Perspectives on functional and hyperkinetic movement disorders

Phenomenology & pathophysiology

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Chapter 1

GENERAL INTRODUCTION
Chapter 1

**FUNCTIONAL MOVEMENT DISORDERS - PHENOMENOLOGY**

Functional movement disorders (FMD) are abnormal movements that are inconsistent with a known organic aetiology.(1) FMD are frequently encountered in the outpatient clinic and comprise between 3% and 15% of patients seen by neurology movement disorder specialists in tertiary referral clinics.(2) FMD phenomenology can resemble tremor, myoclonus, dystonia, gait disorders, or combinations of these abnormal movements. Diagnosis and treatment of FMD is difficult and FMD have therefore been considered to constitute an alarming “crisis in Neurology”.(3) Typical clinical characteristics of FMD are acute onset, fast progression, movement patterns incongruent with organic movement disorders, distractibility, variability, and the simultaneous occurrence of various abnormal movements and dysfunctions.(1)

In general, neurologists are cautious to diagnose FMD in order to avoid misdiagnosis of an organic disorder as conversion disorder. One early seminal study by Slater in 1965 investigated the misdiagnosis rate of “hysteria” and found that 33% of patients originally diagnosed as “hysteria” later turned out to have a confirmed organic disorder.(4) However, a more recent systematic review disproved this high rate of misdiagnosis and demonstrated a 4% misdiagnosis rate in a large cohort (n = 1466) of patients with conversion symptoms.(5) Therefore, the caution to diagnose FMD in order to avoid diagnostic error may be unfounded. In contrast, others have claimed that “undiagnosing” a patient who was first diagnosed with an organic neurological disorder and later considered to have a functional neurological disorder is an equally problematic diagnostic error as the initial misdiagnosis of an organic disorder as FMD.(6)

The diagnostic criteria as initially proposed by Fahn and Williams indicate the diagnostic degree of certainty of FMD as “documented”, “clinically established”, “probable” or “possible”.(7) (see Table 1) Later, the diagnostic certainty criteria were critically revised by Gupta and Lang and they introduced the diagnostic category “laboratory supported definite” FMD.(8) (see Table 2) According to Gupta and Lang, electrophysiological studies are advised to confirm the clinical diagnosis FMD. The diagnosis “laboratory supported” FMD is made in case electrophysiological testing concurs with the clinically established diagnosis of FMD. For example, the diagnosis of functional tremor can be supported with simultaneous EEG and EMG recordings showing entrainment (i.e. the functional tremor synchronizes with the tapping frequency). In case of irregular twitching or jerky movements, jerk-locked back averaging can be used to demonstrate the Bereitschaftspotential (BP or Readinesspotential).(9) The presence of the BP prior to the muscle movement supports the diagnosis of jerky FMD.(9) The purpose of this thesis was to examine the phenomenology and pathophysiology of jerky FMD from a clinical, electrophysiological and neuro-imaging perspective. The diagnostic process towards the FMD diagnosis and the diagnostic value of the BP, as supportive criterion for the diagnosis FMD, were studied in detail.

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**Table 1**

<table>
<thead>
<tr>
<th>Degree of certainty</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically established</td>
<td>The movement disorder is congruent or consistent with a classical movement disorder</td>
</tr>
<tr>
<td>Documented</td>
<td>The movement disorder is incongruent or inconsistent with typical movement disorders or psychiatric disturbance</td>
</tr>
<tr>
<td>Probable</td>
<td>The movement disorder is congruent or consistent with a classical movement disorder or there are inconsistencies in the examination, plus at least one of the following three: other psychogenic signs, multiple somatisations, or an obvious psychiatric disturbance.</td>
</tr>
<tr>
<td>Possible</td>
<td>The movement disorder is incongruent with a classical movement disorder or there are inconsistencies in the examination, without the need for the additional psychiatric disturbance.</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Description</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory supported definite</td>
<td></td>
</tr>
<tr>
<td>Documented</td>
<td>The movement disorder is congruent or consistent with a classical movement disorder</td>
</tr>
<tr>
<td>Probable</td>
<td>The movement disorder is congruent or consistent with a classical movement disorder or there are inconsistencies in the examination, plus at least one of the following three: other psychogenic signs, multiple somatisations, or an obvious psychiatric disturbance.</td>
</tr>
<tr>
<td>Possible</td>
<td>The movement disorder is congruent or consistent with a classical movement disorder or there are inconsistencies in the examination, without the need for the additional psychiatric disturbance.</td>
</tr>
</tbody>
</table>
Chapter 1

