Reviewing an improved evidence base for the treatment of functional neurological disorders

Functional neurological disorders: a treatment-focused review

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Summary

Functional neurological disorders are commonly seen in medical practice. Despite the fact that these conditions are currently poorly understood, the last decade has seen a substantial increase in research into many areas, notably treatment. Thus, there is good evidence supporting physical treatment with emphasis on specific elements. Psychological treatments, for a long time viewed as the mainstay of therapy for these disorders, showed remarkably low levels of evidence until better conducted studies were published recently, with interesting new trends such as interdisciplinarity or self-help. Pharmacological treatments lack clear confirmation of efficacy. Evidence for neuromodulatory treatments is at an embryonic stage, but there have been some encouraging results.

Key words: functional neurological disorder; treatment, physical; psychological; pharmacological; neuromodulation

Introduction

Patients with medically unexplained symptoms present in all medical and surgical settings, acute and chronic, with protean symptomatic manifestations. Whether they present with globus pharyngeus to the otorhinolaryngologist, inflammatory bowel disease to the gastroenterologist, chronic pelvic pain to the gynaecologist or chronic fatigue to the rheumatologist, they occupy more than 30% of all generalists’ and specialists’ practice [1]. In the field of neurology, these patients can present a wide range of symptoms such as paresis, paralysis, abasia, ataxia, paraesthesia, anaesthesia, aphonia, dyskinesia, akinesia, dystonia, tremor, ataxia, vesico-sphincteric symptoms, blindness, amnesia, or seizures [2].

Even naming these conditions is a challenge, and a wide variety of terminology has been used over time, across countries and between health professionals. In a recent survey, patients found the word “functional” to be less offensive than “hysterical”, “psychosomatic”, “medically unexplained”, “stress related”, “depression related”, or “symptoms all in the mind” [3], and we will use the term “functional neurological disorders” in this review in accordance with trends in current diagnostic nomenclature (see below).

UK neurologists have described these patients as “the most difficult to help”, and they came bottom of a recent US neurologists’ inquiry of “most likeable conditions” as a consequence of persistent uncertainties about aetiopathogenesis [4]. That this condition is currently still very poorly understood is all the more surprising given the fact that these disorders provided major building blocks for both the theoretical basis and clinical semiology of the foundation of modern neurology and psychiatry in the late 19th century. Nonetheless, the last decade has seen a substantial increase in research into many aspects of these disorders.

The aim of this paper is to provide a treatment-focused review of ongoing developments in functional neurological disorders.

Methods

A MEDLINE/PubMed and google.scholar literature search was conducted, focusing on treatment studies on functional neurological disorders from 2000 to 2016. The search included articles with the following words in title or abstract: “functional”, “conversion”, “psychogenic”, “somatoform”, “hysteric”, which were combined with the subsequent terms: “treatment”, “management”, “physical”, “physiotherapy”, “psychological”, “psychotherapy”, “pharmacological”, “medication”, “drugs”. Titles and abstracts were reviewed to identify potentially relevant articles of which there were 51; the full articles were then retrieved and reviewed. All results were limited to English-language articles.

Features

Clinical/diagnosis

Uncertainties regarding the definition and causes of these disorders is reflected by the fact that they are currently classified in different diagnostic families in the Diagnostic and Statistic Manual (DSM) established by the American Psychiatry Association [5] and the International Classification of Diseases (ICD) taxonomy put forward by the World Health Organization [6],
being listed among somatoform disorders in the former and among dissociative disorders in the latter. The latest version of DSM-5 removed the diagnostic requirement for a “recent psychological stressor”, as well as the need to exclude feigning, and replaced them with the need for positive physical signs to support the diagnosis [7].

Functional neurological symptom disorder (conversion disorder), DSM-5 [5]

A. One or more symptoms of altered motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognised neurological or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

The ICD 11th revision is due in 2017, and in its current beta draft, functional disorders are for the first time a separate category within the neurological section [8].

