Review

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P R E S S

Learned regulation of brain metabolism

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Self-regulation and voluntary control of circumscribed brain regions using real-time functional MRI (rt-fMRI) allows the establishment of a causal functional link between localized brain activity and behavior and cognition. A long tradition of research has clearly shown the brain's ability to learn volitional control of its own activity and effects on behavior. Yet, the underlying neural mechanism of self-regulation is still not fully understood. Here, we propose that self-regulation of brain activity is akin to skill learning and thus may depend on an intact subcortical motor system. We elaborate on the critical role of the basal ganglia in skill learning and neurofeedback, and clarify that brain-self-regulation need not be an explicit and conscious process as often mistakenly held.

Neurofeedback and brain plasticity

Neurofeedback (see Glossary) is defined as the learned change of a particular neural signal or a combination of neural signals when feedback and reward of these signals are repeatedly presented to the organism. When Joe Kamiya and colleagues published the first report on biofeedback of the alpha waves of the human electroencephalogram (EEG) in 1969 [1], the paper triggered widespread interest not only in the psychophysiological and neuroscientific community, but more so in the public and in the clinical community. The same year Eberhard Fetz demonstrated operant-reward learning of cellular spiking in a monkey: the monkey was rewarded for an increase in neuronal firing recorded from microelectrodes in the motor cortex [2] and learned to activate and deactivate the responses of that cell in isolation, without activating or deactivating the whole brain. These complementary demonstrations of neurofeedback stimulated the notion of unlimited plasticity of the mammalian brain and created hope for the treatment of neurological and neuropsychiatric disorders with learned self-regulation of the disordered brain regions. However, as often is the case in the history of

the biological sciences, the road to clinical success turned out to be much longer and stonier than originally expected (Box 1). Only neurofeedback of intractable epilepsy [3] and attention deficit–hyperactivity disorder (ADHD) [4]

Glossary

Amyotrophic lateral sclerosis (ALS – also called Lou Gehring's disease): progressive atrophy of all voluntary muscles due to degeneration of motor neurons at the motor cortex, brain stem, and spinal cord.
Anterior insula: evolutionarily old cortical area located deep within the sylvian fissure. Often used in neurofeedback experiments because of its strong relationship with perception of emotions and pain.
Blood-oxygen-level-dependent (BOLD) response: a magnetic resonance imaging (MRI) contrast of blood oxyhemoglobin and deoxyhemoglobin. Higher BOLD signal intensities arise from increases in the concentration of oxygenated hemoglobin and decrease in the concentration of deoxyhemoglobin during brain activity.
Brain–machine interface (BMI): control of an external device or computer (brain–computer interface, BCI) with brain activity alone. Neurofeedback is often used to train BMI control.
Completely locked-in syndrome (CLIS): a cognitively intact person without any peripheral motor control.
Curare: a plant alkaloid which blocks muscle nicotine receptors and thus causes paralysis, including paralysis of the respiratory muscles. South American natives killed their prey with curare at the tips of arrows.
Deep brain stimulation (DBS): deep brain stimulation delivers electrical stimulation through a chronically implanted electrode in a target region of the brain. It has evolved from an experimental procedure to a successful reversible surgical treatment for motor disorders (Parkinson's disease, tremor, dystonia), chronic pain, and incipiently for psychiatric conditions (obsessive compulsive disorder, treatment-resistant depression).
Discriminative stimulus (S^D): stimulus or context present during a rewarded response.
Effective connectivity: represents the direction of influence between brain regions. In fMRI, effective connectivity techniques usually include Granger causal mapping, mapping based on psychophysiological interactions, structural equation modelling, and multivariate autoregressive modelling.
Extinction (Pavlovian): progressive weakening of a learned response during repetitive presentation of a conditioned stimulus without the unconditioned stimulus (in classical Pavlovian conditioning).
Extinction (operant): progressive weakening of a learned response (operant) after repetitive responding without occurrence of the anticipated effect.
Functional connectivity: refers to the correlation or partial correlation of time-series of brain signals during a task or rest. This measure takes into account neither causality (the direction of information flow) nor whether structural connections between two brain regions are direct or indirect.
Habit learning (synonymous with skill learning): acquisition and maintenance of motor acts in memory. A form of implicit learning because it requires no active-explicit and conscious search for reproduction and recall.
Neurofeedback: an organism receives continuous information about its own brain activity.
Structural connectivity: represents the physical connections existing between neurons or brain regions. One well known type of physical connection between neurons or brain regions is the axon or a group of axons (axonal bundle).