Functional movement disorders (FMD) are abnormal movements that are inconsistent with
movements and dysfunctions. Diagnosis and treatment of FMD is difficult and FMD have therefore been considered to
distinguish or periodic tremors or dystonias, somatosensory deficits, or a combination of these abnormal
movements.

In general, neurologists are cautious to diagnose FMD in order to avoid misdiagnosis of an
movement disorders, distractibility, variability, and the simultaneous occurrence of various abnormal
movements. Gupta and Lang and they introduced the diagnostic category
psychogenic signs, multiple somatisations, or an obvious psychiatric disturbance.

The diagnostic criteria as initially proposed by Fahn and Williams indicate the diagnostic
degree of certainty of FMD as
be helped by physiotherapy; or the patient was seen without the movement disorder when
believing him- or her-self unobserved.

**Table 1** Fahn-Williams criteria for psychogenic movement disorders (7) (as summarized in (1))

<table>
<thead>
<tr>
<th>Degree of certainty</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented</td>
<td>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 her-self unobserved.</td>
</tr>
<tr>
<td>Clinically established</td>
<td>The movement disorder is incongruent with a classical movement disorder or there are inconsistencies in the examination, plus at least one of the following three: other psychogenic signs, multiple somatisations, or an obvious psychiatric disturbance.</td>
</tr>
<tr>
<td>Probable</td>
<td>The movement disorder is incongruent or inconsistent with typical movement disorders or there are psychogenic signs or multiple somatisations.</td>
</tr>
<tr>
<td>Possible</td>
<td>Evidence of an emotional disturbance.</td>
</tr>
</tbody>
</table>

**Table 2** Revised diagnostic criteria as proposed by Gupta & Lang (8) (as summarized in (1))

<table>
<thead>
<tr>
<th>Degree of certainty</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically definite</td>
<td>Includes Fahn-Williams documented and clinically established categories, and also includes movement disorders that are incongruent with a classical movement disorder or for which there are inconsistencies in the examination, without the need for the additional presence of psychogenic signs, multiple somatisations, or an obvious psychiatric disturbance.</td>
</tr>
<tr>
<td>Possible</td>
<td>Gupta and Lang question the utility of this category. This category is reserved for patients with movement disorders congruent or consistent with a classical movement disorders that also have additional psychogenic signs, somatisations, or evidence of emotional disturbance. Gupta and Lang suggest that this category may then include patients who are pathophysiological different from those with “true” psychogenic movement disorders.</td>
</tr>
<tr>
<td>Laboratory supported definite</td>
<td>Electrophysiological tests that support the presence of a psychogenic movement disorder (primarily evidence of pre-movement potentials (BP) before jerks or entrainment in tremor EEG-EMG recordings).</td>
</tr>
</tbody>
</table>
Chapter 1

**TERMINOLOGY: HYSTERIA AND PSYCHOGENIC**

Historically, “hysteria” has fascinated medical doctors with Charcot as the first prominent medical expert in the field. (10) Hysteria originated from the Greek word *hystera* (uterus) and the term reflected the first pathophysiological model to explain symptoms as originating from “a wondering womb”. (11) Later, the pathophysiological explanations switched from the uterus to the brain as the organ involved in the cause of hysteria. In 18th and 19th centuries symptoms were classified as “neuroses” implying a disorder of function of the nervous system. (11) During this period, *the mind* (as opposed to *the body*) was viewed as an important source of hysterical symptoms and the explanatory framework and terminology shifted to *the psyche*. Accordingly, symptoms were labelled as “psychogenic”, and this term was used interchangeably with conversion disorder. (12,13)