Functional clinical manifestations of the nervous system, ICD 11 Beta draft [6]

Functional paralysis or weakness:
Motor weakness of a limb or body part in which there is positive evidence of either internal inconsistency (e.g., the presence of Hoover’s sign or Hip Abductor sign) or incongruity with other causes of limb or body part weakness.

People with functional neurological disorders present some commonly noted clinical features, such as sudden onset of symptoms, often precipitated by a physical event (e.g., injury or illness), rapid progression, severity increasing with attention and decreasing with distraction, and shifting symptomatology [4]. Two broad entities were classically depicted, functional movement disorders (in decreasing order of prevalence: tremor, dystonia, gait disorder, parkinsonism and myoclonus) and nonepileptic seizures, but these are increasingly considered to overlap and respond to the same treatments [9–11]. It is also increasingly usual to distinguish between negative/loss of function symptoms (e.g., paresis, sensory losses or blindness) and positive/productive symptoms (e.g., functional movement disorders and nonepileptic seizures). Clinical manoeuvres such as Hoover’s sign (fig. 1) gained some empirical credibility in distinguishing functional from organic motor symptoms, and it is more and more often recommended to emphasise positive signs in the diagnosis [12]. The gold standard for diagnosis of nonepileptic seizure remains video-electroencephalogram [4]. In terms of illness representation, people with functional neurological disorders have been found to have illness beliefs similar to those of their counterparts with the corresponding organic disease, except that, paradoxically, they tend to be less likely to attribute their symptoms to stress than patients with organic disease [13].

Epidemiology
The prevalence of functional neurological disorder is notably difficult to establish because of case definition issues. Nevertheless, lower estimates of community prevalence extracted from a population-based case register are at around 50/100 000 [4]. One of the largest multicentre prospective cohort studies of neurology outpatients to date found that up to 30% had neurological symptoms that were either “not at all” or only “somewhat” explained by neurological disease, with a diagnosis of “conversion disorder” in 5.6% of cases [14].
Prognosis is often poor, with long-lasting symptoms in approximately half of the patients leading to distress, disability, social isolation and early work retirement, to a greater extent than in patients with organic disease [8]. For example, functional neurological disorders cause impairments of quality of life that are worse than those experienced by patients with Parkinson’s disease [15]. In the UK, estimates of yearly costs associated with patients with “medically unexplained symptoms” are slightly higher than the annual costs associated with dementia patients [16]. Psychiatric comorbidities such as depression and anxiety are frequent, and there is good evidence that aversive childhood experience is more common in patients with functional neurological disorders than in controls, although not psychiatric controls. The frequency of recent life events around the time of onset is also somewhat increased, but results between studies are incongruent [4].

**Imaging**

Over the last decade, neuroimaging studies examining brain activity with different paradigms have started to explore the neural basis of functional neurological (essentially motor) disorders [17, 18]. Summarising the findings is notably difficult, but three of them fit very broadly with current putative models of these disorders. The first of these findings suggests an alteration/down-regulation of networks involved in planning, execution and interpretation or attribution of movement (insula and motor cortex) by dysregulated areas involved in emotional regulation (orbitofrontal cortex), perhaps reproducing a phylogenetic mechanism of deceiving predators by mimicking illness/disability in presence of intense fear [8]. The second implies potential abnormalities in the sense of agency/self-monitoring control of movement. In patients, motor pathways (e.g., MI) seem less coupled with premotor areas and more with default mode network regions (precuneus, ventromedial prefrontal cortex and other midline regions), suggesting a role for internal self-representations in influencing motor activities in these patients [19]. Aberrant functional connectivity between these networks is thus capable of producing movements or perceptual experiences that are not associated with the normal sense of agency and interpreted therefore as involuntary by patients [20].

The third finding involves arousal and memory alterations. Globally, an overly sensitive amygdala, possibly conditioned by previous learning (early life stress events), seems to drive changes in networks mediating perceptual experiences (temporoparietal junction) and movement plans (supplementary motor area, SMA) [4]. Moreover, during stressful tasks, patients with functional neurological disorders show greater dorsolateral prefrontal cortex (DLPFC) and SMA activity, and decreased hippocampal activity. Interestingly, inferences were made in support of some psychodynamic concepts, such as memory repression (greater DLPFC activity inducing lower hippocampal activity), associated with conversion symptoms (greater SMA activity) [20, 21], although evidence is mixed [22].

