Neurostimulation for the treatment of functional neurological disorder: A systematic review

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Abstract
Functional Neurological Disorder (FND), also known as conversion disorder, is characterized by neurological symptoms that are incompatible with any known structural disorder and best explained by a biopsychosocial model. Evidence-based treatments for FND are limited, with cognitive behavioral therapy (CBT) and physiotherapy being the most effective interventions [1]. In recent years, functional neuroimaging studies have provided robust evidence of alterations in activity and connectivity in multiple brain networks in FND. This body of evidence suggests that neurocircuitry-based interventions, such as non-invasive brain stimulation techniques (NIBS), may also represent an effective therapeutic option for patients with FND.

In this systematic review, we outline the current state of knowledge of NIBS in FND, and discuss limitations and future directions that may help establish the efficacy of NIBS as a therapeutic option for FND.

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FND: From a psychological explanation to a neurocircuitry disease model

Functional neurologic disorder (FND), also known as conversion disorder, is characterized by the presence of ‘one or more symptoms of altered voluntary motor or sensory function which clinical presentation must provide evidence of incompatibility between the symptoms and the recognized neurological or medical condition’, according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM–5) [2]. FND comprises a myriad of different symptoms, including motor symptoms (from hyperkinetic- movement disorders- to loss of motor function- paresis), cognitive symptoms, sensory pathology (including vision, hearing, etc.) and seizures. Functional seizures are one of the most common clinical manifestations of FND. Little has been known regarding the underlying pathophysiology of FND. The original conversion disorder hypothesis suggested that psychological factors (i.e., traumatic and/or stressful events) are converted into neurological symptoms [3]. This has been abandoned in favor of a more comprehensive biopsychosocial framework that considers predisposing, precipitating and perpetuating risk factors [4–7].

A growing number of neuroimaging studies in patients with FND has provided evidence of dysfunction in activity and connectivity in brain networks implicated in cognitive and motor control, emotion regulation, self-awareness and agency [8,9]. Clinical studies have led to the identification of positive neurological signs specific for these disorders (e.g., Hoover’s sign) [10–12], facilitating the diagnostic process. Furthermore, epidemiological studies have shown that a history of trauma or provoking stressor are not necessary but are considered risk factors for FND [13]. This improved understanding of the pathophysiology of FND has not yet been translated into effective treatments. Currently, evidence-based treatments available for FND include physical and psychological therapies, particularly cognitive-behavioral therapy (CBT) – which represents the most effective evidence-based treatment for patients with FND [1,14–16]—along with reassurance and a compassionate explanation of the diagnosis, which are also critical for recovery [17,18]. Interestingly, efficacy of CBT and motor retraining in patients with FND has been associated with changes in the activity and connectivity of several brain regions implicated in FND [19,20]. This evidence suggests that interventions aimed at targeting neurocircuitry dysfunctions, such as non-invasive brain stimulation (NIBS), may be a promising therapeutic strategy for FND.

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two NIBS interventions increasingly studied for clinical use. Both techniques are safe and well-tolerated when delivered according to existing guidelines [21–24] as they do not require general anesthesia, and both have fewer potential side effects when compared with other neuromodulatory techniques such as electroconvulsive therapy (ECT). ECT was the first electrical stimulation technique used to treat neuropsychiatric disorders, including FND [25], however ECT- related side effects and lack of spatial specificity of this intervention limits its efficacy [see Box 1 for overview of neuromodulatory techniques]. Both TMS and tDCS have demonstrated modulation of brain networks and change in clinical and behavioral domains relevant to FND, in both healthy controls and patients with neuropsychiatric disorders [26–33]. In this study, we review the literature on investigations of NIBS as a therapeutic intervention in patients with FND and discuss the implications that study design, stimulation protocols, patient population and treatment outcomes have in determining the efficacy of NIBS for FND.

Methods

A systematic literature search was performed using PubMed for reports published until July 20, 2021. Two sets of search terms were used: one to identify articles on TMS and FND, and the other to identify articles on tDCS and FND. The terms used in each search can be found in Appendix A and Appendix B.

For study on TMS, our initial search was further refined by selecting those articles that used TMS and repetitive TMS (rTMS) – including also accelerated stimulation protocols such as intermit- tental theta burst stimulation (iTBS) - as a treatment tool for any FND phenotype. To ensure accuracy, the literature search was performed at four different time points by the first author (IG). We excluded review/update articles, manuscripts that were not in English, and non-therapeutic studies (including reports that used TMS as a diagnostic tool for FND and/or other disorders as well as those that used TMS to measure cortical excitability). We excluded studies that used other neuromodulation treatments (tDCS, vagus nerve stimulation-VNS, ECT). Another article was excluded as presented duplicate subject data [34] that was incorporated in a later report already included in our review [35]. We also examined previously published reviews [14,36–40] and identified three further studies [41–43] that met our inclusion criteria, which were included in the final data collection. Two of these 3 articles were not originally published in English [41,43] and the third one was an abstract not available through PubMed and localized through a different search engine, WebofScience [42]. Thus, data from these articles were extracted from reviews [36,38,44], instead of the original publications. The selection process is illustrated in Fig. 1.

