Current progress in real-time functional magnetic resonance-based neurofeedback: Methodological challenges and achievements

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ABSTRACT

Neurofeedback (NF) is a research and clinical technique, characterized by live demonstration of brain activation to the subject. The technique has become increasingly popular as a tool for the training of brain self-regulation, fueled by the superiority in spatial resolution and fidelity brought along with real-time analysis of fMRI (functional magnetic resonance imaging) data, compared to the more traditional EEG (electroencephalography) approach. NF learning is a complex phenomenon and a controversial discussion on its feasibility and mechanisms has arisen in the literature. Critical aspects of the design of fMRI-NF studies include the localization of neural targets, cognitive and operant aspects of the training procedure, personalization of training, and the definition of training success, both through neural effects and (for studies with therapeutic aims) through clinical effects. In this paper, we argue that a developmental perspective should inform neural target selection particularly for pediatric populations, and different success metrics may allow in-depth analysis of NF learning. The relevance of the functional neuroanatomy of NF learning for brain target selection is discussed. Furthermore, we address controversial topics such as the role of strategy instructions, sometimes given to subjects in order to facilitate learning, and the timing of feedback. Discussion of these topics opens sight on problems that require further conceptual and empirical work, in order to improve the impact that fMRI-NF could have on basic and applied research in future.

1. Introduction

The last decade has seen significant increase in the number of research groups using real-time, functional magnetic resonance imaging-based neurofeedback (fMRI-NF) to train participants in the self-regulation of brain networks and functions (Sulzer et al., 2013; Thibault et al., 2018). NF utilizes the latest developments of real-time data processing and pattern analysis to train participants in the self-modulation of neural networks (LaConte et al., 2007; Johnston et al., 2010; Johnston et al., 2011; LaConte, 2011; Watanabe et al., 2017). The strength of this technique, compared to other approaches such as EEG (Arns et al., 2017) or functional near-infrared-spectroscopy (fNIRS) (Sitaram et al., 2017), lies in its high spatial resolution, the ability to probe deep subcortical structures and whole-brain coverage, as well as the extraction of information from distributed activation patterns (Sorger et al., 2012), and the mapping of functionally connected networks (Zotev

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et al., 2011). This is critical, as functional brain networks change significantly throughout development (Cohen Kadosh et al., 2011) and the fine-tuning patterns differ for typically and atypically developing populations (Johnson et al., 2002, Cohen Kadosh, Linden et al. 2013). If implemented successfully, the NF approach holds much promise for brain-based intervention approaches that aim to influence and shape the emerging networks in the developing and matured brain. That is, it allows us to target not only cortical and subcortical task-relevant regions with good precision, but it also offers the necessary flexibility to accommodate the frequent changes in brain network configurations that are typical for emerging networks. As a result, a substantial body of "neurofeedback training" research is now available that highlights the potential and versatility of feedback-based approaches to teach participants to control and improve brain functions.

Operant conditioning is widely acknowledged as the leading learning mechanism of brain self-regulation with NF (Black et al., 1977; Caria, 2016), which is mediated by reinforcement of action that results in a desired change in brain activation. The two-process theory (Gaume et al., 2016; Lacroix, 1986) adds a second, parallel process, which focuses on discrimination learning of internal percepts, guided by the identification of correlation between internal (e.g. afferent signals, mental events, affective states) and external signals (i.e. neurofeedback). The integration of internal percepts with NF relies on the allocation of attention to the different sources of these signals, which is moderated by executive function (Gaume et al., 2016). The participant perceives reinforcing feedback and evaluates it with regards to the regulation goal. If accessible to perception, the subject improves his or her perceptual accuracy of internal signals. Depending on the valuation outcome, mental actions such as cognitive strategies are then changed or maintained (Paret & Hendler, in press). A detailed overview of NF learning theories can be found elsewhere (e.g. Arns et al., 2017; Gaume et al., 2016; Sherlin et al., 2011; Strehl, 2014).

With the advent of fMRI-NF, the number of specific brain mechanisms and indications for NF training has broadened considerably (Sulzer et al., 2013). The functional specificity of fMRI might explain the versatility of fMRI-NF, showing modulation effects across a number of domains such as motor function (Sitaram et al., 2012; Scharnowski et al., 2015), prosody (Rota et al., 2011), working memory (Zhang et al., 2013), visual sensitivity training (Shibata et al., 2011; Scharnowski et al., 2012; Sitaram et al., 2012), and emotions (Caria et al., 2010; Johnston et al., 2011; Zotev et al., 2011; Paret et al., 2014; Koush et al., 2017; for a review see Linhartová et al. (2019)).

As a result, the number of studies on fMRI-NF has increased substantially and methodological progress has been considerable (Thibault et al., 2018). We now have seen evidence that fMRI-NF training is feasible in participants across a wide age range, starting with children as young as seven years (Cohen Kadosh et al., 2016b; Alegria et al., 2017) and in a broad range of patient populations (see Thibault et al., 2018 for review), including prevalent psychiatric conditions such as chronic pain (deCharms, Maeda et al., 2005; Guan et al., 2015), depression (Linden et al., 2012; Young et al., 2014; Yuan et al., 2014), borderline personality disorder (Paret et al., 2016a), posttraumatic stress disorder (Gerin et al., 2016; Nicholson et al., 2017) and addiction (Li et al., 2013; Kirsch et al., 2016). Evidence has also accumulated that fMRI-NF training affects responsiveness not only in the specific target region, but that it also modulates the underlying task networks (e.g., Cohen Kadosh et al., 2016b Cohen et al., 2016; Keynan et al., 2016; Ruiz et al., 2013). Further, some studies have now begun to directly modulate brain networks. This has been achieved via functional connectivity (fc)-NF which has been used in both adults (Koush et al., 2013, 2017; Spetter et al., 2017), and adolescents (Zich et al., under review). Finally, more recently, advanced methods such as multivariate pattern analysis (MVPA) and hierarchy indices between network's nodes (Jacob et al., 2018), have been introduced to assess distributed patterns of brain activation and functional correlations (Lubianiker et al., 2019).

While the technical aspects of fMRI-NF have been brought along to great success, which is reflected in advanced software developments and more scanning centers being now set-up to conduct fMRI-based NF experiments, the field finds itself at a crossroads which will not only determine whether the current research activity is sustainable in the future but will also have the impact that is hoped for with regards to interventions and clinical applications (Stoeckel et al., 2014). As with many newly emerging fields, it is important to verify that promises do not overstate the realistic possibilities. While the current evidence is certainly encouraging regarding the feasibility of fMRI-NF with a number of disease-relevant target areas and networks, it is now critical to tighten the strings and develop a methodological framework that can help guide future research, in particular on clinical applications. Furthermore, this will considerably facilitate the shift from feasibility and proof-of-concept studies, which naturally dominate the initial phase of a research field, towards translational studies and clinical trials. Researchers developing NF training protocols cannot avoid to address fundamental questions regarding all steps of planning, conducting and analyzing; starting from the experimental design and leading all the way down to the evaluation of training success (Randell et al., 2018). Broadly, critical questions can be sorted into four domains as they address (1) the neurocognitive function to be changed with the intervention; (2) the information given to participants by professionals beforehand and transmitted via the brain-computer interface; (3) personalizing the training context to the participant and (4) measuring brain self-regulation and training success. Addressed in this paper, these domains and the corresponding questions are visualized in the form of a Floor Map for graphical overview (Fig. 1). The rapid development of NF techniques and applications, a large variety of suggested solutions for current problems, and the lack of gold standards are challenges that, in our view, require a debate considering several procedural aspects underlying the method. With this paper, we hope to contribute to the critical discussion of current progress in fMRI-based NF research and accordingly, to address the considerations and possible solutions the field is currently facing with. Though we focus on fMRI, the large part of critical points stressed in this paper are not limited to NF with fMRI, but pertain to any neuroimaging modality that can be used for this purpose, including EEG, fNIRS or magnetoencephalography (cf. Thibault et al., 2016; Sitaram et al., 2017). However, amongst all neuroimaging modalities, as fMRI-based NF is currently the most rapidly growing field (Watanabe et al., 2017), it also brings up certain aspects that require particular attention and justify focused review. Critically, by providing an overview on the different methodological, cognitive and psychological factors that influence NF training success, we hope to help steer the discussion towards improving and standardizing procedural aspects.

