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Case Report

Identifying and evaluating novel treatment targets for the development of evidence-based interventions for functional neurological disorder

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ABSTRACT

Historically, functional neurological disorder (FND) has been described in psychodynamic terms as the physical manifestation of psychological distress. It is often explained to patients and caregivers as the result of anxiety, stress, trauma or other psychiatric comorbidities. However, recent evidence indicates that targeting mood and stress is not equivalent to the treatment of FND and may have limited to no effect on FND symptoms. Given the few randomized controlled trials for FND treatments and the limited evidence of mood and stress as effective treatment targets, the identification and evaluation of novel treatment targets or mediators is an area of great opportunity and should be the focus of future research. Identifying and targeting modifiable disease mechanisms directly as opposed to only treating psychiatric comorbidities may result in greater efficacy in treating FND symptoms, better patient outcomes and lower healthcare costs. Several novel mechanisms have been identified that warrant additional investigation as potential treatment targets including abnormal attentional focus on the affected area, beliefs and expectations about illness, impairments in habituation, and decreased sense of control over actions. Future intervention studies should take a mechanism-based approach and utilize valid and reliable measures or specific biomarkers to determine whether improvements in FND symptoms are associated with changes in the treatment targets. This transdiagnostic approach will allow researchers to translate the novel mechanistic outcomes emerging from neurophysiological and neuroscience studies into new or improved evidence-based approaches to FND treatment and prevention.

The term "functional neurological disorder" (FND) refers to neurological symptoms which are inconsistent with known neurological diagnoses, and functional seizures (FS; also called dissociative seizures or psychogenic non-epileptic seizures) are a common subtype [1]. FND is the second most common diagnosis in neurology outpatient clinics [2]. It presents in a very high proportion of neurological inpatient units and is a driver of high costs of neurological care via frequent testing and inpatient evaluations [3]. Correct diagnosis, especially in the case of FS, results in >95% reduction in healthcare expenses [4].

Historically, FND has been described in psychodynamic terms as the physical manifestation of psychological distress [5]. It is often explained to patients and caregivers as the result of anxiety, stress, trauma or other psychiatric comorbidities [5]. However, about one-third of adults with FND do not have a specific comorbid psychiatric diagnosis or an identifiable psychological trigger. Further, even for the ones who do, it is unclear whether their psychiatric diagnosis relates to the etiology of their FND, and if yes, how [6]. Additionally, psychiatric comorbidities may be the result of living with FND. Recent etiological models acknowledge the significant heterogeneity in the development of FND. These models use a biopsychosocial etiological explanation that can account for mood and trauma as risk factors for FND without explaining them as the direct cause of FND symptom onset or requiring them to be present in every individual with FND [7–10].

Many treatments for FND target mood or stress to improve FND symptoms. Recently it was suggested that treatments for individuals with FND should be based on the etiological factors associated with each individual's FND, e.g., those with comorbid posttraumatic stress disorder would engage in prolonged exposure therapy while patients with personality disorder symptoms would participate in dialectical behavioral therapy [11]. However, targeting mood or trauma may not necessarily result in treatment of the FND symptoms. This has been demonstrated in trials in which selective serotonin reuptake inhibitors (SSRIs) improved anxiety and depression but resulted in no significant reduction in FS

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frequency compared to controls [12]. Further, the largest randomized controlled trial (RCT) of a treatment for FND used CBT to target fear avoidance for FS [13]. Unfortunately, the primary outcome objective at 12-months after treatment was not achieved – there was no significant difference in FS frequency between those assigned to CBT compared to those assigned to the treatment as usual arm. While several secondary outcome measures were significantly improved in patients treated with CBT, only 20% of patients in the CBT treatment arm achieved freedom from FS at the 12-month follow-up [13].

As a result of the poor long-term efficacy demonstrated in recent FND treatment research, it has been suggested that researchers forgo symptom frequency and severity as primary outcomes and instead aim to improve health-related quality of life or other aspects of mental health [11]. Quality of life in patients with FS is very low and typically lower than in patients with epilepsy [14,15]. As such, this is an important construct, and its improvement is and should continue to be an important secondary target. However, symptom frequency and severity (e.g., frequency of FS or severity of the functional tremor or functional weakness) are primary concerns for patients [16] and are the main reasons they present for treatment. In many patients with FND, these symptoms rather than psychiatric comorbidities are the primary drivers of disability (e.g., the inability to drive and attend work or school) and low quality of life. Therefore, as illustrated in the case report below, improving FND symptoms rather than the comorbidities should be the focus of FND therapies. Further, as FND symptoms decrease and individuals are able to return to work/school and social activities, their health-related quality of life is likely to improve, as disease severity and disease disability are predictors of health-related quality of life for other conditions [17,18]. Finally, although improving health-related quality of life and other secondary outcomes in patients with FND is undeniably beneficial to patients, it is premature to abandon symptom frequency and severity as primary outcomes given there has only been one large, adequately powered RCT assessing a treatment for FND [13].

