Closed-loop brain training: the science of neurofeedback

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Abstract | Neurofeedback is a psychophysiological procedure in which online feedback of neural activation is provided to the participant for the purpose of self-regulation. Learning control over specific neural substrates has been shown to change specific behaviours. As a progenitor of brain–machine interfaces, neurofeedback has provided a novel way to investigate brain function and neuroplasticity. In this Review, we examine the mechanisms underlying neurofeedback, which have started to be uncovered. We also discuss how neurofeedback is being used in novel experimental and clinical paradigms from a multidisciplinary perspective, encompassing neuroscientific, neuroengineering and learning-science viewpoints.

Biofeedback
It provides an explicit indicator of some physiological process, such as heartbeat or brain activation, so that an individual can attempt to regulate that activation or guide behaviour.

Brain–machine interfaces
(BMIs). Brain–machine interfaces, sometimes called direct neural or brain–computer interfaces, are direct communication pathways between the brain and external devices.

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doi:10.1038/nrn.2016.164
Published online 22 Dec 2016

The goal of clinical and behavioural neuroscience is to observe and to understand nervous system mechanisms to manipulate behaviour-related neural processes and to restore or enhance function. Neurofeedback is a type of biofeedback in which neural activity is measured, and a visual, an auditory or another representation of this activity is presented to the participant in real time to facilitate self-regulation of the putative neural substrates that underlie a specific behaviour or pathology (FIG. 1). Neurofeedback began with experiments showing that humans could self-control electroencephalographic signals in real time[1]. These experiments led to the development of the field of brain–machine interfaces (BMIs), also called brain–computer interfaces (BCIs)[2], in which individuals aim to directly regulate external devices instead of neural substrates.

In neurofeedback, brain activation is volitionally regulated through learning; as the activation acts as an independent variable, it allows causal inferences to be made between brain activity and behaviour. The different behavioural changes that have been observed to result from self-manipulation of neural activation indicate that the physiological consequences of neurofeedback may be considered to be a form of endogenous neural stimulation[3]. Thus, neurofeedback has been used to modulate behaviourally relevant functional networks[3–6] and to provide self-administered therapy[7,8]. Concerns have been expressed about how the rapid attempts to use neurofeedback for clinical rehabilitation and therapy have outpaced the development of a proper understanding of the neural mechanisms and neuroplastic changes that underlie neurofeedback. The failure of some clinical trials[9,10] to show that neurofeedback can have treatment effects after promising preliminary studies further emphasizes the need to delineate neurofeedback mechanisms. In this Review, we describe the progress that has been made in understanding these mechanisms by synthesizing developments across neuroimaging modalities and applications in cognitive and clinical neuroscience.

Neural specificity and plasticity

Traditional functional neuroimaging establishes correlative relationships between brain activity and behaviour. By contrast, neurofeedback that involves functional neuroimaging enables the manipulation of neural activity in circumscribed regions, functional connections and spatiotemporal activity patterns as independent variables, and thus represents a way of investigating the relationship between brain activity and behaviour that is comparable to brain stimulation (BOX 1; FIG. 1). In this section, we discuss examples of self-regulation of neural activity with a focus on how learning self-regulation leads to specific neural and behavioural changes.

The neural substrates of self-regulation. Animal experiments that have monitored neural activation have provided the most fine-grained evidence that neural activity can be self-regulated in the context of BMIs and neurofeedback. For example, a study showed that monkeys could be trained to voluntarily increase or decrease the firing rate of neurons in the frontal eye field using auditory feedback and juice rewards[11]. During feedback training, the monkeys received auditory feedback of pure tones with a pitch that was proportional to the

Synchronization
Simultaneous oscillations of membrane potentials in a network of neurons that are connected with electrical synapses.

Biomarkers
Biological features (physical, physiological or behavioural) that act as robust predictors of one or more experimental or clinical outcomes.

Coherence
A measure of how stable the frequency and/or phase relationship is between two neural sites; it reflects the amount of information that is shared between two sensors or channels.

instantaneous firing rate of the multiunit activity at the recording site of the frontal eye field. Increasing neuronal activity in this oculomotor area improved visual attention but not oculomotor preparation, revealing a specific association of voluntarily controlled neural activity. Recent research showed that mice could gain control of spike-related calcium signals, which were recorded with two-photon imaging in motor and sensory cortices[12], and that learning was associated with changes in neural firing at fine spatial locations. Recently, human BMIs have shown that learned control of multiple neurons can operate different types of external devices to facilitate communication and motor control in people with paralysis. For example, on the basis of activity in the primary motor cortex (M1) recorded from intracortical multielectrode arrays, individuals with partial paralysis were able to learn coordinated movements of a seven degrees-of-freedom robotic arm[13], to control a computer cursor[14] or to functionally stimulate muscles[15].

Neurofeedback has been used to self-regulate electroencephalography (EEG) amplitudes, which correlate with the degree of intracortical neuronal synchronization[16]. Indeed, neurofeedback-mediated reductions in parieto-occipital EEG amplitudes boosted visual attention[17] or curbed mind-wandering[18], and neurofeedback-mediated increases in intracortical neuronal synchronization elicited improvements in tasks requiring internal processing, such as mental rotation[19] or musical performance[20].

Functional MRI (fMRI)-based neurofeedback that involved learning to increase or decrease activity in distinct cortical and subcortical regions of interest (ROIs) has been used to modulate behaviour. For instance, upregulation of activity in M1 (REFS 21,22), the dorsolateral prefrontal cortex (dlPFC)[23] and the anterior insula[24] was associated with improved motor performance, working memory and arousal to emotional pictures, respectively. Moreover, one study showed that neurofeedback-mediated downregulation of anterior cingulate cortex (ACC) activity was associated with a decrease in cigarette cue craving[25].

Recent neurofeedback studies have combined electrophysiological and haemodynamic brain signals in innovative ways to make the most of their respective advantages. For example, one study trained participants on less expensive, portable EEG after initially calibrating the location of the signal with spatially precise fMRI of the amygdala[26] (this approach is innovative, as EEG by itself cannot determine where activation occurs in deeper brain regions such as the amygdala). The participants downregulated the EEG correlates of amygdala blood-oxygen-level-dependent (BOLD) activation in the presence of visual stimuli. The authors found that improved downregulation with EEG-based neurofeedback was directly related to downregulation of the amygdala BOLD signal and that the self-regulated activity resulted in improved control of negative emotions. In contrast to this serial approach to multimodal neurofeedback, fMRI and EEG information can be presented simultaneously as two independent signals[27] to take advantage of the dynamic properties of the electrophysiological signal and the spatial specificity of the haemodynamic imaging modality. Similarly, functional near-infrared spectroscopy (fNIRS) has been combined with EEG in neurofeedback to improve sensory motor rhythm control by benefiting from the complementary information available in the two signals in classifying brain states[28]. Classification accuracy increased by 5% with the combined signals compared with the EEG signal alone.

One of the key advantages of non-invasive imaging in neurofeedback is that it allows the feedback of neural activation to be measured over an entire network of distributed brain regions that are involved in a specific function from spatiotemporal pattern of brain activations[3,4,29–32]. Biomarkers of pathological changes in dynamic interactions between brain areas (that is, functional brain networks[33]) that underlie psychiatric and neurological disorders (BOX 2) could be potential targets for neurofeedback training. Thus, the ability to modulate neural dynamics on a network level with neurofeedback may be a more effective method of neural regulation than neurofeedback involving a single area or anatomically unspecific pharmacological interventions.

