

**The Impact of Comorbidities and Expectations on Functional Neurological
Disorder Symptoms (FND)**

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Declaration

This is to certify that:

- I. the thesis comprises only my original work towards the MPhil except where indicated in the Preface,
- II. due acknowledgement has been made in the text to all other material used,
- III. the thesis is fewer than 40 000 words in length, exclusive of tables, maps, bibliographies and appendices,
- IV. the research reported in this thesis was conducted in accordance with the principles of the ethical treatment of human subjects as approved for research by Human Research Ethics Committee at the Austin Health.

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ABSTRACT

Functional Neurological Disorder (FND) is a condition that encompasses a wide spectrum of neurological symptoms that do not have an organic explanation. It is not clear why some patients develop a specific neurological symptom. In our study we considered the most frequent FND sub-types: functional motor disorders (FMD) and non-epileptic seizures (NES). It has been purported that individuals with risk factors, create strong expectations about body sensations based on clinical experiences such as disease, injury or surgery. These expectations would impact the nervous system which in turn lead to functional symptoms. These symptoms are inconsistent in frequency and evolution across time, and they are vulnerable to suggestion. Thus, there are no objective measures that can account for the symptoms.

This thesis aims to determine whether *previous clinical factors* affecting different parts of the body have a relationship with the development of functional motor disorder (FMD) and non-epileptic seizures (NES), and to carry out a preliminary study of a measure capable of identifying *perceptual differences* in patients with functional weakness, the most reported symptom.

In the first study we analysed the medical records of 108 FND patients (52 FMD and 56 NES), and in the second study we applied the Size-Weight Illusion (SWI) to 11 FND patients with functional weakness and 15 healthy controls (HC).

It was found that patients with motor symptoms (FMD) had significantly higher rates of clinical factors that affected their *limbs* prior to the symptom onset than NES. Moreover, contrary to predicted, patients with NES had a similar rate of events that affected their *head* than FMD. However, NES had a higher rate of clinical factors during their lifetime than FMD, such as dissociative symptoms, suicidal ideation, and being victim of bullying, which affect the mind, and from the patients' perspective they can be considered as located in the *head*.

In the second study, FND and HC experienced a similar size-weight illusion. The severity and laterality of the symptom did not impact on the strength of the illusion, nor the dominance of the affected side. However, we propose that it is likely to find an effect in FND with a larger sample size. Otherwise, if similar results were found in future studies, the SWI might be a test that provides an objective assessment to confirm FND has a normal perception of weight relative to size.

CHAPTER 1: INTRODUCTION

Functional Neurological Disorder (FND) is a condition that remains poorly understood despite being the focus of increasing research over the last decade. It is characterised by neurological symptoms of voluntary motor or sensory function which are not compatible with neurological disease (American Psychiatric Association, 2013) and is among the most common causes of disability (Carson & Lehn, 2016). The term “functional” is used to describe symptoms without a neuropathology, and one of its characteristics is the possibility of reversing the deficit because there is no damage to nerve cells, but rather a problem with their function (Lanska, 2006).

FND has a prevalence of 2-5/100,000 people, with estimates varying between 1% to 14% in clinical populations (American Psychiatric Association, 2013; Brown & Lewis-Fernández, 2011; Carson & Lehn, 2016; Anthony Feinstein, 2011). FND represents between 16-20% of neurological outpatients (Lempert, Dieterich, Huppert, & Brandt, 1990; Stone et al., 2010), although others have reported up to 60% (including other unexplained symptoms such as pain) (Nimnuan, Hotopf, & Wessely, 2001). It is the second most common cause of neurological consultation after headache (Stone et al., 2010). Patients with FND have a cost close to \$256 billion per year in the United States (Evens, Vendetta, Krebs, & Herath, 2015). Women were found to represent 73% of the patients in a transcultural study that included the United States and Spain (Cubo et al., 2005). The mean age at onset of symptoms reported has been between 35 and 50 years old, and appears to depend on the symptoms (Gelauff, Stone, Edwards, & Carson, 2014).

The symptoms are generally acute in onset, but often have multiple recurrences. Symptoms are typically classified into *motor symptoms* such as weakness and tremor; *sensory symptoms* such as blindness and tingling; *psychogenic nonepileptic seizures* (Stone, Warlow, Sharpe, et al., 2010) and other sub-categories such as *cognitive*, *balance* and *speech* functional symptoms (Espay et al., 2018). We will focus on *functional motor symptoms* and *nonepileptic seizures*.

The diagnostic criteria for functional neurological disorder according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) include one or more symptoms that affect body movements or senses; symptoms that cannot be explained by a neurological or other medical condition or another mental health disorder; and symptoms cause significant distress or problems in social, work or other areas (American Psychiatric Association, 2013).

Functional motor disorder (FMD) is the most common variant of FND and it is importantly correlated with disability and referrals to neurologists (Carson et al., 2011; Stone et al., 2010). FMD has been reported to be more common than multiple sclerosis, causing similar disability but with higher rates of psychological comorbidity (Carson et al., 2011; Stone et al., 2010). Similar levels of disability and quality of life have been reported between patients with FMD and Parkinson's disease (Anderson et al., 2007). The prognosis of FMD is unfavourable, since in most studies examined in a systematic review (20 out of 24) more than 33% of patients had the same or worse symptoms at follow-up (Gelauff et al., 2014). In the same review they found that specifically weakness and paralysis presented a great variation from 4% to 69% of patients (n= 25 – 60) with same or worse symptoms at follow-up. Like FND in general, there are more women than men in this variant, between 61%-87% (Factor, Podskalny, & Molho, 1995).

The variant of non-epileptic seizures (NES) consists of episodes of seizures that are not caused by epileptiform activity, disrupting daily life functioning (LaFrance & Devinsky, 2004). There are few population-based studies of this variant. Estimated prevalence is between 2 and 33 per 100,000 inhabitants (Hingray, Biberon, El-Hage, & De Toffol, 2016). Video electroencephalography-confirmed cases of NES have an incidence of 1.4 and 4.9 per 100,000 population per year (Espay et al., 2018). Around 5-10% of patients in epilepsy clinic is actually suffering from NES, reaching 20%-40% in tertiary centres (Hingray et al., 2016).

One obstacle to clinical research is the heterogeneity of FND symptoms. It is unclear why some patients present with motor/sensory symptoms while others present with seizures. The aetiology of FND remains unknown and likely involves a complex set of factors. A group of researchers propose that physiological or psychophysiological experiences, such as injuries, panic attacks and illnesses, among others, are intrinsically related to the kind of symptoms that patients develop. These authors suggest a mechanism (to be explained in more detail in the next section) in which these experiences, through incorrect beliefs and expectations of illness, might trigger autonomic physiological responses that generate FND symptoms (Edwards et al., 2012).

Indeed, these patients present with a great variety of precipitating physiological and psychophysiological experiences (Pareés, Kojovic, et al., 2014), which consist of physiological responses based on psychological processes, for instance, a change in heart rate as a result of exposure to a stressful event. However, even though the presence of precipitating factors is a typical clinical presentation and is supported by DSM-V diagnostic

criteria, this occurrence is not always detectable or existing. The occurrence of physical events, including infections, neurological disorders, drug reactions and surgery are very common, occurring in 80% of a sample of 50 FND patients (Pareés, Kojovic, et al., 2014). A systematic review found that physical injuries were reported at the onset of FMD in 37% of a sample of 869 patients (Stone et al., 2009). Organic disease has also been described as common, with up to 60% of co-occurrence (Folks, Ford, & Regan, 1984; Merksey & Buhrich, 1975). Several psychiatric comorbidities are known to be very frequent in FND patients too, the most common ones being depression and anxiety disorder, which includes panic disorder (Kozłowska, 2017; Kroenke, 2003; Sar et al., 2004; Stone, Zeman, & Sharpe, 2002; Wessely, Nimnuan, & Sharpe, 1999).

One study has proposed that FND correlates with common comorbid symptoms and events at the *onset* of the disorder: panic attacks (34% of patients, n=107); followed by dissociative symptoms (that usually occur with panic) (25%), pain (21%), and physical injury (10%) (Stone, Warlow, & Sharpe, 2012). These authors suggest that some motor symptoms might have potential relationships with physical injuries, for example, functional weakness has been found in some patients after experiencing a physical injury that involved immobility and attention focused on a specific body part. Nevertheless, these kinds of interactions have not been thoroughly studied in large samples and it is unclear if the different variants of the disorder are related to different kinds of comorbidities or physical events such as injuries or surgeries.

Therefore, our first goal is to study what kinds of prior clinical factors, such as comorbidities, injuries and surgeries are related to the two variants of FND, namely FMD and NES. To do this, we analysed a database that consists of medical records of 108 patients, which has information about symptoms, diseases and other conditions that patients have reported during the medical appointments. Studying the relationship between clinical factors and functional symptoms is helpful to understand the relationship between these factors and the development and perpetuation of FND. This may inform strategies to enhance current treatment strategies that can help to decrease the risk of developing FND or treat the symptoms when it has already started.

A second obstacle to clinical research is that simple objective measures are not useful in this group of patients, so there are no tests to assess the mechanisms involved and the symptom severity as well as their evolution (Espay et al., 2018). This obstacle is in part because the symptoms are inconsistent with neurological disease, for example, psychogenic

tremor is not continuously oscillatory as in organic disease; dystonia (involuntary contractions of the muscles) is usually unpatterned; and myoclonus (involuntary muscle jerks) tends to be slower and more difficult to classify than the organic myoclonus. Moreover, the symptoms change considerably across time and even during the medical appointment, evolving into another symptom (for instance tremor that evolves into myoclonus) or fluctuating in amplitude, frequency or anatomical distribution (Hallett, 2011).

The complexity of FND lies in an important component of subjectivity, particularly a mismatch between the perception of symptom and measured symptom, which is always performative. For instance, a patient with functional weakness will often show fluctuating signs of weakness, so that when they are asked to make a movement during the clinical appointment they generally perform poorly with their affected limb, although in other circumstances they can perform normally (Edwards & Bhatia, 2012). Normal or abnormal performance under certain conditions does not indicate that the patient is lying but is rather taken as evidence supporting the diagnosis. In these circumstances, the patient may have the *perception* of weakness that is different to the *objective* measure.

For these reasons, the few studies that have attempted to assess symptoms have not found differences between patients and healthy controls using conventional objective measures. For example, testing functional weakness with a dynamometer (van der Ploeg & Oosterhuis, 1991), using electromyography (McComas, Keresi, & Quinlan, 1983; Pillai, Markind, Streletz, Field, & Herbison, 1992), and measuring evoked motor responses by magnetic brain stimulation (Meyer et al., 1992).

The inconsistency of symptoms regarding known neurological disease and a reasonable neurological presentation, in addition to their variability across time, would suggest that performance of patients is highly influenced by other mechanism but nervous system lesion and probably are more based on beliefs about their disease (Pareés et al., 2012; Stone, Mutch, Giannokous, Hoeritzauer, & Carson, 2017). Some authors have reported that patients are particularly prone to suggestions to increase the intensity, frequency or to change kind of symptom (Hallett, 2011; Kenney et al., 2007). In fact, Bell and colleagues (2011) concluded that development of functional motor symptoms is more likely when the subject is highly hypnotisable, and that these symptoms can be modelled by suggestion (Bell, Oakley, Halligan, & Deeley, 2011). Hypnosis, suggestions and saline provocation are procedures that have been used to diagnose FND, however, they are not practised widely because they are currently considered unethical practices (Lafrance, Baker, Duncan, Goldstein, & Reuber,

2013). Thus, the diagnosis of FND is based on medical tests to dismiss other possible causes and diseases, and by characteristics of the patient's symptoms (Espay et al., 2018). However, the specificity and sensitivity of the medical observations might be biased by many factors, including that patients generally cannot describe with enough detail their subjective experience of symptom onset, as well as psychological factors that might be present (Deeley, 2016). Thus, searching for new, unbiased methods that can confirm the diagnosis will be a valuable contribution to this field.

Therefore, the second goal of this study is to find a reliable measure that allows testing the mechanisms underlying FND, particularly in functional weakness, because it is the most reported symptom in the literature (Stone et al., 2002).

Additionally, this measure must not be influenced by the patient's beliefs about how they should answer. To do this we will apply a questionnaire of severity of symptoms and a perceptual illusion called the "size-weight illusion" (Murray, Ellis, Bandomir, & Ross, 1999). The benefit of this illusion is that there is no correct or expected answer that can be predicted by the patient providing a means to directly assess changes in the individual's subjective experience. A reliable measure of changes to subjective experience would make it possible to test the effects of treatments or interventions, if that measure was found to reliably correlate with the individual's FND symptoms.

In sum, we aim to explore the relationship between clinical factors affecting different parts of the body (such as comorbidities, injuries and surgeries) and the two variants of FND; and secondly, we aim to find a reliable measure of perception in functional weakness by addressing the following research questions:

- Which clinical factors are more associated with functional motor disorder (FMD) in comparison to non-epileptic seizures (NES)?
- Do FND patients with functional weakness have a diminished size-weight illusion (SWI)?

ACCOUNTS OF FND MECHANISMS AND SYMPTOMS

Early models of FND, then known as "hysteria", based their assumptions on the presence of an early trauma. For instance, Charcot and Marie (1892) as well as Janet (1921) proposed that a possible mechanism of hysteria was a reaction to childhood trauma through autohypnosis or autosuggestion, resulting in somatoform dissociative symptoms (Charcot & Marie, 1892; Janet, 1921). Breuer and Freud (1955) proposed that hysteria was produced by a

mental process called conversion, which consisted of converting overwhelming emotions of traumatic events into physical symptoms, removing them from consciousness (Breuer & Freud, 1955).

However, little systematic evidence confirms these models, which leave a neurophysiological gap in how a psychological factor such as a trauma can manifest in physical symptoms (Espay et al., 2018; Pareés, Brown, et al., 2014). In addition, even though stressful events and maltreatment are present in a higher rate in patients with FND than in healthy and patient controls, many cases report no stressors (Kuloglu, Atmaca, Tezcan, Gecici, & Bulut, 2003; Ludwig et al., 2018; Roelofs, Keijsers, Hoogduin, Naring, & Moene, 2002; Stone et al., 2011). Conversely, not all people that have suffered trauma develop FND (Rofé, 2008). Thus, the traditional variable of prior experience of adversity is now argued to be a risk factor instead of a direct mechanism (Apazoglou, Mazzola, Wegrzyk, Polara, & Aybek, 2017). FND is now considered a neuropsychiatric condition which neurological symptoms are related to (not caused by) psychological risks and perpetuating factors (Hubschmid et al., 2015; Reuber, Burness, et al., 2007).

Currently, there are a variety of models attempting to explain the possible mechanisms underlying this disorder, and although there is no consensus or unified explanation, neurocognitive and neurophysiological perspectives are receiving increasing support (Demartini, Ricciardi, Crucianelli, Fotopoulou, & Edwards, 2016; Edwards, Moretto, et al., 2011; Espay et al., 2018; Pareés, Kojovic, et al., 2014; Stone, Warlow, Sharpe, et al., 2010). In fact, neurobiological evidence has challenged the notion that psychological mechanisms are the only causes of FND, supporting the replacement of the term *psychogenic* by *functional*, which replaces the erroneous dichotomy of physical/psychological and supports the possibility of reversibility (Stone, Carson, & Sharpe, 2005). Thus, the word functional is a more neutral concept, referring to symptoms, and contributes to understanding and acceptance on the part of the patients (Espay et al., 2018).

Recent studies with neuroimaging have concluded that FND presents with alterations in brain circuits related to emotion processing and emotion-motor processing that could be related to functional symptoms (Ejareh dar & Kanaan, 2016). The limbic system (which includes, among others, *the hippocampus*, *amygdala* and *cingulate cortex*, related to memory and emotions) is abnormally connected to brain areas involved in motor function (the *supplementary motor area* and *right temporo-parietal region*), when dealing with trauma

(Aybek et al., 2014) or emotional stimuli (Aybek et al., 2015; Blakemore, Sinanaj, Galli, Aybek, & Vuilleumier, 2016; Voon et al., 2010).

Higher activity in the *amygdala* has been found while patients faced fearful and happy faces compared to neutral ones, presenting a hyperarousal state (Voon et al., 2010), in a task where the patients had a lack of habituation to negative stimuli (Aybek et al., 2015), and during emotional stimulation and passive movement of the affected hand in FND patients with hemiparesis (Hassa et al., 2017).

Another study found a higher activation in the *supplementary motor area* (SMA) and the *cingulate cortex* when FND patients attempted to move the paralysed limb (Deeley et al., 2013). Increased activation in the *anterior cingulate gyrus* was reported as a result of self-monitoring during a reaction time-task in patients with unilateral paralysis (van Beilen, Vogt, & Leenders, 2010).

A study using biological markers and a measure of motor readiness has confirmed that FND presents with increased brain and body *arousal* (Kozłowska et al., 2017; Lader & Sartorius, 1968) and increased baseline *stress hormone* (cortisol) (Bakvis et al., 2010) .

The brain-body stress system, which is responsible for triggering automatic responses to threat, can be activated by stress, pain, injury or trauma (Arnsten, 2015; Bakvis et al., 2010; Hermans et al., 2011). This system consists of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, immune-inflammatory system, and brain systems related to pain, arousal and emotions. Studies that have compared defensive actions in humans with animals, have found similarities, for example behaviours like protective immobility, freezing before threat and motor arrest (Nijenhuis, Vanderlinden, & Spinhoven, 1998; Whitlock, 1967). High levels of cortisol in monkeys after exposure to psychosocial stressors has been found to drive fear and freezing responses of longer duration (Kalin, Shelton, Rickman, & Davidson, 1998). It is proposed that psychosocial stressors are responsible for non-conscious avoidance and coping mechanisms in FND (Vuilleumier, 2005).

Thus, physiological and psychophysiological experiences may trigger functional neurological symptoms by impacting the stress system. These experiences and their autonomic responses can be taken as abnormal models for body sensations, being able to trigger symptoms in the future as well (Edwards et al., 2012; Pareés, Kojovic, et al., 2014). Interestingly research suggests that the potential connection with the functional symptom is the psychological impact of these experiences rather than the objective severity of the event

(Stone et al., 2009). So that, in a vulnerable person, a mild injury can trigger a cascade of psychological processes leading to functional symptoms.

THE ROLE OF EXPECTATIONS IN FUNCTIONAL NEUROLOGICAL DISORDER (FND)

A neurobiological mechanism has proposed that physiological and neuropsychological experiences can influence beliefs and expectations about how the brain and body work, generating functional symptoms (Edwards, Fotopoulou, & Pareés, 2013). The process starts with an event that leads people to generate abnormally strong *priors*, which are top-down predictions or predictive representations of the self and environment. These priors have a top-down impact on lower-level functions such as senses, triggering physiological arousal and excessive attention to one's own body (interoceptive vigilance) (Barsky & Wyshak, 1990). Higher arousal and interoceptive vigilance can either nullify or overwhelm any "bottom-up" signals (incoming stimulus) that are out of keeping with it, provoking an increase in the probability of the expected symptoms occurring (Edwards, 2016; Edwards et al., 2012). This mismatch between bottom-up sensations and top-down prior beliefs lead to prediction errors that drive functional symptoms (Pareés, Kojovic, et al., 2014).

In other words, catastrophic thoughts about possible consequences of an injury or disease (such as the idea of permanent damage) can generate implicit predictions about body sensations (Stone et al., 2005). As these predictions are incorrect, they lead a patient to infer that normal body sensations are symptoms, increasing attention to the body and therefore perceiving an amplification of sensations (Brown & Reuber, 2016; Stone et al., 2009; Van den Bergh, Witthöft, Petersen, & Brown, 2017). Then, previous somatic symptoms or even normal sensations are reattributed to a current injury or disease, producing medically unexplained symptoms. Thus, incorrectly interpreted body sensations might lead to development of a symptom, for example, developing a fixed dystonia of a leg after a surgery on the same leg (Demartini, Goeta, et al., 2016). Behaviours like extreme rest or disuse of a limb may contribute to the generation and perpetuation of a symptom, since they reinforce the beliefs and expectations of disease (Stone et al., 2009).

Therefore, the way patients perceive and experience their symptoms is not a direct inference of bodily sensations, but instead mediated by biased inferences (Van den Bergh et al., 2017). Previous experiences such as illnesses and physical injury to a limb may cause a person to make implicit predictions about interoceptive information (sensory information

from the body), which when incorrect might result in dysfunctional processes (Pareés et al., 2014; Stone et al., 2009).

To understand what kinds of ideas of symptoms people have, researchers asked healthy people to pretend that they had certain neurological symptoms (Stone et al., 2017). They found that people pretended symptoms based on their beliefs of symptoms instead of, the sometimes-counterintuitive nature of anatomy and physiology. For instance, 80% of the people that pretended to have a paralysed arm thought that this would be accompanied by sensory loss, which is not a characteristic of neurological disease. This presentation is similar to functional paralysis seen in FND, although that is not thought to be voluntarily produced. Incorrect ideas of symptoms, instead of how symptoms really are, might explain the heterogeneity of functional symptoms and their incongruence with neurological disease (Stone & Carson, 2011; Stone et al., 2017).

The role of beliefs and expectations in the generation and remission of symptoms is evident in the positive response of FND patients when placebo is administered (which is very dependent on people's expectations), since in some cases their symptoms get better (Hallett, 2011). Here I mention a case report involving a patient who showed an immediate resolution of dystonia after the administration of an injection of botox toxin that takes at least 24 to 48 hours to relax muscles (Edwards, Bhatia, & Cordivari, 2011). Additionally, some kinds of symptoms are more common in some cultures than others, which is explained by beliefs being culturally influenced. An example is the "whiplash injury" that consists of neck pain after a minor traffic collision, which is much less common in countries where it is not widely known (Ferrari et al., 2001). Frequent exposure to friends or relatives with neurological disease, can also be a model for developing functional symptoms. This was reported in 55% of patients with FMD, and in 7% of patients with NES (Asadi-Pooya & Emami, 2013). This is a feasible explanation so far for those cases of motor symptoms seen in several members of the same family (Stamelou et al., 2013).

Besides the research described above, there are very few studies that focus on clinical events that patients experience and the relationship with symptoms. Nevertheless, by considering these models that state the importance of the ideas that patients have, and how these may affect their bodies, generating functional symptoms, it is very pertinent to study the comorbidities, surgeries and injuries they have had.

Based on this evidence, we think that clinical factors such as diseases, injuries or surgeries are important factors that should be studied, since they can be used as models of

body sensations and symptoms, and through incorrect expectations and beliefs can impact the stress brain-body system, triggering a chain reaction of psychological and physiological processes. Thus, it would be interesting to thoroughly understand their relationship with the FND variants, namely FMD and NES.

In fact, some authors have found a strong relationship between physical events (such as injuries or illnesses) and FND symptoms. Pareés et al. (2014) documented that in 50 patients, physical events preceded about 80% of the FND presentations. Other kinds of physical events reported by these patients were physiological experiences (e.g., hypnic jerks (involuntary twitches when a person is beginning to fall asleep), sleep paralysis (a feeling of being conscious but unable to move while sleeping), pathophysiological experiences (e.g., pain after injury, migraine) or psychophysiological experiences (e.g., panic attacks). These authors suggest that the symptoms the patients develop are consistent with the kinds of priors (previous experiences) that they have had. These symptoms, which are manifested involuntarily, have the same characteristics as those produced voluntarily, thus the presence of priors that define movement patterns that could be triggered involuntarily is plausible (Edwards et al., 2012). The extent to which FMD and NES patients have experienced different types of clinical events in the past remains unknown. Studies of clinical factors in these patients are mainly focused on FND in general, or on one specific symptom variant.

