).

b. Early fMRI experiments

Years later, the first functional MRI experiments were reported (Kwong *et al.*, 1992; Ogawa *et al.*, 1992), and soon, it was shown that functional brain images could be processed in real time (Cox, Jesmanowicz and Hyde, 1995). This demonstration prompted many efforts to develop tools allowing one to conduct pre-processing steps and statistical analyses in real time (Goddard *et al.*, 1997; Cox and Jesmanowicz, 1999; Voyvodic, 1999; Gembris *et al.*, 2000; Cohen, 2001; Mathiak and Posse, 2001; Posse *et al.*, 2001; Smyser *et al.*, 2001; Bagarinao *et al.*, 2003). These tools paved the way for the first fMRI neurofeedback experiments (Yoo and Jolesz, 2002; Posse *et al.*, 2003; Weiskopf *et al.*, 2003; Weiskopf, Mathiak, *et al.*, 2004;

Weiskopf, Scharnowski, *et al.*, 2004; Weiskopf, 2012). In such experiments, participants were commonly trained to continuously modulate their brain activity during experimental blocks lasting from a few seconds to approximately a minute. Using this approach, early experiments showed successful modulation of brain activity in regions such as M1/S1 (Yoo and Jolesz, 2002; Yoo *et al.*, 2004), the amygdala (Posse *et al.*, 2003), anterior cingulate cortex, the supplementary motor area and the parahippocampal place area (Weiskopf *et al.*, 2003; Weiskopf, Mathiak, *et al.*, 2004). These findings prompted a great interest to explore potential therapeutic applications and to better understand underlying principles of neurofeedback.

Recent advances in real-time fMRI

Since these early fMRI studies, many methodological advances have been achieved (Watanabe *et al.*, 2017). Thanks to the recent explosion of research in artificial intelligence and machine learning (LeCun, Bengio and Hinton, 2015) and to the ever increasing power of modern computers (Moore, 2021), there is now considerable momentum for the development of novel and improved neurofeedback methods. In the last few years, a vast repertoire of analytical approaches have been developed for the purpose of real-time brain modulation. In the next sections, we will detail some of these recent advances and pay special attention to developments with potential clinical applications.

a. Decoded fMRI Neurofeedback

In neurofeedback, one persistent challenge is to determine the relevant brain activity to target. This represents a challenge because brain regions are not associated with a unique function. Without explicitly delineating the relationship between brain signal and psychological states, one is at risk of training participants to activate irrelevant brain representations. Decoded neurofeedback aims specifically at addressing this problem using modern machine learning (or

decoding) approaches. Decoded neurofeedback interventions typically involve conducting a first session, called the decoder construction session, where a multivariate decoder is trained to predict the occurrence of a specific psychological state from brain activity. For instance, such decoders have been trained with the brain representation of visual stimuli (Shibata *et al.*, 2011; Amano *et al.*, 2016; Koizumi *et al.*, 2016) or finger movements (LaConte, Peltier and Hu, 2007; Oblak, Sulzer and Lewis-Peacock, 2019). Importantly, the unbiased accuracy of such decoders can be determined using current recommendations in the machine learning literature (Varoquaux, 2018). This can give us confidence in the association between the decoder output and the targeted psychological trait. Once an accurate decoder is trained, it is possible to target this representation in a closed-loop manner (see Fig. 2a). Multiple decoded neurofeedback experiments have now been conducted using this approach and highly specific neural and behavioral effects have been reported (for a review see, (Watanabe *et al.*, 2017)). While decoded fMRI neurofeedback has not yet been used exhaustively with clinical populations, many experiments showed promising applications. These are detailed in the section: “*Promising approaches in the treatment of mental disorders*”.

In the context of clinical interventions, constructing meaningful decoders may however represent a challenge. For instance, one might wish to train a decoder of a specific brain state without having to put a patient in a particularly dreadful situation (Taschereau-Dumouchel *et al.*, 2018). Furthermore, one may want to train a brain decoder even when only a small amount of data can be collected for each participant. In these situations, between-subject decoders can be considered. However, between-subject decoders can also be challenging to train as they require the brain data of different participants to be represented in a common space. One possibility is to perform a structural alignment in a standard space, such as the MNI space (Fonov *et al.*, 2009). This is routinely achieved in offline analyses. However, structural alignment is an extra pre-processing step that can slow down the processing of brain images in real time. Even if data

from the mNI space are projected in the native space of the participant, the performance of decoders trained with structurally aligned data have been shown to be sometimes suboptimal (Haxby *et al.*, 2011).

An interesting alternative is offered by functional alignment methods (Haxby *et al.*, 2011; Chen *et al.*, 2015). This family of approaches aims at aligning brain data coming from different participants using their functional profile. More precisely, these approaches aim at leveraging the response profile of the voxels (obtained in a “calibration” session) in order to perform the between-subject alignment. One advantage of such approaches is that they allow for the data of a group of participants to be represented in the native space of a given participant (see Fig. 2b). This property presents an interesting advantage for real-time interventions as the decoders can be trained in the native space. We previously showed that this approach can be successfully used in a closed-loop experiment (Taschereau-Dumouchel *et al.*, 2018).

b. Decoding EEG fingerprints

EEG is probably the imaging modality most frequently used in order to conduct closed-loop interventions. Here also, machine learning approaches have been successfully used (Bu *et al.*, 2019). However, EEG presents some limitations, such as a limited spatial resolution (Srinivasan *et al.*, 1996). In order to improve the accuracy of EEG interventions, an interesting approach has been to combine EEG with fMRI. Previous work laid down solid foundations for the use of “EEG fingerprints” in neurofeedback (Keynan *et al.*, 2016, 2019). This practice involves training a decoder of EEG activity to predict concurrent fMRI signals (see Fig. 3a). This can be achieved by acquiring fMRI and EEG signals simultaneously. Using this approach, it is possible to train a decoder of the EEG fingerprint that can later be used outside of the scanner for neurofeedback purposes. For instance, successful neurofeedback experiments have been conducted using a decoder of the EEG fingerprint of amygdala activity

(Keynan *et al.*, 2016, 2019). Importantly, approaches leveraging EEG fingerprints present multiple potential clinical applications (Keynan *et al.*, 2019). For instance, one might consider targeting the EEG fingerprint of any decoded fMRI activity (see Fig. 3a). Accordingly, it might also be possible to target decoded fMRI activity using EEG neurofeedback.