**Treatment**

A 2005 Cochrane systematic review of treatment for conversion disorders identified 260 references, including over 100 case reports, and described a “Prévert’s catalogue” of treatment regimens as different as spa treatment, hypnosis, abreaction/cathartic therapy, family therapy, psychodynamic therapy, cognitive behaviour therapy, surgery, drugs, electroconvulsive therapy, transcranial magnetic stimulation, physiotherapy, inpatient psychiatric care and packages of different interventions. The authors found it impossible to draw any conclusions about their potential benefits or harms, and urged researchers to aim towards more reliable evidence [23]. This was of particular importance because patients with functional disorders are notably susceptible to unethical health practices, especially via the web [24].

**One of the major barriers to treatment is the lack of a defined treatment provider and treatment transition strategies.**

Indeed, evidence for effective treatment regimens in functional neurological disorders has grown up in recent years. A large number of new studies have reported marked short-term improvements, mostly in the region of a 60–70% symptom reduction [25], regularly with a class 2 level of evidence. Whatever physical, psychological, neuromodulatory or combination treatments are nowadays proposed to these patients, effective communication with them and their relatives, and providing a shared rational model of the functional symptoms, are now cornerstones of experts’ recommendations [16], given that diagnostic acceptance is a well-documented prognostic factor [26]. One of the major barriers to treatment that remains and that will be difficult to resolve with evidence-based medicine is the lack of a defined treatment provider and treatment transition strategies. The neurologist is often the health professional who makes the
Physical treatment
Physiotherapy has long been considered by neurologists and physical therapists to be an important component of treatment for functional neurological (movement) disorders. Questions about lack of evidence and integration with psychological treatments led to a series of studies in recent years that aimed to overcome these limitations. A systematic review conducted by Nielsen et al. [27] identified a surprisingly low number of patients (373) included in studies relevant to these aspects of treatment, given that 77% of a large survey of neurophysiotherapists in the UK reported working with patients with functional movement disorders [28]. There is, however, increasing sound evidence for the use of physiotherapy for functional neurological (movement) disorders. Expert consensus recommendations [29], alongside the first randomised controlled trial [30] and other recent studies [31–33], offer effective physiotherapeutic treatment protocols described in sufficient detail to allow replication.

There is increasing sound evidence for the use of physiotherapy for functional neurological (movement) disorders.

In contrast to the classical view that physical methods help by providing a “face-saving way out” for patients, new evidence showed that elements of physiotherapy matter. Three points are of particular relevance and are outlined in the 2015 expert consensus recommendations [29].

1. As a rule of thumb, physiotherapy with patients suffering from functional movement disorders draws attention away from the disabled body part. This approach contrasts with physiotherapy of neurological conditions such as stroke, spinal injury or multiple sclerosis, which relies on focused attention on the poorly functioning body part [31]. The challenge here is for the physiotherapist to demonstrate normal movement in the context of a meaningful activity such as walking. Distractions are preferably motor-oriented (finger tapping) rather than cognitively oriented (conversation, music, arithmetic) because they seem more effective.

2. A second element is the strong educational framework given with physical therapy, centred not only on patients’ representations, but also on recognising inconsistencies between their presentation and the work with the physiotherapist [33]. Useful ingredients are, for example: acknowledgement that symptoms are real and not imagined, and that they are relatively common in the general population; explanations that these symptoms can improve and are often reversible (by showing the patient clinical signs of reversibility such as Hoover’s sign, hip abductor sign, or entrainment of tremor); and introduction of the role of the physiotherapist in helping the patients “regain control” over their “nervous system” and voluntary movements.

