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Process-based framework for precise neuromodulation

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Functional MRI neurofeedback (NF) allows humans to self-modulate neural patterns in specific brain areas. This technique is regarded as a promising tool to translate neuroscientific knowledge into brain-guided psychiatric interventions. However, its clinical implementation is restricted by unstandardized methodological practices, by clinical definitions that are poorly grounded in neurobiology, and by lack of a unifying framework that dictates experimental choices. Here we put forward a new framework, termed 'process-based NF', which endorses a process-oriented characterization of mental dysfunctions to form precise and effective psychiatric treatments. This framework relies on targeting specific dysfunctional mental processes by modifying their underlying neural mechanisms and on applying process-specific contextual feedback interfaces. Finally, process-based NF offers designs and a control condition that address the methodological shortcomings of current approaches, thus paving the way for a precise and personalized neuromodulation.

The use of functional MRI (fMRI) in neurofeedback (fMRI-NF) has brought new hope to the field of self-guided neuromodulation. fMRI-NF allows individuals to modulate spatially localized neural patterns in real-time, using contingent rewarding feedback. Accumulating evidence suggests that in many cases, attaining significant neural modulations in line with the task protocol (i.e., NF success) is followed by corresponding mental and behavioural changes[1], thus contributing to bridging the gap between brain functionality and our mental experience. Despite this promising prospect, the utilization of fMRI-NF for basic science as well as for clinical purposes has been slower than expected. This may be due to various methodological constraints, such as the lack of proper control conditions and inadequate blinding and randomization, as well as the relatively small sample sizes that characterize the field. Furthermore, brain-guided interventions do not correspond with current psychiatric categorization, which traditionally relies on subjective reports rather than on neurobehavioral substrates[2,3]. Together, these limitations have hampered tangible conclusions regarding the clinical relevance and efficacy of fMRI-NF[4–6].

It is generally acknowledged that, to improve precision and efficacy of psychiatric treatments, new insights regarding the psychological and neural substrates of maladaptive behaviours should be incorporated into the conceptualization of mental disorders[7,8]. Such insights imply that the brain is functionally organized around several neural circuits that subserve perception, motivation, cognition, emotion, and social behavior[9–12]. In line with this, we put forward a new framework termed 'process-based NF', which suggests that NF interventions should target specific dysfunctional mental processes by modifying their underlying neural mechanisms (Fig. 1a–c).

A crucial organizing principle in process-based NF is that a correspondence should be established between different aspects of the intervention (neural target, feedback interface, outcome measures, and study population) and a specific, functionally defined mental process targeted for modulation, which in turn should generate exact, evidence-based predictions of clinical efficacy. This principle of correspondence and its benefits can be exemplified with the case of NF treatment for major depressive disorder (MDD). In common practice, the main outcome measure for MDD treatments is symptom severity (for example, Dekte et al.[13] and the Hypericum depression trial study group[14]). However, MDD is in fact a clinical syndrome comprised of various distinct groups of symptoms, including mood and motivational dysfunctions (for example, anhedonia), cognitive rumination, anxiety, and abnormal sleep patterns[15]. Importantly, each of these classes of symptoms is associated with a distinct mental process and its associated neural mechanism[16]. By targeting an impaired mental process, such as deficient approach motivation (which is thought to underlie anhedonia), rather than overall depression severity, it is possible to match the intervention's neural target for modulation—for example, certain features of the extensively investigated mesolimbic reward system[11,17,18]—with specific hedonic outcome measures. For the latter, one could apply a subjective report questionnaire of hedonic experience (for example, the Snaith–Hamilton Pleasure Scale[19]) and objective measures of responsivity to reward (for example, the monetary incentive delay task[20]), both known to be specifically mediated by the targeted mesolimbic circuit[21,22]. Furthermore, for the sake of clinical precision, a process-based approach also calls for a shift in the current focus from supposedly pure diagnostic

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Fig. 1 | Process-based NF framework. Three principal elements of process-based NF interventions: functional process and neural target selection; feedback interface; and outcome measures. **a**, Three functional processes, associated with three distinct neural targets (represented schematically): cognitive control (blue), approach motivation (green), and potential threat (brown). Varying greyscale intensities indicate differential involvement of each process in three *Diagnostic and Statistical Manual* categorical disorders: substance use disorder (SUD), MDD, and specific phobia. **b**, Feedback interfaces adapted to correspond with the targeted process, via process-specific multimodal stimuli. In the illustrated example, a participant is navigating a supermarket scenario in VR. For cognitive control deficit in the context of SUD, feedback is displayed through addiction-related appetitive cues that change in size in proportion to modulation of cognitive control network activity. For deficient approach motivation in MDD, a rewarding smiling face of a sales assistant alters in proportion to modulation of the reward mesolimbic circuit neural activity. For potential threat dysfunction in specific phobia, a phobia-related cue changes in size in proportion to modulation of the threat neural circuit activity. **c**, Subjective and objective outcome measures that correspond with the targeted process. For cognitive control deficit, the Conners impulsivity scale and a go/no-go task. For deficient approach motivation, the Snaith–Hamilton Scale (SHAPS) is used to measure hedonic experience and reward responsivity is measured by the monetary incentive delay task. For potential threat, the subjective unit for distress scale and the no shock–predictable shock–unpredictable shock (NPU) task are used.

Diagnostic and Statistical Manual[15] or *International Classification of Diseases*[23] grouping criteria. For instance, when targeting deficient approach motivation, a clinical study could include MDD patients that specifically suffer from anhedonia, as well as individuals without a formal diagnosis of MDD who nevertheless exhibit substantial hedonic deficits, such as patients with Parkinson disease, substance use disorders, or schizophrenia[24–26].