c. Connectivity-based neurofeedback

Brain connectivity analyses gained considerable popularity in recent years (Bassett and Sporns, 2017; Avena-Koenigsberger, Misic and Sporns, 2018). This family of analyses was very successful in establishing links between inter-regional brain connectivity and mental disorders (Whitfield-Gabrieli and Ford, 2012). As a result, closed loop interventions have been designed in order to normalize the connectivity between specific brain regions in hope of also normalizing symptoms. These approaches can be termed connectivity-based neurofeedback. In these studies, the connectivity between two targeted regions is typically computed in real time and used in order to provide feedback to participants (see Fig. 3b). Multiple studies reported that inter-regional brain connectivity could indeed be successfully manipulated using multiple connectivity metrics such as correlational approaches (Megumi *et al.*, 2015; Yamashita *et al.*, 2017), sliding-window analysis (Gembris *et al.*, 2000), the two-point approach (Ramot *et al.*, 2017; Ramot and Gonzalez-Castillo, 2019), dynamic causal modeling (Koush *et al.*, 2013; Koush, Meskaldji, *et al.*, 2017) and tensor independent component analysis (Koush *et al.*, 2019). Importantly, connectivity neurofeedback has been associated with some outcomes relevant to mental health (Ramot *et al.*, 2017). This will be discussed further in the section: *“Promising approaches in the treatment of mental disorders”*.

d. Information transmission analysis

When conducting neurofeedback experiments, researchers are often interested in identifying brain processes involved in the modulation of brain activity. This question can be addressed using an information transmission analysis. This analysis aims at determining if the target of the intervention (e.g., decoded brain activity or regional activity) can be accurately predicted by the activity within other brain regions. Such analyses are often conducted within a searchlight procedure covering the whole brain or within specific regions of interest. In the context of decoded neurofeedback, an information transmission analysis can be seen as a form of multivariate connectivity metric indicating how much a given brain region can predict the occurrence of a multivariate representation elsewhere in the brain. This is an interesting metric that could potentially be used in the future as a target of neurofeedback. For instance, this could be used in order to train a brain region to increase or decrease the expression of a given decoder in another brain region.

e. Co-adaptive systems

Neurofeedback aims at modulating brain activity, possibly through physiological and psychological mechanisms involved in reinforcement learning (see the section: *Investigating the mechanisms of action*). However, this mechanism of action is not the only one capable of driving brain activity in real time. Many other means of interacting with individuals may also facilitate the expression of specific patterns of activity in their brains. Interestingly, it might be possible to optimize the expression of specific patterns of brain activity using modern artificial intelligence algorithms (Taschereau-Dumouchel and Roy, 2020). For instance, Zhang and colleagues trained a reinforcement learning algorithm to reduce the pain-related brain activity of users (Zhang *et al.*, 2020). They first trained a pain decoder and obtained predicted pain ratings in real time while participants were receiving electrical stimulations. They fed this information in real

time to a reinforcement learning algorithm (Fig. 4a). They showed that, after only a few trials, the algorithm learned which of two possible interventions (High-intensity or low-intensity electrical stimulations) could be delivered in order to reduce pain-related brain activity. These results are important as they illustrate the possibility of using artificial intelligence algorithms to devise means of interacting with the brain of users and to facilitate the expression of specific patterns of brain activity. One might envision a similar approach adapted to brain stimulation (either non-invasive or deep brain stimulation). In this scenario, diverse patterns of brain stimulation could be iterated over in order to optimize the expression of specific patterns of brain activity.

Yet another possibility is to leverage deep generative models in order to generate stimuli to be presented to participants in real time (Fig. 4b). This possibility was previously investigated by generating visual stimuli in order to optimise the firing rate of specific neurons in the visual system (Bashivan, Kar and DiCarlo, 2019; Ponce *et al.*, 2019). These experiments, conducted in macaque monkeys, led to two important conclusions. First, such artificially created stimuli can greatly increase the firing rate of specific neurons, even beyond what is expected of natural stimuli. Second, such artificially created stimuli typically depict abstract shapes that do not represent any specific objects or animals. This suggests that artificially-generated stimuli could be used in order to facilitate the expression of specific brain signals in humans without divulging the nature of the targeted brain activity. This is an interesting feature as it would still allow one to conduct double-blind placebo-controlled experiments. As such, these findings are important as they suggest that artificially-generated stimuli might ultimately be used in order to support or complement neurofeedback interventions in mental health.

f. Cloud computing and parallel processing

The real-time processing of standard fMRI neurofeedback experiments can be easily achieved on most desktop computers. However, the speed of modern internet connections

makes it possible to transfer fMRI data to a remote computer (i.e., in the cloud) in order to conduct processing over there in real time (Cohen *et al.*, 2017; Mennen *et al.*, 2021). This allows one to conduct more intensive analyses in real time while using relatively simple desktop computers onsite. This possibility is particularly interesting when combined with parallel computing as it can considerably speed up the analysis of fMRI data (Eklund *et al.*, 2014). The idea of using parallel processing in real time is not new (Goddard *et al.*, 1997), but it is now simpler to include such analyses in real time processing pipelines. This was made possible with the increasing power of graphics processing units (GPUs) and the development of open-source softwares leveraging GPU capabilities (Eklund *et al.*, 2014). Importantly, parallel processing can considerably fasten preprocessing (Eklund *et al.*, 2014) and first-level analyses (Eklund *et al.*, 2014) and can also be used in order to run feature selection (Wang *et al.*, 2016). Such technologies open up multiple opportunities to conduct complex analyses in real time. This was notably shown in a recent proof-of-concept study (Mennen *et al.*, 2021).

Investigating the mechanisms of action

Based on experiments conducted with intracranial recording in animals, we have good reasons to believe that neurofeedback can indeed modulate precise patterns of neural activity (Fetz, 1969; Fetz and Finocchio, 1971; Sadtler *et al.*, 2014). However, fMRI is quite different from intracranial recordings. Notably, it is conducted at the voxel level, not at the neuronal level. This is an important distinction as the haemodynamic signal may or may not reflect the underlying neural activity (Sirotin and Das, 2009). Moreover, at the voxel level, the signal can represent the activation of many different neurons within that voxel. Further, considering the number of voxels recorded in the brain, one might wonder how is it possible for participants to target such precise neural representations? To answer these questions, Shibata and colleagues proposed the targeted neuroplasticity hypothesis (Shibata *et al.*, 2019). This hypothesis

proposes that fMRI neurofeedback does not reinforce brain activity at the voxel level but at the level of a low-dimensional manifold instead. Indeed, multiple lines of evidence indicate that neural activity does not occur completely at random and is rather constrained on a low-dimensional manifold (Ringach, 2009). To test this hypothesis in the context of brain-computer interfaces (BCI), Sadtler and colleagues determined a low-dimensional space from high-dimensional recordings of neuronal activity in macaque monkeys (Sadtler *et al.*, 2014). They showed that the dimensions of that intrinsic manifold considerably constrained learning in a BCI task such that it was more difficult for the monkey to learn to generate patterns of brain activity that would fall outside of the manifold. These findings are important as they indicate that not all patterns of brain activity are equally likely to be trained using BCI or neurofeedback. This finding is corroborated, to some extent, by results in fMRI neurofeedback. More precisely, Shibata and colleagues showed that, during the induction period of decoded neurofeedback experiments, 80% of the variance of the blood oxygen level-dependent (BOLD) signal can be explained by a relatively small number of principal components (Shibata *et al.*, 2019). Taken together, these results suggest that the space of possible activation patterns to explore during neurofeedback may be smaller than expected which could render tractable the complex learning problem posed by neurofeedback experiments (Watanabe *et al.*, 2017).

