PATHOPHYSIOLOGY OF FUNCTIONAL (PSYCHOGENIC) MOVEMENT DISORDERS

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Isabel Pareés Moreno

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Sobell Department of Motor

Neuroscience and Movement Disorders

UCL Institute of Neurology

Queen Square

London

DECLARATION THAT THE WORK PRESENTED IN THIS THESIS IS THE CANDIDATE'S OWN

I, Isabel Pareés Moreno, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

London, December 2014

Signature

Isabel Pareés Moreno

Esta tesis está dedicada a mis padres y a mi hermana por su apoyo y amor desde la distancia, por ser el pilar inamovible de mi vida y estar siempre a mi lado. A Alejandro, por ser mi cómplice, mi compañero de viaje y porque "en la calle codo a codo somos mucho más que dos". Finalmente a Guillermo, mi amor, por teñir cada uno de mis días con su sonrisa y haberme hecho redescubrir la vida como madre.

"Be accustomed to the laws ruling the mind of the hysterics"

Pierre Janet

SUMMARY

This thesis describes a series of studies involving healthy subjects, carefully selected patients with functional movement disorders and organic movement disorders, in which different aspect of the mechanism underlying functional movement disorders were explored:

1. The presence of physical precipitating factors at onset of functional movement disorder by using semistructured interviews. I found that most patients with functional movement disorder have a clear physical event prior to the onset of functional symptoms.

2. The presence of a "jumping to conclusions" reasoning style that may predispose patients with functional movement disorder to accept new hypothesis on the basis of less evidence. They requested less evidence that healthy controls to make a judgement, which is here suggested to influence the manner in which they process novel sensory data occurring during triggering events.

3. The role of attention in symptoms production by using different motor tasks in which the predictability of movements as well as the effect of explicit and implicit strategies in motor control were manipulated. Motor impairment in patients with functional movement disorder was found to be related to the employment of explicit strategies or when pre-planning movements is possible.

4. The intensity and duration of tremor in patients with functional tremor in a real life situation using accelerometers. They were found to fail to perceive

that tremor is not present most of the time compared with patients with organic tremor.

5. Finally, I explored the phenomenon of the sensory attenuation using a force-matching task as a measure of sense of agency for movement in these patients. Patients with functional movement disorders have an abnormal sensory attenuation for movement, which may help to explain the lack of agency for the abnormal movement.

These results contribute to the understanding of the mechanisms underlying functional movement disorders and by extension, other functional neurological symptoms, and demonstrate that they are amenable to neuroscientific study.

STATEMENT OF PARTICIPATION IN STUDIES DESCRIBED

The initial concept for the thesis was generated by Dr Mark Edwards. In what follows, I make a statement of my contribution in each of the studies described here.

Chapter 1 and 2. General introduction and historical view of functional movement disorders. I performed the search of the literature, interpreted and wrote up the findings.

Chapter 4. A study on the physical precipitating factors in functional movement disorders. The conception of the study was generated by Dr Mark Edwards, Dr Jon Stone, Dr Alan Carson and myself. I planned along with Dr Edwards the design of the semi-structured interview and the selection of the questionnaires. I reviewed previous literature on physical events preceding functional movement disorders. Patient ascertainment was conducted by Dr Edwards and myself. Dr Maria Pires, Dr Maja Kojovic and myself contributed to the collection of the data. I performed the analysis of the data and writing up the results. The interpretation of the data was performed by Dr Mark Edwards, Dr Jon Stone, Dr Alan Carson and myself.

Chapter 5. A study on the "jumping to conclusions" bias in functional movement disorders. The conception of the study was generated by Dr Mark Edwards and Katerina Fotopoulou. The experiments were planned by myself. I was involved in the recruitment of participants and participated in all the studies. Dr Pedro Zapater and Dr Horga de la Parte guided me in the statistical analysis and I wrote up the

results. The interpretation of the data was performed by Dr Mark Edwards, Katerina Fotopoulou and myself.

Chapter 6. A study on the effect of explicit strategies and predictability on motor control in functional movement disorders. The conception of the study was generated by Dr Mark Edwards. Sven Bestman and Marco Davare were the mayor contributors to the development of the explicit and implicit motor paradigms and pre-cued task. I was involved in the recruitment of the participants and I run all the experiments. The analysis was performed by Dr Mark Edwards and myself. I wrote up the results. Dr Mark Edwards, Sven Bestman, Professor Rothwell and myself contributed in the interpretation of the data.

Chapter 7. A study assessing functional motor symptoms in real life conditions using a wrist-worn actigraph. The conception of the experiment was generated by Dr Mark Edwards. I designed and planned the study. Dr Saifee and myself conducted the ascertainment of the participants and the collection of the data. I performed the analysis of the data. Dr Pedro Zapater and Dr Horga de la Parte gave substantial input on it, mainly in the Bland-Altman analysis. I wrote up the results. Dr Edwards and myself interpreted the results.

Chapter 8. A study on the lack of sense of agency for movement in functional movement disorders. The concept of the study was generated by myself. Dr Edwards, Atsuo Nuruki and myself planned the study but Atsuo Nuruki was the major contributor programming the robots for the motor task. Marco Davare wrote the script to analyse the results. I performed the analysis and wrote up the results.

Dr Harriet Brown, Dr Rick Adams and Professor Friston provided with substantial input to our interpretation of the results.

Chapter 9. Discussion. I wrote the discussion and Dr Edwards guided me through it.

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ABBREVIATIONS

ANOVA   Analysis of Variance

BOLD   Blood-Oxygen-Level Dependent contrast imaging

BP   Bereitschaftspotential

CBT   Cognitive Behavioural Therapy

DaT SPECT   Dopamine transporter imaging with single-photon

               emission computed tomography

DR   Displacement Ratio

DSM   Diagnostic and Statistical Manual of Mental Disorders

EEG   Electroencephalography

EMG   Electromyography

FMD   Functional Movement Disorder

FT   Functional Tremor

FTM   Fahn-Tolosa-Marin tremor scale

HADS   Hospital Anxiety and Depression Scale

ION   Institute of Neurology

IQ   Intelligence Quotient

JTC   Jumping to Conclusions

LEQ   Life Events Questionnaire

MT   Movement Time

NHNN   National Hospital for Neurology and Neurosurgery

OB   One-back Reaching

OrgT	Organic Tremor
PD	Parkinson's disease
PDI	Peter's Delusions Inventory
ROT	Rotation Learning Task
RT	Reaction Time
SA	Sensory attenuation
SAS	Secondary Attentional System
SD	Standard Deviation
SEP	Somatosensory evoked potentials
SMA	Supplementary Motor Area
TMS	Transcranial Magnetic Stimulation

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ACKNOWLEDGEMENTS

Librarians from the Queen Square Library, who assisted me through the process of searching the precious books from Charcot, Janet and Freud. The readings of those helped me to contextualise functional symptoms and realise that important concepts about them have not significantly changed after more than one century.

Dr Jorge Hernandez Vara from whom I discovered, during my first years of residency, how fascinating movement disorders are.

My second supervisor Professor Kailash Bhatia who more than 5 years ago accepted me as a fellow in Queen Square and whose clinical skills I will never forget.

Finally my supervisor, Dr Mark Edwards. It is extremely difficult to describe what Mark represents to me in a language that is not my mother tongue. When I decided to engage in the experience of doing clinical and research work abroad I would had never thought to come across a person like him. Thank you for taking your time and being so supportive and patient with me at the very beginning when English was not my best skill. Thanks for your guidance and for teaching me to treat my patients as a "whole" and not just as a neurological disease. Thanks for teaching me that brain is more than white and grey matter. Thanks for showing me that one can see interesting things where others see nothing and that simple paradigms in research can provide exciting results. Thanks for your warmness, your kindness and for looking after me when things have not been easy.

THESIS OVERVIEW

A personal view

Before coming to London, I completed my training in Neurology in one of the biggest hospitals in Barcelona, Spain, between 2004 and 2009. During that time, I dealt with the diagnosis and management of most acute and chronic neurological diseases. However, my experience with patients suffering from functional neurological symptoms was limited, not because they were not seen in the emergency department or in the outpatient's clinics, but because most patients were lost to follow up. They usually were managed by explaining that they should not be worried about the symptoms because all tests had come back normal, that they must be anxious and depressed, and that this was the likely cause of their symptoms. I could feel how disappointed most patients were with this explanation and when they were told that they were discharged from the clinic to be referred to the Psychiatry Department. Most patients said that they actually did not feel depressed or anxious, that their symptoms were indeed very disabling and they could not see how their symptoms were going to improve. I could also see how uncomfortable the situation was for clinicians who were not confident in making a diagnosis and explaining the problem to the patient in a positive/explicit way. Also, I could perceive how the assumption of malingering was always (in an implicit manner) present in the discussion.

The truth is that I was struck by how young and disabled many patients were and how little we could offer. Having said that, I would have never expected to do my PhD in functional neurological symptoms. I definitely preferred patients for whose

disorders there was no speculation or explanations that touched the barrier with philosophy.

This impression has notably changed over the last 4 years. A more neuroscientific approach to them has shown me how complicated and fascinating clinical problem functional movement disorders are. The more I read, the more I realised that they represent an enigmatic area of medicine that has always existed but has always been considered the "ugly duckling" of neurology. I think the fear to face these conditions by most clinicians has resulted in a lack of improvement in terms of understanding of pathophysiology and treatment despite all the advances that have occurred in Medicine over the past decades. This fear displayed by neurologists to face functional neurological symptoms is in my opinion more than reasonable as no one teaches you during your career how to manage these patients.

During these 4 years I have learnt the importance of making the diagnosis in a positive fashion rather than as a diagnosis of exclusion. In this regards, patients with functional motor symptoms are ideal because in contrast to patients with symptoms such as sensory loss, pain, fatigue and memory disturbance, these patients have objective signs on examination that are amenable to clinical and experimental measurement. This provides a degree of certainty about the diagnosis which may not be achievable in those whose symptoms are only measurable via self-report.

I have also learnt that once one explains how the diagnosis has been reached, and it is put in context, that patients are open to treatment and may improve with no additional measures. Hostile patients turn out to be pleasant patients that look

forward to collaborating in research to better understand their condition. I have learnt that the brain is more fascinating than I ever thought it was during my neurology training.

I have been amazed how despite all the normal investigations, these patients can inform you about different aspect of motor physiology and about other typical neurological diseases.

From the academic point of view, there is still active debate about what to call this group of patients. In this thesis I have used the term "functional" and this is not something new. In the past, other authors including Yealland in Queen Square (Linden et al., 2013) preferred this term when treating soldiers with functional symptoms. "Hysteria" implies a pejorative meaning and it is not commonly used nowadays. "Non-organic" denotes what one does not have and may infer that the symptoms are imagined or not real. "Medically unexplained" is commonly used in medical circles but when a patient receives this diagnosis they also receive a label of uncertainty: "if my problem cannot be explained, is the doctor missing a rare disease?" In the title of this thesis I have included the term "psychogenic" in parenthesis because it is the most widespread term in the movement disorder community. However, this term implies that the aetiology of the symptoms is purely psychological. This one-dimensional approach is criticised in this thesis and therefore I considered somehow inappropriate to hold this label through the text. "Functional" does not imply aetiology and is not associated with negative connotations (Stone et al., 2002). However, it may be considered to be vague as in the past other conditions such as migraine or epilepsy were labelled as functional

because of the lack of structural abnormalities in the central nervous system. Nevertheless, given the current level of understanding of the underlying pathophysiology, I have considered that the term "functional" is the one that comes closest to my understanding of these perplexing symptoms.

On the other hand, it may sound inconsistent that I have sometime used the term "organic" to designate more typical neurological diseases but not by this I dismiss the possibility that functional symptoms have a neurobiological basis.

Approval was obtained from the National Hospital for Neurology and Neurosurgery/Institute of Neurology (NHNN/ION) Joint Ethics Committee for all the studies included in this thesis and all participants provided written consent to participate according to the Declaration of Helsinki. I have included the methodology and the results of each of my studies in a different chapter, with the hope of simplifying the reading of this thesis.

Chapter 1 is a general introduction to functional movement disorders. This chapter covers the current state of knowledge regarding phenomenology, diagnosis and management of this group of patients.

Chapter 2 is a review of previous literature on the pathophysiology of functional symptoms in general. It covers information from ancient Egypt to the beginning of the 20th century but with special focus on the 19th century and three of the most important authors in this period: Charcot, Janet and Freud. Particular attention is paid to functional movement disorders, when mentioned in their writings.

Chapter 3 describes the specific aims and hypothesis of this thesis.

Chapter 4 describes the methodology and results of a clinical study designed to assess the presence of physical precipitating factors at the onset of functional movement disorders. Psychological factors prior to the development of functional symptoms have been classically highlighted in the past but potential physical triggers to these symptoms have been mostly neglected. In this study, semi-structured interviews were used to retrospectively identify physical events that occurred closely related to the onset of functional movement disorders.

Chapter 5 describes the methodology and results of an experiment assessing the presence of a cognitive bias known as "Jumping to Conclusions" in patients with functional movement disorders. Patients who display this bias are more prone to accept new hypothesis on the basis of limited evidence compare to healthy controls and this might be hypothesised to favour the development of functional symptoms along with other factors.

Chapter 6 describes the methodology and results of two experiments designed to assess the effect of explicit strategies and predictability of events on motor control in patients with functional movement disorders. Clinically attention is known to play an important role in symptoms generation and these experiments are an attempt to study this aspect in experimental conditions.

Chapter 7 describes the methodology and results of a study the assessing duration and intensity of functional tremor in real life conditions compared to patients with other types of tremor. For that, a wrist-watch actigraph that had been previously demonstrated to optimally capture tremor was used for five consecutive days.

Results were compared with the patient's subjective experience of tremor recorded in a diary.

Chapter 8 describes the methodology and results of an experiment assessing the phenomenon of sensory attenuation that has been previously proposed to be an implicit measure of agency for movement. Patients with functional movement disorders report their abnormal movement to be involuntary and it is believed that most of them are not feigning. We sourced for an abnormality in the sensory attenuation phenomena to help and explain the lack of agency for movement in this group of patients.

Chapter 9 contains a description of more modern models about the pathophysiology of functional symptoms (especially functional movement disorders), a more unified discussion of the results presented in this thesis, and an attempt to integrate them within a contemporary theory of brain function.

Chapter 1: General introduction to functional movement disorders

Part of the information presented in this chapter was originally published in the form of a book chapter: Pareés I, Edwards MJ. Psychogenic Movement Disorders. Ed Wolters & Baumman. VU University Press, 2014. Page 675-690.

1.1 Definition

Functional movement disorders (FMD) are part of the broad spectrum of functional neurological symptoms, which together account for 16% of new patients attending neurology outpatients' clinics (Stone *et al.*, 2010). Patients can present with the whole range of abnormal movements, which by definition are incongruous and inconsistent with movement disorders that occur in typical neurological diseases. The different terms used along the history to describe these patients (functional, hysteria, psychogenic, psychosomatic, conversion disorder, somatisation disorder, non-organic, medically unexplained) reflects the lack of understanding of the mechanisms that contribute to FMD.

1.2 Epidemiology

The prevalence of FMD is uncertain due to the lack of consensus on diagnostic criteria and different methodologies used to ascertain cases. It has been estimated between 1% and 9% in general neurological clinics (Marsden, 1986, Lempert *et al.*, 1990, Factor *et al.*, 1995). In adult movement disorders clinic this ranges between 2 and 20% (Hallett, 2006). The mean age at onset is between 37 and 50 years and

usually, women are more commonly affected (Hinson *et al.*, 2005). In approximately 70% of the cases, patients present with tremor or dystonia. Although FMD usually occur as a single neurological diagnosis, they have been reported to be associated with "organic" neurological disorders in 10-15% of the patients (Ranawaya *et al.*, 1990, Stone *et al.*, 2012). This assciation has been called "functional overlay" and has been the topic of recent studies (Onofrj *et al.*, 2010, Onofrj *et al.*, 2011, Stone *et al.*, 2012, Pareés *et al.*, 2013). FMD are thought to be uncommon in the elderly. However, one study has reported that 21% of a large cohort of patients with FMD had an onset of the symptoms after the age of 60 years, which highlights the importance of symptoms recognition in this group of age (Batla *et al.*, 2013). Children can also develop FMD, with gait disorder and tremor the most commonly seen (Schwingenschuh *et al.*, 2008). In a series of children with FMD reported by Schwingenschuh et al the average age at onset was 12.3 years, with a clear predominance of females among the patients (80 %) (Schwingenschuh *et al.*, 2008).

1.3 Clinical Presentation

1.3.1 General clues

Different features from the clinical history and examination findings are commonly noted in patients with FMD irrespective of the type of movement disorder that the patient displays and, although none of these features is entirely specific for FMD and diagnosis should not be based on these features alone, they can be helpful as part of the diagnostic process.

FMD often have a sudden onset with rapid progression to maximum severity, they can present spontaneous remissions, paroxysmal exacerbations, and relapses. Patients may experience a shift in phenomenology over time (tremor turning to abnormal posture for example), and may have a history of previous functional medical symptoms.

General clues on clinical examination include the co-existence of other functional signs such as "give-way" weakness, positive Hoover's sign, non-physiological patterns of sensory loss on clinical examination such as midline splitting of sensory loss or altered vibration across frontal bone. It has recently highlighted the frequent presence of convergence spasm during the examination of patients with FMD (Fekete *et al.*, 2012).

1.3.2 Functional tremor

Functional tremor (FT) is the most common form of FMD (Factor *et al.*, 1995, Hinson and Haren, 2006). A combination of rest, postural and intention tremor is commonly seen, which is an unusual pattern for organic tremor. Arms are the most common body part affected, usually sparing the fingers. Tremor of other body parts, including legs, head or palate, can also be seen. The onset of the tremor is abrupt in a large number of patients, often following a physical injury (Jankovic *et al.*, 2006).

Distracting the patient's attention away from the tremor during examination usually makes FT significantly change in frequency or even stop it. A range of distraction tasks have been assessed including cognitive distracters (serial subtraction), tapping with an unaffected limb at a different frequency to the tremor

and making a sudden ballistic movement with the other hand. With clinical assessment alone (without supplementation with tremor recordings), tapping tasks are most sensitive and specific for distinguishing essential tremor from FT. Self-paced cognitive tasks are not very effective. Also, tapping with the hands may not be a good distractor for tremors affecting legs, head or tongue. In these cases, tapping with one foot or moving the tongue side to side respectively can be of help. Using tremor recordings, tapping tasks have again been shown to be helpful in distinguishing FT from organic tremors. Patients with FT may "entrain" to the tapping frequency, may show a shift in tremor frequency towards the tapping frequency, or may instead be inexplicably unable to perform the tapping task correctly with their normal hand. This illustrates an important point with distractor tasks which is that performance of the task must be adequate to draw attention away from the tremoring limb. This is likely why self-paced tasks (whether cognitive or motor) are not good at discriminating patients with FT from organic tremor (Roper *et al.*, 2013). Ballistic movements of the non-tremoring limb cause a small pause in the tremor in patients with FT. Additional electrophysiological characteristics include a paradoxical worsening of the tremor with loading (which typically damps organic tremor), and co-contraction at the onset of tremor.

Recently these tests have been compared head-to-head in a group of patients with FT and a mixed group of patients with organic tremors (Parkinson's disease (PD), dystonic tremor, essential tremor, neuropathic tremor)(Schwingenschuh *et al.*, 2011). No single test was found to be of sufficient sensitivity and specificity to distinguish FT from organic tremor. However, a cut-off score was devised by combining several of these measures and FT could be successfully distinguished

from "organic" tremor. Nevertheless, these preliminary results are awaiting confirmation in a prospective study.

1.3.3 Functional dystonia

Functional dystonia is the second most common FMD after tremor (Factor *et al.*, 1995). Patients with functional dystonia are usually women who present with fixed abnormal postures typically triggered by apparently minor injury, accompanied by severe pain similar to that noted in chronic regional pain syndrome type 1. Nature of fixed dystonia is under debate and concerns about whether it should be classified as a FMD or as a form of "organic" movement disorder still exists. Recently, it has been proposed that abnormalities in central body schema may be present in these patients, which might contribute to pain and other unusual features, such as the seeking of limb amputation seen in this condition (Edwards *et al.*, 2011).

Clinically, functional dystonia affects predominantly the limbs, and rarely the neck/shoulder region or jaw (Schrag *et al.*, 2004). Functional blepharospasm has been recently reported, which displays different electrophysiological features compared with typical blepharospasm (Schwingenschuh *et al.*, 2011). An unusual distribution of dystonia given the age of onset can be a further clue that points toward functional dystonia. Primary dystonia has a very typical anatomical distribution which depends on age of onset: generalized (with classic limb onset) in individuals younger than 25 years, focal involving upper limb in individuals between 25-45 years and focal involving craniocervical area in individuals of more than 45-50 years. Importantly, unusual distribution given the age of onset age can also be a

clue for secondary/neurodegenerative dystonia and these should be ruled out. In functional dystonia there is typically an absence of task/position specificity commonly seen in "organic" dystonia and patients often do not have sensory tricks. Some patients do develop limb contractures demonstrating maintenance of postures even when unobserved. It can be difficult to demonstrate distractibility in fixed dystonia. This difficulty may occur because fixed dystonia maintenance of postures does not need a similar level of attention as maintenance of tremor. However, a brief give way of muscle activity in the affected limb can be felt with distraction in a number of patients.

It has been recently reported that some patients with fixed dystonia can respond immediately (within minutes) to the botulinum toxin injections (Edwards *et al.*, 2011). This is in contrast to the known physiological effects of botulinum toxin which usually take 36-72 hours to begin to become apparent. The dramatic response seen in these patients is therefore likely to be due to placebo effect and may help to confirm that such patients are different from those with typical dystonia.

1.3.4 Functional myoclonus

Functional myoclonus is reported in about 20% of patients with FMD (Factor *et al.*, 1995). Functional myoclonus can be difficult to differentiate from typical myoclonus as it is difficult to demonstrate distractibility in patients with intermittent movements. Electrophysiological tests can be particularly helpful in supporting the clinical diagnosis. Simple recording of the duration of the jerks can be of benefit, particularly to demonstrate variability in duration and recruitment pattern of

electromyography (EMG) burst, suggestive of a functional cause. Bursts of less than 75ms in duration are unlikely to be functional. However, bursts of more than 75ms do not prove myoclonus to be functional as some forms of "organic" myoclonus (e.g. brainstem myoclonus, spinal segmental myoclonus) may have EMG burst lengths longer than 75ms. The most definitive test to confirm the functional origin of the myoclonus is detection of the readiness potential or Bereitschaftspotential (BP). This electroencephalography (EEG) potential starts around 1.5s before voluntary self-paced movement, and reflects activity in areas associated with movement preparation (Shibasaki and Hallett, 2006). It can be found in patients with functional myoclonus, but has never been reported in patients with typical myoclonus. Three studies assessing the presence of BP have confirmed that most patients carrying a diagnosis of idiopathic spinal myoclonus or propriospinal myoclonus were in fact of functional origin (Esposito *et al.*, 2009, van der Salm *et al.*, 2010, Erro *et al.*, 2013).

1.3.5 Functional gait disorder

Abnormal gait can be an isolated phenomenon in patients with FMD or mixed with other clinical manifestations. In the classical manifestation of functional gait disturbance, patients veer from side to side when walking, often waving the arms at the same time. They seem to be about to lose their balance, but tend not to. This ability to shift their centre of gravity from one side to the other without losing balance is actually a demonstration of good balance in direct opposition to the patient's subjective report of poor balance. This pattern has been termed the "walking on ice" gait. Other features include: narrow base, hesitation, dramatic

response to Romberg's test and tests of postural stability, "uneconomic" postures or excessive slowness. Some patients with typical neurological conditions such as Huntington's disease or generalised dystonia can exhibit bizarre patterns of gait and clinical experience in both functional and "organic" disorders can be required to make a clear diagnosis.

1.3.6 Functional parkinsonism

Functional parkinsonism is relatively rare, accounting for the 10% of cases of FMD (Hallett, 2011). The diagnosis is not always easy and a detailed clinical history and physical examination looking for positive clinical signs of FMD is required. All features of parkinsonism can be present. In a series of 9 patients, 7 had a predominant tremor form and only two had akinetic-rigid form (Benaderette *et al.*, 2006). This indicates that in fact "true" functional parkinsonism, rather than people who have functional rest tremor, is probably very rare. In such patients, rigidity may be present but feels similar to voluntary oppositional resistance against passive movements rather than true cogwheel rigidity. Movements may appear to be very effortful and slow, but true bradykinesia with decrementing amplitude with rapid repetitive movements is not seen. When patients are distracted, velocity of the movements can normalize. Postural stability testing may lead to dramatic loss of balance and falls. Speech often becomes stuttering, "baby-like" or develops a foreign accent. The handwriting is laboured and irregular but without typical micrographia (Jankovic, 2011). It is important to recognise that placebo response can be quite sizeable in patients with PD where it is associated with dopamine release (de la Fuente-Fernandez *et al.*, 2001), so caution needs to be taken in

interpreting response to placebo in patients with suspected functional parkinsonism. Dopamine transporter (DaT) single-photon emission computed tomography (SPECT) scanning is a useful test to investigate the integrity of the nigrostriatal system and discriminate functional parkinsonism from PD. This test will be abnormal in patients with PD and normal in functional parkinsonism. It is important to emphasize that normal DaT scans are seen in patients with "organic" post-synaptic causes for parkinsonism such as drug-induced parkinsonism. Also, it is worth to note that the diagnosis of PD does not exclude the presence of functional symptoms or the reverse. Indeed, it has been suggested that patients with PD are more prone to develop functional symptoms than other neurodegenerative disorders (Onofrj *et al.*, 2010, Onofrj *et al.*, 2011).

1.3.7 Other functional movement disorders: chorea, tics and paroxysmal movement disorders

Functional chorea is distinctly rare. So far, only two patients have been reported, one of them with a family history of Huntington's disease (Fekete and Jankovic, 2010). Here, clues for the diagnosis were normal saccadic eye movements, lack of motor impersistence and marked decrease of chorea when patient was distracted during performance of voluntary repetitive movements.

Functional tics are also rarely described. Surprisingly, in a series of patients with tics reported by Mejia and Jankovic, 16 out of 155 patients with tics (10.3%) were considered to have functional tics (Mejia and Jankovic, 2005). The rather high frequency of functional tics this sample was subsequently questioned, arguing that the criteria used to give the diagnosis of FMD in these patients was not specified

and that typical indicators of FMD such as abrupt onset, response to placebo or suggestion or increase with attention and cessation with distraction may not help differentiate "organic" from functional tics as "organic" tics may begin also abruptly, be under some voluntary control and intensity can vary with attention. This highlighted the need of well-defined criteria to characterize functional tics.