In this Perspective, we attempt to delineate the process-based approach for NF by associating it with various central aspects of the intervention. We begin by addressing the manner in which psychological processes and their underlying neural mechanisms may be ideally targeted and modulated. Following this, we discuss possible ways to optimize process targeting via feedback interface adjustments. Finally, we discuss the NF general processes and offer possible designs and a new control condition for dissociating between NF-general task effects and those specific to the targeted process modulations. We assert that by applying such process specific modifications, the NF field could offer a brain-guided psychiatric intervention with greater scientific validity and enhanced efficacy.

Process-based neural targeting

Accumulating evidence from human neuroimaging studies suggests that psychiatric disorders share common trans-diagnostic structural and functional impairments in neural networks[9,27–29]. In accordance with this notion, a substantial body of work has demonstrated that network-level patterns, rather than focal neural patterns, encode core mental processes. For instance, emotion regulation is thought to be characterized by interplay between core limbic or salience circuits and regulatory prefrontal sets of regions[30], rather than by isolated amygdala or prefrontal cortex (PFC) activity. Likewise, inhibitory control, a dysfunctional process in attention deficit hyperactivity disorder[31] and substance use disorder[32], was suggested to be linked with a set of frontoparietal networks rather than with a specific brain area such as the inferior frontal gyrus[33]. Moreover, recent works using multivariate analyses have shown that subjective experiences and mental states that relate to various pathological conditions are associated with distributed neural activations. This was recently demonstrated in pain[34,35], sustained attention[36], and negative affect[37]. It follows that the dysfunctions of neuropsychological processes in psychiatric syndromes are mediated by distributed, network-level abnormalities, rather than focal impairments[9].

Interestingly, network-level functional changes were shown to occur following single-region fMRI-NF. For example, several studies have demonstrated that PFC and amygdala connectivity was altered following amygdala downregulation NF[38–40]. Likewise, Cohen-Kadosh et al.[41] found that insula fMRI-NF subsequently resulted in functional connectivity changes in an emotion-regulation network. These results indicate that regulation of a single region, based on the classic univariate analysis of blood-oxygen level dependent (BOLD) activity, may conjointly lead to a distributed neural change. Hence the clinical efficacy of fMRI-NF interventions targeting single regions may result from widespread network-level changes (for example, connectivity of the regulated region with other regions or networks), rather than from restricted alterations in the targeted region of interest. Considering these points, we posit that NF interventions should target brain networks (i.e., activity or connectivity indices) or distributed patterns that specifically mediate dysfunctional processes, as outlined below.

Brain network matrices. Various NF targets have been previously applied to modulate network-level functionality, such as functional connectivity between two or more brain regions[42–45], as well as more complex network dynamics indices (for example, dynamic causal modelling NF[46,47]). For instance, Yamada et al. attempted to alter dysfunctional hyper-connected patterns of the default-mode and frontoparietal networks by training participants to decrease functional connectivity between the posterior cingulate cortex and dorsolateral PFC, two respective key hubs of these networks[44]. Such practice resulted in a decrease in depressive symptoms, as measured with the Hamilton Depression Rating Scale, which was correlated with NF success. A different network-NF approach was recently developed by Jacob et al.[48], which trained participants to modify a central region's influence on an entire functional network. Results demonstrated the feasibility of facilitating changes in network functional hierarchy via NF training.

Another method that efficiently measures the neural substrates of mental processes is multivariate or multivoxel pattern analysis (MVPA). MVPA captures neural information that is distributed over many voxels or regions in the brain. It has been used extensively in the attempt to decode mental states from brain activation[49,50], and more recently it has been implemented in real-time imaging[51] and specifically in NF (in decoded neurofeedback, DecNef)[52,53]. Key assumptions of DecNef are that neural patterns that are congruent with a mental state can be manipulated and that the endogenous modulation of a mental state should lead to corresponding mental and behavioural changes. Hence this method may serve as a good surrogate for process-based NF (for a detailed review on DecNef applications see refs. [44,54]). So far, DecNef has been applied to induce perceptual[53], cognitive[55], and affective modifications[56] in healthy individuals. More recently, this concept was clinically applied to individuals suffering from specific phobia[57]. In this study, a neurotypical activity pattern in the ventral temporal area was first calculated based on data from healthy individuals that were exposed to aversive stimuli, representing adaptive emotional processing. Subsequently, participants diagnosed with specific phobia, exhibiting atypical responses to aversive stimuli, were trained to modulate their ventral temporal activity to resemble the predefined neurotypical voxel-wise pattern. Notably, this was achieved via an implicit learning procedure, associating desired changes in activity with positive reward cues, without exposing the patients to the object of their phobia.

Notwithstanding the above, process-based neural targeting may present several challenges. First, it is noteworthy that regulating complex distributed indices requires high signal reliability. To this end, using functional localizer tasks to better target individual network nodes (possibly in combination with predefined anatomical or meta-analytic derived masks) could improve precision of network indices and consequently enhance signal reliability. In the case of dynamic causal modelling-based NF, sufficiently long time windows should be used for the assessments of the different models, to enable precise feedback regarding network causal relationships. Such requirement might be met via intermittent feedback protocols. Another issue revolves around the scalability of the process-based intervention. fMRI holds a critical advantage over other recoding techniques for targeting defined neural mechanisms: its superior spatial resolution. Yet its limited accessibility might hamper fMRI-NF clinical translation. Electroencephalograms (EEG), on the other hand, are cost-effective and mobile. However, due to poor spatial resolution, EEG's ability to target functional processes associated with distributed cortical as well as subcortical areas is severely limited. Hence a measuring tool that offers both precise localization and high accessibility is greatly needed for the applicability of process-based NF (Box 1). Another issue that arises when targeting processes for modulation is the consideration of subjects' developmental stage[58,59], i.e., whether one should attempt to modulate brain regions associated with a cognitive process at the specific developmental stage or simply target the brain networks associated with a given process in healthy mature adults. This is especially important if one considers the developing brain as an adaptive system, in which brain networks that support cognitive abilities change interactively as a result of ongoing brain maturation and cognitive development[60,61]. Finally, although theoretical considerations suggest the