Box 1. The curarized rat tragedy: motor mediation and neurofeedback

Until the 1960s, instrumental learning of autonomous responses was regarded as impossible, because of the understanding that homeostatic functions are regulated by the autonomous nervous system (ANS) independently of voluntary, non-homeostatic motor responses. Neal E. Miller, one of the most influential and productive experimental psychologists of the 20th century challenged the doctrine of the autonomous nervous system as autonomous and argued that even homeostatic functions may be learned instrumentally, at least within their physiological limits (i.e., heart rate [17]). Miller also claimed that brain self-regulation and neurofeedback may be independent of changes in the central and peripheral motor systems [49].

Miller, however, was aware of the crucial argument of traditional physiology that voluntary control of autonomous changes is usually mediated by motor–muscular changes (i.e., increase muscle tension in order to increase heart rate). Even thinking (in the tradition of 'motor theory of thinking' of the 19th century [50]) and brain activity can be considered as part of the motor system's dynamics. To eliminate motor mediation, Miller designed the curarized rat preparation: the awake rat, artificially respirated and fed, completely paralyzed by curare over a long period of time and with an artificially held constant equilibrium of most other physiological functions is rewarded with electrical stimulation of the reward centers in the limbic system for an increase or decrease of one specific physiological response, for example, an increase/decrease in heart rate, peripheral blood flow, renal blood flow, etc., without any concomitant increase or decrease in muscle activity and without unspecific changes of arousal or relaxation in other bodily systems [49].

Miller's laboratory at Rockefeller University was unable to replicate the positive effect over the years [49]. One of the main investigators, Leo Di Cara, left the laboratory and committed suicide and the suspicion that the early positive results were fabricated without Miller's involvement by his graduate student was never proved or disproved. Miller's name was dropped from the Academy's list of Nobel candidates. Barry Dworkin of the Rockefeller laboratory and some other groups tried to replicate the results during the next 40 years without success [49]. Many explanations were tested in order to resolve the puzzle of the curarized rat preparation, none of which provided a satisfactory solution.

Moving from the curarized rat to the completely paralyzed locked-in patient (CLIS), artificially respirated and fed with a more or less constant equilibrium of many bodily systems, Kubler and Birbaumer [51] reviewed all available published cases with CLIS where neurofeedback and BMI were applied to achieve brain communication using operant learning of EEG waves, event-related brain potentials, such as slow cortical potentials (SCP), and direct invasive recording from the cortical surface (electrocorticogram). None of these attempts, even after months of training, achieved reliable brain control and communication, mirroring the curarized rat disaster. A more recent study [52] found indications of systematic brain communication using a BCI based on EEG signals in a CLIS patient when a classical conditioning paradigm involving statements that need to be answered with 'yes' or 'no' was used (e.g., 'The capital of Germany is Rome'; 'The capital of Germany is Berlin'). The supposed 'no'-thinking of the patient was followed by an aversive or negative stimulus. The EEG signals were then classified to recognize 'yes' and 'no' answers from positive and negative brain responses established on the basis of the EEG. When the same patient was later presented with personal questions, 'yes' and 'no' answers were classified with high accuracy, based on positive and negative brain responses classified in some sessions only. Birbaumer *et al.* speculated [53] that extinction of goal directed, output-effect oriented thinking may be responsible for this failure and the failure to train the curarized rat. Patients (and animals) learn that anticipated effects of a particular intention (e.g., 'I want to be turned around') do not occur, and extinction follows.

These unresolved difficulties to achieve instrumental-operant control of brain responses (and autonomic responses) in completely paralyzed organisms may cast doubts on a skill-learning interpretation of brain-control. A single case of a CLIS patient or of a curarized rat learning to produce a brain response 'voluntarily', after neurofeedback training that rewards the response, would disprove the motor mediation hypothesis of neurofeedback and strengthen a skill-learning interpretation of neurofeedback: presently, such a case does not exist. However, the fact that a CLIS patient answers reliably with a yes or no response by producing a change in EEG or in blood oxygenation as described above points towards an operant 'voluntary' component, even in this classical 'reflexive' conditioning procedure. Without volition to answer such questions, reliable responses by these completely paralyzed patients is not possible, and responding at chance level would result.

responded favorably in controlled studies with neurofeedback of slow cortical potentials. With functional MRI (fMRI) allowing access to deep brain systems involved in the regulation of emotion and motivation, these hopes were re-awakened.

In this review, we first present a theoretical framework of the learning mechanism that underlies neurofeedback and then discuss the effects of neurofeedback of the rt-fMRI blood-oxygen-level-dependent (BOLD) response on behavior. Finally, we describe the effects of neurofeedback of local BOLD changes on neurological and psychiatric disorders.