A ''paroxysmal'' component is one of the most important clinical presentations of FMD. However, functional paroxysmal disorders have been rarely mentioned in the literature. Because "organic" paroxysmal disorders such as paroxysmal kinesogenic dyskinesia, paroxysmal non kinesogenic dyskinesia and paroxysmal exercise induced dyskinesia or even focal seizures are by definition brief and reversible the clinical diagnosis can be very difficult. "Organic" counterparts have, however, typical precipitating factors and the length of the attacks is also well defined for each type and incongruous features with them can therefore be suspicions of a paroxysmal FMD (Ganos *et al.*, 2014). Often, EEG and video-recording of the attack are essential to reach the diagnosis.

1.4   Diagnosis

Over the past years, marked emphasis amongst movement disorder specialists has been placed on using positive physical signs and investigation findings to support the diagnosis of FMD, rather than making a diagnosis of exclusion or based on the presence of psychological distress.

The most widely used criteria were developed by Fahn and Williams in 1989 (see Box 1) (Fahn and Williams, 1988). FMD are divided into four categories of diagnostic certainty: documented, clinically established, probable and possible. These criteria

were in fact first developed for functional dystonia alone, but were later expanded to cover all FMD.

Gupta and Lang have suggested revisions to these criteria which delete the "possible" category as being not sufficiently specific for FMD, and also seek to introduce the concept of a laboratory supported level of certainty (Gupta and Lang, 2009). Shill and Gerber proposed alternative criteria, but these have been criticised for relying too heavily on historical factors such as "disease modelling" without reference to the movement disorder phenomenology (Shill and Gerber, 2006).

Recently, these criteria have been assessed with regard to inter-rater reliability, and have been found to demonstrate moderate to poor reliability for the probable and possible categories (Shill and Gerber, 2006). Therefore new criteria, which perhaps include more specific direction as to the positive physical signs that predict FMD rather than the unspecified "incongruency" with typical movement disorders, is urgently needed to improve reliability.

Box 1. Fahn and Williams criteria for functional movement disorders

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1. Documented

> Persistent relief by psychotherapy, suggestion or placebo has been demonstrated, which may be helped by physiotherapy, or the patient was seen without the movement disorder when believing him- or herself unobserved

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2. Clinically established

> The movement disorder is incongruent/inconsistent with typical movement disorder plus at least one of the following three:
> – Other psychogenic signs
> – Multiple somatisations
> – Obvious psychiatric disturbance

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3. Probable

> The movement disorder is incongruent/inconsistent with typical movement disorder
> The movement disorder is incongruent/inconsistent and there are psychogenic signs
> The movement disorder is incongruent/inconsistent and there are multiple somatisations

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4. Possible

> The movement disorder is incongruent/inconsistent and there is evidence of an emotional disturbance

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Giving the diagnosis of a FMD to patients can be sometimes even more challenging than making the diagnosis itself. A poor explanation such as "all the tests have come normal, therefore you are stressed" often causes incredulity and sometimes hostility (mainly because many patients do not consider psychological factors being relevant in their cases and the explanation is therefore no convincing). However, a successful explanation of the diagnosis can be therapeutic itself. Explaining what they do have, what they do not have and why (for example PD), how you have reached the diagnosis (for example explaining the positive signs in the

examination), stating that the diagnosis is very common and that you believe them (you do not think that it is all in their minds or they are putting the symptoms on) are often of help (Stone et al., 2013). It is also important to explain that a potential for reversibility does exist and that treating psychological issues (when relevant) can also help to treat the condition.

1.5 Differential diagnosis

Many clinicians do not feel confident during the diagnostic process and the worry of erroneously labelling a patient as functional is not uncommon. A systematic review of studies of misdiagnosis however found that only 5% of patients had the wrong diagnosis after an average of five years (Stone *et al.*, 2005). This rate is similar to those found for most neurological and psychiatric conditions. However, the diagnosis is not always easy and it is usually prudent to ask a specialist to confirm whether it is correct.

I have detailed general clues in the history and positive signs in the examination for each type of FMD that may help to differentiate them from their "organic" counterparts. Additionally, it have recently discussed general pitfalls in approaching patients with functional symptoms (those that can lead erroneously to diagnosis neurological disease as functional were called "mimics" and those that can lead to diagnosis of functional symptoms in patients that have a typical neurological disease were called "chamaleons") (Stone *et al.*, 2013). Putting too much emphasis in the presence of psychiatric disorders and life events, failure to consider that many patients may have an overlay of functional symptoms and typical neurological diseases, normal imaging or the presence of "la belle indifference" can lead to

misdiagnose patients as functional. Among the chameleon, to rely on the opinion that a patient is "nice, normal, or not stressed" to be functional as well as the fact that symptoms can come after injury or a minor disease or that the patient is too old can be misleading. Finally, assuming that normal neuroimaging exclude neurological diseases or in contrast, assuming that all structural abnormalities are relevant may also result in a misdiagnosis in both directions (Stone *et al.*, 2013).

Because FMD resemble movement that are voluntarily produced, one can always argue that patients are deliberately assuming symptoms in order to gain benefits. It is generally acknowledged to be very difficult to distinguish malingering from "true" FMD, but the consensus of opinion is that malingering is likely to be rare and is not a satisfying explanation for the disorder in the majority of patients (van Beilen *et al.*, 2009, Hallett, 2010). Data arguing against the idea that malingering is the most likely explanation for FMD comes from functional imaging studies in FT and fixed dystonia (Voon *et al.*, 2010, Schrag *et al.*, 2013). Here, patterns of brain activation in patients were different to those seen in subject feigning symptoms.

1.6 Treatment

There are no official guidelines for the treatment of FMD. However, an effective communication of the diagnosis that allows patients to understand their symptoms seems a good start. The benefit of simply explaining the diagnosis, at least in the early stages, has been found to lead to long-term resolution of symptoms in overall functional symptoms (Hall-Patch *et al.*, 2010).

Referral of patients with FMD to physiotherapy services is common practice by neurologists. However, in a recent survey most physiotherapists reported that

although they have interest for this group of patients, they have a low self-judged knowledge about how to treat them. Preliminary evidence for regular low-medium intensity walking exercise has been found in a single-blind study which assessed patients with FMD after a 12 week program (Dallocchio et al., 2010). In a study of 60 patients from the Mayo clinic with functional motor symptoms, a 5 day inpatient physical rehabilitation program produced benefits in over 60% of patients which were sustained in most for over 2 years (Czarnecki et al., 2012). This encourages the development of further studies to provide evidence for how physiotherapy services could best be structured to design and deliver successful treatments to patients with FMD.

Psychological intervention can be helpful in patients who consider psychological factors as relevant in symptom development or maintenance. Indeed, a small study provided preliminary evidence for a positive effect of antidepressant treatment in those patients diagnosed with primary conversion disorder but not in those with somatisation disorder (Voon and Lang, 2005). In patients with clear psychological stressors but who are reluctant to try this strategy, explaining that cognitive techniques are commonly used in medicine to help to control physical symptoms (e.g. modern management of chronic pain) may encourage them to try this approach. Recently, a community- based study of functional neurological symptoms demonstrated that patients receiving cognitive behavioural therapy (CBT)-based guided and usual care had more benefit than those who received usual care alone (Sharpe *et al.*, 2011).

The use of placebo as treatment strategy for FMD is still under debate. Because prognosis and successful treatment of FMD may be highly dependent on the patients' belief that they will get better, some neurologists support the use of placebo in this group of patients. Indeed, dramatic therapeutic benefits mediated through placebo therapy have been described (Edwards *et al.*, 2011). However, loss of patient autonomy and the erosion of doctor-patient relationship are important ethical concerns that should be taken into account. Recently, the need for clinical trials to define optimal regimes for placebo therapy in these patients as well as for health professional education in the use of placebos has been stressed (Rommelfanger, 2013).

Additional treatments have been suggested to be effective in FMD but evidence is poor. For example, intrathecal baclofen was reported to be effective in fixed dystonia compare to placebo (van Hilten *et al.*, 2000). However, placebo control was only used for the initial test dose of intrathecal baclofen, and it is not known whether there was systematic unblinding of the participant by systematic effects of the baclofen. Low frequency repetitive Transcranial Magnetic Stimulation (TMS) has been used as a therapeutical tool in FMD with some promising results (long-lasting clinical improvement immediately after TMS session was seen in many patients) (Dafotakis et al., 2011, Garcin et al., 2013). However, the unmasked nature of the intervention in most of these studies makes placebo effect a likely explanation for the results.

There is limited controlled trial data to guide treatment in FMD but the evidence that is available suggests that a multidisciplinary approach gives the best chance of

benefit. A recent study that retrospectively evaluated a multidisciplinary inpatient programme suggested this approach can provide long-lasting benefit for some patients with treatment-refractory FMD, at least as measured by retrospective self-report (Saifee *et al.*, 2012). However, similar to other studies, most patients failed to return to work and cessation of health-related financial benefits was uncommonly seen despite of reporting clinical benefits.

1.7   Prognosis

Data on long-term prognosis are scarce, but most studies point to significant impact in quality of life. For example, one study comparing patients with FMD and PD patients on different measures of disability and quality of life showed that patients with FMD reported levels of disability similar to those seen in PD (Anderson *et al.*, 2007). In a long-term follow up study, 90% of a group of 80 patients with a range of FMD still had abnormal movements after a mean of 3.2 years since their initial assessment (Feinstein *et al.*, 2001). In other study, a third of patients were employed at the time of follow up, while 11.5% were on disability and 1.3% were involved in litigation (Thomas *et al.*, 2006).

More optimistic studies of long-term outcome in FMD have showed that half of the patients report an improvement in their symptoms at last follow up (3-5 years after presentation)(Jankovic *et al.*, 2006). Factors that predicted a favorable outcome were a short duration of illness, patient's perception of effective treatment by the physician and the presence of a comorbid psychiatric diagnosis of depression or anxiety (which is therefore amenable to treatment) (Feinstein *et al.*, 2001, Thomas *et al.*, 2006). Negative outcome at long-term follow-up is associated with long

standing symptoms (more than 6 months) (Factor *et al.*, 1995), insidious onset of movements and primary psychiatric disorder of hypochondriasis, factitious disorder or malingering (Voon and Lang, 2005).

Chapter 2: The pathophysiology of functional movement disorders – the historical view

An historical review of any illness is always important. It is a very useful instrument to determine what happened in the past to an entity, and how previous contributions made an impact on the modern concept of a particular illness. It also often provides clues on future directions for research.

In this regard, functional symptoms are complex as there is a broad spectrum of manifestation ranging from neurological symptoms such as sensory, motor, memory or visual disturbances to non-neurological manifestation such as gastrointestinal symptoms. Some authors have argued for a common theory accounting for all the symptoms (Brown, 2004) whereas others have suggested a specific mechanism for each one. The proneness of functional patients to develop more than one type of symptoms over the time supports, in my opinion, the view that there should be common underlying mechanisms.

In this chapter I will review different theories that have been proposed to explain functional neurological symptoms. Here, I will use (in contrast with the rest of this thesis), the word "hysteria" to be consistent with the nomenclature used in the past. I have included information from ancient times (even though it is likely that the term hysteria at that time was also employed to describe other entities different from functional symptoms as defined in modern times). I have focused the research mostly on the 19th century and the beginning of the 20th century, a period in which hysteria was widely discussed and a theme of debate in the medical literature. I have concentrated on reading some of the original work of three

important authors who showed a vivid scientific interest in hysteria: Jean-Martin Charcot, Pierre Janet and Sigmund Freud. I present their main theories but I also highlight the specific accounts of FMD when they reported them. By doing this, I do not mean that these three authors are the only important ones. There are other relevant thinkers, who are not mentioned in this thesis, whose contributions were undoubtedly of value. My aim was, however, to read in depth and capture the most illustrative thoughts from that time.

Janet once wrote that most theories have the inconvenience of being transitory, *"of disappearing soon after us, but it would be a singular illusion to seek to do something eternal"* (Janet, 1907)*.* What follows demonstrates that in fact each theory does have in itself something eternal, something that is still undoubtedly influencing our current understanding of these common and disabling symptoms.

2.1   Ancient Egypt, Greece and Rome

It is thought that the first description of hysteria comes from the ancient Egyptians (Kahun Papyrus, 1900 BC) (Tasca *et al.*, 2012). They described them as being due to spontaneous movements of the uterus in women's body but symptoms had not yet been given a specific term.

It was Hippocrates (5th century BC) who first used the term hysteria (Gilman, 1993). He suggested that the causes of the symptoms were poisonous humours which, due to an unsatisfactory sexual life, had never been expelled. He stated that because a women's body was naturally cold and wet, they were predisposed to decomposition of the humours. As a prevention of the disease, the suggestion that even widows and unmarried women should get married and live a satisfactory

sexual life was made. Once women had acquired the disease, they were advised to treat themselves with acrid or fragrant fumigation of the face and genitals (Tasca *et al.*, 2012).

Although the theories on hysteria developed by one of the greatest physician of ancient Rome, Claudius Galen (2nd century AD), were analogous to those of Hippocrates, he was the first who emphasised the difficulties that just one single organ such as the uterus, could cause several different symptoms. He wrote with reference to Hippocrates: "*Ancient physicians and philosophers have called this disease hysteria from the name of the uterus, that organ given by nature to women so that they might conceive. I have examined many hysterical women, some stuporous, others with anxiety attacks [...]: the disease manifests itself with different symptoms, but always refers to the uterus*" (Tasca et al., 2012).

2.2   Middle Ages

The Roman Empire fell but Greco-Roman medical culture survived thanks to, amongst others, the Persian Avicenna (980-1037) and the Andalusian Jew Maimonides (1135-1204). The theories of Hippocrates and Galen were conserved and hysterical symptoms were treated in a "scientific" way with the use of Melissa as a natural remedy (Tasca *et al.*, 2012).

From the 13th century onwards, the Inquisition played an important role in how manifestations of illnesses, especially those due to psychiatric conditions, were interpreted. If a physician was not able to identify the cause of a disease, likely to occur with functional symptoms, it was thought to be due to the presence of a

demon. Therefore, "hysterical" women were commonly exorcised (Tasca *et al.*, 2012).

2.3   Modern Age

During the 16th and 17th century the basis of modern medical science were established. The physician Thomas Willis (1621-1675) referred for the first time to hysteria as being related to the brain and to the nervous system (Tasca *et al.*, 2012). While many of his contemporaries were looking for the causes of psychiatric disorders in other organs, such as the uterus, lungs and spleen, he used to dissect his own patients with the aim of relating the symptoms to brain pathology, including patients with hysteria (Eadie, 2003, Molnar, 2004). It is during this period that a door for a neurological explanation was opened and the suggestion that perhaps hysteria was not a condition exclusive to females and instead, could affect both sexes raised.

2.4   19th and 20th Centuries

In the 19th century, a burst of scientific interest to understand hysteria occurred and France became the epicentre of this study. Prominent physicians developed methods and treatments for hysterical symptoms which sometimes divided the medical community.

2.4.1   Briquet

His Treatise on Hysteria, published in 1859, contains clinical and epidemiologic details of 430 patients with hysteria seen over a decade. He described several etiological factors such as "affective" temperament, family history, low social class,

sexual immorality or poor physical health (Mai and Merskey, 1981). Paul Briquet regarded hysteria as a "Neurosis of the Brain" in which the causative agents can act on the "affective part of the brain" in a susceptible and predisposed individual (Hallett, 2006). In terms of treatment, Briquet emphasized the importance of an improvement in social circumstances and the need to minimize environmental problems. With Briquet the historic association of hysteria and disease of the uterus was finally discredited (Mai and Merskey, 1981).

2.4.2 Charcot

Jean-Martin Charcot (1825-1893) was a pioneer of modern neurology during the 31 years of his working life. His contributions to medical knowledge were based on a systematic use of physiology and pathology accompanied by a rigorous clinical analysis. By the time of his death, the nosology of the main neurological diseases had been carefully and methodologically classified. He tried to apply his methodology to understand also hysteric symptoms and it was him the one who treated, perhaps for the first time, hysteria as an issue worthy of serious study. The Clinical Lectures on the Diseases of the Nervous System summarises all the lectures given by Charcot between 1882 and 1885 in the lecture theatre of the Salpetriere hospital in Paris (Charcot, 1889). Here, he focuses on the difficulties on diagnosing and treating patients with hysteria among other neurological diseases. He gives a detailed description of the phenomenology and care provided to patients admitted on the ward suffering from several functional symptoms such as "hystero-epilepsy", "hysteric mutism", "hysteric amyotrophic", and "hysterical paralysis". Several men are described and this was used by Charcot to demonstrate to his students that

hysteria could occur in men, though he reported the proportion previously suggested by Briquet of 1 man to 20 women was exaggerated (Charcot, 1889).

In these lectures, Charcot also presents cases of FMD. He describes hysterical tics on the lower face in a 15 year-old girl and dedicates extensive work to what he called "hysterical contractures of traumatic origin" highlighting the common presence of physical injuries preceding the abnormal posture, a condition nowadays called fixed dystonia.

In lecture III, he presented the case of a 34 year-old lady with a history of hystero-epilepsy (she displayed in the past both epileptic seizures and non-epileptic attacks). During a period in which non epileptic attacks had completely disappeared, she had a work accident after tripping on the top of a staircase, falling heavily on her left side. Charcot stressed the fact that the injury was mild but the next morning she had a plantar flexion and inversion of the left foot, which in Charcot's words *"attempts to passive movements were useless"* (Charcot, 1889).

With this case, Charcot highlights several typical aspects of functional movement disorders such as the sudden onset of the abnormal movements, that physical triggers are common, that the abnormal movements reach their maximum *"all in a moment"* and comments on the predisposition of functional patients to develop new different symptoms over the time.

In lecture XXV, he also described a man, who after a physical injury and the application of a splint in the arm developed a painful fixed posture with the arm in flexion (Figure 2.1).

Figure 2.1. Man with fixed dystonia after injury and application of a splint described by Charcot in The Clinical Lectures on the Diseases of the Nervous System. Image courtesy of the Queen Square Library, Archive and Museum. Copyright National Hospital for Neurology & Neurosurgery.

Interestingly, this patient underwent an examination under the effect of Chloroform to confirm the hysterical origin and to assess that there were no contractures of his muscles or shortening his tendons. This is the first account for an examination under anaesthetics (which is still nowadays used with the same purposes) that I have come across during my review of the literature. Later on, Breuer will also realise that hysterical contractures may disappear under the effect of anaesthesia after given Chloral to Anna O.

Overall, Charcot pursued the regularities and laws of hysteria, derived from its clinical manifestations. He asserted that hysterical symptoms *"do not form, in pathology, a class apart, governed by other physiological laws than the common one."* (Charcot, 1889). His eagerness to understand the mechanism of hysteria from a neurobiological perspective is clearly reflected in his theory to explain hysterical

contractures. Firstly, he explained the causes of organic contractures and then, the similarities with the functional symptom: "*In hemiplegia consequent on a lesion of the brain […] the limb remains flaccid. But the contracture exists there, in a latent state as it were, as is shown by exaggeration of the tendon-reflexes; and sometimes by repeated blows on the patellar tendon, a temporary contracture lasting several minutes can be produced. Well, under these circumstances, there is an imminence of contracture which can be brought on by the occurrence of a traumatism, and it will manifest itself in the part which is the seat of the contusion, sprain etc. […] Moreover, to determinate a contracture, the injury need not necessarily be violent. The theory which best enables us to fix these facts in the mind is the following: there exists in cases of paralysis due to material lesion a hyper-excitability of the grey substance, and particularly of the motor cells of the anterior horns, a special state. Then, a cutaneous irritation, irritations of the centripetal nerves in general, augments the already excited conditions of the motor cells […]. Now, to return to hysteria, in many hysterical patients […] exists an exaggerated reflex excitability. Hence, it is not astonishing to find that an excitation of the centripetal nerves […] produces the same effects as in cases where there exists a lesion of the nervous system*" (Charcot, 1889).

In the Clinical Lectures on the Diseases of the Nervous System, Charcot argues for the view that hysteria is a brain disease caused by functional rather than structural abnormalities. Interestingly, he also advised his students about the difficulties of differentiating hysteria from individuals simulating symptoms: "*When we are treating of hysteria, the physician should always have present in his mind the possibility of simulation*" (Charcot, 1889). Indeed, he aimed to prove that most

patients with hysterical contractures were actually not feigning their symptoms. For that, he and his colleagues designed an experiment using the following device (Figure 2.2).

Fɪɢ. ɪɢ.—Experiment intended to verify the reality of the contracture
of the hand.
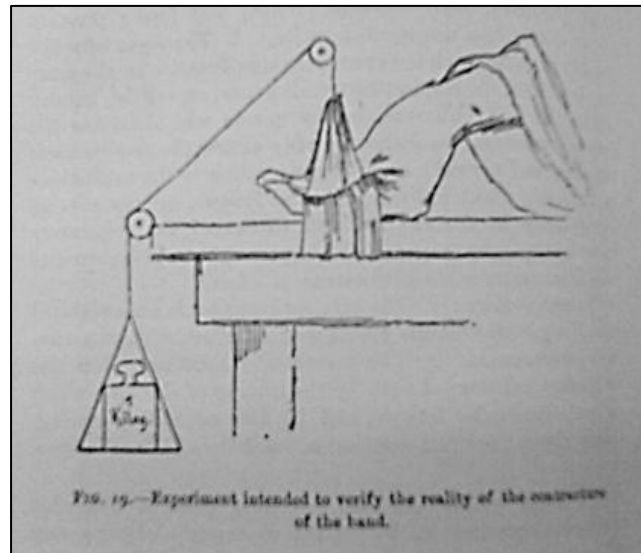
Figure 2.2. Device to demonstrate that patients with fixed dystonia are not feigning described by Charcot at The Clinical Lectures on the Diseases of the Nervous System. Image courtesy of the Queen Square Library, Archive and Museum. Copyright National Hospital for Neurology & Neurosurgery.

They placed the hand affected by hysterical contractures on a table and submitted it to a continuous traction of 1 kg for 30 minutes. They assessed breathing patterns with a plethysmograph-like machine over the 30 minutes of the experiment and they compared the results with those from a "vigorous" young man who was asked to mimic the posture of the patient. Whereas the pattern of breathing of the young healthy man changed over the experiment, it became superficial and irregular, denoting signs of fatigue, the pattern of hysterics remained stable as if no effort was employed.

Nevertheless, the physiological view about mechanism of hysteria employed by Charcot was not incompatible with more complicated psychological views about the aetiology. In 1878 he introduced the technique of hypnotism into this research and there was a shift towards acknowledging that psychological factors were also relevant (Bogousslavsky, 2011).

2.4.3 Janet

Pierre Janet (1859-1947), perhaps due to the influence of his mentor Charcot, also developed an avid interest for hysteria. In the Major Symptoms of Hysteria (1920) (Janet, 1907), fifteen lectures given in the Medical School of Harvard University, he summarises his thoughts about the underlying mechanism of functional symptoms.

Interestingly, his view about the personality of patients with hysteric symptoms differed radically from the conception that most physicians have nowadays. He described hysterics to be "easily managed, not dangerous, on whom we can experiment without any great fear and who like to be observed" (Janet, 1907).

He was one of the first who emphasised the necessity of the early recognition of the symptoms and the impact of communicating the diagnosis in the management. In one of his lectures he advised the audience: *"You must be able quickly to recognise this disease, in order to foresee its evolution, to provide against its dangers, and immediately to begin a rational treatment. This early diagnosis is much more important still from another point of view: it will keep you from making blunders. It is perhaps not very serious not to recognise a hysterical accident and not to treat it, but what is always very serious is to mistake hysterical accident for another one and to treat it for what is not"* (Janet, 1907). These words can be

interpreted as an attempt to protect patients with functional symptoms from unnecessary interventions, if the correct diagnosis is made.

Janet sought a balance between what he called the theories of the "clinical period", referring to Charcot and contemporaries from 19th century, who, in his opinion, tried to give a medical character to hysteria; and what he called "psychological period", meaning by this his contemporaries, who described hysteria as a pure mental phenomenon. He criticised Charcot: *"[…] carried along by his habits as a clinician, he has sought these general laws too much in the physiological domain, which led him to a certain number of regrettable errors"* (Janet, 1907) but he also disagreed with a pure psychological view of hysteria*: "A certain number of authors have been seduced by the psychological explanation. It seemed to them that the mere words "moral" and "thought" were enough to explain everything, and as people generally like simple explanations, physicians are too disposed nowadays to be content with a vaguely mental explanation. Hysteria, they say, is a psychic disease, it is the disease of suggestion, taken in a vague sense […] There is some truth in this view, for it brings into relief the psychic character of affection; but it is quite insufficient. We should, in my opinion, retain something of the precise method of Charcot, of the search after the determination and the laws of hysteria, and apply it only to the psychological facts"* (Janet, 1907)*.*

In these lectures he meticulously described the most common FMD: tremor and dystonia.

He stated that in FT tremor "*the arm has regular little oscillations, of an average rate of five to nine a second. These oscillations are nearly continual. There are some*

subjects with whom they never stop, either when they rest or when they move; there are some others with whom these tremors are intermittent, disappearing at the time of voluntary activity and increasing at the time of diversion and rest. But it is not possible to establish any rule, for you often observe the reverse in the form of intentional trembling, analogous to that of disseminated sclerosis […] These tremors occur under various conditions, sometimes gradually, after paralytic phenomena, very often suddenly, after an emotion. One of the finest cases I have observed is that of a workman, who, in consequence of the breaking of a scaffolding, remained suspended at the height of a sixth floor. […] But in most cases, there is nothing behind the tremor but a vague emotive state and a kind of transformation of the motor function of the limb." (Janet, 1907)

He described functional dystonia as "*a state of moderate contraction of an ensemble of muscles which maintains a limb in a determinate position and that in an involuntary, unconscious, and indefinite manner. Such contractures can be observed on absolutely all the muscles of the body, and in each region they raise medical problems […] First we know that contractures are consequent, like all hysteric phenomena, on thoughts and emotional phenomena. A shock has no action in this direction except when it determines the great phenomena of imagination, I will explain myself. An individual has his legs in a state of contraction because, he says, a carriage ran over them. After verification, it is found that the carriage passed besides him, and that he felt nothing at all. A real shock would do less than this imaginary shock […] The contracture varies with certain psychological facts. If the subject is very quiet, if nobody touches her contractured limb, and if she herself does*

not try to make a voluntary movement, we may see than contracture decrease…"

(Janet, 1907)*.*

Janet highlighted the genuine nature of the symptoms and differentiated them from those that were feigned. He stated*: "You will find that you are much more awkward than a hysteric person, and that unless you have practiced specially to this end, you cannot obtain the same regularity. Try to keep your arm in the position of a hysteric contracture and describe the movement of the arm; you will remark that you have not the same perseverance or courage as the patient. After a short time, your arm trembles and is displaced, while the hysteric contracture has not changed. If therefore we suppose there is a psychic action in these hysteric phenomena, it must be acknowledged that this action is not identical with ours, but that is performed in other conditions. Here is my hypothesis; […] "…Action by becoming unconscious in hysterics, by separating from consciousness, loses something of its dignity, retrograde in a manner and assumes an appearance that recalls the action of visceral muscles, the action of the lower animals, and the movements of fatigued muscles, as if the activity of the sarcoplasm prevailed over that of the fibrils. This is what in my opinion gives to the subconscious action of the hysteric those abnormal characteristics we saw in tremors and contractures"* (Janet, 1907).

