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Review article

Towards therapeutic electrophysiological neurofeedback in Parkinson's disease

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ABSTRACT

Neurofeedback (NF) techniques support individuals to self-regulate specific features of brain activity, which has been shown to impact behavior and potentially ameliorate clinical symptoms. Electrophysiological NF (epNF) may be particularly impactful for patients with Parkinson's disease (PD), as evidence mounts to suggest a central role of pathological neural oscillations underlying symptoms in PD. Exaggerated beta oscillations (12–30 Hz) in the basal ganglia-cortical network are linked to motor symptoms (e.g., bradykinesia, rigidity), and beta is reduced by successful therapy with dopaminergic medication and Deep Brain Stimulation (DBS). PD patients also experience non-motor symptoms related to sleep, mood, motivation, and cognitive control. Although less is known about the mechanisms of non-motor symptoms in PD and how to successfully treat them, low frequency neural oscillations (1–12 Hz) in the basal ganglia-cortical network are particularly implicated in non-motor symptoms. Here, we review how cortical and subcortical epNF could be used to target motor and non-motor specific oscillations, and potentially serve as an adjunct therapy that enables PD patients to endogenously control their own pathological neural activities. Recent studies have demonstrated that epNF protocols can successfully support volitional control of cortical and subcortical beta rhythms. Importantly, this endogenous control of beta has been linked to changes in motor behavior. epNF for PD, as a casual intervention on neural signals, has the potential to increase understanding of the neurophysiology of movement, mood, and cognition and to identify new therapeutic approaches for motor and non-motor symptoms.

1. Introduction

Neurofeedback (NF) is a form of voluntary operant conditioning that has been shown to facilitate individuals to learn to control specific features of their own brain activity [1]. NF also provides a tool for testing causal relationships between neural signals and behavior, and represents a potential therapeutic avenue for modulating neural activity and symptoms across a wide range of pathological brain states [1]. In electrophysiological NF (epNF), invasive or non-invasive electrophysiology recordings are analyzed in real-time, with signals presented back to patients in the form of sensory (e.g., visual, auditory, haptic) feedback (Fig. 1). Such feedback provides individuals with the opportunity to learn to modulate their brain activity, guiding them towards, or away from, specific neural activity patterns, with potential clinical and behavioral impact.

Multiple studies have demonstrated the ability of NF protocols to modulate brain activity in humans and non-human primates [2–7]. By targeting this control to specific patterns of brain activity, NF has successfully been used to influence key behaviors (e.g., motor execution, emotion processing) [8–13]. A growing body of work has assessed a potential therapeutic role for NF across a wide range of neurological and psychiatric disorders, including depression, ADHD, PTSD, stroke, and epilepsy [14–18]. These studies provide support that NF might potentially result in clinically meaningful symptom reduction across a range of neurological and psychiatric disorders. However, issues regarding experimental design and technical challenges have currently limited a full translation of these findings to the clinic [19,20].

We propose that epNF in the context of Parkinson's disease (PD) merits particular attention due to the growing body of evidence pointing towards the pathological role of abnormal neural oscillations in PD [21]. Development of alternative (non-stimulation based) approaches such as epNF in conditions with validated electrophysiological targets, such as

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in PD, presents a promising translational avenue [22–24]. epNF may provide a means for modulating oscillations of different frequencies with more selectivity by enabling individual rhythms to be targeted, as opposed to less selective electrophysiological changes achieved by existing therapies such as Deep Brain Stimulation (DBS) and dopaminergic medication [25]. epNF may provide additional advantages compared to DBS by facilitating up-regulation as well as down-regulation of signals, and allowing patients to endogenously control activity in a way that may over time promote self-regulation or even neural plasticity [16]. That is, with continued practice in sessions guided by epNF, patients may be able to develop strategies to self-modulate their own brain oscillations that can be applied in non-NF settings to regulate their own symptoms. Thus, epNF could serve as an adjunct therapy in PD patients, ameliorating acute symptom exacerbations and reducing long-term dependence on medication and DBS.

Here, we review epNF in PD and discuss its potential for clinical improvement in motor and non-motor domains. For a review of hemodynamic neuroimaging NF in PD, the reader is directed to other syntheses [26,27]. We discuss key features of epNF studies with PD patients, including brain regions and frequency bands of interest, clinical implications, and limitations, and provide recommendations and insights for future studies.