Methodology of rt-fMRI-based neurofeedback

An rt-fMRI neurofeedback system performs the following functions in real-time: brain signal acquisition from an MR scanner, signal processing for extracting relevant features from the region(s) of interest, computation of feedback and/or reward, and presentation of this feedback/reward to the subject (Figure 1). Separate computers connected by a local network typically handle these different functions. An echo planar imaging sequence is used to acquire whole brain images from experimental subjects. With this technique, the three-dimensional brain is divided into a number of two-dimensional slices of specific thickness (e.g., 5 mm)

with a specific gap (e.g., 1 mm) between the slices. The real-time operation requires that feedback be produced immediately after each set of whole-brain images is acquired for each time point (usually 1–2 s). After signal acquisition for each time point, the reconstructed images are transferred to another computer, where the images are pre-processed to improve the signal-to-noise ratio. After the images are generated, the rt-fMRI software performs statistical analysis and generates functional maps. Brain activation in regions of interest is then used for computation of feedback and reward in various ways: from simple arithmetic sums and differences of average activation levels to complex spatio-temporal patterns. Feedback is most commonly presented visually and in a variety of forms, including functional maps, continuously updated curves, graphical thermometers that display activity or virtual reality immersive environments. For a detailed review of the methods, see [5–7]; see also Box 2 for rt-fMRI methodological advances.

Mechanisms of brain regulation and neurofeedback
Learning the skill to regulate one's own brain activity
Skill learning involves a discriminative stimulus (S^D) that activates response planning, the actual response, and an

Box 2. Rt-fMRI methodological advances

Although the majority of the rt-fMRI neurofeedback studies have aimed at training individuals to self-regulate circumscribed brain regions, further advances have enabled feedback of functional connectivity between brain regions [55]. Even more intriguing are studies that have employed pattern classification approaches developed in the field of machine learning to train individuals to self-regulate the spatio-temporal patterns of the specific circuitry involved in motor function, emotion, and perception [20,56,57]. These studies have established that people can learn to regulate patterns in a specific manner that has behavioral consequences.

effect (reward or punishment) that is time contingent upon the response. The response plan is modified based on the difference between the anticipated effect and the actual effect [8]. Skill learning curves, like other forms of procedural learning and repetition priming, usually follow a positive exponential function [9]. During the neurofeedback-based learning of metabolic or neuroelectric responses, no response plan exists at the start of training, because the response and its physiological and behavioral correlates are not in the repertoire of the organism's memory. Further, such responses usually do not fulfill a motivational drive-modulating function – except if brain regions with homeostatic properties are modified. Therefore, they need external reinforcement in order to become stable habits. Sensory feedback of the target physiological response acquires its anticipated effect by motivating learning from instruction (in humans) or through associa-