3. The third element is goal-directed physical rehabilitation that focuses on function and automatic movement (e.g., walking) rather than impairment (e.g., weakness) by creating an expectation of improvement (e.g., by daily or weekly objectives recorded in a rehabilitation diary or workbook) and developing a self-management and relapse prevention plan. The only randomised controlled trial to date on these questions, by Jordbru et al., investigated a 3-week inpatient rehabilitation programme based on adapted physical activity with a strong educational frame of reference [30]. It showed effectiveness on two scales assessing physical and cognitive disability, and functional mobility, respectively; treated patients kept their gains during a 1-year follow-up. Contrary to the previous opinion that recovery would be less likely more than 2 years after disease onset [34], patients with a disease duration as long as 4 years responded well.

An influential study at the Mayo Clinic investigated a short-term (5 day) physical rehabilitation protocol consisting of a twice daily step-by-step strategy establishing elementary movement in the affected body part and then building on this, coupled with distracting motor tasks (e.g., finger tapping, balloon bouncing). This study showed that approximately 70% of the patients were rated by themselves and a neurologist as “markedly improved”, “nearly completely normal” or “in remission” [35].

A retrospective study of 60 patients, conducted in 2013 at the Maudsley Hospital, London, investigated a twice weekly, essentially physiotherapeutic intervention. This included exercises targeting posture with balance and strength, combined with techniques employing...
distraction from the affected limb and assistance for the patient in recognising inconsistencies between presentation and work with the therapist. There was a “marked improvement” in 69% of the patients immediately after treatment with lasting effect at 25 months [33].

More recently, two studies using the physiotherapeutic guidelines issued in the 2015 recommendations have shown positive results. The first, conducted by one of the leading experts involved in the 2015 recommendations, investigated a prospective, brief (5-day) physiotherapeutic programme, and showed again that beneficial outcomes are possible even with patients for whom previous evidence suggested poor prognosis (symptoms for more than 2 years, loss of role, e.g., unemployment or divorce, receipt of disability-related financial benefits) [32]. The second study, published in 2016, was a case series of 35 patients, which again showed positive results, with substantial gains for patients with both acute and chronic presentation, even if the former gained significantly more points on average [31].

Finally, there is certainly a role for other physical therapies apart from work with a physiotherapist. Nonspecific, graded exercise is more and more considered to be a part of general rehabilitation programmes that address reduced exercise tolerance, chronic pain, fatigue, and anxiety and depressive traits [26]. Dallochio et al. observed that a group exercise programme of low to mild intensity could improve functional movement disorders and general well-being in a group of mildly to moderately affected patients [36]. The challenge with these nonspecific group exercises is to have the right exercise intensity to prevent exacerbation of symptoms and build up adherence to the programme [27].

Psychological treatment

Despite the belief, common since the early 20th century, that psychological therapies are the mainstay of treatment of functional neurological disorders, there are very few appropriately powered studies in this area. The 2005 Cochrane systematic review investigating psychosocial interventions for conversion disorder found no convincing support for any treatment, with only slight experimental evidence for two therapies, namely hypnosis and paradoxical intention therapy (symptom prescription where patients are instructed to deliberately increase symptomatic behaviour) [23].

A more recent 2014 Cochrane systematic review on psychological treatment for nonepileptic seizures highlighted that there is little evidence to inform physicians and health practitioners regarding existing psychotherapeutic treatments and how effective they are [37]. Recent randomised controlled trials provided class 2 evidence for psychological treatments of patients suffering from functional neurological disorders, but essentially in the short-term and mostly for nonepileptic seizures, with much less information on functional movement disorders [38–41]. In this domain lessons have yet to be learned from the treatment of similar conditions, especially somatoform disorders (most subjects with a functional neurological disorder fulfil criteria for a somatoform disorder [40]), where the evidence for psychological treatment is wider and more sound [42].