The same procedure was followed to identify publications on tDCS in FND (Fig. 2). We excluded articles not in English, those that used tDCS for pathologies other than FND and reports that did not evaluate tDCS as a therapeutic intervention. Our search led to a single article that used tDCS as a treatment tool for a patient with functional seizures [45]. Additionally, we identified another article describing potential therapeutic benefit of one tDCS session in FND, although the study was not designed to test the efficacy of this intervention [46].

Of note, our search was not limited by age range. No studies were identified that use/studied TMS/rTMS or tDCS in children with functional neurological disorder diagnosis. However, both neurostimulation techniques have been studied in children and adolescents with other neuropsychiatric disorders and determined to be feasible and safe [47–50].

Results

Following our methodology, we divided our results in 2 sections to describe in detail each NIBS technique studied in our review (TMS and tDCS) separately.

1. TMS in FND

We identified a total of 21 studies that investigated the efficacy of TMS/rTMS in FND patients (Fig. 1). Study characteristics are summarized in Table 1.

1.1. Study design

Of the 21 studies identified, 4 were randomized, controlled trials (RCTs) that aimed to assess the efficacy of TMS as a potential treatment for FND. 8 were open label studies (case series and 9 were individual case reports. A total of 82 patients participated in the 4 RCTs (n = 21 [51], n = 33 [52], n = 17 [53] and n = 11
while a total of 138 patients were enrolled in open label studies. A total of 11 patients were included in the individual case reports.

Of note, two of the RCTs identified used sham TMS as the control intervention [53,54], while root magnetic stimulation (RMS) [52] and low-intensity stimulation (below motor threshold) [51] were used as control interventions in the other two RCTs.

1.2. Stimulation parameters

The majority of the TMS studies reviewed used low-frequency (<1Hz) rTMS –considered inhibitory– (9 studies: 3 RCTs and 6 case reports). Five studies (1 RCT, 2 case series and 2 case reports) used high-frequency (>5Hz) rTMS –generally considered excitatory--; and 6 studies (5 case series and 1 case report) used single pulse
**Table 1**
- TMS- study characteristics' description.

| Study (author/ year) | FND Phenotype | Design | N | Parameters of stimulation | Results |
|----------------------|---------------|--------|---|---------------------------|---------|
| **Randomized Controlled Trials** | | | | | |
| Pick et al. [65] | Paresis (unspecified laterality) | Randomized Inactive treatment controlled (rTMS above/below MT) Single blinded | 21 | MC | rTMS 1Hz | Active arm: 120% RMT, Inactive arm: 80% RMT | Outcome Measures: CGI by patient, CGI-Investigator, FIM/FAM (Psychosocial functioning), Barthel Index (Disability). Both groups showed improvement- non-significant further improvement in the active vs inactive treatment groups. Before and immediately after 2nd TMS session- 67% active group vs 20% inactive group reported “much improvement”. 3 months after the first TMS session - 44% active group vs 20% inactive group reported “much improvement”.
| | | | | | |
| Taib et al. [53] | Movement disorder- tremor (unilateral and bilateral) | Randomized Sham controlled (sham rTMS) Double-blinded 2nd phase open label | 17 | MC(hand+leg areas) .Contralateral in unilateral tremor .Bilateral in bilateral tremor | rTMS 1Hz | 90% MT | 800 pulses | Phase 1 (controlled trial): 5 sessions in 1 day (either arm) Phase 2 (open label): 3 sessions in 3 weeks (rTMS+1 hour hypnosis) | CGI-Investigator: Statistically significant improvement in PMDRS tremor subscores and CGI-I in active group only, at 1 month after study inclusion. Maintained decrease in PMDRS in active rTMS group at M2, M6 and M12. No change in PMDRS or tremor subscore at M6 and M12 in control intervention group. Sustained improvement in 56% of all subjects at 1 year. Recurrence in 12 subjects at 6 months who responded to single TMS booster session. |
| Garcin et al. [52] | Movement disorder- unspecified (all unilateral) | Randomized Sham controlled (RMS) Single blinded Cross-over | 33 | TMS: MC- Contralateral (legs +arms area) RMS: Spinal Roots-Homolateral (cervical + lumbar) | rTMS 0.25Hz 250 microsec (each pulse) | 120-150% MT | Average 50 pulses (30-80 pulses) | 2 sessions on consecutive days (interval minimum 18 hours) in cross-over design by group | CGI by patient: Neurological evaluation (blind) FMD score. Both groups showed improvement (60% of subjects were improved by day 3). No difference between TMS and RMS groups. |
| Broersma et al. [54] | Paresis (all unilateral) | Randomized REMP-controlled Single Blinded Cross-over | 11 | MC | rTMS 5Hz 2 sec train ITI 4sec | 80% MT | 9,000 pulses | 10 sessions in 2 weeks .Cross-over: separated conditions by 2 months Repetition of same protocol (10 sessions in 2 weeks) | Dynamometry: Subjective change in muscle strength. Significant increase in objective muscle strength in active group; no significant difference in sham group after 1st 10 sessions (for 8 subjects completing both treatments, increase was larger after active rTMS). No difference in subjective change between the placebo and active rTMS group. |