Overall, Janet summarized the peculiar mental state of hysterical by the words "retraction of the field of consciousness". Janet was one of the originators of the idea of dissociation. He proposed that in the physiological state enormous amounts of sensory information from all the points of our bodies constantly emerge. However, a person never perceives them all. The number of elementary sensations

that can simultaneously reach consciousness depends on the extent of the field of consciousness and this may differ very much within individuals and depends on their state of mind (attention). The sensations which do not reach consciousness must remain in the sub-consciousness, and he calls this "normal absent-mindedness". In the case of hysterics, the field of consciousness is so contracted that the patient reserves the small share of perception for the sensation which is considerate the most important one. For instance, if patients can perceive just two stimuli at the same time and vision and auditory stimuli are prioritised, when someone pinches the left arm of the patient, he cannot feel it consciously: it has become anaesthetic. He considered that this restriction of the field of consciousness was secondary to their fundamental mental state, which was characterised by a *"special moral weakness, consisting in the lack of power, on the part of the feeble subject, to gather, to condense his physiological phenomena and assimilate them to his personality"* (Janet, 1907)*.*

Janet's theory accounted essentially for functional anaesthesia and he found it more difficult to explain other functional symptoms.

Janet also emphasised the importance of physical events preceding the onset of functional symptoms. He believed that the restriction of the field of consciousness usually affected a function that for some reason or other had become weak. He gave examples of cases such as that of a girl with functional paralysis in her right leg, and he believed that the reason was that in her childhood the right leg was affected with rachitis or the case of another girl with paralysis of the leg, which was thought to be due to the fact that in her childhood the leg was affected by a tumour

and was kept wrapped in a bandage (Janet, 1907). He also brought to attention what nowadays is called "functional overlay" by saying that "in certain cases, hysteria makes conspicuous some light symptoms of organic disease of the nervous system quite at the beginning by exaggerating them beyond all measures" (Janet, 1907).

2.4.4 Freud

In popular culture hysteria begins and ends with Sigmund Freud (1856-1939). However, as previously reviewed, there is a tradition of study of hysterical symptoms for more than three thousand year history before his work. Despite being a pupil of Charcot in Paris, Freud rejected any account for hysteria but the pure psychological one. This strong theoretical position is well reflected in Studies on Hysteria (1893-1895) (Breuer and Freud, 1974), a book written with his mentor in Vienna: Joseph Breuer. Here, they wrote *"in what follows, little mention will be made of the brain and none whatever of molecules. Physical processes will be dealt with in the language of psychology; and indeed it cannot possibly be otherwise"*. The purpose of their work was to elucidate the precipitating cause of hysteria, *"the event which provided the first occurrence after many years earlier of the phenomena in question"*. They acknowledged the difficulties that go with it as "*the patient sometimes dislikes discussing, and mainly because they are genuinely unable to recollect it and has no suspicion of the causal connection between the precipitating event and the pathological phenomenon."*

It was clear to me on reading this text that they recognized physical precipitating factors close to the onset of the functional symptoms in several clinical cases

through the book. For instance, in the famous case of Anna O they wrote *"a girl, watching beside a sick-bed in a torment of anxiety, fell into a twilight state and had a terrifying hallucination, while her right arm, which was over the back of her chair went to sleep; from this, she developed a paresis of the same arm accompanied by contracture and anaesthesia"* (Breuer and Freud, 1974). It is possible that in first place, Anna had numbness and a degree of paresis secondary to nerve compression caused by placing her arm on a hard surface (the back of a chair) for a number of hours. Or the case of Miss Lucy R, a girl who suffered from suppurative rhinitis and necrosis of the ethmoid bone and developed later hysterical symptoms in the form of subjective olfactory sensations (Breuer and Freud, 1974). By observations like these, they proposed that the concept of traumatic neurosis from Charcot should be extended to traumatic hysteria. Here, it is not the physical injury but the affect of fright that commonly accompanies the injury, the *psychical trauma*, which is considered the cause of the illness. They neglected the importance of the physical event itself by saying that their investigations reveals *"for many, if not for most hysterical symptoms, precipitating causes [can be identified] which can only described as psychical traumas."* (Breuer and Freud, 1974)

When it was not possible to establish the point of origin of the illness, they hypnotized the patient *"As a rule it is necessary to hypnotize the patient and to arouse his memories under hypnosis of the time at which the symptom made its first appearance"* (Breuer and Freud, 1974) and when patients denied any precipitant or the one interpreted by them, they attempted to persuade the patients to believe the opposite.

In the theoretical part of the Studies on hysteria, they summarize their views after the observation of several hysterical patients. They use the analogy of an electrical system through which there is a constant flow of current to explain what may happen in the brain. In physiological conditions, they argued that the brain tries to keep in a constant excitation *"intracerebral tonic excitation"* at that level which is optimal to be *"accessible to all external stimuli, the reflexes are facilitated, though only to the extent of normal reflex activity, and the store of ideas is capable of being aroused and open to association in the mutual relation between individual ideas which corresponds to a clear and reasonable state of mind"* (Breuer and Freud, 1974). Healthy people can get rid of any increased cerebral excitation associated to emotional situations by using motor discharge or secretions (for instance shouting and jumping for joy or sobs and tears when sadness). If these reactions are suppressed, the affect associated with emotional situations is not "abreacted" and may remain attached to the memory (Breuer and Freud, 1974).

Coming back to the analogy with an electrical system, they argue that there must be resistances through the system, which prevent the general distribution of excitation (mainly in organs which are of vital importance *"the circulatory and digestive organs are separated by strong resistances from the organs of ideation"*). The strength of these resistances varies from one person to another and they suggested that this is the explanation why some people have a strong vegetative reaction with low levels of stress and others do not (Breuer and Freud, 1974).

In the case of hysterics, Breuer and Freud argued that they have an innate idiosyncrasy which is characterised by excess of energy. They understood hysterics

as lively people, full of intellectual interests before they fall ill. They thought that it was uncommon *"to find in them simply, dull intellectual inertia".* During puberty the original excess is increased by additional excitation which arises with the emergence of sexuality. After puberty, they have enormous quantity of free nervous energy available for the production of pathological phenomena. But this predisposition to hysteria does not lie down exclusively on excessive intracerebral excitation. Hysterics were also thought to have abnormal weakness of the *resistances*. These weak resistances were suggested to be determined by the individual's initial constitution, by the long-term excitation itself or by weakening factors, such as the presence of a previous illness of the organ concerned, which may facilitate the paths to and from the brain (Breuer and Freud, 1974).

They suggested that in hysteria, there are difficulties to abreact traumatic experiences and memories of these experiences are repressed from their consciousness. These memories, which have a strong affect attached to them, increase the excitation of the brain and this energy is "converted" into a somatic phenomenon. This discharge *"follows 'the principle of least resistance' and takes place along those paths whose resistances have already been weakened by concurrent circumstances"* (Breuer and Freud, 1974). For instance, in the case of Miss Lucy R, hysteric symptoms were subjective olfactory sensations and she had recently suffered from suppurative rhinitis that might have acted as a weakening factor.

Their therapeutic approach was the use of light hypnosis and suggestion to bring back to consciousness the memory of the traumatic event and arousing its

accompanying affect. They assured readers that when patients had described the event in the greatest possible detail and had put the affect into words, the symptom immediately and permanently disappeared.

Chapter 3: Aims and hypotheses

The background above provides, I hope, a picture of how theories regarding the pathophysiology of functional symptoms have largely focussed on causation (and here have focussed on causation by a psychological trauma), and less on the mechanism by which this event becomes translated into the type of physical symptom experienced by the patient. In other words there has been a focus on "why" rather than "how" symptoms develop. While I believe both questions are very important, my sense at the beginning of the work was that the question of "how" symptoms are produced might be more tractable and relevant. The other key factor that helped in the formulation of the hypotheses I pursued was the patient population that I had access to. These patients had disorders of movement, providing a great opportunity to study symptoms where there are observable clinical signs (in comparison to sensory loss or pain for example). The clinical methods for making a diagnosis in such patients already provided key information on the likely underlying mechanism, especially with regard to the importance of attention. I therefore took as my starting point the manner in which the diagnosis of FMD is made in neurological practice. The diagnosis can be made confidently on the basis of positive physical signs, helped by certain historical features. This, to me, was the most suitable starting point as it removed aetiological speculation, particularly about the role of psychological trauma in causation of functional symptoms, and instead focused on a more mechanistic level. This provided a better fit with investigation of other illnesses where the main tractable areas of study (at least initially) relate to *how* symptoms are produced, rather than *why*.

In addition to a clear role for attention in the generation of functional motor symptoms being apparent from a clinical point of view, two other potentially important mechanistic issues stood out for me. One was that some symptoms (for example tubular visual fields) suggested a key role for beliefs about the way the nervous system might malfunction due to illness which we know are contradicted by basic anatomy and physiology. The other issue was that there must be an abnormality in sense of agency for movement if movement that appears to be voluntarily generated is not experienced as such. Finally, I was also interested in understanding better the circumstances surrounding the onset of the functional symptoms.

I looked for paradigms that might provide ways of exploring these three areas of interest, and in this I was influenced in part by paradigms that had been previously used in patients with delusional beliefs. It was against this background that I developed the following hypotheses:

1. That physical precipitating factors will be common in patients with FMD, as our clinical experience suggested.

2. That patients with FMD will display a reasoning style different to healthy controls that may predispose them to accept new hypothesis on the basis of less evidence.

3. That patients with FMD will have impaired motor control under circumstances in which there is an opportunity for attention to be directed towards movement production.

4. That patients with FMD will display abnormalities in paradigms designed to assess the sense of agency for movement.

Chapter 4: A study on the physical precipitating factors in functional movement disorders

The work presented in this chapter was originally published in the form of a research article:

4.1 Introduction

We have seen that typically, functional neurological symptoms, including FMD, have been explained as resulting from psychological stressors which lead to unconsciously produced physical symptoms. In keeping with this formulation, several authors have found higher rates of childhood trauma in patients with functional symptoms (Alper *et al.*, 1993, Bowman and Markand, 1996, Roelofs *et al.*, 2002) or have highlighted the aetiological importance of emotional stress or recent life events (Binzer *et al.*, 1997, American Psychiatry Association, 2000, Irfan and Badar, 2002). Indeed, it was not possible to make a diagnosis of conversion disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria without the presence of a psychological stressor that precedes the onset of physical symptoms (American Psychiatry Association, 2000).

My impression from my involvement in a specialised clinic for FMD was that many patients did not report psychological stressors prior to the onset of symptoms. Supporting this view, a recent study found few differences in self-reported recent life events or past experience of sexual or physical abuse in patients with FMD,

compared to healthy controls and patients with "organic" movement disorders (Kranick *et al.*, 2011).

In contrast, my experience was that many patients with FMD reported a physical event such as injury or illness at the time of onset of their symptoms. The presence of a physical event was discussed as part of the pathophysiology of FMD at the time of Charcot, who coined for instance the term "traumatic dystonia" to describe hysteric contractures after minor injuries, but since then, the role of physical events triggering functional symptoms has been neglected in favour of more psychological explanations.

After a search of the published literature for the past 25 years, I realised that physical events had been commonly reported in cohort studies of FMD but they had only very rarely been discussed in research articles and had been ignored as a relevant factor for symptoms development. I summarise this data in Table 4.1.

Table 4.1. Examples of studies where physical precipitating factors have been reported in functional movement disorders

Author, year	Type of study	N	Subjects	Main FMD	Patients with PPF, n (%)	Type of PPF (no. of patients, where available)
Koller *et al.*, 1989	Retrospective	24	Adults	Tremor	11 (45.8)	− Head injury (2) − Flu-like illness (2) − Motor vehicle accident (3) − Exposure to Agent Orange (1) − Respiratory infection (1) − Abdominal surgery (1) − Vomiting (1)
Ranawaya *et al.*, 1990	Uncertain	6	Adults	Dyskinesia	6 (100)	− Spasmodic torticollis (2) − Writer's cramp (1) − Whiplash injury (1) − Road traffic accident (1) − 'Pre-existing organic movement disorder' (1)

Monday and Jankovic, 1993	Retrospective	18	Adults	Myoclonus	9 (50)	− Injuries at work (3) − Flu-like symptoms (3) − Motor vehicle accident (2) − 'Slipped in a shopping mall' (1)
Factor et al., 1995	Retrospective	28	Adults	Mixed	13 (46.4)	− Back injury (4) − Back surgery (1) − Fell off ladder (1) − Motor vehicle accident (2) − Carpal tunnel syndrome (1) − Hand caught in a bus door (1) − Exposure to polyvinyl-alcohol and trichloroethylene (1) − Worsening medical condition (1) − Taking erroneous prescription drug (1)
Factor et al., 1995	Retrospective	14	Adults	Parkinsonism	10 (71.4)	− Febrile illness (1) − Work injury (3) − Motor vehicle accident (2) − Head injury and subdural haematoma (1) − Pregnancy (1) − 'Fibrositis' (1) − Exposure Agent Orange? (1)
Lang, 1995	Retrospective	18	Adults	Dystonia	14 (77.8)	− Febrile illness (1) − Hand surgery (1) − Minor head injury (1) − Motor vehicle accident (5) − Work injury (1) − Walking (1) − 'Injury' (1) − HIV (1) − Fall (1) − Fracture (1)
Deuschl et al., 1998	Prospective	25	Adults	Tremor	12 (48)	− Lumbalgia (2) − Neck pain (3) − Periarthropathia humeroscapularis (1) − Myocardial infarction (1) − Asthma (1) − Shell shock (1) − Mild cervical trauma (1) − Meningoencephalitis (1) − Fracture (1)
Kim et al., 1999	Retrospective	70	Adults	Tremor	23 (32.8)	− Physical injury (23)
Verdugo and Ochoa, 2000	Prospective	58	Adults	Dystonia, tremor	55 (94.8)	− Physical injury (55)
Feinstein et al., 2001	Prospective	42	Adults	Mixed	21 (50)	− Surgery (8) − Road traffic accident (7) − Injury (5) − Infection (1)

Study	Design	N	Population	Phenotype	Precipitating event n (%)	Type of precipitating event (n)
Tan and Jankovic, 2001	Retrospective	5	Adults	Hemifacial spasm	1 (20)	− Head injury (1)
Schrag et al., 2004	Retrospective	103	Adults	Fixed dystonia	76 (73.8)	− Peripheral injury or back or neck injury (65) − Arthroscopy (2) − Fracture (1) − Pain (2) − Head injury (1) − Asthma (2) − Abscesses on thigh (1) − 'While in physiotherapy' (1) − Tingling and weakness in legs (1)
Jankovic et al., 2006	Retrospective	127	Adults	Tremor	70 (55.1)	− Trauma (30) − Surgery (12) − Major illness (17) − Reaction to medical treatment/procedure (11)
Benaderette et al., 2006	Prospective	9	Adults	Parkinsonism	3 (33.3)	− Accidental fall at work (2) − Surgery (1)
Espay et al., 2006	Prospective	10	Adults	Dystonia	7 (70)	− Motor vehicle accident (3) − Falling in the bathroom (1) − Chiropractic manipulation (1) − Ankle sprain (1) − Fatigue (1)
Baik and Lang, 2007	Retrospective	279	Children, adults	Mixed	68 (24.4)	− Motor vehicle accident − Surgical procedure
Ferrara and Jankovic, 2008	Retrospective	54	Children	Mixed	29 (53.7)	− Injury or accident (19) − Minor medical illness (e.g. pharyngitis) (5) − Exertion (5)
McKeon et al., 2009	Prospective	33	Adults	Tremor	8 (24.2)	− Medical procedure − Respiratory infection − Back pain
Stamelou et al., 2012	Retrospective	7	Adults	Palatal tremor	7 (100)	− Flu-like illness (1) − Viral labyrinthitis (1) − Tinnitus (1) − Otitis (1) − Endoscopy (1) − Vomiting (1) − Throat infection (1)
Canavese et al., 2012	Retrospective	14	Children	Mixed	1 (7.1)	− Minor teeth surgery (1)
Fasano et al., 2012	Retrospective	61	Adults	Facial FMD	25 (41)	− Physical trauma (9) − Peripheral facial injury (8) − Pain (3) − 'Another disease' (5)

Batla et al., 2013	Retrospective	151	Adults	Mixed	52 (33.4)	− Trauma (34)
						− Surgery (9)
						− Infection (9)

FMD = functional movement disorder; PPF = physical precipitating factor

Only one study, which is a review of previous literature about the role of physical injuries in motor and sensory functional symptoms in general, reported that 34% of patients with FMD had a recent history of physical injury and emphasized the potential role in symptoms generation (Stone *et al.*, 2009). The proportion of physical injuries preceding the onset of the symptom was lower for FMD than those reported for functional sensory loss (45%) and functional paralysis (41%) in this study (Stone *et al.*, 2009).

Based on this previous information, we I aimed for the first time to systematically describe physical events (not just physical injuries), which occurred at the onset of functional symptoms in a cohort of 50 consecutive patients with FMD, as well as exploring other events near to onset.

4.2   Methods

4.2.1   Participants

Fifty patients were recruited in a consecutive way from a specialised Functional Movement Disorder run by Dr Edwards, at the NHNN Queen Square, London, UK, from January 2011 until December 2011.

I used as inclusion criteria:

1. Newly referred patient.

2. Age over 18 years.

3. Diagnosis of clinically established or documented functional movement disorders according to Fahn and Williams criteria (Fahn and Williams, 1988).

I used as exclusion criteria:

1. Age less than 18.

2. Unable to communicate with researcher (e.g. does not speak English).

4.2.2 Semi-structured interviews

We used face to face semi-structured interviews to characterise the circumstances which surrounded the onset of FMD. We used this type of interview because, although it was more time consuming than a structured interview and harder to analyse, it is more flexible and allowed us to collect more detailed data. The interviews were carried out by Dr Edwards and myself. I designed the data collection sheet in which information on sex, age, marital status, presenting symptoms, work status, presence of a disease model either at work or among family and friends, receipt of financial benefits and the presence of litigation were recorded. The interview also provided a retrospective account of the tempo of onset, associated symptoms and circumstances prior to onset of the FMD, which were also recorded.

There is no consensus about the timing between a precipitating event and the onset of a FMD to be sure that there is a good chance that there is a causal relationship. Some authors have considered one year between a physical injury and the development for instance of functional dystonia. Others consider this gap excessive and have reported that most triggers occur within the first few months.

In this study, only physical events within 3 months before the onset of the FMD have been included for consideration.

We used DSM-IV criteria for panic disorder (Box 2) to describe the presence of panic symptoms at the onset of symptoms (American Psychiatry Association, 2000).

Box 2. DSM-IV criteria for panic attack

A discrete period of intense fear or discomfort, in which 4 (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:
1. Palpitations, pounding heart or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, light headed or faint
9. Derealisation or depersonalisation
10. Fear of losing control or going crazy
11. Fear of dying
12. Paresthesias
13. Chills or hot flushes

4.2.3 Questionnaires

Following the interview, I asked participants to complete two questionnaires regarding their mood and the presence of life events within the 3 months prior to the onset of the FMD. When it was not possible for the patients to do it in the clinic, they were allowed to take away the questionnaires and send them back by post if they wished. For those patients who failed to return the questionnaires in two weeks, I phoned them as a reminder.

4.2.3.1 Mood

We used The Hospital Anxiety and Depression rating scale (HADS) with reference to their mood the week prior to testing (Zigmond and Snaith, 1983). There are 7 items for anxiety and 7 for depression. Each item is scored on a 0-3 scale. Therefore, the potential range of scores is 0-21 for both anxiety and depression scales, with higher scores indicating greater emotional disturbance. A cut off level of 9 or more has been found to have similar sensitivity and specificity in cancer patients. We used HADS because it is brief and simple to administer and although it was originally designed to be used with hospital populations, it has been found to perform well with non-hospital groups.

4.2.3.2 Life events

We used the 82 items Life Events Questionnaire (LEQ) (Norbeck, 1984). This is a self-report questionnaire addressing life events in the categories of health, work, school, residence, love and marriage, family and close friends, parenting, personal or social, financial and crime or legal matters. Patients are asked to indicate whether each event is considered "good" or "bad"; and rate the impact of the event on a 4-point scale (0-3). We used the negative events score (the sum of the impact ratings for all items designated as "bad" by the patient: range from 0 (no impact) to a maximum of 246). We chose this 82 items questionnaire because it covers a broad range of life event and includes questions that increase the relevance for adult female respondents of childbearing age, a group which was predicted to be common in our cohort.

4.3   Results

We recruited 11 males and 39 females. Demographic and clinical characteristics are

shown in Table 4.2.

Table 4.2. Demographic characteristics of the patients (n = 50)

Age (years), mean (SD)	39.8 (11.9)
Gender, n (%)	
Female	39 (78)
Male	11 (22)
Marital status, n (%)	
Single	19 (38)
Cohabiting/married	27 (54)
Divorced	4 (8)
Educational level, n (%)	
≤16 years	22 (44)
To 18 years	17 (34)
Graduate	11 (22)
Current employment status, n (%)	
Employed	8 (16)
Unemployed	8 (16)
Off sick	11(22)
Medically retired	16 (32)
Student	3 (6)
Unknown	4 (8)
Symptoms duration (years), mean (SD)	5.7 (6.1)
Type of FMD, n (%)	
Fixed dystonia	15 (30)
Tremor	8 (16)
Myoclonus	4 (8)
Mobile dystonia	3 (6)
Paroxysmal FMD with retained consciousness	2 (4)
Parkinsonism	1 (2)
Gait disturbance	1 (2)
Tics	1 (2)
Combination of ≥2 FMD	15 (30)
Potential sources of symptom modelling, n (%)	
Health care worker	8 (16)
Family/friends	10 (20)
Both	2 (4)
Home disability adaptations, n (%)	21 (42)
Family acting as a career, n (%)	34 (68)
Benefits, n (%)	25 (50)
Litigation, n (%)	3 (6)

FMD = Functional Movement Disorder; SD = standard deviation

4.3.1 Tempo of onset

Twenty seven patients (54%) reported a sudden onset of symptoms (seconds-minutes). Eighteen patients (36%) developed symptoms in hours - 1 day and only 5 patients reported a gradual onset (more than 1 day to maximal symptoms).

4.3.2 Physical precipitating factors

From a total of 50 patients, 40 (80%) patients reported a physical event within the three months prior to the onset of the FMD. Three patients did report a physical event which was related to the functional symptom (injuries in the same limb where the FMD appeared) but these occurred before the 3 months period that we set as inclusion criteria. One patient did not remember the exact timing between the physical event and the onset of the symptoms.

Time from physical event to onset of FMD in those 41 patients was minutes in 8 (16%) patients, approximately one day in 6 (12%) patients, two days in 4 (8%) patients, within the first week in 7 (14%) patients, one month in 9 (18%) patients and within the 3 months prior to onset in 6 (13%) patients.

The FMD occurred after an injury in 11 (22%) patients. The injuries were mainly of soft tissues, but some patients experienced more serious injury leading to fracture. In 9 (18%) patients, FMD first started after an infection, most commonly a flu-like illness. In another 8 (16%) patients functional symptoms appeared following a neurological disorder (severe episode of migraine (n=3), brachial neuritis (n=1), Bell's palsy (n=1), carpal tunnel syndrome (n=1), restless legs syndrome (n=1) and after a pituitary haemorrhage (n=1)). In 4 (8%) patients, pain appeared to be an important factor at onset (either an episode of acute pain even though there was

no specific injury, or exacerbation of chronic pain). Three (6%) patients presented with functional symptoms after experiencing a drug reaction, two of them after an acute dystonic reaction secondary to dopamine receptor blockers used as antiemetic and one patient after jerks induced by fluoxetine. Three (6%) patients developed FMD after major surgery (tendon transfer operation, surgery to relieve cauda equina syndrome and a tensor fascia lata release). Finally, 2 (4%) patients developed FMD after an episode of vasovagal syncope. We sought associations between types of physical event and subsequent functional phenomenology but no clear relationship was found (Table 4.3).

Table 4.3. Number of patients with a particular physical precipitating factor for each type of functional movement disorder (n = 50)

	Operation	Physical injury	Drug reaction	Infection	Neurological disease	Vasovagal	Pain	None
Fixed dystonia	3	3	0	4	2	0	1	1
Tremor	0	1	0	1	2	1	2	1
Myoclonus	0	3	0	1	0	0	0	0
Mobile dystonia	0	0	2	0	0	0	0	0
Paroxysmal FMD with retained consciousness	0	0	0	0	0	1	1	0
Parkinsonism	0	0	0	0	1	0	0	0
Gait disturbance	0	0	0	1	0	0	0	0
Tics	0	1	0	0	0	0	0	0
Combination of ≥ 2 FMD	0	3	1	2	3	0	0	4

FMD = functional movement disorder

4.3.3   Case examples

4.3.3.1   Case 1

This 34-year-old gentleman was fit and well until February 2010 when he was at work and started to feel sick and light headed. He was diagnosed with a "sickness bug" and was prescribed prochlorperazine to be taken four times a day. By the following morning when he had taken four doses or so of the medication he noticed the beginning of abnormal movements. This started with twitching and tightening of the left arm so that it moved out at the shoulder. He continued to take the tablets, but the movement problems worsened and progressed to his legs stiffening and moving involuntarily as well as jerking of his head backwards. He remembers his throat and face feeling tight and he developed involuntary tongue protrusion. He went to the minor injury unit on the following morning but he was told to seek advice from his GP again in a few days. No advice was given to stop medication. He continued with the drugs and movement problems worsened. When he saw his GP, he was told he had had a medication reaction and was advised to stop taking the drug which he did right away.

His movements persisted and he again attended A &E where blood tests were taken. He recalled being asked whether he had taken any illicit drugs and he was given diazepam which decreased the severity of some of his movements.

About four weeks after the onset of symptoms he had the first episode of what later became regular attacks of abnormal movements. He developed spasms around the face and arms and severe gait disturbance. By this time, the original movement disorder had almost completely resolved. Attacks could last from 10

minutes to 2 hours. He retained consciousness throughout these attacks. He was admitted and various investigations were performed including imaging and an EEG and no abnormality was found. He was discharged still on treatment with Clonazepam. He continued to have attacks on most days. A few months later, he had his worst ever attack which occurred at work. He became unable to speak and also had a period of time lasting a couple of weeks where he was virtually unable to walk. During this time, he received psychological input but he did not feel that the emphasis on potential psychological triggering factors were of much relevance to him. Our formulation was that he had experienced some extrapyramidal side effects from prochlorperazine which had settled within days of the initial reaction but which had triggered a functional movement disorder'.

4.3.3.2   Case 2

This 59 year old lady who previously worked as a child-minder attended our Clinic. Ten years previously she had painful bunions on both feet and had an operation to help with this. Post operatively both feet became infected and for unclear reasons both legs below the knees were put in plaster for about 7 weeks. When the plaster was taken off she had a problem with going over on her ankles when she was walking. Because of this, she underwent a bilateral tendon transfer operation. The right leg improved, but on the left immediately post-operatively she developed a fixed abnormal posture of the foot which on examination had typical features of functional fixed dystonia.