Cognitive behavioural therapy (CBT) is the most studied psychotherapeutic modality in functional neurological disorders. It is a form of psychotherapy that can be administered in a limited time-frame to help patients become aware of their dysfunctional thoughts and maximise function by practicing new ways to think about their symptoms and learning new ways to respond to these symptoms. Most of the literature on the use of CBT in functional neurological disorders involves nonepileptic seizures [43]. The rationale is that functional neurological disorders represent dissociative responses to arousal, occurring when the person is faced with fearful or intolerable circumstances [38]. Two pilot clinical trials had promising results. The first, in 2010, showed a reduction in seizures in patients with nonepileptic seizures as compared with a treatment-as-usual control group, but the benefit was not maintained at 6-month follow-up [38]. The second trial, in 2014, demonstrated that manualised psychotherapy for patients with nonepileptic seizures reduced seizures and other somatic symptoms, improved psychiatric symptoms including depression and anxiety, and improved quality of life and overall functioning [39].

Psychoanalytic psychotherapy is a modernised form of psychoanalytic cure aimed at reshaping personality structure. It is based on the articulation between early life experiences, parenting dynamics, negative emotions, current life experiences and enduring personality traits. It showed promising benefits in a 2006 single-blind clinical trial investigating brief (12-week) psychodynamic psychotherapy in 10 patients, with improvement in movements, and depression, anxiety and global functioning scales [44]. However, a 2014 randomised controlled trial developed to build on the results of this previous study found no specific benefit in the brief psychodynamic psychotherapy group, as opposed to the active control group with neurological observation and support [40].

Adaptations of the previous models to overcome limitations such as shortage of qualified therapists, low
A current trend in expert opinion emphasises interdisciplinarity between neurologists and psychiatrists [48–53], with opportunities for renewed collaboration around this paradigmatic “neuropsychiatric” disorder between specialties that were separated during much of the 20th century [54]. Joint neurological and psychiatric consultation in an inpatient setting is the cornerstone of this multidisciplinary model, and serves several purposes: better initial contact with psychiatry services by avoiding feelings of rejection and incomprehension by patients when referred to a psychiatrist by their neurologist or general practitioner; a sense of coherence and shared understanding, thus helping medical and paramedical staff (physiotherapists) to work more appropriately with the patient’s representations [55]. The main results that emerged from this trend in the literature were the likely sustained benefits of the interventions (as long as 3 years [55]) in the follow-up studies, and diminished healthcare use during the follow-up period.

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A last word on hypnosis, which shares a long and storied history with functional neurological disorders. Notable psychiatric personalities (Charcot, Bernheim, Janet, Freud, Breuer) from the latter 19th century treated these patients with hypnosis, noting similarities between hypnotic response and conversion symptoms. By the end of the 20th century, hypnosis-based interventions had experienced a revival in medical practice, as they appeared to be an effective form of adjunctive treatment in a number of medical situations, such as pain management, smoking cessation, or trauma-related syndromes [2]. Similar alterations of brain function in functional neurological disorders and hypnotic states have been suggested, and this shaped the modern rationale for the effects of hypnosis on these disorders [26]. However, these hypothetical links are not supported by recent brain imaging studies specifically comparing both phenomena in motor paresis [55]. Evidence remains very scarce and mixed: Moene et al. conducted two studies in the early 2000s, observing improvement in an open-label study [2], but no difference in a randomised controlled trial on the additional effect of hypnosis on a comprehensive treatment programme for patients with functional movement disorders [56].

Pharmacological treatment

Evidence concerning pharmacological treatments in functional neurological disorders is scarce. There are no data to support use of drugs that are routinely used for treating nonfunctional movement disorders, such as antiparkinsonian medications. A recent Cochrane review assessing pharmacological interventions for somatoform disorders in adults found only low- or very low-quality evidence for their efficacy, and that solely for two specific classes, namely new-generation antidepressants and natural products [57]. Thus an essential part of the sound medical treatment of functional patients is often removal and avoidance of unnecessary medications [16], such as antiepileptic drugs in patients with exclusively nonepileptic seizures [58]. Nonetheless, psychopharmacological treatments, especially antidepressants, are used frequently in patients with functional neurological disorders, presumably targeting underlying depressive or anxiety symptoms. Voon et al. conducted a widely cited open-label study [59] evaluating antidepressant (citalopram, paroxetine, venlafaxine) treatment outcomes in functional neurological (movement) disorders. They found that patients with chronic primary conversion syndromes (rather than primary somatoform disorders, hypochondriasis or malingering) and recent or current depression or anxiety may respond to antidepressants, which confirmed that the target of antidepressants is the depression and/or anxiety associated with functional movement disorders.