2. Electrophysiological biomarkers in Parkinson's disease

Synchronization throughout the basal ganglia-cortical network, reflected by enhanced beta (12–30 Hz) oscillations [21], is posited to relate to many key motor manifestations of PD [28]. Features of enhanced beta activity have been observed within the basal ganglia (e.g., STN [22], STN-GPi [29]), within the cortex (e.g., motor cortico-cortical coherence [30]), and between the basal ganglia and the cortex (e.g., STN-motor cortex [31,32]). Basal ganglia beta has been identified as a clinically relevant and promising biomarker, as its suppression by either dopaminergic medication or DBS has been found to correlate with motor symptom improvements, including with bradykinesia and rigidity [22–24,33,34]. Beta oscillations have been more recently characterized as short bursts of phasic activity, or beta bursts [35,36], and a number of studies have established that the dynamics of subcortical beta bursts are of particular importance in motor impairment in PD [37,38].

Several noteworthy high order features of cortical beta have also been described in PD, including beta waveform asymmetry [39] and elevated beta-gamma phase-amplitude coupling (PAC) [40,41]. Additionally, cortical beta desynchronization in motor cortex prior to movement appears to be somewhat enhanced in PD [42,43]. This has been postulated to reflect a compensatory mechanism developed by patients to facilitate movement initiation, as a similar but less exaggerated pattern is described in healthy individuals before the initiation of movement [44–46]. However, resting motor cortical beta has not been consistently found to be elevated in PD [41], nor does motor cortical beta predictably decrease with DBS or dopaminergic medication as compared with subcortical beta [47,48]. This suggests that cortical epNF protocols to treat motor symptoms may need to target signals differently than protocols using subcortical signals.

Although most research in the motor domain in PD has focused on beta oscillations, signals in other frequency bands may also serve as valuable biomarkers. Narrowband gamma activity in motor cortex and the STN has been linked to ON dopaminergic medication states and dyskinesia [49]. Broadband gamma in the motor cortex is elevated during rest and movement, which may reflect a state of increased motor cortical spiking and metabolic activity, though its exact clinical significance remains to be determined [50,51]. Theta activity in the STN has been linked clinically to resting tremor [52].

PD was historically characterized and managed purely as a movement disorder. However, it is now well recognized that patients also experience disabling non-motor symptoms including dysfunction of sleep, mood, motivation, and cognition [53–56]. The oscillatory mechanisms of cognitive and affective domains are significantly less well understood than those related to movement. This represents an important area of further research given the severe impact these symptoms