The correlated activation of two neural substrates is termed 'functional connectivity' in haemodynamic modalities and 'coherence' in electrophysiological terms. One recent study examined functional connectivity-based neurofeedback and ROI-based neurofeedback in heavy smokers[8]. The performance of ROI-based feedback in anterior brain regions (comprising the ACC, medial PFC and orbital frontal cortex) and the posterior brain regions (comprising the posterior cingulate and precuneus) — all brain areas related to craving — were compared with functional connectivity-based feedback involving the same anterior and posterior regions. The study found greater volitional control with connectivity feedback than with activity-based feedback, but, more importantly, reductions in craving scores were better correlated with

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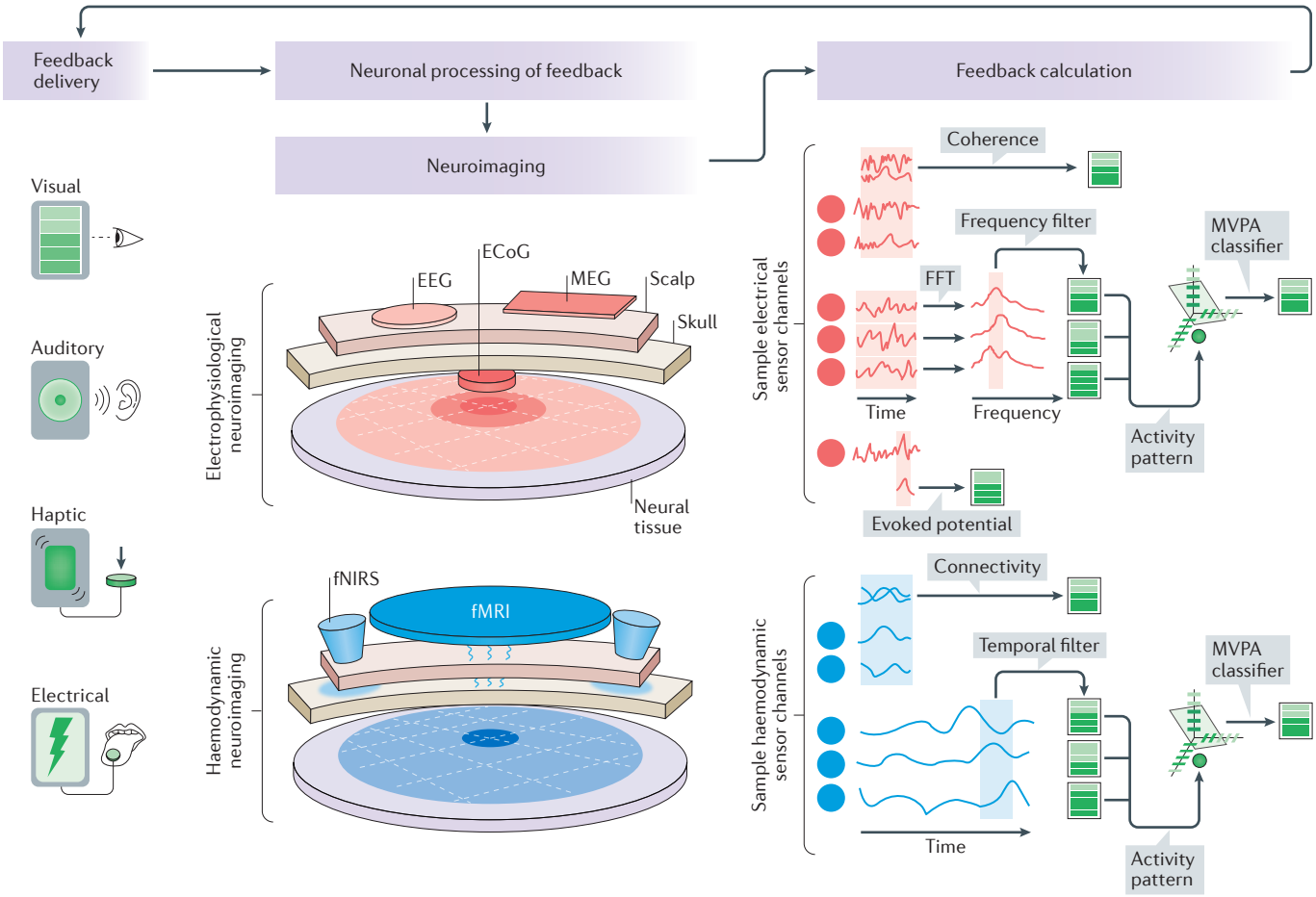

Figure 1 | **Overview of the procedure of neurofeedback.** Neurofeedback begins with observation of neural activity. Electrophysiological methods to detect such activity include electroencephalography (EEG), magnetoencephalography (MEG) and invasive electrocorticography (ECoG), and haemodynamic imaging methods for detecting neural activity include functional MRI (fMRI) and functional near-infrared spectroscopy (fNIRS). The grids on canonical neural tissues provide a qualitative reference for the relative spatial resolutions of the various imaging technologies. Sample signals that are extracted from both types of these sensor channels provide a qualitative representation of the difference in temporal resolution. Electrophysiological and haemodynamic signals can be processed in similar ways. Univariate approaches extract a signal from a single channel or region of interest, for example, an evoked potential. Calculation of coherence or connectivity between two channels as a measure of functional connectivity is another common feedback method. Features from a set of sensors, such as the power at a frequency window or the level of activation, can be classified as multivariate patterns of activity (MVPAs). The calculated signal is then presented to the individual via visual, auditory[72], haptic[139] or electrical stimulation[210] feedback, allowing the user to alter neural function and complete the loop with neural processing of feedback. The advantages and disadvantages of these modalities, as well as how their signals are processed for neurofeedback, are discussed in BOX 1. FFT, fast Fourier transformation.

functional connectivity outcome scores than ROI activity. A change in functional connectivity, from a negative correlation before neurofeedback training to a positive correlation after training, was observed to last for more than 2 months between the lateral parietal cortex and the primary motor area, regions that belong to different intrinsic networks (that is, the default mode network (DMN) and the visuo–spatial–motor network, respectively[33]). This study demonstrates that neurofeedback is able not only to alter connectivity between two functionally distinct brain networks but also to exert long-term effects.

Network reorganization resulting from neurofeedback training of single regions was observed in earlier studies[34,35], whereas recent studies have attempted neurofeedback training of functional connectivity between brain regions. For example, in one study, participants were trained to be able to alter the level of interhemispheric motor cortical coherence through the use of contingent magnetoencephalography-based neurofeedback, leading to proportional changes in asynchronous finger tapping[36,37]. Moreover, connectivity-based neurofeedback training has recently been used to increase subjective emotional valence ratings by strengthening top-down connectivity from cognitive control areas in the dorsomedial PFC to the amygdala, which is involved in emotion processing[38].

Multivariate pattern analyses (MVPAs) afford more sensitive detection of distributed patterns of brain activity corresponding to specific sensory, behavioural or mental processes[29–31,39]. Patterns of voxel activity in circumscribed

Multivariate pattern analyses
(MVPAs). These are statistical and mathematical approaches for finding regularities and patterns in the data.