Another outstanding question pertains to the precise mechanisms responsible for the regulation of brain activity. A meta-analysis of previous fMRI neurofeedback studies indicated that, across multiple neurofeedback targets, regulation primarily engaged the anterior insular cortex, the basal ganglia (primarily the striatum), the temporo-parietal area, the anterior cingulate cortex, the dorsolateral prefrontal cortex and the ventrolateral prefrontal cortex (Emmert *et al.*, 2016). Similarly, a meta-analysis conducted exclusively on decoded fMRI neurofeedback studies also highlighted the involvement of the insular cortex, dorsal striatum, posterior parietal cortex, supplementary motor area and cerebellum (Shibata *et al.*, 2019). One

possibility is that these structures mediate reinforcement learning during the task. Here the feedback may act as a reward capable of reinforcing the occurrence of specific brain activity. In line with what we saw above, reinforcement learning may operate at the level of a low-dimensional manifold of neural activity (Sadtlter *et al.*, 2014; Shibata *et al.*, 2019). Yet another possibility is that reinforcement learning might occur at the voxel level. Oblak and colleagues showed that, in simulated voxels, reinforcement could facilitate the expression of the targeted pattern of brain activity when spontaneous correlated activity was also present (Oblak, Sulzer and Lewis-Peacock, 2019). As such, these simulations indicate a potential mechanism capable of reinforcing specific patterns of brain activity using decoded fMRI neurofeedback (For a discussion of other theories of neurofeedback learning, see Sitaram *et al.*, 2017).

Yet another outstanding question pertains to the mechanisms mediating therapeutic effects. This is of course of great importance to interventions specifically designed for mental disorders. Most interventions carried out attempted to “regularize” or “normalize” specific brain targets that have been identified as problematic in a clinical population. For instance, the amygdala reactivity in major depressive disorder (Young *et al.*, 2014; Young, Misaki, *et al.*, 2017; Young, Siegle, *et al.*, 2017) or the functional connectivity between the superior temporal sulcus and the somatosensory cortex in autism spectrum disorder (Ramot *et al.*, 2017). Of course, precise biomarkers of psychopathologies are still hotly debated. However, if neurofeedback training leads to clinical improvements, this could further indicate the link between the specific brain target and the clinical outcome at hand.

Decoded fMRI neurofeedback also presents interesting clinical applications as it makes it possible to target distributed brain representations rather than regional brain activity. Previous experiments indicated that it might be possible to target brain representations with specific significance for pathology, like representations of feared stimuli (Taschereau-Dumouchel *et al.*, 2018; Chiba *et al.*, 2019). Using this approach, it might be possible to achieve therapeutic

effects by pairing, for instance, such representations with a reward or by training participants to repeatedly activate such representations in their brain. Concrete clinical applications will be discussed in the section: *Promising approaches in the treatment of mental disorders*.

Common methodological considerations in the neurofeedback literature

Multiple factors are expected to modulate brain activity and behavior in neurofeedback experiments. If such confounds are not delineated properly, one is at risk of falsely attributing observed effects to neurofeedback interventions. Such considerations led researchers to mobilise and to develop guidelines in an attempt to bring more experimental rigour to the field (Ros *et al.*, 2020). Below, we provide an overview of commonly discussed methodological considerations and some helpful guidelines to improve the interpretability of the results. Importantly, if such guidelines are observed, it is often possible to conduct experiments with the utmost scientific rigour.

a. Control conditions and the possibility for double-blind interventions

Control conditions are essential in order to isolate the intended effects of neurofeedback experiments. The control condition to be used is often defined by the goal of each individual experiment (Sorger *et al.*, 2019). In a literature review, Thibault and colleagues reported that about 38% of fMRI neurofeedback experiments did not include a control group (Thibault *et al.*, 2018). Such designs are appropriate when one primarily aims at studying the modulation of brain activity between regulation and rest blocks. However, when it comes to studying behavioral outcomes, control groups or control conditions are necessary in order to rule out the effect of confounds such as the placebo effect, the passage of time, non-specific effects of training and interaction with the research personnel (Sorger *et al.*, 2019). A good strategy is to provide a control group with placebo neurofeedback. For instance, one can provide feedback

using the activity of another brain region (Young *et al.*, 2014; Young, Siegle, *et al.*, 2017) or simply by inverting the feedback provided to the experimental group (Shibata *et al.*, 2016). In these situations, the task demands and reward contingencies should be very similar between groups, which should provide adequate control of the placebo effect.

However, a control group is not always the best option. In fact, within-subject controls have the potential to be even more powerful as they also control for any other factor that could vary between groups and affect the results. They also require considerably less resources than control groups as they only require one experimental group to go through the training. Notably, such designs are appropriate when the effect of the intervention can be observed on specific experimental conditions but not on others (Shibata *et al.*, 2011; Koizumi *et al.*, 2016; Taschereau-Dumouchel *et al.*, 2018; Taschereau-Dumouchel, Liu and Lau, 2018).

Within-subject designs can also be devised such that participants will take part both in up-and down-regulation sessions (crossover design) (Cortese *et al.*, 2016). In this context, participants act as their own control. When appropriate, within-subject designs can bring the strongest scientific demonstration while minimizing the resources required.

Further, in order to fully control for the placebo effect, it is important to make sure that both patients and experimenters are blind to the experimental conditions. Such experimental designs, termed double-blind experiments, represent the highest scientific standards but few psychological interventions can actually be conducted in such settings, as experimenters can often make educated guesses regarding the nature of the intervention. This is not the case with neurofeedback as blinding the experimenters is generally relatively straightforward. Once real-time processing pipelines are created, group membership can be randomly selected without the experimenters' knowledge. This is a simple step with important implications as it can shield researchers from unwittingly influencing participants' behavior. Surprisingly, this important feature of neurofeedback has been underappreciated in the past. As Thibault and colleagues

reported, out of the many studies using placebo-controlled neurofeedback, only a handful were also reported to be conducted in double-blind settings (Paret *et al.*, 2014; Young *et al.*, 2014; Yuan *et al.*, 2014; Guan *et al.*, 2015; Hamilton *et al.*, 2016; Paret, Ruf, *et al.*, 2016; Yao *et al.*, 2016; Zotev *et al.*, 2016; Young, Misaki, *et al.*, 2017; Young, Siegle, *et al.*, 2017; Taschereau-Dumouchel *et al.*, 2018).