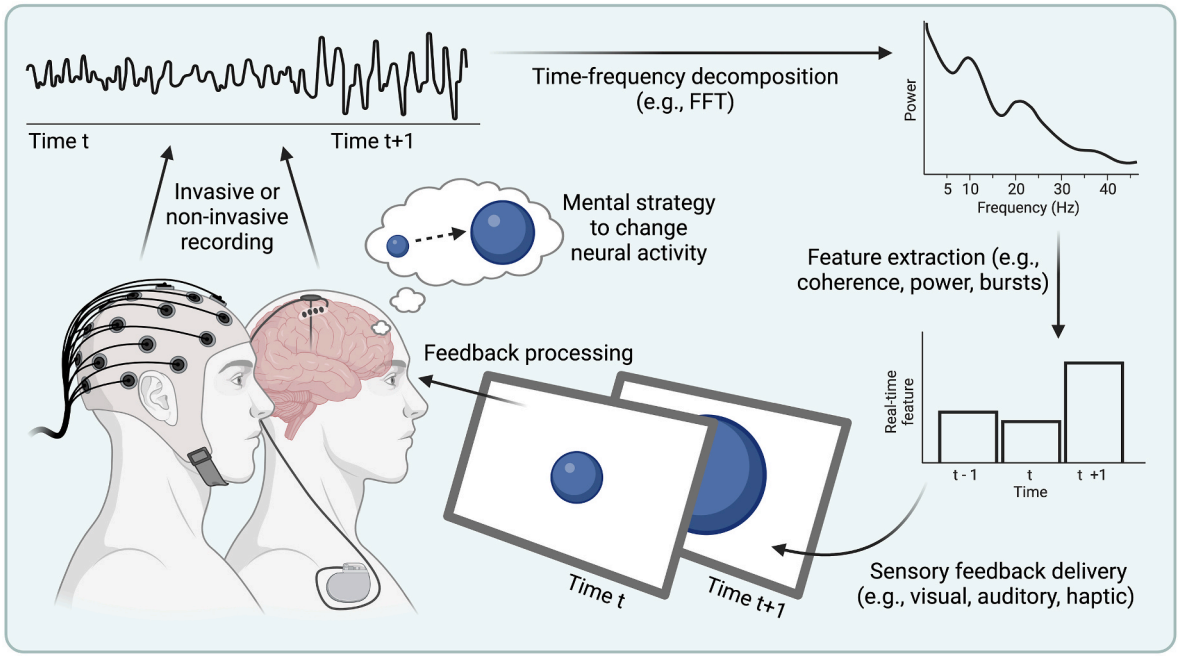

Fig. 1. Electrophysiological neurofeedback (epNF) in patients with Parkinson's disease (PD). In epNF, invasive or non-invasive electrophysiological recordings are analyzed in real-time, and sensory feedback is delivered to patients in order for them to learn to regulate their own brain activity. Raw electrophysiological data can be recorded from the cortex with scalp electroencephalography (EEG) or electrocorticography (ECoG), or from subcortical Deep Brain Stimulation (DBS) electrodes. In this schematic, a raw signal is decomposed into the time-frequency domain using the fast Fourier transformation (FFT), a frequency band of interest is then selected, and changes in neural activity in that frequency band control the diameter of a ball on a computer screen. Figure created with Biorender.com.

have on patients' quality of life [53]. Many different candidate frequencies have been described in non-motor tasks or contexts with PD patients, such as STN alpha in depression [57], theta-alpha and high gamma in prefrontal cortex during emotional processing [58], STN theta in conflict [59], and prefrontal beta in cognitive control [47]. However, further research is required to validate and integrate findings from non-motor domains.

Collectively, evidence suggests that the pathophysiological consequences of PD can be seen electrophysiologically at a cortico-basal network level, characterized by multiple changes in neural oscillatory signals that relate to motor and non-motor symptoms. Causal interventions, including epNF, have the potential to modulate these signals, to evaluate their impact on PD patients' behavior and to be therapeutic adjuncts to current treatments.

3. Cortical epNF with non-invasive electrophysiology

Non-invasive cortical electrophysiology presents a potentially cost-effective and accessible method for epNF. Synchronization in the basal ganglia-cortical network in PD has previously been effectively targeted by DBS [22–24], but DBS for PD is usually restricted to patients with more advanced symptoms. Therefore, targeting this network through epNF with non-invasive cortically recorded signals could potentially benefit a significant proportion of patients. Additionally, although non-invasive electrophysiology provides less spatial resolution than invasive recordings, this may conversely allow for monitoring and targeting of less restrictive cortical areas in the search for effective biomarkers for both motor and non-motor domains. To date, a number of studies have assessed the efficacy of epNF with scalp electroencephalography (EEG-NF) in PD. These provide initial evidence that patients can modulate beta and other frequencies with EEG-NF, although current impact on behavioral and clinical metrics is less clear.

Supporting the potential of EEG-NF as a safe and possibly effective adjunct therapy in PD, two case studies used EEG-NF protocols in PD patients to up-regulate beta activity in sensorimotor cortex [60,61]. The first case study investigated EEG-NF targeting low beta activity combined with a breathing-based biofeedback technique, with 30 regular sessions over the course of 6 months and 12 more sporadic sessions over the course of the next 18 months [60]. The patient in this protocol successfully up-regulated sensorimotor beta power and reported subjective symptomatic improvement, including an improved quality of life and reduced dystonic symptoms [60]. A more recent case study used visual EEG-NF to modulate low beta power in sensorimotor cortex, and demonstrated successful up-regulation of beta burst rate and duration with training [61]. This patient reported improvement in their rigidity and gait, along with a perceived "sense of control" over their neural activity [61]. Although the results of case studies should be interpreted with caution, these two are compatible with findings that increased motor cortical beta activity may relate to motor symptom improvements in PD in certain scenarios [48].