4.3.4 Panic symptoms

Most patients reported physical symptoms of panic at the onset of the FMD, which were concurrent with the functional symptoms in the majority of them. Eighteen (38%) fulfilled criteria for panic attack. Of those, 10 (55%) had an onset of the functional symptoms in seconds/minutes and 7 (39%) had an onset in hours/day.

4.3.5 HADS

Twenty nine (58%) patients completed the HADS (Zigmond and Snaith, 1983). Mean score for depression was 11.8 ±4.6 and mean score for anxiety was 6.7 ±3.8.

4.3.6 Life events

Twenty eight (56%) patients filled the in LEQ (Norbeck, 1984). The mean negative score for life events within three months before symptom onset was 15.7±16.6 (maximum score 246). Figure 4.1 shows the characteristics of life events experienced among patients. 14% of the patients that completed the questionnaire did not report any life event, and 21% reported life events exclusively related to health issues.
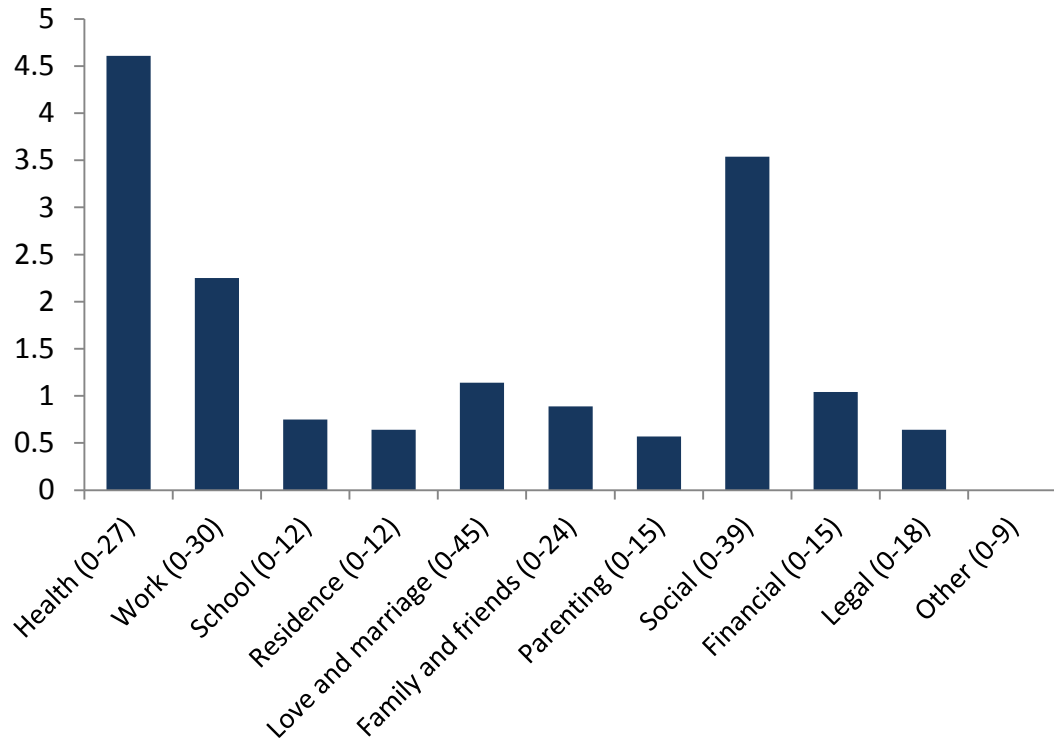
Figure 4.1. Mean negative events scores (in points) across the patients for each of the categories recorded in the Life Event Questionnaire. The range of possible points for each category is given along the name.

4.4 Discussion

In this case series, I assessed the presence of physical events preceding the onset of FMD in 50 consecutive patients. Eighty per cent of patients described a physical event temporally related to the onset of the FMD. Physical injuries were the most common precipitating event prior to the onset of the functional illness, as previously reported in the literature (Stone *et al.*, 2009). However, a range of other physical events including infections, drug reactions and episodes of acute or exacerbated chronic pain were commonly associated with onset of FMD. There were examples where the phenomenology of the functional symptoms was

plausibly related with the physical trigger. For example two patients who had a clear acute dystonic reaction secondary to drugs developed a functional dystonia which affected the same body parts as the original acute dystonic reaction. Also, most patients with fixed dystonia developed symptoms in the limb that was injured, where surgery had been performed or where neurological symptoms were present (e.g. from brachial neuritis or carpal tunnel syndrome). This is in line with other reports suggesting that the nature of the physical precipitating and the affected body parts during the physical illness may influence the subsequent functional symptom (Moss-Morris and Spence, 2006). For instance, a prospective study showed that during follow up, patients who had suffered from Campylobacter gastroenteritis had a greater risk for developing irritable bowel syndrome than those who had an infectious mononucleosis, whereas infectious mononucleosis patients had more significant risk to develop chronic fatigue (Moss-Morris and Spence, 2006). We may remember that this potential association was also noted by Breuer and Freud, for instance when they described the patient suffering from hysteric olfactory symptoms, who previously had had severe infections of the nasal cavity (Breuer and Freud, 1974).

Others have highlighted the occurrence and potential aetiological importance of physical events preceding onset of functional neurological symptoms for example physical injury to the limb which commonly precedes the onset of limb paralysis (Stone *et al.*, 2010).

As I have previously mentioned, in a review of the literature, it was suggested that physical events were more common in functional paralysis (41%) than in FMD (34%)

but physical events in these studies were limited to physical injuries. Our results suggest that a broader spectrum of physical events might be present at the onset of FMD.

We found that 38% of patients with FMD fulfilled criteria for the diagnosis of a panic attack during the physical triggering event, which is similar to that found in patients with functional paralysis (34% of 107) (Stone *et al.*, 2010). Similar to patients with functional paralysis, most patients who fulfilled criteria of a panic attack had an acute onset of the functional symptoms, suggesting a potential link.

Because of the uncontrolled design of our study we cannot conclude with confidence that the physical events reported were causal in the development of FMD. We only can conclude that most patients with FMD report a physical event before the onset of the functional symptoms, and this is often accompanied by physical symptoms of a panic attack. We hypothesise that physical events can be of relevance themselves in the development of functional symptoms by providing new sensory data which may be abnormally processed and could provide the substrate for the development of an abnormal movement. However, most people do not develop FMD after common physical events such as injuries or flu-like illness. Therefore, there should be other predisposing factors, perhaps at a cognitive level, which may influence the way initial sensory data is processed.

The presence of symptoms related to panic during the physical triggering event may play also a role. It may provide an additional factor that could increase the salience of the sensory information occurring during a coincident physical precipitating event or could generate additional physical symptoms in itself (e.g. tremor).

There is clearly still a role for past and recent life events in generating vulnerability in individual patients. In addition, no physical event can be experienced without a concomitant psychological experience. Our impression is that in many patients it is the physical triggering event itself which may be best thought of as the most important "recent stressor" related to the symptom, rather than hunting in the history for an emotional life event which reflects the general vulnerability of the patient.

In this regard, we assessed the presence of life events three months prior to the onset of the functional symptoms by using a self-report questionnaire (LEQ) (Norbeck, 1984), which addressed several categories. We found that patients scored low in the negative score for life events within three months before symptom onset (15.7±16.6), which is similar to the score reported by others, for instance in patients with colon polyps and normal controls (Ashktorab *et al.*, 2013). A sizable proportion of patients who reported life events mainly scored in the health-related subscore, which linked with the high proportion reporting a physical precipitating factor. This is in line with other studies of patients with FMD and other functional neurological symptoms where patients do not commonly report adverse life events (other than those associated with their physical health) close to onset of FMD (Binzer *et al.*, 1997, Kranick *et al.*, 2011). However, it should be noted that the retrospective assessment of life events is difficult especially with regard to recall bias. This, along with the low response rate that we obtained for the LEQ questionnaire, does not allow us to draw clear conclusions about the presence of potential psychological stressors.

I acknowledge a number of other methodological limitations. First, we did not include a control group and our result should be interpreted with caution in terms of causality. The ideal control population would have been "organic" movement disorder counterparts with a sudden onset. However, the vast majority of "organic" movement disorders start gradually and this made any attempt at comparison difficult. Second, there is the problem of recall bias. We cannot rule out that patients have over reported physical events and/or under reported life events at the onset of the FMD. In this regards, alexithymia has recently been found to be common in patients with functional motor symptoms (Demartini *et al.,* 2014). We cannot rule out that potential difficulties to identify emotions were also influencing the results of the LEQ.   Also, the retrospective design of the study has difficulties distinguishing a physical event and onset of functional symptoms. Third, because patients were recruited in a specialist centre, one can argue that the data may not be representative of all patients with FMD. However, I do not feel that the clinical histories of the patients we included significantly differ from case series of patients with FMD collected from less specialist services. In addition, recruitment was consecutive in order to minimize a selection bias. Fourth, the response rate for questionnaires was low, which makes it difficult to comment on more psychological aspects. Fifth, we set an arbitrary limit of 3 months for both physical events and life events to be included. A specific timing is not well established but we believe that with this selection, we have assured a reasonable temporal relationship.

In summary, physical triggering events are common in FMD and an appreciation of their role may help to move forward our understanding of the mechanism of FMD

beyond simplistic notions related to "psychological stressors" towards a more truly

biopsychosocial model of these common and disabling symptoms.

Chapter 5: A study on the "jumping to conclusions" bias in functional movement disorders

The work presented in this chapter was originally published in the form of a research article:

5.1   Introduction

In the previous chapter, we have seen that most patients with FMD report a physical event temporarily close to the onset of the functional symptoms which often are phenomenologically related. We suggested that they may be of relevance in symptom development by providing new sensory information which may be the substrate for the functional symptom in question. However, the physical events that we reported, particularly painful injury or flu-like illness, are almost universal occurrences that do not trigger functional symptoms in most people who experience them. Therefore, I wondered whether there should be differences in the manner in which patients process novel information and use it to guide future behaviour.

As a preliminary exploration of this question I assessed a well-known cognitive reasoning model in psychiatric research, the "jumping-to-conclusions" (JTC) bias. For that, I used the "bead task" (Garety *et al.*, 1991). In this paradigm, participants assess (within a Bayesian reasoning framework) the probabilities of events on the

basis of empirical evidence. Deluded patients have been found to exhibit a tendency to the early acceptance of hypotheses formed in this task based on much more limited evidence than controls. This style of reasoning has been suggested to favour the formation of abnormal inferences, ultimately leading to the adoption of abnormal beliefs (Fine *et al.*, 2007). In this study, we hypothesised that similar reasoning abnormalities might be present in patients with FMD which would favour formation of abnormal inferences about the sensory data arising during the physical event and could contribute to the development of functional symptoms.

5.2   Methods

5.2.1   Participants

Eighteen patients with FMD were recruited by two methods:

1. They were recruited from a pre-existing database of patients with movement disorders who had previously given the consent for their medical data to be stored in the ION Queen Square (Movement disorders Research Database) and to be contacted regarding participation in research studies by doctors authorised by Professor Bhatia or Dr Mark Edwards. These patients were contacted by telephone and the specific study was discussed with them. If the patient expressed interest in participating, a formal letter with a full description of the study and stating the date and location of the experiment was sent.

2. Patients were directly recruited from the General Movement Disorder clinic of Dr Mark Edwards or Professor Kailash Bhatia as well as from the specialised Functional Movement Disorder run by Dr Edwards, at the NHNN

Queen Square, London, UK. The specific study was personally explained in detail and if the patient expressed interest in participating, a formal letter with a full description of the study and stating the date and location of the experiment was sent.

I used as inclusion criteria:

1. Age over 18 years.

2. Diagnosis of clinically established or documented functional movement disorders according to Fahn and Williams criteria (Fahn and Williams, 1988).

I used as exclusion criteria:

1. Age less than 18.

2. Unable to communicate with researcher (e.g. does not speak English).

Eighteen healthy subjects who were matched by age and gender were also recruited from a departmental register of volunteers and patient's relatives.

5.2.2   Design and measures

5.2.2.1 Bead task

The reasoning task was similar to previous designs (Garety *et al.*, 1991). Participants were presented with two jars each containing 100 beads: Jar A with 85 red and 15 blue beads and Jar B with 85 blue and 15 red beads. Both jars were then hidden from view. Participants were told that the experimenter would choose one jar and draw beads one at a time from this jar. Beads would be replaced in the jar after each draw.

Two conditions were performed in the same order in each participant. In condition 1 (Figure 5.1), "draws to decision" methodology was employed. Here, participants requested as many beads as they deemed necessary to decide from which jar the beads were being drawn. Beads (red: R; blue: B) were presented in the following sequence: RRRBRRRRRBBRRRRRRRRB. After each draw, participants were asked if they were certain which jar had been chosen. Participants were told that they were allowed as many trials as they needed to be completely sure. The dependent variable was the number of draws taken to reach a decision (draws to decision). We classified as "extreme responding" participants who required two or fewer draws before making a decision (Garety *et al.*, 1991).
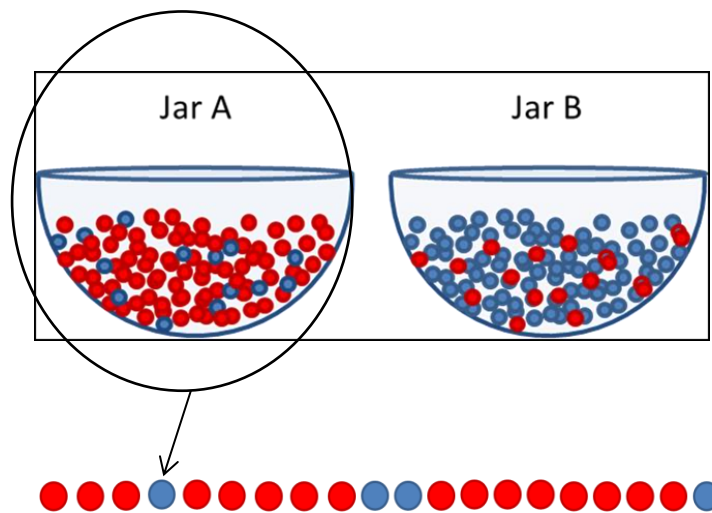
Figire 5.1. Schematic representation of the jars and the sequence used to drawn the beads in condition 1.

In condition 2 (Figure 5.2), "draws to certainty" methodology was used to assess the response to confirmatory or contradictory evidence. All participants saw the same 20 beads sequence: RRRBRRRRRBRBBBBRBBBBBRB. After each draw, participants

were asked to indicate their estimates of the likelihood of Jar A or Jar B having been chosen by placing a mobile pointer along a scale. The first 10 trials supported the hypothesis that beads were being drawn from Jar A (predominantly red beads), but the final 10 beads were inconsistent with this hypothesis. In this condition the trial continued for 20 draws for all participants. The dependent variables were: 1) effect of confirmatory evidence: the estimate given after the second bead (red) was drawn minus the estimate given after first bead (red) was drawn; 2) effect of disconfirmatory evidence: the estimate given after the third bead (red) was drawn minus the estimate given after fourth bead (blue) was drawn (positive values indicate reduction in confidence); and 3) final decision after the last draw with respect to the probability that Jar A had been chosen.
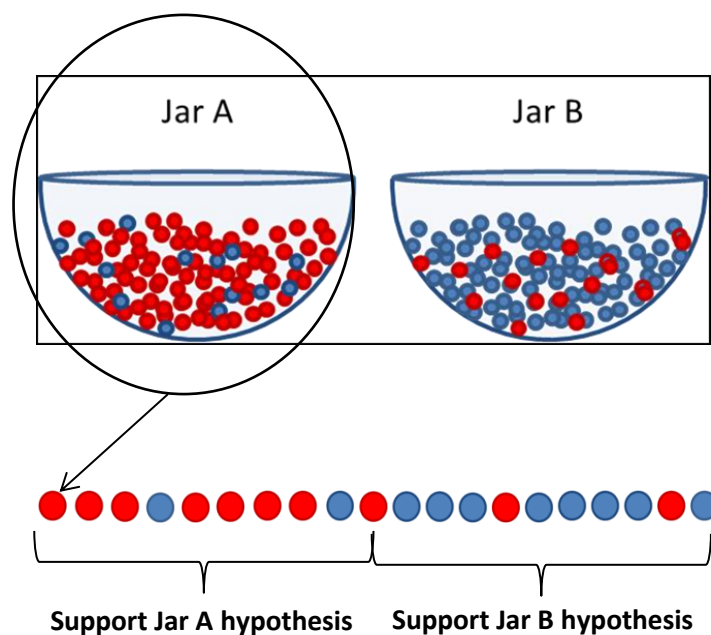
Figre 5.2. Schematic representation of the jars and the sequence used to drawn beads in condition 2.

5.2.2.2 Questionnaires

5.2.2.2.1 Intelligence level

To estimate the intelligence level of participants, we used the 12 items short form of Raven's Progressive Matrices test (Raven JC, 1977). This is a classic test of abstract or non-verbal reasoning in which a variety of figures, relationships and transformations are presented and the person must select the best of multiple choice alternatives to fill the empty corner (Figure 5.3).
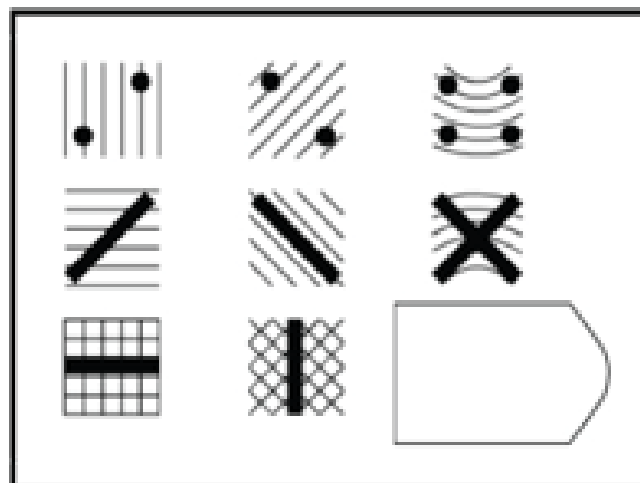
Figure 5.3. Example of one of the items used in the short version of the Raven's Progressive Matrices.

I used this test because many of the participants of this study were non-native English speakers and therefore we thought that a test avoiding verbal intelligence would be more appropriate.

5.2.2.2.2 Delusional ideation

Delusional patients have been found to have the "jumping to conclusion" bias and therefore delusional ideation was assessed in our participants. We used the Peters et al. Delusions Inventory (PDI-21) which has been designed to assess delusional ideation in general population (Peters *et al.*, 2004). It includes 21 questions asking whether or not the participant has a particular idea, incorporating measures of the distress, preoccupation and conviction associated with delusional beliefs. For each question participants answer yes/no and 1 point is assigned to each "yes" answer and a 0 to each "no" answer. Therefore, the possible range of scores was 0 to 21. The distress, preoccupation, and conviction ratings ranged from 0 to 5 for each item. A "no" answer automatically scored 0 on each of the three dimensions. A rating between 1 and 5 was obtained if the item had been answered "yes". Total score of the questionnaire range from 0 to 336. Higher scores indicate higher delusional ideation.

5.2.2.2.3 Mood

Some authors have suggested that mood disturbances may influence results in this cognitive task (Garety *et al.*, 2005). Therefore participants completed the Hospital Anxiety and Depression rating scale (HADS) (Zigmond and Snaith, 1983) with reference to their mood the week prior to testing, which has been already explained in the previous chapter.

5.2.3   Statistical analyses

I used PASW statistical package (version 18) for statistical analysis. P values reported for categorical variables were calculated with the use of Fisher's Exact

Test. Mann-Whitney U test was used to compare differences for numerical variables between groups. In order to determine the independent contribution of Raven's matrices scores, delusional ideation, and anxiety and depression subscales of the HADS to bead task performance, a simple linear regression analysis was first performed. Those variables which were contributing factors to the results of the task in this analysis were entered en bloc as independent variables in a subsequent multiple linear regression analysis. A two-tailed α level of 0.05 was used as the criterion for significance in all analyses.

5.3   Results

Baseline clinical and demographic features of the participants are given in Table 5.1.

Table 5.1. Clinical and demographic characteristics of patients in the bead task

	FMD (n=18)	*Controls (n=18)*	*P-value*
Age (years)			
Mean ± SD	43.5 ± 12	48.2 ± 14	0.33
Female / Male	12 / 6	10 / 8	0.73
Disease duration (years)			
Mean ± SD	5.4 ± 4.5	–	–
Type of FMD, n (%)			
Tremor	12 (67)	–	–
Dystonia	5 (28)	–	–
Myoclonus	1 (5)	–	–
Treatment, n (%)			
SSRIs	4 (22)	–	–
Benzodiazepines	2 (11)	–	–
None	12 (67)	–	–
Raven's Matrices score			
Mean ± SD	7.6 ± 2.3	8.7 ± 2.7	0.13
PDI-21 total score			
Mean ± SD	35.7 ± 32.9	18.9 ± 21.2	0.34
HADS score, mean ± SD			
Anxiety subscale	11.0 ± 3.9	5.6 ± 3.4	0.001
Depression subscale	9.2 ± 4.2	3.0 ±1.8	< 0.001
Total	20.2 ± 7.3	8.1 ± 4.2	< 0.001

FMD = functional movement disorder; SD = standard deviation

In condition 1, a significant difference between groups was found for draws to decision: patients requested significantly fewer draws before making a decision than controls (U=33.50, z=-4.21, p<0.001) (Figure 5.4 and Table 5.2). Seven patients (40%) but no control participants met criteria for "extreme responding".

In condition 2 (Table 5.2), a significant difference between groups was found when confronted with potentially disconfirmatory evidence: patients had significantly greater reduction in confidence, whereas controls were more likely to make no change or to continue to affirm their initial hypothesis by increasing their degree of certainty (U=94.5, z=-2.28, p=0.02). There were no significant differences between groups regarding the effect of confirmatory evidence. Ten patients and only three controls chose Jar B as their final decision (p=0.03).
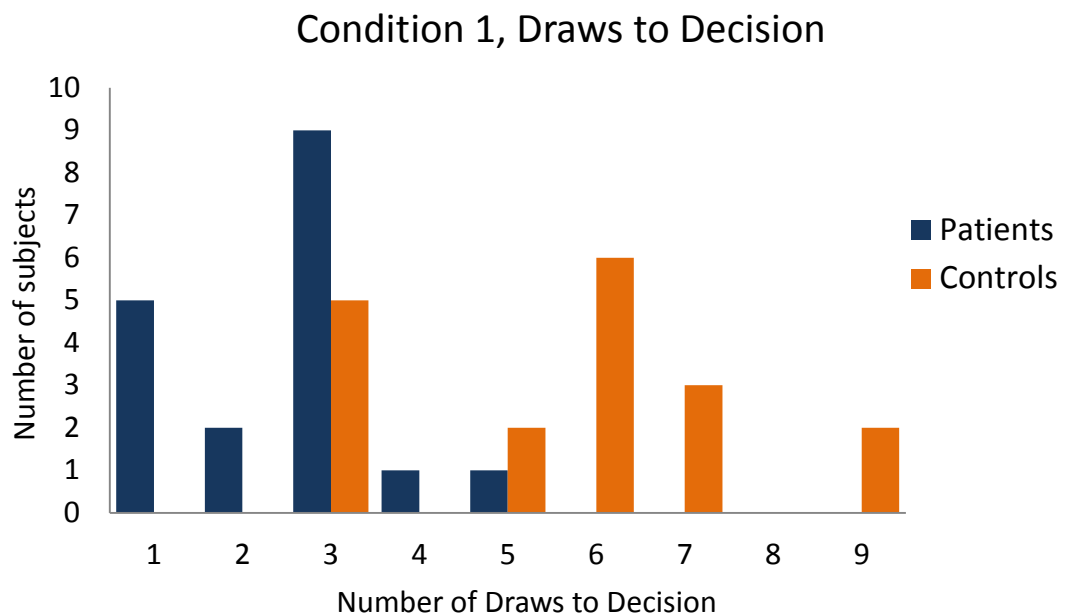
Figure 5.4. Results of functional patients and healthy controls in condition 1 of the bead task.

Table 5.2. Results in condition 1 and condition 2 of the bead task

	FMD (n=18)	*Controls (n=18)*	*P value*
Draws to decision			
Mean ± SD	2.5 ± 1.2	5.56 ± 2.0	< 0.001
Effect of confirmatory evidence [*]			
Mean ± SD	0.5 ± 15.4	5.5 ± 2.2	0.32
Effect of disconfirmatory evidence [†]			
Mean ± SD	4.8 ± 33.2	-2.6 ± 5.4	0.02
Final decision (Jar B chosen)			
n (%)	10 (56)	3 (17)	0.03

*Effect of confirmatory evidence: the estimate given after the second bead (red) was drawn minus the estimate given after first bead (red) was drawn; positive values indicate an increase in confidence.

†Effect of disconfirmatory evidence: the estimate given after the third bead (red) was drawn minus the estimate given after fourth bead (blue) was drawn; positive values indicate a reduction in confidence.

FMD = functional movement disorder; HADS = Hospital Anxiety and Depression Scale; SD = Standard Deviation; SSRIs = selective serotonin reuptake inhibitors.

There were no significant differences between groups in Raven's matrices scores (U=87.0, z=-1.50, p=0.13) or PDI-21 scores (U=74.0, z=-0.79, p=0.43) (see Table 5.1). Patients scored significantly higher than controls on anxiety and depression subscales of the HADS (U=52.5, z=-3.47, p<0.001; U=30.0, z=-4.2, p<0.001; respectively). We assessed whether Raven's matrices, PDI-21, anxiety and depression scores were individual predictors of the reasoning performance. In the simple linear regression analysis, only anxiety and depression scores were contributing factors to draws to decision (R^2=0.22, p=0.004; R^2=0.27, p=0.001; respectively). Since anxiety and depression scores were significantly higher in patients than in controls, we

investigated in more detail whether belonging to one group or the other was a potential confounder factor. When both anxiety and depression scores were considered in a multiple linear regression analysis and their contribution was adjusted in a second step by group as a possible confounder neither anxiety nor depression scores were predictive factors to draws to decision (β= −0.06, p=0.73; β= −0.036, p=0.87; respectively).

5.4   Discussion

In this study we assessed probabilistic reasoning in patients with FMD using the bead task, a classic paradigm in psychiatry research for the study of belief formation under conditions of uncertainty (Garety *et al.*, 1991, Fine *et al.*, 2007). We found differences in probabilistic reasoning between patients with FMD and healthy participants. First, patients required less evidence before making a definite decision on the task. Second, patients integrated new, potentially discomfirmatory evidence into their decision making differently than controls. They were more likely to make changes in their probability estimates in the direction suggested by the new evidence, and to make a final decision consistent with this new evidence. Both aspects of the bead task are conceptually related to frontal lobe functions such as set shifting and impulsivity, and similar abnormalities have been found in delusional patients. These data appear not to be influenced by the higher levels of depression and anxiety found in the patient group.