B. Explicit vs implicit neurofeedback

Many previous neurofeedback experiments provided participants with an explicit training strategy such as instructions to engage in mental imagery or to retrieve positive affective memories (Sitaram *et al.*, 2011; Scharnowski *et al.*, 2012; Young *et al.*, 2014; Zilverstand *et al.*, 2015). It is commonly assumed that such strategies should help to create the desired effect. This approach is appropriate when the control and experimental groups are provided with the same strategies. However, if they are not, this is likely to create an interpretation problem as the effect of the strategy will be interwoven with the effect of neurofeedback.

Another approach has been to use implicit neurofeedback approaches, meaning that participants are not provided with any induction strategy in order to modulate their brain activity. This approach assumes that pairing the feedback with a monetary reward should be sufficient to reinforce the targeted brain activity. Importantly, this approach has been shown to outperform explicit neurofeedback in a study directly comparing implicit and explicit approaches (Sepulveda *et al.*, 2016). Furthermore, multiple studies have reported substantial behavioral and neural effects using implicit approaches (Shibata *et al.*, 2011; Cortese *et al.*, 2016; Koizumi *et al.*, 2016; Ramot *et al.*, 2016, 2017). As such, implicit neurofeedback presents many advantages over explicit approaches. However, this should be taken with caution as only one study has directly compared implicit and explicit approaches.

C. Physiological artifacts

fMRI neurofeedback experiments provide feedback based on the BOLD signal. Physiological artifacts can drastically influence this metric. For instance, the BOLD signal can be substantially modulated when participants are holding their breath (Kastrup *et al.*, 1999; Abbott *et al.*, 2005; Thomason *et al.*, 2005). Furthermore, some have suggested that, during real time functional connectivity neurofeedback, regularity of breathing accounted for most of the correlation observed between brain regions (Weiss *et al.*, 2020). As a result, participants could essentially learn, likely unconsciously, to modulate their breathing rate in order to perform better at the task. Such increased performance would not reflect a true modulation of brain activity, but rather a global change in blood oxygenation. In order to correct for such artifacts, some have suggested regressing out physiological signals and, in the case of functional connectivity neurofeedback, regressing out the global signal (Weiss *et al.*, 2020). It is important to note however that not all neurofeedback approaches are equally likely to be affected. For instance, results of within-subject control designs are unlikely to be explained by such artifacts as experimental conditions are expected to be affected in similar ways by such physiological artifacts. Furthermore, decoded neurofeedback (see section *Decoded Neurofeedback*) relies both on positive and negative weights attributed to voxels within a given brain region. As a result, a global modulation of BOLD activity is not expected to affect the feedback in a straightforward manner (Shibata *et al.*, 2019). This is an empirical question that should be addressed in future research.

Promising approaches in the treatment of mental disorders

Over the years, multiple psychopathologies have been targeted by fMRI neurofeedback interventions and great literature reviews have been written (Stoeckel *et al.*, 2014; Tursic *et al.*, 2020; Pindi *et al.*, 2021). Here, we aim at presenting an overview of this literature by

sub-selecting only the most scientifically rigorous studies. Based on two recent systematic reviews of the field (Tursic *et al.*, 2020; Pindi *et al.*, 2021), we sub-selected studies targeting a mental health disorder where: (1) patients were blinded to experimental goals and (2) a control group or control condition was included. Our approach is not meant to diminish the usefulness of proof-of-principle studies that may not fulfil these criteria (Paret, Kluetsch, *et al.*, 2016; Orlov *et al.*, 2018; Chiba *et al.*, 2019; Zaehringer *et al.*, 2019; Takamura *et al.*, 2020; Mennen *et al.*, 2021). Such studies are crucial in order to show target engagement before more extensive funding can be secured for larger clinical studies. However, when it comes to clinical efficacy, studies need to be on par with clinical research guidelines and present multiple experimental controls. As such, our approach aims at providing a bird's-eye view of the field based on minimally confounded studies (Thibault, Lifshitz and Raz, 2017). Further, we also included some studies conducted in subclinical populations that could potentially inform future clinical targets for neurofeedback.

Our selection method yielded 25 studies, all of which have been published since 2013. Only a few studies have been conducted within each individual disorder and few have been pre-registered. As such, we propose to provide a qualitative assessment of this young field of research, noting the strengths and weaknesses of the studies conducted so far. Following the terminology used by the American Psychological Association, we found that treatment strategies using fMRI neurofeedback do not yet meet criteria for “well-established” treatments, but some approaches could be considered “probably efficacious” treatments (Chambless and Hollon, 1998; APA Presidential Task Force on Evidence-Based Practice, 2006). So far, fMRI neurofeedback interventions for major depressive disorder present the most empirical support.

a. Major depressive disorder

Previous work indicated that depressed patients present a blunted activity of the amygdala when processing positive stimuli (Victor *et al.*, 2010). Such findings inspired a treatment strategy aiming at increasing the activity of the amygdala during the processing of happy memories. Using this approach, multiple experiments have reported that the emotional state of patients in the active group can be improved in comparison to a control group (Young *et al.*, 2014; Yuan *et al.*, 2014; Zotev *et al.*, 2016; Young, Siegle, *et al.*, 2017). Importantly, this demonstration has been achieved in double-blind placebo-controlled experiments (Young *et al.*, 2014; Yuan *et al.*, 2014; Young, Siegle, *et al.*, 2017). This constitutes a strong scientific demonstration of the usefulness of amygdala neurofeedback in order to improve the emotional state of depressed patients. Relatedly, other researchers attempted to modulate the affective bias of depressed patients by targeting the activity within the salience network. For instance, Hamilton and colleagues (2016) trained patients to regulate the activity within the insula and dorsal anterior cingulate cortex in hope of regularizing their perceptual bias. They showed, again in a double-blind placebo-controlled study, that their intervention decreased negative affects reported by patients when confronted with negative images. Taken together, these results constitute a strong scientific demonstration that fMRI neurofeedback may be useful in order to improve the emotional state of patients and to regularize their perceptual biases. It is however important to note that other approaches were not as successful (Mehler *et al.*, 2018; Zotev *et al.*, 2020).

b. Anxiety disorders

Other fMRI neurofeedback studies aimed at regularizing symptoms of anxiety disorders. In a study conducted with spider phobic patients, Zilverstand and colleagues reported that dual neurofeedback of the dorsolateral prefrontal cortex and insula decreased anxiety during

exposure to the feared animal following the intervention (Zilverstand *et al.*, 2015). While these results are very informative, it is important to note that different induction strategies were provided to the active and control groups (cognitive reappraisal vs rest). As such, the reported results may be partly attributed to the cognitive reappraisal strategy used in the active group.