2. How to choose the training target?

2.1. Target regions

One of the most critical decisions facing fMRI-based NF research is without a doubt the choice of target and control region(s). Among others this involves the question whether fMRI-based NF should focus on local activation in a specific target region (typically a change in average blood oxygenation level dependent [BOLD] response), or rather metrics related to a network function or organization. Either approach has been shown to be feasible, yet a couple of theoretical aspects need to be considered.

If a single target region is chosen to be modulated with NF training, it is important to consider whether the main goal of the training is to regulate activation in a region that is disturbed, such as for example modifying amygdala BOLD activity in an emotion regulation context (Zotev et al., 2011; Linden et al., 2012; Paret et al., 2014), reducing ventral striatum reactivity to alcohol cues (Kirsch et al., 2016), or in a region that is associated with increased food cravings (Ihssen et al., 2016). The regional approach has governed the fMRI-NF practice, led by the assumption that some regions might be critical for a specific symptom or disorder. Yet, the critical issue here is to use a region that is vastly
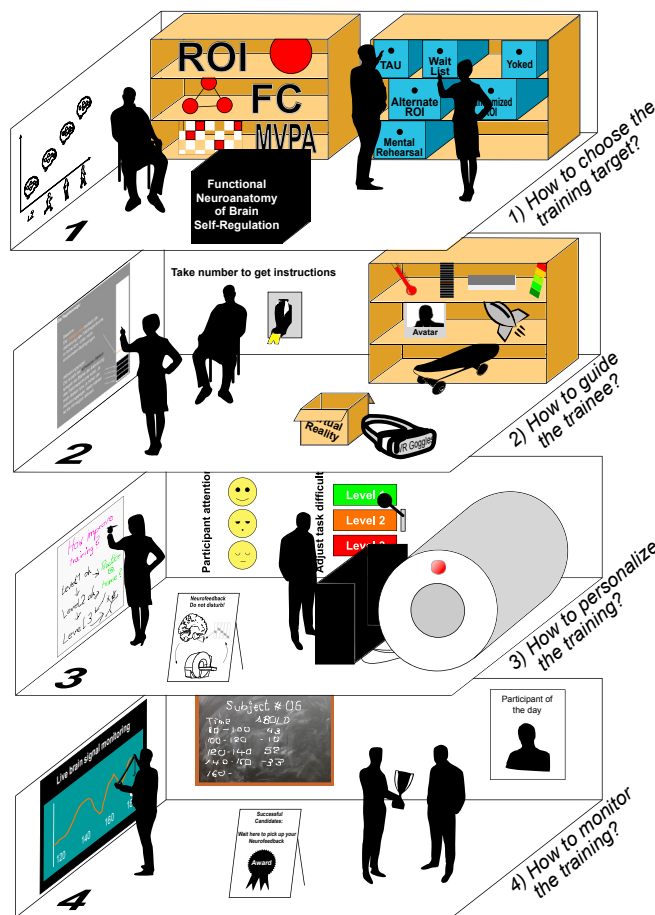
Fig. 1. "Floor plan", illustrating domains of neurofeedback procedures of current debate and discussed in this article.

connected and could be considered as a hub, assuming that its modulation will result in a large functional impact through its network (Table 1).

It has become increasingly accepted among neuroscientists that functionally inter-connected networks of regions mediate brain processes (Broyd et al., 2009; Bullmore and Sporns, 2009; Menon, 2011; Barrett and Satpute, 2013) especially regulatory ones (Kober et al., 2008; Raz et al., 2012). According to this view, communication between and within largely segregated neural modules is essential to the transfer and processing of information in the brain, and it would make sense to target parameters of this communication with NF. One possible network metric that can be probed with NF is functional connectivity (fc) between regions, aiming to differentially change the co-activation patterns between two or more regions (Watanabe et al., 2017). This approach is possibly the more physiologically valid given that the brain is naturally organized

Table 1
Overview on combinations of brain target and outcome analysis with single region and network NF trainings.

		Neurofeedback brain target	
		Single region	Network of regions
Outcome	Single region	Training of single region regulation, assess activation of same region as outcome	Regulation training of network activity with two or more regions, assess activation of single region
	Network of regions	Training of single region regulation, assess functional network of trained region as outcome	Regulation training of network activity with two or more regions, assess same functional network as outcome

in networks of regions that work together to support behaviour (Fair et al., 2007; Broyd et al., 2009; Fair et al., 2009; Cao et al., 2014). It is however important to recognize that network NF approaches should not neglect the behaviour of single brain regions within that network. Thus, for example, it can be assessed whether a specific brain region within the network is driving the modulatory change, as shown in a study which used fc-NF to change effective connectivity between the prefrontal cortex and the amygdala in an emotional reappraisal context (Zich et al., under review). In this study, Zich and colleagues found that fc-NF modulated the prefrontal cortex (PFC)-amygdala fc towards a more negative fc pattern, and that this modulation was driven predominantly by changes in PFC activity. The authors also found that this fc change, which is related to more control and less anxiety, correlated with the change in thought control ability as assessed before and after the MRI session.

2.2. Consider functional neuroanatomy of neurofeedback learning

In a recent paper, Sitaram and colleagues presented three different NF brain network modules that support the overall NF process (Sitaram et al., 2017). Focusing on key brain regions that have been repeatedly shown to be activated in previous NF studies, they differentiated between network regions associated with *control of visual NF*, such as the dorsolateral PFC (dlPFC), thalamus, lateral occipital cortex and posterior parietal cortex, *NF learning* regions such as the dorsal striatum, and finally, *NF reward* processing regions, such as the ventral striatum, the anterior cingulate cortex (ACC) and the anterior insula. Moreover, neural activations related to NF control and those related to the monitoring of feedback such as reward signals could be recently differentiated (Paret et al., 2018). In this study, healthy individuals viewed emotional pictures and regulated their amygdala response, visualized via the temperature of a thermometer presented next to the pictures. The task involved two conditions, requiring individuals to regulate NF either up or down. That is, they needed to evaluate NF with respect to the task-condition (e.g. rise in temperature is rewarding during up-regulation but punishing during down-regulation). In line with Sitaram et al.'s model, the dlPFC, lateral occipital cortex, and lateral thalamus were involved in NF control, whereas the ventral striatum was involved in reward processing. This finding aligns well with other empirical study of NF-related reward signals (Ramot et al., 2016; Shibata et al., 2019; Skottnik et al., 2019). In contrast to Sitaram et al.'s suggestion, the insula was not involved in reward processing but rather in NF control (Shibata et al., 2019; Paret et al., 2018). In addition, the ventromedial PFC (vmPFC) was involved in feedback monitoring (Radua et al., 2016; Paret et al., 2018; Shibata et al., 2019), as were the medial thalamus and the rostral PFC (Paret et al., 2018). Notably, these regions did not differentiate between rewarding or non-rewarding feedback, whereas the orbitofrontal cortex was found to respond to failure feedback selectively (Paret et al., 2019). Instead, the vmPFC and medial thalamus exhibit a more general feedback response, suggesting a role in attentional control. The vmPFC may also support the learning of associations between emotional arousal and feedback (Paret et al., 2016a,b; see also Radua et al., 2016 for vmPFC response to NF). In contrast, the rostral PFC showed a marked response when subjects were instructed to up-regulate feedback but not during down-regulation (Paret et al., 2018). A positive correlation of this response pattern with regulation success, as well as functional connectivity between rostral PFC and ventral striatum further support a role of rostral PFC in the monitoring of contextual information such as instructions (Paret et al., 2018). Rostral PFC resting-state connectivity predicted anxiety reduction with fMRI-NF (Scheinost et al., 2014), a finding that further emphasizes the importance of this neural node for the ability to effectively process feedback in order to inform brain self-regulation. Involvement of rostral PFC may therefore reflect effortful model-based reinforcement learning of regulation strategies (Gaume et al., 2016).