How might these preliminary data help to inform our understanding of the underlying mechanism of symptom production in FMD? This experiment was prompted by the association between physical triggering events and the production

of phenomenologically related symptoms in patients with functional neurological disorders. The process of making inferences on the causes of sensory data and incorporating these into an internal model of the world is central to a modern Bayesian approach to understanding the brain (Friston, 2010). Impulsivity in decision-making may reflect an abnormal overweighting of the importance of sensory data which causes an inappropriate updating of internal models relating to the data. Extrapolating such a reasoning style to sensory data occurring during a physical triggering event, this might produce inappropriate updating of expectations regarding future sensory data, for example an expectation of pain, abnormal movement or weakness, which might drive future physical symptoms. This initial formulation, although speculative, could form the basis of a testable biopsychosocial framework for FMD.

Patients were more likely to respond to potentially disconfirmatory evidence by changing their probability decision in the direction of the new evidence, seemingly at odds with the fixity with which illness beliefs are sustained by this patients group. Indeed, a similar question has been raised by those studying delusions. Here the suggestion has been, supported by experimental evidence, that over time beliefs shift from a more flexible "goal-directed" ventral corticostriatal system to a more inflexible "habit-related" dorsal striatal system (Corlett *et al.*, 2010). If this is also relevant to functional disorders, then the period of time following the initial triggering event must be important in creating persistence and fixity of abnormal beliefs. This would be consistent with the, negative correlation between time to diagnosis and chance of recovery previously found in functional disorders (Wyllie *et al.*, 1990) and the fact that, at least in the early stages, simply explaining the

diagnosis can lead to long-term resolution of symptoms (Hall-Patch *et al.*, 2010). In contrast, fixity of illness belief is associated with poor long-term outcome (Buchanan and Snars, 1993). Though we highlight the similarity of performance of patients with FMD on this task and previous studies of patients with delusions, the lack of difference between FMD patients and controls in the PDI-21 inventory indicates that patients with FMD are not suffering generally from delusional beliefs.

Limitations

We acknowledge limitations to our study. First, the sample size is small and we cannot exclude that in a larger cohort data may be different. However, we chose patients with clinically typical FMD using standardized criteria and feel that they do accurately represent patients with these diagnoses. Second, FMD patients tend to have concomitant mood abnormalities as measured by HADS. However, multiple regression analysis revealed that anxiety and depression scores were not independent predictors of the draws to decision. This is in line with several reports which have failed to find an, association between performance on the bead task and mood disturbance. Future studies could nevertheless compare the cognitive style of FMD patients with depressed and anxious patients without FMD. Third, while we have controlled for the presence of delusions in general, we have not measured other psychiatric comorbidities such as personality disorder that could be confounding the results.

In conclusion, we present preliminary evidence of a "'jumping to conclusions" style of cognitive reasoning in patients with FMD. These data may have relevance to the manner with which patients with functional symptoms process novel sensory data

occurring during physical triggering events commonly reported at onset of symptoms.

Chapter 6: A study on the effect of explicit strategies and predictability on motor control in functional movement disorders

The work presented in this chapter was originally published in the form of a research article:

Pareés I, Kassavetis P, Saifee TA, Sadnicka A, Davare M, Bhatia KP, Rothwell JC, Bestmann S, Edwards MJ. Failure of explicit movement control in patients with functional motor symptoms. Movement Disorders 2013; 28: 517-23.

6.1   Introduction

I emphasized in Chapter 3 that one of the aims of this thesis is to better understand mechanism of symptom production and that I have taken as the starting point the manner in which the diagnosis of FMD is made in neurological practice.

In this regard, the clinical basis for making a positive diagnosis in this group of patients is quite clear: movement becomes normal when attention is diverted away from the movement, or when movement is triggered covertly. This typically occurs during implicit motor control which is engaged in 'automatic' movements where attentional processes have limited contribution. In contrast, motor impairments are manifest only during periods of explicit attention to movement. Therefore, it would seem a priori that an understanding of the mechanism underlying these robust clinical phenomena would be essential to explain symptom generation in patients with FMD. However, these apparently simple clinical tests are in fact complex tasks when viewed from an experimental perspective, and at the present time it is not

clear which aspects of movement control might be important in generating impairment.

Taking all these considerations into account, I decided to investigate the distinction between implicit and explicit motor control in patients with FMD. Two different experiments were designed in which voluntary movements were made either with an opportunity for explicit awareness/control, or were performed in a largely implicit fashion. We hypothesized that, even within the same limb, implicit influences on movement would be preserved whereas explicit control would be abnormal in patients with FMD.

6.2 Methods

6.2.1 Participants

Eleven patients were directly recruited from the General Movement Disorder clinic of Dr Mark Edwards or Professor Kailash Bhatia as well as from the specialised Functional Movement Disorder run by Dr Edwards, at the NHNN Queen Square, London, UK. The specific study was personally explained in detail and if the patient expressed interest in participating, a formal letter with a full description of the study and stating the date and location of the experiment was sent.

I used as inclusion criteria:

1. Age over 18 years.

2. Diagnosis of clinically established or documented FMD according to Fahn and Williams criteria (Fahn and Williams, 1988).

I used as exclusion criteria:

1. Age less than 18.

2. Unable to communicate with researcher (e.g. does not speak English).

The control group consisted of 11 healthy participants matched with respect to gender, age, and handedness.

Demographic and clinical details, including HADs (Zigmond and Snaith, 1983), are shown in Table 6.1.

Table 6.1. Baseline characteristics of patients with functional movement disorders in experiments 1 and 2 of the motor learning tasks

Patient	Gender	Age (y)	Handedness	Diagnosis	DD (y)	HADs	OB	ROT	Pre-cued task
1	F	43	R	Tremor (R hand)	4	22	+	+	+
2	F	30	R	Tremor (R hand)	1	13	+	+	+
3	M	39	R	Tremor (R hand)	18	19	+	+	+
4	F	61	R	Tremor (R hand)	4	29	+	+	+
5	M	52	L	Tremor (L hand)	9	12	+	+	+
6	F	26	R	Paroxysmal ballism (arms)	4	8	+	+	+
7	M	41	R	Tremor (R hand)	3	27	+	+	+
8	F	50	R	Tremor (R hand)	1	20	+	+	+
9	F	18	R	Dystonia (generalized)	1	24	+	+	+
10	M	64	R	Tremor (R hand)	12	27	+	+	
11	M	42	R	Tremor (R hand)	5	20			+

F = female; M = male; R = right; L = left; DD = disease duration; HADs = Hospital Anxiety and Depression Scale total score; OB = one-back reaching task; ROT = rotation learning task. + = participation in the experiment

6.2.2 Experimental Procedure

6.2.2.1 Experiment 1: one-back reaching and rotation learning tasks

Participants sat in front of a 17 inch computer monitor (refresh rate 50Hz, distance from subject to screen 45cm). A joystick was placed in front of them. The monitor displayed eight targets arranged in a circle with a radius of 13cm at intervals of 45°. A similar square target marked the centre of the circle, and a small yellow circular cursor indicated the joystick position. The experiment was programmed within MatLab version 7.0.1 with the Cogent Toolbox (http://www.vislab.ucl.ac.uk /cogent.php).

In the baseline condition, 4 blocks of 40 trials were presented. At the start of each trial, the target to be aimed for turned red, and participants were instructed to move the joystick so that the yellow cursor was inside the target square (Figure 6.1). Once the cursor was kept within the target square for 1 second, the target changed colour from red to green, and participants were instructed to move the joystick back to the centre square to start the next trial. Targets were always visible and presented in a random pattern in each block. Participants were instructed to move to the target as quickly as possible. Temporal and spatial variables used to characterize task performance were reaction time (RT: time in ms from target presentation to movement onset), movement time (MT: time in ms from movement onset to stabilisation of the cursor in the target), and displacement ratio (DR: ratio between the length –measured in pixels– of a straight line "perfect path" between the starting point and the target, and the length of the actual path taken by the participant, with higher values of DR indicating increasing deviation from the

perfect path). Participants then performed in a randomised order a one-back reaching task (OB), or a rotation learning task (ROT).
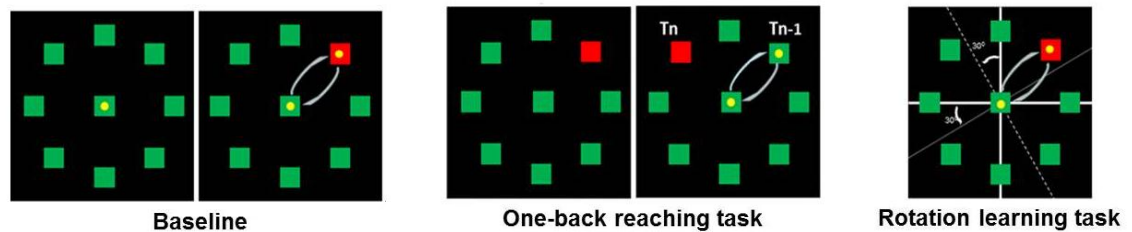
Figire 6.1. Schematic representation of the three conditions of experiment 1.

In the OB task, explicit motor control was tested (Mazzoni and Wexler, 2009). Participants were instructed to move the cursor to the target displayed in the previous trial (Figure 6.1). One block of 40 trials was performed. Targets were presented in a random pattern during the block. Improvement in motor performance during the task was defined as the ratio of each of the temporal and spatial variables in the first ten trials and the last ten trials. A ratio of < 1 for RT, MT and DR variables indicated improvement. Target selection errors, the number of which would reflect working memory performance required to perform the task (Mazzoni and Wexler, 2009), was monitored by using directional error. This was defined as the difference (in degrees) between the cursor direction and the target direction at peak velocity. Based on previous research, we set the size of the range outside of which directional error was assumed to represent incorrect target selection as ±6times the standard deviation of the directional error in the baseline condition (Mazzoni and Wexler, 2009).

In the ROT task, implicit motor control was tested (Mazzoni and Wexler, 2009). This task measured the ability of participants to adapt to a visuomotor perturbation. A constant 30° anticlockwise rotation was introduced into the path of the cursor displayed on the screen (Figure 6.1). Targets were displayed in a randomised order, and participants had to move the cursor to the highlighted target as quickly as possible. Participants were not instructed how to compensate for the rotation. Improvement would be indicated by a ratio in the first ten trials and the last ten trials of < 1 for RT, MT and DR.

6.2.2.2 Experiment 2: pre-cued choice reaction time with varying cue validity

In this experiment we manipulated the predictability of an upcoming movement (Bestmann *et al.*, 2008). Participants sat in front of a 17 inch computer monitor (refresh rate 50Hz, distance from subject to screen 45cm). A standard QWERTY computer keyboard was placed in front of them. Their left index finger was placed over the "Z" key and the right index finger was placed over the "M" key.

In a training session, participants were required to respond with one or other key to the presentation of two different symbols. They were told that "Z" was associated with one symbol, and "M" with the other. Feedback was given on the accuracy of their choice, and 40 trials were conducted. This ensured accurate response mapping of keypress to symbol, with all subjects achieving a 100% correct response level by the end of training.

There were three experimental conditions each performed twice in a randomised order across participants. Each trial started with a fixation cross in the centre of the

screen, followed 450ms later by presentation of the preparation cue for 200ms: one of the two symbols seen in the practice session coloured white. The fixation cross was then displayed for a fixed delay period of 1500ms. Finally, the "go" cue was displayed, which was one of the two symbols from the practice session coloured green (Figure 6.2). Participants were instructed to press the key corresponding to the go cue as quickly as possible. Each condition consisted of 80 trials. No feedback was given.
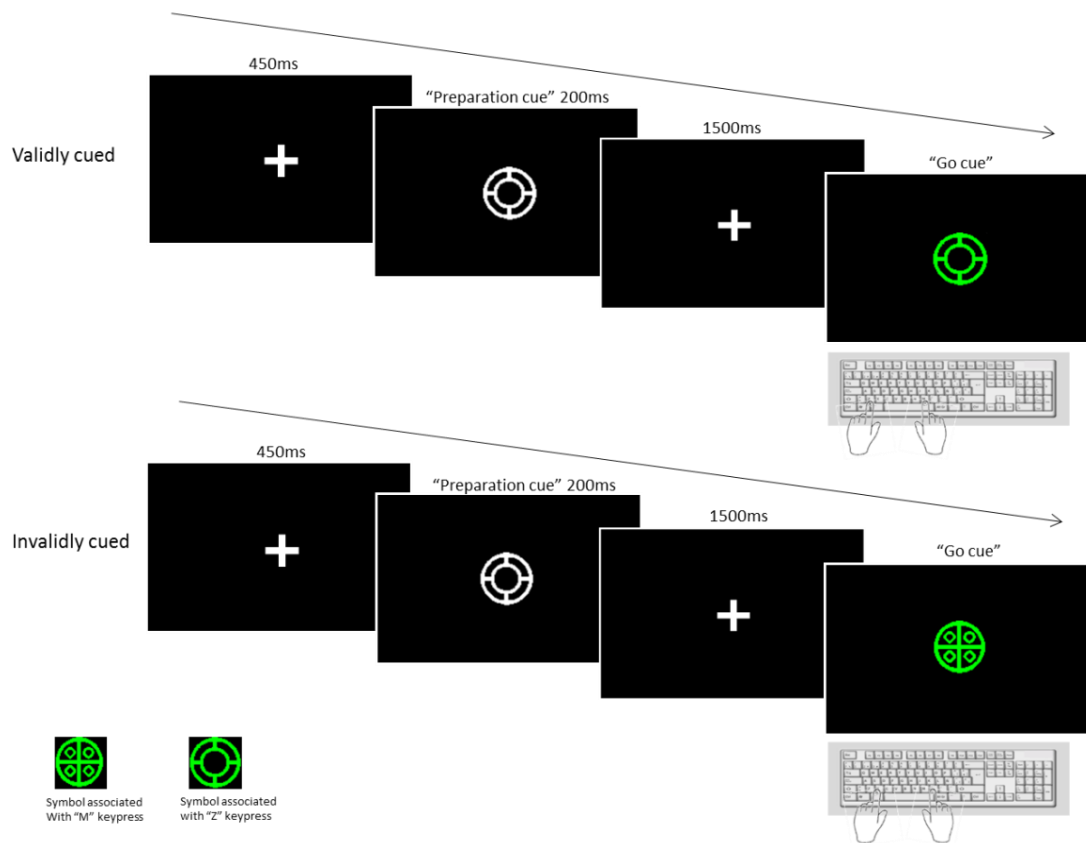
Figure 6.2. Schematic representation of experiment 2 (Pre-cued Choice Reaction Time with Varying Cue Validity).

In the 50% validity condition (50v), the preparation cue accurately predicted the "go" cue in 50% of trials, i.e. it had no predictive value. In the 75% validity (75v) and the 95% validity (95v) conditions, the preparation cue accurately predicted the "go" cue in 75% and 95% of trials, respectively.

We calculated response time in ms (time from presentation of the "go" cue to key press) for each trial. Trials where the preparation cue accurately predicted the "go" cue (valid trials) were separated from those where the prediction was incorrect (invalid trials). We then averaged response times for valid and invalid trials separately across all trials performed for each of the three conditions. We expected that response times for valid trials would become shorter for conditions with increasing validity of the preparation cue.

6.2.3 Statistical analysis

We used the PASW statistical package (version 18). P values for categorical variables were calculated with Fisher's Exact T. Kolmogorov-Smirnov test was used to assess the normal distribution of the data. Analysis of variance (ANOVA) was used to compare differences in means for numerical data when parametric assumptions were met. Post-hoc T-tests with Bonferroni corrections were used. When data were not normally distributed, non-parametric tests (Mann-Whitney U test, Friedman ANOVA, Wilcoxon test and Spearman correlation) were used. Statistical significance of $p < 0.05$ was assumed.

6.3   Results

6.3.1   Experiment 1: one-back reaching and rotation learning tasks

Ten patients and ten healthy controls participated. All patients performed the experiments with the affected (dominant) hand except for one patient who was unable to adequately control the joystick because of the severity of the tremor affecting the dominant hand. The results of this patient did not differ systematically from the others. All controls used their dominant hand. Exploration of the data revealed them to be not normally distributed, and therefore non-parametric tests were used.

6.3.1.1   Baseline Performance

Patients with FMD had a significant change over the four blocks of the baseline condition in MT ($\chi2$ (3)=17.16, p<0.001) and in DR ($\chi2$ (3)=18.84, p<0.001). Post hoc analysis using Wilcoxon tests showed improvement in performance from Block 1 to Block 4 for MT (median Block 1=1695.5ms, median Block 4=1363.7ms; Z= -2.8, p=0.002) and for DR (median Block 1=5.45, median Block 4=4.57; Z= -2.8, p=0.002). There was no difference in these parameters between Block 3 and 4, indicating a ceiling effect in baseline motor performance. In the control group, there was a trend for improvement in performance across the 4 blocks. Comparison of temporal and spatial variables in Block 4 of the baseline condition between patients and control participants revealed that there was no difference in RT between groups (323.9ms vs 286.5ms; U=24.0, Z= -1.07, p=0.32) but the patients were slower in MT (1363.7ms vs 1036.3ms; U=24.0, Z= -2.34, p=0.02) and had poorer accuracy measured as DR (4.57 vs 3.48; U=8.0, Z= -2.64, p=0.003).

6.3.1.1.1 One-Back Reaching

Patients and control participants differed in performance in the OB condition. Both patients and controls had a similar improvement in RT and DR between the first and the last ten trials (U=32.0, Z= -1.36, p=0.18 and U=39.0, Z= -0.83, p=0.42, respectively). However, while MT also improved in control participants, it did not in patients and a ratio of MT in first ten and last ten trials was greater than 1, indicating a deterioration in performance over the course of the block (U=38.0, Z= -2.19, p=0.03). Results of ratios are shown in Table 6.2 and illustrated in Figure 6.3. There was no difference between number of target selection errors seen in patients and control participants (U=29.5, Z= -1.64, p=0.12).

6.3.1.1.2 Rotation Learning

In the ROT condition both groups improved their performance across the block when comparing the results of the temporal and spatial variables in the first 10 and last 10 trials: RT ($\chi2$ (1) =5.0, p=0.041); MT ($\chi2$ (1)=7.2, p=0.012) and DR ($\chi2$ (1)=9.8, p=0.003). The amount of improvement in each variable, measured as the ratio of the first 10 and last 10 trials, did not differ between groups. Results of ratios are shown in Table 6.2 and illustrated in Figure 6.3.

Spearman correlation coefficient revealed no association between HADs scores and target selection errors or temporal or spatial variables in patients or healthy controls in either task.

Table 6.2. One-Back Reaching and Rotation Learning Tasks Results

	Patients with FMD	Healthy controls	P value
OB (explicit motor control); ratio (median)			
Reaction time	0.96	0.81	0.18
Movement time	1.10	0.78	0.03
Displacement ratio	0.95	0.90	0.42
ROT (implicit motor control); ratio (median)			
Reaction time	0.87	0.91	0.39
Movement time	0.91	0.82	0.32
Displacement ratio	0.84	0.77	0.28

FMD = Functional movement disorder
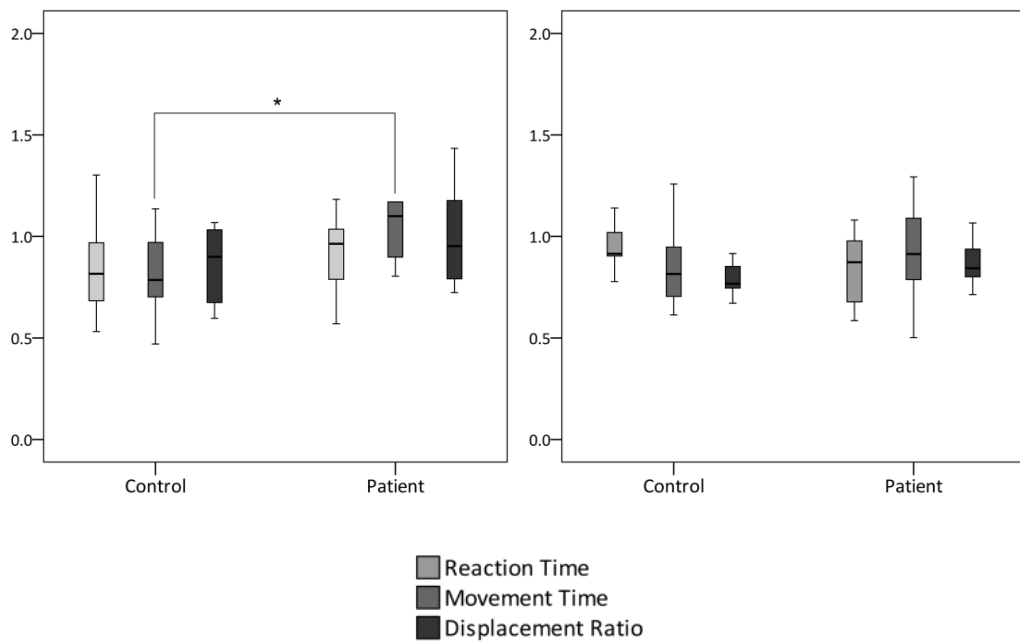
Figure 6.3. Results of Experiment 1. Boxplot presenting ratios between the first ten trials and the last ten trials of the temporal and spatial variables for patients with functional movement disorders and controls (A: One-back Reaching task and B: Rotation learning task). Improvement in motor control is indicated by a ratio <1. Thick black lines represent medians. Box edges represent the upper and lower quartiles. The whiskers represent the minimum and maximum values.*p<0.05

6.3.2 Experiment 2: pre-cued choice reaction time with variable cue validity

Ten patients and ten healthy controls participated in this experiment. We first performed an ANOVA with PROBABILITY (0.5, 0.75, 0.95) and VALIDITY (Valid/Invalid cue) as main factors, and with GROUP (Patients, Controls) as a between subjects factor. This revealed a PROBABILITY x VALIDITY x GROUP interaction ($F_{(2,17)}=12.2$; $p=0.001$). We explored this interaction with separate ANOVAs on the data in each of the three conditions (50v, 75v, 95v) with VALIDITY (valid cue, invalid cue) as main factor and GROUP (patients, controls) as a between subjects factor. In the 50v condition, there was no effect of validity ($p=0.39$), nor a Group x Validity interaction ($p=0.36$). In the 75v condition there was an effect of validity ($F_{(1,18)}=32.7$; $p<0.0001$) due to faster response times to valid cues compared with invalid cues. There was, however, no GROUP x VALIDITY interaction ($p=0.14$). In the 95v condition, there was no effect of VALIDITY ($p=0.51$), but there was a GROUP x VALIDITY interaction ($F_{(1,18)}=18.8$; $p<0.0001$). Exploration of this effect with post-hoc tests with Bonferroni corrections revealed this to be due to a faster response time for valid cues compared with invalid cues in controls ($t=-4.5$; $p=0.001$), but slower response time for valid compared with invalid cues in patients ($t=2.2$; $p=0.05$) (response time ratios between valid and invalid cues for each validity condition are shown in Figure 6.4). There were no differences in the number of errors made (incorrect key presses) between patients and controls.
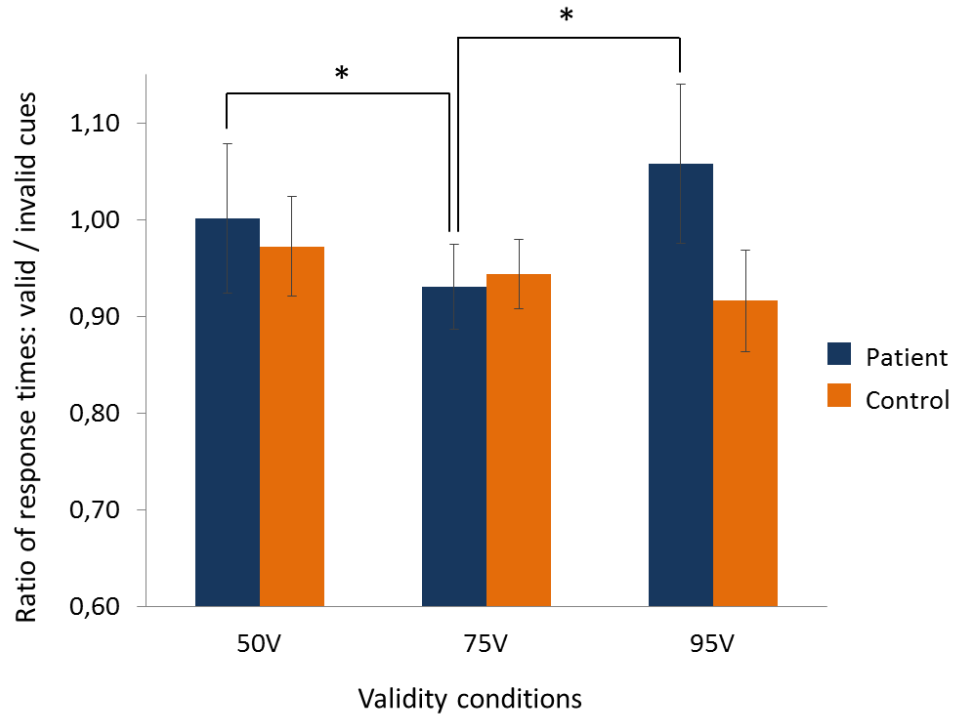
Figure 6.4. Results of experiment 2. Ratios of the response time (ms) for valid/invalid cues in each validity condition. Ratio < 1 indicates faster response time for valid cues compared with invalid cues. Ration >1 indicates slower response time for valid cues compared with invalid cues. *p<0.05

6.4 Discussion

These experiments aimed to dissect experimentally the basis of the clinical examination techniques used to make a positive diagnosis of FMD by examining how motor performance is affected when automaticity of movement changes. I found that performance in FMD was specifically impaired in situations where movements were highly predictable and there was opportunity for explicit control. In the OB task, which explores explicit movement control under conditions of maximal certainty about the movement required, performance of patients was impaired: although they had a similar improvement in RT and DR compared to controls, there was a clear deterioration in the execution of the movement

measured as MT over the course of the block. Patients did not make more errors in target selection compared with controls, suggesting poor performance was not due to problems in the working memory requirement of the task. In contrast, performance was similar to healthy subjects in the rotation learning task which tests implicit motor performance.

Likewise, when I manipulated the predictability of an upcoming movement by changing the validity of a pre-cue in a pre-cued reaction time task, patients had a paradoxical slowing of response times to valid cues when they were highly predictive of the movement required, despite normal performance in conditions where cues were non-predictive or 75% predictive.

I have therefore demonstrated that under conditions of increasing certainty regarding the movement to be performed, and crucially when the nature of the task is one where pre-planning of movement can occur, impairment is seen in patients. This is supported by previous work in functional paralysis where impaired reaction time was seen after pre-cuing by a consciously perceived "endogenous" cue, but a normal response to a non-consciously perceived "exogenous" cue (Roelofs *et al.*, 2003). The same group has reported increased N2 event-related potential amplitude during an explicitly-cued movement task, interpreted as reflecting enhanced "action monitoring" (Roelofs *et al.*, 2006).