Other approaches aimed at targeting brain structures involved in the regulation of physiological defensive responses to threat. For instance, in a subclinical population presenting high contamination-related anxiety, Scheinost and colleagues reported that fMRI neurofeedback of the orbitofrontal cortex was associated with an increased perception of control over contamination anxiety (Scheinost *et al.*, 2013). Relatedly, Zhao and colleagues showed that neurofeedback of the functional connectivity between the amygdala and the ventromedial prefrontal cortex decreased self-reported anxiety in a subclinical population presenting high trait anxiety (Zhao *et al.*, 2019). Taken together, these findings strongly suggest that fMRI neurofeedback can help regulate anxiety symptoms in subclinical populations.

Yet another approach might be to target upstream the association between sensory representations and physiological defensive responses. For instance, we showed, in a double-blind fMRI neurofeedback experiment, that it is possible to decrease physiological defensive responses to feared animals (i.e., amygdala and skin conductance reactivity). This was achieved by training participants to pair a reward with the activation likelihood of the brain decoder of a feared animal (Taschereau-Dumouchel *et al.*, 2018). These results are important as they indicate that it might be possible to change unconsciously how sensory representations generate physiological defensive responses. This intervention was carried out in a subclinical population and further investigations will be needed in order to establish the potential for clinical applications.

c. Substance abuse

fMRI neurofeedback has also been used in order to decrease cravings in substance abuse. Two studies were conducted with nicotine-dependent smokers. The goal of the first one was to reduce cravings by training participants to regulate the activity within craving-related regions located in the anterior cingulate cortex and medial prefrontal cortex. The results showed a between-group effect with participants in the active group presenting a greater decrease in the urge to smoke following the intervention (Hartwell *et al.*, 2016). In the second study, Kim and colleagues investigated the added value of including a functional connectivity component to the feedback. To do so, they provided two groups of heavy smokers with different feedback. The first group received feedback from the anterior cingulate cortex, medial prefrontal cortex and orbitofrontal cortex. The second one received feedback from the same regions but also from the functional connectivity between these regions and the posterior cingulate cortex and precuneus. They showed that including information about functional connectivity may have an effect on reducing cravings (Kim *et al.*, 2015). However, the between-group effect was not reported. These results indicate that fMRI neurofeedback may be helpful in order to decrease cravings in nicotine-dependent smokers, but further investigations conducted in double-blind placebo-controlled interventions are currently needed.

d. Attention deficit / hyperactivity disorder

Multiple studies suggested that EEG neurofeedback might be a potential treatment for attention deficit / hyperactivity disorder (Arns *et al.*, 2009; Sonuga-Barke *et al.*, 2013; Holtmann *et al.*, 2014). However, surprisingly little evidence also supports this possibility when it comes to fMRI neurofeedback. For instance, Alegria and colleagues conducted an fMRI neurofeedback study with adolescents presenting attention deficit / hyperactivity disorder. They showed that patients could learn to regulate brain activity within the right inferior frontal gyrus. However, they

reported no between-group effect on the main clinical outcomes (Alegria *et al.*, 2017). Similar results were also obtained by Zilverstand and colleagues (Zilverstand *et al.*, 2017). They showed that patients can learn to modulate the activity within the dorsal anterior cingulate cortex. However, while they observed some improvements in cognitive functioning (i.e., sustained visual attention and visual working memory), they did not observe between-group effects on the main clinical outcomes.

Such discrepancies between EEG and fMRI approaches may be partly explained by methodological differences as the two imaging methods are vastly different. This begs the question: could other fMRI approaches also present therapeutic effects? Interestingly, a decoded fMRI neurofeedback experiment indicated that sustained visual attention might be efficiently trained in healthy participants. De Bettencourt and colleagues designed an intervention where mixture images composed of face and scene stimuli were presented in the fMRI scanner and updated in real time as a function of the decoded brain activity (deBettencourt *et al.*, 2015). If the decoder output indicated a greater representation of the task-relevant category (either face or scene) the mixture image was updated in order to represent this category more clearly on the computer screen. Importantly, this intervention was shown to increase sensitivity in a sustained attention task following neurofeedback training. These results suggest the possibility of training sustained attention in healthy individuals and might present interesting clinical applications for attention deficit / hyperactivity disorder but also for major depressive disorder. For instance, a recent proof-of-concept study showed the potential of this approach to reduce the negative attentional bias in depressed patients (This study was not included in Table 1 and in the section on Major depressive disorders as we could not establish if the study was single-blind) (Mennen *et al.*, 2021).

e. Autism spectrum disorder

Autism spectrum disorder has been associated with various dysregulations in the functional connectivity of the brain. Notably, under-connectivity has been reported between various brain regions (Müller *et al.*, 2011). As such, one possibility for symptom management might be to reinforce some connections using functional connectivity neurofeedback. Ramot and colleagues designed an experiment to achieve this goal (Ramot *et al.*, 2017). First, they leveraged resting-state connectivity data from participants presenting autism spectrum disorder and from typically developing individuals. Using this data, they established that autism spectrum participants presented with decreased connectivity between the superior temporal sulcus and the somatosensory cortex. Using a new feedback method called the two-point approach (see Fig. 3b), they trained autism spectrum participants to increase the connectivity between these two regions while decreasing the connectivity between these regions and a control region. Importantly, the intervention was carried in such a way that participants were not even aware of taking part in a neurofeedback experiment. Ramot and colleagues showed that autism spectrum participants learned, completely unconsciously, to increase the connectivity between the two target regions. Furthermore, the change in resting state connectivity following the intervention was associated with positive behavioral changes in the autism spectrum participants. While it is still unclear if this approach can also lead to between-group effects, these results are nevertheless very informative and warrant further investigations of the approach.

f. Post-traumatic stress disorder

Another mental health disorder that represents a considerable therapeutic challenge is post-traumatic stress disorder. Previous neurofeedback approaches have been used with mixed results in this population. For instance, Zotev and colleagues conducted an fMRI / EEG neurofeedback experiment with patients presenting post-traumatic stress disorder (Zotev *et al.*,

2018). They did not observe any between-group effect on clinically meaningful outcomes (such as CAPS scores), but they did observe a trend towards significance. Furthermore, the intervention helped to regulate the functional connectivity of the amygdala with diverse regions of the prefrontal cortex including the dorsolateral prefrontal cortex. As such, further investigations using a pre-registered intervention appear to be warranted.