CLINICAL FACTORS IN FUNCTIONAL MOTOR DISORDER (FMD) AND NON-EPILEPTIC SEIZURES (NES)

Studies of the FMD variant of FND have found high rates of comorbid psychiatric syndromes (33%), personality disorders (50%), and pain (50%) (Stone, Warlow, Sharpe, et al., 2010). In one meta-analysis, the authors reported that physical injury prior to symptom onset was the most common characteristic of these patients (37% of 324 patients) (Stone et al., 2009). Similar rates have been seen in patients with symptoms such as functional dystonia (Schrage, Trimble, Quinn, & Bhatia, 2004). Physiological triggers such as sleep paralysis, general anaesthesia and long bed rest have been reported as common in functional weakness (Stone et al., 2012). Somatic symptom disorders, that consist of distressing somatic symptoms and abnormal thoughts, feelings and behaviours about these symptoms, including pain disorder and hypochondriasis (American Psychiatric Association, 2013), have been found in 25% of patients in a sample of 500 (Guze, Woodrugg, & Clayton, 1971), and other

studies have reported from 8% to 43% (Kapfhammer, Buchheim, Bove, & Wagner, 1992; Wilson-Barnett & Trimble, 1985).

There are no studies that specifically report on the presence of surgeries, however in a study looking at factors relevant to FMD, 12% of patients were found to present with functional motor symptoms after drug reaction or major surgery (Pareés, Kojovic, et al., 2014). There are a few case studies that describe the occurrence of functional motor symptoms, particularly paraplegia, after general anaesthesia for breast surgery (Mason, 2017); difficulty speaking, numbness, weakness and paralysis 1 hour after general anaesthesia (Afolabi et al., 2016); two cases of psychogenic paralysis after spinal surgery (Zhu, Ni, & Guo, 2012); and a case of motor and sensory symptoms on upper extremities and face after a brain tumour surgery (Szota, Ogłodek, & Araszkiewicz, 2013).

Regarding NES, a study of 158 patients reported that 66% presented with at least one of the following disorders: somatic syndromes including fibromyalgia; chronic fatigue syndrome; chronic pain syndrome; tension headaches; irritable bowel syndrome, and chronic diseases such as migraine; asthma and gastroesophageal reflux disease (Dixit, Popescu, Bagić, Ghearing, & Hendrickson, 2013). These chronic diseases have similar characteristics to seizures, as they are chronic, have intermittent attacks and may be interpreted as seizures, being considered risk factors to develop FND (Dixit et al., 2013). Another study reported somatic symptoms in between 22% and 84% of patients with FND; dissociative symptoms in 22% to 91%; post-traumatic stress in 35% to 49%; depressive disorders in 57% to 85%; and anxiety disorders in 11% to 50% (Bowman, 1993; Bowman & Markand, 1996; Griffith, 1990; Kanner et al., 1999; Krishnamoorthy, Brown, & Trimble, 2001; Mökleby et al., 2002; Reuber, Fernández, Helmstaedter, Qurishi, & Elger, 2002; Reuber, Howlett, Khan, & Grünewald, 2007). There are case studies that report episodes of psychogenic NES after recovering from anaesthesia for gynaecologic surgery (Ramos & Brull, 2013); after epilepsy (Reuber et al., 2003); epilepsy surgery (Glosser, Roberts, & Glosser, 1999); head injury (Barry et al., 1998; Westbrook, Devinsky, & Geocadin, 1998); and intracranial surgery (Reuber, Kral, Kurthen, & Elger, 2002).

There are no comparisons between comorbidities, injuries or surgeries in patients with FMD and NES so far. By comparing other variables, studies have found similarities in their characteristics, suggesting they are part of the same clinical spectrum (Erro et al., 2016; Hopp, Anderson, Krumholz, Gruber-Baldini, & Shulman, 2012), while others have stated a great heterogeneity (Reuber, Howlett, et al., 2007; Stone, Sharpe, & Binzer, 2004). A review

studying differences between FMD and NES to determine if NES is just another symptom of FND, found 8 studies comparing them directly (Kanaan, Duncan, Goldstein, Jankovic, & Cavanna, 2017). They proposed that the variants are different disorders - while FMD is an acute response to immediate trauma, NES has a slow development across life. Table 1 shows the main variables compared in different studies.

Table 1. *Variables of Functional Motor disorder compared with Non epileptic seizures.*

Variable	NES	FMD
* Education level (Driver-Dunckley, Stonnington, Locke, & Noe, 2011; Hopp et al., 2012)	36% incomplete high school 64%-43% college	15% incomplete high school 85%-41% college
Female predominance (Abubakr, Kablinger, & Caldito, 2003; Factor et al., 1995; Lancman, Brotherton, Asconapé, & Kiffin Penry, 1993)	74%-90%	61%-87%
Employed or retired / Unemployed / Disabled (Driver-Dunckley et al., 2011; Hopp et al., 2012)	47% / 19% / 34% respectively	44% / 33% / 24% respectively
* Age at onset (Abubakr et al., 2003; Driver-Dunckley et al., 2011; Hopp et al., 2012; Lempert et al., 1990; Stone et al., 2004)	30s	30s – 50s
Depression and anxiety (Driver-Dunckley et al., 2011; Hopp et al., 2012)	42% and 16% respectively	41% and 48% respectively
Histrionic and borderline personality disorders (Baillés et al., 2004; A Feinstein, Stergiopoulos, Fine, & Lang, 2001)	60%	45%
Chronic pain syndrome (Driver-Dunckley et al., 2011)	67%	75%
Fibromyalgia (Driver-Dunckley et al., 2011)	18%	16%
Subjective fatigue (Driver-Dunckley et al., 2011)	41%	57%
Sleep disorders (Driver-Dunckley et al., 2011)	21%	34%
Physical injury (Driver-Dunckley et al., 2011)	12%	13%
Substance / alcohol abuse in the family (Driver-Dunckley et al., 2011)	33% / 26%	30% / 20%
* Sexual abuse (Driver-Dunckley et al., 2011)	31%	16%
* Childhood abuse (Driver-Dunckley et al., 2011)	41%	21%
Physical abuse (Driver-Dunckley et al., 2011; Pareés, Kojovic, et al., 2014; Reilly, Baker, Rhodes, & Salmon, 1999; Reuber, Howlett, et al., 2007)	35% - 80%	21%

* Statistically significant < 0.005

The authors that advocate that the variants are the same disorder but located at two ends of a continuum, presenting with different symptoms, based this on similarities in age and sex distribution, psychiatric comorbidities, psychological profiles, and rates of chronic pain and somatization disorders (Erro et al., 2016). In particular, there is evidence of similar levels of depression and anxiety (Hopp et al., 2012) and similar rates of subjective fatigue and sleep disorders (Driver-Dunckley et al., 2011). Moreover, it has been reported that both groups present with previous surgery or physical trauma, dysfunctional family relationships and stressful life events (Lancman et al., 1993).

Among the differences, studies have stated higher rates of trauma and physical abuse in NES (Reilly et al., 1999; Reuber, Howlett, et al., 2007), finding up to 63% of patients reporting previous trauma (Dixit et al., 2013). Others have reported higher rates of emotional, physical or sexual abuse in NES (Driver-Dunckley et al., 2011; Kranick et al., 2011).

The evidence available suggests similarities and differences between FMD and NES in several variables. In our study we will analyse these factors and compare comorbidities, injuries and surgeries that both groups of patients have reported, since these are proposed to have a key role in the formation of ideas of disease as they are present prior and during the disease, being considered risk and perpetuating factors.

If the symptoms are influenced by clinical factors that lead to different expectations of body sensations, we anticipate that FMD would have a higher proportion of disorders, surgeries and injuries related to legs and arms, since their symptoms are located mainly in the limbs, while NES would have a higher proportion of disorders related to the head, such as psychiatric and neurological comorbidities, since dissociative symptoms present in NES are located in the brain.

We believe that studying comorbidities, injuries and surgeries can shed some light on whether the variants of FND are more related to some kinds of physical events than others. We would expect to have a larger sample than previous studies, and to have recruited and assessed both variants from the same sample. This information may be helpful to future studies aimed at identifying suitable treatment strategies that tackle not only the symptoms of FND, but other associated comorbidities. This is especially relevant since it is still unclear which kind of treatment should be the best for the patients and for how long it should last (Espay et al., 2018). Moreover, this knowledge may help patients to understand their disorder better, by offering an explanation of the diagnosis that validates the disease allows the patient to understand and accept it, which is very important for therapeutic success (Stone, 2016).

MEASURES OF FUNCTIONAL WEAKNESS

PREVIOUS ATTEMPTS OF MEASURING FUNCTIONAL WEAKNESS

FND symptoms are difficult to measure objectively due to their inconsistency compared to neurological disease and the fact that the symptoms can fluctuate across time. These characteristics are suggested to be influenced by beliefs about disease and desirability about performance (Pareés et al., 2012; Stone, Mutch, Giannokous, Hoeritzauer, & Carson, 2017). Since the symptoms have inconsistent presentation over time, increasing and decreasing intensity between appointments or even in the same examination, the patients' perception of the symptoms does not correspond with the symptom measured in an objective fashion (Espay et al., 2018). For these reasons there are very few studies that have attempted to assess symptoms objectively (using dynamometer, electromyography, evoked motor responses, etc.), and those few have produced inconsistent results (McComas et al., 1983; Meyer et al., 1992; Pillai et al., 1992; van der Ploeg & Oosterhuis, 1991).

So far, there are very few objective tests or reliable measures available to study the symptoms and their evolution, and these few are not well suited to assessing severity or changes in symptoms. The diagnosis is based on positive evidence of internal inconsistency, other characteristics of the disorder and by excluding other possible causes (Espay et al., 2018). However, the specificity and sensitivity of the medical observations might be biased by many factors (Deeley, 2016). There are many cases in the literature in which neurological diseases have been misdiagnosed as functional neurological disorder, particularly in those patients that present with characteristics that are typical of FND, such as anxiety, recent stressful event, and psychiatric comorbidities (Stone, Reuber, & Carson, 2013). The opposite has also been seen, for instance, a patient that does not meet the common features because they are “male”, are “too old” or “do not have psychiatric disorders”, for example, may cause the doctors to think that they must have a neurological disease (Stone et al., 2013).

We aim to identify a reliable perceptual measure that does not have desirable answers, as is the case for measuring force or speed, which can be manipulated by applying less force or being slower with the most affected limb. To overcome this issue, we chose the “size-weight illusion”, a perceptual measure where the subject cannot predict the answers, is related to relevant sensory and perceptual mechanisms without needing to ask patients directly to perform a task that obviously assess their reported deficit.

THE SIZE-WEIGHT ILLUSION (SWI): A POSSIBLE MEASURE OF MECHANISMS INVOLVED IN FUNCTIONAL SYMPTOMS?

The size-weight illusion is a well-described task that allows us to study the different pathways thought to be involved in FND: cognitive pathways, such as attention and expectations (Buckingham & Goodale, 2010a), perceptual pathways (Flanagan & Beltzner, 2000), and sensorimotor pathways (Murray et al., 1999). This illusion occurs when lifting a small and a large object that have the same weight, and the typical result is that the smaller object feels consistently heavier than the large one (Murray et al., 1999). Before lifting two objects, people predict that the large one will be heavier than the small one and will use grip and lift forces according to this (Ellis & Lederman, 1998). Then, when lifting the objects, there is a mismatch between the expectation (the large object will be heavier) and the sensory feedback, where applying more force to the large object produces the sensation that it is lighter than it really is, and conversely, applying less force to the small one produces the sensation that is heavier than really is (Buckingham & Goodale, 2010b; Davis & Brickett, 1977; Gordon, Forssberg, Johansson, & Westling, 1991).

The illusion is thought to depend on long-term expectations, since prior knowledge does not integrate with the current sensory evidence after repeated lifting or after learning that the objects weigh the same (Flanagan & Beltzner, 2000). Furthermore, people experience the illusion after seeing the objects and then lifting them with their eyes closed (Buckingham & Goodale, 2010a). However, if people cannot see or touch the objects at any time (for example lifting them by a wire or strip), they do not experience the illusion, which means that visual or tactile perception (cues of size) added to expectations play an important role (Dijker, 2008; Ellis & Lederman, 1993).

People lift objects applying forces according to their expectations, which are based on experience, where weight is relatively correlated with size (Dijker, 2014). The brain learns constancies through sensorimotor interaction, this is, through integration of daily life actions and sensations (Guillery, 2017). Without this integration, sensory messages on their own have little meaning for the brain. Accordingly, actions and their sensory consequences are anticipated. These expectations lead to the adaptiveness of the behavioural mechanism, which forces people to perceive in a particular way rather than voluntarily discovering properties of the objects (Dijker, 2014). This is consistent with the view of internal models that suggests that organisms utilize their knowledge of past events to deal with the present and future (Craik, 1943), so that the central nervous system exercises control (called the inverse model)

and prediction (called forward model) to produce motor actions and perception (Figure 1) (Kandel, Schwartz, Jessell, Siegelbaum, 2014).

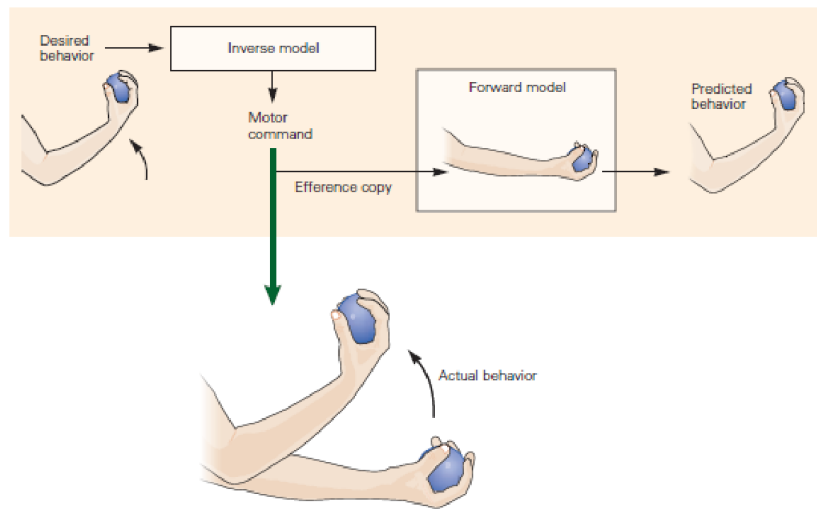


Figure 1. The inverse model determines the motor commands to do an action towards a goal, then a descending motor command goes through the musculoskeletal system to produce motor output. A copy of this motor command is passed to a forward model, which simulates the interaction between the motor system and the world to predict behaviour. If the system works correctly, both the predicted and the desired action (forward and inverse model) will be the same (Kandel, Schwartz, Jessell, Siegelbaum, 2014).

This neurocognitive mechanism is a predictive system of motor control, and its role is to allow people to anticipate their own movements and sensations (Blakemore, Wolpert, & Frith, 1998). This system is responsible for anticipating the sensory consequences of one's own movements; as a consequence, the perceptions of these sensations become attenuated and the sensations from external sources become salient. This sensory attenuation is important to perceive movements and actions as self-generated, and its loss is suggested to be caused by a temporal and spatial offsetting between the movement and the sensations, resulting in a pathological perception of one's own movements (Blakemore, Frith, & Wolpert, 1999; Blakemore, Wolpert, & Frith, 2002). The predictive mechanism has been reported to be related to symptoms in schizophrenia (Shergill, Samson, Bays, Frith, & Wolpert, 2005) and recently in FND (Edwards, Moretto, et al., 2011; Macerollo et al., 2015; Pareés, Brown, et al., 2014). In the case of schizophrenia, it has been associated with one of the characteristics of this disorder, which consists of some symptoms perceived as those of an external agent. In the FND group it has been proposed to be related to the perception that the motor symptoms are out of their control (Kranick et al., 2013). The difference between both

groups might be that patients with schizophrenia rely on external cues, whereas patients with FND depend more on internal pathological predictions regarding movement (Edwards et al., 2012). Thus, sensory attenuation allows us to differentiate between perceptions coming from self-produced motor actions and sensory changes produced by external triggers (Cullen, 2004). Furthermore, the belief of authorship of actions is attributed to sensory attenuation, which is the belief of being the cause of sensory changes in the environment (Blakemore et al., 2002; Weiss, Herwig, & Schütz-Bosbach, 2011).

Specifically, FND patients have been reported to not attenuate the sensory consequences of their own actions (Pareés, Brown, et al., 2014). In that study the patients did not reduce the force they needed to press directly on their own finger, unlike the control group. Another study suggesting the same underlying mechanism reported that patients with FMD had a decreased intensity of sensory experience and sensory evoked potentials amplitude when movements were self-generated (Macerollo et al., 2015). This deficit is related to abnormal self-directed attention that is key to detecting sensory information coming from one's own body. It is suggested that FND patients have difficulty in focussing their attention on relevant stimuli and inhibiting irrelevant ones, including their own body movements (Roelofs, van Galen, Keijsers, & Hoogduin, 2002). This is important for voluntary movement and is proposed to be an implicit measure of sense of agency (Pareés, Brown, et al., 2014).

Furthermore, FND, in comparison to healthy controls, has been reported to have decreased action-effect binding for normal voluntary movements (Haggard, Clark, & Kalogeras, 2002; Kranick et al., 2013). In the same line of research, a study using fMRI to study brain activity in FND patients during an episode of tremor, compared functional tremor with voluntary mimicked tremor, found that FND tremor had right temporoparietal junction (TPJ) hypoactivation and lower functional connectivity of this area with sensorimotor regions (involved in movement) and limbic regions (involved in emotional processing and memory) (Voon et al., 2010). Since the TPJ is involved in the comparison between internal predictions and outcomes, they suggest that FND patients have a lack of appropriate sensory prediction signals, consequently occurring a mismatch with proprioceptive feedback, leading to a lack of control for movements or sensation that is not self-generated.

Research regarding medically unexplained symptoms suggests that the perceptual system generates and tests hypotheses about the causes of sensory inputs, and this mechanism can make incorrect inferences, producing symptoms. They propose that medically unexplained

symptoms are similar to visual illusions, and are in fact “somato-visceral” illusions (Norman, Berntson, & Cacioppo, 2014; Van den Bergh et al., 2017).

It has been suggested that when incorrect predictions are made, confusing perceptions and sensations regarding movement are produced and that this might lead to FND symptoms (Pareés, Brown, et al., 2014). The confused or absent perceptions of sensory and/or motor function in FND patients are proposed to reflect a failure in the prediction systems, which leads to wrong perceptual inferences being produced (such as, believing these sensations or movements are products of an illness). These lead to the creation of imprecise expectations, which in turn lead to overwhelming bottom-up sensory information and to increased attention towards the incorrect sensations, reinforcing the process (Edwards et al., 2013). For example, in the case of patients with functional weakness, their wrong expectations about lack of force (caused by previous injury or a physical event) lead them to perceive difficulty in generating movement (power, direction or speed), thereby inhibiting their motor function. Since the attention to their symptom increases, there is an association between the belief and the sensation, perpetuating the symptom (Edwards et al., 2012).

Therefore, we propose that the size-weight illusion allows us to test the predictive sensory-motor mechanism involved in FND in a reliable fashion. The assumed misperception of body sensations along with lack of control of movements might produce a wrong perception of internal stimuli, which might impact the performance in the SWI.

THE SIZE-WEIGHT ILLUSION (SWI) IN CLINICAL POPULATIONS

The SWI has been widely tested in healthy populations, however there are some research articles that have studied the illusion in patients with unilateral brain damage (with and without apraxia) (Li, Randerath, Goldenberg, & Hermsdörfer, 2011), patients with unilateral damage (with apraxia) (Buckingham, Bieńkiewicz, Rohrbach, & Hermsdörfer, 2015), patients with isolated cerebellar degeneration (Rabe et al., 2009) and a non-clinical sample varying in autism like traits (Buckingham, Michelakakis, & Rajendran, 2016). They found the illusion to be present in the patients, which is to say that they perceived the small object to be heavier than the large one.

However, this task had different results in patients with anorexia (Case, Wilson, & Ramachandran, 2012) and schizophrenia (Williams, Ramachandran, Hubbard, Braff, & Light, 2010). In these studies, the researchers found the point of subjective equality, which is the point where participants could not differentiate which of the objects was heavier. By this

measure, they found a weaker illusion in the patient groups than in healthy controls. In other words, patients reported that the larger object was similar to the smaller object when their weights were indeed similar to each other, being more precise than the control groups. These results were attributed to a decreased integration of visual and proprioceptive information and a possible sensory prediction deficit (Case et al., 2012; Shergill et al., 2005; Williams et al., 2010).

Even though FND, anorexia and schizophrenia are different disorders, they are proposed to have a deficit in the predictive process of motor control and sensory integration. This process is thought to be involved in the lack of control of movements, in the misperception of body image and sensations and in the perception that symptoms are produced by an external agent, respectively, which may generate similar perceptions in the SWI, a perceptual illusion that depends on this process.

Therefore, we hypothesise that FND patients experience a diminished illusion in the SWI than healthy controls (HC), which means that they should be more accurate in estimating weights. Moreover, we expect that patients with greater symptoms might experience a more diminished illusion in comparison to those with lesser symptoms.

Using this task, we may have a numerical measure of their deficit, which might be used as a consistent measure for future research. Moreover, this task provides information about the perception of FND patients without asking them directly, which would be unreliable as they tend to be driven by their abnormal beliefs of what is desirable to respond.

CONTROVERSIES ABOUT THE ROLE OF EXPECTATIONS IN THE SIZE-WEIGHT ILLUSION (SWI)

In spite of over more than 100 years of research, there is still controversy around an explanation that would fully account for the size-weight illusion. There were authors that proposed a crucial role of expectations (Davis, 1973; Dijkster, 2008; Koseleff, 1958), while others admitted a small role without consequences for sensorimotor processes, or denied any role at all (Amazeen & Turvey, 1996; Gibson, 1979; Turvey & Shaw, 1995).

The role of expectations has been supported by several studies. One of them found that when people lift two equal-weight objects via an attached handle or string, without being aware of the objects' sizes, the differences in weight are not perceived. However, when people are exposed to visual cues, that is, they can see the size of the objects while lifting, they experience the illusion, with the perceived weight being negatively influenced by size. In this case, perception of size must have a role, instead of differences in mass (Lancman et

al., 1993). Along the same lines, one of the first studies of the illusion proposed that people tend to avoid looking at the objects while lifting them in order to have a more accurate perception of weight, suggesting that visual perception, and in turn expectations, does affect sensory perception (Ross, 1969). Dijker (2008) found that the perception of size affected the perception of weight of same-weight objects, and this relationship was mediated by expectations of weight. In this study, participants compared dolls of equal weight and different sex. Participants did not perceive differences in weight when dolls were lifted without seeing them, but they did perceive different weight when they saw the dolls while lifting, being aware of their sex. Thus, expectancies of weight according to dolls' sex mediated the effect of perception of size on the perception of weight. The role of expectations was also demonstrated in another study which found that the illusion could be diminished by altering lifters' expectations, through perceptual training (Flanagan, Bittner, & Johansson, 2008).

These kinds of evidence lead to the most predominant explanation for the SWI: that people create expectations through experience, where larger objects are heavier than smaller ones. When different sized objects of the same weight show up, the expectations are violated leading to incorrect weight perceptions (Buckingham & Goodale, 2010a; Dijker, 2008; Murray et al., 1999).