**Frequency:** If data not included, information was not provided in the original article

**AC:** Anterior Cingulate; **CGI:** clinical global impression; **FMD:** Functional Movement Disorders; **FIM/FAM:** Functional Independence Measure/ Functional Assessment Measure; **ITI:** inter-train interval; **MC:** (primary) Motor Cortex; **MT:** Motor Threshold; **M2,M6,M12:** month; **PMDRS:** Psychogenic Movement Disorders Rating Scale; **REMP:** real electromagnetic placebo; **RMS:** Root Magnetic Stimulation; **RMT:** Resting Motor Threshold.
| Study (author/year) | FND Phenotype | Design | N | Parameters of stimulation | Results | Outcome Time point 1** | Outcome Time point 2*** |
|---------------------|---------------|--------|---|---------------------------|---------|------------------------|------------------------|
| Spagnolo et al. [56] | Movement disorder - unspecified | Open label | 6 | Left DLPFC Individualized fMRI imaging guided iTBS 120%RMT 3600 pulses total of 6 sessions 2 visits - 24h interval 3 iTBS sessions each visit, >20min between sessions 30 sessions in 3 weeks 2 sessions/day-15min between sessions | Functional MRI data S-FMDRS Decrease functional connectivity between the left amygdala and DLPFC Significant FMDRS decrease within each stimulation visit (pre and post treatment) | | Significant FMDRS decrease between baseline (pre TMS) and 24h after last stimulation |
| Peterson et al. [62] | Functional seizures | Open label | 7 | Right TPJ rTMS 10Hz 5 sec trains ITI 30sec 110% MT 3000 pulses | Functional seizures count Decrease in weekly functional seizures frequency in all subjects throughout treatment. | | All participants sustained improvement up to 3 months post-treatment. 4 out of 7 subjects remained seizure free at 3 months. Improvement not sustained After 3 months all subjects’ symptoms had recurred |
| McWhirter et al. [58] | Upper limb weakness (all unilateral) | Open label | 10 | MC Contralateral Single pulses Up to 0.3Hz Sets of 4–5 pulses 3–4 sec interval 120-150% MT depending on subject tolerance 46-70 single pulses 1 session | Measures of disability (SF-12 and MRS). Self-reported symptom severity (5-point Likert Scale). Grip strength hand dynamometer. Tapping frequency | | Significant reduction in self-report symptoms severity in 4 out of 10 subjects. No differences in objective measures. |
| Shah et al. (2015) | Movement disorder - unspecified (bilateral) | Open label | 6 | Phase1: MC- Dominant Phase2: Dorsal PMC-Dominant Single pulses 0.33Hz 150 sec 90% MT 50 pulses Phase1: 5 sessions Phase2: 10 sessions total | WHOLQOL-BREF Improvement in physical symptoms after both phase 1 and phase 2 Improvement in psychological symptoms only after phase 2. No changes in the social relationship and environmental domains in either phase. | | Data only available in 2 subjects who reported sustained improvement after “many months” |
| Garcin et al. [57] | Movement Disorder - unspecified (9 unilateral; 15 bilateral) | Open label | 24 | MC Contralateral- unilateral FMD Bilateral-bilateral FMD Single pulse 0.25Hz 120% MT 20 pulses (average) 1 session | AIMS (modified). Burke-Fahn-Marsden scale (walking disability subscore). CGI- Improvement (by patient) 75% of subjects improved by >50% immediately after TMS (a third with complete resolution of motor symptoms) | | Sustained improvement in 71% of subjects at 1-year follow-up (4 subjects returned to work). 10 subjects relapsed during f/u period but all improved again after boost TMS |
| Study                  | FND Phenotype                        | Design       | N  | Parameters of stimulation                                                                 | Results                                                                 | Outcome Time point 1** | Outcome Time point 2*** |
|------------------------|--------------------------------------|--------------|----|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------|-------------------------|
| Dafotakis et al. [43]  | Movement Disorder - tremor (3 unilateral; 8 bilateral) | Open label   | 11 | MC Laterality not specified                                                                | Kinetic Motion Analysis                                                 | Immediate reduction of symptoms in 97% of subjects | Sustained recovery in 4 subjects at 8-12 months Remaining subjects had recurrence |
| Chastan and Parain [60]| Paresis (paraparesis 40; monoparesis 26; quadriparesis 2; hemiparesis 2) | Open label   | 70 | MC Contralateral in unilateral paralysis Bilateral in bilateral paralysis                   | None reported                                                          | Effective in 89% of subjects (total recovery in 59 subjects) immediately or within hours after rTMS. | Sustained improvement in most patients. Recurrence in 8 subjects at 6 months; 6 received and responded to rTMS booster sessions |
| Schönfeldt-Lecuona et al [35] | Paresis (3 unilateral; 1 bilateral) | Case Series  | 4  | PMC Contralateral to paralytic limb Laterality not specified for subject with bilateral paresis | None reported                                                          | 3 of 4 cases improved by week 2-3 and recovered or improved significantly by week 5-12 | Sustained improvement after 1 year |

Frequency: if data not included, information was not provided in the original article