A pilot pharmacological randomised controlled trial in nonepileptic seizures, conducted by LaFrance et al.,
reported reduced seizure frequency in a group receiving a selective serotonin-reuptake inhibitor (SSRI: sertraline) compared with a placebo control group. Intriguingly, the findings provided preliminary evidence for a serotoninergic-mediated intervention acting directly on nonepileptic seizures, because the improvement in the SSRI group was not accompanied by a reduction in comorbidities such as depression or anxiety [60].

A 2014 short communication reported that therapeutic sedation had positive results in severely disabled functional neurological patients with spastic paraplegia or fixed dystonia, rehabilitating one of the first modern treatment methods for conversion disorders, which was used massively during the First World War on soldiers who presented these symptoms. Potential mechanisms of the video-recorded propofol-induced sedation protocol are demonstration of reversibility, helping the patient to trust in possible recovery, and cerebral state alteration inducing temporary interruption of altered cognitive, motor and emotional pathways [61].

Neuromodulation

Noninvasive brain stimulation methods such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and electroconvulsive therapy (ECT) have been used in past decades to treat various mental disorders, and have been introduced or re-evaluated as potentially helpful in the treatment of functional neurological disorders. As a reminder, the use of electricity or magnetic fields in medical practice has a long history dating back to the 18th century, and is closely linked to discoveries in the nascent neurological fields and paradigmatic shifts away from ancient Galenism [62].

Especially rTMS has been the subject of much recent interest. When applied at suprathreshold motor intensities to the contralateral motor cortex, rTMS can induce movements in the functionally weak, dystonic or tremulous limb [63, 64]. Two recent systematic reviews by Pollak et al. [65] and Schönfeldt-Lecuona et al. [25] provide preliminary evidence that rTMS could be beneficial in the treatment of functional movement disorders, despite heterogeneous protocols and the poor overall quality of examined studies. The mechanism of action of rTMS in functional neurological disorders remains uncertain. One hypothesis is a possible direct effect on neuronal firing rate, but this idea seems at present to be preliminary, because of protocols that are not intense enough to result in these events and because benefits lasted far longer than those seen in some of the better sham-controlled blinded trials of rTMS in Parkinson’s disease or dystonia. Some authors emphasise the crucial influence of patients observing an externally triggered muscle contraction, which is not the case with tDCS and ECT, for which evidence remains anecdotal [25].

Finally, transcutaneous electrical nerve stimulation (TENS) devices, which emit low-voltage current to the skin and are widely used to treat various acute and chronic pain conditions such as musculoskeletal disease, neuropathy, surgery and childbirth, have also been examined. Two open-label studies found benefits on motor symptoms in the short term [66, 67]. The portability and focus of TENS makes it, in any case, a useful tool in the armamentarium of physiotherapists working with patients with functional neurological disorders, especially for those with sensory symptoms such as paraesthesia or allodynia [8].

Conclusions

Functional neurological disorders are commonly seen in medical practice, but the field has only recently moved forward to using proper methodologies to explore the question of treatment. Current expert recommendations emphasise physical therapy aimed at drawing attention away from the disabled body part and focusing on automatic movement (e.g., walking) rather than the impairment, within a strong goal-directed framework in order to create an expectation of improvement. Multidisciplinarity between neurologists and psychiatrists is another cornerstone of existing guidelines, with particular emphasis on effective communication to provide a shared rational model of the functional symptoms. Data show promising results, and should encourage neurologists, psychiatrists, physiotherapists and other health practitioners to work together, sometimes in new and original ways, to promote and improve health, prognosis and quality of life of these patients.

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References

The full list of references is included in the online article at www.sanp.ch.