Nevertheless, this explanation has been questioned by researchers who have investigated whether resistant forces or inertia perceived during lifting also contributes to the perceived weights. These resistances depend on mass distribution in three dimensional space, suggesting that prior expectations about weight do not have a key role (Amazeen & Turvey, 1996; Gibson, 1986; Turvey, Shockley, & Carello, 1999). It is clear that the weight of hidden objects depends on their volume and mass distribution, for example, when cylinders attached to a wire increased their length but keeping their mass were perceived as heavier. Therefore, the manner in which objects are used affects perception of inertia, and in turn weight (Amazeen, 1997). However, these studies did not allow participants to explore the object's shape visually or haptically as in the SWI studies (Lederman & Klatzky, 1993). Experiments that demonstrate the influence of expectations have used models where resistances are constant and where participants can perceive differences in size by seeing and/or touching the objects (reversing the perception and producing a typical SWI) (Dijker, 2008; Ellis & Lederman, 1993).

A second controversy arises from the idea that, since expectations of weight are potentially modifiable when new information is available, perception should also change. This is different to what happens in the SWI, where participants continue experiencing the illusion even after being given new sensory-motor or verbal information about the actual weight of the objects (Buckingham & Goodale, 2010a; Flanagan & Beltzner, 2000; Gordon et al., 1991; Johansson & Westling, 1988). Furthermore, evidence supports that the SWI is dependent on visual perception of size, since when people lift the objects hidden from view after having seen them for only 1 or 2 seconds, the SWI disappears (Masin & Crestoni, 1988). Therefore, according to this view, the SWI depends on sensory information instead of expectations. This is because, if expectations were important, they would affect weight judgements through top-down processing. In another similar experiment they found different results, arguing against the importance of continuous visual exposure to size cues. Here, the participants experienced the SWI when lifting the objects blindly after being briefly exposed to the objects (Buckingham & Goodale, 2010a). In this study, participants lifted one single cube without being aware that they were lifting the same object in every trial. The experiment consisted of priming participants' expectations, so that they felt that the object was much heavier when they expected to lift a large cube. However, the difference between both experiments is that the first one used 15 objects of different weight and size, which is a complex task for working memory, while the second one used only 3. Therefore, it is argued that these studies seem to indicate that the SWI does need visual cues (real, memorized or imagined) to be experienced.

Finally, if expectations are key, and these are created and modified through experience, they should be stronger with age. Although previous developmental studies found that the SWI decreases with age (Gordon, Forssberg, Johansson, Eliasson, & Westling, 1992; Pick & Pick, 1967; Robinson, 1964), new research supports the notion that SWI increases with age (Chouinard et al., 2019).

In an attempt to integrate this controversial evidence, Dijkers (2014) has proposed that the sensorimotor mechanism influences perception and behaviour from early life, leading to formation of weight-size expectations that are very difficult to modify by verbal or visual information. These expectations are in part responsible for the unexpected weight relative to size perceived in the SWI, added to the lifting movements necessary to judge weight, which are not voluntarily determined. Therefore, this mechanism is activated and deactivated through unexpected size-weight patterns in the SWI, generating inappropriate motor output in

a constant fashion. When new evidence is available, these expectations are modifiable but without removing the older adaptive and reactive mechanisms, so that the motor response is still based on internal representations instead of on current sensory motor information (Dijker, 2014).

Outline

To summarize, this thesis consists of two main objectives. The first one is to study whether there is a relationship between the two main variants of functional neurological disorder (FND), namely, functional motor disorder (FMD) and non-epileptic seizures (NES), and previous clinical factors. Among these factors are diseases, injuries and surgeries that affect different parts of the body and other psychiatric comorbidities. We anticipate that FMD would have a higher proportion of disorders, surgeries and injuries related to legs and arms, since their symptoms are located mainly in the limbs, while NES would have a higher proportion of disorders related to the head, such as psychiatric and neurological comorbidities, since dissociative symptoms present in NES are located in the brain.

The second aim is to consider the size-weight illusion (SWI) as a possible objective measure to identify perceptual differences in FND patients that present with weakness. We hypothesise that FND patients experience a diminished illusion in the SWI than healthy controls (HC), which means that they should be more accurate in estimating weights. Moreover, we expect that patients with greater symptoms might experience a more diminished illusion in comparison to those with lesser symptoms.

This thesis is structured in three further sections: chapter 2 will present the methodology, results and discussion of the clinical factors associated with functional motor symptoms and non-epileptic seizures. Chapter 3 will present the methodology, results and discussion of a preliminary study exploring the capacity for the SWI to objectively measure functional weakness. Finally, chapter 4 will discuss the main results and practical implications of this thesis.

CHAPTER 2: CLINICAL FACTORS IN PATIENTS WITH FUNCTIONAL MOTOR DISORDER AND NON-EPILEPTIC SEIZURES

INTRODUCTION

FND symptoms are inconsistent with neurological diseases or other medical conditions. They disappear with distraction or suggestibility, or may evolve into other symptoms (Hallett, 2011; Kenney et al., 2007). Thus, some researchers purport that FND symptoms are dependent on the individual's *idea* of disease and are heavily influenced by expectations of how the brain and body work (Edwards, 2016; Edwards et al., 2013; Pareés et al., 2012). If this is correct, it may explain why FND patients develop some symptoms instead of others.

The generation of these expectations are thought to be based on the previous patients' experiences. Among these experiences there are several risk factors or vulnerabilities that make the appearance of functional symptoms more probable (Stone et al., 2005). Biological, psychological and social factors have been found relevant, for instance: genetic influences that affect the personality, coping styles and childhood neglect or abuse, respectively. Additionally, some of these play a role as predisposing (e.g. biological vulnerability of the central nervous system), precipitating (e.g. hyperventilation, physical injury) or perpetuating factors (e.g. depression, anxiety, etc).

There are studies that highlight the relevance of certain factors over others, such as previous life events (Nicholson et al., 2016) and traumatic experiences such as physical, emotional or sexual abuse (Breuer & Freud, 1955; Roelofs, Spinhoven, Sandijck, Moene, & Hoogduin, 2005), while others suggest that experiences such as physical events and diseases can trigger the symptoms by impacting the stress pathways within the brain and body (Apazoglou, Mazzola, Wegrzyk, Polara, & Aybek, 2017; Pareés, Kojovic, et al., 2014; Stone et al., 2009).

The high number of comorbid diseases and physical events in FND may be linked to the type of symptoms patients develop (Baillés et al., 2004; Dixit et al., 2013; Gupta & Lang, 2009; Kuloglu et al., 2003; Pareés, Kojovic, et al., 2014). From a neurobiological perspective, it is suggested that prior physical events (such as injuries or surgeries) and psychological experiences that trigger physiological responses (e.g., panic, sleep paralysis, etc.) can have a psychological impact on vulnerable people, triggering physiological processes (Edwards et al., 2012). In fact, Stone and colleagues (2012) have proposed that functional weakness might

be associated with physical injury, such as immobility and attention focused to a specific body part.

Studies have shown higher prevalence of chronic post-concussive syndrome after a minor head injury in people of countries where expectations of symptoms are higher (Ferrari et al., 2001). The same evidence was reported regarding chronic symptoms of whiplash injury (Ferrari et al., 2002). This phenomenon is explained from a biopsychosocial view that acknowledges the key role of expectations, that is, the belief that an acute head injury will lead to chronic symptoms and even disability (Aubrey, Dobbs, & Rule, 1989; Mittenberg, DiGiulio, Perrin, & Bass, 1992). These authors found that the symptoms of a post-concussion syndrome were very consistent with what people expected (Aubrey et al., 1989). These are examples of how the generation of beliefs along with incorrect expectations of body sensations are taken as models of how the body must perceive and behave. Accordingly, top-down cognitions overwhelm bottom-up sensations leading to incorrect perceptions of normal body functioning, generating a sensation of lack of control of movements (Edwards et al., 2012; Pareés, Kojovic, et al., 2014). Increased attention to the body contributes to the amplification of the importance attributed to sensations (Brown & Reuber, 2016; Stone et al., 2009; Van den Bergh, Witthöft, Petersen, & Brown, 2017).

The most common factors occurring alongside initial FND symptoms are panic attacks (34% of patients), dissociative symptoms (that usually occur with panic) (25%), pain (21%), and physical injury (10%) (Stone, Warlow, & Sharpe, 2012). Dissociation means a disruption of psychological functions such as body representation and motor control, including a loss of the sense of ownership of actions and sensations (American Psychiatric Association, 2013; Stone et al., 2002). A further study has identified physical events, including infections, neurological disorders, drug reactions and surgery to be highly prevalent on the onset of FMD symptoms (80%) (Pareés, Kojovic, et al., 2014). A systematic review found physical injuries at onset in 37% of a sample of 869 FMD patients (Stone et al., 2009). Organic disease has additionally been described as common, occurring in up to 60% (Folks, Ford, & Regan, 1984; Merksey & Buhrich, 1975). In patients with NES in particular, up to 70% have reported pre-existing epilepsy (Wissel et al., 2016), between 10% - 15% have coexisting epilepsy (Alper et al., 1997; Benbadis, Agrawal, & Tatum IV, 2001) and 32% have reported antecedent head injury (Westbrook et al., 1998). Interestingly, all patients believed that the head injury had caused their seizures (Westbrook et al., 1998).

The reported time between physical events and symptoms' onset has varied from minutes (16% of FMD patients), to days (34%) to months (13%) (Pareés, Kojovic, et al., 2014). The studies reporting head injury before NES varied from immediately before to 9 years before, with 81% of cases happening over the last year (Westbrook et al., 1998).

There are very few studies, however, that have compared the precise relationship between previous diseases, surgeries, injuries in the two main variants of FND. However, the literature has identified similarities and differences between FMD and NES in other variables of interest to the current study. For example, among the similarities are age and sex distribution, psychiatric comorbidities and rates of somatisation disorder (Erro et al., 2016). There is also evidence of similar levels of depression and anxiety (Hopp et al., 2012), chronic pain syndrome, subjective fatigue and sleep disorders (Driver-Dunckley et al., 2011). Moreover, it has been reported that both groups have high rates of previous surgery or physical trauma, dysfunctional family relationships and stressful life events (Lancman et al., 1993). Among the differences, studies have reported higher rates of trauma and physical abuse in NES (Reilly et al., 1999; Reuber, Howlett, et al., 2007), finding up to 63% of patients reporting previous trauma (Dixit et al., 2013). Others have reported higher rates of emotional, physical or sexual abuse in NES (Driver-Dunckley et al., 2011; Kanaan et al., 2017; Kranick et al., 2011).

The main aim of the current study was to determine whether clinical events that impact different parts of the body prior to FND onset are related to the development of either motor symptoms or non-epileptic seizures. This information will shed some light regarding the relationship between body parts affected and the kinds of symptoms presented, which has not been studied so far. Additionally, we aim to confirm the specific similarities and differences previously described in the literature between both groups regarding psychiatric disorders and rates of trauma, respectively.

Since it has been proposed that symptoms are influenced by clinical factors that lead to different expectations of body sensations, we hypothesise that FMD patients will have a higher proportion of disorders, injuries and surgeries related to limbs, while NES patients will have a higher proportion of events related to the head, such as neurological and psychiatric disorders. We hope this will help us understand the impact of these variables on the development of symptoms.

METHODS

In this study the medical records of 108 patients diagnosed with FND were reviewed. The diagnosis was made by a consultant psychiatrist specialising in FND in the outpatient Functional Neurology Clinic at the Austin Hospital located in Melbourne, Australia. The clinic accepts referrals from specialists or primary care physicians anywhere in Australia. Referrals must have undergone a neurology assessment that concluded a probable diagnosis of FND, and they are expected to have had all necessary investigations completed. Patients whose primary symptoms are pain or fatigue are not accepted, but any other neurological symptoms are.

The medical records reviewed consisted of letters written by psychiatrists and neurologists. Since these letters were based on the clinical interviews and clinical reports for each patient, there is a degree of subjectivity. For this reason, records were extracted and reviewed by the current author and a second graduate student within the research team with any discrepancies resolved by the treating psychiatrist, professor Richard Kanaan. Data that required more precision, such as dates of diseases, were confirmed from past medical records.

Patients were classified as either FMD or NES according to the diagnosis given by the clinic. Patients over 18 years old, whose primary diagnosis was FMD or NES were included, and those whose had symptoms of both FMD and NES or only sensory or cognitive symptoms, were excluded.

The following variables were collected: age, gender, employment status, education history, symptoms, traumatic events, subjective daily life stress, medical comorbidities, surgeries, psychiatric history in the family, and date of FND onset. The information collected represented any period of their lives, but for the analyses regarding events prior to FND onset, any events that could not be confidently identified as preceding the onset of symptoms were excluded. Information about disability pension, socioeconomic status, ethnicity, and neurological or neuropsychological assessment was excluded because was unavailable for many patients.

PROCEDURE

Firstly, every medical letter was read to find demographic information about the patients and the presence of the three kinds of clinical events prior to FND onset considered for this study: comorbidities, injuries and surgeries.

Secondly, according to the information written in the medical records, the clinical events were classified into the body parts they impacted: head, trunk, limbs, back or whole body. Psychiatric and psychological disorders were included in “head”. Events that affected internal organs (e.g. stomach, liver) were classified as “trunk”, and those impacting the spine were grouped into “back”. Events that were not clearly identified within the limbs or back, because they could have affected both or the affected area was unclear, were included in the category “limbs + back”. This classification (which can be found in [Appendix 1A](#)) would allow us to study if the body parts affected by any clinical factor previous to FND onset would be related to the developing of a specific FND variant.

Thirdly, in a more exploratory fashion, comorbidities and injuries were examined first, and surgeries second, to determine the extent to which these two groups of events contributed to the formation of symptoms, discriminating between FMD and NES. For this analysis, comorbidities and injuries were grouped into the same category because they share common characteristics, such as both being clinical events that occur unexpectedly. Meanwhile, surgeries were considered separately because they are a different kind of clinical event, since they are invasive procedures that are generally scheduled in advance and that require general or local anaesthesia. Sensory/motor changes in the body are triggered by anaesthesia, and these changes can be associated with strong expectations of symptoms in the short and long term.

Then, to determine if the moment when the clinical factors occurred was a relevant factor that could differentiate FMD from NES, the time between clinical factors and symptoms onset was analysed.

Finally, other characteristics of both groups were examined: symptoms (cognitive, motor, sensory, dissociative, pain and fatigue); lifetime psychiatric disorders (somatoform disorders, sleep disorders, depression, anxiety, suicidal ideation, chronic fatigue syndrome); and life events (domestic violence, bullying, sexual abuse, death of relative or friend, divorce or separation).

The collected data was coded and entered into Jamovi version 1.0.5 downloaded from <https://www.jamovi.org/download.html>, using Mann-Whitney U for continuous variables and Chi-square χ^2 for categorical variables and Fisher’s exact tests when the subjects in any of the cells of the contingency table were below 5 (Larntz, 1978). Alpha was set to 0.05. Since we performed multiple comparisons to study the main variables, we adjusted the false discovery rate using the Benjamini-Hochberg method to reduce the probability of finding

significant results that might occur by chance (false positives) (table of adjusted p -values in [Appendix 2A to 5A](#)) (Benjamini & Hochberg, 1995; Simes, 1986).

This study was approved by the Human Research Ethics Committee (HREC) of the Austin Hospital (reference number: 48818).

RESULTS

DEMOGRAPHICS

FMD and NES patients were compared regarding gender, age, age at FND onset, education and employment. Nineteen patients were excluded with primary diagnoses of instead chronic fatigue syndrome; multiple sclerosis; functional blindness; or had a dual diagnosis of FMD and NES. A total sample of 108 FMD and NES patients were compared regarding gender, age, age at FND onset, education and employment. The groups had similar demographic characteristics, as shown in Table 2. There was no education information available for 16 individuals. Interestingly, 65% of the patients reported being unemployed or unemployed due to illness, and only 24% were employed (there was no employment information available in the medical records for 5 individuals).

Table 2. *Demographics*

	FMD <i>n</i> (%)	NES <i>n</i> (%)	Total <i>n</i> (%)	<i>p</i> value
Gender ^a	<i>n</i> = 56	<i>n</i> = 52	<i>n</i> = 108	0.811
Female	41 (73%)	37 (71%)	78 (72%)	
Male	15 (27%)	15 (29%)	30 (28%)	
Age (years) ^b	<i>n</i> = 56	<i>n</i> = 52	<i>n</i> = 108	0.113
Mean	48	43	--	
Age at FND onset (years) ^b	<i>n</i> = 56	<i>n</i> = 52	<i>n</i> = 108	0.058
Mean	40	34	--	
Employment ^a	<i>n</i> = 52	<i>n</i> = 51	<i>n</i> = 103	0.448
Employed	16 (31%)	9 (18%)	25 (27%)	
Unemployed	17 (33%)	17 (33%)	34 (33%)	
Unemployed due to illness	16 (31%)	17 (33%)	33 (32%)	
Retired ^c	2 (4%)	3 (6%)	5 (5%)	--
Student ^c	1 (2%)	5 (10%)	6 (6%)	--
Education ^a	<i>n</i> = 49	<i>n</i> = 43	<i>n</i> = 92	0.292
≤ Year 12	28 (57%)	18 (42%)	46 (50%)	
Certificate I-IV or Diploma	10 (21%)	14 (33%)	24 (26%)	
Bachelor's degree or above	11 (22%)	11 (26%)	22 (24%)	

FMD = functional motor disorder; NES = non-epileptic seizures.

^a Chi-square

^b Mann-Whitney U

^c Variables not included in the statistics because there were less than 5 cases.

* $p < 0.05$

CLINICAL FACTORS

Ninety three percent of patients reported a clinical event before the onset of symptoms, which were classified into comorbid diseases (reported by 85%), surgeries (reported by 50%) and injuries (reported by 22%).

As shown in Figure 2, by examining the kinds of events, we found that FMD patients had a significantly higher proportion of injuries occurring prior to symptom onset than NES (30% compared to 14% respectively), $X^2(1, N = 24) = 4.45, p = 0.035$, which included fractures, falls, dislocations and carpal tunnel syndrome. There were no differences between groups regarding comorbidities and surgeries.

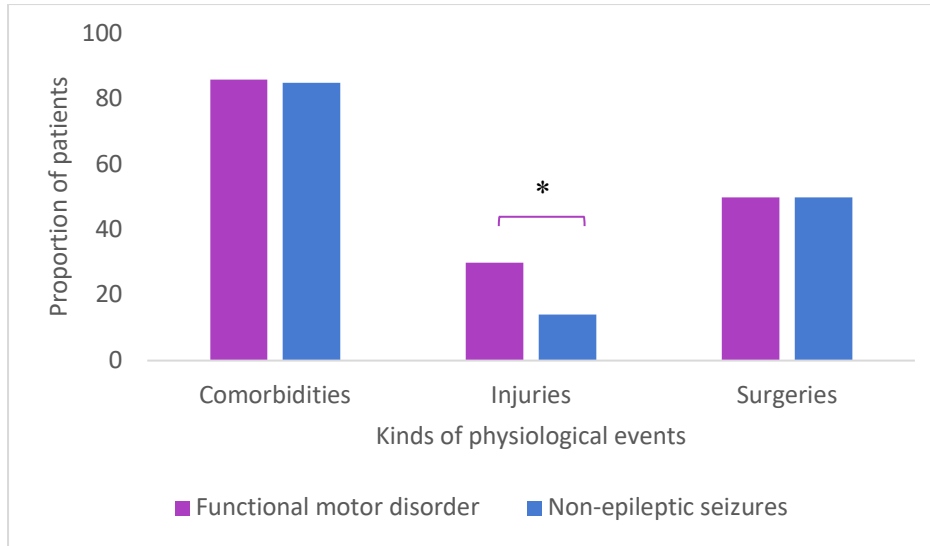


Figure 2. Proportion of patients that reported different kinds of clinical events before FND onset. * $p < 0.05$.

CLINICAL FACTORS PER BODY PARTS

a. Comorbidities, injuries or surgeries per body parts

As illustrated in Figure 3, a high proportion of patients reported *diseases, injuries or surgeries* before FND onset, classified by body regions. Specifically, it was found that clinical events that impacted the limbs or back were significantly higher in FMD than NES (46% and 21% respectively), $\chi^2 (1, N = 37) = 7.65, p = 0.006$. Events impacting the head and whole body were similar in both groups, 70% and 81%, and 54% and 48%, respectively.

Although there was a tendency towards more events impacting the trunk in NES, 71% compared to 54%, the difference was not quite significant $\chi^2 (1, N = 67) = 3.54, p = 0.06$.

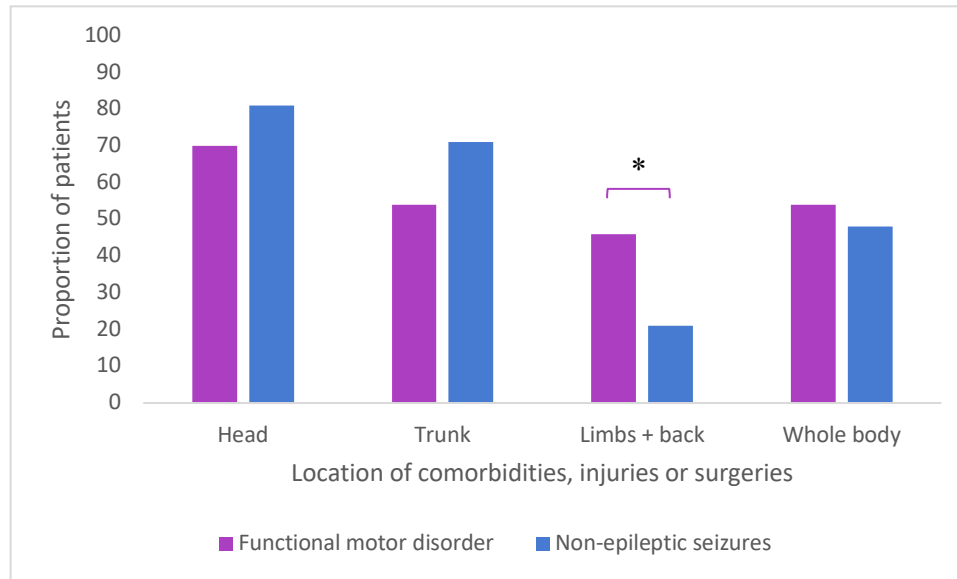


Figure 3. Proportion of patients that reported *comorbidities, injuries or surgeries* affecting different parts of the body before the onset of FND. * $p < 0.05$.

Table 3 shows the main body parts belonging to every category shown in the figure above. Every specific body part belonging to each category and subcategory can be found in [Appendix 6A](#).

Since events impacting limbs and back were grouped together (limbs + back) and were significantly different between groups, we separated them to determine which of both limbs or back, would be more important to this relationship. Thus, we additionally analysed events that had a clear impact only on the limbs and only on the back.

As shown in table 3, events impacting limbs were found to be higher in FMD (34% and 14% respectively), $\chi^2 (1, N = 26) = 6.18, p = 0.013$, and there was no difference regarding events impacting only the back.

Table 3. *Comorbidities, injuries and surgeries per part of the body*

Body region	FMD (%)	NES (%)	Total (%)	p-value
Head	39 (70%)	42 (81%)	81 (75%)	0.182
Trunk	30 (54%)	37 (71%)	67 (62%)	0.060
Limbs + back	26 (46%)	11 (21%)	37 (34%)	0.006*
Limbs	19 (34%)	7 (14%)	26 (24%)	0.013*
Back	11 (20%)	8 (15%)	19 (18%)	0.561

FMD = functional motor disorder; NES = non-epileptic seizures. * $p < 0.05$

b. Comorbidities and injuries per body parts

To determine to what extent comorbidities and injuries contributed to the differences found in the body regions described above, they were examined separately, excluding surgeries.