Brain self-regulation with NF is an active task and involves interlocked psychological processes. In addition to regions involved in feedback monitoring, regions involved in active NF control show great

overlap between studies (Emmert et al., 2016). The network comprises regions from the cognitive control network including lateral PFC and posterior parietal cortex (Gaume et al., 2016), the ACC which is assumed to implement error monitoring of NF (Gaume et al., 2016), insula and lateral thalamus (Emmert et al., 2016; Paret et al., 2018). As these regions are activated when subjects try to control NF, down-regulation training with these regions seems incompatible with the psychobiological dynamics of the system. In line with this assumption, Veit et al. (2012) showed that down-regulation of anterior insula activation was associated with lower activation compared to up-regulation, but insula was still activated above baseline in both conditions. Instead of down-regulation below baseline, alternating up- and down-regulation of dlPFC can increase speed of deliberate dlPFC regulation and may lead to more flexible recruitment of cognitive control (Van den Boom et al., 2018). Feeding back activation from regions while they are themselves involved in NF may introduce problems for learning regulation, and should be considered in study planning (Lubianiker et al., 2019). Taken together, several neural networks are involved in NF monitoring and control and feeding back activation from these networks may interfere with the actual treatment goal.

2.3. Control aspects

In order to show specificity of training, studies introduce control groups that, instead of feedback from target brain activation, receive some other kind of intervention or feedback protocol. The most commonly adopted choice of feedback control is to feedback signal stemming from a different brain region (other approaches include: no feedback; feedback based on the activity from the same region, but from a different point in time; feedback from the same region, but from a different individual; feedback based on artificially created irrelevant randomized signals, also sometimes called sham feedback). Here, similar concerns apply to the choice of a region from which the participant receives sham feedback in order to assess the sensitivity and specificity of the NF training. Generally, the control feedback region should be independent of the NF network that is to be trained. Given that most cognitive and behavioral functions depend on intertwined networks, this is a challenge that has yet to be addressed satisfactorily (Cohen Kadosh, Linden et al., 2013; Staunton and Cohen Kadosh, 2019; Cohen Kadosh et al., 2016b). Recently published taxonomies (Sorger et al., 2019, Lubianiker et al., 2019) survey the advantages and disadvantages of the different ways of designing control conditions and selecting control groups. For example, not involving a control group or comparison to a no-training control group allow slim and less costly study designs, and are favorable in early phase studies (e.g. to identify endpoints for future clinical trials (Sorger et al., 2019)). If NF is given in order to facilitate mental strategy learning, a control group practicing a mental strategy without NF is necessary to reveal additive effects from treatment (Sorger et al., 2019). In contrast, placebo control is required to conclude on causality of brain self-regulation (e.g. with a randomized control group design). Like placebos in pharmacology research, NF placebo conditions should control for psychosocial effects (e.g. attention by staff, receiving high-tech treatment, and so on) without altering the process targeted with the intervention (e.g. emotion regulation with amygdala neurofeedback). However, brain self-regulation with NF is a complex phenomenon and involves several processes itself such as perception, valuation of feedback, implementation of control and learning (see section 1.2 above). Therefore, placebo would need to invoke all these "NF general" processes, without addressing the target process (Lubianiker et al., 2019). With current state of knowledge, an informed selection for placebo NF considering all the above points is difficult, if not impossible. A solution still to be tested may be "randomized ROI NF" (suggested in Lubianiker et al., 2019), where different control regions-of-interest are assigned to participants of the control group. Moreover, ethical considerations may prevent usage of some control groups, particularly in patient treatment. For example, there is concern that sham feedback might

encourage participants to abandon an otherwise successful strategy, simply because the feedback does not seem to support using it. Schabus (2017) suggested that yoked feedback might introduce learned helplessness, with adverse consequences on motivation and learning with subsequent real feedback. Moreover, a recent study by Goldway et al. (2019) provided additional support for the suitability of sham feedback to distill specific NF effects, after they observed subjective improvement after sham feedback in patients with chronic pain that faded in follow-up measurements.

Similarly, given the changes in recruitment patterns of different brain regions in the developing brain, it is likely that brain regions that are used at an earlier developmental stage are not necessarily relevant at a later stage (Johnson et al., 2009; Johnson et al., 2015). As a result of this, it would be extremely difficult to find a control brain region that would support a comparable function across different ages. A possible solution for this problem could be to provide authentic feedback during the regulation conditions and to compare the regulation success against a 'dry' regulation baseline (where feedback is not given). This would allow us to assess the extent to which participants rely on the live feedback signal to both learn and maintain their regulation strategies.

2.4. Population aspects

The selection of region(s), as well as other parameters, is of particular importance when training children with or without psychopathology (Cohen Kadosh, Linden et al., 2013; Cohen Kadosh et al., 2016a), although it does apply also to adults. For example, it is currently unclear whether one should teach young individuals to regulate brain responses that would support a cognitive function at the specific developmental stage, or, instead teach them directly to use the brain network that supports this ability in healthy mature adults (Fig. 2). This may seem especially important if one considers the developing brain as an adaptive system, where the networks of brain regions that support cognitive abilities change interactively as a result of on-going brain maturation and cognitive development (Cohen Kadosh and Johnson, 2007; Johnson et al., 2009). Hence, the temporary use of an alternative brain network during development can be considered both logical and adaptive and it remains to be determined whether NF should target these current alternatives instead of future key regions. This is also relevant for other clinical populations (e.g. stroke patients), where brain networks may well have specialized in a way that is most adaptive for the individual. This has not only theoretical and practical, but also ethical, implications. More precisely, the main choice lies between increasing responsiveness in compensatory networks, or in attempting to shape brain networks towards more typical functioning. While either approach could be argued for, a definite decision should be best based on scientific evidence of mechanisms of plasticity and rehabilitation that is currently lacking. One promising solution may be to focus on brain regions that help with acquiring new skills, such as the inferior frontal gyrus for example, whose involvement in executive functions makes it a frequently reported brain region in developmental neuroimaging studies that observe age-dependent differences in brain activation (Johnson et al., 2009; Cohen Kadosh, Johnson et al., 2013).