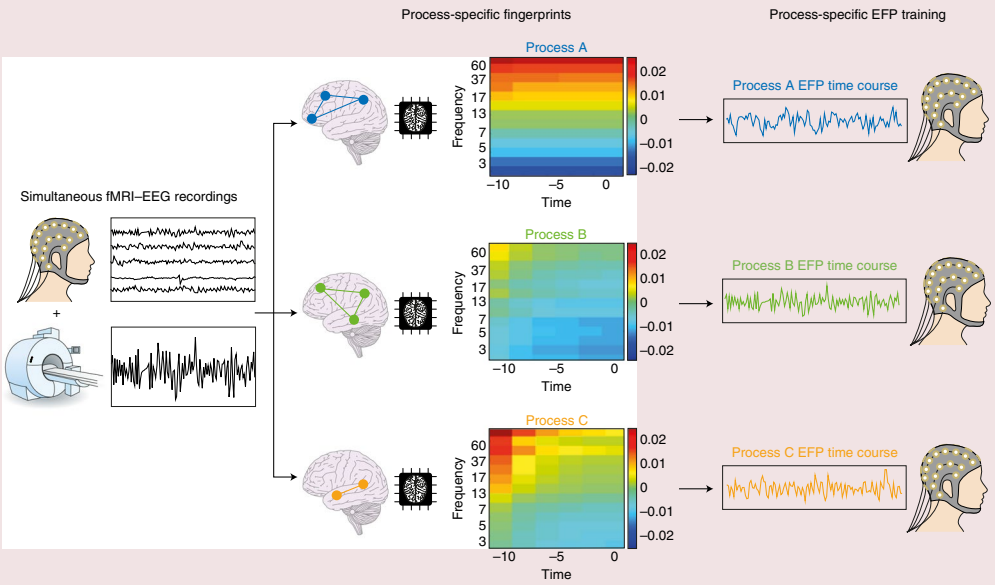
Box 1 | Process-based NF accessibility

EEG is an accessible and widely used NF recording device. However, it does not allow precise signal localization. Recent computational advancements have been used to overcome this issue by enhancing the spatial resolution of EEG recordings. These included low-resolution electromagnetic tomography (LORETA)[108] or its variants[109]. However, LORETA necessitates the use of a dense grid of electrodes, limiting its mobility and accessibility, while being highly sensitive to noise, particularly for deep subcortical areas[110]. Other approaches have used fMRI to improve EEG localization in an attempt to develop a forward model that traces neuronal activity from both recording channels[111]. However, such a model-based approach relies on somewhat unsubstantiated a priori assumptions regarding the biophysical origins of the EEG and fMRI signals. To overcome this, data-driven approaches were applied to associate the two signal-types[112], using either simple correlations between EEG frequency bands and localized BOLD activity[88,113,114] or linear regression in which a combination of frequency bands predicts BOLD activity, which showed improved results[115].

A general framework adopting the linear regression approach was recently developed using signal-processing and machine-learning techniques, based on temporal and frequency analyses. This approach, termed EFP, successfully predicted fMRI BOLD activations in the amygdala and medial prefrontal cortex using only EEG data from single channels[66,116]. Furthermore, the amygdala EFP model was used in a NF design, yielding the first ever EEG-NF intervention that enabled precise modulation of a subcortical region[78,117,118]. Results from a validation experiment demonstrated that participants who were trained outside the fMRI scanner to downregulate their amygdala EFP index not only successfully decreased amygdala BOLD activity during fMRI-NF in a following session but also showed reduced amygdala reactivity to threatening visual stimuli[117]. More recently, this method was applied in two studies, one involving healthy individuals undergoing a stressful military training program[119] and one involving chronic pain patients[120]. Results indicated that repeated amygdala EFP training sessions had a beneficial effect on neural and behavioural indices of stress resilience and chronic pain symptoms, respectively.

This method and others that may follow hold important advantages for process-based NF over existing techniques. Most importantly, they combine the strengths of EEG and fMRI, providing both high accessibility and precise spatial localization. From a clinical perspective, the studies presented above pave the way for the development of additional 'fingerprints' for various target regions (for example, see Klovatch-Podlipsky et al.[121], which present a right inferior frontal gyrus electrical finger print (EFP) model development), network-level indices, or multivoxel-based patterns. Furthermore, to maximize process targeting, various improvements of the feedback interface could be introduced, including the use of immersive virtual reality (VR) technologies that simulate highly naturalistic environments that facilitate improved learning, generalizability, and process-specificity (discussed in detail below). Many of these beneficial modifications are more suited to portable recording devises such as EEG than to the restricting clinical setting of magnetic resonance scanning.

However, the EFP approach contains some limitations. First, it does not monitor a specific region exclusively, but rather a set of regions that are co-activated along with the traced region. For instance, when examining the BOLD correlates of the amygdala EFP in an EEG–fMRI experiment, it was found that the EFP was associated not only with the signal fluctuations within the amygdala but also with additional functionally related regions[117]. Second, even though an EFP model was developed and validated for BOLD activations in a single region, fingerprinting more complex neural indices (for example, MVPA, network connectivity, etc.) might prove to be more challenging in terms of susceptibility to movement and/or physiological artefacts or other factors influencing signal to noise ratios. Future empirical work is expected to demonstrate whether reliable fingerprint models for such indices are feasible. Finally, it is assumed that an EFP index is a correlate of BOLD activations in a specific target region. However, this raises the question of whether an EFP model can be generalized to multiple contexts (for example, NF task, clinical outcome tasks, resting state scans, etc.). Future studies should provide evidence for the generalizability of the model across various functional datasets.