As shown in Figure 4, differences in diseases and injuries that impacted the limbs or back were found non-significant when adjusted with Benjamini-Hochberg procedure (table in [Appendix 2A](#)), where FMD had 34% in comparison to 17% of NES, $\chi^2(1, N = 28) = 3.88, p = 0.049$.

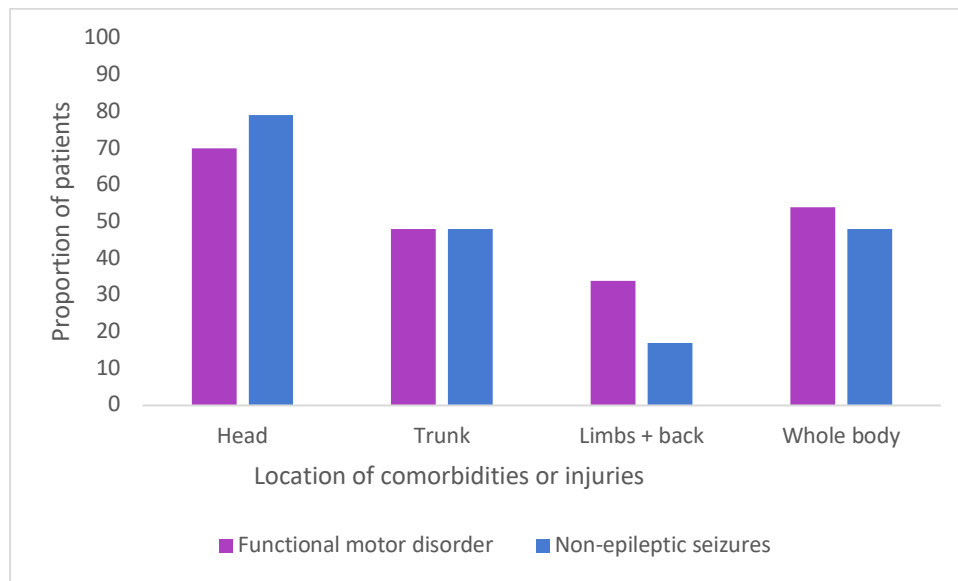


Figure 4. Proportion of patients that reported *comorbidities or injuries* affecting different parts of the body.

Table 4 summarizes the proportion of comorbidities and injuries that occurred in the main parts of the body in both groups. Every specific body part belonging to each category and subcategory can be found in [Appendix 7A](#).

To determine if comorbidities and injuries occurring in the limbs or back were more important, they were studied individually. It was found that diseases and injuries that affected the limbs were not significantly different between groups - 27% of FMD and 12% of NES, $\chi^2(1, N = 21) = 4.00, p = 0.045$. There was no difference regarding these kinds of events occurring in the back.

Table 4. *Comorbidities and injuries per part of the body*

	FMD (%)	NES (%)	Total (%)	<i>p</i> -value
Head	39 (70%)	41 (79%)	80 (74%)	0.275
Trunk	27 (48%)	25 (48%)	52 (48%)	0.989
Limbs + back	19 (34%)	9 (17%)	28 (26%)	0.049
Limbs	15 (27%)	6 (12%)	21 (19%)	0.045
Back	7 (13%)	8 (15%)	15 (14%)	0.665
Whole body	30 (54%)	25 (48%)	55 (51%)	0.568

FMD = functional motor disorder; NES = non-epileptic seizures. * $p < 0.05$

c. Surgeries per body parts

To determine to what extent surgeries affected the body regions, we treated them separately from comorbidities and injuries.

Figure 5 depicts a significant difference between FMD and NES regarding surgeries occurring in the limbs or back, which was higher for FMD (23%) in comparison to NES (8%), $p = .035$, Fisher's exact test. Similar proportions were found regarding surgeries located in the head and trunk.

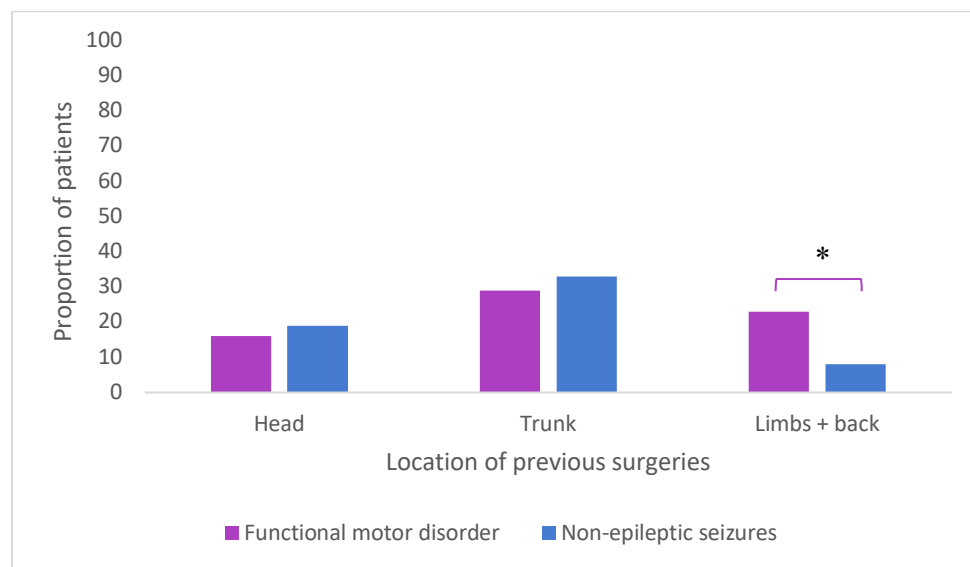


Figure 5. Proportion of patients that reported surgeries previous to the onset of FMD affecting different parts of the body. * $p < 0.05$.

Table 5 summarises the main body regions affected by surgeries. Every specific body part belonging to each category and subcategory can be found in [Appendix 8A](#).

Although the numbers were considerably lower than diseases and injuries shown above, the data shows that surgeries that affected the limbs or back were significantly higher in FMD than NES, although there was no significant difference regarding surgeries affecting only limbs and only back.

Table 5. *Surgeries per part of the body*

	FMD (%)	NES (%)	Total (%)	<i>p</i> -value
Head	9 (16%)	10 (19%)	19 (18%)	0.667
Trunk	16 (29%)	17 (33%)	33 (31%)	0.642
Limbs + back	13 (23%)	4 (8%)	17 (16%)	0.035*
Limbs	8 (14%)	2 (4%)	10 (10%)	0.095
Back	5 (9%)	2 (4%)	7 (6%)	0.440

FMD = functional motor disorder; NES = non-epileptic seizures. * $p < 0.05$

TIME BETWEEN CLINICAL FACTORS AND SYMPTOMS ONSET

Figure 6 depicts the proportion of patients that had a clinical event prior to symptom onset, divided into three timeframes: up to a week; 1 week to 1 year; more than 1 year. Only the most recent clinical event was considered.

More than half of the patients (54%) reported having had any kind of clinical event between 1 week and 1 year prior to the symptom onset.

Interestingly, there was a tendency for more of NES to have had a clinical event over the same day or week of the symptom onset (37% compared to 21% of FMD), however, this difference was not significantly different, $\chi^2 (1, N = 31) = 3.01, p = 0.083$.

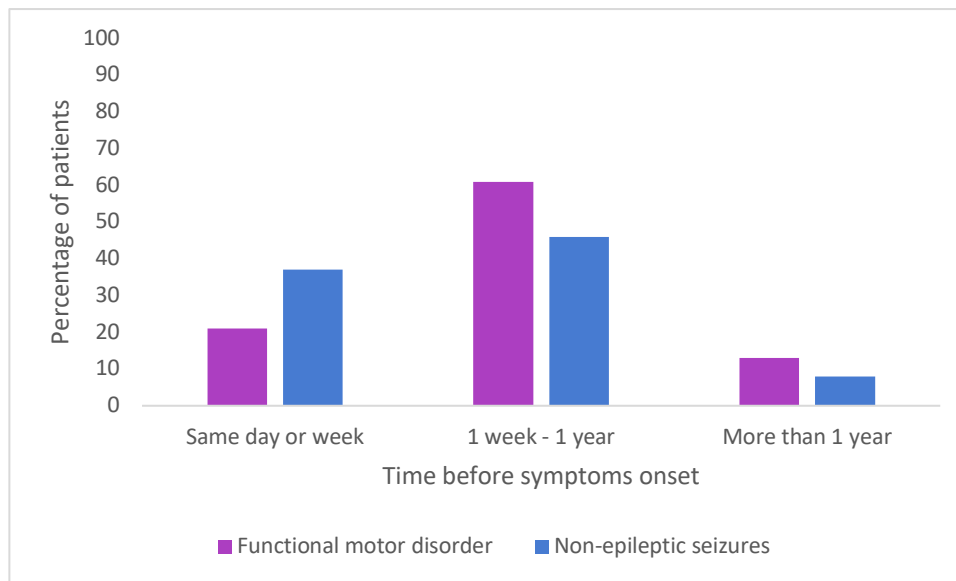


Figure 6. Proportion of patients that reported any kind of clinical events (including surgery, injury or disease) prior to the symptom onset. Only the last event of every patient was considered.

OTHER IMPORTANT CHARACTERISTICS

Symptoms

As illustrated in Figure 7, both groups of patients reported a wide variety of symptoms, which were classified into fatigue, cognitive symptoms, motor symptoms, sensory symptoms, dissociative and panic symptoms, and pain.

Among the most commonly reported symptoms we found sensory symptoms (81% of patients), motor symptoms (70% of patients), cognitive impairment (61% of patients) and dissociative symptoms (60% of patients).

The main differences were found in motor symptoms where FMD had significantly more than NES (93% and 46%, respectively), $\chi^2 (1, N = 76) = 28.2, p < 0.001$, and dissociative symptoms and panic where significantly higher in NES than FMD (90% and 30%), $\chi^2 (1, N = 64) = 40.2, p < .001$.

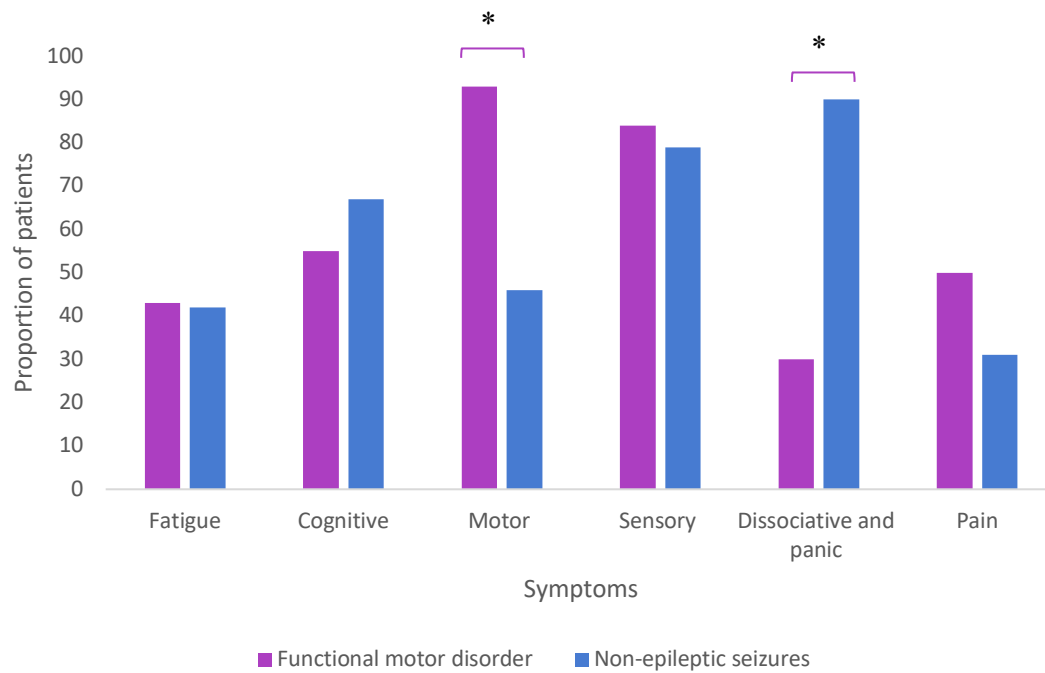


Figure 7. Proportion of patients that reported each kind of symptom. * $p < 0.05$

Table 6 shows a detailed list of symptoms present in each group. Weakness was the most common, reported by 56%, followed by spasms and twitching (49%) and temperature changes, numbness and reduced sensation (45%).

Among the differences, we found that NES had significantly higher rates of loss of awareness or depersonalization (31% compared to 4% of FMD), $X^2(1, N = 18) = 14.4, p < .001$, and seizures (75% in comparison to 5% of FMD), $X^2(1, N = 42) = 55.0, p < .001$.

Table 6. *Symptoms present in patients with FMD and NES*

	FMD <i>n</i> (%)	NES <i>n</i> (%)	Total <i>n</i> (%)	<i>p</i> -value
	<i>n</i> = 56	<i>n</i> = 52	<i>n</i> = 108	
Cognitive symptoms	31 (55%)	35 (67%)	66 (61%)	0.203
Attention and memory	21 (38%)	22 (42%)	43 (40%)	0.610
Language	20 (36%)	27 (52%)	47 (44%)	0.090
Motor symptoms	52 (93%)	24 (46%)	76 (70%)	<.001*
Weakness	29 (52%)	31 (60%)	60 (56%)	0.413
Tremor	28 (50%)	15 (29%)	43 (40%)	0.025
Spasms / Twitching	29 (52%)	24 (46%)	53 (49%)	0.559
Gait difficulties	35 (45%)	11 (21%)	36 (33%)	0.010
Coordination / balance	18 (32%)	11 (21%)	29 (27%)	0.198
Sensory symptoms	47 (84%)	41 (79%)	88 (81%)	0.497
Temp. changes/numbness/reduced sensation	27 (48%)	22 (42%)	49 (45%)	0.538
Electric sensations / pins, needles / pulsations	10 (18%)	6 (12%)	16 (15%)	0.356
Visual blurring / flashing lights / visual loss	14 (25%)	13 (25%)	27 (25%)	1.00
Vertigo/ dizziness / nausea	12 (21%)	21 (40%)	33 (31%)	0.033
Dissociative symptoms and panic	17 (30%)	47 (90%)	64 (60%)	<.001*
Loss of awareness/depersonalization	2 (4%)	16 (31%)	18 (17%)	<.001*
Seizures	3 (5%)	39 (75%)	42 (39%)	<.001*
Panic / fear	10 (18%)	9 (17%)	19 (18%)	0.940
Hyperventilation/shortness of breath	6 (11%)	6 (12%)	12 (11%)	0.892
Pain	28 (50%)	16 (31%)	44 (41%)	0.042
Fatigue	24 (43%)	22 (42%)	46 (43%)	0.954

FMD = functional motor disorder; NES = non-epileptic seizures. * $p < 0.05$.

Psychiatric Disorders

A history of psychiatric disorders in the patient's family was reported by 33%, with depression (19%), anxiety disorders (anxiety, panic attack, obsessive-compulsive disorder) (19%) and addictions (17%) being the most commonly reported. All were similar between groups.

Regarding the patients themselves, NES and FMD had similar rates of psychiatric comorbidities during their lifetime (94%).

As shown in Figure 8, we found a significant difference between groups in functional somatic syndromes (which includes fibromyalgia, chronic pain syndrome, chronic fatigue syndrome and irritable bowel syndrome), where FMD had a higher rate than NES (46% and 27% respectively), $\chi^2 (1, N = 40) = 4.40, p = 0.036$. By contrast, suicidal ideation (which included suicide attempts) was significantly more common in NES (56% and 32% respectively), $\chi^2 (1, N = 47) = 6.12, p = 0.013$. The groups had similar rates of depression, anxiety disorders, sleep disorders and subjective fatigue.

[Appendix 9A](#) shows all the psychiatric comorbidities reported by FND patients.

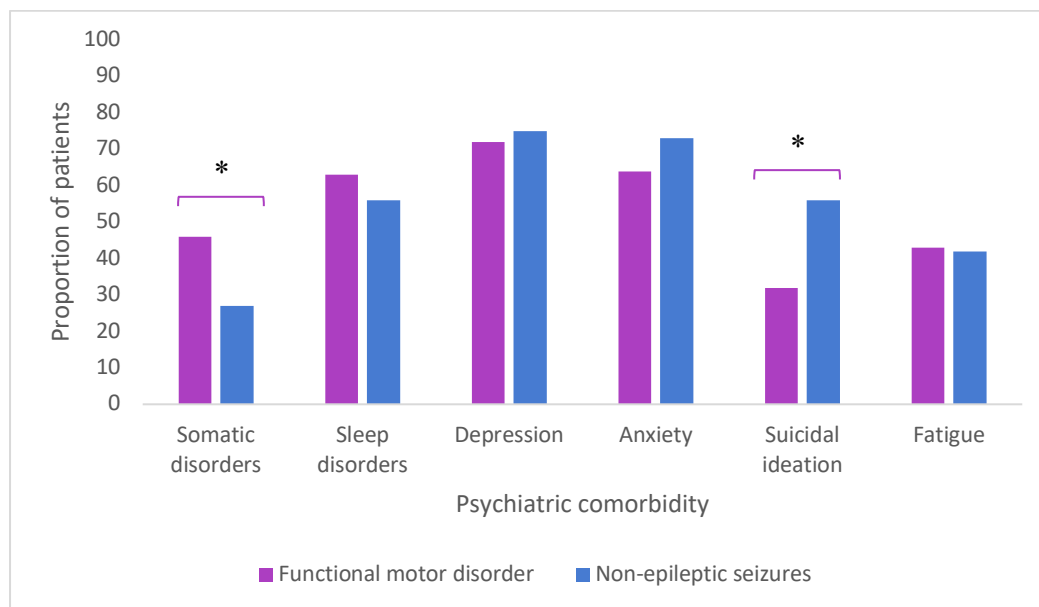


Figure 8. Main psychiatric comorbidities reported by FND patients. * $p < 0.05$.

Life Events

Patients with NES reported a trend towards more traumatic life events (81% compared to 64% of FMD, which included domestic violence, bullying, sexual abuse, death or disease of relative or friend, and separation or divorce, $\chi^2 (1, N = 78) = 3.65, p = 0.056$). The groups reported similar rates of daily life stress (71% of FMD and 78% of NES). Daily life stress was defined as all the situations that the patients considered as concerning or problematic in their daily life, for example, toxic relationships or unpleasant situations at work.

We took the total number of traumatic events reported, that is, the sum of the events in every kind of event rather than presence / absence as reported before, and we found that patients with NES ($M = 1.69, SD = 1.16$) reported significantly higher number of events than FMD ($M = 1.13, SD = 1.05$); $t (106) = -2.67, p = 0.009$, with medians 2 and 1, respectively.

Figure 9 illustrates the proportion of patients that reported different kinds of traumatic life events. NES patients presented higher rates of being victims of bullying than FMD (49% and 24% respectively), $X^2(1, N = 38) = 7.97, p = 0.008$.

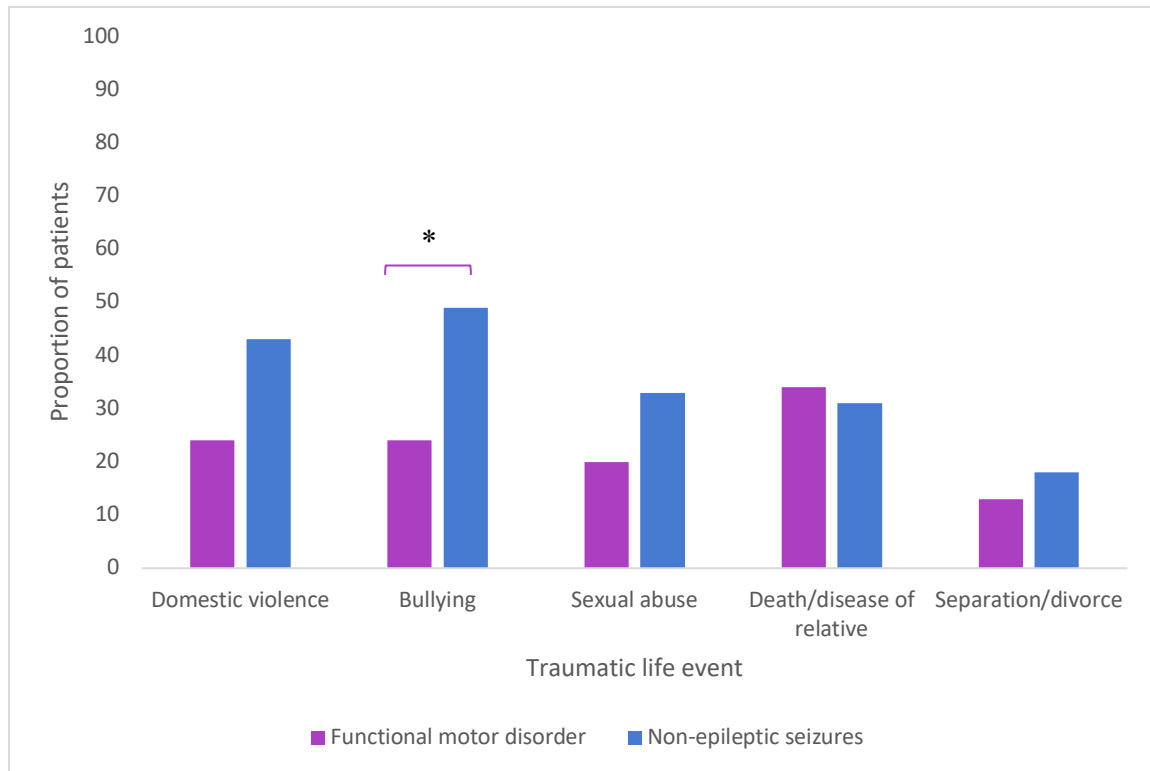


Figure 9. Proportion of patients that reported different traumatic life events before FND onset. * $p < 0.05$.

DISCUSSION

DEMOGRAPHICS

In this study we retrospectively examined the medical records of 56 FMD patients and 52 NES patients, to determine whether there was a relationship between clinical events such as diseases, surgeries and injuries in different body parts and their symptomatic presentation. Additionally, we compared other factors of interest, including demographics, psychiatric disorders and life events to examine other possible variables that might help to explain their different symptomatology.

Consistent with the literature, our sample consisted of more women than men in both groups (72%) (Erro et al., 2016; Factor et al., 1995; Hopp et al., 2012) and NES patients had a tendency to present with the first symptoms at a younger age than FMD (34 years old in comparison to 40 years old) (Abubakr et al., 2003; Driver-Dunckley et al., 2011; Hopp et al., 2012; Ludwig, Whitehead, Sharpe, Reuber, & Stone, 2015; Stone et al., 2004).

Both groups had similar employment status, as reported in previous studies, although we found a considerably higher rate of unemployment, 64% compared to 19% and 33% previously reported (Driver-Dunckley et al., 2011; Hopp et al., 2012). This difference might be attributed to different kinds of disability support pensions in different countries where the studies were carried out.

Our sample had a similar level of education between groups, where 50% had 12 or less years of education. This is in contrast to previous reports of individuals with FMD having higher years of education than NES (Driver-Dunckley et al., 2011; Hopp et al., 2012).

CLINICAL EVENTS AND OTHER VARIABLES OF FMD AND NES

We found that *prior to the disease onset*, FMD was more affected by clinical events that impact the individual's *limbs*, compared to NES. Additionally, FMD had a higher prevalence of *injuries* prior to the disorder onset than NES, which is consistent with previous studies that have indicated that FMD had a high prevalence of injuries, although they did not compare with NES (Pareés, Kojovic, et al., 2014; Stone et al., 2009). While past research has not examined these events per body parts, there are a few study cases that reported a relationship between clinical events and FMD, e.g. a patient who had an organic problem in their leg and subsequently developed paralysis of the same leg (Demartini, Goeta, et al., 2016); a patient that developed functional paraplegia after general anaesthesia (Mason, 2017); and a patient that had weakness, numbness and paralysis 1 hour after general anaesthesia (Afolabi et al., 2016).