**Time Point 1: Assessments performed during the TMS treatment course

***Time Point 2: Assessments performed as follow up after TMS treatment- goal to assess durability of improvement

AC: Anterior Cingulate; AIMS: Abnormal Voluntary Movement Scale; CCI: clinician's clinical impression; CGI: clinical global impression; DLPFC: Dorsolateral Pre-Frontal Cortex; FMD: Functional Movement Disorders; ITI: inter-train interval; MC: (primary) Motor Cortex; MRS: Modified Rankin Scale; MT: (resting) Motor Threshold; PMC: Premotor Cortex; PMDRS: Psychogenic Movement Disorders Rating Scale; SF-12:
| Study (author/year) | FND Phenotype | Design | N | Parameters of stimulation | # Sessions | Outcome Measures | Outcome Time point 1** | Outcome Time point 2*** |
|---------------------|---------------|--------|---|---------------------------|------------|-----------------|------------------------|------------------------|
| Bottemanne et al. [66] | Tetraparesis | Case report | 1 | MC | rTMS 1Hz | 20 sessions 2 sessions/day 10 days | MRC | Symptoms improved between 8th and 12th session, with paresis improving first. Magnitude and frequency of the myoclonus were strongly reduced based on EMG data |
| Naro et al. [61] | Functional myoclonus | Case report | 1 | Left PMC | rTMS 1Hz | 30 sessions 6 weeks 5 sessions/ week | EEG  EMG | Patient-reported improvement in myoclonus severity after 2 weeks of rTMS treatment. This improvement consolidated at the end of the rTMS paradigm and persisted up to 2 months later. Sustained improvement after 2 months leading to return to active duty. |
| Blades et al. [63] | Functional seizures, Functional dystonia -head and neck Dissociative PTSD | Case report | 1 | Primary target: AC Secondary target: SMA + PMC Laterality not specified | rTMS 1Hz | 36 sessions in 2 months, multiple locations in each session: 36 cingulate, 2 PMC (right+left), and 32 SMA | BDI-2 GAD-7 PHQ-9 BAIT WSTRS | Improvement in speech, motor twitching, mood and global change after all TMS treatments |
| Agarwal [55] | Functional seizures | Case report | 1 | Right TPJ 1 cm lateral to CP4 | iTBS "excitatory" No other specifics given | 10 sessions in 7 days 2 sessions/day | PNES scale HAM-D HAM-A | Decrease functional seizures frequency and in all scales immediately after treatment. Sustained improvement in all scales one week after treatment and functional seizures remission 2 weeks after treatment. Complete recovery at 12 (sudden recovery after 8 months) and 15 months in each case (improvement attributed to head injury) |
| Yeo et al. [64] | Visual loss | Case report | 2 | Central occipital cortex | rTMS 10Hz 10 trains 10 sec trains | Case 1: 3 sessions over 3 months Case 2: 6 sessions over 1 year [frequency not specified] | None reported | Improvement in sight in both cases |
| Portaro et al. [67] | Flaccid paraparesis | Case report | 1 | MCBilateral (hand+leg area) | rTMS 1Hz | 36 sessions in 12 weeks | Psychological evaluation Gait analysis | Improvement in mood, weakness, pain and gait immediately after rTMS. Progressive improvement (CGI-I = 1.5), two subsequent recurrences responded to booster treatment (CGI-I = 2.5 and 2 respectively) |
| Gaillard et al. [41] (in French) [Schonfeldt-Lecuona et al. [36]] | Quadriplegia | Case report | 1 | MC Bilateral limb areas | rTMS 1Hz | 40 sessions in 8 weeks initially-then 2 sessions/ week *total duration of treatment not specified | CCI-CGI | Recurrence at f/u (timeline not specified) with medical complications (phlebitis, PE and pressure sores) |

(continued on next page)
We observed great heterogeneity among studies in terms of duration of the stimulation session, total number of sessions and total duration of the study (including the time period between pre- and post- treatment measurements). Four studies entailed a single session and applied single pulse TMS [42,43,57,58], while the remaining studies used either high or low frequency rTMS used multiple sessions, ranging from 2 [59,60] up to 70 sessions [35]. There was a wide range of pulses depending on the frequency: 12–70 pulses in one session of single pulse TMS, 30–4,000 pulses in low frequency rTMS, and 1,000–9,000 in high frequency rTMS. The 2 studies using iTBS applied a total of 600 pulses and 3600 pulses respectively. Some studies reported patients receiving additional TMS session(s) between end of treatment and follow-up visit due to incomplete response, which could impact the outcome at the follow up timepoints [41,52,60].

1.3. Stimulation targets and study population

The majority of the studies included in our review evaluated TMS effects on functional motor disorders (FMD) with negative symptoms (paresis, weakness, paralysis, myoclonus) (see Table 1). In these trials, the primary motor cortex contralateral to the symptom (bilateral in the case of bilateral motor symptoms) represented the most frequently selected anatomical target, with the exception of 2 studies in which the premotor cortex – contralateral to the affected limb [35,61] – and the vertex [42] were stimulated.

Five studies investigated TMS efficacy on FMD with hyperkinetic motor symptoms (2 RCTs, 1 pilot study and 2 case series – Table 1), and they all used the primary motor cortex as the stimulation site, except for one study using an individualized, functional neuroimaging-guided stimulation target within the left dorsolateral prefrontal cortex [56]. Although the TMS protocol used was different between studies (single pulse TMS, low frequency rTMS and iTBS), all reported positive outcomes that persisted through their follow-up timepoint.