Randomized sham-controlled trials have also now evaluated EEG-NF in PD patients. In one study, nine PD patients with levodopa-induced dyskinesia were randomly assigned to either an active EEG-NF (N = 5) or sham (N = 4) group [62]. Patients in the active group were trained to simultaneously up-regulate low beta (8–15 Hz) and down-regulate both theta (4–8 Hz) and high beta (23–34 Hz) in sensorimotor cortex. However, theta EEG-NF was linked to a patient reported reduction of well-being and subjective worsening of PD symptoms and was therefore suspended. After 24 30-min sessions of beta EEG-NF, patients in the active group successfully up-regulated low beta and down-regulated high beta, but showed no significant improvement in dyskinesia severity ratings. However, the study also reported a trend towards improved motor fluctuations and sense of well-being in patient home diaries. In another randomized sham-controlled study, 16 PD patients were divided equally between a sham-NF group and an active NF group [63]. The NF group was trained to up-regulate low beta (12–15 Hz) and down-regulate theta (4–7 Hz) in the occipital cortex in an attempt to improve balance. After eight 30-min training sessions, PD patients in the active group successfully modulated the targeted neural activity, and showed significant improvements in both static and dynamic assessments of balance. These studies suggest that PD patients can modulate cortical activity at multiple sites with active EEG-NF, but the impact on motor symptoms is not yet definitive. This warrants further studies with strong experimental designs motivated by knowledge of cortical biomarkers, potentially using single biomarkers before combination biomarkers, as well as objective outcome measures and longer-term follow-up [20].

4. Cortical epNF with invasive electrophysiology

Compared to non-invasive protocols, epNF protocols using invasive electrocorticography (ECoG-NF) are more spatially focal and have potential advantages of an increased signal-to-noise ratio. In a study with MPTP-induced parkinsonian non-human primates, an ECoG-NF protocol was used to up-regulate low beta (12–17 Hz) power in sensorimotor cortex [64]. One group of monkeys underwent 9–12 epNF sessions prior to the induction of PD symptoms via MPTP. Following training, both the experimental group and a control group of monkeys underwent MPTP dopaminergic depletion. Importantly, both groups of monkeys had equivalent neural cell loss in the substantia nigra. However, the experimental group that had received ECoG-NF training on up-regulating low beta power had significantly improved motor scores when ON and OFF dopaminergic medication, as compared to the control group. Less severe symptoms were also described during the induction phase of parkinsonism in the ECoG-NF group. This study uniquely performed ECoG-NF training prior to PD onset, while other studies have considered models or patients with more advanced PD. The positive effects reported here suggest that it might be particularly useful to use epNF early, that effects achieved with epNF may vary according to disease progression, and that epNF may modify or even lessen the behavioral consequences of dopaminergic loss in the basal ganglia.

An ECoG-NF study in human patients with PD (N = 3) also demonstrated that all patients were able to successfully modulate cortical beta power in sensorimotor cortex [65]. The ECoG-NF protocol involved up- and down-regulating sensorimotor beta, and was achieved within 1–2 h of training, although no assessment was made to the longevity of this effect nor its impact on motor symptoms. Importantly, the ECoG signal used in this study was derived from chronically implanted devices, making it the first study to successfully demonstrate that chronically implanted devices (rather than intra-operative recordings, as have been more widely used for invasive recordings in humans) could be used for epNF training. However, given the rapidity of training in this group, it is possible that humans use different strategies compared to non-human primates. Consideration should be given in NF protocols design regarding explicit (e.g., visualization) versus implicit strategies for neural signal modulation, as these may recruit different circuits and have different short and long term behavioral effects.

Overall, these studies demonstrate that intracranial cortical signals can be successfully modulated in PD patients and non-human primate models of PD. While the definitive impact on clinical symptoms in humans has yet to be explored, these results stand as a promising pointer for the potential utility of ECoG-NF.

5. Subcortical epNF with invasive electrophysiology

Therapeutic DBS of the STN and GPi provides a window into basal ganglia neurophysiology that can be leveraged for subcortical epNF investigations. The use of these signals for epNF is of particular interest in PD, which is usually considered primarily as a subcortical disorder. Therefore, directly targeting pathological signals in this region might prove to be more efficacious than targeting signals in cortex.

Recent work modulating subcortical electrophysiological signals

with epNF has demonstrated proof-of-principle of neural signal modulation over short time scales. Thus far, most of these studies have specifically focused on modulating STN beta activity, with some utilizing beta power as a target and others focusing on beta bursts. In the first published study of its kind, Fukuma et al. studied eight PD patients with bilateral STN DBS who were undergoing pulse generator replacement surgery [66]. Patients were ON dopaminergic medication, and trained to modulate subcortical beta power through epNF. In a 10 min visual feedback session, patients were required to either up- (N = 4) or down-regulate (N = 4) STN beta power to reduce the radius of a black circle on a screen (Fig. 2A). All four patients in the down-regulation condition showed significantly reduced resting STN beta power post-feedback compared to pre-feedback. Whereas, only two out of four patients in the up-regulation condition showed significantly increased resting STN beta power post-feedback, possibly related to ceiling effects in the beta signal despite regular dopaminergic medication (Fig. 2B).