Development of process-specific electrical fingerprints. A functional dataset of simultaneous EEG-fMRI recordings is collected. Subsequently, machine-learning algorithms are applied on the data to extract EEG features that correspond with the defined BOLD neural patterns of each target process. Based on these BOLD-predicting features, a scalable and process-specific NF training is enabled using only EEG. For detailed information regarding the EFP model development, see Meir-Hasson et al.[64,106].

superiority of network-based or distributed-pattern-based NF over single-region NF interventions, it is yet to be established that such indices may indeed lead to improved NF modulations and enhanced clinical outcomes. Future studies should thus compare between network NF and single-region NF in terms of modulation success and clinical benefits.

Process-based feedback interfaces

The feedback interface forms the environmental setting of the intervention. To date, the majority of NF studies have used simple forms of interfaces solely to indicate the level of neural activity change (for example, thermometer[62,63], a visual analogue scale[64,65], or sound[66,67]). These interfaces are usually one-dimensional (size or height; volume or pitch), unimodal (visual or auditory), and affectively neutral. Therefore, they hardly evoke a specific process by themselves. In contrast, process-specific adjustment of the feedback interface can considerably contribute to the targeting of dysfunctional processes in two ways: (i) by inducing an environmental context in which deficits are typically expressed, individuals may be guided to practice process-relevant strategies in situations similar to those they naturally struggle with, but in a safe and controlled clinical setting; and (ii) as the underlying neural mechanisms one is trying to alter are dysfunctional, provoking them in a process-specific manner might assist in recruiting them and thus promote the desired neurobehavioral changes. Consequently, process targeting may become more precise, ecological, and clinically effective. In an attempt to promote such an approach, we discuss possible modes of context induction: the incorporation of multimodal contextual cues into the interface and the utilization of immersive feedback interfaces (Fig. 1b).

Contextual interfaces. Several NF studies have incorporated process-specific contextual cues into a neutral feedback interface, creating an emotional context for affective processes[38,68–70]. Paret et al.[69] trained healthy participants to downregulate their amygdala, a region involved in emotion processing and regulation, while viewing aversive photos with a thermometer indicating the level of neural activity from both sides of the image. Participants successfully regulated amygdala activity, and furthermore, NF success was correlated with post-practice amygdala regulation with no feedback (i.e., transfer effects, which indicate the generalization of acquired regulation skills). In two clinical studies, patients with borderline personality disorder and post-traumatic stress disorder (PTSD)[39,40] practiced amygdala downregulation while watching affective stimuli (pictures with affectively disturbing content or trauma-related words, respectively). Both groups exhibited widely distributed neural changes along with reduced dissociative symptoms.

Other than using process-specific contextual cues along with a neutral feedback display (for example, a thermometer), the feedback itself could represent the neural changes in a process-specific manner. For example, Sokunbi et al.[71] and Ihssen et al.[72] employed 'motivational feedback' interfaces, in which participants are presented with reward-related stimuli (for example, appetizing food) that change in size in proportion to BOLD fluctuations in regions involved in motivational aspects of craving. Hence the attempt to up- or downregulate neural activity in itself facilitates process-specific motivational consequences. A similar approach might be taken with an 'emotional feedback' interface. Even though evidence of efficacy is still scarce, we can cautiously assume that if the undesired patterns of an affective neural target were represented by an aversive emotional feedback, participants may be specifically motivated to downregulate it. This might be true not only due to contextual affective induction, but also as successful regulation results in attenuation of the aversive feedback. Furthermore, since affective interfaces may facilitate a stressful or unpleasant context that resembles process-relevant real-life situations, the acquired neural regulation skills may therefore be better generalized. Conversely, one could argue that such approach might encourage maladaptive avoidance tendencies that are inherent to the psychopathology, as is the case in obsessive–compulsive disorder and PTSD. A possible solution for this issue could be altering the content of the stimuli rather than its size or simulated distance from the trainee. For instance, in the case of motivational feedback for substance use disorder, alcoholic beverages could be gradually replaced with soft drinks.

Importantly, both modes of context induction are particularly relevant for the modulation of neural 'hubs' that underlie several processes (for example, insula, amygdala, etc.). For instance, Young et al.[73] employed a hedonic-related context (via instructions: retrieving positive memories) to guide amygdala upregulation for MDD patients with hedonic deficits. Alternatively, by incorporating negative affective stimuli cues into the interface, the amygdala was targeted for downregulation both for PTSD[40] and borderline personality disorder[39] patients. Further research should try to reveal in which cases could neural hubs that are involved in several processes be provoked in a process-specific manner via different types of context induction.

Aside from contextualizing the feedback interface, other feedback interface factors may be harnessed for process induction. These include the utilization of different feedback protocols for process targeting (Box 2) as well as NF task instructions (i.e., providing participants with suggestions for specific process-related imageries)[74,75].