Three further studies evaluated the efficacy of TMS on functional seizures. Peterson et al (2018) [62] and Agarwal et al (2019) [55] used right tempo-parietal junction (TPJ) as the anatomical stimulation target, whereas Blades et al (2020) [63] used the anterior cingulate cortex as the target. Although all three studies used different TMS protocols (rTMS excitatory, iTBS inhibitory and iTBS excitatory respectively) and different parameters of stimulation, all three reported positive outcomes with significant improvement after treatment and sustained improved in symptoms at subsequent follow-up timepoints.

There were two studies on other FND phenotypes: one case report that described a case of aphonia, which targeted the left prefrontal cortex and right motor cortex with an inhibitory protocol [59] and another report with 2 cases of visual loss, which stimulated (excitatory rTMS) the central occipital cortex[84].

1.4. Outcome measures

Study outcome measures varied significantly among studies. Some studies used validated outcome scales (e.g., clinical global impression scales [CGI]) to measure change in symptom severity, while others provided a descriptive report. Study outcomes were measured immediately after patients received rTMS and at follow-up in the majority of the studies (Table 1). The interval between the last stimulation session and the follow-up was highly variable among studies, ranging from 24 hours to 12 months. None of the studies consistently incorporated the core outcome measures outlined by the FND-COM group– Clinical Global

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Table 1.3 (continued)
Impression—Improvement scale (CGI-I); core FND symptoms change; Patient Health Questionnaire-15 (PHQ-15); other physical symptoms; Hospital Anxiety and Depression Scale/ Beck Depression Inventory (HADS/BDI); psychological symptoms; Short Form-36 Health Survey Questionnaire/ Work and Social Adjustment Scale (SF-36/WSAS); life impact; Health economics: health-care resource use [65] — although it is worth noting that many studies were published prior to the FND-COM group recommendations.

Several studies also assessed secondary outcome measures related to mood, pain, functioning, and cognitive complaints. Imaging and/or physiological measures (e.g., functional MRI, EEG) to evaluate target engagement were not included in the studies identified, with the exception of a recent pilot study which used resting-state functional connectivity data to identify an individualized stimulation target and evaluate neurocircuitry engagement [56].

1.5. Efficacy measures

Two of the 4 RCTs evaluated TMS efficacy in terms of objective improvement in muscle strength between subjects receiving active versus sham TMS [53,54]. In the other two RCTs, efficacy was measured as between-group differences in subjective improvement based on patient- and/or investigator-rated CGI scale. Garcia and colleagues [52] found improvement in both active and control (RMS) groups, with no statistical difference between them. Similarly, Pick et al.[51] found subjective improvement within both active and inactive treatment groups. Efficacy from open label studies and case series were reported as a decrease in symptom severity and frequency, as well as complete resolution of symptoms in some cases [55,59,64,66]. In addition, nineteen out of 21 studies included reported results from follow-up assessments. Of these studies, only 2 described no TMS effects on study outcomes at follow-up [54,67], and 16 reported prolonged effects of TMS on primary and/or secondary study outcomes. However, it is important to note that time at follow-up varied greatly among studies (from 24 hours to 1 year after last TMS session). In some of the studies with positive follow-up outcomes, patients received further TMS sessions if exhibiting symptoms at follow-up [52,57,60], thus affecting the validity of follow-up data at a later timepoint.

2. tDCS in FND

We identified 2 studies investigating the effects of tDCS on FND (Fig. 2). Study characteristics are summarized in Table 2. The first study is a case report describing the effects of 30 sessions of anodal (excitatory) tDCS stimulation over the F3 EEG position (left dorso-lateral prefrontal cortex-DLPFC), over 15 consecutive working days, with a duration of 30 minutes per session. Interestingly, the stimulation target was selected using a FDG-PET (fluorodeoxyglucose-positron emission tomography) guided approach; which in this case showed hypometabolism in the frontal region [45]. The authors reported reduction in functional neurological symptoms as well as mild improvement in psychiatric symptoms. Symptom improvement was observed for 8 weeks after treatment, although the patient required additional tDCS sessions within those 8 weeks due to incomplete response.

As mentioned above, we included a further case-control study that aimed to measure improvement in interoceptive sensitivity and spatial attention and used tDCS as a neurocircuitry probe [46]. The authors investigated the effects of one anodal tDCS session (20 minutes) over the posterior parietal cortex on interoceptive sensitivity (by a heart rate detection task) and spatial attention (using the Posner paradigm [68]). There was a significant decrease in interoceptive sensitivity in the FND group after the tDCS session, while no significant difference was found in the healthy control group. The authors suggest a potential translation of these positive results to a hypothetical therapeutic effect of tDCS in FND. The authors also demonstrated a negative correlation between interoceptive sensitivity and scales measuring alexithymia, depression, and anxiety in the active but not in the control group. There was no effect of tDCS on spatial attention in either group, which could be due to the study’s small sample.

Discussion

In this systematic review we examined a total of 23 studies investigating the therapeutic potential of tDCS and rTMS for FND: 21 used TMS/rTMS and 2 used tDCS. These studies were small in sample size, variable in design, and differed in terms of stimulation protocols, FND phenotype, and outcome measures.