tion with primary or secondary rewarding or punishing stimuli. As training progresses, however, an idiosyncratic response plan develops, usually hidden from the experimenter: participants use imagery and other abstract cognitive activities, which become more and more 'pruned' from irrelevant response elements until a final response concept reliably evokes the desired effect [10]. The hidden nature and idiosyncrasy of the initial response plan leads to large differences in variability of the learning curves in neurofeedback experiments, particularly during the initial training phases. Visual or auditory feedback stimuli that represent the response strength of the desired brain response are used most frequently in neurofeedback. Instructions to the participant may play a critical role in self-control of brain activity: if ambiguous instructions are given (e.g., 'try to produce an increase of the red colored bar on the screen'), the initially unstructured response plan may appear even less specific for the participant. Ambiguities in instruction and initial responses could lead to high variability, often extended training periods, and a substantial rate of non-learners in neurofeedback [10,11]. Neurofeedback of the BOLD signal and other metabolic brain signals, for example, as measured with near infrared spectroscopy (NIRS), may produce smoother and more exponential learning curves than neuroelectric responses, comparable to motor skill acquisition, because feedback from the brain's vascular system to the critical brain areas responsible for skill learning (e.g., the striatum and basal ganglia structures) constrains the abstract nature of the
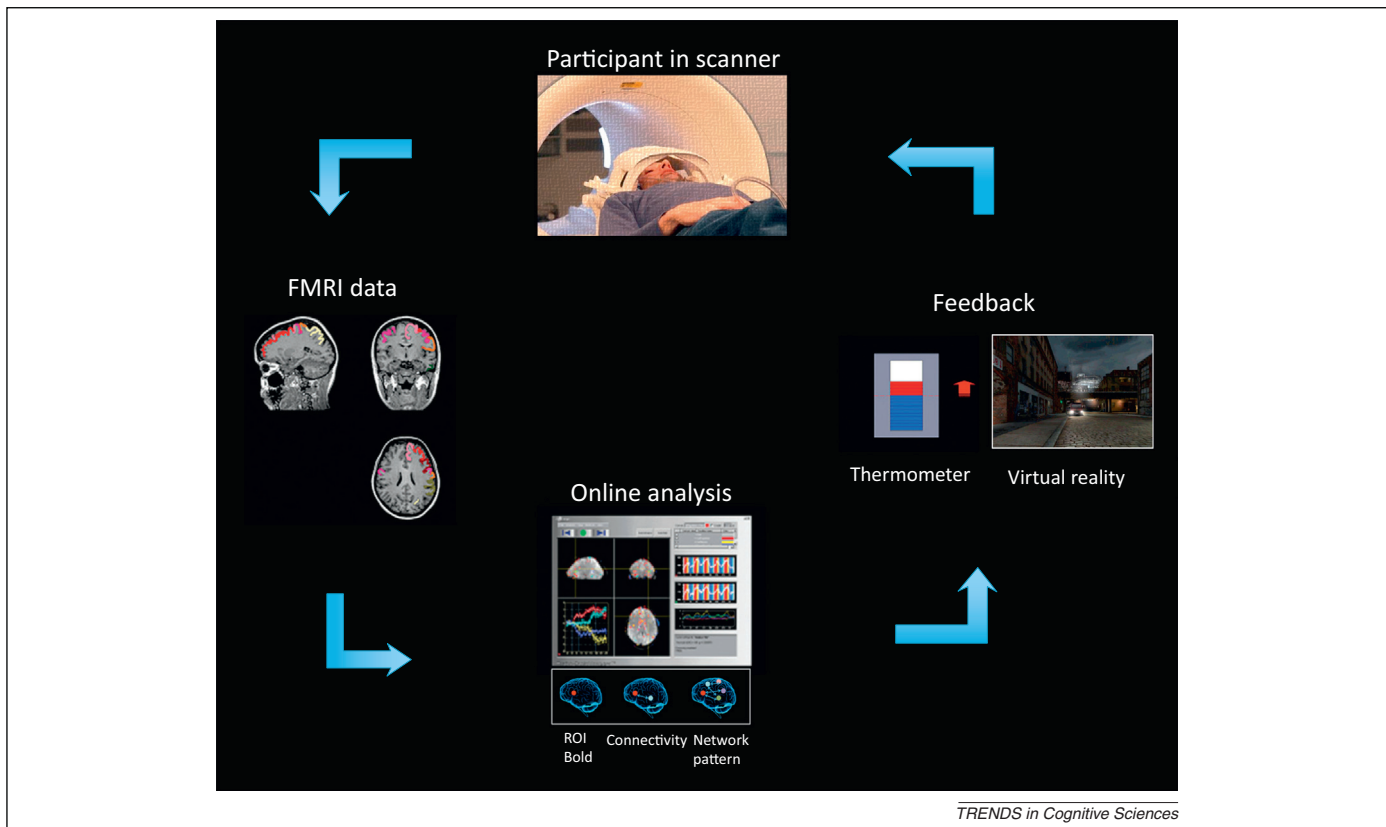

TRENDS in Cognitive Sciences

Figure 1. Overview of an rt-fMRI neurofeedback system. Ongoing BOLD signals from the participant, lying in the MR scanner, is acquired, processed, and presented as visual feedback (auditory or haptic feedback is also possible). Feedback can be provided as changes in amplitude from individual brain regions (e.g., primary motor cortex), functional connectivity measures from two or more brain regions (e.g., between Broca's and Wernicke's areas), or decoded spatio-temporal patterns of brain activity in distributed brain regions that represent a network (e.g., fear network). Real-time feedback can be provided as a simple increase/decrease in levels of activation (e.g., in a thermometer) or in the form of a complex and immersive virtual reality environment. Part of this figure is reproduced, with permission, from [54].
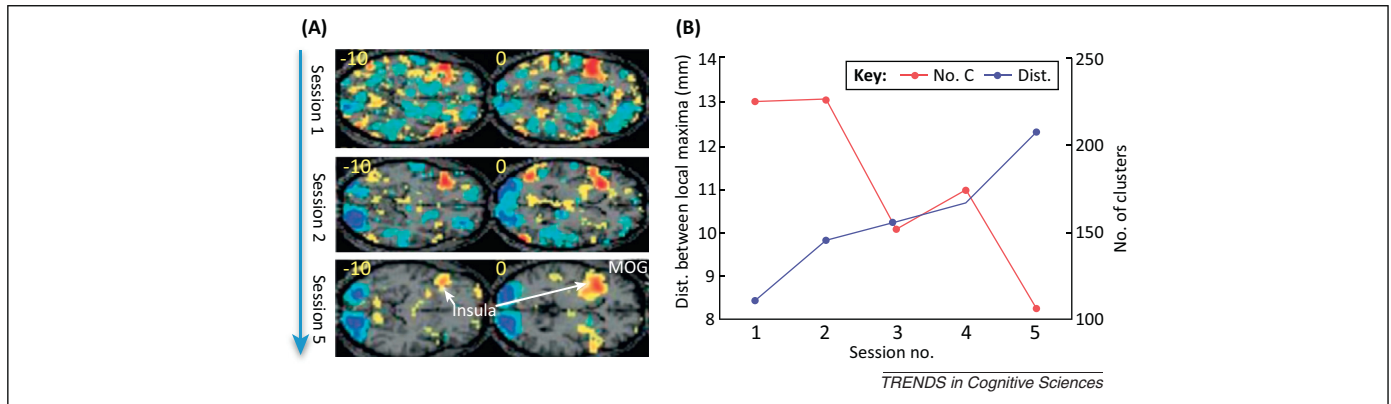
Figure 2. Brain reorganisation due to rt-fMRI neurofeedback training of the anterior insula [13]. The results depicted in these two panels are from a multivariate analysis of the data from a previous study [14], in which participants were trained to regulate their own BOLD responses in the anterior insula with rt-fMRI feedback. **(A)** Neurofeedback training from session 1 to session 5 (top to bottom; sessions 3–4 are not shown) results in focusing of brain activity. **(B)** This effect is represented quantitatively as a decrease in the number of activation clusters and simultaneous increase in the average distance between the clusters. Reproduced, with permission, from [13].