Box 1 | **Neuroimaging methods of neurofeedback**

Real-time functional neuroimaging includes electrophysiological and haemodynamic methods that represent the same underlying neural activation[158]. Electrophysiological signals[159], which directly measure extracellular field potentials, are measured by electrocorticography (ECoG), electroencephalography (EEG) or magnetoencephalography (MEG). These approaches have relatively high temporal resolution (~1 ms). Measurements from ECoG electrodes, which are placed on the cortical surface, have relatively high spatial resolution (~5 mm^2), whereas non-invasive MEG and EEG can cover the entire cortex, albeit with reductions in resolution (10 mm^2 (REF. 160) and 5 cm^2 (REF. 161), respectively). Neurofeedback studies in animals have used single-unit activity at a spatial resolution of ~0.05 mm, multiunit activity at ~0.1 mm and local field potentials at ~0.5 mm, and all at a very high temporal resolution of ~3 ms (REFS 162,163). In real-time analysis, the signal that is extracted from these methods is typically transformed into the frequency domain and decomposed into a specific frequency (for example, delta (0–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (>30 Hz) bands) before feature extraction. Examples of feature extraction include coherence, power spectral density and their combinations for input to multivariate patterns, event-related potentials and slow cortical potentials. The signals can be processed either in sensor space (that is, individual electrodes) or source space (for example, beam formers[164] or LORETA[165]) that enables a more accurate estimate of the activity in cortical regions that then is transformed into the feedback signal[165].

Most haemodynamic methods of neuroimaging detect the concentration of oxygenated and deoxygenated haemoglobin in the neural vasculature, are reflective of the metabolic demands of the underlying neural activation and are more closely related to postsynaptic activity and field potentials than action potentials[158,166]. The relatively slow response of blood oxygenation to neuronal activity is known as the haemodynamic response function (HRF). The HRF peaks at about 5 seconds after stimulus onset (FIG. 1). The HRF is detected by functional MRI (fMRI) as the blood-oxygen-level-dependent (BOLD) signal over the whole brain, with a spatial resolution typically of up to 2 mm^3. The spatial specificity, also known as the point spread function of the BOLD signal, as obtained by fMRI, is around 2 mm (REF. 167), a value that may be improved by suppressing macrovascular signals and contrasting different experimental conditions appropriately. The regions of interest (ROIs) are initially selected using a 'localizer' scan, which is based on anatomical or functionally defined voxels. Another type of haemodynamic acquisition, functional near-infrared spectroscopy (fNIRS), measures infrared light absorption of haemodynamic signals in the brain by scalp optodes at a spatial resolution of 2–5 cm^2 (REF. 168). The fNIRS signal is acquired by multiple pairs (channels) of emitter and detector optodes. Feature selection includes a summary activation from selected ROIs that are then used alone, as seed regions in functional connectivity, or used as features in multivariate pattern analyses. Feedback in electrophysiological or haemodynamic imaging modalities can be based on visual, haptic, electrotactile and/or auditory displays. EEG and fNIRS are portable and lowest in cost, whereas MEG and fMRI require more-sophisticated equipment with shielded rooms and are priced accordingly.

There is evidence of correspondence between electrophysiological and haemodynamic imaging modalities. For instance, intrinsic networks (for example, sensorimotor, visual and default-mode) that are derived from haemodynamic BOLD fluctuations seem to spatially overlap with those of MEG power envelopes[169,170]. This overlap extends to the temporal domain, in which coherence between fMRI and EEG power peaks between 0.01 and 0.1 Hz (REF. 171), generally revealing positive and negative correlations between BOLD and high- and low-frequency EEG rhythms, respectively[172,173]. Moreover, as a result of phase–amplitude coupling[174,175], BOLD fluctuations can also be directly related to the phase (rather than to the power) of EEG slow cortical potentials[176]. Despite these commonalities, the level of correspondence of neural activation between modalities varies between regions or networks[172] and has yet to be fully clarified.

regions have been found to distinguish visual orientations[40] and motor sequences[41], whereas averaged voxel activity in those regions does not provide useful information. In neurofeedback, MVPA was initially used in fMRI-based studies[32] but is now also being applied to electrophysiological neurofeedback methods[42]. In a seminal neurofeedback investigation in which perceptual learning of grating orientations was induced in the primary visual cortex[3] individual orientation columns were below the resolution of fMRI but could be detected from subthreshold population activity using an MVPA[40]. In the absence of visual stimulation except for a neurofeedback signal, participants learned to self-induce patterns of activity in the primary visual cortex that corresponded to a particular orientation of a Gabor grating. The participants received visual feedback of the correspondence between the brain activity patterns and the desired brain state (but not the actual stimulus). Increased correspondence paralleled perceptual learning of the specific orientation, providing an example of the behavioural specificity of neurofeedback training. In another innovative application of such adaptive neurofeedback[6], an MVPA was used to decode whole brain states associated with sustained attention while participants performed a cognitive task. The level of difficulty of this task was automatically adjusted based on the decoded brain state to improve vigilance. The task-relevant representations in attentional networks in the brain showed more distinctive and focused activity after neurofeedback training[43]. In summary, MVPA neurofeedback studies have provided convincing evidence of specific causal brain–behaviour relationships, but the underlying neurophysiological mechanisms of the brain state being regulated require further exploration.

Adaptive neurofeedback
Previously, and perhaps imprecisely, referred to as 'closed-loop', adaptive neurofeedback changes an experimental task in real time on the basis of neural activity.

Neural plasticity and specificity. The persistence of functional reorganization of the brain after the termination of neurofeedback training is an indicator of neuroplasticity. The specificity of the trained neural substrate was first noted in a study involving non-human primates[44], which showed that the regulation of single-cell firing in the motor cortex could be learned. The local specificity of learned physiological regulation at the microscopic level was later confirmed by a series of impressive experiments in which rats were rewarded for increasing the firing rate of a cell in the motor cortex and simultaneously decreasing the firing rate of an adjacent cell[45]. Another study in rats showed that neurofeedback could be used to induce selective temporal coherence between neurons in M1 and in the dorsal striatum[46]. In a study in monkeys, an electronic implant, called NeuroChip[47,48], used action potentials recorded in one location of the motor cortex to trigger electric stimulation delivered at another location in the motor cortex. After 2 days of continuous stimulation, the activity at the recording site resembled the activity at

Fractional anisotropy
A property of white matter pathways of the brain that relates to the diffusion of water molecules along axonal pathways and is measured by diffusion tensor imaging; it is represented by a value ranging from 0, indicating no specific directionality, to 1, indicating one prominent directionality.

Homeostatic plasticity
The capacity of neurons to regulate their own excitability relative to network activity; it is observed in neurofeedback as an opposite and paradoxical change in brain activity after the training.

the stimulation site, showing that functional reorganization had occurred *in vivo*; this functional reorganization remained for more than a week after stimulation was terminated. Importantly, long-term (neuroplastic) changes occurred only when the duration between recording and stimulation was less than 50 ms (BOX 3).

At the level of large cell assemblies, there is abundant evidence indicating that neurofeedback can have specific neural effects. Comparable to invasive recordings, local neuroanatomical specificity in the modulation of EEG in healthy adults has been described[49]. In fMRI-based neurofeedback, an MVPA and an effective connectivity analysis that were performed on fMRI signals acquired during training of the anterior insula showed that learning self-regulation results in a gradual reduction in the spatial extent of activation clusters ('pruning') in the brain and in an increase in the separation of these clusters ('focusing')[43]. Similar cortical changes have been observed with extensive practice and learning of complex cognitive tasks[50], such as verbal learning, mirror reading, motor learning and artificial grammar learning. However, as cognitive strategies activate a network (see below), neural specificity can be experimentally addressed using control conditions such as opposing directions of regulation[37], differential feedback[51], inverted feedback[52], sham feedback[53], mental imagery without any feedback[53] or feedback from a different neural substrate[54].

Neurofeedback-induced neuroplasticity, in the form of cortical excitability changes, has been demonstrated in humans by using transcranial magnetic stimulation (TMS) on the trained brain region[55,56]. TMS pulses were applied to the motor cortex to measure motor-evoked potentials after learned self-regulation, without regulation or under other control conditions to probe for neuroplastic changes in the strength (that is, the excitability) of the corticospinal pathway. It was discovered that neurofeedback was associated with sustained (that is, lasting more than 20 min) decreases in intracortical inhibition following single[55] or repeated[56] training sessions.