Prior to the release in May 2013 of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5), the term “psychogenic” movement disorders was commonly used in publications. (14) In the DSM-5 the idiom “functional neurological” has been introduced to replace conversion disorder. (14) In Neurology, opposition to the term “psychogenic” movement disorders has been based on a seminal paper that showed that “psychogenic” is considered offensive by patients. (15) The “number (of patients) needed to offend” was lowest for hysteria, implying that after communicating the diagnosis as “hysteria” to a low number of patients, many were offended. (15) The “number needed to offend” was highest when the diagnosis was communicated by the doctor as “functional”, implying that the diagnosis could be told to many patients before 1 was offended. (15) Thus, in the consensus of DSM–5 “functional neurological symptom disorder” is the preferred term. In this thesis, that was written during this change in terminology, we will use the “psychogenic movement disorder” in the initial publications and “functional movement disorder” in later publications.

**FUNCTIONAL MOVEMENT DISORDERS - PATHOPHYSIOLOGY**

The historical emphasis on psychological causes is demonstrated by the previously applied terminology for FMD. Based on late 19th and early 20th century observations, psychological hypotheses of conversion, somatisation and dissociation posed that inner emotional conflicts often form the basis for psychiatric diagnoses in these disorders. However, research on the pathophysiological mechanisms underlying conversion disorders is scarce.

At the start of the current studies described in this thesis no pathophysiological models of FMD had been published. (16) During the studies in the current thesis, new insights were published which changed the explanatory paradigm shift of FMD from “psychogenic” to “functional”. (1) The term “psychogenic” implies a psychological cause of FMD. However, recent reports demonstrate that patients with FMD do not have the expected rates of psychological trauma or psychiatric co-morbidity. (17) The absence of psychiatric co-
morbidity has fuelled insights into the pathophysiology of FMD and support the use of the term FMD instead of “psychogenic”. In recent years much emphasis has been put on the involvement of the voluntary motor system, based on the fact that in FMD patients their involuntary movements have features that are usually associated with voluntary movement (for instance distractibility), and are associated with the presence of the pre-movement BP. The BP entails a slow negative electroencephalographic (EEG) activity that is commonly found preceding the execution of voluntary movements in healthy subjects. Based on experiments by Libet, the BP has been assumed to be neuroscientific proof against free will, because the BP precedes the timing of the experience of “will” or volition of consecutive movement by 1 or 2 seconds. Moreover, a BP can precede jerky movement induced by FMD. The presence of the BP in FMD supports involvement of the voluntary motor circuit in the generation of hyperkinetic jerky FMD. Despite these features and the BP pointing towards involvement of voluntary motor circuits, FMD patients experience the movements as involuntary. Thus, the pathophysiology of FMD presumably encompasses the voluntary motor circuit and the areas related to the subjective experience of control over movement. The current pathophysiological models postulate three mechanisms underlying FMD: 1) an abnormal sense of self-agency (or the sense of being in control of one’s actions), 2) abnormal focus of attention, and 3) abnormal prior beliefs and expectation of movements. Over the recent years several neuro-imaging and experimental studies support these three mechanisms in FMD.

**Differential Diagnosis – Other Hyperkinetic Movement Disorders**

In order to avoid misdiagnosis of FMD, the treating physician needs to be familiar with the differential diagnosis consisting of other movement disorders, needs to detect the incongruences and inconsistencies typical for FMD, and needs to distinguish FMD from these other movement disorders. In case of jerky FMD, tics (usually within the scope of Gilles de la Tourette Syndrome (GTS)) and myoclonus are the main differential diagnoses to consider.

GTS is a neuropsychiatric disorder with motor and vocal tics as clinical hallmarks. Diagnosis is based solely on clinical criteria, with the required presence of 2 or more motor tics and 1 or more vocal tics before the age of 18 years old, for the duration of more than 1 year. The prevalence of GTS is estimated between one and ten per 1,000 children and adolescents and the outcome is generally favorable; most patients improve by their late teens or early adulthood. The ability of tic suppression differentiates GTS from other movement disorders. However, tics can usually only be suppressed temporarily, and need to be released eventually. Common comorbidity in GTS encompass attention deficit and hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). Despite indications that GTS is an inherited disorder, the exact genetic defect is unidentified. The pathophysiology of GTS tics is unknown. The major prevailing hypothesis for tics
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encompasses deficient inhibitory control through the cortical-striatal-thalamic-cortical motor loop. Imaging studies using positron emission tomography (PET) and more recent fMRI studies have shown functional abnormalities in the striatum, thalamus and related cortical regions. In addition, recent evidence suggests prefrontal dopaminergic abnormalities. Currently, there is no diagnostic or neurophysiological test to support the diagnosis of GTS.