3. How to guide the trainee?

3.1. Feedback interface

Interfaces of different complexity have been applied, ranging from simple, thermometer-like displays (Cohen Kadosh et al., 2016b) to more complex reality interfaces (Yamin et al., 2017). Integrating realistic virtual environments in NF can enhance learning and improve user's experience (Cohen et al., 2016), for discussion see (Lubianiker et al., 2019). Yet, complexity can also prove to be distractive as it introduces additional attentional task demands, especially in pediatric or clinical populations which may present with reduced cognitive functions
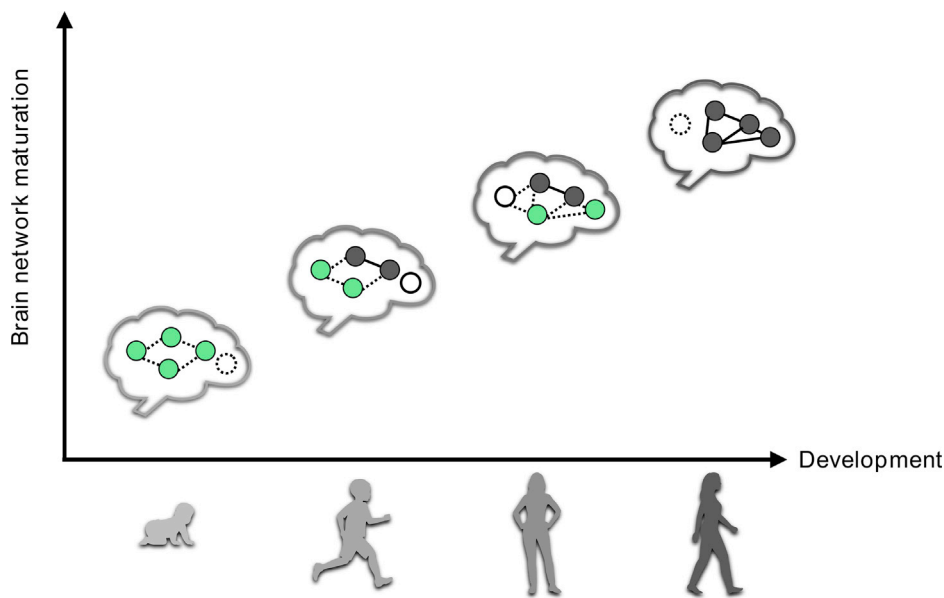
Fig. 2. How to treat the maturing brain: train networks specific for a particular developmental stage or reinforce adult healthy brain function? Brain networks undergo considerable maturation throughout the first two decades of life (Fair et al., 2009; Cohen Kadosh, Cohen Kadosh et al., 2011), a change which is reflected in the functional and structural connectivity patterns across the age range. For the design of effective NF protocols, this could mean that different brain regions may support a specific cognitive function at each age point. The question therefore arises whether one should teach young individuals to regulate brain responses that would support a cognitive function *at the specific developmental stage*, or, instead teach them directly to use the brain network that supports this ability in healthy mature adults. This may seem especially important if one considers the developing brain as an adaptive system, where the networks of brain regions that support cognitive abilities change interactively as a result of on-going brain maturation and cognitive development (Cohen Kadosh and Johnson, 2007; Johnson et al., 2009). The same principle applies for clinical populations, which may rely on alternative brain networks to perform a task. Hence, the (temporary) use of an alternative brain network can be considered both logical and adaptive and it remains to be determined whether NF should target these (current) alternatives instead of typical key regions (see also discussion in Lubianiker et al., 2019).

Table 2
Pros and cons of simple and more complex NF interfaces.

	Simple interface	Virtual reality environment
Examples	Thermometer, sound/music jingle, rocket space ship, virtual fire	Interact with avatar, reach a coffee mug, navigate in computer game
Pros	Distractors are reduced to minimum	Improved learning Better sustainability Better transferability Increased motivation
Cons	May produce fatigue	May distract from task More complex scenarios come with higher cognitive demands and may turn out difficult for some populations

('entertainment' vs. 'treatment' problem, see (Arns et al., 2014)). The optimal feedback modality (e.g., visual, auditory, tactile) and the complexity of their transmission (one dimensional courser movement to virtual reality environment) have to be chosen based on the objective, population and task (Table 2).

3.2. Instruction

Previous NF studies have varied as to whether participants were given explicit strategy instructions to regulate their brain responses or whether an implicit strategy was expected, i.e., with participants being asked to develop their own effective strategies. Most fMRI-NF studies to date have opted for implicit strategies (e.g. Paret et al., 2014), and only some patient studies suggested the use of mental imagery (e.g. Zilverstand et al., 2015). Others have only offered simple and relatively unconstrained instructions, in order to allow participants across a wide age range (7–17 years) to perform well. This was the case in a recent NF study where children and adolescents were asked to increase the response in a key emotion regulation region by trying 'to think happy thoughts; to think about something that would make them happy' (Cohen Kadosh et al., 2016a,b). Keeping instructions simple may also be important for patient

populations, when ability levels to use different strategies are likely to vary significantly. The same study also found that whereas the instruction worked in the first instance, this lasted only for a couple of runs, with some participants failing to up-regulate in the later runs. Understanding the motivational-contextual factors that modulate NF regulation is critical. Identifying individual differences in the use of different regulation strategies is also important, if we want to enhance the effectiveness of these procedures. In fact, a collection of post-training feedback from subjects across experiments may be helpful with identifying any trends in strategy formation/usage.

NF can also be used to support the selection of an instrumental mental strategy from a pool of potentially useful strategies (Lawrence et al., 2014). Patients can identify effective strategies for ACC control from a pool of skills they had previously learned during cognitive behaviour therapy treatment (MacDuffie et al., 2018). Mental strategies during training are diverse and depend on the NF signal; for example, motor imagery can be used to control sensorimotor electrocortical rhythms (Halder et al., 2011; Nan et al., 2012) and cognitive appraisals of emotional contents are instrumental for amygdala regulation (Brühl et al., 2014; Zotev et al., 2011). It was shown that strategy knowledge can facilitate NF learning (Bray et al., 2007; Lawrence et al., 2014; Zilverstand et al., 2015; Kober et al., 2017), and strategy instructions may decrease the risk of non-learning with limited duration of an experiment (Scharnowski and Weiskopf, 2015) or in face of erroneous control beliefs, as shown in EEG-NF (Witte et al., 2013). Furthermore, practicing anterior insula up-regulation with NF helped subjects to identify helpful mental strategies, while subjects repeating strategies without NF did not learn anterior insula regulation (Caria et al., 2010).

On the downside, strategies can have undesired effects. For example, when subjects identify an instrumental strategy right away, there is no need to explore new strategies, which would potentially lead to even stronger activation. Some support for this critique of strategy suggestions comes from EEG-NF research, where Hardman et al. (1997) observed a steeper learning curve in subjects without instructed strategies to control feedback from slow cortical potentials, compared to another group of subjects who were told to use emotional strategies. However, significant

post-hoc tests were not reported to show whether the no-strategies group in the last of three blocks outperformed subjects from the instructed-strategies group. In line with a possible advantage not to instruct strategies, strongest learning effects were observed for fMRI-based NF without strategy instruction, followed by NF with strategy instruction; but group differences were not significant (Sepulveda et al., 2016). These results need a careful interpretation, because the authors of the latter study introduced another variable (additional rewards) and statistical tests of group differences may have lacked adequate power. Though these studies lend some support to the notion that strategy instructions may (negatively) influence NF regulation learning, these results may also indicate that subjects were able to overcome initial ignorance of strategies to regulate NF, while subjects who received strategy instructions start with a higher level of regulation success, which they maintain over the course of the experiment.