Structural changes in grey matter volume and white matter connectivity, previously used to reveal neuroplastic changes resulting from different forms of skill training[50,57], have also been examined now in neurofeedback. Increases in fractional anisotropy in white matter pathways and grey matter volume were found 1 week after the neurofeedback training of beta waves (15–18Hz) in the frontal and parietal regions of the brain[58]. The structural changes were associated with large improvements in visual and auditory attention after training in the experimental group.

Are the resulting neuroplastic changes from neurofeedback predictable and stable? A concept found in the EEG neurofeedback literature challenges simple models of Hebbian plasticity. Evidence for homeostasis in neural activity (such as, firing rate and synchronization) has been noted in some neuroimaging studies with such measures remaining in physiologically confined ranges[59,60]. In these studies, Hebbian plasticity was counterbalanced by (non-Hebbian) homeostatic plasticity that seemed to prevent extremes in excitation or inhibition. Remarkably, there is emerging evidence for homeostatic reversal or 'rebound' of neural function after neurofeedback training[61]. For instance, after undergoing alpha desynchronization neurofeedback, individuals with post-traumatic stress disorder showed a rebound in EEG synchronization[62], which may be explained by the fact that such individuals present with abnormally decreased alpha power at baseline. However, it is not clear to what extent homeostatic plasticity affects long-term changes in brain activity and behaviour, as evidence exists for such changes after periods of days[63], months[33,64] and even years after training[65]. Further research may shed light on the interaction between homeostatic and Hebbian forms of plasticity in the context of neurofeedback.

Neurofeedback training may not always result in behavioural modifications. Studies in monkeys showed that the response of neurons in the motor cortex to operantly learned rewards are initially associated with active limb movements, but, as the monkey continues to activate the reward-linked neurons, the movements drop out entirely[66,67]. Further investigations should resolve the two alternative explanations for this cessation

Box 2 | **Network models of neuropsychiatric disorders**

In recent years, there has been a major shift in how neuropsychiatric disorders are conceptualized: from a largely categorical perspective using descriptive diagnostic criteria to an approach that is based on observable behavioural and neurobiological characteristics (that is, an 'experimental medicine' approach embodied by the Research Domain Criteria[177]). According to this framework, many neuropsychiatric disorders are thought to share common, transdiagnostic disease mechanisms that are often represented in a set of brain regions and networks that may be disrupted in space[178] and time[179] as a function of the disorder across its lifespan.

Complementing this shift in neuropsychiatry, 'connectomics' is emerging as the predominant scientific philosophy for understanding human brain function and dysfunction[180]. Even what seems to be a localized brain damage (for example, isolated stroke) can have downstream effects on entire brain networks[181]. An example of one such model of network-based pathology is the 'triple network model' of neuropsychiatric disorders[178]. Dysfunction in three large-scale brain networks (the default mode network (DMN), the executive control network (ECN) and the salience network (SN)) seems to be crucial for the development and maintenance of a series of neuropsychiatric disorders, including schizophrenia[178], Alzheimer disease[182] and addiction[183,184]. The DMN includes a set of midline (the medial prefrontal cortex and the posterior cingulate cortex) and lateral (parahippocampal gyrus) brain networks that have been implicate d in internal self-referential processes (rumination, and episodic and prospective memory). The ECN includes lateral (the dorsolateral prefrontal cortex and the posterior parietal cortex) brain networks that govern external responses to the environment to organize and execute complex goal-directed behaviours. Activity in the DMN and ECN seems to be anti-correlated and may serve to respond to information-processing demands from internal (DMN) and external (ECN) environments. The brain system that accounts for allocation of attentional resources and facilitation of switching between the DMN and the ECN is the SN, which consists of the anterior insula, the dorsal anterior cingulate and, occasionally, the central reward or motivation system, including the ventral tegmental area, the nucleus accumbens–ventral striatum, the amygdala and the ventromedial prefrontal cortex[183].

One research group[184] has proposed the use of a composite index termed 'resource allocation index' to quantify the association between the SN–DMN and the SN–ECN and explained how this 'triple network' might be affected in the context of neuropsychiatric disease. These large-scale brain networks are emerging as potential targets for neurofeedback. Training patients to normalize individual nodes, functional connectivity or spatiotemporal patterns of activity in order to optimize the interactions across these networks could be a potential treatment strategy for neuropsychiatric diseases.

Box 3 | **Neurobiology of learning**

To understand the specific mechanisms that underlie neurofeedback learning, one needs to first understand the general theoretical and experimental bases of learning. Operant conditioning (that is, instrumental learning or reinforcement learning) and classical conditioning (that is, Pavlovian conditioning) are two major types of associative learning. Hebb[185] hypothesized that, if the activity in a presynaptic neuron repeatedly led to the firing of a postsynaptic neuron, an enduring modification of the synaptic structure follows, such that subsequent activity of the presynaptic neuron has a high probability to excite the postsynaptic neuron ('neurons that fire together wire together'). Extant literature holds that long-term potentiation (LTP) is a central mechanism underlying associative learning[186]. Recent research has focused on a form of LTP called spike timing-dependent plasticity (STDP)[187]. According to STDP, a modification in synaptic transmission occurs owing to variations in the timing of weak and strong synaptic inputs over tens of milliseconds. For some inputs, transmission increases — that is, a presynaptic response produces a stronger ('potentiated') postsynaptic response — and, for others, the transmission decreases ('depresses') postsynaptic responses. In essence, STDP depends on the sequence of firing times of the presynaptic and postsynaptic neurons.

Dopamine is an intermediary that relates STDP to behavioural changes by gating plasticity at corticostriatal and cortical synapses. However, opposing evidence and conceptual arguments suggest that LTP is not sufficient or even not involved in association formation[188]. Studies conducted in behaving mammals to relate the experimentally evoked LTP and activity-dependent changes in synaptic strength show that hippocampal synapses are selectively modified in strength during the acquisition of classical conditioning but not of instrumental conditioning, whereas striatal regions are activated during instrumental conditioning but not during classical conditioning[189]. In both of these two types of learning, NMDA receptors, other neurotransmitters and transcription factors participate.

Prediction error is a cardinal concept in associative learning that is defined as the difference between expected and actual rewards[190]. The prediction error that is generated by an outcome, for example, the juice reward in an animal neurofeedback experiment, is a measure of how unexpected or surprising the outcome is with respect to an expected signal. This error signal is communicated to the striatum and cortical areas. Dopaminergic neurons respond with short-latency plastic bursts to unexpected rewards and reward predicting stimuli[191] in proportion to the reward prediction error signal[192,193].

Learning results from the concurrent occurrence of a strong presynaptic and postsynaptic activation and dopamine release[194]. According to this postulation, which is called 'three factor learning', synaptic transmission is strengthened only in those neurons that simultaneously receive input coding some aspect of an event in the environment and dopaminergic input proportional to the reward prediction error[195]. Hence, on the basis of contingent feedback, dopaminergic projections to the striatum are able to modify behaviour in response to salient stimuli and contingent feedback.

of movement: one states that the movement drops out owing to pruning, whereas the other states that it stops because of the decoupling of the association between neural activity and movement; the latter suggests that motor circuits exert independent effects on driving cell activity and generating limb movements[67]. Future investigations should investigate these hypotheses in light of the evidence indicating that neurofeedback-induced changes in neuroplasticity may persist and lead to long-term behavioural improvements in humans[64].