My results fit within a body of research which has explored the effect of explicit strategies in motor control (Fourneret and Jeannerod, 1998). Healthy people do not pay much attention to many aspects of their actions and normal movement is associated with a remarkable lack of activity in brain areas that correspond to high-

level executive control (Jueptner *et al.*, 1997). During motor learning, prefrontal and anterior cingulate activity that is present early in the task disappears with increasing movement automaticity. If over-trained subjects are then asked to attend to their actions, prefrontal activity and anterior cingulate activity returns, and there is deterioration in performance (Jueptner *et al.*, 1997). Factors that have previously been reported to favour a shift to attentive manner of movement control include those associated with risk of development of functional symptoms, such as injury, physical illness, anxiety, depression and childhood trauma (Woody, 1996, Orrell *et al.*, 2009, Edwards and Rothwell, 2011).

I suggest that a shift from a normal procedural mode of movement to an attentive self-focused action monitoring mode may occur in patients with FMD, which could impair movement kinematics in a similar fashion to that reported in sportspeople "choking" under pressure (Beilock and Carr, 2001). Such a shift would only be possible during preparation for movement that was highly predictable and accessible to pre-planning. This would explain my data showing no impairment where movement parameters were likely governed by implicit processes or when movement was not highly predictable. This explanation would be consistent with resolution of functional motor symptoms when attention is distracted away revealing an intact procedural memory for movement.

I acknowledge several limitations to these studies. We have studied a small cohort of patients, and we cannot exclude that in a larger cohort data may be different. I have interpreted the findings with reference to ideas of explicit versus automatic (implicit) control of movement. These are well-researched topics within motor

control, but I also accept that they are not precisely defined. I have speculated that increasing predictability of a required movement allows opportunity for explicit control, but we are not able to measure it within this experimental framework, and therefore this remains a speculative interpretation. I did not compare patients with FMD and patients affected by "organic" movement disorders. It might be argued that they can also develop an abnormal awareness of movement which could specifically interfere with explicit motor control and with movements that are predictable. However, previous studies in patients with well recognized "organic" disorders such as Huntington's disease and PD have reported abnormalities in both explicit and implicit motor learning tasks (Ghilardi *et al.*, 2003, Siegert *et al.*, 2006, Wilkinson and Jahanshahi, 2007, Ghilardi *et al.*, 2008). Also, patients with PD have been found to show similar improvements in RT as healthy controls in the context of highly predictable events (Galea *et al.*, 2012). Patients did not make more errors in target selection compared with controls in the OB task, and I suggested that poor performance here was not due to impairments in working memory. However, formal assessment of working memory was not performed in these patients and we acknowledge this would have been appropriate. Finally, I did not compare our results with people feigning symptoms. However, previous work in volunteers feigning found them to be poor at moving "slightly" slow: movements were often performed with long delays (at least 500ms in duration) (Willison and Tombaugh, 2006, Reicker, 2008). In contrast, the impairments in movement and response times in our patients were small (of the order of 50-100ms), and in our view not likely to be consistent with malingered poor performance.

Conclusions

These data demonstrate that movement impairment in patients with FMD is restricted to tasks where the predictability of movement is high and is therefore accessible to pre-planning, and not where movement is unpredictable or where movement occurs in an implicit fashion. This suggests that a shift to a conscious attentive control of may play a relevant role in symptom generation.

Chapter 7: A study assessing functional motor symptoms in real life conditions using a wrist-worn actigraph

7.1   Introduction

In the previous chapter, I explored (in an experimental setting) the role of explicit strategies in motor control in FMD. I demonstrated that the motor impairment seen in these patients seems to be restricted to tasks where the movement is accessible to pre-planning, suggesting that a shift to a conscious attentive control of movement may play a relevant role in symptoms generation. This fits with the findings during the clinical examination that the symptom improves or even disappears when attention is diverted away from the symptom.

However, the reality reported by most patients in the clinic is different: they typically report abnormal movements to be present constantly often causing severe disability and affecting their day to day life.

In this chapter, I describe the results of a study aimed to assess FMD, outside of the clinic, in real life conditions. I decided to study patients with FT, as this is the most common FMD, is relatively distractible and patients usually describe it as very disabling. I took advantage of the ability to assess the duration and intensity of

tremor accurately, remotely and for long periods of time using a wrist-worn actigraph device (Van Someren *et al.*, 2006). In contrast to cumbersome devices used in the past for ambulatory tremor monitoring (Spieker *et al.*, 1997, Spieker *et al.*, 1998), this device is small and has been demonstrated to accurately differentiate tremor from other movements. We used this device in a cohort of patients with FT and patients with "organic" tremor (OrgT) in a natural setting over 5 days, and we compared these data with self-report of tremor duration over the same period and a standardised face-to-face clinical assessment of tremor severity.

7.2 Methods

7.2.1 Participants

I recruited 10 patients with FT from the Movement Disorder outpatient clinics run by Dr Edwards and Professor Bhatia at the NHNN, London, UK.

Inclusion criteria were:

1. Age over 18 years.

2. Diagnosis of clinically established or documented FT according to Fahn and Williams criteria (Fahn and Williams, 1988).

3. Tremor in at least one arm at rest, on posture or both of a moderate/severe level judged by a score of at least two on Part A of the Fahn-Tolosa-Marin (FTM) scale (Fahn S, 1988).

Exclusion criteria were:

1. Patients with any major concurrent neurological disorder

I also recruited eight patients with OrgT who served as a control group.

Inclusion criteria were:

1. Age over 18 years.

2. Presence of clinically typical tremor and course of illness for their diagnosis.

3. Moderate/severe tremor (at rest, on posture or both) in at least one arm judged by a score of at least two on Part A of the FTM scale (Fahn S, 1988).

Exclusion criteria:

1. Patients with marked clinical fluctuations in response to medication.

The purpose of the study was explicitly explained to the participants.

7.2.2 Questionnaires and scales

7.2.2.1 Fahn-Tolosa-Marin scale for tremor (FMT)

At the inclusion visit, tremor was rated using the FTM (Fahn S, 1988). This is a widely used clinical rating scale in which severity of tremor is rated by body part from 0 (none) to 4 (severe). It has three subscales: Part A assesses examiner-reported tremor location and severity. In part B examiner reports the ability of the patient to perform specific motor tasks (writing, drawing, and pouring with dominant and non-dominant hands). Finally, in part C patient reports functional disabilities due to tremor (speaking, eating, drinking, hygiene, dressing, writing, working, and social activities). Participants were videotaped during clinical assessment.

7.2.2.2 Handedness

Hand dominance was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). This is a ten-item questionnaire in which individuals have to self-report the preferred hand for carrying out common activities such as writing and drawing, throwing, and using utensils such as a toothbrush, knife, and spoon. Individuals have to place 1 or 2 check marks under "left" or "right" to specify the strength of preference for each activity (2 checks indicate the largest preference: the individual "would never try to use the other hand unless absolutely forced to"). A laterality measure can be calculated where a score of 100 indicates complete dextrality, and a score of −100 indicates complete sinistrals.

7.2.2.3 Quality of life

EuroQol ED-5Q was used to assess quality of life (Brooks R, 2003). It assesses five dimensions of functioning and quality of life (mobility, self-care, usual activities, pain and anxiety and depression). All dimensions are divided into three levels reflecting 'no problem', 'some problem' and extreme problem', with the focus of that dimension. EuroQoL ED-5Q also includes a 20 cm visual analogue scale as a means of valuing the participant's health state. The end-points of the scale are labelled 'best imaginable health state' and 'worse imaginable health state' anchored at 100 and 0, respectively. Participants were asked to indicate how they rate their own health state by drawing a line from an anchor box to that point on the scale which best represents their own health.

7.2.2.4 Post-study questionnaire

I designed a post-study questionnaire to assure that participants had understood the purpose of the study. Patients were retrospectively contacted by telephone and were asked two questions: a) "What do you think was the purpose of wearing the watch?" and b) "For how much of the time that you were wearing the watch do you think it was turned on?"

7.2.3 Tremor recording

I used Actiwatch (Cambridge Technology, Cambridge UK) to objectively motorize tremor. The Actiwatch contains a uniaxial accelerometer consisting of a small mass fixed to a piezoceramic bar. When the piezoceramic bar is distorted by acceleration, a current is induced that is proportional to acceleration. The device continuously samples the output of this internal accelerometer at 64Hz, with an 8-bit resolution covering -5 to +5G. The algorithm programmed in the Actiwatch has been validated to discriminate tremor from other movements with high sensitivity and specificity (Van Someren *et al.*, 2006). Continuous recording of duration and intensity of tremor for up to 22 days is possible. Optimal sensitivity is achieved for tremor of a frequency equal to or above 3 Hz. Tremor duration is reported by the Actiwatch software as seconds of tremor per minute of recording. Tremor intensity is reported as the highest amplitude of tremulous movement in each minute measured as counts (25 counts/second representing approximately an acceleration of 1G) (The Actiwatch User Manual, version 7.2; http:www.camntech.com).

Participants were instructed to wear the actigraph on the wrist of the most tremulous arm constantly for five consecutive days. They were instructed that the

actigraph should only be taken off when the hands were exposed to water (e.g. showering or swimming).

7.2.4 Diaries

I designed a self-completed diary for the participants to subjectively rate their tremor for the same days as the actigraph was worn. This had five sheets, each sheet covering one day. On each sheet participants were asked to record the time of waking up and going to bed, as well as any time that they spent without wearing the actigraph. For three pre-defined intervals per day (time from waking to 1:00 pm, from 1:00 pm to 7 pm, and time from 7:00 pm to bedtime) they were asked to mark the percentage of time they estimated themselves as having tremor on a visual analogue scale marked from 0 (no tremor) to 100 (tremor 100% of the time interval). I termed these 'intra-day interval estimations'. I also asked participants to estimate on average the proportion of the whole waking day that they had experienced tremor by using the same type of visual scale. I termed this the 'whole day period estimation'. Finally, I asked subjects to record whether they felt that the day had been typical for them in terms of the amount of tremor they experienced.

7.2.5 Data analysis and statistics

Duration of the waking day was defined as the time from waking up to bedtime minus the amount of time that each participant took the actigraph off in minutes. Duration of tremor was calculated as the total amount of seconds with tremor as measured by the actigraph during the waking day. The results were expressed both in minutes and as percentage of the duration of the waking day. To compare intra-day interval estimations reported in the daily diary with the results of the actigraph,

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I converted the amount of time with tremor measured by the actigraph to a percentage of each interval of time.

We used the PASW statistical package (version 18) and MedCalc (version 11.6) for statistical analysis. P values for categorical variables were calculated with the use of Fisher's Exact Test. T-Tests were used to compare differences in means for numerical data when parametric assumptions were met and Mann-Whitney U tests when data was not normally distributed. Statistical significance of $p<0.05$ was assumed. Bland-Altman analysis corrected for repeated measurements was used to assess the agreement between 'intra-day interval estimations' and tremor measured by actigraphy (Bland and Altman, 2007). Results are expressed as the mean bias (difference between tremor reported in diaries minus tremor recorded by actigraphy: positive values indicating overestimation in diaries, negative values indicating underestimation in diaries) and 95% confidence intervals. We plotted these against the geometric mean of the two measures (calculated by multiplying 'intra-day interval' estimations and results from the actigraphy and taking the nth root, where n was the number of values to average), giving me an opportunity to assess bias when diary and actigraphy scores were at different levels. Intra-day interval estimations not clearly reported were excluded from this analysis.

7.3   Results

7.3.1   Baseline characteristics

Eight patients with FT and 8 patients with OrgT completed the study. After initially agreeing to take part, two patients with FT decided not to complete the study. One reported severe pain in the affected arm meaning he could not wear the watch and

the other reported an allergic skin reaction due to the watch strap. In the OrgT group, five (62.5%) patients had PD, two (25%) had dystonic tremor and one (12.5%) had Wilson's disease.

Table 7.1 summarises the clinical and demographic data.

Table 7.1. Baseline characteristics of patients

	FT (n=8)	OrgT (n=8)	P value
Age (years)			
Mean (SD)	52.3 (12.1)	66.1 (14.1)	0.054
Sex, n (%)			
Male	4 (50)	6 (75)	0.61
Female	4 (50)	2 (25)	
Handedness, n (%)			
Right	6 (75)	7 (88)	1.0
Left	2 (25)	1 (12)	
Disease duration (years)			
Mean (SD)	10.7 (11.8)	7.6 (4.7)	0.92
Triggering event prior to onset of tremor			
Yes	6 (75)	0	0.007
No	2 (25)	8 (100)	
Fahn-Tolosa-Marin tremor scale, mean (SD)			
Subscale A	9.1 (3.7)	12.5 (7.8)	0.29
Subscale B	9.5 (6.0)	10.6 (4.8)	0.69
Subscale C	15.2 (4.4)	8.1 (5.4)	0.01
Total	34.0 (11.3)	31.1 (13.8)	0.66
EQ-5D (dimensions), n (%)*			
Mobility	8 (100)	3 (37.5)	0.03
Self-care	8 (100)	1 (12.5)	0.001
Usual activities	8 (100)	5 (62.5)	0.001
Pain	7 (88.5)	0	0.2
Anxiety/depression	6 (75)	2 (25)	0.13
EQ-5D visual analogue scale			
Mean (SD)	42.6 (22.0)	75.4 (8.0)	0.002
Treatment for tremor, n (%)			
No	6 (75)	2 (25)	0.13
Yes	2 (25)	6 (75)	
Active compensation/litigation	0	0	

SD = Standard deviation

The OrgT group was slightly older than the FT group (66.1yrs vs. 52.3yrs; p=0.0054), but they were matched on tremor severity as judged by the FTM scale. Two (25%) functional patients and six (75%) "organic" patients had tremor elsewhere apart from the arm wearing the actigraph. FT patients rated their quality of life as significantly more impaired than OrgT patients. Two (25%) functional patients were receiving treatment for tremor at the time of the study (propranolol in both cases) whereas six (75%) "organic" patients were on treatment (antiparkinsonian drugs in five cases and propranolol in one).

7.3.2   Comparison between actigraphy and self-report of tremor

There were no differences between groups regarding their reported duration of the waking day and the amount of time they were not wearing the actigraph (Table 7.2).

Table 7.2. Results of the wrist-worn actigraph study

	FT (n=8)	OrgT (n=8)	P value
Waking day duration (minutes)			
Mean (SD)	860.8 (222.6)	975.6 (47.3)	0.93
Time without the actigraph (minutes)			
Mean (SD)	36.2 (25.7)	24.4 (21.4)	0.42
No of representative days*			
Mean (SD)	5 (0)	4.4 (1.1)	0.64
Tremor intensity (counts/sec)			
Mean (SD)	13.6 (10.25)	12.2 (5.84)	0.83
Waking day Tremor duration			
Diary (%), mean (SD)	83.5 (14.0)	58.0 (19.8)	0.01
Actigraphy (%), mean (SD)	3.9 (3.7)	24.8 (7.7)	0.001
Actigraphy (minutes), mean (SD)	31.1 (30.7)	240.0 (70.1)	0.001

SD = Standard deviation

Patients with FT reported the five-day period of the study as 100% representative of a normal day in terms of tremor whereas patients with OrgT considered 87.5% of the five-day period as representative. None of the actigraphs ran out of power during the experiment.

In diaries, 'whole day period' estimation for duration of tremor, as percentage of the waking day, was significantly higher in patients with FT than patients with OrgT (83.5% ±14.0 vs. 58.0% ±19, respectively; p<0.01). However, mean percentage of the waking day with tremor measured by actigraphy was significantly lower in the FT group (3.9% ±3.7; 31.1 ±30.7 minutes) compared with the OrgT group (24.8% ±7.7; 240.0 ±70.1 minutes) (p=0.001). The mismatch between diary estimates and actigraphy measures is illustrated in Figure 7.1. When tremor was present, there was no difference between groups in the intensity of tremor measured by the actigraph (p=0.83).

Since both patients with FT and OrgT overestimated the amount of time with tremor in the 'whole day period' estimations, I analysed the agreement between diary and actigraphy measures in more detail by assessing each of the 'intra-day interval' estimations as recorded in diaries and actigraphy over the five days (Figure 7.2). Bland-Altman analysis showed a significantly better agreement between methods in the OrgT group compared to the FT group (OrgT: mean bias = +27.6%, 95% CI −26.0 to 81.2; FT: mean bias = +64.7%, 95% CI 1.2 to 128.1). According to this analysis, intra-day interval estimations of patients with OrgT showed approximately 28% more tremor duration in diaries than by actigraphy. In contrast, patients with FT showed 65% more tremor duration in diaries than by actigraphy.

The fairly random spread of data points in Figure 7.2 with regard to the x axis indicates that bias was not proportional to the mean of tremor duration estimates and actigraphy, but rather subjects had an absolute systematic bias towards overestimation of tremor.
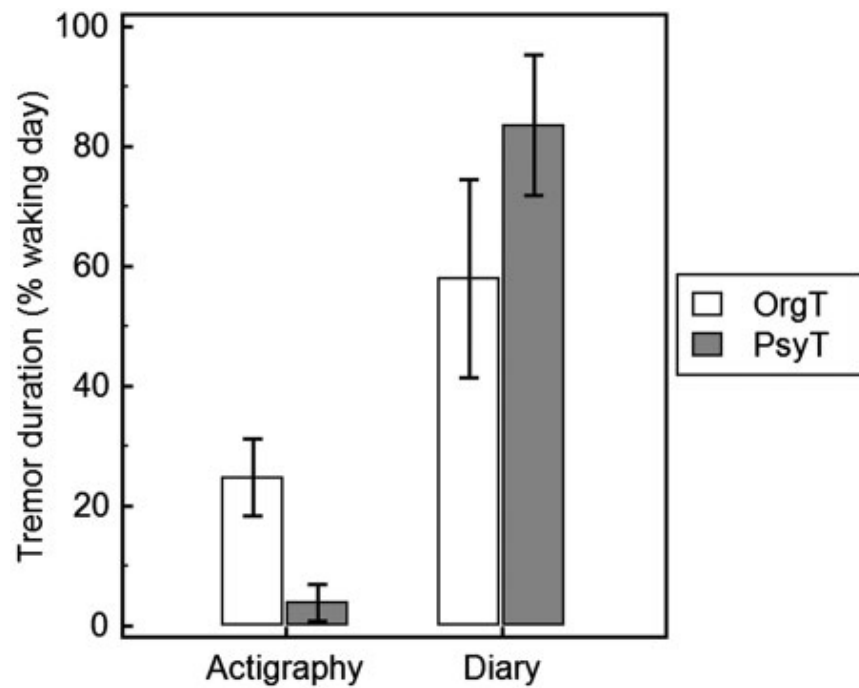
Figure 7.1. Tremor duration as percentage of the waking day (mean ±standard deviation), as recorded in self-report diaries and by actigraphy, in patients with "organic" tremor (OrgT) and Functional tremor (FT).
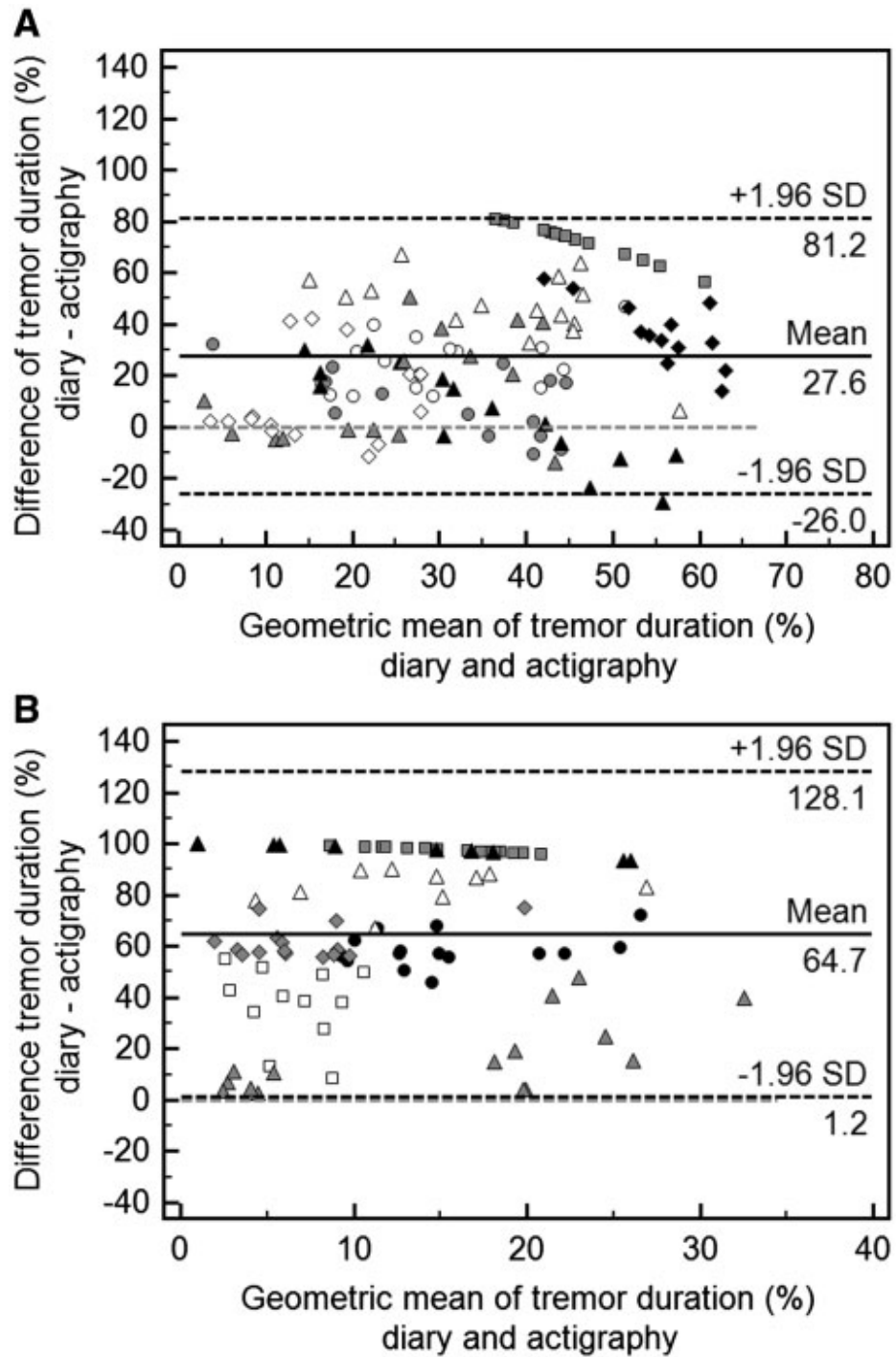
Figure 7.2. Bland-Altman plots for tremor duration as percentage of the intra-day intervals, recorded in self-report diaries and by actigraphy, in patients with "organic" tremor (OrgT) (A) and functional tremor (FT) (B). All values from each participant are represented by the same symbol. Bias is expressed by the mean of the differences between methods and 95% confidence intervals (±1.96 SD). A difference of 0 (dotted grey line) represents the perfect agreement between both methods. Differences with positive values indicate an overestimation of tremor duration in diaries compared with actigraphy. Differences with negative values indicate an underestimation of tremor duration in diaries.

I additionally assessed intensity and duration of tremor at the time when patients were supposed to be filling in the diaries. Although I gave them instructions to fill in the diary at particular times of the day, I cannot be completely sure that they strictly followed the instructions. The most reliable moment that we believe we can be certain that the patients were filling the questionnaire was at bedtime. I therefore analysed the intensity and duration of tremor during the 30 minutes before going to bed. I did not find any increase in the intensity of tremor during this period in either group. However, for tremor duration, when I calculated the ratio between the percentage time with tremor over the 30 minutes before going to bed compared with the percentage time with tremor over the whole third interval (from 7:00pm to bedtime), I observed significant differences between groups (p=0.01). The FT group had a ratio of 1.7 (indicating an increase of tremor during the 30 minutes before going to bed with respect to the rest of the interval) whereas the OrgT group had a ratio of 0.7 (indicating a decrease of tremor in the 30 minutes before going to bed).

In the post-study questionnaire, all patients answered that they believed that the purpose of the study was to monitor tremor, and that the watch was recording tremor 24 hours a day.

7.4   Discussion

In this study I have assessed duration and intensity of tremor in patients with FT and OrgT by using a validated long-term actigraph during five days and simultaneous self-rated measurements. I have demonstrated a remarkable absence of tremor during most of the waking day in patients with FT. Despite this, patients

with FT reported tremor to be present the majority of the time. In comparison with OrgT patients, they reported tremor to be present a significantly higher proportion of the waking day, and compared with the results of actigraphy showed a significantly greater bias towards over-estimation of tremor.

Patient groups were well matched in terms of objective clinical assessment of tremor severity at baseline. In line with their estimates of tremor duration, but not with the actigraphy data, patients with FT rated themselves as significantly more disabled by tremor (Sub-scale C of the FTM scale), and as having a significantly poorer quality of life as rated by the EQ-5D (Brooks R, 2003).

7.4.1 Implications for understanding the pathophysiology of functional tremor

I suggest that these data provide supportive evidence that the majority of patients with FT (and perhaps by inference other functional disorders) are not malingering. I was explicit in my explanation of the study to the patients, specifically explaining that we were using a "tremor watch" to record the actual duration of their tremor and were comparing this with patients' own estimates of tremor duration. I gave patients the opportunity to abort the study at any point. Two of the patients with FT we approached for the study initially accepted our invitation to take part, but then returned the actigraph to us without wearing it or completing diaries. The reasons given for this (arm pain, allergic reaction) may be genuine, but could also be hypothesised to be excuses to avoid revealing that tremor was not present when unobserved, compatible with the diagnosis of factitious disorder/malingering. However, in the rest of the FT group patients completed the study in a similar

fashion to "organic" patients. This behaviour, given the explicit study design, seems incompatible with malingering or factitious disorder, and instead suggests a genuine perception that tremor was present to the extent reported in the diaries.

If malingering/factitious disorders are not explanations for the tremor in this group of functional patients, how might these data inform our understanding of the mechanism of symptom production? I believe that these data reflect the interaction between perception (diary assessments) and real sensory data (actigraph measurements). In an ideal neural model these would be identical (i.e. all sensory data is correctly translated into perceived tremor), but it is clear from personal experience and numerous experimental studies that perception of sensory data is dramatically altered by expectation (Koyama *et al.*, 2005, Colloca *et al.*, 2008, Bulsing *et al.*, 2010). For example, perception of pain can be radically altered by expectation of the intensity of the pain stimulus (Koyama *et al.*, 2005, Colloca *et al.*, 2008).

Similarly, I suggest that my data reflect prior expectations about tremor in both functional and "organic" patients and how this can influence the way they estimated their tremor. Both patient groups overestimated their time with tremor, and this could be conceptualised as an over-weighting of prior expectancy about having tremor over actual sensory data. Such overvaluing of prior expectancy is indeed the norm in most studies of perception in healthy populations, and may reflect an evolutionarily beneficial tendency to value past experience over new sensory information (Elze *et al.*, 2011).