One unanticipated finding was that the occurrence of *prior events* impacting the *head* in NES was surprisingly similar to FMD. Previous studies have reported head trauma as a precipitant to NES (Barry et al., 1998; Westbrook et al., 1998), as well as developing epilepsy as a common premorbid brain-disorder (Reuber et al., 2003) and having epilepsy surgery (Glosser et al., 1999; Pillai & Haut, 2012; Westbrook et al., 1998; Wissel et al., 2016). However, there are no studies that have compared the frequency of such events with FMD.

Regarding other important factors occurring during the patients' lives, we confirmed findings reported in the literature. The data showed that FMD has a higher rate of *motor symptoms* (Erro et al., 2016) and *somatic disorders* (Demartini, Goeta, et al., 2016), compared to patients with NES. Indeed, there are structural alterations in common brain areas

in somatic symptom disorders and FND, raising the possibility that they have an overlapping pathophysiology (Bègue, Adams, Stone, & Perez, 2019).

NES on the other hand, had a higher prevalence of *suicidal ideation*, and in agreement with previous studies, higher prevalence of *dissociative symptoms* (Demartini, Goeta, et al., 2016; Hendrickson, Popescu, Ghearing, & Bagic, 2015) and *traumatic life events* (Dixit et al., 2013; Driver-Dunckley et al., 2011; Kanaan et al., 2017; Kranick et al., 2011), specifically *domestic violence* and *bullying* (Reilly et al., 1999; Reuber, Howlett, et al., 2007).

These findings confirm that FND patients present with a wide range of clinical events, and that previous events that impacted the *limbs* were more related to FMD than NES, although previous events impacting the *head* were not more related to NES than FMD as we had hypothesised. Additionally, we confirmed differences between FMD and NES in the literature. Specifically, somatic and motor symptoms during the lifetime were higher in FMD than NES, and psychiatric disorders and traumatic life events (that have psychological consequences) were higher in NES than FMD, which can be considered variables that impact the *mind* and can be physically located in the *head*. None of these events is enough by itself to generate a symptom, but they are part of a complex neurophysiological mechanism. This mechanism consists of three different kinds of factors: *predisposing*, *precipitating* and *perpetuating factors*.

A higher sensitivity to stress and emotional hyperarousal are typical *predisposing factors* (Apazoglou et al., 2017). Among *precipitating factors* are diseases, injuries and surgeries that impact the brain-body stress system triggering autonomic responses to threat, which when dysregulated produce aberrant functioning of the central nervous system (Kozłowska, 2017). Finally, *perpetuating factors*, that might contribute to that these autonomic responses become abnormal and long-lasting, are symptom modelling and catastrophizing thoughts about the cause of the symptoms (Stone et al., 2005).

Thus, our results suggest that events impacting the limbs prior to FND onset might be considered *predisposing factors* for FMD, while events such as somatic and motor symptoms that might be present before and during the disease might be considered *predisposing* and *perpetuating factors* for FMD. Suicidal ideation, dissociative symptoms and traumatic life events on the other hand, might be considered *predisposing* or *perpetuating factors* for NES. Suicidal ideation might be a consequence of the condition though. Either way, the association with this variable is important for treating clinicians to be mindful of the increase likelihood

for suicidal ideation so that appropriate steps can be put in place to reduce the risk in this group.

The relationship of these events with FND symptoms are proposed to be related to the generation of expectations and cognitive biases that impact the neurobiology of the brain (Edwards et al., 2012; Kozłowska, 2017; Pareés, Kassavetis, et al., 2012). According to neurobiological models, physiological and psychophysiological experiences are crucial for the generation of expectations and cognitive biases. Psychophysiological experiences consist of physiological responses based on psychological processes, for instance, a change in heart rate as a result of exposure to a stressful event. These events, through hypervigilance and attention to one's own body, might lead the subject to develop abnormal beliefs or expectations regarding their body sensations and motor behaviour, for example thoughts that they are sick (Edwards et al., 2013). There is an inferential leap between a physical event and how it is interpreted by the subject, which creates implicit incorrect predictions about body sensations (Van den Bergh et al., 2017).

For instance, in a study that measured illusory tactile perceptions by delivering near-threshold tactile stimuli to the fingertip with a probability of 50%, it was found that people with more functional neurological symptoms (including paralysis, seizures, sensory loss and somatoform symptoms) had a higher number of false alarms or illusory touch experiences (Brown, Brunt, Poliakoff, & Lloyd, 2010; Katzer, Oberfeld, Hiller, Gerlach, & Witthöft, 2012). Similar to what it is proposed to happen in FND, these results suggest a jump between the physical stimulation and the interpretation of it, namely, the perception.

Additionally, FND patients have been reported to show a “jumping to conclusions” cognitive bias (Pareés, Kassavetis, et al., 2012). This bias consists of using less information to estimate the probability of events, and easily changing opinion based on new evidence. This reasoning may help to explain why a single event might lead to a sensory prediction becoming ingrained, and consequently in how the sensations are experienced, instead of how they are anatomically (Stone et al., 2017). Therefore, biased thinking might favour abnormal inferences about body sensations coming from a physical event, contributing to the genesis of functional motor symptoms. A similar mechanism might be present in the case of NES but triggered by different kinds of events.

These models together may explain how patients who have suffered from a physiological event in their limbs or a psychophysiological event subsequently develop functional symptoms, which we found and was mentioned in other studies (Pareés, Kojovic, et al., 2014;

Stone et al., 2009). Hence, people that have vulnerabilities such as higher arousal and response to stress, caused by traumatic experiences or genetics for example, might have several unusual body sensations which are reinforced by new clinical events. Then, diseases, injuries or surgeries that impact different body parts lead the person to a hypervigilant state regarding their own sensations. When attention towards their body is high, these body sensations are inadequately interpreted, leading to incorrect expectations and misperceptions. Thus, the difficulty in predicting body sensations and movements, lead the patient to experience strange perceptions and a lack of movement control.

For these reasons, it was expected that clinical events impacting the limbs would be more common in patients with motor symptoms in their limbs, and that clinical events impacting the head would be more common in NES, since non-epileptic seizures are thought to be related to the brain. Possible explanations for this discrepancy with our predictions include the exclusion of all the events with uncertain dates from our analysis, and that our data depended mainly on what patients reported in their medical appointments and was noted by their doctors. For example, there were events such as head injuries or epilepsy surgeries that could not be clearly identified as occurring before FND onset that were excluded from the analysis. Additionally, as patients with epilepsy are more likely to be seen through other services, since the functional neurology clinic sees patients with FND as a primary diagnosis, it is possible the relative proportion of patients with epilepsy will have been reduced.

Overall, these results suggest that previous events that impact the limbs might explain why some patients are more likely to develop the motor variant of FND, while psychiatric and psychological events during the lifetime make NES more likely.

TIME BETWEEN EVENTS AND FND ONSET

The descriptive data shows possible similarities between groups in the time difference between clinical events and symptom onset. Twenty nine percent of patients had a comorbidity, injury or surgery during the same day or week of symptom onset, while 64% had an event more than one week prior to FND onset. Seven percent of patients were excluded from this analysis because their reported events had unclear dates of occurrence. Although there are no studies that have compared these variables between FMD and NES, the available studies in each group independently show different prevalence. For instance, 28% of NES and 50% of FMD patients had events coincident with FND onset or during the same week, 72% of NES' events occurred more than 1 year before and 38% of FMD' between 1-3

months before (Pareés, Kojovic, et al., 2014; Stone et al., 2009). Even though it is not possible to conclude a strong relationship between the timing of occurrence and symptom onset, these findings support the idea that past acute clinical events are important risk factors of FND.

LIMITATIONS

One of the main limitations of our study is that the medical letters, have a degree of subjectivity, since they are based on clinical interviews. These interviews do not have a unified criteria or structure; therefore, the interviewers may have different parameters when asking questions, exploring certain topics or issues more which were considered more relevant. Besides this, some events, including the onset of the symptoms, could have occurred a long time before patients consulted a specialist, which might lead to a recall bias. To address these flaws, future studies could collect information through direct interviews with the patients to compare with the information from medical records.

CONCLUSION AND FUTURE DIRECTIONS

In summary, FMD and NES present with similar demographic characteristics; rates of clinical factors, namely, injuries, surgeries and comorbidities; and psychiatric comorbidities such as depression, anxiety disorders, sleep disorders and fatigue. On the other hand, FMD had a higher rate of previous clinical events that impacted the limbs, with injuries being the most common, while NES showed a trend of events that impacted the trunk. FMD had higher rates of motor symptoms and somatic disorders during their lifetime, while NES had a higher prevalence of dissociative symptoms, suicidal ideation and bullying. These findings together suggest that every symptomatic presentation is influenced by variables impacting different parts of the body, where FMD has more events affecting the limbs prior to the disorder onset, and NES is more impacted by traumatic experiences related to violence, dissociative symptoms and suicidal ideation, events considered as impacting the “mind” or “head” during their lifetime.

Regardless of these limitations, this research examines clinical events affecting different parts of the body and their relationship with symptomatic presentation of the two main variants of FND in a substantial sample size for the first-time.

It would be interesting to contrast our data with prevalence of the same variables in the healthy population, so that we could more confidently determine if FND patients had higher

rates of diseases, injuries and surgeries. This would help clarify whether having more events impacting the body is one of the risk factors for developing FND. In future studies, we would therefore suggest including additional disease controls and healthy controls to understand the specificity of the differences identified, as well as a more structured data collection procedure, such as through an interview or questionnaire.

CHAPTER 3: A PRELIMINARY STUDY TO IDENTIFY PERCEPTUAL DIFFERENCES ASSOCIATED WITH FUNCTIONAL WEAKNESS

INTRODUCTION

FND is characterized by motor or sensory symptoms that do not have organic causes. The diagnosis of FND is based on neurological symptoms (e.g. tremor, seizures) that typically have certain characteristics, such as internal inconsistency, and are usually preceded by stressful events, and by excluding other possible causes (e.g. by electroencephalograms or brain scans). The prognosis of FND is poor, since treatments commonly consisting of physiotherapy and cognitive-behavioural therapy, with medications to treat the symptoms of comorbid disorders, among others, are only partially successful (Gelauff et al., 2014; Lancman et al., 1993).

The functional symptoms have characteristics that differ from organic diseases (for instance, sensory loss occurring with weakness) and they can evolve from one kind of symptom to another (Hallett, 2011; Stone & Carson, 2011). Furthermore, functional symptoms typically get better with distraction (Hallett, 2010; Kenney et al., 2007; Wolfsegger, Pischinger, & Topakian, 2013), and are thought to be influenced by suggestion (Bell et al., 2011; Hallett, 2011; Kenney et al., 2007). It is proposed that patients, through their expectations or ideas of disease and over-attention to their body, may lead to changes of symptom intensity and frequency (Edwards et al., 2012; Stone et al., 2017).

This unpredictability of symptoms is a problem both for diagnosis and follow-up, since they cannot be tested. So, the presence or absence of signs do not allow us to confirm the diagnosis. Since we cannot rely on objective instruments, the diagnosis of FND may be affected by the biases of medical practitioners (Deeley, 2016). For instance, neurological diseases might be misdiagnosed as FND when the patients have typical characteristics, such as anxiety, recent stressful event or psychiatric comorbidities (Stone, Reuber, & Carson, 2013). The opposite is also possible, for instance, the physician might dismiss FND when the patient does not meet the common features of the disorder (Stone et al., 2013). For example, the patient is male, “too old” or does not have the typical psychiatric disorders.

A few studies have tried to measure functional symptoms in an objective fashion, but they have had limited success. One study tested functional weakness with a dynamometer (van der Ploeg & Oosterhuis, 1991), others used electromyography (McComas, Kereshi, & Quinlan, 1983; Pillai, Markind, Streletz, Field, & Herbison, 1992), or measured evoked

motor responses using magnetic brain stimulation (Meyer et al., 1992). However, none of these studies were able to measure the symptom or differentiate FND from healthy controls or other disorders.

One of the most frequently reported symptoms of FND is weakness in the upper or lower limbs, which can sometimes be seen objectively (e.g. a patient that reports weakness in their arm and can barely move it), but not always (e.g. the patient reports weakness in their arm but there is no difference in performance compared to the normal arm). A clinical test for the presence of unilateral functional weakness in the lower limb is Hoover's test, which reveals a weak hip extension when tested directly, but normal extension when the patient is asked to flex the opposite hip, which is used to corroborate that the weak leg can show normal power in certain situations but not in others (Diukova, Ljachovetckaja, Begljaro, & Gavrileyko, 2013; Ziv, Djalde, Zoldan, Avraham, & Melamed, 1998). Another example is the arm-drop, which is used to assess if the patients will protect themselves from their paralysed or weak arm when it is dropped over their face (Knutsson & Mårtensson, 1985). However, these signs are not always present, so they are not a consistent way to show the presence of weakness. Therefore, due to the characteristics of functional symptoms, it has been very difficult to find a test that can measure them.

Moreover, the progress of FND across time is challenging to quantify. Quantitative measurement is important for clinical research, to study, for example, the impact of a medication, or variables that are thought to be involved, such as attention and expectation (Edwards et al., 2012; McIntosh, McWhirter, Ludwig, Carson, & Stone, 2017; Ricciardi et al., 2016). While the patient's experience is important and provides helpful information, it is not sufficient to study the evolution and development of symptoms in a reliable fashion.

In this study we aim to test a potential measure for functional weakness, that could provide a means to quantify symptom severity. To do this, we looked for a task that did not directly ask patients their perception of their weakness, nor measure the symptom directly, because if we did this, patients' expectations of how they *should* perform on the test might influence their performance. Instead, we selected a perceptual task that does not have subject-predictable responses and that does not directly measure their symptoms, such as measuring force or reaction time. This is the size-weight illusion (SWI), which is a perceptual illusion that we believe will be sensitive to the sensory and perceptual mechanisms present in functional weakness.

The size-weight illusion has been extensively studied and has robust effects. It consists of the misperception that a small object is heavier than a larger one when both weigh the same (Buckingham & Goodale, 2010a; Charpentier, 1891; Christopher M. Davis, 1973; Ellis & Lederman, 1993; Flanagan & Beltzner, 2000; Murray et al., 1999). It has been proposed that the SWI is cognitively impenetrable, since people continue experiencing the illusion even when they are shown that the two objects weigh the same (Ellis & Lederman, 1998). The most common explanation is that people, based on their experiences, have expectations that larger objects are heavier, since in daily life weight is relatively correlated to size (Dijker, 2014). Thus, in the SWI people overestimate the force they need to lift the large object and underestimate the force they need to lift the small object (Gordon et al., 1991). Therefore, the SWI violates expectations, leading to an incorrect perception of weight of the objects (Ross, 1969)

The SWI is pertinent to FND because it consists of judging which of two objects of different size is heavier, which involves sensorimotor integration and expectations. Since the task consists of comparing a small reference with large objects of different weights, there are no obviously correct answers. Moreover, this illusion, which is consistently experienced by healthy controls, involves fundamental processes that are thought to be related to FND.

One of these processes is the prediction system of motor control, which integrates daily life experience and generates expectations of the sensory consequences of one's own movements (Blakemore, Wolpert, & Frith, 1998). When predictions are incorrect, perceptions and sensations regarding movement are confusing, which is one of the problems that is proposed to be happening to patients with FND (Pareés, Brown, et al., 2014). Particularly, it is proposed that FND patients, unlike healthy controls, do not attenuate the sensations coming from their own body, so that they do not correctly predict the sensations that are caused by their own movements, leading to pathological perceptions (Blakemore, Frith, & Wolpert, 1999; Blakemore, Wolpert, & Frith, 2002). Similar results have been reported, where patients with FND displayed decreased intensity of sensory experience and sensory evoked potential amplitude when movement was self-generated (Macerollo et al., 2015). This deficit is related to abnormal self-directed attention that is key to detecting sensory information coming from one's body (Pareés, Brown, et al., 2014).

This predictive process has been implicated in the symptoms of schizophrenia as well (Shergill et al., 2005). In schizophrenia, this process may explain how symptoms are perceived as those of an external agent, which is similar to how motor symptoms are felt out

of control, or patients feel that they lack agency for their movement in FND (Pareés, Brown, et al., 2014). Williams, Ramachandran, Hubbard, Braff & Light (2010), tested the SWI in patients with schizophrenia, and found they had a reduced illusion, meaning they were more accurate than healthy controls. The task they used consisted of comparisons between a small reference and larger objects of increasing weight. To know the strength of the illusion in control participants and patients with schizophrenia, they calculated the point of subjective equality (PSE), which is the exact point where the participants could not decide which of the disks was heavier. This point is where the illusion is nulled, and the weights are perceived as equal. In other words, the PSE is the point where a subject comparing between a stimulus and a reference is equally likely to choose one of the two as higher or lower (Figure 10). Patients with schizophrenia had a lighter PSE than the healthy control group.

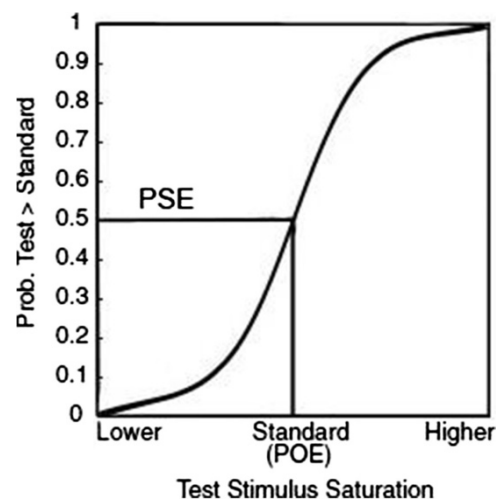


Figure 10. The point of subjective equality (PSE) is the 0.5 probability point. The point of objective equality (POE) is the point at which the test and standard stimulus are objectively equal (Kim et al., 2014). In the case of the SWI, the X axis corresponds to the grams of the comparison stimuli and the Y axis corresponds to the proportion of correct judgements, where 50% is the PSE. Therefore, the PSE is when a standard stimulus and a test are perceived subjectively the same, so that an observer is not able to choose which is higher or lower (heavier or lighter weight than the reference disk in this the context of this study), choosing randomly between them.

Another measure that is calculated from the SWI is sigma (σ), the weight discrimination sensitivity. This is calculated as the standard deviation, where higher is less sensitive.

Even though schizophrenia and FND are different disorders, both are suggested to have a deficit in the prediction system. Hence, we propose that FND will have a similar SWI. We hypothesize that FND patients with functional weakness will experience a reduced SWI than healthy controls (HC), being more accurate in estimating weight in regard to size. Additionally, we hypothesize that patients with a higher severity of weakness will have a reduced SWI, and patients with lateralized weakness will have a reduced SWI on their affected side.

METHODS

PARTICIPANTS

This study was approved by the Human Research Ethics Committee (HREC) of the Austin Hospital (reference number: 48818). Eleven patients diagnosed with FND by a consultant psychiatrist at the Functional Neurology Clinic of the Austin Hospital and 15 healthy control (HC) subjects at the University of Melbourne were recruited. Patients were recruited after their appointment with their psychiatrist, by asking them verbally. All participants were over 18 years old, provided written informed consent to participate in this study ([Appendix B](#)) and were paid \$15 as compensation for their time. Inclusion criteria comprised being over 18 years old and exclusion criteria comprised having symptoms or diseases that would interfere with the study (such as a tremor in upper limbs or blindness), and incapacity to read and communicate with the researcher.

Healthy controls were recruited by word of mouth through the University of Melbourne and matched to FND patients by sex and age. The subjects were excluded if they had any psychiatric or neurological condition other than anxiety disorder or depression, since these are the main comorbidities of FND, or if they had consumed illegal drugs in the previous 48 hours.

PSYCHOMETRIC MEASURES

The Hospital Anxiety and Depression Scale (HADS)

After the task was finished, participants were asked to complete “The Hospital Anxiety and Depression Scale” (Zigmond & Snaith, 1983), which assesses anxiety and depression, two of the main comorbidities of FND. This scale is appropriate for this group of patients because it was designed for people with physical health problems, such as tiredness or slowness, which

might confound the ratings. The questionnaire has 14 items and has proven reliability and validity (Bjelland, Dahl, Haug, & Neckelmann, 2002). It takes 5 minutes to complete ([Appendix C](#)).

Questionnaire of Severity of Weakness and Demographics

A Likert scale of intensity of weakness created for this study was applied, to determine the severity of weakness perceived in the upper limbs ([Appendix D](#)). We were interested in upper limbs only because the task tests perception while using the hands. Some demographic and clinical questions (psychiatric diagnoses) were asked of each participant. It takes 10 minutes to complete.

Edinburgh Handedness Inventory

A short questionnaire on the laterality of participants was given. This is an inventory of 12 questions that lasts 5 minutes (Oldfield, 1971) ([Appendix E](#)).

Size-weight Illusion (SWI) Task

The participants were asked to compare pairs of grey plastic disks to judge which was heavier. The comparison was between a smaller 90g reference disk of 5 cm in diameter and larger disks of 11 cm in diameter of variable weight, all of them 3.8 cm height (Figure 11).

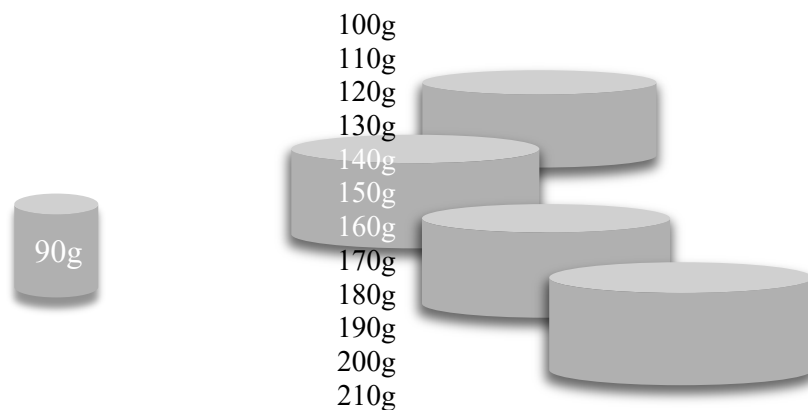


Figure 11. People compared a 90g small disk to large disks of increasing weights (100 to 210 grams in 10 grams increments) by lifting them with both hands at the same time.

The mass of every disk was evenly distributed around the centre, by gluing small heavy metal balls just in the middle, and the material was uniformly produced by 3D printing.

The participants were instructed to lift the disks in the same way every trial and look at them the entire time. They had up to 10 seconds to judge which disk was heavier. The comparisons were counterbalanced for hand and there were 4 trials per comparison: 2 trials with the comparison disk in the left hand, and 2 trials with the comparison disk in the right hand. This 20-minute task included 48 trials (comparisons) in total. These comparisons were applied randomly to participants in five pre-determined orders ([Appendix F](#)).

First, to identify the weight discrimination sensitivity and the point at which the illusion starts to disappear in FND and HC we calculated sigma (σ) (standard deviation) and the point of subjective equality (PSE), the mean of the underlying normal distribution.

Secondly, to understand the impact of the symptom on the illusion, we calculated the PSE of 8 patients with unilateral weakness while using their *weak* hand versus their *no-weak hand*. In this and the following analysis we did not calculate sigma since the analysis was related to one hand only and hence the number of trials was half (2 trials instead of 4).