Immersive interfaces. Recent applications in the rapidly evolving fields of VR and augmented reality (AR) may be used to simulate highly naturalistic environments enriched with process-relevant cues. Unlike the common one-dimensional and unimodal feedback, three-dimensional game-like interfaces enable presentations of multimodal dynamic stimuli[76] that may improve learning and user experience[77]. Cohen et al. directly compared a unimodal thermometer with a multimodal game-like NF interface and showed that the latter indeed resulted in improved learning, generalizability, and user experience[78]. Mathiak et al. compared simple visual feedback (a bar) with VR-based social reward feedback (a smile on an avatar face that is altered as a function of dorsal anterior cingulate cortex BOLD activity); results demonstrated that the VR interface induced increased target engagement and promoted learning[79]. Notably, immersive VR and AR environments allow substantial flexibility in context representation[80], which may be highly beneficial in certain cases. For instance, people suffering from dysfunctions in threat processing (for example, social anxiety disorders, PTSD, etc.) could be trained by associating their experienced virtual environment with their neural state, such that gaining control over threat-related neural targets would result in a more tranquil simulated environment that corresponds with their specific phobia (social- or trauma-related, etc.). This could further strengthen adaptive behaviours, for example, approach towards phobia-related cues (Fig. 1b). Such applications correspond with the growing practice in psychiatry of applying VR environments in exposure procedures, mainly for the treatment of PTSD and phobias[81–83]. Several studies have used VR or AR to create process-specific contexts in the treatment of psychiatric and neurologic disorders[84–86], demonstrating the feasibility of applying such therapeutic interventions. Yet these studies serve as small-scale proofs-of-concept that rely on EEG frequency bands with poor localization. Hence further research is needed to realize the full clinical potential and efficacy of VR and AR technologies for NF training in general and within the process-based framework specifically.

Process-based NF specificity

To determine NF treatment specificity, the effects resulting from modulation of a specific target process must be differentiated from those of mere NF practice. To this end, five types of control conditions have been applied thus far: (i) alternative NF, providing feedback from an alternative region; (ii) inverse NF, modulation of the

Box 2 | NF interface protocols

The most common form of a NF task is explicit (participants know they are receiving neural feedback and are given explicit task instructions) and continuous (i.e., feedback is calculated for each acquired functional brain volume and presented to the participant in real-time). Nonetheless, NF protocols vary in these important aspects, which may be used for process targeting. First, NF interventions may be explicit or implicit to the subject. During an experiment using an implicit feedback protocol, participants receive rewarding feedback without conscious knowledge of its origin and without instructions for regulating it. Instead, they may either passively watch these target-contingent cues or conjointly perform an unrelated simple task (for example, a button-press). These features have the appeal of avoiding confounds of effort and of other cognitive demands. Importantly, such confounds are critical specifically when trying to dissociate effects deriving from neuromodulation of attentional and executive functions (for an elaboration, see Fig. 3a). Moreover, implicit NF may be more suited to certain pathological conditions in which participants' cognitive resources are limited, such as severe attention deficits, dissociative tendencies, or young or aged populations. On the other hand, one of the advantages of NF is the possibility of using it to reinforce specific imageries in patients[122]. To achieve this, explicit feedback presentation combined with patients' awareness of the contingencies between neural activation changes and rewarding feedback is necessary. Arguably, such explicit training may support patients' ability to generalize their applied strategies to real-life situations. Furthermore, as explicit NF protocols demand patients' active participation in the therapeutic process, they may promote participant engagement and possibly increase adherence to the therapeutic intervention. Finally, the use of contextual feedback interfaces (discussed here under "Process-based feedback interfaces") may elicit awareness of the nature of the feedback, rendering it overt. This point should be taken into consideration when tailoring NF designs for processes and pathological conditions that require covertness. Initial evidence has indicated that in some cases, implicit feedback protocols are effective[43] and possibly preferable to explicit ones[123] (i.e., explicit task instructions may be counterproductive), while in other cases explicit designs were found to facilitate better results[124]. Future studies using implicit and explicit feedback protocols for different target processes should provide empirical evidence for these still-speculative pros and cons.

Another aspect that varies between NF designs that could be meaningful for process targeting is the timing of feedback presentation. Instead of the common continuous NF protocol, several studies have applied an intermittent design, in which participants are presented with feedback once every few acquired functional brain volumes or solely following the actual NF regulation block (for example, refs. [46,64,125]; see Fig. 3a for an example time course). Intermittent feedback protocols hold the potential of minimizing reward-related confounds, which becomes particularly important when trying to determine specificity when targeting motivational processes (Fig. 3a). Furthermore, one can assume that the practice of process-specific imageries that require internally rather than externally oriented attention might benefit more from an intermittent rather than a continuous feedback, since constantly tracking and processing dynamically changing stimuli might be distracting. In such cases, less information might allow better learning. This was recently demonstrated for motor regions[125] and for amygdala downregulation[126]. In the case of NF interventions for tinnitus, however, differential effects were observed: while intermittent feedback facilitated better regulation after a single session, continuous feedback was more effective for multisession interventions[64]. Moreover, even though artefact removal algorithms are applied on the data in real-time, continuous feedback is more affected by physiological and movement-related noise than the intermittent feedback, which is averaged over several functional time points, thus reflecting neuronal activity more reliably. This may be particularly important for complex indices such as network connectivity, MVPA, or dynamic causal modelling. Conversely, continuous feedback tends to be more engaging and interactive, an important feature for treatment adherence in general and especially for young populations. In addition, continuous feedback presentation might prove to facilitate a more ecological and coherent measure for mental experiences, which unfold in seconds-long time scales and may change rapidly.

These deliberations regarding the link between process targeting and feedback protocols still await further empirical evidence. Nonetheless, in face of the pros and cons debated here, the choice between implicit-versus-explicit and continuous-versus-intermittent NF protocols should take the wider therapeutic context of the intervention into account to maximize process targeting.

experimental neural target in the opposite direction; (iii) yoked sham NF, presenting participants with sham feedback recorded from a matched subject from the experimental group; (iv) mental rehearsal, applying mental strategies with no feedback presentation; and (v) no treatment, a natural history control condition[4]. We note that there is a tendency to evaluate novel interventions such as NF according to the experimental standards of pharmacological randomized controlled trials. However, this is misleading, as pharmacotherapeutic placebo interventions affect only the underlying mechanisms of non-specific affective processes, generally in the same manner as the real drug[87]. Active NF control conditions, on the other hand, manipulate sensory, cognitive, and affective aspects that may introduce two main classes of confounds: (i) modulations of additional processes that are not engaged in the experimental intervention and (ii) modulations of NF-general processes that substantially vary from the experimental intervention. To eliminate these confounds, NF control conditions must involve the same general processes modulations as those of the experimental condition, without any additional processes engagements (Fig. 2).