In a study by Bichsel et al., 10 PD patients OFF dopaminergic medication and OFF DBS during bilateral STN DBS implantation underwent three epNF sessions involving both up-regulation (move a cursor to the right) and down-regulation (move a cursor to the left) of STN beta power [67]. Patients were prompted with an initial strategy to imagine a bradykinetic movement when trying to move the cursor to the right (up-regulation) and to imagine a fluid movement when trying to move the cursor to the left (down-regulation), but were also encouraged to personalize their strategies. Here, patients significantly reduced STN beta in the down-regulation condition, doing so within 6 min of epNF and becoming more effective with subsequent trials. Patients were also able to increase STN beta in the up-regulation condition, though this increase was not significant, echoing the findings of Fukuma et al. and supporting the notion that there may be a ceiling effect. Alternatively, it may be the case that the up-regulation of STN beta requires a different strategy compared to down-regulation, that may be less immediately intuitive, and that patients need more personalized epNF protocols to access the appropriate circuitry to induce beta up-regulation. In this study, the researchers also considered the impact of epNF on motor behaviors, cueing patients to pronate and supinate their hand following their third neurofeedback session, and again two days later without concurrent epNF. Motor performance was improved by using down-regulation strategies at both timepoints, although without concurrent epNF it yielded more variable results than with concurrent epNF (Fig. 3D).

In a preliminary study by He et al. targeting beta bursts, rather than conventional beta power, three PD patients underwent five sessions (10 training trials per session) in order to down-regulate STN beta bursts (represented through the vertical position of a basketball on a screen) and 10 no-training trials (in which subjects simply watched a basketball move) [68]. Two out of the three patients had significantly fewer STN beta bursts in the training trials compared to no-training trials. Following this, in another study by the same group, 12 PD patients off dopaminergic medication with temporarily externalized bilateral STN DBS implants were trained to down-regulate STN beta bursts across at least four sessions and this study included a motor task [69]. Patients similarly underwent 10 training and 10 no-training trials per session, though here each trial was followed by a brief delay and a cued finger pinch, measured via accelerometry (Fig. 2C). These PD patients were able to significantly decrease STN beta bursts with training, with group-level analyses showing lower beta power in the training condition compared to the no-training condition (Fig. 2D).

In this study, the reduction in STN beta burst activity was accompanied by a reduction in reaction times (RT) in the cued pinch movement – a proxy for bradykinesia – following training compared to no-training trials (Fig. 3B) [69]. This supports the interpretation that decreasing STN beta bursts improves movement initiation. Following subcortical beta epNF training, these patients also notably had increased STN gamma power which has been considered previously as a prokinetic rhythm (Fig. 2D) and decreased beta coupling between STN and motor