Yet another approach conducted in a healthy population might present interesting clinical applications in the future. Keynan and colleagues used an EEG-fingerprint approach (see Fig. 3a) to train stress resilience in men enrolled in military training (Keynan *et al.*, 2019). Their goal was to provide neurofeedback training in order to prevent stress-induced psychopathologies. They showed that training participants to regulate the EEG-fingerprint of the amygdala could improve emotion regulation as evidenced by decreased alexithymia and improved emotional stroop task performances. This could represent an interesting avenue in order to prevent the effect of stressful situations on mental health.

g. Schizophrenia

Lastly, some researchers also aimed at reducing auditory hallucinations in schizophrenia patients using fMRI neurofeedback. For instance, Zweerings and colleagues conducted an intervention where schizophrenia patients were trained to regulate the activity within the Inferior frontal gyrus and the superior temporal gyrus (Zweerings *et al.*, 2019). Following this intervention, the authors observed a negative association between the connectivity between these two regions and the global severity index. Further, two recent studies reported a decrease in auditory hallucinations following interventions targeting the superior temporal gyrus and the ratio of activation between the central executive network and the default mode network (Bauer *et al.*, 2020; Okano *et al.*, 2020). While these studies were conducted in rigorous designs it is important to note that these effects were observed within-groups (or within-conditions) and that

no between-group (or between-conditions) effects were reported. Nevertheless, these findings warrants further investigation into the possibility of reducing auditory hallucinations with fMRI neurofeedback.

Future directions and conclusion

The field of fMRI neurofeedback is still young. Recently, multiple initiatives have been taken to bring more scientific rigour to the field (Ros *et al.*, 2020). Such concerns are being taken seriously and, as a result, the full scientific potential of neurofeedback interventions has started to show. Recent studies conducted with stringent scientific rigour have indeed shown the potential to achieve very specific therapeutic effects in clinical populations (Young, Siegle, *et al.*, 2017). Moving forward, this should pave the way for more pre-registered clinical trials conducted in double-blind placebo-controlled settings. At this stage, such diligent empirical demonstrations are necessary in order to further establish the usefulness of fMRI neurofeedback as a general treatment strategy in mental health.

Moving forward, one can imagine multiple ways to improve current neurofeedback approaches. For instance, only a few studies previously used advanced neurofeedback approaches such as decoded neurofeedback and EEG-fingerprinting with clinical populations. Using such methods, it should be possible to improve the sensitivity and specificity of neurofeedback interventions and to simultaneously improve therapeutic effects. Furthermore, one can imagine multiple new therapeutic approaches based on current research findings in the field. For instance, Cortese and colleagues showed that neurofeedback might be used in order to improve meta-cognition and the capacity to perceive one's own brain activity (Cortese *et al.*, 2016; Cortese, Lau and Kawato, 2020). Notably, such approaches might be leveraged in order to train meta-cognitive deficits in clinical populations. Other future applications might include targeting the production of specific neurotransmitters (MacInnes *et al.*, 2016). For instance,

MacInnes and colleagues showed that participants can be trained to increase the activity within the ventral tegmental area, a brain region associated with striatal dopamine release (Schott *et al.*, 2008). While further investigations are still needed in order to precisely document changes in dopamine release, such an approach presents an interesting future avenue for intervention. Clinical populations presenting a dysregulation of the dopamine system could potentially regulate neurotransmitter levels without medication. The targeted specificity of such a neurofeedback approach could avoid the undesirable side effects of common neurotransmitter-regulating medications. Lastly, another means of intervention might be to combine neurofeedback with in-scanner virtual reality (Lorenzetti *et al.*, 2018). This approach could notably be used to improve the decoding of specific brain states and to devise new reinforcing environments capable of improving learning beyond current approaches.

We have come a long way since the first demonstrations to suggest the direct reinforcement of neural responses in the brain. However, devising effective therapeutic strategies using neurofeedback techniques is a complex endeavor requiring multiple iterations. We now have multiple lines of evidence suggesting that neurofeedback interventions can have very precise therapeutic effects in mental health. Considering that new machine learning approaches can potentially potentiate the effects in the field, we are optimistic that multiple new approaches will be successfully tested in the future. Importantly, we have entered an era of research where such interventions will be evaluated with the utmost scientific rigor. As such, we are confident that future studies will be able to further delineate the usefulness of fMRI neurofeedback as a therapeutic approach in mental health.

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Terms and Definitions

Closed-loop brain imaging: General family of approaches leveraging real-time brain imaging for the purpose of brain regulation.

Neurofeedback: A kind of biofeedback where participants are provided with information regarding their own brain activity for the purpose of regulation.

Decoded neurofeedback: A neurofeedback approach that uses machine learning to determine the intervention target. It also involves monetary rewards and implicit strategies.

Brain-computer interface: A real-time brain imaging approach aiming at controlling an external device through the modulation of brain activity.

Co-adaptive systems: Closed-loop systems where the user and the machine aim at regulating brain activity by adapting their behavior or neural activity.

Related Resources

The DecNef Collection: A database regrouping the data of multiple previous decoded neurofeedback experiments (<https://bicr-resource.atr.jp/drmd/>) (Cortese *et al.*, 2021).

Softwares available to conduct neurofeedback experiments:

ATR toolbox: This free software can be used for the purpose of conducting experiments in decoded neurofeedback and functional connectivity neurofeedback (<https://bicr.atr.jp/decnefpro/>).

BrainIAK: This free software can be used to conduct multiple real-time brain imaging experiments. Notably, it can be used to conduct cloud-based interventions (https://brainiak.org/examples/rtcloud_notebook.html) (Kumar *et al.*, 2020).

MURFI: This free software can be used to conduct multivariate and univariate neurofeedback interventions (<https://github.com/gablab/murfi2>) (Hinds *et al.*, 2011).

OpenNFT: This free software can be used to conduct diverse neurofeedback experiments such as univariate, multivariate and connectivity neurofeedback (<http://opennft.org>) (Koush, Ashburner, *et al.*, 2017).

Pyneal: This free software can be used to conduct univariate neurofeedback experiments. It includes a tool to transform mask from MNI space to the native space of a participant (<https://github.com/jeffmacinnes/pyneal>) (MacInnes *et al.*, 2020).

Turbo BrainVoyager: This paid software can be used to conduct multiple neurofeedback experiments (https://www.brainvoyager.com/downloads/install_turbobrainvoyager.html) (Goebel, Esposito and Formisano, 2006).