Evidence has now accumulated showing that explicit strategy knowledge is not required for acquisition of NF control per se (Shibata, Watanabe et al. 2011, 2016; Kober et al., 2013; Amano et al., 2016; Koizumi et al., 2016; Ramot et al., 2016) for a review see Shibata et al. (2019). Nonetheless, instructed strategies may be useful when using NF for certain applications, e.g. emotion regulation purposes. For instance, individuals who habitually use specific emotion regulation strategies, such as the reappraisal of emotional material, have better functioning levels and higher well-being compared to others, who tend to suppress emotions (Gross and John, 2003). Reappraisal is a cognitive strategy to change the emotional impact of an affective stimulus via re-interpretation of, or taking a detached perspective from the stimulus (Powers and LaBar, 2019). Healthy individuals prefer to distance from emotional stimuli with high affective intensity, but rather reappraise low intensity stimuli (Sheppes, Scheibe et al. 2011, 2014). Deviations from this pattern may relate to psychopathology, such as borderline personality disorder (Sauer et al., 2016). Hence, NF with explicit strategy instructions may help patients to overcome deficits in the use of effective emotion regulation strategies, through neural reinforcement of desirable mental strategies (Herwig et al., 2019). The question of whether explicit or implicit task instructions are most efficient remains to be determined, yet given the importance of this methodological aspect (Birbaumer et al., 2008), the need for a more systematic research and possible standardization is evident.

4. How to personalize the training?

Based on the questions above, it has also become clear that methodological approaches may need to be additionally adapted for different populations, as requirements are likely to vary not only across different ages or clinical populations, but also with regard to subject-specific psychological variables which we will discuss in the next section. There are a number of cognitive and psychological factors that can affect NF performance. Gaining a better understanding of these factors is not only important in order to improve training outcome but also to help address the *inefficiency problem*. The inefficiency problem refers to the often reported finding that not all participants in NF studies are able to influence their brain activity. These people are often referred to in the literature as non-responders, non-performers or non-regulators and represent 30–50% of the population (Alkoby et al., 2018). In the following, we discuss a number of methodological, cognitive and psychological factors that all contribute to NF efficiency. While by no means complete, these provide first starting points for further optimizing NF interventions for a specific sample and thereby reducing the inefficiency problem.

4.1. Protocol aspects

An area of NF research that requires more in-depth research is the development of both time and cost-effective training regimes. For example, the number and length of each training session varies considerably across the different studies, with some studies testing participants repeatedly over several days (e.g. Spetter et al., 2017) whereas others used a single testing session only (e.g., Cohen Kadosh et al., 2016b). Some individuals might achieve the maximum level of control already after a single session, notably not only in fMRI-NF but also in EEG-NF (Schabus, 2017; Schabus et al., 2017; MacDuffie et al., 2018). The former is surprising as EEG-NF is usually thought to require higher training dosage than fMRI-NF (Sulzer et al., 2013). The lack of reported data on within-session brain signal regulation is currently a major obstacle for comprehensive review (Thibault and Raz, 2016). A more systematic investigation of optimal training length is urgently needed to avoid training regimes that are too short, or too long to be effective. To date, only one study has considered individual criteria for training length (Scharnowski et al., 2012). More research, across a range of populations and tasks would now be needed to provide reliable standards for effective and efficient NF training. Similarly, when considering training length and intensity, the option of combining NF training with out-of-scanner practice should be considered, as has been done in some studies with clinical samples (Subramanian et al., 2011; Linden et al., 2012), possibly in combination with a therapeutic intervention, such as cognitive-behavioral therapy (CBT), which would allow for a cross-over and mutual reinforcement of intervention approaches. NF could augment psychotherapy as illustrated by MacDuffie et al. (2018), who let patients regulate ACC after completion of CBT, using strategies they had learned in psychotherapy. The one-session protocol was instrumental for patients to identify strategies that were more effective than others for neural regulation. Furthermore, Herwig et al. (2019) show that NF may augment the neural effect of behavioral instructions.

Finally, a number of contextual and individual factors such as at what time of the day participants are tested, age, the amount of sleep that the participant had, physical exercise and general fitness, nutrition and menstrual cycle could influence the optimal training regime. At this time, we have no data available to address these questions conclusively. In addition to finding an ideal NF protocol, it might be helpful to try and implement an adaptive NF protocol that could maximizes neural regulation abilities. One example of such an approach to support optimal regulation performance could involve the individual NF range to keep participants challenged and engaged by varying scales of neural activity representation via the interface. Adaptive task difficulty was previously applied in other types of tasks, such as the tracking stop task (Rubia et al., 2003) by using a computer algorithm that adjusts the paradigm difficulty level according to the participant's performance. Using this approach, feedback range would not be fixed for all participants, rather it will be set according to the participant's performance in previous blocks/sessions. Such "shaping" of behaviour conforms to learning theory principles (Sherlin et al., 2011). For example, if the participant was very successful in previous sessions, the feedback will be presented with a higher demand range of neural activity in order to achieve the optimal performance.

Another approach to maximize regulation performance is the use of adaptive NF protocols that contain fewer challenge levels. According to this approach, individual progress in NF training is determined by the participant achieving a pre-determined goal, rather than by going through a fixed number of sessions. This kind of protocol may include fewer stages, each carrying different level of challenge. The first stage of such NF protocol may include a neutral feedback interface (e.g. bar/ neutral sound) while more advanced stages may include gradually more challenging (i.e., stressful or intriguing) feedback interfaces. In this setup participants are required to meet pre-determined success criteria (e.g. three successful sessions), in order to progress from one stage to the next (see Table 3 for an overview). Whilst adopting an individually tailored feedback approach may be more optimal from a learning perspective, it significantly limits comparability between sessions (either within or between individuals), and in turn reduces the informative value of, especially, between-subject designs.

Table 3
Selective summary of protocol aspects that may increase efficiency of NF training.

Measure	Current state-of-the-art	Suggestions
Limit training to number of sessions that are needed for learning.	Empirical data on optimal number of session is lacking. Studies are designed based on similar studies already published and expert suggestions from the literature.	Future studies should report between-session success and/or learning curve. Studies are needed to identify learning curves and define threshold-criteria.
Improve learning with additional out-of-scanner treatment	Initial studies show feasibility and benefits in clinical samples.	Conduct more studies to test benefits and feasibility of out-of-scanner practice. Identify maximum number of NF sessions needed in such protocols.
Adapt feedback range to the subject's performance	Some studies use an adaptive range and find successful learning. Studies to assess benefits of adaptive versus fixed feedback range and baseline levels are missing.	Investigate effect of adaptive feedback on brain self-regulation and assess potential additive benefits for transfer of learning.
Introduce performance-level criterion (e.g. A: regulation without challenge; B: regulation with mild stressor; C: regulation with strong stressor). Use performance-levels for decisions such as passing to next level of difficulty, or to stop training.	Not yet tested.	Studies should assess potential improvements when using training with levels.

4.2. Person aspects

Cognitive factors such as general intelligence levels, executive functions and the ability to focus on a task are to be considered when adjusting task designs for different populations (Hammer et al., 2012; Jeunet, N'Kaoua et al., 2016). It may be useful for example to simplify both task instructions and feedback display for younger participants in order to reduce the task demands and cognitive load (Gaume et al., 2016). A study by Alegria et al. used a simple rocket to display brain activity in a sample of adolescents (Alegria et al., 2017). In another recent study, Zich and colleagues trained a sample of adolescent girls to simultaneously increase activation in the dorsolateral prefrontal cortex and to decrease activation in the amygdala (Zich et al., under review), yet to simplify these complex changes for the participants, a simple thermometer was displayed, which increased with increasing negative correlation between the two regions.

A recent systematic review of the NF literature where 281 articles were reviewed (Staunton and Cohen Kadosh, 2019) found that attention indices such as the ability to focus, as well as length of attention span influenced NF learning outcomes, yet more research needs to be conducted to explore this further.