In terms of stimulation paradigms, most studies used rTMS, with sessions ranging between 10 and 20 minutes. The majority of the studies used high frequency stimulation, but overall the frequency varied from 1 to 20 Hz. The intensity, measured as a percentage of resting motor threshold, ranged from 80% to 140% and the motor threshold was usually determined visually and only in a few cases using electromyography (EMG), which is more accurate and reproducible. The total number of pulses, an essential parameter for tMS efficacy [69], varied between 600 and 2000 in most trials.

A further critical source of variability was represented by the stimulation target. In the majority of studies, the motor cortex was selected as target site, despite lack of motor cortex abnormalities in patients with FND based on a large body of neurophysiological and neuroimaging studies (for a review see Spagnolo, Garvey and Hallett, 2021 [56]). Current evidence suggests that functional neurological symptoms are associated with abnormalities in activity and connectivity in motor-limbic circuitry (i.e., amygdala, insula, supplementary motor area) as well brain areas implicated in agency (right temporoparietal junction – rTPJ– and precuneus) [60,61]. Therefore, modulation of these areas via NIBS may represent a novel and effective therapeutic strategy for FND. Furthermore, studies targeting these regions via NIBS may allow to directly probe a causal link between dysfunction in distinct brain networks and clinical and behavioral manifestations of FND. Neuroimaging studies alone do not provide such causal connections. As our understanding of the neurobiological basis of FND grows, NIBS may play a pivotal role in facilitating the translation of this knowledge into neurobiologically-informed therapeutic interventions for FND.

In addition to the rationale for choosing a given brain region, the procedure to identify the specific stimulation site within said region needs to be considered. The majority of previous TMS studies in FND selected the target areas using scalp landmarks or skull coordinates based on an EEG electrode system. These approaches can lead to inaccurate targeting compared to MRI-based neuronavigation methods [70] and do not account for the complex functional organization of the brain and for disease-specific alterations in neurocircuitry. Neuroimaging-guided target selection currently represents the gold standard for NIBS studies, as this method allows for an accurate and reproducible identification of the stimulation site. Importantly, mounting evidence indicates that clinical response to NIBS, particularly rTMS, relates to the functional connectivity between the cortical stimulation site and distal brain regions, which are part of the same neurocircuitry. For example, in patients with depressive disorders, the connectivity...
| Study (author/year) | FND Phenotype | Design | N | Location | Current | Electrode size | Duration | # Sessions | Outcome Scales | Outcome Time point 1 | Outcome Time point 2 |
|---------------------|---------------|--------|---|----------|---------|----------------|----------|------------|----------------|---------------------|--------------------|
| Leroy et al. 2019   | Functional Seizures | Case report | 1 | PET-guided | 2 mA | Anode 35 cm² Cathode 35 cm² | 30 min | 30 sessions in 15 working days | AIMS, Seizure episodes, MADRS, TAS | Progressive decrease of involuntary movements beginning at week 2 of treatment. Mild improvement in psychiatric symptoms overall. After 5 weeks: AIMS < 63%; PNES < 80%; MADRS < 20%; TAS < 8% | No follow up |
| Demartini et al. 2019 | FMS: Tremor, Parkinsonism, Dystonia, Weakness | Randomized Double blind Cross-over Sham + healthy controls | 9FMS 7 Healthy controls | Anode: R-PPC Cathode: Supraorbital (laterality not specified) | 1.5 mA | Anode 25 cm² Cathode 35 cm² | 20 min | 1 tDCS 1 sham tDCS (2 day minimum interval) | Heartbeat Detection Task (interoceptive sensitivity), Posner Paradigm (spatial attention), HAM-A, HAM-D, TAS-20 | Significant decrease in interoceptive sensitivity in the FND group vs healthy control. No significant change in spatial attention task after intervention in either group | No follow up |

*Time Point 1: Assessments performed during the tDCS treatment course.
**Time Point 2: Assessments performed as follow up after tDCS treatment - goal to assess durability of improvement.
AIMS: abnormal involuntary movement scale; FMS: functional movement symptoms; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D: Hamilton Rating Scale for depression; mA: milliampere; MADRS: Montgomery-Asberg Depression Rating Scale; PNES: psychogenic non-epileptogenic seizures; PPC: posterior parietal cortex; TAS: Toronto Alexithymia Scale; tDCS: transcranial direct current stimulation.
between the stimulation target in the left dorsolateral prefrontal cortex and the subgenual cingulate cortex has been shown to predict clinical response to rTMS. These observations have prompted the investigation of a novel, individualized connectivity-based targeting strategy, which allows to tailor the stimulation target to each patient. This approach has already been used in several studies, including a study in patients with Alzheimer’s disease and a recent study in patients with FMD [56,71].

Interpretation of the results of rTMS and tDCS is also limited by the size and characteristics of the sample. The majority of the reviewed trials consisted of small sample sizes with clinically heterogeneous populations. Patients enrolled in these studies were affected by different phenotypes within the FND spectrum, such as FMD and functional seizures; and within the FMD group, studies evaluated patients with both positive and negative motor symptoms, raising the question whether NIBS in FND should be approached considering the specific FND phenotype. Studies on the neurobiology of FND usually consist of small samples of patients with similar FND symptoms [9,72]. Therefore, our current understanding of the neurobiology of FND is based on samples that at least share some phenotypic resemblance. Note that this may be overcome if, as suggested above, anatomical targets can be individualized based on functional neuroimaging, allowing for more flexible anatomical target and protocol selection.