Another neurological disorder resembling jerky hyperkinetic FMD is myoclonus. Myoclonus is defined as brief, involuntary jerks. The myoclonic jerks usually present as short muscle contractions resulting in a shock-like movement (so-called 'positive' myoclonus). The causes of myoclonus are diverse, ranging from physiological, essential, epileptic, and symptomatic myoclonus. The latter is by far the largest group, containing a wide range of diagnoses ranging from post-anoxic myoclonus and metabolic encephalopathies to various genetic causes. Based on clinical and neurophysiological clues, myoclonus can be subdivided according to its neuro-anatomical origin: the cortex, subcortical structures, brainstem, spinal cord or peripheral nervous system. Localisation of the origin of the myoclonic jerks narrows down the differential diagnosis for the underlying disorder. Electrophysiological tests can provide support for the localization of the myoclonus. For instance, a brief duration of the EMG bursts (<100ms) and a giant somatosensory evoked potential (SSEP) supports a cortical origin.

TREATMENT

Treatment of FMD is difficult and often consists of a combination of psychiatric counseling and physiotherapy. Only few studies have systematically investigated treatment strategies of FMD. There is some indication that cognitive behavioral therapy, whether or not combined with physical activity, might be beneficial. Prognosis is poor in case of chronic FMD. Factors associated with a more favorable prognosis include short duration of symptoms, early diagnosis, and high patient satisfaction with the provided care. These findings clearly show the need for effective early recognition, diagnosis and intervention strategies in FMD.
AIMS AND OUTLINE OF THIS THESIS

The main objective of this thesis is to elucidate the phenomenology and pathophysiology of jerky FMD from a clinical, electrophysiological and neuro-imaging perspective. The aim is to identify features that help to differentiate patients with FMD from patients with other hyperkinetic movement disorders, in particular myoclonus and tics. Moreover, EEG-EMG and EMG-fMRI are applied to study the generation of voluntary and involuntary movements to reveal the underlying pathophysiological mechanism in FMD.

Chapter 2 investigates the inter-rater agreement of renowned clinical experts on a case-series of patients with various jerky hyperkinetic movement disorders (FMD, tics and myoclonus). In chapter 3, the clinical decision making of the expert panel is investigated to deduce how the diagnosis FMD, tics and myoclonus is made. Chapter 4 reviews the clinical features of all published cases of patients with propriospinal myoclonus (PSM). The incentive for this review was the publication of several case series that described that patients referred with PSM-like truncal jerks were diagnosed as FMD instead of PSM. We therefore reviewed all published case reports of PSM to assess clinical characteristics commonly associated with FMD. In chapter 5 the diagnostic value of the BP in the decision making process is investigated by means of electrophysiological testing of patients with FMD, tics and myoclonus in comparison to healthy control subjects who voluntarily imitate these disorders. In chapter 6, a neurophilosophical phenomenological perspective on FMD and free will is provided. In philosophy, the term phenomenology is used for the objective study of subjective topics, for instance consciousness and conscious experiences (e.g. judgements and perceptions). The connection of voluntary and involuntary movement disorders and free will are explored both from a clinicians’ and patients’ perspective and contemplated upon. Because the BP is considered as the neuroscientific proof against free will, in chapter 6 we also test the hypothesis that the presence of the BP is correlated with a higher degree of perceived volition in patients with FMD and tics. Chapter 7 takes a neuro-imaging perspective on the pathophysiology of FMD. In this chapter, we investigate why patients with FMD have difficulty to perform a voluntary task. During functional MRI a finger tapping task is performed by FMD patients, healthy controls and GTS patients that serve as a hyperkinetic control group. The results of all studies in this thesis are summarized and discussed in chapter 8 and recommendations for future studies are proposed.
REFERENCES

Chapter 1