The contribution of psychological factors has been less explored and the results so far are not conclusive. In the recent systematic review mentioned above, only two factors emerged: motivation and mood (Staunton and Cohen Kadosh, 2019). Understanding a participant's motivational preference is important because it can help explain how participants will respond to the training paradigm. However, motivation is likely to vary between and within participants, but also as a function of age and across contexts. Specifically, it was found that while motivation to learn is important, there may be a need to balance individual levels of intrinsic motivation with the reward that is received. For example, Leeb and colleagues (2007) found that whereas highly motivated participants performed initially better on a simple NF training task than less motivated students, this performance difference was reversed when the NF training paradigm was switched to a virtual environment and became more immersive and hence, more interesting for subjects. This suggests that external factors such as learning paradigms can interact with an individual's motivation to learn.

With regard to mood, it has been shown that anxiety and depression can have a negative influence on performance (Zich et al., under review). In a recent study, Zich and colleagues found that low state anxiety levels in adolescent girls at the beginning of the training predicted better NF training outcomes (Zich et al., under review). While more research is needed to replicate this finding, future studies could explore the use of anxiety reducing exercises prior to the NF training in order to maximize its effectiveness. Similarly, it may be useful to monitor anxiety levels in participants throughout the training and to adjust when a certain threshold is reached, rather than continuing with the training.

Further, being susceptible to other people's emotion appears to play a part in emotional regulation learning. For example, susceptibility to anger has been found to impair NF success in two studies (Zotev et al., 2011; Marxen et al., 2016). Moreover, under specific circumstances, the ability to label emotions may be important in NF-based emotion regulation learning, such as in the case of children and adolescents who exhibit prolonged developmental trajectories for both emotion recognition and regulation abilities (Thomas et al., 2007; Ahmed et al., 2015). Introspective ability to perceive one's emotions more generally relates to the ability to discriminate percepts of internal signals, which is a key aspect of the two-process theory of NF learning. As suggested by Gaume et al. (2016), the ability of participants to perceive internal signals may be a good predictor for learning success and transfer of learning. However, behavioral measures of the ability to perceive brain states are still to be developed.

The evidence reviewed above highlights the important role that psychological factors can play in the successful implementation of NF training (see also Staunton and Cohen Kadosh, 2019). In the same vein, neural markers were found successful to predict EEG-NF performance (Gevensleben et al., 2009; Blankertz et al., 2010) and could be distilled from pretraining fMRI measures such as resting-state connectivity (Scheinost et al., 2014) to predict NF response and optimize treatment protocols. Clearly, more research is needed to develop recommendation that would allow us to personalize training programs for each individual in order to achieve maximum effectiveness.

5. How to monitor training?

5.1. Signal calculation

There is currently no standardized approach of calculating feedback, a problem which makes it difficult to compare NF signal and, in turn, NF training effectiveness across studies. To quantify signal change, BOLD signal drifts require corrections such as signal detrending and/or usage of a baseline where signal drifts only have negligible influence. For example, baseline activation can be retrieved from an epoch preceding the regulation block such as a 'rest'-period of a few seconds where subjects are instructed to refrain from cognitive efforts (Veit et al., 2012), and activation can be quantified relative to the mean baseline activation. BOLD signal changes have considerable interpersonal and intrapersonal variance that renders quantification problematic, though. To deal with this problem, the BOLD signal can be sampled during a baseline period (e.g. 60 s) to receive the mean and standard deviation, which can then be used as reference for quantification of signal variability (e.g. Keynan et al., 2016). This method seems optimal to receive maximally informative feedback in terms of variability, but a sufficiently long baseline period needs to be recorded in order to receive reliable statistics. Notwithstanding the problems of BOLD quantification, absolute quantification of BOLD signal change for feedback appears feasible (e.g. Paret et al., 2014; Zotev et al., 2011), at least for some applications (Fig. 3).
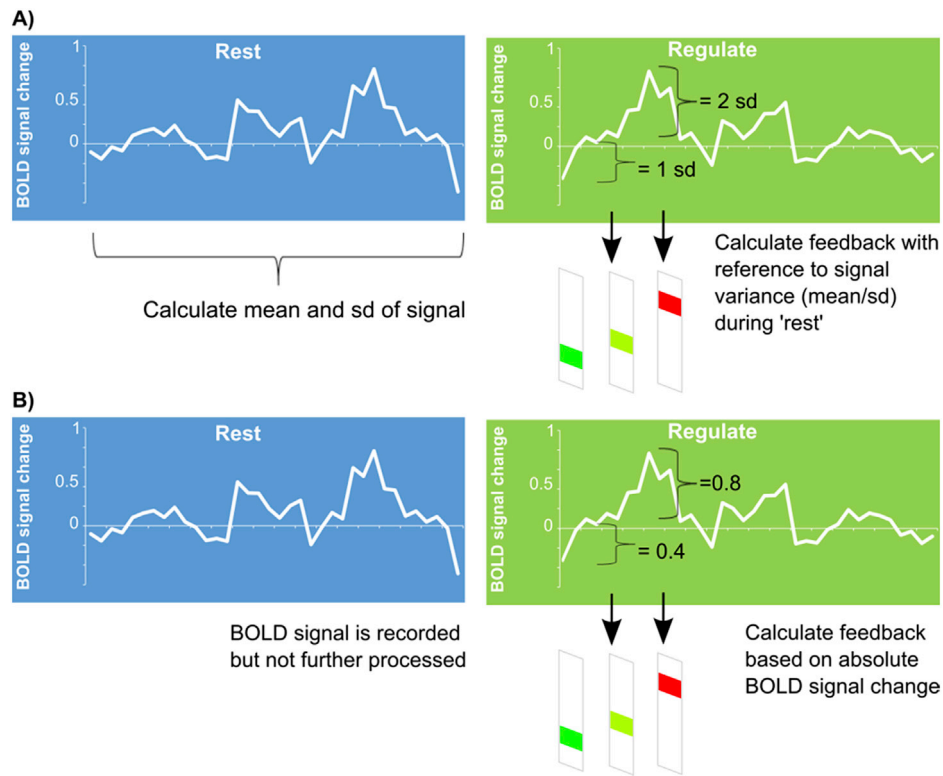
Fig. 3. Feedback is calculated based on the subject's BOLD signal variance or based on absolute signal change. A) The BOLD signal is sampled during a period (e.g. during 'rest', left area in blue). Mean and standard deviation (sd) is calculated and used to standardize feedback during the 'regulate' trial (right area in green). B) An absolute threshold is set to decide, whether BOLD signal change is followed by a change in the feedback thermometer.
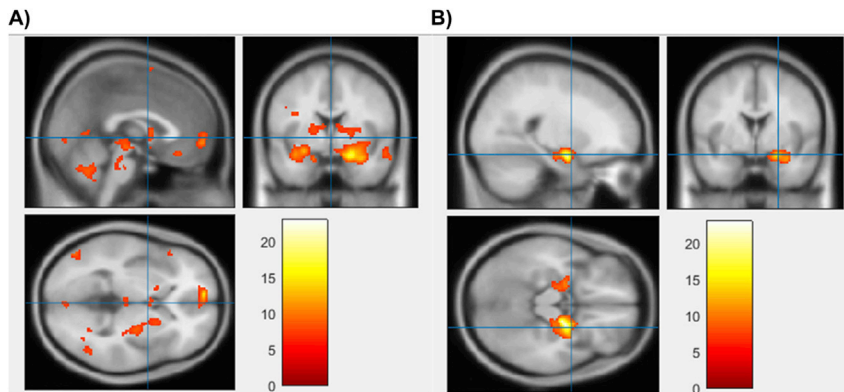

Fig. 4. Different real-time signal processing pipelines yield feedback that is correlated with different regional activation patterns. For illustration, right amygdala activation was calculated with two different real-time preprocessing routines, based on prerecorded fMRI data of N = 17 subjects who were administered a fMRI emotion regulation experiment (Linhartová, Gerchen & Paret, unpublished data). The resulting amygdala-signal was used as a predictor in a whole-brain statistical parametric mapping analysis. The maps show results from the group t-test (P < 0.05 FWE-corrected; colour-scale: t-values). Shown are regions that were significantly correlated with the amygdala signal as it was received by real-time analyses. Hence, activation of these brain regions is represented in this signal, and would have been reflected in feedback from this signal (note that subjects in this study did not receive feedback). A) The amygdala signal was cleaned by real-time regression of movement parameters and "censoring" of super-threshold movements, based on realignment regressors. B) Activation from a rectangular control region was subtracted from the amygdala signal (see Paret et al., 2018 for comprehensive description of methods).