However, my data with regard to the significantly greater estimation/actigraph mismatch in patients with FT fits with an abnormal weighting of prior expectancy in this patient group such that it overwhelms sensory data that should inform the patient that they do not have tremor. I hypothesise that whenever patients' attention is turned towards the symptom (for example during clinical examination or as demonstrated in the present study, around the time they had to fill in the diaries) the expectation of the sensory consequences of the symptom is of sufficient strength to drive the abnormal motor behaviour. On the contrary, when attention is diverted away from the symptom (for example during most day-to-day behaviour away from the clinic) tremor stops. However the patient's perception, which is moulded by the dominance of the abnormally strong prior expectation over sensory data, remains that tremor is present most of the time.

7.4.2 Implications for clinical trials in functional tremor

This is the first study to assess FT objectively in a "real-life" ambulatory fashion. To date, information regarding severity of symptoms in FT has been provided by objective face-to-face clinical observation using standardised rating scales such as the FTM or from patient self-report (Jankovic *et al.*, 2006, McKeon *et al.*, 2009). My data demonstrate that although intensity and severity of FT, when present, is similar to OrgT measured by actigraphy and rated using standardised scales, patients' self-reports do not capture the reality of tremor duration in day-to-day life. This finding has implications for design of future clinical trials. In essence, my data suggest that the disability reported by patients with FT is not due to the tremor itself, but more to their abnormal perception that the tremor is continually

present. This would argue for the use of global disability and quality of life measures along with specific tremor assessments, as outcomes in clinical trials in this condition.

7.4.3 Limitations

I acknowledge some limitations to this study. Firstly, I have studied a small cohort of functional and "organic" tremor patients, and I cannot exclude that in a larger cohort data may be different. However, I chose patients with clinically typical (albeit longstanding) functional and "organic" tremor diagnosed using standardised criteria and feel that they do accurately represent patients with these diagnoses. Secondly, I cannot rule out that the actigraph was underestimating tremor in both groups as in a previous study 71% of 10 minutes of tremor observation were classified as tremor by the actigraph (Van Someren *et al.*, 2006). However, studies using EMG, which is more sensitive to tremor than actigraphy (Spieker *et al.*, 1997), have found patients with PD to have tremor 28.9% of a 24 hour period and patients with Essential Tremor to have 15.8%. These results are similar to my data in the OrgT group. Thirdly, I cannot completely exclude the possibility that tremor was not accurately recorded by actigraphy in patients with FT because of the known variability in FT frequency. However, this seems to be unlikely since the filters for tremor were set over a wide range (3 to 11Hz). Fourth, even though participants were clearly instructed, we cannot exclude that they overestimated tremor duration because tremor involving other body parts was also reported. Nevertheless, the majority of patients with FT had tremor only in the arm wearing the actigraph, and consequently, this explanation is unlikely to account for the

excessive overestimation of tremor in the FT group. Fifth, I set up arbitrarily only three intra-day interval estimations. It is possible that with shorter intervals, results would have been different as participants would have thought about the tremor more often. However, I wanted to assure the correct completion of the study and I felt three times a day was an achievable number for most of the participants. Six, I studied patients with FT and no other FMD and one can argue that these results do not apply for other FMD. Indeed, it seems less likely that patients with functional fixed dystonia display their symptoms for short periods of time due to the presence of muscle contractures and shortening of tendons commonly seen in some of these patients (which would reflect somehow that the abnormal movement is present most of the time). Seven, although on average patients with FT had 31 minutes of tremor a day, there may well be patients with FT who have more tremor, if their attention is turned towards it more often. Finally, I acknowledge that assessment of the presence or absence of malingering is very difficult and my data cannot fully exclude this possibility and therefore that there was some purposeful embellishment in the way functional patients completed the diaries. However, a post-study questionnaire indicated their understanding of the nature of the study and I feel malingering is an unlikely explanation of my results.

7.5   Conclusions

In this study, I have demonstrated a dramatic overestimation of duration of tremor in patients with FT compared with estimates of patients with OrgT and ambulatory actigraphy. Our data do not support the hypothesis that these patients are malingering. Instead, these data may reflect an abnormal perception of tremor in

patients with FT who might overweight their expectancies regarding tremor duration.

Chapter 8: A study assessing the lack of sense of agency for movement in functional movement disorders.

8.1   Introduction

So far, I have provided evidence for an abnormal attentional focus towards movement in patients with FMD. However, this requirement of attending to the movement for the dysfunction to manifest might be expected to be associated with a strong sense of "voluntariness" or agency for the movement, which is in marked contrast to what patients with FMD report: they experience the abnormal movement as involuntary. This issue is at the heart of a centuries old debate on the level conscious fabrication/manufacturing of functional symptoms. If feigning is not an explanation for the vast majority of patients with FMD, then the logical conclusion must be that these patients have an impairment of the mechanisms implicated in the ability to recognize that one is initiating and controlling one's own actions, i.e. the sense of agency for movement.

After reviewing the literature, I decided to assess the phenomenon of sensory attenuation (SA), which is considered to be an implicit measure of the sense of agency (Blakemore *et al.*, 2002).

In brief, SA is the phenomenon whereby the intensity of sensation generated by self-generated movement is reduced (Blakemore *et al.*, 1998, Blakemore *et al.*, 2000, Shergill *et al.*, 2003). A common example of this is the observation that while one cannot tickle oneself, one can be tickled by others. The experience of SA is important in labelling movements as self-generated and a loss of SA has been proposed to lead to a loss of agency for movement (Blakemore *et al.*, 2002). In the experimental setting, SA has been most commonly assessed with a force matching paradigm (Shergill *et al.*, 2003, Shergill *et al.*, 2005, Voss *et al.*, 2007, Teufel *et al.*, 2010). Here, subjects are asked to match a force delivered to their finger, either by pressing directly on their own finger with the other hand, or by operating a joystick that, via a non-linear transform, causes a robot arm to press down on their finger. Healthy subjects consistently generate more force than required when directly pressing on their finger compared with using the joystick, where they are much more accurate. It has been proposed that the excess force exerted in the first condition reflects SA of the sensory consequences of self-generated movements, something not present in the second condition, where the highly nonlinear transform between movement and sensation disrupts the sense of agency.

I felt that exploring SA in patients with FMD would provide an opportunity to assess a key psychophysical property of movement that is experienced as self-generated or voluntary in this group of patients. I predicted that if patients with FMD had impairment in the sensory attenuation mechanism, they would be more accurate than controls matching forces when directly pressing on their finger.

8.2   Methods

8.2.1   Participants

Fourteen patients with FMD were selected from the General Movement Disorder clinic of Dr Mark Edwards or Professor Kailash Bhatia as well as from the specialised Functional Movement Disorder run by Dr Edwards, at the NHNN Queen Square, London, UK. The specific study was personally explained in detail and if the patient expressed interest in participating, a formal letter with a full description of the study and stating the date and location of the experiment was sent.

Inclusion criteria were:

1. Age over 18 years.

2. Diagnosis of clinically established or documented FMD according to Fahn and Williams criteria (Fahn and Williams, 1988).

3. The FMD was not affecting the upper limbs to ensure the correct accomplishment of the motor task.

I used as exclusion criteria:

1. Age less than 18 years.

2. Unable to communicate with researcher (e.g. does not speak English).

3. Presence of sensory symptoms or sensory abnormalities (detected on physical examination).

The control group consisted of 14 healthy participants who were recruited from a Departmental pool of volunteers and from patients' relatives who wished to

collaborate with the research. They were matched with respect to gender, age, and handedness.

8.2.2 Questionnaires

8.2.2.1 Handedness

Hand dominance was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), which has been previously described in this thesis.

8.2.2.2 Mood

We administered the HADs to all participants to assess their mood the week prior to testing, which has been also previously described in this thesis (Zigmond and Snaith, 1983).

8.2.2.3 Intelligence level

To estimate the non-verbal intelligence level (IQ) of participants, the 12 items short form of Raven's Progressive Matrices test was used, previously described in this thesis (Raven JC, 1977).

8.2.2.4 Delusional ideation

Delusional ideation was assessed using the PDI-21, as previously described (Peters *et al.*, 2004). I decided to match both groups by delusional ideation because healthy individuals with higher scores in delusional questionnaires have been previously found to have a less amount of SA (Teufel *et al.*, 2010).

8.2.3 Materials

A small, desk-mounted force-feedback robot arm (PHANTOM® Desktop™ Haptic Device, Sensible Technologies, Cambridge, MA, USA) was programmed to apply different forces over a custom-made force transducer, which was placed on the top of the subject's left index finger. The force output was recorded by a programmable output system (Spike 2, version 6, Cambridge Electronic Design (CED), UK).

8.2.4 Experimental Design

I tested each participant in a single experimental session consisting of two main conditions: matching a target force, either by 1) pressing on themselves with the right index finger on the left index finger (self-condition) or 2) by manipulating a robot which pressed down on the left index finger (external-condition). Five different target forces (16 trials of each), increasing in increments of 0.5 Newton (N) from 1N to 3N, were randomly presented in both conditions. All subjects completed a total of four blocks of 20 trials each (80 trials in total) for each condition. The order of conditions was counterbalanced across participants.

8.2.5 Procedure

Participants sat in front of a table and placed the tip of their left index finger under the force transducer. The finger was taped to the table to avoid any movement. In the self-condition, the robot exerted one of the five constant target forces in each trial for 3s. After 2s of rest, an auditory "go" signal told the participants when to start matching the target force – by directly pressing with their right index finger for 3s onto the force transducer resting on the left index finger (Figure 8.1). A "stop"

auditory signal marked the end of the trial. In the external-condition the robot exerted one of the five constant target forces in each trial for 3s. After 2s, an auditory "go" signal warned the participant to start matching the target force by moving the arm of a second robot horizontally, which controlled the output of the other robot that applied a force vertically to the left index finger (Figure 8.1).
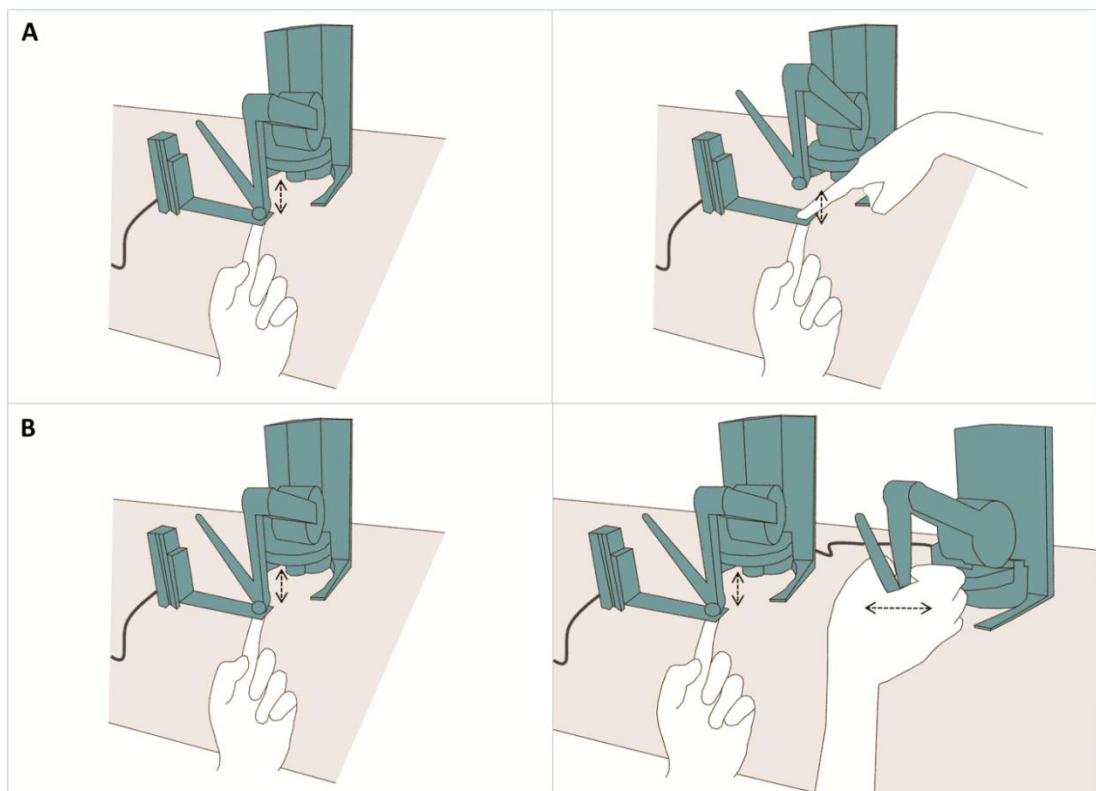
Figure 8.1. Experiment set-up. A) Self-condition. A constant force is delivered by one of the robots on the participant's left index finger. Immediately afterwards, participants had to match the force by pressing with their contralateral index finger. B) External-condition. A constant force is delivered by one of the robots on the participant's left index finger. Immediately afterwards, participants had to match the force by moving the arm of the second robot horizontally – to control the first robot's output.

The force level generated by the subject was calculated for each trial by taking the mean force recorded by the force sensor between 2000 and 2500ms after the go-signal. We calculated the ratio between the matched force and the target force for both conditions (ratio > 1 indicating generation of excessive force) and this was our measure of SA. This measure was averaged across trials to give the mean attenuation for each force level and condition.

8.2.6   Statistical analysis

SPSS Statistics software (version 21.0.0) was used for the statistical analysis. Normality of errors was assessed by using the Kolmogorov-Smirnoff test. When not normally distributed, the data were subjected to a Log10 transformation. P-values for categorical variables were calculated with the use of Fisher's exact test. U-Mann-Whitney test was used to compare differences in means for numerical data in baseline characteristics.

A repeated-measures ANOVA was used to compare the results of the main experiment with CONDITION (Self vs. External) and FORCE (1N, 1.5N, 2N, 2.5N, 3N) as main factors and GROUP (patients vs. healthy participants) as a between-subjects factor. Post-hoc tests were conducted with Bonferroni corrections for multiple comparisons. We calculated potential associations between IQ, PDI-21 and HADs and the amount of SA (calculated as the mean of the ratios for each force level in the self-condition) by using Pearson's correlation. Statistical significance of $p < 0.05$ was assumed.

8.3   Results

Baseline characteristics of the participants are shown in Table 8.1. Patients and healthy participants were matched for age, gender, handedness, Raven's and PDI scores. Most patients had fixed dystonia of the lower limbs as FMD. Clinical features included an acute onset and rapid escalation of the symptoms. Most presented dramatic response to placebo or following examination under anaesthesia and dystonic symptoms often disappeared for a period of time to recur later on. Most patients were females which is consistent with the majority of them having fixed dystonia, as there is female predominance in this group of patients. None of the patients was treated with antipsychotic medication.

Table 8.1. Demographic and clinical characteristics of the participants in the sensory attenuation study

	FMD	Healthy control	P value
Age (years)			
Median (range)	38.1 (30 - 67)	34.5 (29-58)	0.12
Sex, n (%)			
Male	1	4	0.32
Female	13	10	
Handedness			
Right	12	14	0.48
Left	2	0	
Type of FMD, n (%)			
Fixed dystonia	10	NA	
Functional tics	1	NA	
Functional palatal tremor	1	NA	
Functional hemifacial spasm	1	NA	
Paroxysmal movement disorder	1	NA	
HADS total score			
Median (range)	13 (0-28)	4 (0-28)	0.002
Raven's score			
Median (range)	10 (6-12)	11 (9-12)	0.94
PDI-21 score			
Median (range)	12.5 (0-63)	12.5 (0-30)	0.98

FMD = Functional movement disorder

A repeated-measures ANOVA showed a significant CONDITION x GROUP interaction (F=6.54, df=1, 26, p=0.017). Post-hoc explorations of this interaction revealed that this was due to the patients having significantly less attenuation than healthy controls in the self-condition (F=8.47, df=1, p=0.007) but no significant difference from healthy controls in the external condition (F=0.145, df=1, p=0.706).

When I analysed patients alone, I found no significant differences in their performance when self and external-conditions were compared (F=2.62, df=1, 13,

p=0.129). In contrast, healthy controls significantly overestimated the force required in the self- condition compared to the external-condition (F=26.64, df=1, 13, p<0.001).

I present the raw data in Figure 8.2.
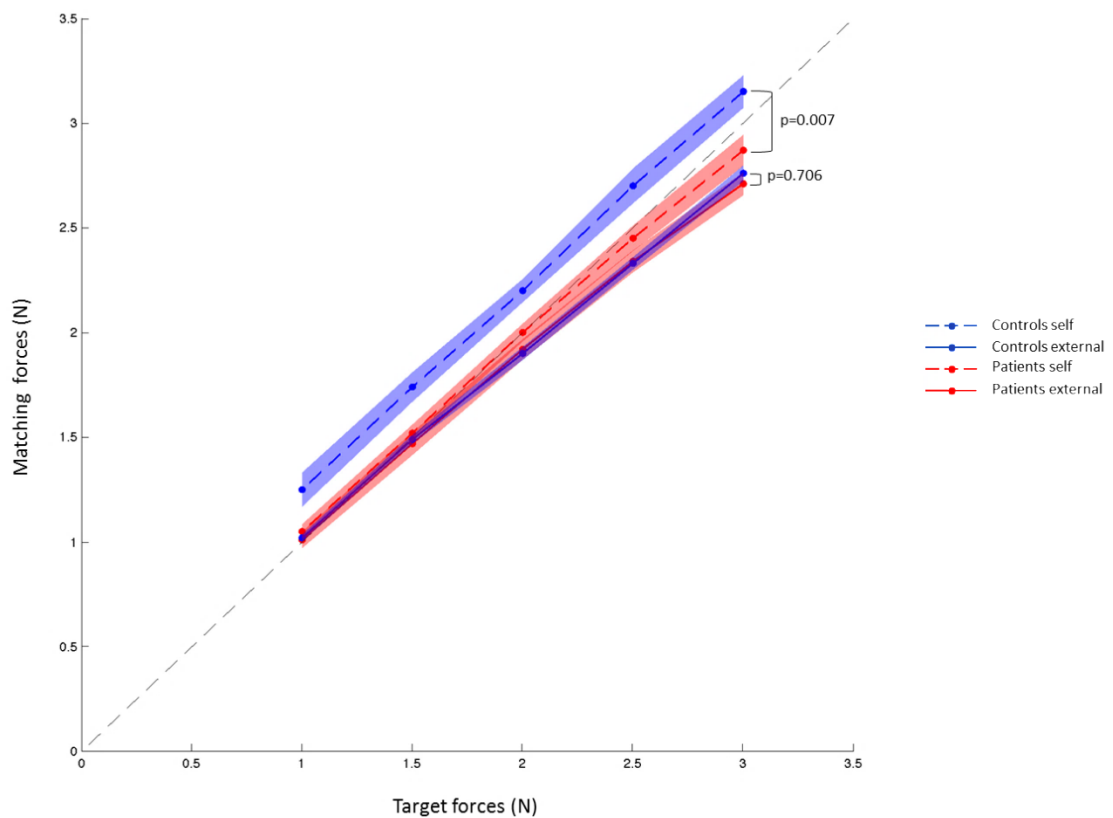
Figure 8.2. Results of the force matching paradigm. Healthy controls (dashed blue line) significantly overestimated target forces in the self-condition compared with patients with functional motor symptoms (dashed red line). There were no differences in the external-condition between healthy controls (solid blue line) and patients (solid red line). Colour shadows represent the standard error of the mean for each condition.

I found no significant correlation between duration of symptoms and SA (r=0.007, p=0.98). There were no correlations between HADs or Raven's scores and SA

(r=0.29, p=0.91; r=0.147, p=0.62 respectively). PDI-21 total score did not correlate with the amount of SA (r=-0.67, p=0.82). We calculated a new score as the sum of the score of just those items in the PDI-21 that imply somehow passivity experience (i.e. questions 10, 18, 19, 20 and 21). No significant correlation was found between this score and the amount of SA.

8.4   Discussion

In this study, I have assessed the phenomenon of SA as a measure of self-agency, in patients with FMD. I have demonstrated that patients with FMD have a loss of SA in a force-matching task compared with healthy control subjects. As expected, healthy controls consistently overestimated the force required in the self-condition, whereas patients did not, and were actually extremely accurate in their force estimation performance when using their own contralateral index finger. In contrast, both patients and control behaved exactly the same in the external or control condition, when they manipulated a second robot to match the different forces.

SA has been observed in auditory, visual and tactile domains (Martikainen *et al.*, 2005, Cardoso-Leite *et al.*, 2010, Hughes and Waszak, 2011, Desantis *et al.*, 2012) and attenuation of Blood Oxygen Level-Dependent (BOLD) responses and Somatosensor Evoked Potentials (SEP) related to self-generated sensations has also been demonstrated (Cohen and Starr, 1987, Blakemore *et al.*, 2000). Over the past decade, the most prominent theoretical account of the phenomenon has been based on motor control theory, where an efference copy of a motor command is used to generate a "corollary discharge" – a prediction of the likely sensory

consequences of that movement (Blakemore *et al.*, 1999). When movement occurs, sensory feedback is compared with the sensory prediction and – after a "subtraction" process – any mismatch can be used to update future commands. It is proposed that in voluntary movements, predictions of sensory consequences are very accurate and therefore there is little or no mismatch between predicted and actual sensation. This lack of mismatch is assumed to attenuate the perceptual consequences of self-produced movements and may be the cause of force overestimation in the force matching task. Temporal and spatial offsetting between the movement and its sensory consequences causes a gradual decline in SA (Blakemore *et al.*, 1999) Thus the degree of SA is proposed to index in some manner the "voluntariness" of movement. Conversely, lack of SA has been proposed to reflect a lack of agency for self-generated movement (Shergill *et al.*, 2005).

However, some difficulties with the classical model of SA have recently been highlighted (Brown *et al.*, 2013). For instance, different experiments have demonstrated that attenuation of externally generated sensations is possible, which, by definition, cannot be predicted by the forward model of the sensory consequences of movement. Also, SA commences before the onset of a movement (Bays *et al.*, 2006), and is not related to the predictability of the stimulus (Bass *et al.*, 2008). A different approach based on a Bayesian model of the brain has been recently developed to explain SA (Brown *et al.*, 2013). Under this framework, attention plays an important role modulating the suppression of the sensory consequences of voluntary movement and inferring about internally and externally generated sensations. This will be discussed in more detail in the next chapter.

Patients with schizophrenia and healthy individuals with high scores delusional on questionnaires probing delusional beliefs have been also found to have reduced SA using a similar paradigm (Shergill *et al.*, 2005, Teufel *et al.*, 2010). These results have been explained on the basis of a dysfunction in generation of accurate internal predictive models related to movement, which might be responsible for delusions of control (or the abnormal belief that one's own actions are controlled by an external force). Despite this, psychotic symptoms are not a feature of patients with FMD, and I did not find differences between delusional ideation measured by PDI-21 between my patients and healthy controls. It is therefore likely that although patients with schizophrenia and FMD share the same abnormalities in the SA, they have different primary causes.

It is important to note that other studies have aimed to explore agency for movement in patients with functional motor symptoms. However, the employed methodology makes interpretation difficult. For instance, in a study using fMRI, a relative reduction in activation of the right inferior parietal lobule was found in patients with functional tremor comparing activation patterns while they were tremoring and when they were voluntarily producing tremor (Voon *et al.*, 2010). Although right inferior parietal lobule is considered to be important in sense of agency, these data only indirectly address the question of reduced sense of agency in patients with functional motor symptoms. Two other studies have shown that patients with FMD judged the feeling of intention to move significantly closer to the action of moving compared to control participants and had a decreased action-effect binding when making voluntary movements compared with healthy volunteers (Edwards *et al.*, 2011, Kranick *et al.*, 2013). However, both studies rely

on subjective self-report and are clearly susceptible to important biases. Finally, a recent study has shown that patients with functional paresis display distinct electroencephalographic markers compared to feigners (Blakemore *et al.*, 2013). Among other results, they found that P3 event-related EEG potentials component was enhanced when the symptomatic hand was moving in contrast to feigners, and they suggested that this might be related to the lack of awareness that patients have about the origin of their symptoms. Unlike the previous studies, I believe that the paradigm employed in my study provides a more direct demonstration that a key component of normal movement related to sense of agency, and which is immune to feigned poor performance, differs from healthy controls. Patients fail to attenuate the sensory consequences of self-produced movement and therefore they were extremely accurate matching forces as compared to healthy controls. Data such as these support that feigning is not a satisfactory explanation for the majority of patients with functional symptoms and support that abnormalities in the sense of agency for movement underlie this disorder.

I acknowledge a number of limitations of this study. First, the sample size is small and I cannot exclude that in a larger cohort data may have greater statistical efficiency. However, we chose patients with clinically typical FMD using standardized criteria and feel that they do accurately represent patients with this diagnosis. Furthermore, the fact that I was able to show a significant group by condition interaction with a relatively small sample size suggests the effect sizes in question are relatively large. Secondly, it is important to note that functional tremor is considered the most common FMD and that in our sample, most patients suffered from functional fixed dystonia, which is considered to be the second

commonest diagnosis. This is likely to be due to the exclusion criteria used in this study. Patients with FMD involving upper limbs were not included and this is the body part usually affected by functional tremor. Thirdly, while the self and external-conditions were significantly different in controls we did not find the same amount of SA in healthy controls compared with previous studies (Shergill *et al.*, 2003, Shergill *et al.*, 2005). One possible explanation is that the experimental set-up differed from that used in previous literature. Fourthly, this study does not resolve the important question of why patients with FMD showed impaired SA in the force-matching task using non-affected body parts. I believe that one possible explanation is that lack of SA is a trait (perhaps related to the self-focussed attention that these patients display), which predisposes them to develop functional symptoms. It is of note that a proportion of patients with functional symptoms develop progression and spread of symptoms over time, and while the initial onset of symptoms is quite commonly associated with a physical or psychological trigger, spread of symptoms is often apparently spontaneous. Further studies in asymptomatic patients with a previous history of FMD would clarify this important question.

In conclusion, patients with FMD display impairment in SA mechanism measured by a force matching task. This might contribute to explaining the paradox of why movements that superficially resemble voluntary movements are experienced as involuntary in this group of patients.

Chapter 9: General discussion and conclusions

Part of the discussion described in this chapter has been also written as a review article:

Edwards MJ, Fotopoulou A, Pareés I. Neurobiology of functional (psychogenic) movement disorders. Current Opinion in Neurology 2013; 26: 442-7.

In this thesis I have explored different aspects of the pathophysiology of FMD. As I mentioned in the introduction, I took as my starting point the manner in which the diagnosis of FMD is made in neurological practice and I focused on a mechanistic rather than on an etiological level.

The findings of the different studies described here suggest that physical illnesses preceding the onset of FMD, abnormal focus of attention to movement, abnormal beliefs about the symptoms as well as an impairment in the sense of agency for movement are elements that play an important role in the mechanism underlying FMD and that it would be important to incorporate these concepts in any model seeking to explain this perplexing condition.

In this final chapter I will discuss my results in the light of previous theories, I will discuss in more detail the methodological limitations of each of my studies and make suggestions for improvements. Finally, I will suggest directions for future research.

I started saying that one of the main aims of this work was to try to better understand the circumstances surrounding the onset of FMD. I have mentioned how functional symptoms have been typically interpreted as a result of previous psychological stressors, even if they preceded the onset of symptoms by decades.