Converging evidence from various animal and human studies[46,82,83,88] indicate that fMRI-NF involves three general processes[1]: (i) control: applying different mental strategies in the attempt to modulate the presented feedback, associated with the lateral occipital cortex, posterior cingulate cortex, and dorsolateral PFC; (ii) reward: valuation of positive or negative outcomes of applied strategies, associated with anterior cingulate cortex, anterior insula, and ventral striatum; and (iii) learning: the consolidation of associations between rewarding feedback cues and a desired neural activity pattern (or specific mental imageries), which may occur through operant learning mechanisms that involve the dorsal striatum. A recent meta-analysis by Emmert et al.[89] revealed a network of regions activated during NF practice regardless of a specific neural target, composed mainly of prefrontal, mesolimbic, and striatal regions. This network corresponds with the underlying mechanisms of NF-general processes mentioned above and may be considered a general network of fMRI-NF. However, studies investigating NF general processes are still scarce and have yet to resolve disagreements between different NF learning models (for example, skill learning versus operant learning; see ref. [1]). Notably, Paret et al.[90] employed amygdala fMRI-NF and succeeded in dissociating feedback congruency monitoring (i.e., tracking feedback

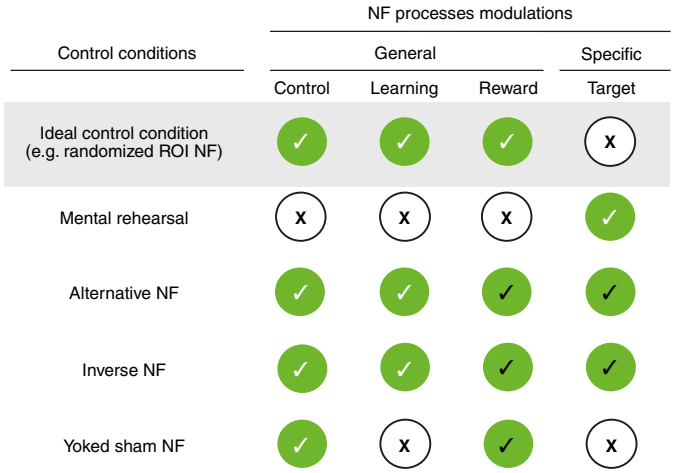


Fig. 2 | NF control conditions from a process-based perspective. Each control condition is characterized by the manner in which it manipulates the NF-general processes and by whether it also manipulates a distinct target process (far-right column). Green circles with a white check mark indicate a process modulation that is similar to the experimental condition; a black check mark indicates a process modulation that varies from the experimental condition; white circles with *x* marks indicate no process modulation. The ideal control condition (marked in grey) should manipulate the general task processes in the same manner as the experimental condition, without specifically modulating any other target process, as may be accomplished by the suggested randomized ROI NF condition.

correspondence with task instructions; associated with the ventral striatum), feedback context monitoring (i.e., responses to differing task instructions; associated with rostral PFC), feedback activity monitoring (i.e., general feedback fluctuations; associated with thalamus and ventromedial PFC), and other task-related activations (including insula, anterior cingulate, and lateral PFC), thus providing a more intricate map of NF underlying mechanisms. Importantly, different NF protocols (Box 2) vary in their manipulations of the general task processes. These differences could be capitalized to investigate the NF underlying mechanisms and to advance a more precise understanding as to which of the NF general processes hold unique contribution in terms of modulation success and clinical benefits. Figure 3a presents two protocols that may be used to isolate reward and control processes. NF learning, however, presents a more complex challenge, as multiple learning processes may co-occur during NF[1]. One design that may unravel the involvement of stimulus–response contingencies in NF learning (the stimulus being the contingent feedback and the response being the neural target activations) could be an implicit NF design that excludes the voluntary use of regulation strategies, in which stimulus–response contingencies are varied between conditions via differential feedback timing protocols: a continuous condition, an intermediate intermittent condition (in which feedback is presented once every few functional time points), and a fully intermittent condition.

Dissociating NF-general from target processes. As Fig. 2 shows, confounds of both NF-general and additional processes are particularly relevant to inverse NF and alternative NF. First, these control conditions involve not only NF-general processes but also an additional target process that is not manipulated in the experimental condition. Second, some targets are inherently harder to modulate than others[91], as has been shown to occur in many cases[90,92–94]. Differences in 'modulability' between experimental and control neural targets incur discrepancies in task difficulty and, as a result, in the level of reward participants receive. An indication of both confounds has been recently shown by Alegria et al[94]. This study controlled for right inferior frontal gyrus fMRI-NF intervention for attention deficit–hyperactivity disorder patients, with alternative NF to the left parahippocampal cortex. Specifically, this alternative NF group exhibited increased activations in bilateral parahippocampal cortex, right supplementary motor area, and additional frontotemporal regions involved in various motor and cognitive functions[95–97], which were not activated in the right inferior frontal gyrus NF group. Moreover, substantial differences between conditions were exhibited both in the absolute value of NF success (the level of positive feedback differed between groups) and in transfer effects, possibly leading to confounds of reward processes. Consequently, treatment efficacy cannot be specifically attributed to the target process engagement with such control groups.

In contrast, yoked sham NF only manipulates NF-general processes, but in a different manner than the experimental condition. First, the lack of contingency between feedback and neural patterns could lead to major differences in NF reward processes, as participants may deduce they are not receiving veritable feedback[98] and thus may reduce their motivation, task engagement, and positive expectations in relation to a genuine feedback group. Second, even when matching feedback variability between groups by 'yoking' in a double-blinded manner, there would still exist differences in NF learning, as no learning based on contingencies between neural patterns and feedback would occur. Corresponding to this last confound are the models of NF learning that stress the importance of associative (i.e., Hebbian) learning mechanisms that rely on contingencies between stimulus and response. Thus, yoked-sham NF also cannot isolate the hypothesized factor.