A further source of variability is represented by psychiatric comorbidities. Functional seizures, for example, are associated with high frequency and severity of depression, anxiety, post-traumatic stress, dissociation, and somatic distress [73]. Many of these comorbid disorders have well-established neurocircuitry dysfunction that may converge (or not) with the proposed neurocircuitry dysfunction in FND, such as brain areas involved in emotion regulation and cognitive control [74]. Understanding the overlap in neurocircuitry alteration between FND and comorbid conditions could potentially further reinforce target selection. This suggestion should be cautiously considered, as evidence already exists that well-proven therapies for comorbid psychopathology do not automatically translate into improvement in FND symptoms [75] and vice versa [76].

Future directions

Our review of the extant literature on NIBS for FND shows that efficacy and real indications for the use of tDCS and rTMS in this patient population need confirmation. Many critical questions remain unanswered, including the optimal stimulation parameters, the appropriate patient population, and the opportunity to combine other treatments. Larger studies are needed, and these should be based on specific, testable pathophysiological hypotheses and robust electrophysiological effects. Physiological measures, including EEG, PET and functional MRI, should be included in such studies to provide evidence of target engagement, that is that the stimulation protocol selected is able to modulate activity and/or connectivity in the selected site and related neurocircuitry. Furthermore, combining these measures with clinical outcomes can provide mechanistic insights and better characterize the neurocircuitry underlying FND.

To fully uncover the therapeutic potential of NIBS for FND, other aspects should also be considered and investigated. First, it will be important to assess the effects of NIBS combined with other therapeutic strategies. For instance, engagement in specific activities (for example, FND-specific physical therapy or CBT) or tasks (e.g., cognitive tasks, cue exposure tasks) immediately before, during or after neurostimulation has the potential to directly engage the neurocircuitry targeted by NIBS, thus reinforcing neuroplastic effects, as suggested by studies in depressed patients [74,75]. For example, CBT for functional seizures utilizes distraction, relaxation techniques, exposure to avoided or feared situations and development of more flexible thinking patterns [1]. Exposing patients to this learning around the time of neurostimulation would therapeutically exploit the neuroplastic changes induced by NIBS and could potentially solidify or amplify therapeutic gains from CBT. A similar approach may be considered for a treatment protocol pairing FND-informed physical therapy with NIBS [77]. Having the experience of moving a limb again, recovering speech, or decreasing a positive sensory symptom through neurostimulation could serve as a powerful “catalytic inducer of change,” especially if coupled with behaviors and/or cognitions that help reinforce the positive experience. An equivalent mechanism has been described in phantom limb pain phenomena, where stimulating the motor cortex [78] or the sensory cortex [79] contralateral to the amputated limb can “reset” altered perception. A related approach using a virtual reality-delivered mirror and exposure therapy protocol, without neurostimulation, has been described in FND [80]. These studies support the hypothesis that exposure to a rectified motor or sensory experience (which may be facilitated by neurostimulation) offers therapeutic potential. More recently, this hypothesis was tested by Bottemanne and colleagues [76], who used a biofeedback protocol coupled with rTMS in which a patient visualized motor activity of her upper limbs during stimulation of the primary motor area, with promising results. It is also critical to consider the cognitive pre-conditioning that may occur before neurostimulation treatment (patients hear “TMS will most likely help you”). The therapeutic effect of a suggestion is well documented and participants in TMS studies and actual treatment are known to gain confidence in recovery due to guidance from study staff [64]. A placebo effect should be further examined, and therapeutically exploited in FND if beneficial, as it has been shown to be an influencing factor in treatment response in TMS studies for different pathologies [81–84]. Investigation of the added benefit of NIBS to proven therapies for FND would require properly designed powered sham-controlled studies.

Finally, future studies should use a reliable and widely validated set of outcomes measures, as recommended by the FND-COM group, to assess treatment response and to facilitate comparisons between NIBS studies using different stimulation targets or protocols [65]. These outcomes should be evaluated immediately after patients receive NIBS and at follow-up intervals to establish both the acute and long-term effects of NIBS.

Conclusions

In conclusion, the efficacy of rTMS and tDCS as potential treatments for FND still needs to be confirmed. Existing NIBS studies in FND are heterogeneous in design. Many critical questions regarding development of future NIBS treatment protocols remain unanswered, such as what the optimal stimulation parameters are, who the appropriate patient population should be, and how to combine NIBS with other treatments. More work and larger studies are needed, but these studies should be based on our current understanding of the neurobiology of FND and should be designed to assess both clinical and brain-level effects. Physiological measurements (functional MRI, EEG) should be associated with clinical outcomes, to provide evidence of target engagement, as well as to better characterize the neurocircuitry underlying FND. Ultimately, the future of NIBS for FND and other psychiatric disorders depends on the design of studies that will provide answers for these crucial questions.
Box 1
TMS and tDCS: an overview:

Transcranial Magnetic Stimulation (TMS) is a non-invasive technique that uses an electromagnetic coil to generate electrical activity in targeted brain regions through the application of magnetic pulses. It is used to study brain physiology and plasticity when delivered as a single pulse TMS, or to elicit neuromodulation and neuroplasticity throughout train of pulses, repetitive TMS (rTMS) [85,86]. Neurostimulation with rTMS increases cortical excitability when delivered via high frequency stimulation (≥5 Hz) or intermittent theta burst stimulation (ITBS- a variation of high frequency rTMS) or decreases cortical excitability when delivered via low frequency (1 Hz) rTMS or continuous theta burst stimulation [87–89]. All these variants of stimulation frequencies could translate into prolonged excitability that outlasts the stimulation period [85,90–92]. The different coil shapes and the strength of the field determine which brain structures the stimulation can reach. Classical figure-of-eight coil targets brain regions at a depth of 3–4 cm while newer coils (H-coil) could reach areas 5–7 cm deep [93]. Muscle pain surrounding the area of the stimulation along with self-limited scalp pain and headache following the stimulation are the main side effects reported in rTMS [86]. The most serious concern is the potential risk of inducing an epileptic seizure, which translates into a minimal risk once following proper screening processes (by medical professionals) and TMS guidelines [23,94]. In terms of therapeutic applicability, TMS has been approved by the FDA for the treatment of major depressive disorder (2008) [95], migraine (2013) [96] and most recently OCD (2018) [97], and will likely continue to expand as TMS continues to show benefit for the treatment of many other disorders including post-traumatic stress disorder (PTSD) [98] substance use disorders [99], schizophrenia [100], cognitive abnormalities in Alzheimer’s Disease (AD) [101], etc.

Transcranial direct current stimulation (tDCS) is a non-invasive technique that uses a low-amplitude direct current (0.5–2 mA) through a pair of saline-soaked electrode pads placed directly over the scalp and connected to a battery device. It appears that tDCS modifies cortical excitability through subthreshold modulation of neuronal membrane potentials [102,103], and also can induce lasting plasticity changes [104]. Direction of cortical modulation (facilitation vs inhibition) depends on duration, intensity, and polarity of stimulation [105]. In addition, effects of tDCS could be altered depending on electrode positioning and configuration as well as skull thickness and composition [106]. tDCS’s most common side effects are skin irritation and a sensation of burning [107].

It is important to note that both TMS and tDCS are overall safer and better tolerated than medications, especially in specific populations such as pregnant or women of child-bearing age, older adults, and those subjects with medical conditions impacting the absorption, distribution, or metabolism of drugs. To date, tDCS is not an FDA-approved treatment for any pathologies.

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.

Appendix A - terminology used for TMS study search

("functional neurological disorders"[Text Word] OR “functional neurological symptom disorders”[Text Word]) OR “conversion disordeorder”[Text Word] OR “hysterical symptoms”[Text Word] OR “psychogenic symptoms”[Text Word] OR “psychogenic disorders”[Text Word] OR “functional weakness”[Text Word] OR “psychogenic weakness”[Text Word] OR “conversion paralysis”[Text Word] OR “psychogenic paralysis”[Text Word] OR “functional movement disorder”[Text Word] OR “functional movement disorders”[Text Word] OR “psychogenic movement disorder”[Text Word] OR “psychogenic movement disorders”[Text Word] OR “functional gait”[Text Word] OR “psychogenic gait”[Text Word] OR “functional neurological paresis”[Text Word] OR “psychogenic paresis”[Text Word] OR “conversion paresis”[Text Word] OR “functional motor”[Text Word] OR “psychogenic motor”[Text Word] OR “conversion motor”[Text Word] OR “PNES”[Text Word] OR “psychogenic nonepileptic seizures”[Text Word] OR “nonepileptic seizures”[Text Word] OR “dissociative seizures”[Text Word] AND (((“TMS”[Text Word] OR “transcranial magnetic stimulation”[Text Word]) OR “rTMS”[Text Word]) OR “neuromodulation”[Text Word]))

Appendix B - terminology used for tDCS study search

(“functional neurological disorders”[Text Word] OR “functional neurological symptom disorders”[Text Word]) OR “conversion disorder”[Text Word] OR “hysterical symptoms”[Text Word] OR “psychogenic symptoms”[Text Word] OR “psychogenic disorders”[Text Word] OR “functional weakness”[Text Word] OR “psychogenic weakness”[Text Word] OR “conversion paralysis”[Text Word] OR “psychogenic paralysis”[Text Word] OR “functional movement disorder”[Text Word] OR “functional movement disorders”[Text Word] OR “psychogenic movement disorder”[Text Word] OR “psychogenic movement disorders”[Text Word] OR “functional gait”[Text Word] OR “psychogenic gait”[Text Word] OR “functional neurological paresis”[Text Word] OR “psychogenic paresis”[Text Word] OR “conversion paresis”[Text Word] OR “functional motor”[Text Word] OR “psychogenic motor”[Text Word] OR “conversion motor”[Text Word] OR “PNES”[Text Word] OR “psychogenic nonepileptic seizures”[Text Word] OR “nonepileptic seizures”[Text Word]) AND (((“TDCS”[Text Word] OR “transcranial direct current stimulation”[Text Word]) OR “neuromodulation”[Text Word]))

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