Finally, in a more exploratory analysis, to know if the laterality impacted on the illusion (the dominant hand used for most things), we grouped patients into those whose affected hand was their dominant hand, and patients whose affected hand was their non-dominant hand. Thus, we compared the PSE of 2 patients while using their *dominant weak hand* and 5 patients using their *non-dominant weak hand*, compared to HC (while using their dominant and non-dominant hand).

PROCEDURE

The Size-Weight Illusion (SWI) version of Williams, Ramachandran, Hubbard, Braff, & Light (2010) was performed first. After this the participants completed the Hospital Anxiety and Depression Scale (Bjelland et al., 2002) to control for the main comorbidities of FND, a questionnaire about the intensity of their symptoms and some demographic questions. The session lasted between 30-40 minutes. They were told that if they felt unwell and needed to leave or if they needed a break not to hesitate to let the researcher know.

The collected data was coded and entered into Jamovi version 1.0.5 downloaded from <https://www.jamovi.org/download.html>, and analysed using Mann-Whitney U for continuous variables, χ^2 and Fisher's exact tests for categorical variables, and repeated measures ANOVA (post-hoc test), T-Tests and Mann-Whitney to compare means across groups. Alpha was set to 0.05.

To calculate the point of subjective equality (PSE) and sigma (σ) the data was entered into R (version 3.6.1), specifically using “Psychometric function” package.

To perform the power analysis we used G*Power version 3.1.

RESULTS

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

We recruited 26 participants, 11 FND patients (5 patients with non-epileptic seizures and 6 patients with functional motor disorder) and 15 HC, as shown in Table 7. Demographic data for 1 FND patient was missing, since they were unable to complete the questionnaires as they felt unwell at the completion of the task. FND and HC were similar in education level.

The groups had similar levels of anxiety and depression in the HADS, with anxiety normal and depression borderline (abnormal). However, when asked about psychiatric diagnoses, FND reported having more diagnoses of depression and anxiety than the HC subjects.

Table 7. Participant characteristics and HADS scores

	FND (n=10)	HC (n=15)	p-value
Female / Male ^a	9 / 2	10 / 5	0.611
Age average (SD), years ^b	45.5 (16.4)	40.7 (14.7)	0.476
Maximum education level completed ^a:			
≤ Year 12 / Certificate or Diploma / Bachelor's degree	6 / 2 / 2	4 / 2 / 9	0.134
Mean (SD) HADS ^b	14 (8.12)	11 (5.59)	0.359
Mean (SD) HADS anxiety score	5.3 (3.9)	4.5 (2.8)	0.696
Mean (SD) HADS depression score	7.5 (4.2)	8.8 (3.7)	0.558
Edinburgh Handedness inventory	FND (n =11)	HC (n =15)	p-value
right / left / ambidextrous	9 / 2 / 0	15 / 0 / 0	--
	11	0	--
Weakness in upper limbs	4	0	--
Right side weakness	2 / 2 / 0	0	--
mild / moderate / severe	4	0	--
Left side weakness	1 / 3 / 0	0	--
mild / moderate / severe	3	0	--
Bilateral weakness	2 / 1 / 0	0	--
mild / moderate / severe			

FND = functional neurological disorder; HC = healthy controls.

^a Chi-square

^b Mann-Whitney U

a. Size-weight Illusion

To determine the strength of the illusion we calculated the point of subjective equality (PSE), which is the exact point where the comparison feels the same as the standard. The higher the PSE, the stronger the illusion, and, conversely, the lower the PSE, the weaker the illusion (Figure 12).

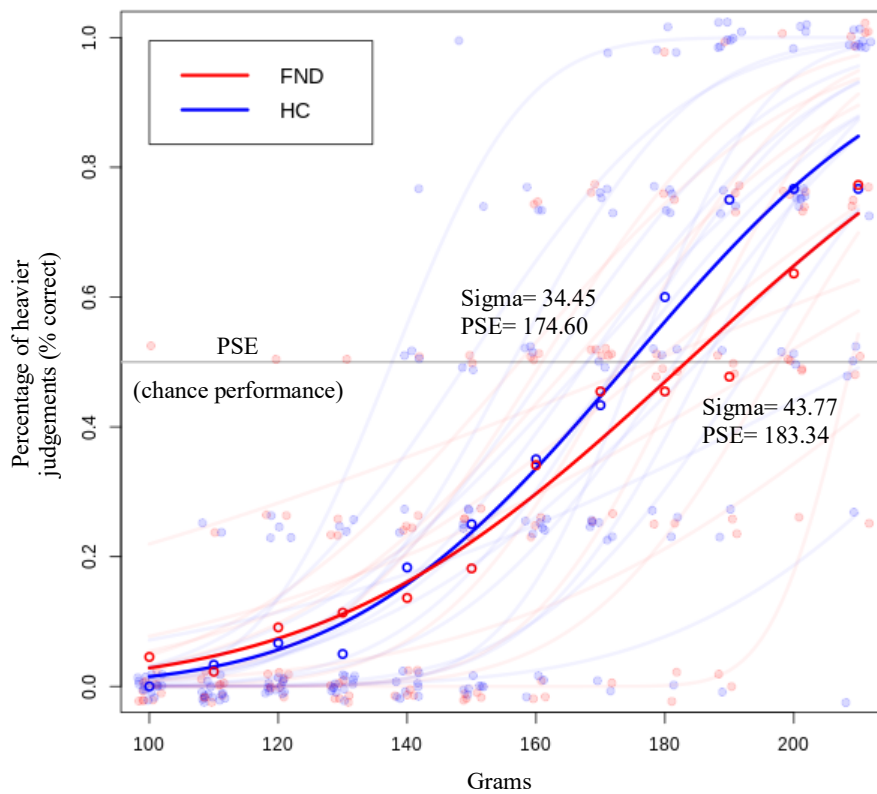


Figure 12. Performance of the healthy control group (HC, $n=15$) and patients with functional neurological disorder (FND, $n=11$) in the size-weight illusion (SWI). The graph depicts the SWI trials, where a 90g disk is compared to larger disks of increasing weights, from 100 to 210 grams. The lines depict average percent heavier values (correct answers). The PSE is the point of subjective equality, where the weights of both disks are perceived as equal. Sigma (σ) is the weight discrimination sensitivity, which corresponds to the standard deviation, where higher values reflect less consistent responding.

The figure shows that 174g is the average point at which HC start to say that the comparison object is heavier than the 90g-reference, and at which FND are still likely to say it is lighter. On the contrary, 183g is the point at which FND patients report the comparison object to feel equal to the 90g-reference. However, independent samples T-tests found this difference in PSE to be non significant between FND ($M=183$, $SD= 20.2$) and HC ($M=173$, $SD=19.5$), $t(24)=1.06$, $p=0.301$. Additionally, we quantified the evidence to support the

alternative hypothesis by computing a Bayes factor, which resulted in $BF_{10} = 0.550$ that corresponds to “anecdotal evidence” (see the table of categories in [Appendix G](#)). This means that the results are not robust enough to support the alternative hypothesis.

Interestingly, looking at the individual data it seems that FND patients have more variable responses than HC, since some of them show a very flat slope. To ascertain if the groups really had a difference in ability to discriminate weights, we calculated Sigma (σ). FND had a sigma of 43.77 ($M = 34.7$, $SD = 25.6$) and HC had a sigma of 34.4 ($M = 38.6$, $SD = 38.7$), which was again not found to reach statistical significance, $t(24) = -0.292$, $p = 0.773$, indicating that this data is not able to determine that they have different weight discrimination sensitivity.

Post-hoc Power Analysis

As the sample size was relatively small, a post-hoc power analysis was performed to determine how many participants would be required given the degree of variability in participant responses.

Using the means and the standard deviations of the two groups compared, we considered the difference between both as they had a medium effect size of 0.43333 and an alpha value of 0.05. These parameters showed that the power of our study did not reach 30% (Power = 0.27), so the probability of detecting a significant effect, if our hypothesis was true, would be extremely low.

Assuming that our hypothesis was true, we found that for 80% power we require a minimum of 67 cases per group to find a medium effect size (0.43333).

The sensitivity of our current design could only have detected significant differences if the effect size was large.

b. Unilateral Weakness and Strength of the Size-weight Illusion

Figure 13 depicts the SWI of patients with *unilateral weakness*, where one hand was more affected than the other one ($n = 8$, with three patients excluded because they reported bilateral weakness). Of these patients, 4 presented with mild weakness in one side and no weakness in the other one, 2 presented with moderate weakness in one side and mild weakness in the other one, and 2 with moderate weakness in one side and no weakness in the other one.

The figure shows the strength of the SWI while holding the comparison disk with the *weak hand* and with the *not weak hand* (or *less weak hand*), to determine if the illusion was impacted by the symptom.

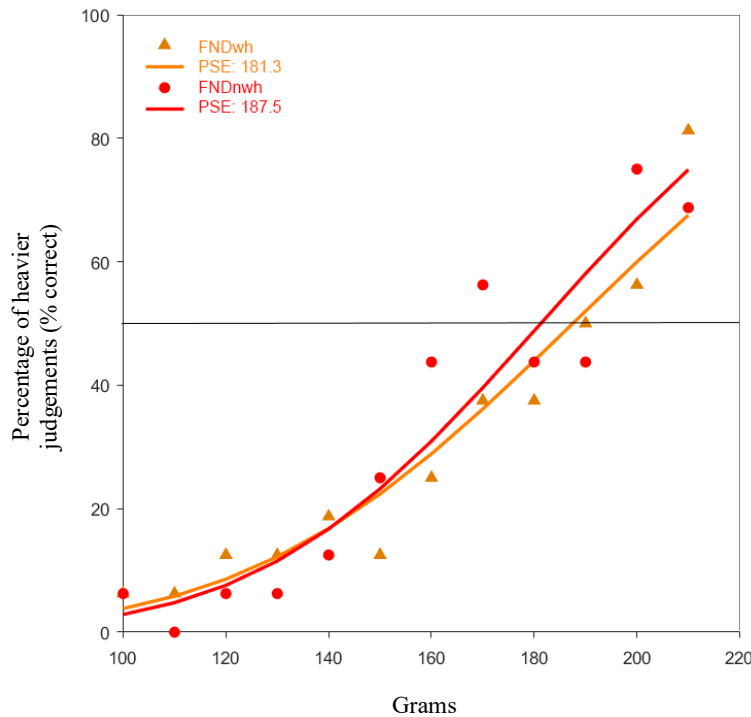


Figure 13. Size weight illusion (SWI) of FND patients with unilateral weakness ($n=8$). The red line represents the SWI of FND while holding the comparison disk with the *weak hand* (FNDwh), while the orange line corresponds to FND holding the comparison disk with the *non-weak hand* or *less weak hand* (FNDnwh). Since this analysis was in relation to one hand, the number of trials is half, having only 2 trials per weight comparison.

Mann-Whitney shows that the point of subjective equality (PSE) between patients using their *weak hand* (Mdn= 172) and their *non-weak hand* (Mdn= 175) was not significantly different, $U=23.0$, $p=0.902$. Therefore, the illusion was not impacted by the dominance of the hand affected by the symptom.

c. Dominance of the Affected Hand and Strength of the Size-weight Illusion

As shown in figure 14, we analysed if functional weakness had a different effect on the illusion depending on whether the weak hand was the dominant or non-dominant hand.

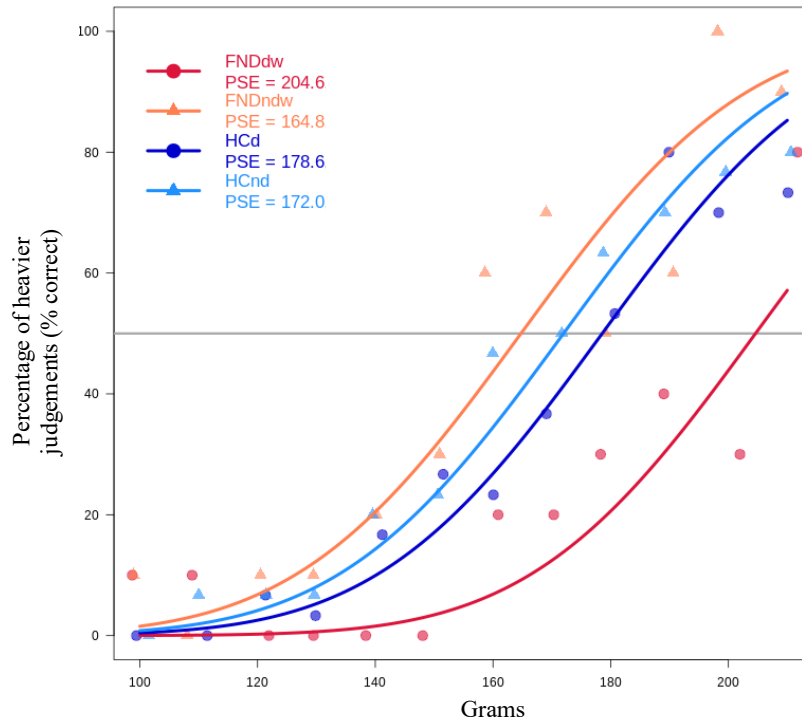


Figure 14. Performance in the size-weight illusion (SWI) of FND patients with unilateral weakness that present with *weakness in their dominant hand* (FNDdw) while holding the comparison disk with that hand ($n = 2$, with 1 excluded patient because they had a very extreme PSE), patients with *weakness in their non-dominant hand* (FNDndw) while holding the comparison disk with that hand ($n = 5$) and HC while holding the disk with their dominant and non-dominant hand ($n = 14$, with 1 excluded subject because they had a very extreme PSE). The red and orange lines correspond to FND and blue and light blue lines to HC. Since this analysis was done in relation to one hand, the number of trials is half, having only 2 trials per weight comparison.

The point of subjective equality (PSE) of FND patients while holding the comparison disk with their *weak dominant hand* (SD= 41) was 205 and FND patients with their *weak non-dominant hand* (SD= 27.6) was 165. PSE of HC while holding the comparison disk with their *dominant hand* (SD=24) was 179, and for HC while holding the disk with their *non-dominant hand* (SD=25) was 172.

Due to the small sample size in this section (as one group had only 2 patients) it was inappropriate to run any statistical analysis.

d. Severity of Functional Weakness and the Size-weight Illusion

Since we did not find differences between hands (*weak* vs *non-weak*) neither between patients with their weakness in the *dominant* vs *non-dominant hand*, nor between patients and HC, we did not analyse the impact of severity of the symptom on the SWI.

DISCUSSION

Since there are no reliable measures to account for functional symptoms, we tested the size-weight illusion (SWI) as a possible measure to identify perceptual differences in patients with functional weakness, the most reported symptom of FND. Eleven patients who reported functional weakness and 15 healthy controls (HC) underwent the size-weight illusion paradigm, using a version created by Williams et al., (2010).

We found that as long as the comparison disks were increasing in weight, correct judgements were also increasing, which means that the participants needed higher weights to perceive that they were heavier than the small reference disk. Thus, consistent with previous studies, all participants experienced the size-weight illusion (Flanagan & Beltzner, 2000; Gordon et al., 1991; Nicolas, Ross, & Murray, 2012).

The point of subjective equality (PSE), which is the point where the illusion is overcome and the objects are perceived as equal, namely, the *strength* of the illusion, was 174 grams for HC. It is notable that this is exactly the same as reported for the healthy controls tested in Williams, Ramachandran, Hubbard, Braff & Light (2010). In comparison the point of subjective equality for the FND group was 183 grams (over double the 90g weight of the smaller disk). We expected that FND would have a reduced illusion, namely a lower PSE than HC. While the difference between groups was not found to be significant, it is noteworthy that the pattern of responses went in the opposite direction as that expected with the average PSE being heavier (indicative of a stronger illusion). It will be important to test a larger participant sample to see if this pattern of responses persists.

Non-significant differences were also found regarding the weight discrimination sensitivity, namely sigma.

Although FND patients and HC had a similar PSE and Sigma, according to the individual data, we proposed that FND does have a different perception but that could not be detected in this study due to the small sample size and that the participants had relatively more diagnoses of anxiety and depression (although they reported similar levels in the questionnaires), which might have affected the results. If this proposal was corroborated, we

might think that FND has a more variable perception and hence unreliable responses compared to HC, being less likely to report the objects as heavier regardless of how much heavier they are. In this context, the illusion would appear to be working differently at the very highest weights, where the perception of patients is different from the HC. In fact, the point at which HC start to report that the comparison object as heavier than the reference is 170g, at which point FND are more likely to say it is still lighter. However, these are only assumptions based on our hypothesis and on observations of the individual data, which have not been found to be true in our study. If FND patients are indeed less consistent in their responses it might also be important to increase the number of trials per participant as the within person variability itself might be more distinct than any change in average PSE.

A second analysis could not reveal a difference between the illusion with the *weak hand* and with the *less weak hand*, therefore it is not possible to suggest that the location of the symptom impacts on the strength of the illusion. Several patients reported weakness in both hands, so to do this comparison we considered only those patients that had unilateral weakness and those that had one side weaker than the other, thus this analysis relied on even less participants.

Finally, when looking at the patients according to if their weak hand was dominant or non-dominant, it was observed that patients using their *dominant weak hand* might have a different performance from patients using their *non-dominant weak hand* and HC using their *dominant hand*. This descriptive analysis indicates that it is worth testing more participants.

The assumption behind our hypotheses was that bodily sensations were strongly impacted by expectations of motor or sensory symptoms, which have been suggested to be affected in FND (Blakemore et al., 1998; Edwards et al., 2012; Pareés, Brown, et al., 2014). Thus, if expectations are at play, bodily perceptions of patients with FND should be different to HC. Since they do not attenuate the sensations coming from their own body, that is, they have a loss of sensory attenuation (Macerollo et al., 2015; Pareés, Brown, et al., 2014), we predicted that they would have a reduced illusion similar to other patients with loss of sensory attenuation (Williams et al., 2010). So, we also expected that if a patient presented with lateralized weakness, the perceptions coming from the (more) affected side would be different to those coming from the unaffected (or less affected) side.

Though we did not find the hypothesised results, these data do not allow us to conclude with certainty that functional weakness does not impact on FND perception, since our sample size was small, and even smaller when comparing affected and unaffected sides. If these

results were confirmed in the future, that is, that FND have similar performance to HC it would be very surprising, since in the literature it has been reported that FND has different perception of their own body, for instance, being purportedly affected by suggestions and expectations of illness and symptoms (Bell et al., 2011; Hallett, 2011; Kenney et al., 2007). However, it would be interesting to find that they had similar results, since patients with FND often have poor performance compared to HC on other kinds of tasks, such as those that examine cognitive functioning, for instance measures of attention (McIntosh et al., 2017); executive function (Brown, Nicholson, Aybek, Kanaan, & David, 2014; Niemi, Portin, Aalto, Hakala, & Karlsson, 2002); and memory (Williamson, Holsman, Chaytor, Miller, & Drane, 2012).

In terms of perceptual processes underlying this illusion, cognitive mechanisms in charge of violation of expectations of heaviness of objects haptically explored appear to be unaffected in FND patients in our preliminary data. Following the explanation proposed by the forward model of motor control, when people lift objects the brain sends motor commands necessary to do an action through the musculoskeletal system (Miall & Wolpert, 1996). However, just before this happens, a copy of this command is integrated into the forward model, which computes the interaction between the predicted behaviour and the world. In general, both the motor command and the prediction are the same, so that the actions can be performed voluntarily and the sensations are normal because they can be predicted (Kandel, Schwartz, Jessell, Siegelbaum, 2014). Nevertheless, in the case of the SWI, the prediction and the actual stimuli are different, producing an incorrect perception of the weight of the small object regarding the large object in healthy population (Buckingham et al., 2016). In the case of FND, if in future studies we found the hypothesized effect, this would be different, showing a poorer performance, that is, a stronger illusion (lower correct judgements in the heaviest weights).

On the other hand, if the similarity between FND and HC was confirmed, it is possible that these predictive processes are involved in the development of symptoms as proposed in previous studies, (Blakemore et al., 1998; Macerollo et al., 2015; Pareés, Brown, et al., 2014; Shergill, 2003) but not in the way we thought. Perceptual and sensory mechanisms that make patients feel that their movements are not self-controlled or that their sensations are abnormal, are related to low interoceptive awareness, particularly, to incorrect interpretation of implicit expectations of sensations coming from their own body (Ricciardi et al., 2016). However, unlike internal stimuli, it might be that patients perceive and interpret the cues

from their environment normally, and consequently experience the same SWI as healthy people. The deficit involved in their ambiguous sensations might be related to incorrect interpretations of interoceptive rather than exteroceptive stimuli, which might be exacerbated by a tendency to divert attentional resources onto themselves (Brown, Danquah, Miles, Holmes, & Poliakoff, 2010) and hyper-vigilance towards their body (Kumru, Begeman, Tolosa, & Valls-Sole, 2007; Van Poppelen et al., 2011). It would be interesting to study the impact of directing attention to internal or external cues on the prediction of movement and sensations, and whether other predictive processes are involved instead - for example, to study if sensorimotor adaptation of grip force to the actual weight of the objects in the SWI occurs as has been found in the healthy population (Baylis, Tipper, & Houghton, 1997; Buckingham et al., 2016; Flanagan & Beltzner, 2000).

Another explanation of these results is that predictive processes in FND, such as the loss of sensory attenuation, are not constantly disrupted - that is, they might be processes that are intermitently “deactivated” or “malfunctioning”. If they worked in this manner, their consequences would be the appearance and disappearance of symptoms in an inconsistent fashion. Moreover, this process might be selective to the side or part of the body affected. To test these possibilities in future studies, there should be two groups of patients, one presenting with the symptom during the task and one with no symptoms. Furthermore, these groups should be studied according to the side of the body affected, as we did, but with a larger sample to allow for appropriate statistical analysis to be performed.

Finally, another possibility is that the SWI does not test the predictive system at all. Some authors propose that the SWI is not produced by processes related to expectations, supporting the bottom-up hypothesis, that the illusion is produced by a misinterpretation of the relationship between mass and volume (Ross & Di Lollo, 1970; Stevens & Rubin, 1970). This hypothesis supports the notion that the higher density of a small object in comparison to a larger one of equal weight is incorrectly interpreted as greater in weight.

However, there is substantial evidence indicating this perspective itself cannot account for the illusion. Other authors have shown consistent evidence supporting the top-down hypothesis, where expectations are involved in interpretation of sensations. Flanagan et al. (2008) showed that participants who experienced inverse-density objects (larger objects had a lighter mass) had a smaller than usual SWI, explaining that this result was caused by manipulated expectations. Furthermore, and more convincingly, after experiencing this for 11 days, the participants reported an inverted SWI, that is, they felt that the large objects were

heavier than the equal-weighted smaller reference. Another study reported that the participants experienced a strong size-weight illusion when lifting a unique medium size cube without looking, after having previewed a small, medium or large cube, which primed their perception of weight (Buckingham & Goodale, 2010a). It is proposed that the SWI can be explained as a combination of top-down and bottom-up effects, namely expectations and sensations coming from external stimuli (Buckingham, 2014). Based on this evidence, we think that the SWI is an adequate test for the prediction system, and that our results are important, since there are no other studies that have measured the impact of lateralized functional weakness on perception, and very few have studied the prediction process in FND.

LIMITATIONS

It is important to highlight that this study has limitations that if addressed should lead to clearer results. We found that the variability in responses elicited by the task meant that it would only be possible to detect large effects with a small participant sample. Therefore, assuming that our hypothesis is correct, we would require a design with many more cases per group to identify significant differences. Additionally, due to time restrictions, even though the patients reported not being tired or in a hurry, they were tested after the medical appointment with their consultant psychiatrist, which could have affected their attention level in the task and, in turn, their performance. Another limitation is that we did not compare between affected and truly unaffected hand, since most cases had mild weakness rather than absence of symptom.