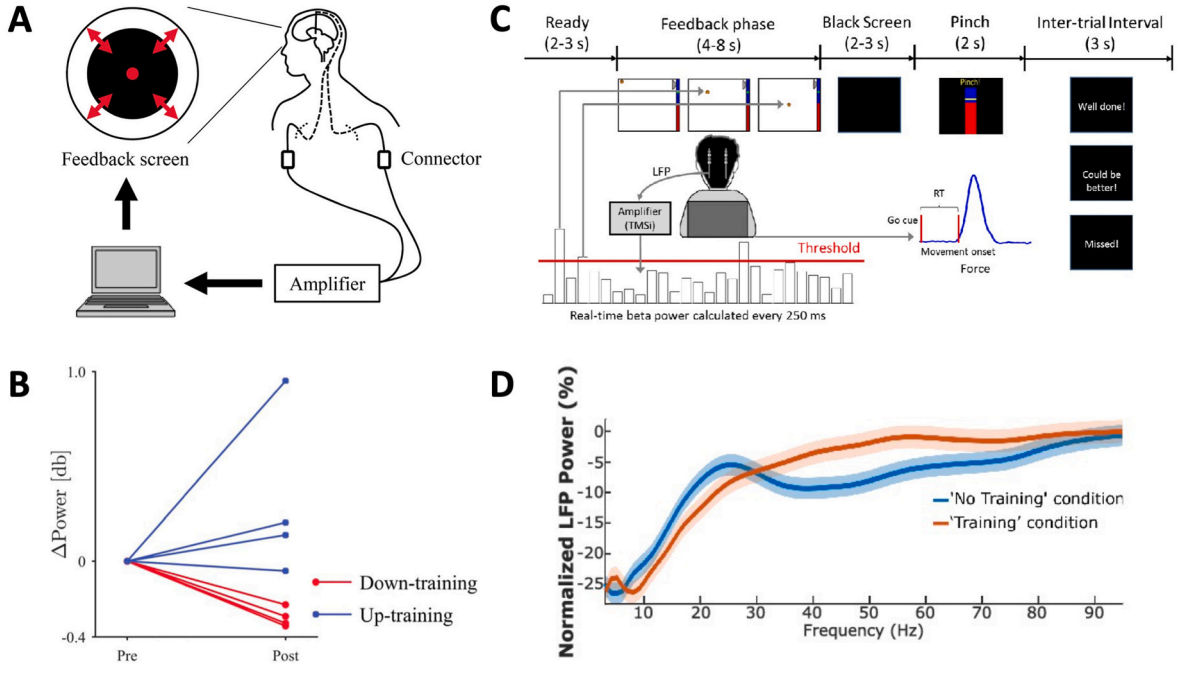

Fig. 2. Subcortical epNF can be used to modulate STN beta activity. (A) Schematic of neurofeedback training protocol used in study with eight PD patients, where patients trained to either up- (N = 4) or down-regulate (N = 4) STN beta power to increase the diameter of a black circle on a screen. (B) Down-regulation training resulted in significantly lower beta power in post-compared to pre-training in all four patients in that condition, while up-regulation training resulted in significantly higher beta power in post-compared to pre-training in two out of four patients. (C) Schematic of beta burst neurofeedback training protocol used in study with twelve PD patients, where all patients completed 10 training trials (down-regulate STN beta bursts to keep a basketball in a high position on a screen) and 10 no-training trials (watch a basketball move on a screen). (D) epNF training to down-regulate STN beta bursts resulted in lower beta power and higher gamma power on average (N = 12). (A) and (B) reproduced from Fukuma et al. [66]. (C) and (D) reproduced from He et al. [69].