Another question regards the specificity of BOLD signal changes. First, the BOLD signal is prone to changes in blood oxygenation that are not related to neural activations, for example produced by changes in respiratory patterns, which need adequate control (see Thibault et al., 2018 for a comprehensive review). Second, although most NF studies use some sort of artifact correction to control for noise, few studies tried to confirm specificity of feedback. It is usual practice to carefully select the anatomical location of a region of interest via a functional localizer experiment and/or anatomical masks. However, the fMRI signal of the whole brain is considerably inter-correlated and only few studies analyze correlations of the feedback signal with brain-wide activations post-hoc. For instance, Ramot et al. (2016) state that feedback-correlated brain activation was indeed not confined to the target region in the fusiform

face area, but was instead widespread and included regions such as thalamus, cerebellum and posterior cingulate cortex. In a recent study, we recorded background noise from a rectangular control region located few millimeters from the amygdala, and subtracted the signal from the right amygdala's BOLD signal. A post-hoc whole-brain regression analysis with feedback as predictor showed strongest correlation of the target region, while left amygdala and two regions in the right and left cerebellum were also correlated (Paret et al., 2018). In conclusion, though feedback is given from a region of interest, the feedback signal is likely not restricted to the anatomical boundaries drawn by the experimenter. Instead, feedback more or less carries information on activation from other regions throughout the brain, beyond the a priori selected target region. In cases of increasing co-activation, feedback becomes more

representative for neural network activity. Conceptually, the difference between regional and connectivity feedback is blurred under these circumstances (Fig. 4). Notwithstanding efforts to yield anatomically precise signal, it is even not clear whether an NF signal with high anatomic specificity (e.g. from the right amygdala only) is superior to a less localized signal. It is even possible that the latter is more helpful for regulation learning, as a less anatomically restricted signal may be more representative of functional networks of interconnected brain regions, and provide greater ecological validity. In future, studies could clarify this matter by providing whole-brain maps of feedback-correlated brain activation in addition to regulation success indices, and with verbal feedback from subjects about the perceived regulation success.

Feedback can be presented continuously or with a delay, and both approaches have been shown to be feasible in allowing participants to learn and to modify their brain response. For some feedback modalities such as dynamic causal modeling (Koush et al., 2017), continuous feedback is not feasible and intermittent/end-of-block feedback turned out to be sufficient for NF training. Only few studies compared continuous and intermittent feedback, and evaluated effects on neuromodulation. Results are inconsistent: two groups stated that continuous feedback was superior for premotor cortex regulation (Johnson et al., 2012) and amygdala regulation (Hellrung et al., 2018), while others tentatively suggest better auditory cortex regulation with continuous feedback (Emmert et al., 2017). In fact, two of the studies did not find significant differences between both types of feedback in primary data analyses (Emmert et al., 2017; Hellrung et al., 2018), and the other study did not report the required statistical group comparison (Johnson et al., 2012). Thus, no clear evidence is currently available on the superiority of continuous or intermittent feedback. Better knowledge of the functional neuroanatomy underlying brain self-regulation could inform decision of continuous vs. intermittent. For example, if the target region shows an event-related response to feedback, it is probably better to give feedback intermittently, because otherwise, NF monitoring may interfere with NF control (Lubianiker et al., 2019).

5.2. Success metrics

The ultimate question for brain self-regulation training is whether the training was successful or not. However, there is currently no established practice of how success is measured. A number of approaches have been taken so far. Some studies have looked at the number of successful trials (Chiew et al., 2012; Koush et al., 2013) an effect size of up/down regulation (Cohen et al., 2016) or a combined index which compared regulation vs. rest activity in the target regions (Cohen Kadosh et al., 2016b; Zotev et al., 2011). Further considerations are whether success is measured by changes in the NF training sessions only or at a follow-up testing appointment. Alternatively, success can be operationalized as improvements in related tasks, i.e. behavioral transfer effects. One could also look at subsequent functional changes in the brain, such as changes in local or global connectivity (Shibata et al., 2011; Zotev et al., 2013; Cohen Kadosh et al., 2016b). Similarly, training effects could be observed at the structural brain level, i.e. in change in white or grey matter.

Assessing NF training success will also depend on the statistical approach. The optimal approach will depend on whether the training consists of a single session or multiple sessions. For a single session, a simple *t*-test or Wilcoxon *t*-test ("fixed threshold") can be used to compare activation during a passive baseline condition (e.g. where subjects were instructed to 'rest') and regulation conditions (Fig. 5A), or between NF-based regulation during exposure to visual stimuli and a "mirror run" (passive viewing of the same/matched stimuli) (Ihssen et al., 2016). However, whereas this measure is straightforward, it is also quite insensitive as it provides binary yes/no answers regarding the question if the NF session was successful or not (Krause et al., 2017). Moreover, global changes in brain signals during training (see above) might mask the true difference between 'rest' and 'regulate' conditions. To overcome this issue, one can perform the same statistical test but with one difference: instead of comparing average brain activity during 'rest' to average brain activity during 'regulate', compare each regulation condition to the previous rest condition. In this case, instead of having a binary score for the session, one can constitute a more fine-grained type of measure we call "success rate" (Fig. 5B). However, this measure is not continuous, as it depends on the number of NF blocks in each session, thus provides fixed levels of success that preclude parametric testing. To overcome the lack of continuity, one could simply calculate the difference (delta) between the mean activity levels in the rest and regulate conditions. In addition to adding continuity, this measure allows for a straightforward interpretation of the results. There are several drawbacks however, as this measure is highly noise sensitive and affected by outliers. Furthermore, it overlooks differences in within-session variance of the signal. For example, while two participants may have equal delta they could differ in the signal variance. Thus, the same delta might not reflect equal performance. One possible solution is the use of a "personal effect
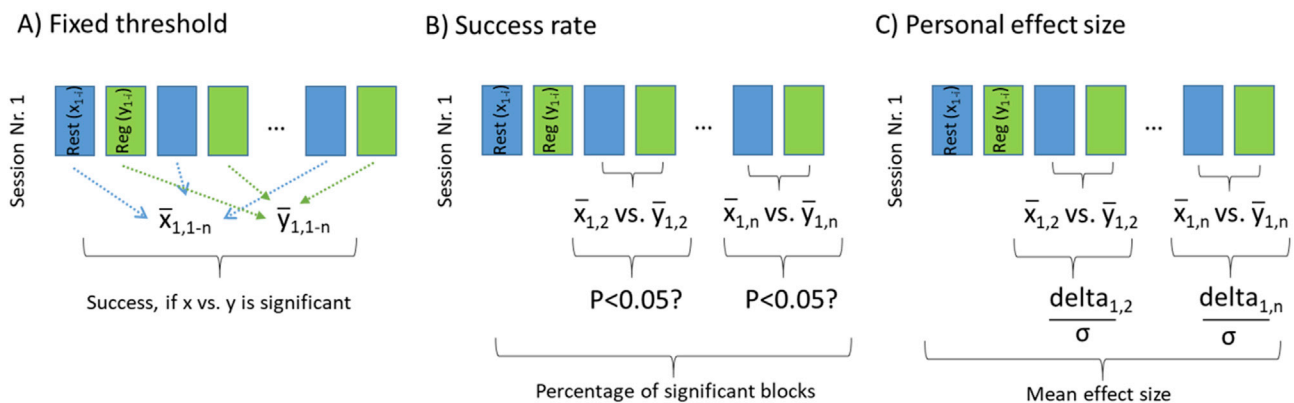