Finally, mental rehearsal control does not tease apart the specific effects of the neural target modulations, but rather the additive value of the interface and feedback presentation themselves. A no-treatment control may be useful for determining whether there are clinical effects that justify further investigations, but it does not isolate any non-specific effects.

On top of these condition-specific confounds, two general confounds may occur that could possibly be dealt with. First, it is known that subjects vary in their ability to regulate brain activation. These individual differences in NF learning capabilities may be predicted via behavioural[99], functional[100,101], or anatomical[102,103] indices and therefore should be taken into consideration when allocating participants to study groups. Second, a unique methodological issue arises when specifically targeting the NF-general processes for modulation (for example, reward[93,104,105] and control[94,106,107]). Such targets are even more problematic to control for, as they are recruited by the mere performance of a NF task, with every possible matched control involving the target process (for a possible solution, see Fig. 3a).

Hence it appears that each of the four common NF control conditions consist of process engagements that do not allow for the disentanglement of target from NF-general effects. An ideal control condition requires a genuine NF intervention that manipulates the same general processes, but without any specific modulations over and above the general NF processes (Fig. 2). In line with the process-based framework, we suggest a control condition that should produce such a psychophysiological state, termed 'randomized region of interest (ROI) NF' (Fig. 3b). In a randomized ROI NF group, participants would be randomly allocated to one of several subgroups of different target processes. The resulting group, matched in numbers of participants to the experimental group, would have participants modulating the NF-general processes with authentic feedback, just as in the experimental group, but with the specific effects of the different neural targets averaged out across all subgroups, as each would receive a different neural target to regulate.

This may lead to the cancelling-out of confounds related to additional processes modulations. Nonetheless, the same reward-related modulability confound that affects alternative NF and inverse NF