Alternatively, the limited efficacy in improving FND symptoms by treatments targeting psychiatric comorbidities may suggest that mood and stress are not the most effective treatment targets for FND. While psychiatric comorbidities appear to increase the risk of an FND diagnosis, there remains significant heterogeneity in the etiology for FND [7,19]. Given that similar rates of psychiatric comorbidities are present in patients with illnesses such as coronary heart disease, stroke and Parkinson's disease [20,21], there may be other factors which mediate the relationship between psychiatric comorbidities and FND. Using a transdiagnostic approach in which these mediating factors are identified and targeted directly as opposed to treating comorbidities may result in greater efficacy in treating FND symptoms and, as an end effect, better patient outcomes and lower healthcare costs. The identification and evaluation of novel treatment targets or mediators is an area of great opportunity and should be the focus of future research.

Multidisciplinary care is an important part of treatment, and better understanding of effective treatment targets will also be beneficial to the multidisciplinary clinical team diagnosing and treating FND. The physician plays an important part in obtaining a thorough history, evaluating and identifying the positive signs of FND, and providing hope for successful resolution of the symptoms [22], and clear communication from the physician to the patient about the diagnosis and treatment help facilitate acceptance of the diagnosis and follow-through with recommended treatment appointments with other disciplines, including psychiatry/psychology and physical, occupational and/or speech therapy. The current lack of understanding of the neuropsychopathology of FND, the uncertainty in effective treatment targets, and the lack of evidence-based treatments for FND often result in differing explanations for the symptoms among providers and make it difficult for the clinical team to clearly explain what the patient should expect in the treatment process. Confirming effective treatment targets will inform the etiological explanation and help develop clear guidelines for clinical practice.

One area in which the identification of effective treatment targets or mediators would be beneficial is cognitive behavioral therapy (CBT) for FND. CBT is considered to be a promising treatment for FND [23]. However, individual CBT interventions for FND target different mechanisms [13,24–27], and effective treatment targets by which CBT can be effective for FND have not been established. Although CBT is often thought to be a single specific treatment, CBT is a principle-based treatment model that generally targets cognitions and behavior and encompasses a wide range of techniques that are tailored to the individual patient and the disorder being treated [28]. Therefore, if one CBT treatment is ineffective for FND, it does not mean that all types of CBT treatments will be ineffective, and if one CBT treatment is effective for FND, it does not mean that all CBT treatments will be effective for all patients if the treatment targets are different. If we step outside of FND treatments to look at examples, Acceptance and Commitment Therapy (ACT) and original Beck CBT are both CBTs used to treat similar disorders, but they vary significantly in their methods and treatment targets. Instead of teaching people how to control their thoughts and feelings like Beck CBT, ACT helps individuals to simply notice, accept and embrace their thoughts and feelings, and therefore efficacies of Beck CBT and ACT vary [29]. Similarly, current CBT interventions for FND focus on treating various targets, and although most of the studies have not confirmed efficacy of these treatments via well powered RCTs, the differing treatment targets may account for the variation in reported outcomes. As mentioned above, results from the largest RCT for a CBT intervention for FND suggest targeting fear avoidance or anxiety has poor long-term success in treating FND symptoms [13]. However, a pilot RCT for a different CBT intervention for FS that was not powered to detect between-group differences found significant within-group improvements for the CBT and CBT + sertraline arms but no significant improvement in the sertraline alone and treatment as usual arms [24]. Additionally, studies have found differing outcomes for CBT interventions for motor FND. In a retrospective study assessing treatment outcomes for patients with motor FND with symptoms such as tremors, weakness and gait disorders, about 50% of patients demonstrated symptom improvement after CBT that used a psychological etiological explanation and sometimes linked past and present experiences with physical symptoms. The number of patients with symptom remission was not reported [27]. Another prospective study using a different CBT treatment to treat patients with functional tremor demonstrated about 73% with short-term remission/near remission after treatment [26]. Overall, there are few reported studies using CBT for FND that include an attention control group for post-intervention comparison, and most have small sample sizes. Further, no studies assessing FND treatments have identified and confirmed the mechanism by which the treatment improves FND symptoms. Future research should use controlled studies with attention control groups (e.g., equal time spent in CBT vs. a support group) or symptom specific (seizures in FS vs. seizures in epilepsy) control groups to assess treatment efficacy and confirm the treatment targets by which CBT treatments are effective.

Neuroimaging studies in FS and other FND symptoms suggest a network approach for identifying treatment targets [30], and future intervention studies should take a mechanism-based approach in which valid and reliable measures or specific biomarkers are utilized to determine whether improvements in FND symptoms are associated with changes in the treatment targets [31].