skill to be acquired [12]. The brain processes information from its vascular system, but it has no sensors for its neuroelectric responses. Changes in blood oxygenation, flow, and pressure are readily processed in the brain and thus may compensate for the lack of motor response components in brain self-regulation and allow faster 'sharpening' of the response properties and pruning of irrelevant response components through feedback and reward. Figure 2 shows different aspects of the change in brain activation in participants who learned to regulate their own BOLD response in the anterior insula via rt-fMRI feedback [13,14]. Figure 2A shows the gradual focusing of brain activations, especially in and around the anterior insula. Figure 2B shows a quantification of the focusing effect, in terms of the number of clusters of brain activation and the distance between the activation clusters. It is evident that with increasing BOLD feedback training, there is a decrease in the number of clusters and an increase in the distance between the clusters.

The role of the basal ganglia in the learned acquisition of brain control
Brain responses are learned, stored, and retained in a manner that is comparable to a motor skill, following the rules of implicit learning [15]. In contrast to explicit learning, implicit learning and memory do not require conscious and effortful search. In the neurofeedback situation, implicit learning is usually negatively defined by providing no explicit instruction to participants as to how they may control the brain activity represented by the feedback stimulus, such as imagery and other mental strategies. In animals, learned control of neuroelectric responses that range from single cell firing [2] to cortical EEG [16] have clearly indicated that neither instructions nor explicit mental strategies – as far as they can be assessed in animals – are necessary to learn brain control. Instrumental (operant) learning of regulation of peripheral vascular responses was also demonstrated in animal preparations [17] (Box 1). A discriminative stimulus (S^D) that indicates to the animal the occurrence of a reward after the particular physiological change is sufficient to guarantee learning. Whereas self-regulation and operant learning of peripheral vascular responses, such as blood pressure,

blood flow, vascular diameter, and blood oxygenation, are well documented, instrumental learning of brain vascular responses in animals has not been investigated, but there is no evident reason to expect a difference in outcome for brain vascular responses and peripheral vascularity.

The most compelling evidence for the procedural nature of neurofeedback-based learning and the critical role of cortical–basal ganglia loops responsible for procedural learning in learned brain control comes from a neurofeedback study with rodents [12]. For motor skills, the role of the cortical–basal ganglia loop is well established, but brain self-regulation does not involve any movement: subjects have to learn the abstract skill of changing brain activity while motionless, to move a neuroprosthetic device or a computer cursor without activating the motor periphery. Koralek *et al.* [12], using intracellular recordings, trained rats to modulate the firing rate of two adjacent neural ensembles in the primary motor cortex (M1) in order to obtain a reward. Modulation of activity in the two ensembles resulted in changes in the pitch of an auditory cursor, which provided constant auditory feedback of the task to the rodents. Reward was delivered when rodents precisely increased activity in one ensemble and decreased it in another ensemble, or vice versa, in order to move the auditory cursor to one of two target tones. When a successful effort was made to any of the targets, the rodent was rewarded with a sucrose solution for one target and with a food pellet for the other. Within 11 days of training, rats became proficient in both tasks and exhibited typical skill-learning acquisition rates. Omitting the feedback but retaining the reward did not result in learning. Degradation of the food–reward contingency or degradation of reward by satiety also rapidly impaired learning, even if correct auditory feedback was provided. Both feedback and reward are necessary for acquisition of the brain response (Figure 3).