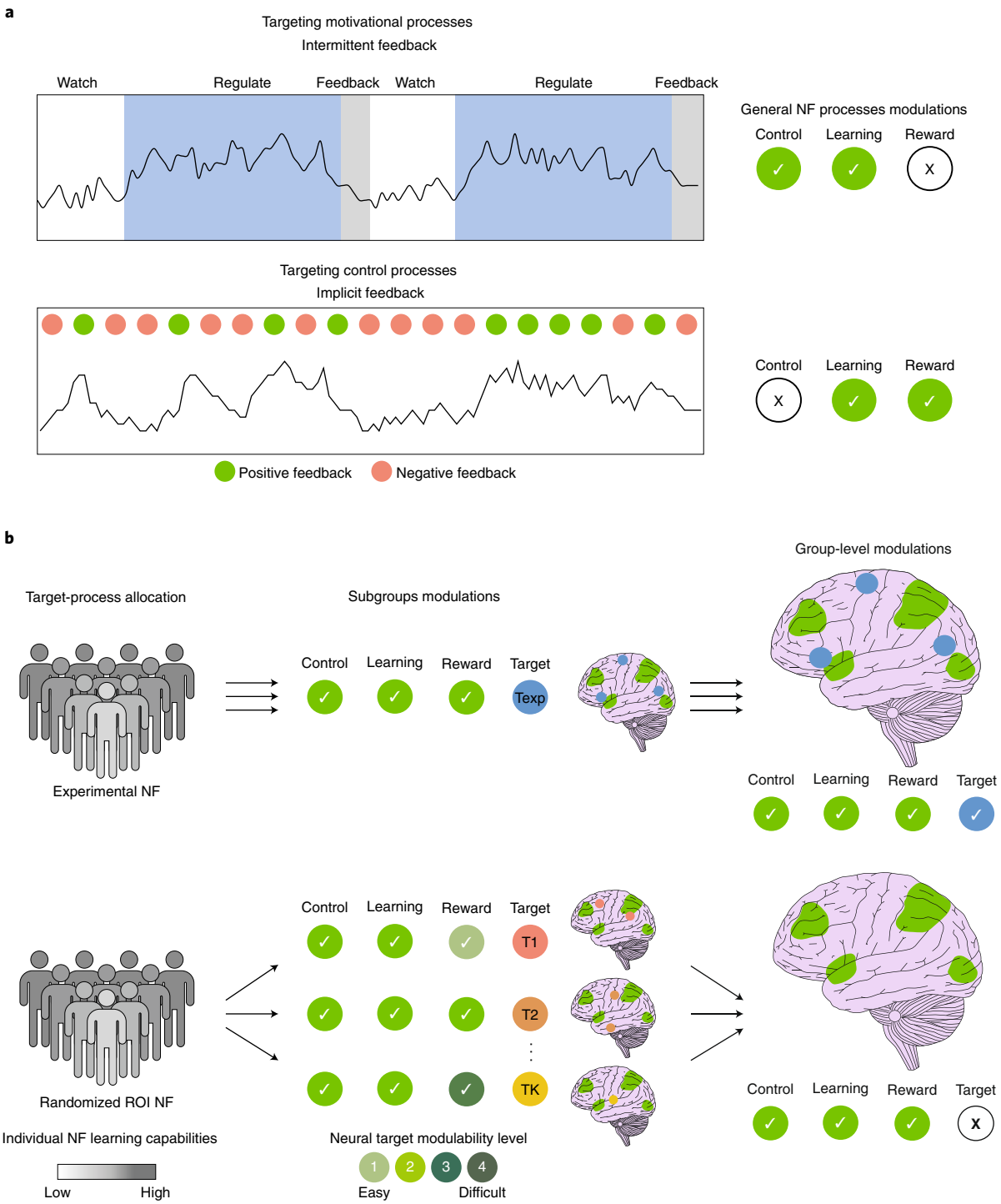


Fig. 3 | Process-based experimental designs. a, Differentiating NF general processes. To distinctly target motivational processes without contaminating control conditions with the target process, one may employ an intermittent protocol, which excludes rewarding feedback from the regulation phase and presents it in a separate feedback block. Thus, neural activation during the 'regulate' screen should be specific to the targeted process in each group. Similarly, targeting attentional or executive functions entails an implicit NF protocol[43,55] that reduces recruitment of cognitive resources in relation to standard explicit NF protocols, thus preventing, to a substantial extent, the contamination of control conditions with such target processes. These protocols may serve both in clinical settings that aim to determine specificity and in basic investigation of NF underlying mechanisms. **b**, Randomized ROI NF control condition. In randomized ROI NF, each participant is randomly assigned to one of *K* subgroups of different target processes (red, brown, and yellow). While in each subgroup a specific neural target is modulated along with the general task processes (green), group-level modulations (right panel) include only the averaged mutual general processes (with no specific target process). Conversely, in an experimental NF group, all participants modulate both the general and target processes (green and blue, respectively). Therefore, group-level modulations include both the general and the reoccurring target processes. Consequently, by comparing both groups, target-specific effects could be teased apart from the general NF effects. To prevent reward-related confounds, modulability levels of randomized ROI NF targets should be as similar to the experimental target as possible, to the extent that current literature suggests. Similarly, to avoid undesirable learning discrepancies, allocation into study groups could be counterbalanced with respect to predicted individual learning capabilities.

should apply here. However, in randomized ROI NF, this confound is moderated by the same concept of averaging out varying task effects between subgroups. While each subgroup may differ in its reward modulations, the overall group reward modulations should average to the mean level of all selected targets. It follows that differences in reward modulations between an experimental target NF and a randomized ROI NF group would be restricted to the difference from a mean reward modulation value, corresponding to the mean level of task difficulty. This contrasts with alternative and inverse NF that may coincidently produce large and unaccounted-for reward-related differences, as shown above. Hence given no prior knowledge on targets modulability, randomized ROI NF should yield a preferable psychophysiological state in terms of general NF processes modulations.

Moreover, future methodological studies could provide essential information on NF targets modulability in two ways: one, different neural targets may be directly compared to one another, as has been recently demonstrated for NF to visual areas[91]; second, modulability of different neural targets could be inspected in a meta-analysis or a critical review, by assessing NF success across all applied neural targets in fMRI-NF studies, thus composing a 'modulability index' for NF targets (Fig. 3b). Such studies should enable informed target selection in the future, such that control targets could resemble the experimental target in their level of modulability, thereby further minimizing reward-related confounds, for randomized ROI NF as well as for alternative NF control condition.

Finally, it is advisable to avoid major differences in the complexity of the interfaces employed to accommodate each randomized ROI NF subgroup and the interface used by the experimental group. To achieve this without forfeiting process specificity, one could induce process-specific contexts via simple contextual interface, similar to the one employed by Paret et al.[69]. For example, subgroups for neural targets of emotion regulation, approach motivation, and potential threat could be contextualized via aversive, appetitive, and threat-related stimuli, respectively, changing only the content of the pictures with all other interface features remaining constant. Alternatively, one could establish a modular immersive scenario (Fig. 1b) that can differentially accommodate several functional processes.

Consequently, a randomized ROI NF control group should differ from an experimental NF group only in the lack of a specific target process. Therefore, it should enable dissociation between target process effects and NF general effects, supporting a more concise conclusion regarding treatment specificity of NF interventions, using only two study groups.

Conclusions and future avenues of research

In the current perspective, we presented a new framework for NF, termed process-based NF. This framework suggests that NF interventions should target dysfunctional processes with defined neural substrates rather than clusters of symptoms, thus adopting a dimensional approach toward mental disorders. Accordingly, the different aspects of the intervention (neural target selection, feedback interface, and clinical outcome measures) should correspond with the target process to optimally ameliorate dysfunctions. Specifically, we suggest that process targeting could be maximized by relying on current neuroscientific theoretical and practical knowledge regarding the neural substrates of functional processes, moving beyond single-region NF toward alterations in network activity and connectivity patterns. We further suggest the development of process-specific interfaces with contextual cues and the enhancement of process engagement via immersive VR and/or AR technologies. Additionally, we show that a process-based approach allows a more precise methodology for determining the specificity of NF effects. To that end, we propose several methodological designs and a new control condition that may enable the disentanglement of general from target-specific effects, an unresolved issue in current NF methodology.

Some current developments that are discussed above, such as dynamic causal modelling NF, DecNef, and simple contextual feedback interfaces are initial instances that relate to the process-based NF approach, each dealing with separate aspects of NF. Our outlined framework integrates these developments into a unifying schema that provides a clear rationale for the construction of all critical stages of NF interventions. The framework further prescribes other suggestions, such as the utilization of immersive VR and AR technologies for process targeting and the process-based application of EFP models for improved accessibility, as well as the use of different feedback protocols and a new control condition for determining specificity. These new propositions, however, have yet to be fully developed and validated. Thus, future interventional NF studies that adopt the proposed framework may enhance our knowledge of the efficacy of NF across neuropsychological domains and diagnostic groups and may further refine the framework's features. Importantly, the process-based framework calls for many modifications; however, it is not mandatory to bind them together. Researchers who wish to enhance NF efficacy or to better determine specificity may adopt some suggestions while passing over other advocated guidelines. Nonetheless, based on the considerations in this paper, we would argue that a process-based approach that harmonizes neural targets, feedback interfaces, and outcome measures is crucial for the further development of NF into a scientifically precise and clinically applicable neuromodulation tool.

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Author contributions

All authors contributed to the writing of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information