Neural mechanisms of self-regulation

Despite its promise, neurofeedback faces several challenges, including the failure of some individuals to achieve self-regulation, inter-individual differences in learning capacity, uncertain long-term effects and unclear transfer benefits. Indeed, a substantial proportion — up to 30% — of participants in neurofeedback and BCI studies fail to self-regulate specific brain activity, even after repeated training[68,69]. Better knowledge of the neural mechanisms underpinning self-regulation will likely assist in the design of more-efficient experimental and clinical protocols, tools and technologies for neurofeedback, and in developing greater knowledge of neurophysiology. In this section, we address the psychophysiological factors that influence learning, the functional and structural brain mechanisms of self-regulation, and the theoretical models of learning and memory that can be applied to neurofeedback training.

Factors influencing neurofeedback learning. Learning to control brain activity in humans is determined by contingent feedback and reward, and potentially by verbal instructions and mental strategies (for example, use of imagery) that are suggested by the experimenter to the participant (BOXES 3,4). In an attempt to compare the influence of the above-described factors on learning to control brain activity and behavioural effects, a recent study examined four groups of participants who were given feedback, explicit instructions, reward or all these factors over 2 days of neurofeedback training to volitionally control the BOLD signal in the bilateral supplementary motor area (SMA)[70]. The members of the group that received only feedback achieved marked increases in BOLD signal amplitudes and learning effects in terms of percentage BOLD change over the training period. Although the group members who were given both feedback and reward showed the highest signal amplitudes in the SMA, they did not show any learning effect. Remarkably, the two groups who were instructed to use motor imagery and received feedback (with or without reward) did not show learning effects after the 2 days of training. These results suggest that contingent feedback without explicit instructions to use specific mental imagery enables more effective learning. Further comparison studies of this kind in different brain regions and pertaining to different brain functions would be necessary to establish the influence of feedback, reward and instructions in learning brain self-regulation.

A recent EEG neurofeedback study that investigated the effects of different mental strategies on neurofeedback performance[71] trained participants to use any mental strategy of choice to increase sensorimotor rhythm (SMR) activity. Participants who reported no specific strategy showed better SMR control than participants who reported specific mental strategies. These results indicate that successful SMR control was not related to the use of explicit, verbalizable mental strategies.

If implicit learning can help regulate brain activation, is any explicit strategy needed at all? Recent research aimed to answer this question by intentionally not providing any explicit strategy and eliminating any possibility for subjects to become aware of the neurofeedback signal. Researchers provided two types of auditory signals that varied in proportion to the BOLD activity in two circumscribed brain areas, the fusiform face area and the parahippocampal place area. Individuals were instructed to perform a task that was unrelated to neurofeedback: to press two different buttons depending on the type of the auditory signal[72]. After 3 days of training,

Operant conditioning
A process by which an organism learns a new association between two paired stimuli: a neutral stimulus and one that already evoked a reflexive response.

10 of the 16 participants exhibited an average increase in activity in the upregulated region relative to the downregulated region, and this change correlated with spontaneous activity within this subset of participants. No effect of learning was observed between sessions. Further study is needed to confirm whether this 'covert feedback' can induce neurofeedback-mediated learning and to confirm the hypotheses regarding the sufficiency of automatic processing of the neurofeedback reward signal[3,73].

Contrary evidence from other studies supports the notion that explicit instructions to perform mental imagery may be necessary to control the neurofeedback signal. For instance, one study showed that simultaneous control of ongoing brain activity in the SMA and the parahippocampal cortex was not initially feasible when participants used their own mental strategies[51]. Indeed, self-regulation was possible only when the experimenters suggested the strategies that were related to the functional role of the ROIs. Conflicts in older EEG neurofeedback literature can be found regarding whether mental strategies or no strategies at all lead to the most successful control of the feedback signal[74–77].

An interesting case illustrating the complexity of control strategies comes from a recent set of studies investigating the mesolimbic dopaminergic system. One study[52] found that cognitive strategies activated the midbrain and that neurofeedback further enhanced midbrain activity, but self-regulation was not effective during the 'transfer' session when participants attempted to perform volitional control in the absence of feedback. Similar results were found for self-regulation of the nucleus accumbens, which is part of the same network[78]. However, recent work[79] used feedback from both substrates separately — that is, one region encompassing the midbrain and the other comprising the nucleus accumbens — for two different groups of healthy participants and found conflicting results. Both groups could not activate these regions without feedback initially, and only the midbrain

Box 4 | **Models of neurofeedback learning**

Here we present extant theories and models that have been proposed to explain neurofeedback learning and its underlying mechanisms. There are overlaps and compatibilities among the theories; for example, the operant (or instrumental) learning theory can be considered to form a part of the dual process view, and motor learning and skill learning theories may have commonalities, whereas the global workspace theory, which presupposes the conscious awareness of reinforcement (feedback) for learning, seems to be compatible with some aspects of the awareness theory. Future, hypothesis-based experiments should shed new light on the validity of the above-mentioned theories in neurofeedback learning and performance.

Operant (or instrumental) learning

The operant learning theory[196], as applied to neurofeedback, states that control of brain activity proceeds when correct or desired brain responses are reinforced by contingent feedback and/or reward[67,197]. The theory considers three main elements in its description of the procedure, discriminative stimuli, responses and reinforcers. A large extant literature of operant learning in humans and animals has elucidated the neurophysiological correlates of operant learning and highlighted the selective involvement of prefrontal and striatal synapses[189,198]. However, experimental instructions and subjective reports of the use of mental strategies in human studies have led some researchers to propose other explanatory mechanisms of neurofeedback learning.

Motor learning

According to this model[199], acquiring control over neurophysiological signals is similar to the acquisition of motor learning involving a well-organized sequence of movements and symbolic information. Although there has been much scientific and clinical investigation of this theory in different types of motor learning[200], there is no specific application of this model to neurofeedback training in recent times.

Dual process theory

The dual process theory attempts to integrate feedforward and feedback learning processes in explaining neurofeedback learning[201,202]. In this model, the naive learner searches for an effective mental strategy, either on their own or based on the experimental instructions. If the learner does not find the strategy to be effective to control the feedback signal, they may search for a new one until an effective strategy is discovered. Upon successive reinforcement, the strategy that best matches the feedback may become automatic. Alternately, the learner may never learn to find an effective strategy, upon which the brain may rely on the feedback signal alone to guide learning, or the subject may fail to learn at all. An experimental investigation of this hypothesis would involve neurofeedback training in the presence or absence of explicit instructions for attaining control while monitoring participants' reports of mental strategies that are used and their brain and behavioural correlates.

Awareness theory

The awareness theory competes directly with the instrumental learning model in biofeedback literature[203]. The theory states that the feedback signal provides information about a physiological response (that is, brain activity) to which the subject becomes aware of, and this leads to voluntary control over the response. The model considers three elements, awareness of reinforcers (feedback and reward), the reinforcer response contingency and the response itself. However, theoretical analyses and later tests in animals and humans concluded that awareness of the response is neither necessary nor sufficient to acquire control over the brain activity[203].

Global workspace theory

The global workspace theory of neurofeedback learning[61] proposes that learning control of neural activity is enabled by the wide, global distribution of the feedback signal in the brain so that it becomes conscious. A testable prediction of this theory is that a non-conscious or subliminal feedback signal, for example, by backward masking, does not help in acquiring control of the brain activity being trained[61]. However, the hypothesis should also be evaluated in light of the existing evidence for subliminal instrumental learning[204], unconscious processing of reward stimuli[205], and the distinctions between conscious and non-conscious representations on the one hand, and automatic and deliberate processing on the other[206].