CONCLUSION AND FUTURE DIRECTIONS

In summary, the present preliminary results show that patients with functional neurological disorder are able to experience the size-weight illusion, similar to healthy controls. Due to the low power of our data, findings were inconclusive regarding differences between affected and unaffected hand, and between dominant and non-dominant affected hands. That is, they perceived that small objects are heavier than large ones of the same weight, needing heavier large objects to nullify this effect. If these results are replicated in future studies, it will allow us to determine with greater certainty that FND patients do not have abnormal prediction processes and perceptions, and that other kinds of mechanisms might be involved.

To further explore the nature of the deficit, future studies may include the SWI with heavier weights, for example disks heavier than 210g, since it seems that the difference between FND and HC seems to be largest at the heavier weights (e.g., in the comparisons above 160g). Moreover, it would be interesting to compare the SWI of FND with organic movement disorders that present with similar symptoms, which would provide us further understanding as to whether perceptual processes of FND work normally or are really different in their functioning impacting on the generation of symptoms. Additionally, if this showed a difference, the task could be taken as a measure of the deficit that can differentiate FND from medically explained disorders, confirming that this disorder has perceptual mechanisms involved beyond of what can be explained through objective tests and medical examinations.

CHAPTER 4: DISCUSSION AND IMPLICATIONS

Functional neurological disorder (FND) is a complex disorder that has a long history of controversy, and despite being studied for more than a century has not been fully understood. During the first decades of research, at the end of the 19th century, neurologists such as Joseph Breuer and Sigmund Freud, to name a few, called this disorder *hysteria*, and argued that it was caused by traumatic events. Their observations suggested that dissociative processes were responsible for the disorder by removing negative emotions about trauma from consciousness and converting them into hysterical symptoms (Breuer & Freud, 1955; Charcot & Marie, 1892; Janet, 1921). However, it is currently thought that not all patients with FND have undergone traumatic events, and conversely, not all people who suffer a trauma develop FND (Rofé, 2008). Furthermore, it has been recently argued that FND is related to psychological risks, but not necessarily caused by them. This has led some to argue for a change of name from *conversion/psychogenic disorder* to *functional neurological disorder (FND)* (Espay et al., 2018).

Some of the neurobiological evidence surrounding FND comprises body and brain high-arousal states (Kozłowska et al., 2017) and abnormal connection between the limbic system (responsible for emotion, motivation and memory), the supplementary motor area and the right temporo-parietal region (in charge of motor control) when dealing with trauma (Aybek et al., 2014) or emotional stimuli (Aybek et al., 2015; Blakemore, Sinanaj, Galli, Aybek, & Vuilleumier, 2016; Valerie Voon et al., 2010). Moreover, activation of the hypothalamic-pituitary-adrenal (HPA) axis has been evidenced, possibly as a consequence of pain, injury or trauma (Apazoglou et al., 2017; Arnsten, 2015; Bakvis et al., 2010; Hermans et al., 2011).

Even though neurobiological mechanisms are involved in the development of FND, recent evidence demonstrates that *cognitive processes* may impact the *kinds of symptoms* that patients develop. It is suggested that, besides the presence of risk factors such as traumatic events and psychiatric comorbidities, different experiences may influence whether a patient develops either FMD or NES, through the generation of expectations about body sensations and movements (Edwards, Fotopoulou, & Pareés, 2013; Pareés, Kojovic, et al., 2014). For example, when the systems implicated in stress and arousal are activated, they generate autonomic responses, such as hyperventilation or an increase in heart rate. These responses can be taken as models for body sensations, driving the generation of functional symptoms in vulnerable subjects. However, there are very few studies that have investigated the relationship between clinical events and kinds of symptoms developed by FND patients. So

far, we know that: physical events can precipitate functional motor symptoms (FMD) (Pareés, Kojovic, et al., 2014); ideas of disease might increase the probability of expected symptoms occurring (Edwards, 2016; Edwards et al., 2012; Pareés et al., 2012); the generation and remission of symptoms can be affected by the placebo effect (Edwards, Bhatia, & Cordivari, 2011; Hallett, 2011), distraction techniques and suggestion (Hallett, 2011; Kenney et al., 2007). Additionally, we know that traumatic life events are more common in NES than FMD (Alper et al., 1997; Bakvis et al., 2009; Kanaan et al., 2017).

Thus, the *first aim* of this research was to investigate if *clinical events* such as comorbidities, injuries and surgeries influenced the kind of symptoms that patients developed, namely, *functional movement disorder* (FMD) or *non-epileptic seizures* (NES). To do this, we examined the medical records of 56 FMD patients and 52 NES patients, which consisted largely of letters written by their psychiatrists and neurologists.

In line with predictions, our study demonstrated that some clinical events occurring in certain body areas were more common in one variant than the other. Thus, patients with FMD had significantly higher rates of *previous clinical experiences* that affected the *limbs* compared to NES. Among these events, *injuries* had a higher prevalence in FMD, which has been found as common in FMD by Pareés, Kojovic, et al. (2014). However, patients with NES had similar rates of previous events related to the *head* than FMD, contrary to what we predicted based on the higher prevalence of head trauma and epilepsy found in previous research (Glosser et al., 1999; Pillai & Haut, 2012; Westbrook et al., 1998; Wissel et al., 2016).

Regarding other occurrences during patients' lifetimes our findings were consistent with the literature. FMD presented with higher rates of *somatic disorders* (Bègue et al., 2019; Demartini, Goeta, et al., 2016) and *motor symptoms* (Erro et al., 2016) compared to patients with NES. NES, on the other hand, presented with more *suicidal ideation* and *dissociative symptoms* (Demartini, Goeta, et al., 2016; Hendrickson et al., 2015), and marginally higher rates of *traumatic life events* than FMD (Dixit et al., 2013; Driver-Dunckley et al., 2011; Kanaan et al., 2017; Kranick et al., 2011), among which *bullying* in particular was higher than in FMD (Reilly et al., 1999; Reuber, Howlett, et al., 2007).

Additionally, we collected information about how long prior to symptom onset the events occurred. The data showed a similar timeframe between the event and symptom onset in FMD and NES. More than half of the patients had a clinical event (surgery, injury or disease)

between one week and one year prior. Interestingly, a substantial portion of the patients, almost a third of them, had an event the *same day or week* of the symptom's onset.

In summary, events impacting the *limbs* prior to FND onset, which corresponded mostly to injuries, were more related to FMD than NES, and events impacting the *mind* (which, from the patients' perspective, can be located in the *head*) during their lifetime, were more related to NES than FMD. Patients with FMD had higher rates of somatic and motor symptoms during their lifetimes than in NES. Of the events that occurred before FND onset, most happened during the last year and a substantial proportion of patients reported an event during the same day or week of FND onset, equally for FMD and NES.

Most of these results are consistent with traditional notions of the influence of the ideas of disease on FND symptoms, for instance, with the concept of "somatic compliance" created by Freud to refer to pathological mental processes connected with bodily organs, leading to a physical outlet (Freud, 1963). These notions are consistent with recent literature and can be explained from neurobiological perspectives, supporting the impact of expectations on FND symptoms (Edwards et al., 2012; Stone et al., 2017). Beliefs based on previous experiences lead to expectations of body sensations, movements and interpretation of external stimuli so that we are prepared in advance for our perceptions and sensations. In other words, the brain contains internal representations of the sensory signals expected as a result of movement (Kandel, Schwartz, Jessell, Siegelbaum, 2014). Thus, it is reasonable to think that vulnerable subjects might generate an aberrant model of perception and sensation in an affected body part, and then when similar circumstances come up, or reminders of those circumstances, the brain unconsciously repeats these patterns, generating confusing perceptions and sensations, including the lack of control of movements (Brown & Reuber, 2016; Pareés, Brown, et al., 2014; Stone et al., 2009; Van den Bergh, Witthöft, Petersen, & Brown, 2017).

We suggest that FMD patients, for instance, by having more events that impact their *arms and legs*, are more vulnerable to generate motor symptoms in their *limbs*. Patients with NES on the other hand, by having more events that impact them *psychologically* or that have more *psychiatric* consequences in their lifetime, are more vulnerable to develop symptoms related to the *head*, such as seizures or fainting. Thus, events impacting limbs might be considered *predisposing* factors for FMD, and events impacting the *head* might be considered *predisposing and perpetuating* factors of NES.

Hence, we propose that clinical events affecting different parts of the body have a relationship with the kinds of symptoms patients develop, through expectations of symptoms.

Moreover, these expectations might explain the inconsistency of symptoms compared with neurological disease, and their changes over time, which make them very difficult to be measured, and therefore, to be studied (Edwards, 2016; Edwards et al., 2013; Pareés et al., 2012). Thus, our *second aim* was to investigate a *measure* to identify *perceptual processes implied* that work differently in *functional weakness* - the most common symptom of FND.

The second study was a preliminary approach to objectively measuring the prediction system involved in functional weakness through the size-weight illusion (SWI). We applied this illusion to 11 FND patients (6 patients with motor symptoms and 5 patients with non-epileptic seizures) and 15 healthy controls (HC), along with questionnaires to control anxiety and depression, the main comorbidities of FND.

Based on the study of Williams, Ramachandran, Hubbard, Braff, & Light (2010), which applied the SWI to patients proposed to have a similar deficit in prediction processes to FND, we predicted that FND would have a reduced SWI than HC, and that this effect would be most pronounced when using their most affected hand.

Unexpectedly, our results showed that FND patients with functional weakness had a *similar SWI* to HC. Moreover, the illusion was similar in both the *weak* and *non-weak* hand regardless of the *dominance* of the affected hand.

Even though our sample was too small to reach any conclusions with certainty, if this data were consistently supported in future research, it would argue that FND patients have similar perceptions of weight in relation to size to HC, and that their predictive processes work normally, contrary to what has been proposed in studies that show a loss of sensory attenuation (Macerollo et al., 2015; Pareés, Brown, et al., 2014). A loss of sensory attenuation is supposed to be caused by a problem in predicting sensations of one's own movements, and it is thought to be the reason why patients feel as though their movements are out of their control, leading to a disturbed self-agency (Blakemore, Frith, & Wolpert, 1999; Brown, Adams, Parees, Edwards, & Friston, 2013) or belief of authorship (Desantis, Weiss, Schütz-Bosbach, & Waszak, 2012).

An alternative explanation that is worth exploring in the future is that the prediction system might indeed be affected but not in the way we think. Thus, one possibility is that a dysfunction in the prediction process might not impact the whole body but only some parts, or perhaps that it is not consistently affected all the time, which might explain the appearance and disappearance of symptoms. Another possibility is that the prediction mechanism is not the same for patients with different variants.

Furthermore, other mechanisms different from the prediction system might be involved in FND. For instance, high arousal (Kozłowska et al., 2017; Lader & Sartorius, 1968) and cortisol levels (Bakvis et al., 2010) generating an over-reaction to stress (Apazoglou, Mazzola, Wegrzyk, Polara, & Aybek, 2017) might be more relevant for the generation of symptoms than the prediction mechanism proposed. These reactions can occur even when there are no objective stressful events, since it has been suggested the psychological impact of the situation is more important than the severity of the events (Stone et al., 2009). Added to this, a lack of sensitivity to internal cues, such as heartbeat or temperature changes, among others, might be more significant for symptoms, consistent with Ricciardi et al.'s (2016) finding of lower interoceptive accuracy in FND than healthy subjects.

It cannot be ruled out that the SWI might not be linked to loss of sensory attenuation or that it might not test the prediction model as proposed. This would be consistent with the researchers that suggest that the SWI is not produced by wrong expectations or top-down processes, but by bottom-up processes, which refer to an incorrect relationship between mass and volume (Ross & Di Lollo, 1970; Stevens & Rubin, 1970). However, even though we must be cautious, we do not support this notion because there is robust evidence that suggests the illusion depends mostly on top-down processing, particularly expectations (Buckingham & Goodale, 2010a; Flanagan & Beltzner, 2000).

In contrast, therefore, if future research confirmed our hypothesis that FND has a decreased SWI than HC, we would argue that there is indeed a problem in the prediction system and a difficulty with integrating sensory-motor cues. In that case, the SWI could be used as a task that provides an objective number of the deficit. But, assuming our essentially negative results were corroborated in the future, we would suggest that FND patients do have a similar perception to HC when it comes to predicting sensory-motor stimuli.

LIMITATIONS AND FUTURE DIRECTIONS

Regarding the first study, of clinical events and symptoms, there is no certainty that the measures collected are characteristic of FND or whether they also occur in the healthy population at similar frequencies. It would be interesting to collect data about comorbidities, injuries and surgeries in healthy people and compare the rates to FND. If they are more common in FND, we could be confident that clinical events are one of the relevant factors of functional symptoms development. Otherwise, it would support the idea that clinical events are unable to generate symptoms in isolation, but instead require other additional

characteristics. Nevertheless, this similarity would not rule out the possibility that clinical factors are key in determining which symptoms the patients develop. To determine the latter with more certainty, it would be necessary to collect the same data as this study but in a more reliable fashion. For example, checking the missing or unclear information with the patients and their doctors, addressing some of the limitations of information subjectivity.

Another limitation is that we cannot determine which factors are characteristic of FND or are also present in other pathologies. Therefore, it would be interesting to collect all variables that possibly affect FND and compare them with the data of patients with an organic pathology that present with similar symptoms. For example, neurological disorders such as epilepsy, or other diseases proposed to have a similar pathophysiology, such as somatoform disorders, which also present with “medically unexplained” symptoms. These comparisons would allow us to understand which variables are common to FND and organic diseases, and to FND and medically unexplained disorders, and which are specific to FND, shedding some light on the determining factors for functional symptoms.

Regarding the second study, a larger sample for both groups would clearly be of benefit. Moreover, to test the alternative explanations of the functioning of the prediction mechanism, it would be crucial to have two groups of patients - with and without functional weakness - as well as two subgroups of patients, of which one group presented with the symptom while doing the task and the other group did not. Moreover, the task should be done on a different day or before the medical appointment, so that performance is not affected by tiredness or lack of concentration.

CONCLUSION

Overall, these findings show that FND patients present with a history of clinical events in body parts that are related to the formation of functional symptoms in those body parts, and that, if confirmed in the future obtaining a larger sample size, they do not have the different SWI than HC as we hypothesised. This might indicate that the relationship between clinical events and FND symptoms in similar body parts is not related to an abnormality in the prediction system responsible for motor control, which seems to work normally. Therefore, the hypothesis that misinterpretations of body sensations drive expectations of symptoms, misperceptions of the body, leading to the appearance of functional symptoms, might be incorrect.

However, to conclude with certainty, further studies would be necessary, which should test the prediction system addressing the limitations proposed, such as increasing the sample size and testing patients that present with more severe symptoms during the task.

In summary, the present studies demonstrate that the occurrence of clinical events in different body parts might partly determine the location and kind of functional symptoms that a patient develops. However, since the sensory-motor predictions that drive the perception of unusual size-weight relationships were not found to be different in FND, there was no evidence found for a role of abnormal prediction mechanisms underlying the relationship between clinical events and the formation of symptoms.

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APPENDIX A: TABLES OF STUDY 1 “CLINICAL FACTORS IN PATIENTS WITH FUNCTIONAL MOTOR DISORDER AND NON-EPILEPTIC SEIZURES”

TABLE 1A. LIST OF COMORBIDITIES, SURGERIES AND INJURIES GROUPED BY AFFECTED BODY PARTS

Body part	Disease / injury / surgery
Head (brain / mind)	Depression
	Anxiety disorder
	Panic attack
	Post-traumatic stress disorder (PTSD)
	Suicidal ideation / attempt
	Sleep disorders
	Bipolar personality disorder
	Obsessive compulsive disorder
	Borderline personality disorder
	Schizophrenia
	Addictions
	Migraine / headache
	Epilepsy
	Syncope
	Meningitis
	Pseudo meningocele
	Progressive multifocal leukoencephalopathy
	Encephalopathy
	Encephalitis
	Cerebrovascular accident (CVA)
	Spasticity
	Concussion
	Head injury
	Anterior temporal lobectomy
	Amygdalotomy
Head (Ears / eyes / face)	Bell's palsy
	Ophthalmic aneurysm
	Sinus polypectomy
	Adenoidectomy
	Myringotomy
	Cataract surgery
	Jaw operation
	Nose surgery
	Corneal transplant
	Hypothyroidism
Head (throat)	Hyperthyroidism
	Tonsillitis
	Goitre
	Tonsillectomy
Back and limbs	Lumbar spinal injury (back and limbs)
	Organic movement disorder (back and limbs)
	Carpal tunnel syndrome (arms)
	Raynaud's syndrome (arms)

Trunk

Fracture (depend on the part affected)
Bursitis (depend on the part affected)
Phlebolympheidema (legs)
Shoulders injury (arms)
Whiplash injury (back)
Cramp-fasciculation syndrome (legs)
Cervical radiculopathy (back and arms)
Locked up joints (limbs)
Lumbar bulge disc surgery (back and limbs)
Shoulder reconstruction (arms)
Spinal cord stimulator insertion
Microdiscectomy (back)
Meniscectomy / arthroscopy (legs)
Cervical spine surgery (back and limbs)
Heart disease
Asthma
Respiratory infection
Chronic obstructive pulmonary disease
Pulmonary oedema
Sleep apnoea
Pulmonary embolism
Gastritis
Gastric ulcer
Gastric infection
Colon polyp
Hiatus hernia
Diverticulosis
Coeliac disease
Irritable bowel syndrome (IBS)
Gastroesophageal disease (GORD)
Gastroparesis
Renal failure
Hepatitis
Cirrhosis
Fatty liver
Pancreatitis
Endometriosis
Polycystic ovarian syndrome
Fibroids
Cervical cancer
Miscarriage
Colonoscopy
Cholecystectomy
Myomectomy
Abdominoplasty
Hysterectomy / tubal ligation
Appendicectomy
Mastectomy
Replacement of the aorta
Gastric banding

Whole body	Lupus Leukaemia Multiple sclerosis Anaemia Haemochromatosis Idiopathic neutropenia Hypercholesterolaemia Hypertension Willebrand disease Orthostatic tachycardia Diabetes Glandular fever Lyme disease Osteoarthritis Osteoporosis Hormones deficiency Addison's disease Pituitary disorder Pre-eclampsia Neurofibromatosis 1 Grave's disease Sarcoidosis Obesity Anorexia Parkinson's disease Allergy to medication Eczema Fibromyalgia Chronic fatigue syndrome (CFS)
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TABLE 2A. BENJAMINI-HOCHBERG ADJUSTMENT CORRESPONDING TO SECTIONS “CLINICAL FACTORS” AND “CLINICAL FACTORS PER BODY PARTS”

Variable	<i>p</i> -value	ranking	(l/m)*q
Comorbidities, injuries, surgeries in limbs + back	0.006*	1	0.01
Comorbidities, injuries, surgeries in limbs	0.013*	2	0.03
Injuries	0.035*	3	0.04
Surgeries in limbs + back	0.035*	4	0.05
Comorbidities, injuries in limbs	0.045	5	0.07
Comorbidities, injuries in limbs + back	0.049	6	0.08
Comorbidities, injuries, surgeries in trunk	0.06	7	0.09
Surgeries in limbs	0.095	8	0.11
Comorbidities, injuries, surgeries in head	0.182	9	0.12
Comorbidities, injuries in head	0.275	10	0.13
Surgeries in back	0.44	11	0.14
Comorbidities, injuries, surgeries in back	0.561	12	0.16
Comorbidities, injuries in whole body	0.568	13	0.17
trunk	0.642	14	0.18
Comorbidities, injuries in back	0.665	15	0.20
Surgeries in head	0.667	16	0.21
Comorbidities	0.82	17	0.22
Comorbidities, injuries in trunk	0.989	18	0.24
Surgeries	1	19	0.25

* statistically significant

l = rank

m = number of tests

q = false discovery rate (chosen)

TABLE 3A. BENJAMINI-HOCHBERG ADJUSTMENT CORRESPONDING TO SECTION “SYMPTOMS”

Variable	<i>p</i>-value	rank	(<i>l</i>/<i>m</i>)*<i>q</i>
Motor symptoms	0.001*	1	0.01
Dissociative symptoms and panic	0.001*	2	0.02
Loss of awareness/depersonalization	0.001*	3	0.04
Seizures	0.001*	4	0.05
Gait difficulties	0.01	5	0.06
Tremor	0.025	6	0.07
Vertigo/ dizziness / nausea	0.033	7	0.08
Pain	0.042	8	0.10
Language	0.09	9	0.11
Coordination / balance	0.198	10	0.12
Cognitive symptoms	0.203	11	0.13
Electric sensations / pins, needles / pulsations	0.356	12	0.14
Weakness	0.413	13	0.15
Sensory symptoms	0.497	14	0.17
Temp. changes/numbness/reduced sensation	0.538	15	0.18
Spasms / Twitching	0.559	16	0.19
Attention and memory	0.61	17	0.20
Hyperventilation/shortness of breath	0.892	18	0.21
Panic / fear	0.94	19	0.23
Fatigue	0.954	20	0.24
Visual blurring / flashing lights / visual loss	1	21	0.25

* statistically significant

l = rank

m = number of tests

q = false discovery rate (chosen)

TABLE 4A. BENJAMINI-HOCHBERG ADJUSTMENT CORRESPONDING TO SECTION “PSYCHIATRIC DISORDERS”

Variable	<i>p</i> -value	rank	(<i>l</i> / <i>m</i>)* <i>q</i>
Suicidal ideation / attempt	0.013	1	0.01
Somatic disorders	0.036	2	0.03
Substance consumption	0.143	3	0.04
Chronic fatigue	0.144	4	0.05
Anxiety disorder	0.326	5	0.07
Fibromyalgia	0.356	6	0.08
Insomnia	0.432	7	0.09
Irritable bowel syndrome	0.454	8	0.11
Sleep disorder	0.477	9	0.12
Panic attacks	0.499	10	0.13
Depression	0.676	11	0.14
Borderline personality disorder	0.736	12	0.16
Psychiatric disorders	0.772	13	0.17
Post-traumatic stress disorder	0.872	14	0.18
Fatigue	0.954	15	0.20
Obsessive compulsive disorder	1	16	0.21
Bipolar personality disorder	1	17	0.22
Schizophrenia	1	18	0.24
Chronic pain syndrome	1	19	0.25

* statistically significant

l = rank

m = number of tests

q = false discovery rate (chosen)

TABLE 5A. BENJAMINI-HOCHBERG ADJUSTMENT CORRESPONDING TO SECTION “LIFE EVENTS”

Variable	<i>p</i>-value	rank	(l/m)*q
Bullying	0.008*	1	0.05
Domestic violence	0.038	2	0.10
Sexual abuse	0.133	3	0.15
Separation divorce	0.504	4	0.20
Death/disease of relative or friend	0.726	5	0.25

TABLE 6A. COMPARISON BETWEEN FMD AND NES REGARDING COMORBIDITIES, INJURIES AND SURGERIES
PER BODY PARTS

Body region	FMD <i>n</i> (%)	NES <i>n</i> (%)	Total <i>n</i> (%)
	<i>n</i> = 56	<i>n</i> = 52	<i>n</i> =108
Head	39 (70%)	42 (81%)	81 (75%)
Ears / eyes / face	11 (20%)	7 (14%)	18 (17%)
Brain / mind	36 (64%)	40 (77%)	76 (70%)
Brain	16 (29%)	21 (40%)	37 (34%)
Mind	41 (73%)	41 (79%)	82 (76%)
Throat	4 (7%)	6 (12%)	10 (9%)
Trunk	30 (54%)	37 (71%)	67 (62%)
Limbs + back	26 (46%)	11 (21%)	37 (34%)
Limbs	19 (34%)	7 (14%)	26 (24%)
Arms	14 (25%)	4 (8%)	18 (17%)
Legs	13 (23%)	4 (8%)	17 (16%)
Back	11 (20%)	8 (15%)	19 (18%)

FMD = Functional Motor Disorder; NES = Non-epileptic seizures. * $p < 0.05$

TABLE 7A. COMPARISON BETWEEN FMD AND NES REGARDING COMORBIDITIES AND INJURIES PER BODY PARTS

	FMD <i>n</i> (%)	NES <i>n</i> (%)	Total <i>n</i> (%)
	<i>n</i> = 56	<i>n</i> = 52	<i>n</i> =108
Head	39 (70%)	41 (79%)	80 (74%)
Ears / eyes / face	6 (11%)	4 (8%)	10 (9%)
Brain / mind	37 (66%)	40 (77%)	77 (71%)
Throat	3 (5%)	2 (4%)	5 (5%)
Trunk	27 (48%)	25 (48%)	52 (48%)
Limbs + back	19 (34%)	9 (17%)	28 (26%)
Limbs	15 (27%)	6 (12%)	21 (19%)
Arms	12 (21%)	4 (8%)	16 (15%)
Legs	9 (16%)	3 (6%)	12 (11%)
Back	7 (13%)	8 (15%)	15 (14%)
Whole body	30 (54%)	25 (48%)	55 (51%)

FMD = Functional Motor Disorder; NES = Non-epileptic seizures.