Striatal neuroplasticity in natural motor skills proved to be critical for learning of the neurofeedback task: cross correlations between the motor cortical cells and striatal neurons revealed increased oscillatory coupling in the 4–8 Hz range with learning. Finally, knockout rats that lacked N-methyl-D-aspartate receptors (NMDARs) – necessary for long-term potentiation in striatal neurons – did
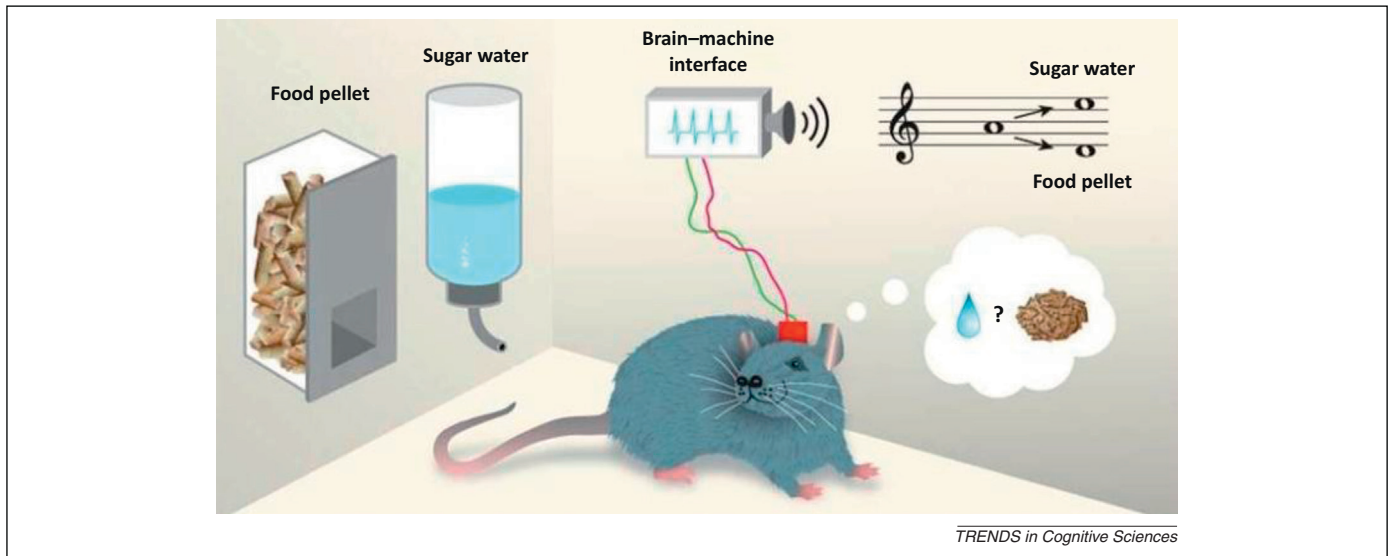
Figure 3. Skill learning in rodents. Koralek *et al.* [12] implanted electrodes into the brains of live rats to record the neuronal activity of the motor cortex and the striatum. Depending on certain features of motor cortex activity, a tonal sound with a specific pitch was automatically generated. The rats learned to make the pitch of the sound rise or fall by modifying their brain activity, because they were rewarded with sugar water or food pellets if the pitch changed successfully. By using genetically modified mice in similar experiments, the authors showed that activity of the striatum was required for the animals to learn the task. Reproduced, with permission, from [12]..

not learn the self-regulation task, despite intact movement (for the role of motor mediation in neurofeedback, see Box 1). Pharmacological blockade of NMDARs in the dorsal striatum also impaired the task in the same way.

These compelling data are complemented by earlier fMRI-brain imaging evidence in humans during learning of self-regulation of slow cortical potentials (SCP). Comparing good learners with poor learners in this neurofeedback task revealed activity of the basal ganglia and cortical motor structures in proficient learners [18].The participants received visual feedback of the amplitude of their SCP: increased cortical negativity (indicating stronger activation of the brain at central sites) moved a cursor up on the screen and decreased negativity moved the curser down, both movements being proportional to the change in amplitude of the SCP. Using neurofeedback and brain–machine interface (BMI) training of sensorimotor (8–15 Hz) rhythms, Halder *et al.* [19] demonstrated that learned control of sensorimotor areas, which are an essential part of the cortico-basal-ganglia-loop, can be predicted from BOLD-response increase in those areas during pre-training motor imagery, particularly while observing movement in others. Overall, this converging evidence from animal and human neurofeedback paradigms strengthens the theoretical position that brain self-regulation and BMI-control can be viewed as skill learning. Whereas an intact subcortical extrapyramidal motor system and dorsal striatum seem to be a *conditio sine qua non* for brain-regulation skill acquisition, the impact of the peripheral and central 'pyramidal' voluntary motor system remains an open question (Box 1).