Skill learning

Recently, there have been proposals to view neurofeedback and brain–computer interfaces (BCI) or brain–machine interfaces (BMI) learning[45,207] within the framework of cognitive skill learning[208,209]. According to this proposal, neurofeedback learning involves an initial phase of rapid change in performance and a late phase of more gradual improvement[209] as the skill is consolidated and performance asymptotes. Functional and structural changes in the dorsomedial striatum have been shown to be associated with the early phase, whereas such changes in the dorsolateral striatum have been shown to be associated with the late phase. Recently, similar changes have been observed in neurofeedback learning in animals[45] and humans[85] (FIG. 2), providing support to this theory.

group could attain self-regulation once feedback was provided. Furthermore, the midbrain group was able to sustain activation and display self-control into transfer. Although there are some differences in methodology (such as repetition time, instructed cognitive strategy and physiological correction) between the studies, it is hard to explain what accounts for the disparities in the results. The transfer of neurofeedback learning from the laboratory (where the discriminating cues may be provided but feedback is not available) to real-world conditions (where neither may exist) could be influenced by the learning curve during neurofeedback training[80]. A systematic investigation is needed to better understand the parameters of neurofeedback training and cognitive strategies and how they affect learning.

The effectiveness of neurofeedback learning determines post-training performance in the transfer session. However, further investigations into how transfer is influenced by learning procedures, cognitive strategies and context are necessary. Other factors that require investigation are: the relevance of the instruction; the aptitude and cognitive ability of the participants in following the instructions; how much attention is paid to the feedback signal; how the signal is presented; and the flexibility that is allowed to vary mental strategies in conjunction with feedback. The effect of multiple tasks may influence neurofeedback control — that is, paying attention to the neurofeedback signal and imagery simultaneously — and some preliminary evidence suggests that such multitasking could have deleterious effects[81]. Further hypothesis-driven experimental work and theoretical models would shed more light on this important issue (BOX 4).

Psychological factors such as the locus of control and the sense of agency could influence an individual's ability to learn to control brain activity. Studies found that the locus of control[82] was negatively correlated with the power of SMR self-regulation[83], leading to the conclusion that instructions should be given to individuals undergoing neurofeedback training to avoid forcing mastery over self-regulation and to aim for a state of focused relaxation. The sense of agency for BMI control decreased when the incongruence between the predicted and actual sensory feedback was high[84]. Other factors that are likely to affect self-regulation and that require more investigation are degree of concentration, mood, confidence in control, and motivation.

Neural substrates of self-regulation. An early study attempted to elucidate the neuronal mechanisms and anatomical sources of self-regulation of slow cortical potentials (SCPs)[85] using an EEG–BCI simultaneously with fMRI acquisition. Successful learning of SCP change was associated with the activation of the basal ganglia. The study showed that learning SCP control correlates with the activation of striatal and motor networks that are related to the associative binding of behaviour to the reward. These human studies are complemented by animal work[45,46] demonstrating complete abolition of neurofeedback learning with NMDA receptor (NMDAR) blockade in the basal ganglia (see below and BOX 3).

Evidence for a 'neurofeedback control network' has been provided by two recent studies that adopted different approaches. One study examined fMRI correlates of brain self-regulation during sham feedback derived from prior EEG recordings of some other participants, although participants were made to believe that they were provided real feedback of their brain activity[86]. A comparison of the sham condition to another condition of passive watching of the feedback bars revealed that the latter was associated with activation of the bilateral anterior insular cortex (AIC), ACC, SMA, dorsomedial and lateral PFC, and superior parietal lobule, suggesting that a network exists for the cognitive act of self-regulation. Another study conducted a meta-analysis by reanalysing data from 12 studies comprising 149 participants who performed fMRI neurofeedback with different target regions using different mental strategies[87]. Although the latter study was based on fMRI neurofeedback, the results were remarkably similar to the aforementioned EEG neurofeedback study, as similar activations were observed in the AIC, ACC, dlPFC and ventrolateral PFC, inferior parietal lobule, basal ganglia and thalamus. Previous findings indicate that the PFC and posterior parietal cortex are part of the executive control network for neurofeedback (BOX 2), whereas the AIC is related to the guiding of attention to cognitive strategies and feedback error[88,89].

Despite these findings, we do not yet know whether neurofeedback engages two distinct neural networks — one pertaining to the self-regulation of brain activity and the other relating to the use of mental imagery of a similar task in the absence of feedback — or overlapping networks. For example, similar regions are activated during neurofeedback control[87], as in tasks involving motor imagery[90], with the exception of the ACC and ventral striatum, which are involved in neurofeedback control but not motor imagery[90]. These differences could be explained in light of the reward processing that occurs with neurofeedback. The ACC is involved in cognitive, explicit processing of reward[91,92], such as a neurofeedback signal. However, the ventral striatum is activated even when no awareness of feedback is present[72], indicating an implicit role of this brain region in neurofeedback processing. These findings indicate that the ACC and ventral striatum may have different roles in neurofeedback processing along cognitive and automatic lines, respectively (FIG. 2).

Brain processes that are involved in learning self-regulation are beginning to be identified (BOXES 3,4). The most compelling evidence for the procedural and implicit nature of neurofeedback learning and for the crucial role of cortical–basal ganglia loops that are responsible for procedural learning comes from a study in rodents[45]. Rats were given food pellets or a sucrose solution as a reward when they increased activity in one cell ensemble in M1 and decreased activity simultaneously in an adjacent ensemble, or vice versa, by moving an auditory cursor to one of two target tones. With feedback training, rats became proficient in this task. Remarkably, omitting the auditory feedback but retaining the reward did not influence performance.

Locus of control
A psychological construct that determines the subjective feeling of being in control.

Sense of agency
The feeling that the individual causes the change.

Slow cortical potentials
(SCPs). These are slow event-related direct-current shifts that can be detected on the electroencephalogram. Slow cortical potential shifts in the electrical negative direction reflect the depolarization of large cortical cell assemblies, reducing their excitation threshold.

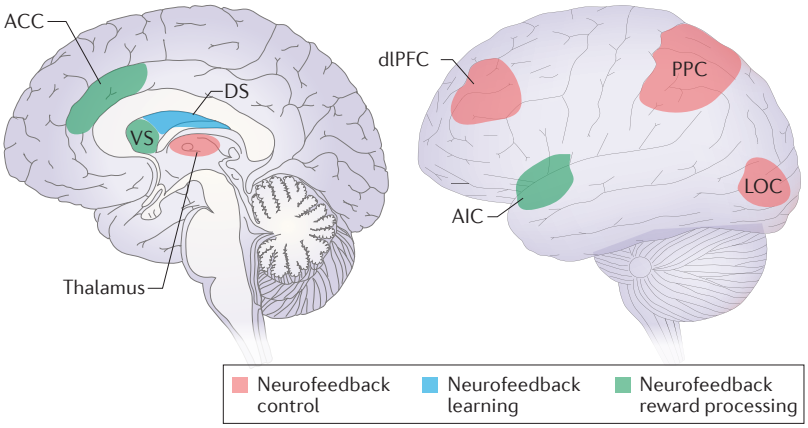

Figure 2 | **Neurofeedback reward processing, control and learning networks.** Accumulated evidence[72,85,86,92,152] indicates the key brain areas that are involved in different aspects of neurofeedback. The anterior insular cortex (AIC), dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC) and posterior parietal cortex (PPC) are active during generalized neurofeedback when feedback is presented visually. Likewise, deep brain regions such as the thalamus and basal ganglia have been implicated in brain self-regulation of different regions of interest. In the case of visual feedback, attention to the signal is governed by the lateral occipital cortex (LOC)[211]. The dlPFC[212] and PPC[213] are involved in performing executive tasks, such as imagery[214], which connects with the thalamus to regulate cortical arousal[215]. The ACC and AIC form part of the salience network and are involved in conscious perception of feedback and reward[88,91,92]. Unconscious reward processing involves the ventral striatum (VS)[72]. The dorsal striatum (DS) has been linked to neurofeedback learning. Taken together, this information suggests that neurofeedback involves a reward processing network (comprising the ACC, AIC and VS), a control network (comprising the LOC, dlPFC, PPC and thalamus) and a learning network (the DS).