This was the main argument of most of 19th/early 20th century theories, especially the Freudian one and is still ingrained within much of modern medical practice. Likewise, I have highlighted how physical events closely preceding the onset of functional symptoms have been previously described in the literature although their role in symptom generation has remained less defined. For instance, Janet proposed in his dissociation theory that the restriction of the field of consciousness usually affects a function that has previously become weak. He proposed that previous physical illness involving the same body part affected by the functional symptom was a potential causes for this weakening. In the case of Freud, he proposed that it is actually the psychological stress that accompanies the physical trauma that is the cause of the functional symptoms rather than the physical injury itself. As part of the analogy with an electrical system that Freud used to explain brain function, he considered that any physical illness affecting the body part concerned could work as by potentially weakening the resistances that prevent the distribution of the abnormally increased brain excitation in patients with function

al symptoms to other organs.

Based on these observations, in the first study of this thesis I aimed to investigate how often patients with FMD report a physical event close to the onset of functional symptoms in a systematic way. I recruited 50 consecutive patients and studied them with a semi-structured interview. I found that most patients that attended our clinic described a clear physical problem closely preceding the FMD and that often, these were phenomenologically related to the functional symptom. Rather than weakening factors, as proposed by 19th century's theories, I speculated

on the potential role of physical events in generation of functional symptoms. I suggested that they may provide initial sensory information that, along with other cognitive and psychological factors, form the substrate for the development of a specific FMD in vulnerable subjects.

However, it is important to acknowledge that although the causality between the physical illness and the subsequent FMD sounds plausible, it cannot be established with the results of a retrospective study and therefore my results should be interpreted with caution. Important methodological limitations that need to be underlined are: first, that I relied on the information obtained during a semi-structured interview and I did not verify the biopsychosocial background of the patients as well as their previous history including medical details of the physical event and the onset of the functional symptoms by accessing patients' medical records from the two medical contact points initially used by most patients (GP surgeries and A&E Services). Second, although it was not the main scope of my study, I assessed life events occurring within the same time window used to assess the presence of physical event by using a standard questionnaire. I have already acknowledged how difficult the assessment of life events is, especially with regard to recall bias. One way to decrease the recall bias would have been the use of a more reliable method, for instance the Life Events and Difficulties Schedule (Brown GW, Harris TO, 1979). Here, information about specific life events, timing and relevant contextual information is collected by a panel of raters but the participant's report of his or her reaction to the event at that time is ignored. Based on the contextual information, the threat for each event is rated.

However, the ultimate approach to avoid any recall bias and clarify the potential causality between physical events and the generation of FMD would have been to design a prospective multicentre study. Further studies could, for instance, recruit patients presenting in different GP surgeries or A&E Services with some of the most commonly physical events found in my study. Regular follow ups during the next month and examination of suspected cases of FMD within that period by trained neurologists would permit the identification of the cases and draw conclusions about causality. However, the large cohort required in order to obtain a reasonable number of cases as well as the likely costs of such a study make this approach less feasible.

The second study described in this thesis aimed to explore the role of attention in the generation of FMD. In one way, this was not a new area of study. We have seen how the role of attention in functional symptoms dates back to the dissociation theory of Janet. He proposed that in the case of patients with functional symptoms, the amount of sensations that can be perceived consciously is limited. He proposed that this is due to a spontaneous narrowing of their attention. The part of the mind that become "unattended" is then "dissociated" from consciousness, and the function of the resulting body part is impaired.

Contradicting somehow this theory, we have seen that it is clinically obvious that in the case of FMD directing attention to the affected body part exacerbates functional symptoms and when attention is distracted away they often improve or disappear. In the study described in Chapter 6 I aimed to translate this clinical

observation to a more experimental setting. I used paradigms that had been previously used in motor physiology literature. For instance, I explored the capability of the brain to adapt to visuomotor distortions. Adaptation in this context is the reduction in systematic errors introduced by a 30 degree counterclockwise angle in the direction used to reach a target in order to return to the former level of performance. Adaptation to visuomotor rotation is widely considered a form of implicit motor learning. One reason is that subjects can adapt whilst being unaware that they are making systematic directional errors. Also, the adaptation occurs even when subjects are given explicit strategies to override it (Mazzoni P, Krakauer JW, 2006). Adaptation to visuomotor rotation has been found to be normal in patients with other movement disorders such as patients with primary cervical dystonia (Katschnig-Winter P, et al, 2014) and asymptomatic carriers with the genetic mutation for Huntington's disease (Mazzoni P, Krakauer JW, 2009). In contrast, visuomotor adaptation has been found abnormal in patients with PD tested with similar paradigms (Venkatakrishnan A et al, 2011). I found that patients with FMD can adapt to visuomotor distortion to the same level than healthy subjects, suggesting that implicit motor control is intact.

The paradigm used to explore explicit motor strategies in FMD was based in the n-back task, previously used to assess working memory. Here, participants are fully conscious of the underlying task structure and therefore movement pre-planning is possible. This paradigm had been previously tested in healthy participants and patients with the genetic mutation for Huntington's disease who performed with no difficulties (Mazzoni P, Krakauer JW, 2009). In contrast, I found that patients with FMD were impaired in this task, and had slower movement times than controls.

Interestingly, RT and accuracy to the trajectory did not differ from controls, suggesting that the execution of the movement was specifically affected.

Finally, I used a cued choice reaction time task to assess how predictability about the movement may impact motor control en patients with FMD. I used a motor task that had been previously designed in the Sobell Department as an adaptation of the classical visual attention paradigm (Posner paradigm) for a motor setting. Briefly, in the classical Posner's paradigm two levels of spatial attention are explored. In the first condition, voluntary/explicit orientating of attention to a visual target is assessed. Here, the target is preceded by an arrow located in the centre of the visual field (cue) which represents potential direction of the location where the subsequent target may appear. The interpretation of this cue requires a voluntary/explicit processing by the cognitive system. In the second condition, a more reflexively/automatic way to orientate attention to a visual target is assessed. The cue in this case is a peripheral cue displayed in the position where the target may appear. It automatically attracts attention in a more reflexive way without a clear voluntary/explicit processing by the cognitive system. In both conditions, cues can predict or not correctly the position of the target. Valid cues result in a decrease of the RT when participants respond about the position of the target compared with invalid cues. In the paradigm used in my experiment, the subjects were asked to make a fast movement as soon as they detect a target in their visual field but instead of being presented with cues providing spatial information, the cues were arbitrarily mapped onto required finger movement responses. The advantage of this paradigm to study motor control was that attention is cued to the aspects of movement itself and not only to spatial attention. I hypothesised that

increasing predictability of a required movement would allow the opportunity for controlling the movement in a more explicit way. Therefore, I predicted that patients would exhibit a paradoxical motor impairment for the valid cues only in those conditions where the movement would be predictable. I found interesting results in this paradigm that deserve further comments. First, I found that the performance of patients with FMD was impaired only in the condition with higher predictability for the movement (95V). However, patients' performance did not differ from healthy participants in the 75V condition, where the movement was also predictable although to a lesser extent. One can argue that this must be due to the fact that patients only employed explicit strategies when they were almost certain about the movement to perform. However, the possibility that these results are due to chance or other factors cannot be excluded. In this regard it would be interesting to test additional levels of predictability (i.e. 50V, 65V, 75V, 85V, 95V) to confirm these results. Also, it would be important to test other group of patients with other movement disorders to explore how having an abnormal movement itself may impact in this paradigm. Likewise, there is no data about how affective disorders may influence the results of this paradigm. The patients included in my study scored higher in HADs than healthy controls and it would be important for further studies to include a control group matched by affective symptoms.

Taking into account all these limitations, the results suggest that movement impairment is restricted to tasks where conscious movement control in the setting of explicit movement production is possible, and not where movement occurs in a more automatic, implicit fashion. This is in agreement with the clinical observation

of these patients but it would argue against the classical "dissociation" theory that proposes that it is the inability to attend to the affected body part the likely cause of functional symptoms. Instead, I propose that it is an abnormal focusing of attention towards the movement (in case of FMD) which is essential for the generation of the symptoms.

This view is in keeping with more recent theories about functional symptoms. Richard J Brown formulated in 2004 a novel theoretical framework for functional symptoms in which attention plays a central role (Brown, 2004). He suggested that in the normal physiological state, an attentional system controls the selection of the relevant sensory information from our body and the environment for further processing and control of actions. He proposed the primary attentional system as the one used to organize relevant sensory information into integrated multimodal perceptual units (primary representations) that provide a working account of the environment for the control of actions. When actions are well learned or become into routine behaviours, they are controlled by a hierarchical system of procedural representations (schemata) specifying the attentional, cognitive and motoric processes involved in executing well-learned actions. This is a rapid system which consumes few processing resources. Behaviours controlled in this way are experienced as effortless. In situations where the system does not have the appropriate schemata such as in novel actions, these are controlled by a secondary attentional system (SAS) in a higher level of the system. Actions controlled by SAS are perceived as mentally demanding and associated with a sense of conscious volition and self-awareness (Brown, 2004). Brown explained the vulnerability of

some people to develop functional symptoms on the basis of self-focused attention. In the proposed model, the recurrent redirection of attention onto symptoms by the SAS is the primary pathogenic factor. Allocation of high level attention to symptoms serves to increase the activation of their brain representations and decrease the amount of activation required for it to be selected in the future. In this context, anything that increases self-focused attention can contribute to the development and maintenance of functional symptoms such as misattribution of symptoms to physical illness, negative affectivity such as anxiety and depression, illness worry and rumination, as well as previous traumatic experiences (Brown, 2004).

My results are also in keeping with more recent studies. For instance, patients with FT have been shown to spend significantly more time directly looking at their affected limb during clinical examination compared to patients with "organic" tremor, suggesting a role for self-directed visual attention in generation of motor symptoms (van Poppelen et al., 2011). Also, a recent study that compared positron emission tomography of regional cerebral blood flow in a small cohort of patients with "fixed" functional dystonia and genetically-characterised primary dystonia as well as healthy controls showed that fixed dystonia patients had reduced blood flow in primary motor cortex and increased blood flow in basal ganglia and cerebellum, which was contrary to that seen in patients with genetic primary dystonia (Schrag et al., 2013). The authors suggested that the abnormal subcortical activations in functional patients could reflect problems with self-directed

attention/monitoring, perhaps related to fronto-subcortical circuits mediating motor attention.

Along with attention, there is another element that emerges in this thesis and can play an important role in symptoms generation and have an important effect altering the sensory experience of them: the presence of symptom-related abnormal beliefs (understanding the concept of belief in this context as expectations about the symptoms).

If we go back to the historical view about the pathophysiology of functional symptoms, we may remember that it was Janet himself who first acknowledged how expectations about symptoms may play a role in symptom generation. He described a patient who developed fixed dystonia in both legs because he thought a carriage had run over his legs although it was later demonstrated that no injury actually occurred.

Interestingly, in this thesis I have found that patients with FMD required significantly less evidence than controls to make a judgement in the JTC paradigm, which could predispose them to appraise anomalous or ambiguous information rapidly and produce (abnormal) beliefs on the basis of limited evidence, without a thorough consideration of alternatives or a review of the evidence. One could suggest that such a reasoning style, along with other factors, may predispose patients with FMD to abnormally process sensory data arising from a triggering event (which we have seen can be often a physical illness) and easily form the abnormal belief that the sensation represents a symptom of a neurological disease.

One important limitation of this study is that patients with FMD scored higher than healthy controls in the HADS. I acknowledged in chapter 5 that affective disturbances were not a predictor of the results obtained in my sample (as assessed by a regression analysis) and this would fit with other studies that also failed to find a relationship between affective disturbances and the JTC bias. However, the specific impact of affective symptoms in probabilistic reasoning bias is still to be elucidated and I cannot exclude that they partially explain my results. Further studies will therefor need to clarify whether the JTC bias is specific to the functional condition itself or instead relates to the affective symptoms that commonly accompany FMD. Either comparing patients with FMD with and without depression/anxiety symptoms and a healthy control group or matching by affective symptoms a group of patients with FMD and a group of depression/anxiety patients with no FMD would help to answer this question. Also, I used only one combination of beads in my study and it has been shown that task difficulty may influence the results of in the probabilistic reasoning task (Young HF, Bentall RP, 1997). Participants are more certain in easier (85:15 ratio) than in difficult versions of the bead task (60:40 ratio). Therefore, I cannot exclude that manipulating the ratios of the beads in the containers the results in patients with FMD might be different. Further studies could then assess the performance of these patients with different ratios. One could argue that if these patients display a JTC bias because they weight the initial information differently from normal subjects (as I have proposed), they would express greater certainty in easier conditions (85:15) compared with the most difficult one (60:40).

A reflection that abnormal beliefs about symptoms may be implicated in symptom generation also comes from the study described in Chapter 7 assessing FT in real life conditions. Here, I demonstrated that when patients with functional and "organic" tremor were asked to wear an accelerometer in their most affected hand in term of tremor, which constantly recorded and stored data over 5 days, both patient groups subjectively overestimated the amount of time they had tremor, but functional tremor patients did this to a much greater extent. I suggested that this significant exaggeration of a natural bias in tremor patients to overestimate tremor duration could reflect abnormal high level beliefs about there being constant tremor present. An abnormally strong prediction or expectation about the symptom may override the real sensory data from the affected limb tremor that should alert the patient that tremor is not there most of the time. Therefore, periods without tremor are simply not perceived. I have already acknowledged limitations in to this study but I think it is important to consider two additional aspects when interpreting my results. First, most patients with "organic" tremor had idiopathic PD. Although I matched both group by tremor characteristics and severity by using the FTM scale, it is likely that PD patients had predominantly rest tremor. One could argue that because rest tremor causes almost no functional disability it can be unnoticed and not reported in the diary. This could explain partially why the "organic" group did not overestimate tremor duration at the same level than functional patients. Second, there was a statistical trend for patients with "organic" tremor to be older than patients with FT. Although our patients did not have significant cognitive impairment, I cannot rule out that this factor was also influencing the way patients were reporting subjectively their tremors. Therefore, if

similar studies are designed in the future to replicate my results, it would be important, apart from increasing the sample size, to match groups by age and select a more homogenised control group with predominately postural tremor, which is clearly functionally disabling and are less likely to be unnoticed (i.e. patients with essential or dystonic tremor).

The last element emerging from this thesis is the sense of agency relating to movement (in other words that one is or is not the cause of the movement of one's body). This is perhaps the most intriguing aspect of patients with FMD, and the one which perhaps has caused most difficulty in their interaction with healthcare. Their movement abnormalities have features typical of voluntary movement and yet they report them to be involuntary. The question of whether they are in fact malingering symptoms is impossible to resolve in most ordinary clinical situations. Indeed, it has been always the centre of debate. We have seen how Charcot and Janet advised about the difficulties of differentiating patients with functional symptoms from feigners. We have also seen how some of them, as in the case of Charcot, argued that most patients with functional symptoms were actually not feigning and aimed to prove it experimentally by designing specific devices (a plethysmograph-like machine to assess breathing regularity and fatigue in patients with fixed dystonia and healthy subjects maintaining voluntarily the same abnormal posture against a continuous traction).

In this thesis, I have shown that the SA phenomenon (proposed to be a measure of the sense of agency for movement) is impaired in patients with FMD. I used the

force matching paradigm which has been largely assessed in healthy volunteers and has been demonstrated to be abnormal in patients with delusions or at high risk of delusional state. I have shown that patients with FMD, similar to those with delusions and in contrast with healthy controls, did not overestimate the amount of force applied to match a target force in the self-condition suggesting a deficit in the SA mechanisms and therefore in the sense of agency for movement. This suggests that malingering is not an explanation for all these patients and instead, they display abnormalities in the mechanisms implicated in the experience of oneself as the agent controlling one's own movements.

However, when interpreting these results it is important to highlight three important aspects regarding the methodology used:

First, although SA is a well-recognised phenomenon, the underlying mechanisms and its link with the sense of agency is not well understood. Studies using functional neuroimaging have shown differences in brain activity during self-generated relative to externally generated tactile stimulation in healthy controls: an increase in activity of the secondary somatosensory cortex and the anterior cingulate gyrus when subjects experienced an externally produced tactile stimulus relative to a self-produced tactile stimulus has been found. Also, the right anterior cerebellar cortex was selectively deactivated by self-produced movement resulting in a tactile stimulus and was activated by externally produced tactile stimulation. Patients with schizophrenia, in contrast, do not demonstrate attenuation in somatosensory cortical activation in association with self-generated movement. This may provide a cerebral basis for the increasing body of behavioural evidence that suggests that

misjudgement of agency leads to a set of symptoms of schizophrenia such as delusions of control, but the evidence is largely indirect.

Second, I have assessed for the first time with this paradigm a clinical population different to patients with schizophrenia and delusions. Therefore data for comparing with other patients, especially those with other involuntary movements, and interpreting my results is lacking.

Third, patients with FMD commonly display emotional disturbances and so far little is known about how different components of emotions may determine agency processing at different stages.

Therefore, further studies comparing patients with FMD, patients with other movement disorders and a group of patients with affective disorders are encouraged. In this regard, additional work assessing SA with other non-behavioural paradigms would be also important. They could study for instance the physiological phenomenon of SEPs at the onset of self-generated movements as this has been proposed to be the plausible electrophysiological correlate of the psychophysiological reduction in intensity of self-generated stimuli probed by the force matching and other behavioural paradigms of SA.

A new model for functional symptoms

Taking all the elements emerging from this thesis and summarised in this chapter, it seems reasonable to suggest that any model seeking to explain FMD and by extension, other functional neurological disorders, must be able to clarify how a physical neurological symptom is adopted by an "a priori" normal neurological system and also explain the paradox of a symptom that requires attention to clinically manifest (which one can argue that it should be associated with a strong sense of "voluntariness") and that, by contrast, it is felt as involuntary.

There is a contemporary theory, which is based on active inference and a hierarchical Bayesian formulation of the brain, that could accommodate all findings described in this thesis (Friston, 2010). There is a robust mathematical framework that underpins this theory, which can explain the brain from a cellular to a more behavioural perspective. However, in what follows, I will try to summarize the main concepts of this theory in a more qualitative, non-mathematical manner.

Within this theory the brain is understood as an inference machine. Here, perception arises from the interaction of the internal model of the world (predictions/expectations/beliefs that the brain has about the world) and the sensory data that the brain receives from the environment. Any mismatch between the expectations/beliefs and the real sensory data from the environment is known as prediction error. The aim of the brain is to minimise this mismatch through interactions between multiple levels of the cortical hierarchy of the neuronal system. The critical issue with this system is that it is possible to "weight" sensory data and predictions about that data differently, so one may have more or less

influence on the other. Imagine navigating from your bed to the door to the bedroom in the dark. If it is your own bedroom which you know well, you are likely to "trust" (i.e. weight) your predictions about the structure of the room over any sensory information, and so walk boldly (and hopefully correctly) towards the door. If it is an unfamiliar room you are more likely to weight your sensory feedback, and so feel carefully along the wall with your hand to try to find the door. Here attention plays an important role. 'Attended' expectations/beliefs or sensations are granted high weight or precision and perception (and movement control) is adjusted accordingly.

Within this framework, it can be suggested that sensory data, for instance that arising from physical events prior to the onset of FMD, combined with many other factors, including panic or affective and cognitive biases, are afforded excessive precision (weight) and may lead to the formation of abnormal expectations/beliefs trying to explain or predict those sensations. This abnormal expectation/belief whose content would be an abnormal movement or sensation may be rendered resistant to extinction through the unusually high levels of precision enjoyed during its formation.

When combined with self-directed attention, precision of these expectations are high enough to overwhelm contrary sensory data from lower levels and automatically produce the abnormal movement consistent with the content of the expectation. This would fit with my results suggesting that the motor impairment occurs when conscious attentive control of movement is possible or when attention is directed to the symptom.

It is not clear at present exactly how one can place the phenomenon of SA within this framework, and therefore how one can explain the way in which SA, sense of agency and this Bayesian model of the brain all interact. One suggestion is that abnormal attention towards the body in patients with FMD may itself disrupt SA (Brown *et al.*, 2013). If SA is part of the mechanism whereby a movement is signalled as intended/willed or not, then its disruption by abnormal attention towards the body in FMD may be in part a mechanism for why patients might be more likely to lose a sense of agency for their actions (it is of note that a proportion of patients with FMD develop progression and spread of symptoms over time with no particular trigger).

This conclusion raises two crucial questions. First, is the loss of SA in FMD patients a 'trait': is it present before and after their motor symptoms? Second, what further factors are required to transform a trait loss of SA into a state loss of agency for a particular action? Hopefully, further work will help to provide answers.

9.1   Conclusions

FMD and functional neurological symptoms in general are common and disabling and represent one of the most enigmatic disorders of the brain. Surprisingly, we are still in the infancy of understanding the underlying pathophysiological mechanism. The finding of the studies described in this thesis may go some way to enlightening us on how these symptoms are generated and why they may feel involuntary. Although these studies may be interpreted as snapshots of what may be occurring in this group of patients, they do not, unfortunately, provide a clear explanation for why these perplexing symptoms occur. It was Sigmund Freud himself who recognized *"if by doing this research we have taken a step forward along the path first traced so successfully by Charcot with his explanation of hysteria, we cannot conceal from ourselves that this has brought nearer to an understanding only of the mechanism of hysterical symptoms and not of the internal causes of hysteria. We have done no more than touch upon the aetiology of hysteria"* (Breuer and Freud, 1974)*.*

9.2   Implications for further research

As I mentioned at the very beginning of this thesis, I have assessed different aspects of the pathophysiology of FMD in each of the studies included. In this last chapter I have gone through each of them and I have suggested further work to improve them from a methodological perspective. One step forward would be to look at them before and after recovery from symptoms. This could help to identify whether they are actually important in symptom generation or not.

For instance, if I was asked to start more studies on FMD, I would assess SA in patients before and after recovery. In this way, I could better interpret whether reduced SA is a trait which makes one vulnerable to developing FMD or it is a state that is only present when patients are symptomatic. This work would be important to be more confident about the underlying mechanisms of this condition and also to develop biomarkers which could then be used as surrogate markers in clinical trials or perhaps even as predictive markers of likely treatment response or poor prognosis.

Finally, new areas to explore in the future would be to demonstrate whether other functional neurological symptoms share common underlying mechanisms of symptom production. I have only assessed patients with FMD in my work and generalizability of my results to other functional patient samples is not possible. An interesting aspect would be to demonstrate that abnormally focussed attention is also present, for instance, in the generation of symptoms characterised by loss of function such as weakness and hypoesthesia. From the clinical point of view it is often possible to demonstrate that functional paresis may improve with distraction

but demonstration that functional anaesthesia may depend on the presence of attention is more difficult. This is because attention is unavoidably directed to the symptom when one assesses sensation. In this regard, further studies could combine functional imaging and evoked potentials to explore different attentional responses when manipulating attention towards/away the symptoms in patients with functional sensory loss.

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APPENDIX

The author's publications in scientific journals in relation to functional movement disorders (those not included in this thesis are also listed).

1. **Pareés I**, Brown H, Nuruki A, Adams RA, Davare M, Bhatia KP, Friston K, Edwards MJ. Loss of sensory attenuation in patients with functional (psychogenic) movement disorders. Brain 2014; 137:2916-21

2. **Pareés I**, Kojovic M, Pires C, Rubio-Agusti I, Saifee TA, Sadnicka A, Kassavetis P, Macerollo A, Bhatia KP, Carson A, Stone J, Edwards MJ. Physical precipitating factors in functional movement disorders. J Neurol Sci 2014; 338:174-7

3. **Pareés I,** Saifee TA, Edwards MJ. Functional motor or somatoform disorders in PD? Mov Disord 2013. [Epub ahead of print].

4. Batla A, Panicker J, Edwards M, Stamelou M, **Pareés I,** Kasavetis P, Bhatia K. Lower urinary tract symptoms in functional movement disorders. J Neurol Neurosurg Psychiatry 2013. [Epub ahead of print].

5. **Pareés I,** Kassavetis P, Saifee TA, Sadnicka A, Davare M, Bhatia KP, Rothwell JC, Bestmann S, Edwards MJ. Failure of explicit movement control in patients with functional motor symptoms. Mov Disord 2013; 28:517-23.

6. Batla A, Stamelou M, Edwards MJ, **Pareés I,** Saifee TA, Fox Z, Bhatia KP. Functional movement disorders are not uncommon in the elderly. Mov Disord 2013; 28:540-3.

7. Stamelou M, Cossu G, Edwards MJ, Murgia D, **Pareés I**, Melis M, Bhatia KP. Familial psychogenic movement disorders. Mov Disord. 2013; 28:1295-8.

8. **Pareés I,** Saifee TA, Kojovic M, Kassavetis P, Rubio-Agusti I, Sadnicka A, Bhatia KP, Edwards MJ. Functional (psychogenic) symptoms in Parkinson's disease. Mov Disord 2013. [Epub ahead of print].

9. Brown H, Adams RA, **Pareés I**, Edwards M, Friston K. Active inference, sensory attenuation and illusions. Cogn Process 2013 [Epub ahead of print].

10. Roper LS, Saifee TA, **Pareés I,** Rickards H, Edwards MJ. How to use the entrainment test in the diagnosis of functional tremor. Pract Neurol 2013 [Epub ahead of print].

11. Edwards MJ, Fotopoulou A, **Pareés I**. Neurobiology of functional (psychogenic) movement disorders. Curr Opin Neurol 2013; 26:442-7.

12. **Pareés I,** Saifee TA, Kassavetis P, Kojovic M, Rubio-Agusti I, Rothwell JC, Bhatia KP, Edwards MJ. Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor. Brain 2012; 135:117-23.

13. **Pareés I,** Kassavetis P, Saifee TA, Sadnicka A, Bhatia KP, Fotopoulou A, Edwards MJ. 'Jumping to conclusions' bias in functional movement disorders. J Neurol Neurosurg Psychiatry 2012; 83:460-3.

14. Kassavetis P, Batla A, **Pareés I**, Saifee TA, Schrag A, Cordivari C, Bhatia KP, Edwards MJ. Joint hypermobility syndrome: a risk factor for fixed dystonia? Mov Disord 2012; 27:1070

15. Saifee TA, Kassavetis P, **Pareés I**, Kojovic M, Fisher L, Morton L, Foong J, Price G, Joyce EM, Edwards MJ. Inpatient treatment of functional motor symptoms: a long-term follow-up study. J Neurol 2012; 259:1958-63.

16. Edwards MJ, Adams RA, Brown H, **Pareés I**, Friston KJ. A Bayesian account of 'hysteria'. Brain 2012; 135:3495-512.

The author's contribution in books in relation to functional movement disorders:

1. **Pareés** and M.J. Edwards. Psychogenic Movement Disorders. In: Baumann and Wolters (ed). Parkinson's disease and other Movement Disorders. VU University Press (2014).

2. **Pareés** and M.J. Edwards. Psychogenic Movement Disorders. In: David J Burn, Christopher Kennard (ed). Oxford Textbook of Movement Disorders. Oxford University Press (2012).