TABLE 8A. COMPARISON BETWEEN FMD AND NES REGARDING SURGERIES PER BODY PARTS

	FMD <i>n</i> (%)	NES <i>n</i> (%)	Total <i>n</i> (%)
	<i>n</i> = 53	<i>n</i> = 52	<i>n</i> =105
Head	9 (16%)	10 (19%)	19 (18%)
Ears / eyes / face	7 (13%)	4 (8%)	11 (10%)
Brain	1 (2%)	3 (6%)	4 (4%)
Throat	1 (2%)	5 (10%)	6 (6%)
Trunk	16 (29%)	17 (33%)	33 (31%)
Limbs + back	13 (23%)	4 (8%)	17 (16%)
Limbs	8 (14%)	2 (4%)	10 (10%)
Arms	3 (5%)	0 (0%)	3 (3%)
Legs	6 (11%)	2 (4%)	8 (8%)
Back	5 (9%)	2 (4%)	7 (6%)

FMD = Functional Motor Disorder; NES = Non-epileptic seizures.

TABLE 9A. COMPARISON BETWEEN FMD AND NES REGARDING PSYCHIATRIC COMORBIDITIES

	FMD <i>n</i> (%)	NES <i>n</i> (%)	Total <i>n</i> (%)	<i>p</i> -value
	<i>n</i> = 56	<i>n</i> = 52	<i>n</i> = 108	
Psychiatric disorders	52 (93%)	49 (94%)	101 (94%)	0.772
Depression	40 (71%)	39 (75%)	79 (73%)	0.676
Anxiety disorder	36 (64%)	38 (73%)	74 (69%)	0.326
Panic attacks	16 (29%)	18 (35%)	34 (31%)	0.499
Obsessive compulsive disorder	3 (5%)	3 (6%)	6 (6%)	1.000
Bipolar personality disorder	3 (5%)	2 (4%)	5 (5%)	1.000
Borderline personality disorder	4 (7%)	5 (10%)	9 (8%)	0.736
Schizophrenia	2 (4%)	1 (2%)	3 (3%)	1.000
Substance consumption	11 (20%)	5 (10%)	16 (15%)	0.143
Sleep disorder	35 (63%)	29 (56%)	64 (59%)	0.477
Insomnia	29 (52%)	23 (44%)	52 (48%)	0.432
Fatigue	24 (43%)	22 (42%)	46 (43%)	0.954
Somatic disorders	26 (46%)	14 (27%)	40 (37%)	0.036*
Fibromyalgia	10 (18%)	6 (12%)	16 (15%)	0.356
Chronic pain syndrome	14 (25%)	13 (25%)	27 (25%)	1.000
Chronic fatigue	8 (14%)	3 (6%)	11 (10%)	0.144
Irritable bowel syndrome	5 (9%)	7 (14%)	12 (11%)	0.454
Post-traumatic stress disorder	8 (14%)	8 (15%)	16 (15%)	0.872
Suicidal ideation / attempt	18 (32%)	29 (56%)	47 (44%)	0.013*

FMD = Functional Motor Disorder; NES = Non-epileptic seizures. * $p < 0.05$

**APPENDIX B: PARTICIPANT INFORMATION SHEET AND CONSENT FORM OF STUDY 2 “A
PRELIMINARY STUDY TO MEASURE FUNCTIONAL WEAKNESS”**

Participant Information Sheet/Consent Form

Interventional Study - Adult providing own consent

Title	A perceptual measure for Functional Neurological Disorder
Short Title	A PM for FND
Protocol Number	1
Project Sponsor	Austin Health
Coordinating Principal Investigator/ Principal Investigator	Professor Richard Kanaan
Associate Investigator(s)	A/Prof. Olivia Carter PhD student Daniela Huepe
Location	Austin Health / University of Melbourne

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project to understand the mechanisms underlying Functional Neurological Disorder (FND).

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tasks that are described
- If you are a patient with FND, consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Functional Neurological Disorder (FND) is hard to study thoroughly, as most tests to measure the evolution of the symptoms are not reliable and consistent. We think that a task that consists of perception of the weights of different objects can provide useful information about changes in the symptoms. This study is to see if this task is related to the presence of symptoms in patients with FND, so that we can use it to study the symptoms in the future. The results of this research will be used by the PhD student Daniela Huepe to obtain a Doctor degree.

3 What does participation in this research involve?

If you decide to take part in this study, we will ask you to sign a consent form. Then, we will ask you to fill in some questionnaires that tell us more about your health and how you feel. This will take about 10 minutes. Then, we will proceed to show you the task, which consists of picking up some objects and determine which ones are heavier. You will be asked to make multiple comparisons. This will take about 40 minutes approximately. All the participants of this study will undertake these questionnaires and task. We will compare the results of the control participants with the participants with FND. If you feel fatigued or do not feel well, please just let the researcher know that you need to take a break or to stop the session and continue another day if possible. There are no additional costs associated with participating in this research project. However, you will be paid \$15 for your time and travel expenses.

4 What do I have to do?

Taking part in this study does not require you to change any aspect of your lifestyle or any medical treatment. You can't participate in this project if you have symptoms that interfere with the task, such as tremor in upper limbs.

5 Other relevant information about the research project

We hope to recruit 60 participants, 40 participants with FND through Austin Health and 20 control participants. This project also includes researchers from The University of Melbourne.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

If you are a participant with FND, your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Austin Health.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. You may continue to receive all the standard treatments whether you participate or not. Your participation in this project will not affect that.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, the knowledge gained may benefit future patients with FND.

9 What are the possible risks and disadvantages of taking part?

If you feel uncomfortable or concerned we advise you to talk with a member of the research team.

10 What if I withdraw from this research project?

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly.

11 What happens when the research project ends?

Please let your study team if you would like to be informed of the results of the study, and you will be invited to attend the presentation of the results.

Part 2 How is the research project being conducted?

12 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. The questionnaire forms will be kept in a locked cabinet, in a room kept locked. The data from these will be kept on a password protected computer without your name or other identifying details attached, but identified only by a code. Only the research team will have access to your data, and it will be securely destroyed after 10 years. Your information will be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. We may wish to use the data for future projects related to this one, with the permission of the Ethics Committee. Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

In accordance with relevant Australian and/or Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research described in this section that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

13 Complaints and compensation

You will not suffer any injuries or complications as a result of this research project. If you have any complaint about this study please contact in the first instance, Chelsea Webster, Manager Ethics and Governance, Office for Research, Austin Health.

14 Who is organising and funding the research?

This research project is being conducted by Professor Richard Kanaan. No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages). It is being funded by the University of Melbourne.

15 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Austin Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

16 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the principal study doctor on Professor Richard Kanaan, telephone: +61 3 9496 3351 or any of the following people:

Clinical contact person

Name	Richard Kanaan
Position	Chair of Psychiatry, Psychiatrist.
Telephone	+61 3 9496 3351
Email	richard.kanaan@unimelb.edu.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Complaints contact person

Position	Complaints Officer
Telephone	(03) 9496 4090
Email	ethics@austin.org.au

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Complaints Officer
HREC Executive Officer	Ethics and Research Governance Manager
Telephone	(03) 9496 4090
Email	ethics@austin.org.au

Consent Form - *Adult providing own consent*

Title	A perceptual measure for Functional Neurological Disorder
Short Title	A PM for FND
Protocol Number	1
Project Sponsor	Austin Health
Coordinating Principal Investigator/ Principal	Professor Richard Kanaan
Associate Investigator(s)	Prof. Olivia Carter PhD student Daniela Huepe
Location	Austin Health / University of Melbourne

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors (if I am a patient at Austin Hospital), other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand I will be reimbursed \$15 on cash for my time.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____	
Signature _____	Date _____

Optional Consent (please circle and sign accordingly):

I do / do not agree to be contacted in the future if I am suitable for other ethically approved research projects.

Signature: _____ Date: _____

(If you do, please provide your contact details to the researcher.)

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher [†] (please print) _____	
Signature _____	Date _____

[†] A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	A perceptual measure for Functional Neurological Disorder
Short Title	A PM for FND
Protocol Number	1
Project Sponsor	Austin Health
Coordinating Principal Investigator/ Principal Investigator	Professor Richard Kanaan
Associate Investigator(s)	Prof. Olivia Carter PhD student Daniela Huepe
Location	Austin Health / University of Melbourne

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Austin Health.

Name of Participant (please print) _____
Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

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Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher [†] (please print) _____
Signature _____ Date _____

[†] A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

APPENDIX C: QUESTIONNAIRE OF ANXIETY AND DEPRESSION OF STUDY 2: A PRELIMINARY STUDY TO MEASURE FUNCTIONAL WEAKNESS

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.

Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

APPENDIX D: QUESTIONNAIRE OF SEVERITY OF WEAKNESS AND DEMOGRAPHICS OF STUDY 2: A PRELIMINARY STUDY TO MEASURE FUNCTIONAL WEAKNESS

WEAKNESS IN UPER LIMBS

In this section we will ask you about the **weakness** you experience in your **hands or arms**. Please circle the answer that best reflects your agreement with each statement. Answer as honestly as possible, there are no correct or incorrect answers.

- Please indicate the intensity of **weakness** you have been experiencing **today** in each hand/arm today:

Considering:

- “mild weakness” refers to when the weakness does not disturb your daily life;
- “moderate weakness” refers to when the weakness can be noticed and disrupts your daily life;
- “severe weakness” refers to when the weakness prevents you from performing the majority of your daily life activities.

	NO WEAKNESS	MILD WEAKNESS	MODERATE WEAKNESS	SEVERE WEAKNESS
Left hand/arm	0	1	2	3
Right hand/arm	0	1	2	3

- Please circle the answer that best indicates the frequency of each statement in your right hand/arm today:

	NEVER	SOMETIMES	OFTEN	ALWAYS
I could pick things up almost as per normal, although I felt a slight tiredness in my hand(s).	0	1	2	3
I could pick things up but with difficulty (for example I could pick up a cup of tea or a book, but I had to make an effort).	0	1	2	3
I could not pick things up (for example a cup of tea or a book are too heavy to pick them up).	0	1	2	3

3. Please circle the answer that best indicates the frequency of each statement in your left hand/arm today:

	NEVER	SOMETIMES	OFTEN	ALWAYS
I could pick things up almost as per normal, although I felt a slight tiredness in my hand(s).	0	1	2	3
I could pick things up but with difficulty (for example I could pick up a cup of tea or a book, but I had to make an effort).	0	1	2	3
I could not pick things up (for example a cup of tea or a book were too heavy to pick them up).	0	1	2	3

1. Whom do you usually live with?

- Husband/wife/steady partner 1
- Spouse/partner and children 2
- Children (but no spouse/partner) 3
- Parents 4
- Alone 5
- Other _____ 6

2. Employment status

- Paid employment – full time 1
- Paid employment – part time 2
- Voluntary work (unpaid) 3
- Sheltered work 4
- Registered as unemployed but available for work 5
- Unemployed due to illness 6
- Retired 7
- Student 8
- Stay-at-home parent 9
- Other _____ 10

3. What is the highest level of education that you have completed?

- Left school during Year 9 or earlier ☐
- Left school during Year 10 ☐
- Left school during Year 11 or 12 ☐
- Certificate I-IV ☐
- Advanced Diploma or Diploma ☐
- Bachelor degree (e.g. BA or BSc) ☐
- Above Bachelor degree ☐
- Other _____ ☐

Date of birth: _____

Sex: _____

Have you consumed any illegal drug in the last 24 hours? NO / YES (which one): _____

Have you consumed alcohol in the last 24 hours? NO / YES: _____ (drinks)

Do you have a psychiatric diagnosis? NO / YES: _____ Do you have
a neurological diagnosis? NO / YES: _____

APPENDIX E: QUESTIONNAIRE OF LATERALITY OF STUDY 2: A PRELIMINARY STUDY TO MEASURE FUNCTIONAL WEAKNESS

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R. C. OLDFIELD

APPENDIX II

Medical Research Council Speech & Communication Unit

EDINBURGH HANDEDNESS INVENTORY

Surname..... Given Names.....

Date of Birth.....

Sex.....

Please indicate your preferences in the use of hands in the following activities *by putting + in the appropriate column*. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, *put ++*. If in any case you are really indifferent *put + in both columns*.

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking Match (match)		
10	Opening box (lid)		
i	Which foot do you prefer to kick with?		
ii	Which eye do you use when using only one?		

L.Q.

Leave these spaces blank

DECILE

APPENDIX F: PROTOCOL SIZE-WEIGHT ILLUSION OF STUDY 2 “A PRELIMINARY STUDY TO MEASURE FUNCTIONAL WEAKNESS”

SIZE-WEIGHT ILLUSION RESPONSES (Random order 1)

ID: _____

Date: _____

INSTRUCTIONS: You will compare pairs of grey disks and report which is heavier. On some trials you will compare two disks of the same size, that is, two large or two small disks; and on some trials you will have one of each size.

- You will have 10 seconds to respond.
- You cannot shake the disks.
- You must look at them every time you lift them up.

Which of the two disks is heavier?

The researcher will mark the response of the participant in the following table.

Comparisons

TRIAL	LEFT HAND	RIGHT HAND
1	Small90	Large100
2	Small90	Large110
3	Large120	Small90
4	Large170	Small90
5	Small90	Large150
6	Small90	Large120
7	Large130	Small90
8	Small90	Large160
9	Large150	Small90
10	Large160	Small90
11	Large100	Small90
12	Small90	Large150
13	Small90	Large130
14	Large190	Small90
15	Small90	Large190
16	Large200	Small90
17	Small90	Large180
18	Small90	Large210
19	Large190	Small90
20	Small90	Large100
21	Large200	Small90
22	Large100	Small90
23	Large170	Small90
24	Small90	Large110
25	Large210	Small90
26	Large180	Small90
27	Small90	Large170

28	Small90	Large200
29	Large160	Small90
30	Large110	Small90
31	Large150	Small90
32	Small90	Large120
33	Large210	Small90
34	Small90	Large140
35	Large140	Small90
36	Small90	Large140
37	Large180	Small90
38	Large110	Small90
39	Large120	Small90
40	Small90	Large180
41	Small90	Large210
42	Large140	Small90
43	Small90	Large130
44	Small90	Large190
45	Small90	Large160
46	Large130	Small90
47	Small90	Large200
48	Small90	Large170

SIZE-WEIGHT ILLUSION RESPONSES (Random order 2)

ID: _____

Date: _____

INSTRUCTIONS: You will compare pairs of grey disks and report which is heavier. On some trials you will compare two disks of the same size, that is, two large or two small disks; and on some trials you will have one of each size.

- You will have 10 seconds to respond.
- You cannot shake the disks.
- You must look at them every time you lift them up.

Which of the two disks is heavier?

The researcher will mark the response of the participant in the following table.

Comparisons

TRIAL	LEFT HAND	RIGHT HAND
1	Small90	Large170
2	Small90	Large200
3	Large130	Small90
4	Small90	Large160
5	Small90	Large190
6	Small90	Large130
7	Large140	Small90
8	Small90	Large210
9	Small90	Large180
10	Large120	Small90
11	Large110	Small90
12	Large180	Small90
13	Small90	Large140
14	Large140	Small90
15	Small90	Large140
16	Large210	Small90
17	Small90	Large120
18	Large150	Small90
19	Large110	Small90
20	Large160	Small90
21	Small90	Large200
22	Small90	Large170
23	Large180	Small90
24	Large210	Small90
25	Small90	Large110
26	Large170	Small90
27	Large100	Small90
28	Large200	Small90
29	Small90	Large100
30	Large190	Small90
31	Small90	Large210

32	Small90	Large180
33	Large200	Small90
34	Small90	Large190
35	Large190	Small90
36	Small90	Large130
37	Small90	Large150
38	Large100	Small90
39	Large160	Small90
40	Large150	Small90
41	Small90	Large160
42	Large130	Small90
43	Small90	Large120
44	Small90	Large150
45	Large170	Small90
46	Large120	Small90
47	Small90	Large110
48	Small90	Large100

SIZE-WEIGHT ILLUSION RESPONSES (Random order 3)

ID: _____

Date: _____

INSTRUCTIONS: You will compare pairs of grey disks and report which is heavier. On some trials you will compare two disks of the same size, that is, two large or two small disks; and on some trials you will have one of each size.

- You will have 10 seconds to respond.
- You cannot shake the disks.
- You must look at them every time you lift them up.

Which of the two disks is heavier?

The researcher will mark the response of the participant in the following table.

Comparisons

TRIAL	LEFT HAND	RIGHT HAND
1	Large210	Small90
2	Large170	Small90
3	Large130	Small90
4	Small90	Large180
5	Small90	Large110
6	Large190	Small90
7	Large150	Small90
8	Small90	Large210
9	Large200	Small90
10	Small90	Large150
11	Small90	Large150
12	Large150	Small90
13	Large110	Small90
14	Small90	Large130
15	Small90	Large210
16	Large190	Small90
17	Small90	Large100
18	Large180	Small90
19	Small90	Large160
20	Large160	Small90
21	Small90	Large190
22	Small90	Large130
23	Large200	Small90
24	Small90	Large120
25	Small90	Large100
26	Small90	Large170
27	Small90	Large190
28	Large100	Small90
29	Small90	Large110

30	Large170	Small90
31	Small90	Large200
32	Large120	Small90
33	Small90	Large170
34	Small90	Large120
35	Large140	Small90
36	Large180	Small90
37	Small90	Large180
38	Large160	Small90
39	Large130	Small90
40	Large210	Small90
41	Small90	Large140
42	Small90	Large140
43	Large100	Small90
44	Small90	Large160
45	Small90	Large200
46	Large110	Small90
47	Large120	Small90
48	Large140	Small90

SIZE-WEIGHT ILLUSION RESPONSES (Random order 4)

ID: _____

Date: _____

INSTRUCTIONS: You will compare pairs of grey disks and report which is heavier. On some trials you will compare two disks of the same size, that is, two large or two small disks; and on some trials you will have one of each size.

- You will have 10 seconds to respond.
- You cannot shake the disks.
- You must look at them every time you lift them up.

Which of the two disks is heavier?

The researcher will mark the response of the participant in the following table.

Comparisons

TRIAL	LEFT HAND	RIGHT HAND			
1	Large140	Small90	30	Small90	Large160
2	Large120	Small90	31	Large180	Small90
3	Large110	Small90	32	Small90	Large100
4	Small90	Large200	33	Large190	Small90
5	Small90	Large160	34	Small90	Large210
6	Large100	Small90	35	Small90	Large130
7	Small90	Large140	36	Large110	Small90
8	Small90	Large140	37	Large150	Small90
9	Large210	Small90	38	Small90	Large150
10	Large130	Small90	39	Small90	Large150
11	Large160	Small90	40	Large200	Small90
12	Small90	Large180	41	Small90	Large210
13	Large180	Small90	42	Large150	Small90
14	Large140	Small90	43	Large190	Small90
15	Small90	Large120	44	Small90	Large110
16	Small90	Large170	45	Small90	Large180
17	Large120	Small90	46	Large130	Small90
18	Small90	Large200	47	Large170	Small90
19	Large170	Small90	48	Large210	Small90
20	Small90	Large110			
21	Large100	Small90			
22	Small90	Large190			
23	Small90	Large170			
24	Small90	Large100			
25	Small90	Large120			
26	Large200	Small90			
27	Small90	Large130			
28	Small90	Large190			
29	Large160	Small90			

SIZE-WEIGHT ILLUSION RESPONSES (Random order 5)

ID: _____

Date: _____

INSTRUCTIONS: You will compare pairs of grey disks and report which is heavier. On some trials you will compare two disks of the same size, that is, two large or two small disks; and on some trials you will have one of each size.

- You will have 10 seconds to respond.
- You cannot shake the disks.
- You must look at them every time you lift them up.

Which of the two disks is heavier?

The researcher will mark the response of the participant in the following table.

Comparisons

TRIAL	LEFT HAND	RIGHT HAND
1	Large210	Small90
2	Large190	Small90
3	Large170	Small90
4	Large150	Small90
5	Large130	Small90
6	Large110	Small90
7	Small90	Large210
8	Small90	Large190
9	Small90	Large170
10	Small90	Large150
11	Small90	Large130
12	Small90	Large110
13	Large210	Small90
14	Large190	Small90
15	Large170	Small90
16	Large150	Small90
17	Large130	Small90
18	Large110	Small90
19	Small90	Large210
20	Small90	Large190
21	Small90	Large170
22	Small90	Large150
23	Small90	Large130
24	Small90	Large110
25	Small90	Large100
26	Small90	Large120
27	Small90	Large140
28	Small90	Large160
29	Small90	Large180
30	Small90	Large200
31	Large100	Small90

32	Large120	Small90
33	Large140	Small90
34	Large160	Small90
35	Large180	Small90
36	Large200	Small90
37	Small90	Large100
38	Small90	Large120
39	Small90	Large140
40	Small90	Large160
41	Small90	Large180
42	Small90	Large200
43	Large100	Small90
44	Large120	Small90
45	Large140	Small90
46	Large160	Small90
47	Large180	Small90
48	Large200	Small90

APPENDIX G: TABLES OF STUDY 2 “A PRELIMINARY STUDY TO IDENTIFY PERCEPTUAL DIFFERENCES ASSOCIATED WITH FUNCTIONAL WEAKNESS”

TABLE 1G. CATEGORIES OF BAYES FACTOR

Bayes factor			Interpretation
	>	100	Extreme evidence for H_a
30	–	100	Very strong evidence for H_a
10	–	30	Strong evidence for H_a
3	–	10	Moderate evidence for H_a
1	–	3	Anecdotal evidence for H_a
1			No evidence
1/3	–	1	Anecdotal evidence for H_0
1/10	–	1/3	Moderate evidence for H_0
1/30	–	1/10	Strong evidence for H_0
1/100	–	1/30	Very strong evidence for H_0
	<	1/100	Extreme evidence for H_0

Adapted from Jeffreys [51, p. 433], and Lee and Wagenmakers (2013, p. 105).

Table 1. Evidence categories for the Bayes factor.¹

(Lakatos, 2014; Ortega & Navarrete, 2017)