Implicit nature of brain-regulation learning
Several human studies using neurofeedback of BOLD responses with rt-fMRI have demonstrated that neither explicit instructions nor explicit imagery and particular mental strategies are mandatory for learned BOLD control. Shibata *et al.* [20] asked their healthy participants 'to

increase the size of a green disc as much as possible' over 6–10 daily sessions. The size of the feedback stimulus was determined – unknown to the participant – by the BOLD response belonging to one of three target line orientations of Gabor patches of the discriminative stimulus. Post-experimental questioning clearly showed that none of the participants was aware of the contingency between line orientation and the feedback. However, they all learned to improve discrimination of line orientation through BOLD neurofeedback. Even more impressive seems to be a demonstration by Kim and colleagues (see [5], for a discussion of this work) that subliminal perception of emotional faces becomes conscious after rt-fMRI training to upregulate the fronto-parietal brain network, including visual cortex, fusiform face area, insula, and prefrontal cortex, without any instructions. Learned down-regulation in the same network was also possible in the same participants, this time leading to reduced conscious recognition of the emotional stimuli.

Behavioral effects of learned brain regulation
The emphasis in recent rt-fMRI studies has shifted from an earlier focus on ascertaining self-regulation capability in different brain regions to investigating the behavioral consequences of learned regulation. Motor regions have received much attention in these studies, indicating that volitional modulation of motor regions could be achieved by rt-fMRI training, with some studies showing changes in motor function as a consequence of training [21–28].

A series of rt-fMRI experiments on manipulating emotions trained individuals to up- or downregulate activity in the anterior insular cortex [14,29] and showed that upregulation leads to increase in the valence ratings of aversion-inducing images, but not neutral images [30], increase in the recognition of faces displaying the emotion of disgust emotion, and decrease in the recognition of faces showing happy emotion, as well as an increase in connection strength in the emotion network [31]. Self-regulation of

language-related brain regions was studied by Rota and colleagues, who reported that upregulation of the right inferior frontal gyrus (the homolog of left Broca's area) resulted in enhancement of prosodic language processing [32] and was also simultaneously associated with a strengthening of connectivity of this brain region to the right prefrontal cortex [33]. Volitional upregulation is also possible in the amygdala [34,35], whereas downregulation of the subgenual anterior cingulate could be achieved by positive imagery and contingent feedback, but not sham feedback [36]. Scharnowski *et al.* found improvements in perceptual sensitivity when they trained participants to upregulate the retinotopic visual cortex with rt-fMRI neurofeedback [37]. An exciting new path to motor rehabilitation was suggested by Sulzer *et al.* [38], who obtained the first positive results showing that the dopaminergic midbrain regions, namely, the substantia nigra and ventral tegmental area, can be upregulated by rt-fMRI feedback. An innovative use of rt-fMRI already mentioned above has been in the operant conditioning of the brain's response to sub-threshold stimuli as a means of modifying conscious perception and awareness [5].

Rt-fMRI neurofeedback in neurological diseases

deCharms and colleagues [39] investigated the clinical impact of self-regulation of rostral anterior cingulate cortex (rACC), a region putatively involved in pain perception. Patients with chronic pain achieved volitional control of rACC activation with rt-fMRI training and subsequently reported a decrease in the level of ongoing pain (an effect that was significantly larger than for control groups trained without rt-fMRI feedback). This important study could not be replicated by deCharms, however (personal communication). Haller and colleagues [40] conducted a pilot experiment in which six patients with chronic tinnitus were trained to reduce the activity of the auditory cortex. Most of the patients learned to downregulate activations in the ROI aided by contingent feedback, and two of them reported a decrease in the subjective experience of tinnitus. Sitaram and colleagues [41] applied rt-fMRI neurofeedback in two stroke patients with right hemiparesis to achieve volitional control of ventral premotor cortex (PMv). Participants demonstrated a progressive increase of the BOLD signal in the PMv over the training, following which a reduction in intracortical inhibition was evident, pointing towards the beneficial effect of self-regulation on motor cortical outputs. Subramanian and colleagues [42] trained five patients at early stages of Parkinson's disease (PD) to upregulate the supplementary motor area and showed a subsequent improvement in both motor speed (in a finger tapping task) and clinical ratings. An equal number of patients trained without fMRI feedback information neither achieved control of the SMA nor displayed any behavioral modification.

Rt-fMRI neurofeedback in psychiatric/psychological disorders

Neuropsychiatric disorders are highly prevalent and burdensome conditions for which rt-fMRI neurofeedback could offer a new therapeutic option. In a proof of concept study, Linden and colleagues [43] used rt-fMRI neurofeedback in eight patients with unipolar depression, who were instructed to upregulate brain regions of emotion control. Both successful regulation and a significant clinical improvement were observed, which were not detected in a control group of patients trained without rt-fMRI feedback. Sitaram *et al.* [44] trained six psychopaths with criminal records to self-regulate the anterior insula. Criminal psychopaths show reduced or absent activation of the fear circuit, including the anterior insula [45]. Subjects with higher psychopathic scores were less successful at self-regulation than those with lower scores. Learned self-regulation led to an enhancement in the number of effective connections in the emotional network and to a more prominent a role of the insula as a causal source of neural connections. No consistent behavioral changes were found, however.