However, degradation of the food reward contingency or degradation of the reward by inducing satiety rapidly impaired learning, even if the correct auditory feedback was provided. Learning led to increased oscillatory coupling in the 4–8 Hz range between motor cortical cells and striatal neurons. In control experiments, rats that lacked NMDARs, which are necessary for long-term potentiation, and animals in which NMDARs in the dorsal striatum were blocked pharmacologically showed impaired learning. These results demonstrate the essential role of striatal neuroplasticity for learning neurofeedback contingencies.

Clinical applications of neurofeedback

Whereas neuroscience applications of neurofeedback have attempted to elucidate the causal relationship between brain and behaviour, clinical applications have attempted to exploit neurofeedback for the treatment of brain and behavioural disorders. In this section, we cover progress and emerging approaches in neurofeedback research in the context of one psychiatric and one neurological disorder. We examine attention deficit hyperactivity disorder (ADHD) because of the better understanding of time-frequency domain characteristics of its neural substrates, the high number of neurofeedback studies that have been performed on this disorder and a history of randomized controlled trials (RCTs). We then discuss stroke because of the spatial localization of its neural substrates and the range of neurofeedback approaches that have been explored for this disorder. These cases illustrate the importance in clinical neurofeedback research of understanding the effects of patient heterogeneity, of identifying the putative neural mechanism of disease protocol efficacy and the severity of the deficit, and of evaluating how neurofeedback can be combined with other treatments.

Attention deficit hyperactivity disorder. The rationale for using neurofeedback to treat ADHD emerged from early observations that children with learning disabilities[93] or ADHD[94], in their resting state, showed excessively high amplitudes of low-frequency EEG oscillations (for example, delta and theta bands) compared with healthy developing children[95,96].

In many children with ADHD, these high amplitudes of oscillations can be reduced through the use of pharmacotherapy[97,98]. Seminal work demonstrated that neurofeedback could be used to reduce the elevated low-frequency synchronization that is observed in ADHD[93]. Subsequent studies in children showed that neurofeedback-mediated decreases in low-frequency amplitudes were associated with improvements in ADHD symptoms[98–100]. Some recent RCTs have provided evidence that the clinical effect size of neurofeedback can be superior to computerized attention training[101,102] or match the one of standard pharmacotherapy[103,104]. Importantly, improvements in the neurofeedback group at 6-month follow-up remained larger than those in the computerized attention group and were comparable to the effects at the end of the training[64]. These studies, among others, were the subject of several meta-analyses[105–107], which included hundreds of patients but yielded inconsistent findings: one study found that neurofeedback treatment was "efficacious and specific" (REF. 105), a second claimed that it was ineffective when assessed with blinded measures[106], and a third concluded that neurofeedback treatment was more effective than active control conditions[107].

Despite the mechanistic findings described above, some recent placebo-controlled RCTs could not find any difference between neurofeedback training and sham neurofeedback training in lowering ADHD scores[108,109], and these results have led to a debate over the best way to evaluate and conduct neurofeedback research[110,111]. Likewise, several RCTs have failed to confirm protocol-specific effects[112,113], reporting anticipated decreases[114] in low frequencies but also increases[9]. These outcomes highlight two potentially critical issues in neurofeedback treatment of ADHD, patient heterogeneity and neurofeedback protocol efficacy. In relation to the former, new evidence suggests that a mixture of abnormal EEG resting-state signatures characterizes ADHD[97,115–117]. Task-related EEG anomalies in individuals with ADHD have also been noted in theta and alpha oscillations[115,118,119] during visual attention[115] and in attenuated SCPs during anticipatory attention[73]. Indeed, neurofeedback treatment involving the increase in negative SCP amplitude was associated with improved clinical symptoms[120–122]. Interestingly, comparisons between oscillatory and SCP-based neurofeedback protocols revealed comparable effect sizes (0.4–0.7)[102,123], thereby leaving an open question

as to which approach is ultimately more favourable[110]. Moreover, ADHD neurofeedback research highlights the importance of clinical study design, specifically in relation to placebo control. The placebo effect is heightened under numerous conditions related to neurofeedback, including seeing a clinician, using expensive, technologically advanced equipment, being exposed to numerous training sessions and having the need to sit still and pay close attention[124]. By contrast, sham feedback used in placebos can be detected by participants as false feedback, and ethical issues may prevent its use in clinical populations. Options such as active control conditions (for example, computerized training) might be more suitable substitutes[92,125] to sham feedback.

Of equal importance is ensuring that the putative neural mechanisms are accurately identified and validated by multiple neuroimaging modalities and experimental conditions to generate more-efficacious neurofeedback protocols. Neuroimaging studies[126–128] have shown that individuals with ADHD have reduced functional independence between task-positive networks and the task-negative DMN compared with individuals without ADHD; these networks have an anti-correlated relationship during successful spatial attention[129] and cognitive control[130] (BOX 2). By contrast, combined EEG–fMRI studies in healthy subjects have found positive correlations between the functional activity of the DMN and the amplitude of EEG theta–alpha rhythms (4–12 Hz)[131–133]. Hence, an excess of task-related theta–alpha rhythms[115,134], which may be reflective of an abnormally upregulated DMN, might be one candidate mechanism responsible for attentional deficits in ADHD. Interestingly, a recent EEG–fMRI study showed that suppressed alpha-rhythm amplitudes after neurofeedback training predicted reduced mind-wandering and were associated with upregulation of task-positive networks and downregulation of the DMN[18]. Thus, combined EEG–fMRI markers could inform future neurofeedback protocols based more explicitly on inter- or intra-network dynamics.

ADHD is one of the most well-investigated clinical neurofeedback applications; however, we still lack definitive evidence of efficacy for neurofeedback-mediated treatment of this condition. Although issues such as proper control conditions have stymied progress, network-based approaches and the combination of neurofeedback with other functional neuroimaging modalities may enable further advances in this area.

Rehabilitation in stroke. Neurofeedback has shown recent success in the initial RCTs for the use of this application in rehabilitation after stroke. The findings from these trials underline the importance of understanding the severity of the injury and how to combine neurofeedback with existing therapeutic approaches. Cases of stroke vary in terms of location affected and size of the lesion, but only weak associations exist between these anatomical changes and symptoms. One of the prevailing models of motor recovery in ischaemic stroke is compensatory excitation of the contralesional hemisphere that is causing pathological disinhibition of transcallosal pathways[135]. Consequently, concurrent stimulation of the lesioned hemisphere and inhibition of the non-lesioned hemisphere (that is, through the use of TMS) may have beneficial effects on recovery[136]. Active patient participation in the therapy is another guiding principle of rehabilitation that is derived from studies employing forced use of the affected limb[137] and robotic therapy that minimizes assistance to encourage greater patient effort[138]. One promising avenue for stroke rehabilitation involves exoskeletal training that uses real-time signals from sensorimotor areas[139].