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Table 1. Controlled and blinded studies using fMRI neurofeedback in mental health.

Disorder	Study	Population	N	Brain target	Control	Single / double-blind	Random-ization	Explicit strategy	Continuous / Intermittent feedback	Effect on brain target	Effect on clinically relevant outcomes	Effect size
ADHD	(Alegria <i>et al.</i> , 2017; Rubia <i>et al.</i> , 2019)	Children with ADHD	N active = 18 N control = 13	Right inferior frontal gyrus	Active control group (left middle parahippocampal gyrus)	Single-blind	Yes	No	Continuous	Yes	No between-group effect on clinical outcomes, but some transfert effects.	N/A
	(deBettencourt <i>et al.</i> , 2015)	Healthy individuals	N active = 16 N control = 16	Whole-brain decoder of task-relevant object category (face or scene)	Active control group, the no-feedback behavioral group, the RT-feedback behavioral group and the RT-control behavioral group	Single-blind	No	Yes. Instructed to pay attention.	Continuous	Yes	Between-group and within-group effects on sensitivity in a sustained attention task	N/A
	(Zilverstand <i>et al.</i> , 2017)	Adults with ADHD	N active = 7 N control = 6	Dorsal anterior cingulate cortex	Control cognitive training	Single-blind	Yes	Yes. Mental calculation.	Continuous	Not different from the control group.	No between-group effect on clinical outcomes, but some effects on cognitive functioning (i.e., sustained visual attention and visual working memory)	sustained visual attention: $\eta^2 = 0.50$ visual working memory: $\eta^2 = 0.56$
Anxiety	(Scheinost <i>et al.</i> , 2013)	Subclinical population with high contamination-related anxiety	N active = 10 N control = 10	Orbitofrontal cortex	Sham control group	Single-blind	Yes	No	Continuous	Yes. Changes in the functional connectivity of the targeted region.	Between-group and within-group effects on reported control over contamination anxiety.	N/A
	(Tascherrou-Dumouchel <i>et al.</i>)	Subclinical population reporting	N = 16	Decoded activity of the targeted feared animal in	Within-subject control condition (brain decoder of	Double-blind	Yes	No	Intermittent	Yes. Increased	Between-group and within-group	Amygdala reactivity: Cohen's d =

	<i>al.</i> , 2018)	high fear of specific animals.		the ventral temporal cortex.	another feared animal)					likelihood of the active condition during induction (with respect to control).	effects on decreased amygdala reactivity and physiological defensive responses.	0.62 Skin conductance response: Cohen's d = 0.55
	(Zhao <i>et al.</i> , 2019)	Subclinical population with high trait anxiety	N = 26	Connectivity between the vIPFC and the amygdala	crossover sham-controlled design	Single-blind	Yes	Yes. Emotional control strategy.	Continuous	Yes. Increase in connectivity within the active but not the control pathway.	Between-group and within-group effects on self-reported anxiety level (marginally significant interaction)	Within-group effect size = 0.46
	(Zilverstand <i>et al.</i> , 2015)	Spider phobia	N active = 9 N control = 9	Dual neurofeedback (dIPFC and insula)	No-feedback control group	Single-blind	Yes	Yes. Cognitive reappraisal. Note that the control group was not provided with the same strategy.	Intermittent	Yes for the Insula. No for the dIPFC.	Between-group and within-group effects on subjective anxiety levels during exposure.	$\eta^2 = 0.34$
Autism spectrum disorder	(Ramot <i>et al.</i> , 2017)	Adults with Autism spectrum disorder	N patients = 19 N Healthy controls = 10	two-point approach (Target 1: STS; Target 2: Somatosensory; Control: IPL)	Active control group (Healthy participants)	Single-blind	No	No	Continuous	Yes	Within-subject association between the Social Responsiveness Scale and changes in resting-state connectivity. No between-group effect.	Within-group $r = 0.56$
Major	(Hamilton)	Adults with	N active =	Localizer in	Sham control	Double-blind	No	Yes.	Intermittent	Yes	Between-group	Between-group

Depressive disorder	<i>et al.</i> , 2016)	major depressive disorder	10 N control = 10	dACC and fronto-insular cortex	group			strategies involving cognitive reappraisal, attentional redirection, and imagery.			and within-group effects on decreased negative affective bias and ratings of self-relevance of the negative adjectives	up effect of decreased negative bias: Cohen's $d = .78$ and ratings of self-relevance of the negative adjective: Cohen's $d = 0.73$
	(Mehler <i>et al.</i> , 2018)	Adults with major depressive disorder	N active = 16 N control = 16	Localizer in anterior brain areas (e.g., insula and striatum)	Active control group (PPA)	Single-blind	Yes	Yes. Potential starting strategies: the active group: imagery of positive stimuli. The control group: imagery of scenes.	Continuous	Yes	No between-group effect on clinical outcomes, but within-group effects are observed.	Within-group effect of $g = 1.46$
	(Young <i>et al.</i> , 2014; Yuan <i>et al.</i> , 2014)	Adults with major depressive disorder	N active = 14 N control = 7	Left amygdala	Active control group (Intraparietal sulcus)	Double-blind	No	Yes. Happy Memories, Count, and Rest conditions.	Continuous	Yes	Between-group effect on mood scales (VAS Happiness ratings, and STAI state anxiety)	N/A
	(Young, Siegle, <i>et al.</i> , 2017)	Adults with major depressive disorder	N active = 19 N control = 17	Left amygdala	Active control group (Intraparietal sulcus)	Double-blind	Yes	Yes. Happy Memories, Count, and Rest conditions.	Continuous	Yes	Between-group effect on multiple clinical scores (MADRS, BDI-II, and HAM-D).	Mean between-group effect on MADRS: Cohen's $d = 1.03$ BDI-II: Cohen's $d = 0.73$ HAM-D: Cohen's $d = 0.79$