Given the limited efficacy of treating mood for FND symptoms, several novel mechanisms beyond mood, stress, and trauma have been identified that warrant additional investigation as potential treatment targets. Some of these include abnormal attentional focus on the affected area, beliefs and expectations about illness, impairments in habituation, and decreased sense of control over actions [7,32]. FS have also been proposed as a network disorder [30], and there may be other novel pathophysiological mechanisms on a proteomic, epigenetic or genetic level [33,34]. One or several of these mechanisms could be more directly related to patients' FND symptoms and could be the key to the development of more effective, evidence-based treatments.

Recent research has demonstrated some initial successes with treatments for FND that target these mechanisms as opposed to psychiatric comorbidities. A randomized feasibility study for physiotherapy aimed at retraining functional motor symptoms demonstrated promising clinical effect sizes. Using a physically-based etiology, participants engaged in movement retraining intended to redirect the focus of motor attention from symptoms. This resulted in moderate to large effect sizes in physical function compared to controls [35]. Retraining of physical symptoms has also been demonstrated to be effective for pediatric FS. Retraining and Control Therapy (ReACT), a CBT-based intervention using a biopsychosocial explanation and targeting catastrophic symptom expectations and sense of control, resulted in a significant decrease in FS in children, even in the absence of decreased anxiety or depression symptoms [25]. However, no studies have assessed the targets by which either of these treatments are effective, and both need additional research to confirm their treatment targets. Below is a case example in which psychiatric comorbidities were present but treatment targeting other factors was successful in treating FS and mood.

Case example: An 18-year-old white female presented for treatment of functional seizures (FS) characterized by a variety of symptoms including loss of consciousness, jerking, memory loss, temporary blindness, crying, laughing, and shortness of breath. The FS had begun 4 years prior and were currently occurring every 7–10 days, lasting approximately 1 hour. She noted many triggers associated with her episodes including stress, interacting with her mother, being at church, and separating from her friends or boyfriend after spending time together. She was currently not able to attend college or work due to the FS. She reported experiencing significant physical, verbal and emotional abuse from her mother from ages 8 to 15. She had a previous diagnosis of depression, a history of attempted suicide and an inpatient psychiatric admission. At age 15, she moved in with her aunt and uncle who then had full custody. She had completed several courses of therapy for FS over the last 3 years, mainly focused on addressing depression and her significant trauma history, which resulted in little improvement in FS. She endorsed ongoing passive suicidal ideation and hopelessness. She began ReACT, which targeted control over symptoms by developing opposing responses to the FS symptoms and catastrophic symptom expectations. After the first session, she reported being able to prevent the onset of 2 FS. After 8 sessions, she experienced no FS for 3.5 months. She then experienced 4 FS over a 2-week period, followed by complete FS remission for at least 6 months. At her final treatment session, she was driving independently, was enrolled in college, had a job and was about to move into her own apartment. She denied symptoms of depression and no longer endorsed suicidal ideation.

Overall, results of studies targeting novel factors are promising and suggest these and additional treatments targeting novel mechanisms may be effective in reducing FND symptoms. Due to the high rate of psychiatric comorbidities of FND, many patients may need treatment for comorbid mood or trauma diagnoses, but current evidence from RCTs indicates that treatment of comorbid diagnoses is not equivalent to the treatment of FND and may have limited to no effect on FND symptoms [12,24]. Future studies of FND treatments should use an experimental therapeutics approach to confirm the mechanism by which FND symptoms improve with treatment. This transdiagnostic approach will allow researchers to translate the novel mechanistic outcomes emerging from neurophysiological and neuroscience studies into new or improved approaches to FND treatment and prevention. Further, as pediatric- and adult-onset FND appear to differ in many ways [36], this approach may also help determine if the target mechanisms for effective treatment outcomes differ by age or other etiological factors. Due to the heterogeneity in the risk factors for FND, the benefit of individualizing treatment for FND has been highlighted [37,38]. Identifying the targets by which interventions are effective will facilitate the development of adaptive interventions for FND which tailor treatment to individuals based on the presence or absence of certain predisposing factors. Adaptive treatments for FND may include the determination of the need for a certain course of therapy (e.g. CBT for comorbid mood diagnosis) or whether the individual may benefit from inpatient vs. outpatient treatment. Interventions may even be developed to tailor the treatment received at each individual session (e.g. based on the change in frequency or severity of the symptoms and the patient's ability to engage in activities over the previous week). As experimental therapeutics has been advocated by the National Institutes of Health (NIMH) in their Strategic Plan for Research, this may increase the ability of FND research to be funded by the National Institutes of Health, providing needed resources for rigorous trials. The development of evidence-based interventions for FND will have significant implications for patients who are provided with few (and often ineffective) treatment options, allowing them to return to school and work, reducing the stigma associated with the FND diagnosis and relieving the financial strain of frequent healthcare visits.

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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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