Few RCTs have been attempted for the use of neurofeedback on patients with stroke. One RCT compared a BCI-augmented robotic arm therapy, based on the detection of movement intention with SMR desynchronization by a real-time Bayesian classifier, with a standalone robotic arm therapy[140]. Both treatment groups showed improvements in terms of their Fugl-Meyer scores, but there was no marked difference between the two groups. Promising evidence of neurofeedback efficacy after stroke has come from a sham-controlled, double-blind RCT in severely impaired, chronic (>6 months after injury) patients with stroke that took a novel neurofeedback–BMI approach with adjuvant physiotherapy (that is, a supplement to normal physiotherapy). Patients learned to upregulate ipsilesional sensorimotor areas by reinforcing successful mu-rhythm desynchronization with robotically assisted hand manipulation[141]. The study compared this treatment to a sham group receiving non-contingent neurofeedback and therefore unrelated, randomized robotic stimulation. Only the experimental group improved ipsilesional mu-rhythm activation, and these patients showed a functional improvement of 3.4 points on the upper-limb Fugl-Meyer scale, representing a change from no to some hand movement (the sham control group showed no functional improvement). A similar approach using SMR-EEG neurofeedback with action-observation therapy[142] instead of robotic stimulation in a subacute-stroke RCT found a remarkable 8.1 point improvement in upper-limb Fugl-Meyer score relative to controls who used only mental imagery[143]. Patients in the feedback group received continuous verbal and motivational feedback from therapists who were observing neural activation followed by movement of a co-located virtual hand if the trial was a success. Although these findings are promising, both the uncontrolled placebo effect and the provision of motivational feedback from therapists make it difficult to ascertain the mechanism of recovery in this trial.

BCI therapy has also been compared with robotic therapy. One study examined the effects of upper-extremity robot-assisted rehabilitation versus an EEG-BCI approach on the relationship between functional reorganization and behavioural outcomes in patients with stroke. Resting-state fMRI analysis showed that BCI training elicited increases in functional connectivity in ipsilesional and contralesional motor cortices, the SMA, parts of the visuospatial system and the cerebellum, and that these changes were associated with motor recovery[144]. The goal of such BCI studies is to combine neurofeedback with functional stimulation to restore lost connections between the brain regions that are involved in intention, planning and movement as a behavioural treatment to aid in the transfer of

Fugl-Meyer scores
Performance-based impairment index for assessing motor functioning, balance, sensation and joint functioning in patients with post-stroke hemiplegia.

the learned effect to improvements in movement outside the laboratory. More evidence is necessary, but the use of neurofeedback as an adjunct therapy to physiotherapy[141] or as part of a multimodal intervention[143] is a promising development for rehabilitation of patients with stroke, which has traditionally maintained focus on activating limbs without engaging brain activity.

Applications of fMRI-based neurofeedback for rehabilitation after stroke are not as well developed, but fMRI spatial precision and whole-brain coverage may better target the neurophysiological substrate of the injury. For instance, fMRI neurofeedback was applied to modulate the activity of a spatially distinct region of the brain that was not affected by stroke (for example, the ventral premotor cortex) to induce intracortical facilitation in the affected M1 (REF. 56) and to directly enhance ipsilesional thalamo–cortical connectivity[145]. Modulation of interhemispheric laterality[80,146] by fMRI-based neurofeedback is being pursued in the context of stroke, although further work is needed to establish the clinical benefits of this approach.

Many challenges remain in generating strong and well-controlled evidence for the general clinical utility of neurofeedback, including the difficulty of identifying responders, the scarcity of homogenous patient populations and the medically oriented efforts to combine different approaches to maximize treatment effects that are often not properly controlled. All these outstanding issues would benefit from more fundamental neuroscientific research. Clinical phenotyping may help to identify responders, and neurofeedback protocols could be designed based on network models of neural dysfunction[147] (BOX 2) rather than on patient interviews and self-reports as in current practice[148]. Finally, training protocols could be tailored to individual patients based on predictions of neurofeedback performance from resting-state activity[149], anatomical brain structure[150,151] and personality traits[152].

Conclusions and outlook

Recent neurofeedback research has led to advances in the knowledge of neural function by using brain activation as the independent variable and behaviour and thought as dependent variables. Learning brain control with neurofeedback is similar to skill acquisition and involves the corticostriatal loop with its dopaminergic and glutamatergic synaptic organization. The promise of neurofeedback as a scientific tool is now beginning to be realized. Real-time connectivity and multivariate methods enable modulation of patterns of neural activation, which may better represent the underlying neural function than activity in single brain regions. Modulation of deep brain structures and neural oscillations (EEG, electrocorticography and single-cell recording) can also be performed using neurofeedback based on electrophysiological activities of subcortical regions. New evidence suggests that modulation of neural circuitry even occurs without conscious awareness of the neurofeedback signal. In addition, we now understand more about how neurofeedback is regulated, its specificity and some of its effects on neuroplasticity. Learned modulation of activity in specific brain regions, connections and patterns can lead to specific behavioural changes. Technological developments on the horizon[153–157] will accelerate neurofeedback experimentation even further. Much remains to be investigated, including the integration of the vast knowledge of training and learning psychology into neurofeedback protocols (BOXES 3,4), the long-term impact of neurofeedback on neuroplasticity and behaviour, and its positive and negative side effects. The range of neural circuitry that can be modulated in neurofeedback, from single cells and connectivity between regions to multivariate patterns, is unparalleled in neuroscience and will continue to provide new ways to understand brain–behaviour relationships.

From a clinical standpoint, neurofeedback remains in early development. There is a need for more placebo-controlled clinical trials that address the behavioural specificity of the learned regulation. However, ongoing large-scale clinical trials may clarify the highly variable effects of neurofeedback. Perhaps the best example for such a large-scale undertaking in neurofeedback is the BRAINTRAIN project that was funded by the European Commission. Some future areas of clinical investigation involve comparing or combining neurofeedback with other interventions, such as pharmacotherapy, neurostimulation and behavioural therapy. The research community is still not informed of comparable effect sizes, side effects and differential effectiveness for diagnostic subcategories. Ultimately, the clinical application of neurofeedback will depend on the value that it brings to the patient and caregiver, and therefore double-blind RCTs of neurofeedback and systematic analyses of its cost–effectiveness should be conducted.

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Acknowledgements
The authors thank S. Ruiz and D. Schnyer for their valuable help in reviewing the manuscript before submission. R.S. is supported by the Comisión Nacional de Investigación Científica neurofeedback Tecnológica de Chile (Conicyt) through Fondo Nacional de Desarrollo Científico neurofeedback Tecnológico, Fondecyt (project number 11121153); Vicerrectoría de Investigación de la Pontificia Universidad Católica de Chile (Proyecto de Investigación Interdisciplina number 15/2013); Institute for Medical and Biological Engineering and Department of Psychiatry, Pontificia Universidad Católica de Chile; the Medical Faculty of the University of Tübingen through the Fortüne funding (project number 2114-1-0); the Singapore–Bäden–Württemberg Life Sciences grant; the ERA-Net (European Research Area)–New INDIGO project funded by the Bundesministerium für Bildung und Forschung (BMBF) (project number 01DQ13004). N.W. is supported by the BRAINTRAIN European research network (Collaborative Project, grant agreement number 602186); the European Research Council (ERC) (grant agreement number 616905); and a Centre Grant by the Wellcome Trust (0915/Z/10/Z). F.S. is supported by the Swiss National Science Foundation (BSSG10_155915). L.S. is supported by the US National Institutes of Health (NIH) (K23DA032612); the Norman E. Zinberg Fellowship in Addiction Psychiatry at Harvard Medical School; the Charles A. King Trust; the McGovern Institute Neurotechnology Program; and private funds to the Massachusetts General Hospital Department of Psychiatry. N.B. is supported by Deutsche Forschungsgemeinschaft (DFG); EU Project LUMINOUS; BMBF, MOTOR-BIC und EMOIO; Eva und Horst Köhler Stiftung; Baden–Württemberg-Stiftung; and EU Project BRAINTRAIN. J.S. is supported by NIH 5K12HD073945-02.

Competing interests statement
The authors declare competing interests: see Web version for details.

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