	(Zotef <i>et al.</i> , 2016)	Adults with major depressive disorder	N active = 13 N control = 11	Left amygdala	Active control group (Intraparietal sulcus)	Single-blind	No	Yes. Happy Memories, Count, and Rest conditions.	Continuous	Yes. Group effect for the Happy vs Count contrast.	Between-group effect on emotional state improvement.	N/A
	(Zotef <i>et al.</i> , 2020)	Adults with major depressive disorder	N active = 16 N control = 8	Left amygdala, left rostral anterior cingulate cortex, and frontal EEG asymmetries.	Sham control group	Single-blind	Yes	Yes. Happy Memories, Count, and Rest conditions.	Continuous	Yes	No between-group effect. Within-group effects on emotional states.	Average within-group Cohen's d = 0.62
	(Mennen <i>et al.</i> , 2021)	Adults with major depressive disorder	N patients = 14 N Healthy controls = 12	Whole-brain decoder of task-relevant object category (face or scene)	Active control Group (Healthy individuals)	Single-blind	No	Yes. Informed informed that the change in opacity was determined by their brain activity.	Continuous	Yes	Between-group and within-group effects on the probability to get stuck in the most negative State (negative faces).	N/A
Post-traumatic stress disorder	(Keynan <i>et al.</i> , 2019)	Healthy man going through military training	N active = 90 N control = 45 N no feedback control = 45	EEG-fingerprint of the amygdala	Active control group (Alpha-Theta training) No feedback group	Double-blind	Yes	No	Continuous	Yes	Between-group and within-group effects on emotion regulation (emotional stroop and alexithymia questionnaire)	Emotional stroop: $\eta^2 = 0.06$ Alexithymia questionnaire : $\eta^2 = 0.12$
	(Misaki <i>et al.</i> , 2018; Zotef <i>et al.</i> , 2018)	Veterans with combat-related PTSD	N active = 20 N control = 11	Left amygdala	Active control group (Intraparietal sulcus)	Single-blind	Yes	Yes. Happy Memories, Count, and Rest conditions.	Continuous	Not a clear learning effect.	No between-group effect. Within-group effect on CAPS scores.	N/A
Schizophrenia	(Bauer <i>et al.</i> , 2020)	Schizophrenia or	N = 11	Central Executive	Active control condition	Single-blind	No	Yes. Meditation	Continuous	Not available	Effect reported on auditory	Active condition:

		schizoaffective disorder		Network minus the default mode network	(crossover design)			(Mental noting)		e	hallucinations following the active condition. No direct comparison with the control condition.	Cohen's d = 0.57
	(Okano <i>et al.</i> , 2020)	Schizophrenia or schizoaffective disorder	N = 10	Superior temporal gyrus	Active control condition (crossover design)	Single-blind	No	Yes. Listen or ignore spoken sentences.	Intermittent	Effect reported in the active group. No test reporting the interaction.	Effect reported on auditory hallucinations following the active condition. No direct comparison with the control condition.	N/A
	(Zweerings <i>et al.</i> , 2019)	Adults with schizophrenia	N patients = 21 N Healthy controls = 35	Inferior frontal gyrus and posterior superior temporal gyrus	Randomized cross-over design (up-regulate and down-regulate) with active control group	Double-blind	Yes. Condition order.	Yes. (1) recalling positive autobiographic memories, (2) imagining spoken language or (3) imagining a relaxing situation	Intermittent	Within-group. No between-group effect.	No between-group effect. Within-group association between the change in functional connectivity and the change in the global severity index.	N/A
Substance abuse	(Hartwell <i>et al.</i> , 2016)	Nicotine-dependent smokers	N active = 21 N control = 23	Anterior cingulate cortex and orbitofrontal cortex	No feedback control group	Single-blind	Yes	Yes. Reduce craving during cue exposure.	Intermittent	Yes	Between-group effect on the Questionnaire of Smoking Urges (Factor 1)	N/A
	(Kim <i>et al.</i> , 2015)	Heavy smokers	N active = 7; N control = 7	Anterior cingulate cortex, medial prefrontal cortex and orbitofrontal cortex and their connectivity with	Active control group (Anterior cingulate cortex, medial prefrontal cortex and orbitofrontal cortex)	Single-blind	Yes	Yes. Asked to resist the urge to smoke without any explicit strategy	Continuous	Within-group. No between-group effect.	No between-group effect. Within-group effect of changes in neural activity	N/A

				bilateral posterior cingulate cortex and precuneus areas.				provided.			on craving scores.	
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If not directly mentioned in the text, single-blind was inferred when patients were unaware of group membership or of experimental conditions (in within-subject designs). Single-blind was not automatically inferred when a healthy control group was used. Double-blind was never inferred and needed to be explicitly stated in the manuscript.

Figure 1. Principle of closed-loop neurofeedback interventions. In closed-loop experiments, a neurofeedback target is processed in real time and fed back to the participant, often in the visual modality. For instance, previous experiments represented the decoded brain activity through the diameter of a circle (right). This feedback process is thought to trigger neurophysiological and psychological mechanisms, possibly related to reinforcement learning, that can over time lead to an increased expression of the targeted brain activity.

Figure 2 A) Schematic representations of decoded fMRI neurofeedback and B) principle of Hyperalignment. A) Brain activity is pre-processed in real time (i.e., incoming data) and decoded using a pre-trained brain decoder of a specific psychological state. For instance, such a brain decoder can be trained to predict attention to a specific stimulus or the visual presentation of a feared animal. The output of such decoders can for instance indicate how closely the brain activity matches the one of the targeted representations (e.g., activation likelihood). This information is then displayed visually in real time and paired with a monetary reward. This is achieved in order to mobilise neurophysiological and psychological mechanisms facilitating the expression of the targeted brain representation. It could also associate the brain representation with a reward. B) Using Hyperalignment it is possible to represent the brain data of different participants in a common space. The common space is determined by functionally aligning the responses of a group of voxels. This is achieved by presenting participants with a task expected to generate similar response profiles across participants. For instance, the presentation of a movie is expected to generate similar response profiles in the visual system. Once the common space is determined, it is then possible to transform data from the native space of participants to the common space. Importantly, it is also possible to reverse that transformation and to bring data from the common space to the native space of a specific participant. This can notably be achieved for the purpose of neurofeedback training (bottom).

Figure 3. A) Decoding an EEG fingerprint and B) principle of connectivity-based neurofeedback. A) When EEG and fMRI signals are acquired simultaneously, it is possible to train a decoder of EEG activity (i.e., “Decoder of the EEG fingerprint”) to predict the fMRI activity. This decoder can later be used outside of the fMRI scanner for neurofeedback purposes. B) Connectivity neurofeedback is conducted in order to reinforce the connectivity between two brain regions (e.g., target 1 and 2). Multiple strategies were used for the purpose of connectivity neurofeedback. An interesting approach involves training participants to increase the connectivity between two target regions while decreasing the connectivity between the targets and a control region (see (Ramot *et al.*, 2017))

Figure 4 The principle of co-adaptive systems. A) Decoded brain activity can be used in order to train a reinforcement learning model to interact with the user. As described in the main text, an algorithm can learn to interact with the user in order to optimise or minimise the decoded brain activity. B) Similarly, a deep generative model can be used to generate visual stimuli that will optimise or minimise decoded brain activity (Adapted from (Taschereau-Dumouchel and Roy, 2020)).