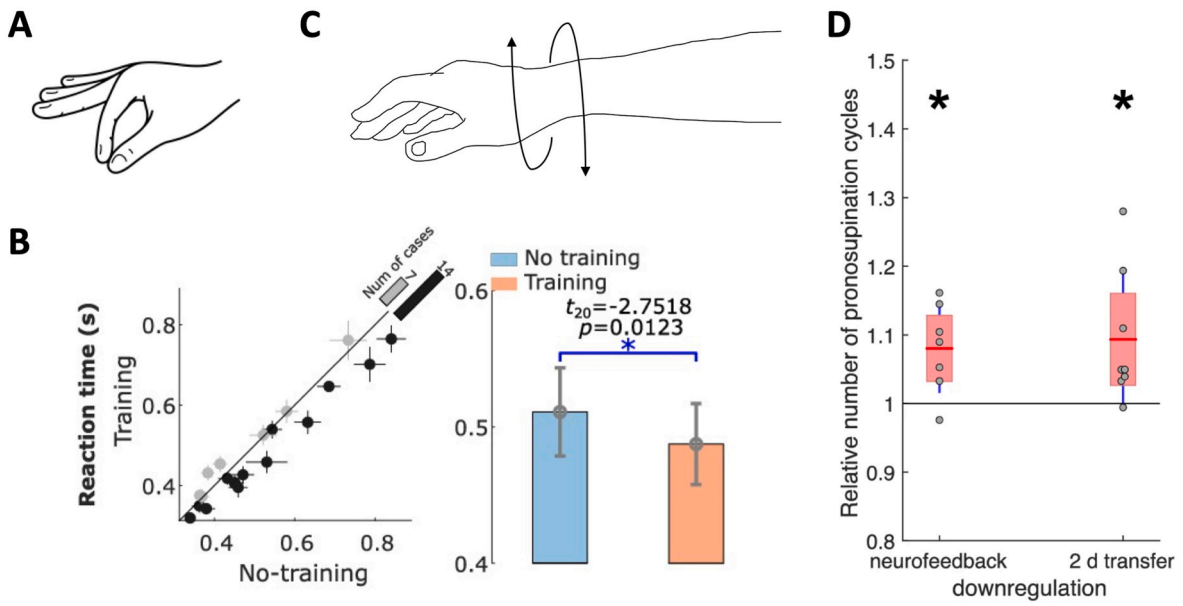

Fig. 3. STN beta modulation via subcortical epNF may improve motor behavior. (A) Parkinson's patients in the study by He et al. [69] were cued to perform a simple finger pinch task following neurofeedback training trials (down-regulate STN beta bursts to keep a basketball in a high position on a screen) or no-training trials (watch a basketball move on a screen). (B) Reaction times on the finger pinch task were significantly faster following training compared to no training [69]. (C) Parkinson's patients in the study by Bichsel et al. [67] were cued to pronate and supinate their more severely affected hand as fast as possible following their third epNF session, and two days later without concurrent epNF during a transfer test. (D) After utilizing STN beta power down-regulation strategies, patients had a significantly greater number of pronosupination cycles compared to rest in the third epNF session and in the transfer test. (B) Reproduced from He et al. [69]. (D) Reproduced from Bichsel et al. [67].

cortex (observed via concurrently recorded scalp EEG) [69]. Notably, decreased STN beta and increased STN gamma were predictors for the RT improvement in cued movement. These features were also more pronounced in later sessions, suggesting that practice leads to improved control over neural activity. However, in patients with pre-existing tremor, the subcortical epNF training significantly increased tremor severity, which was associated with increased STN theta. This suggests that epNF that targets oscillations in a particular frequency band and region may also impact activity in other frequencies and regions affecting non-directly targeted symptoms, and calls into question whether the motor improvements that were observed truly correspond to the decrease in STN beta activity or whether they may play a "bystander" role, with other circuitry changes leading to the observed motor symptom improvement. Future epNF studies that record wide band electrophysiology in addition to multiple behavioral outcome measures can further uncover these interactions.

These studies support beta as a target for subcortical epNF, and there is evidence to suggest a positive impact on motor behavior. However, further investigation is required to understand the immediate and long-term positive and negative influences on clinical outcomes and more complex motor behaviors, as well as interactions between different brain rhythms during epNF. Long-term subcortical epNF protocols notably can and should be investigated as more fully implanted sensing-enabled DBS devices become commercially available. For example, a recent preprint reports successful down-regulation of subcortical beta power in a small cohort of patients with the fully embedded, sensing-enabled Percept™ device from Medtronic [70].

6. Limitations and recommendations

Recent invasive and non-invasive epNF studies have demonstrated that PD patients can learn to modulate cortical and subcortical beta activity, features of which have been associated with disease severity in PD [21,28]. Some studies have shown improved motor outcomes with beta epNF [63,67], with others finding mixed results [61,69] or no significant relationship with behavior [62], and many have not included behavioral or clinical metrics [64–66,68,70]. The field of NF has now developed consensus guidelines encouraging best practices in NF studies particularly relating to 1) pre-registration, 2) control groups and measures, 3) feedback specifications, 4) outcome measures, and 5) data storage and sharing [20], which collectively should reduce variability of outcomes reported thus far. Here we focus on four areas of limitations, with interpretation and recommendations in the context of epNF in PD: sample sizes, control groups and conditions, epNF strategies employed, and behavioral and clinical outcome measures.

Sample sizes. epNF protocols in PD have primarily been with small cohorts. Scalp EEG is a relatively cheap and accessible method for human electrophysiology, and a handful of EEG-NF studies in PD patients have shown success in modulating neural activity and impacting behavior. Although smaller cohort studies are beneficial at the discovery stage, future research should include larger samples of PD patients with EEG-NF protocols to formally investigate its potential as a mechanism for decreasing pathological oscillations in the basal ganglia-cortical network. Smaller sample sizes may be the only option with some epNF protocols, such as those with invasive electrophysiology with ECoG or DBS leads. In such cases, N-of-1 style designs [71] can be utilized with multiple sessions/trials and appropriate within-subject statistical analyses, as is typical in non-human primate electrophysiology. However, the increasing commercial availability of fully implanted DBS devices opens up the possibility of epNF in larger cohorts on a longer, chronic time scale.