Ruiz and colleagues [31] showed that patients with paranoid schizophrenia were able to learn volitional control of the anterior insula and showed an improvement in the recognition rate of disgusted faces, in line with previous evidence of the role of the insula in face disgust recognition. Li and colleagues [46] trained ten nicotine-dependent smokers with rt-fMRI in a 'reduce craving paradigm' and reported that participants successfully managed to reduce their craving response towards craving-inducing pictures, while decreasing the activation of the anterior cingulate cortex. A significant correlation between the induced changes in ACC activation and the corresponding difference in craving ratings was also found.

So far, there is ample evidence that brain self-regulation is achievable with rt-fMRI, even in severe chronic brain disorders. However, for clinical applications, many crucial questions still need to be addressed (Box 3). The efficacy and cost-effectiveness of an expensive methodology like this needs to be examined further, with larger samples and extensive training times. Inconsistent results stress the

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Box 3. Future directions

Priorities for future research include:

- Investigating which feedback modality is the most suitable and how much of feedback training is optimal for learning.
- Testing whether brain self-regulation persists following training when feedback is not provided and whether symptom modification is clinically significant in the long term outside the fMRI laboratory.
- Performing animal studies that employ simultaneous microelectrode recordings during metabolic (i.e., BOLD) self-control learning to clarify the neurophysiological mechanism of metabolic neurofeedback training.
- Self-regulation training of larger but anatomically clearly defined neuronal networks and their functional connections with a thorough measurement of specific behavioral consequences.
- Conducting systematic variations of timing and modality of feedback and reward schedules to establish strong metabolic neurofeedback–behavior relationships.
- Documenting stable and specific long-term effects of metabolic neurofeedback and its behavioral consequences comparable to DBS.
- Developing and testing experimentally more affordable alternatives to fMRI, such as optical imaging (fNIRS) and EEG.
- Performing large scale multi-center controlled clinical trials with well defined clinical groups and adequate comparison groups receiving placebo treatment and the best available alternative treatments, such as drug therapy, DBS, and behavior therapy.

need for replication of the previous findings and inclusion of double-blind experimental designs.

Concluding remarks

Further animal studies, preferably with non-human primates, are necessary in order to clarify the relationship between BOLD self-regulation (BOLD neurofeedback) and intracellular and extracellular activities of the involved neuronal structures (Box 3). In particular, firing patterns and local field potentials (LFP) with simultaneous measurement of BOLD should establish a causal chain between voluntary regulation of BOLD and its cellular bases. The experimental realization of such simultaneous recordings in the awake monkey is difficult and only one laboratory has published extensively about neuro-vascular coupling using such a paradigm [47]

The contribution of physiological mechanisms and structures of the different components of the motor systems to brain-regulation learning need to be clarified. Consistent with a skill learning theory of neurofeedback, blockade of basal ganglia structures eliminated voluntary operant control of cortical spiking [12]. However, the specific role of the cortical, spinal, and peripheral motor system in brain-regulation learning is still not understood. The curarized rat with paralyzed peripheral motor output and the completely locked-in patient suffering from amyotrophic lateral sclerosis (ALS) destroying the motor system at all levels except the basal ganglia were unable to learn neuroelectric responses, but may acquire learned control of the vascular motor system underlying BOLD and brain blood oxygenation (Box 1).

Before neurofeedback of metabolic brain activity becomes a viable supplement to or even an alternative for deep brain stimulation (DBS) [48], it has to demonstrate efficiency in large controlled outcome studies or – as happened in the past with DBS – through cumulative evidence of clinically meaningful long-term (over years) effects outside the clinic or laboratory. Comparable to DBS in Parkinson's disease, the clinical evidence for rt-fMRI neurofeedback should be gathered in disorders for which no efficient long-term treatment is available (e.g., drug resistant generalized temporal lobe epilepsy or chronic stroke without residual movement) or when undesired side-effects severely hamper outcomes, such as neuroleptic drugs in schizophrenia, methylphenidate (ritalin) in children with ADHD, or electroconvulsive shock treatment in depression. For psychological and psychiatric disorders, control groups receiving the established psychotherapeutic (usually behavior therapy) or pharmacological treatment are mandatory. The same recommendation holds for metabolic neurofeedback as a strategy to enhance cognitive functions, such as memory, attention, and motor skills (neuroenhancement). Well-researched training strategies for cognitive enhancement should serve as controls. DBS is usually active 24 hours a day over months and years, wherever the patient lives and whatever he/she does. Neurofeedback cannot be expected to produce comparable effects after a few training sessions in a sterile laboratory environment.

Metabolic neurofeedback has now received its healthy birth certificate through a sufficient number of excellent proof-of-principle studies reviewed here. Whether this healthy baby survives and grows depends more on nutritional support (funding) and educational persistency (long-term controlled outcome studies).

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