Fig. 5. Illustrates different approaches to calculate success metrics. An experiment of alternating 'rest' (blue) and 'regulate' (reg; green) trials is shown. A 'rest' and subsequent 'reg' trial form together a block-unit. The signal of each trial is congregated for 'rest' (i.e., samples 1, 2, …, i; x_{1-i}) and 'reg' (i.e., samples 1, 2, …, i; y_{1-i}) to result in a mean value (e.g. $\bar{x}_{1,n}$ is the mean of all 'rest'-samples in session 1, block n; $\bar{y}_{1,n}$ is the mean of all 'reg'-samples in session 1, block n). A) For the 'fixed threshold' index, the mean of all samples in 'rest' ($\bar{x}_{1,n}$) and 'reg' ($\bar{y}_{1,n}$) is calculated and passed to a statistical test. If significant, regulation was successful. B) For the 'success rate', 'reg' and 'rest' conditions are compared in a block-wise manner. One receives a statistic for each block showing whether samples in the 'reg' trial differed significantly from the preceding 'rest' trial. The success rate of a session is reflected by the percentage of blocks with significant difference. C) For calculation of 'personal effect size', we take the difference (delta) between the 'reg' and 'rest' mean of each block. To account for differences in signal-variance, one may divide each delta by the pooled standard deviation σ of this block, and receive block-wise effect size estimates. The mean of these is the personal effect size of the session.

Table 4
NF training success indices.

Index Type	Pros	Cons
Single session		
Fixed Threshold; T-test comparing between average 'rest' and 'regulate'	Provides definitive yes/no answer	Does not reflect higher/lower levels of success Threshold is often arbitrary; might cause mislabeling in ambiguous situations Cannot be used to test correlations with outcome measures
Success rate; Based on comparison of 'regulate' to the previous 'rest' condition using a *t*-test. The final result is the sum/ratio of significant 'regulate'-'rest' blocks.	Assesses the consistency of regulation Less arbitrary, avoids mislabeling in ambiguous situations	Ordinal: cannot be used for parametric tests
Personal effect size; Based on difference between means of regulate and rest conditions, divided by pooled standard deviation. The result is the mean of these effect sizes.	Continuous Noise "insensitive"	Instable; Sensitive to block duration and sampling rate
Multiple sessions		
Mean Performance; The average score of the selected success index across all sessions	"global score" of brain regulation ability Contains information regarding all the sessions	Insensitive to temporal dynamics
Last–first session; The delta between the first and last session	Quantifies over all learning progress	Assumes that the last session is necessarily the best one. Ignores additional information from the rest of the sessions
Learning Slope; Linear regression/repeated measures ANOVA with number of session as independent/within-subject factor	Accounts for temporal dynamics Contains information regarding all the sessions	Assumes linear improvement in NF performance, that is not supported by all models of neurofeedback learning (see Sitaram et al., 2017)
Best Performance; The best session/block throughout the NF training	Reflects maximum individual potential	Noise sensitive

size" that divides the "delta" by the pooled standard deviation of 'rest' and 'regulate' conditions (Fig. 5C). This measure is continuous and accounts for differences in individual variance. However, this measure is quite sensitive to the block duration and sampling rate – with greater sampling rate leading to a reduction in variance, thereby making it difficult to compare different designs and interfaces (for a summary see Table 4).

In order to account for global performance throughout the NF training course, there is a need to create an index that would capture NF performance not only during a single session but across the entire training procedure. There are currently few approaches to address this issue: the first option is to calculate the "mean performance", i.e. an averaged success index across sessions. This index assesses the participant's performance in a global manner throughout the NF training and is relatively noise-insensitive. One problem with this approach is that the mean performance index does not take into account whether the participant's performance improves from one session to the next. In order to account for any change in regulation ability, one can use the difference between the first and last session. However, this would only provide an index of change from the first to the last session, which would mask any change throughout the training day, a problem which is more obvious when we consider that some participants will exhibit their best performance during the intermediate sessions of the training, followed by a decrease due to tiredness or boredom (Cohen Kadosh et al., 2016b). One way to access this additional information is to calculate the "learning slope", i.e. the slope of a regression of success index on session number. While this measure may account in the best way for learning dynamics, it suffers from two major drawbacks: first, it assumes that learning follows a linear trajectory, which is an assumption that is not supported in current learning theories. For example, skill learning theory for NF learning predicts rapid initial change in performance and more moderate improvement at later phases (Yin et al., 2009; Sitaram et al., 2017). Secondly, this measure is noise sensitive, meaning that one failed NF session can affect the overall model fit. An additional measure that has different conceptual framing is "best performance". This measure refers only to the best session in the NF training course and might even refer to the best block. The rationale underlying this measure is that it reflects the subjects' best potential of neural regulation. With that, this measure is highly sensitive to noise but prone to outliers (see Table 4). Altogether, it

seems that selecting success indices based on theoretical considerations constitutes a helpful initial starting point. We now urgently require systematic research into the mechanisms that relate to changes in NF learning indices and neural/behavioral outcome measures.

6. Conclusion

Researchers about to design and conduct an NF experiment need to find answers on a variety of questions for which clear guidelines are missing. In the above, we addressed several questions regarding NF procedures and reviewed the current state of the literature. For the selection of brain targets, one should consider aspects such as developmental trajectories in brain development and the functional neuroanatomy of NF learning. Virtual reality interfaces have the potential to increase training efficiency by keeping subjects motivated, yet the specific advantages over more simple interfaces that currently prevail require further study. Whether or not to provide overt strategies for NF regulation is still a controversial question and evidence for clear recommendations is lacking. There are virtually infinite ways to calculate NF signals. Control for nuisance and global brain signals is necessary for reliable NF, but the way in which the brain signal is "cleaned" from other influences can have unintended effects. Calculating both the absolute and relative quantification of BOLD signal change for fMRI-NF is feasible and suitable for training. Moreover, criteria for quantification of neural regulation success are lacking, as are success measures, which are necessary in order to evaluate training efficiency. Here we discuss different success metrics that may help to evaluate and compare training regimes in future. We also addressed options to personalize training regimes and to make training more effective, considering aspects of NF protocols as well as characteristics of persons undergoing training. Therefore, in order to maintain the current momentum in the field and the considerable progress as evident by the ever-increasing number of studies that are being published on NF research, a two-pronged approach will be needed. Specifically, we envision an active basic science approach which systematically strives to explore and optimize NF designs by investigating the effect of methodological, cognitive and psychological factors. Such an approach could also focus on establishing a comprehensive testing protocol that would enable us to compare NF training outcomes across populations and research centers. One crucial step

towards this goal is adherence to reporting guidelines such as the CRED-nf (Ros et al. 2019) in future publications. This first approach would then inform the translational work in the field by providing authoritative guidelines for the design of more effective brain training for cognitive enhancement more generally, and the treatment of clinical populations more specifically.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116107.

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