Control groups and/or conditions. Many epNF studies in PD have not assigned robust control conditions, and there have been relatively few randomized controlled trials to date [20]. Establishing sham control is of particular importance in epNF studies in PD, as without controls, it is difficult to determine to what extent the benefit is derived from the epNF specifically versus non-specific effects of the protocol (e.g., using motor imagery, paying attention, sitting still). An ideal sham condition should not compromise study blinding, although that can sometimes be difficult to achieve. Including multiple epNF training conditions, such as both up- and down-regulation of neural signals, is another feature that supports strong inferences regarding specificity of epNF on behavioral outcomes.

Strategies employed. In beta epNF, motor imagery is often recommended to subjects as an initial strategy. This may increase the ease and rapidity with which patients begin to obtain control over neural signals, but may also bias or limit patients developing optimal individual strategies. It is possible that patients may achieve better control or even achieve control by involving different circuit pathways if they are given time to develop implicit strategies. Electrophysiological signals are inherently high dimensional with interactions between spatial, frequency, and connectivity components. Therefore, targeting a relevant and optimal signal is both critical and likely complex. Future studies can attempt protocols without providing explicit strategies, or directly test the long-term effects of utilizing experimenter provided strategies versus strategies developed or learned by the patient. An interesting open question is whether explicit strategies interfere with, boost, or are independent from implicit learning processes in epNF with PD patients.

Behavioral and clinical metrics. It is essential that epNF studies with PD patients include appropriate behavioral and/or clinical outcome metrics. Studies thus far without behavioral or clinical measures have been foundational for testing the safety and feasibility of epNF in PD. However, now that those features are more established, it is critical to test the impact of epNF on relevant motor and non-motor outcomes, to evaluate its feasibility as an adjunct therapy in PD.

7. Future directions

The potential applications of epNF in PD are exciting and promising. epNF protocols in PD have been shown to successfully impact brain signals, and also have shown early evidence of impact on behavioral metrics. However, potential translation of this approach into a viable therapy requires robust testing.

epNF protocols that target pathological beta to address motor symptoms in PD have primarily used beta power and bursts as feedback signals. However, other features of beta have been shown to be pathological in PD patients, such as waveform symmetry [39], which could be targeted with newer methods such as those that analyze waveform shape [72]. Frequencies in addition to beta are also potential candidates for successful epNF in PD. Elevated beta-gamma PAC, for example, is detectable with EEG as well as ECoG, discriminates between on- and off-medication states, and is reduced by therapeutic DBS [39,40]. An epNF protocol could train the down-regulation of beta-gamma PAC and measure short- and long-term behavioral impact. Resting tremor has been linked to theta and beta co-activity [52], suggesting that epNF protocols to simultaneously train activity in multiple frequency bands might be effective, though more work is necessary to find appropriate biomarkers for different symptoms.

Lastly, it is important to explore whether epNF protocols can be meaningful for targeting and treating non-motor symptoms in PD, which are traditionally overlooked by existing therapies and which pose significant impairments in patient quality of life. Protocols that target pathological beta oscillations in PD patients for the primary purpose of targeting motor symptoms may influence non-motor domains as well, as the brain likely recruits overlapping networks for putatively different functions. As one example, the cognitive control literature has implicated cortical and subcortical beta activity in inhibitory control of motoric responses, and a growing body of evidence suggests beta-instantiated inhibitory control is also recruited in non-motor domains such as memory suppression and conflict [73,74]. Targeting pathological beta in cortical and subcortical networks in PD may therefore also impact non-motor domains. First combining epNF with computational behavioral paradigms that assay cognitive control, mood, and motivation may be required to index these clinical features with sufficient precision to demonstrate behavioral impact in the laboratory.

8. Conclusions

PD is a notably promising area to apply epNF in light of the established body of literature linking abnormal brain oscillations to symptoms. Current work suggests cortical and subcortical epNF is feasible, and that protocols involving EEG-NF, ECoG-NF, or subcortical epNF can enable volitional beta modulation. Notably, this has been associated with motor speeding in both patients and animal models. However, the pathway towards therapeutic translation requires robust, well-designed experimental epNF paradigms, as well as precise measurement of their impact on motor and non-motor symptoms.

CRediT authorship contribution statement

Elena Ubeda Matzilevich: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Pria Lauren Daniel:** Conceptualization, Data curation, Visualization, Writing – review & editing. **Simon Little:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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