Perspectives on functional and hyperkinetic movement disorders

Phenomenology & pathophysiology

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Chapter 8

SUMMARY AND GENERAL DISCUSSION
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**Perspectives of the Thesis**

Functional movement disorders (FMD), previously known as conversion disorders or psychogenic movement disorders, are frequently encountered in movement disorder outpatient clinics.\(^{(1,2)}\) Yet, most neurologists consider FMD difficult to diagnose. Clinically, the phenomenology of jerky movement disorders ranges from FMD to tics and myoclonus. 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.

The first chapters (chapter 2 to 4) of the thesis entail several studies on the clinical phenomenology of FMD, tics and myoclonus. In chapter 5, we assess the diagnostic value of the Bereitschaftspotential (BP). Next, a neurophilosophical perspective on the phenomenology of movement disorders is given in chapter 6. Phenomenology, in philosophical terms, is the objective study of subjective topics such as conscious experiences (judgments, perceptions, and emotions). We report the findings of the phenomenological study on FMD, measuring the perceived voluntariness of FMD, tics and myoclonus as perceived by clinicians and patients and explored the relationship of perceived voluntariness and the BP. Chapter 7 aims to elucidate the pathophysiological mechanisms of FMD using neuro-imaging.

The studies presented in this thesis are conducted in a group of patients with jerky hyperkinetic movements of functional origin. This FMD patient sample with homogenous jerky phenotype can serve as a model to study pathophysiological mechanisms for all functional neurological disorders. Agreement on the phenomenological classification of jerky movements facilitates an accurate and fast diagnostic process, which is important because delayed diagnosis in FMD is associated with a poor prognosis.\(^{(3, 4)}\) Insight into the pathophysiology of FMD can direct future therapeutic strategies in FMD.

The current chapter summarizes the main findings as described in this thesis, places the results into a broader perspective and provides suggestions for future studies.
DIAGNOSTIC PERSPECTIVE

The first studies in this thesis evaluate the clinical phenomenology of FMD from a diagnostic perspective. The study in chapter 2 examines the inter-rater agreement among internationally renowned movement disorder experts. To diagnose FMD, clinicians must have knowledge of signs typical of FMD and must distinguish these features from signs in other hyperkinetic disorders. Patients with jerky FMD, myoclonus or tics were rated by the experts using an online diagnostic approach. For each case we provided the following diagnostic items in a stepwise manner: a first impression of the patient’s movements on video, medical history, and the results of a neurological examination, the electrophysiology results (BP recordings) and the findings of the psychiatric diagnostic interview. After each step the most likely diagnosis (jerky FMD, myoclonus or tics) and the level of perceived diagnostic certainty were scored. Remarkably, we found only moderate (kappa = 0.56 ± 0.1) inter-rater agreement on the final diagnosis. Moreover, only in 20% of cases absolute agreement (100%) of experts on the final diagnosis and in 72% of the patients reasonable agreement (>75%) was reached. Overall, the inter-rater agreement on the diagnosis of tics was highest and of myoclonus was the lowest, with FMD scoring in-between. Thus, functional or psychogenic movement disorders (FMD) present a diagnostic challenge.

The moderate inter-rater agreement that was found might be explained in different ways. First, it is known that several aspects of the neurological examination are hampered by moderate inter-rater agreement. For instance, the inter-rater agreement of Babinski sign, a hallmark in the neurological examinations, is only fair (kappa = 0.30). Further, with respect to movement disorders, inter-rater agreement on the distribution of dystonia is moderate for blepharospasm (kappa = 0.51) and cervical dystonia (kappa = 0.52), fair for writer’s cramp (kappa = 0.29), and low for oromandibular dystonia (kappa = 0.20). Therefore, our finding of moderate inter-rater agreement on the phenomenology of FMD is in line with these reports of fair to moderate inter-rater agreement. A small study on inter-rater agreement in FMD (14 patients) demonstrated that the agreement was ‘slight’ (kappa = 0.34 and 0.4) while comparing FMD with organic movement disorders. In contrast, in a study of 29 videos posted on the internet (YouTube) that show people with movement disorders, 66% of the videos were rated as psychogenic and 34% as organic. In this study, a remarkable almost perfect inter-rater agreement (kappa = 0.98) was found. One explanation could be that in that study a dichotomous (organic/psychogenic) choice in rating was given to the expert, which is more likely to lead to higher agreement than 3 options (FMD, tics, myoclonus). Moreover, patients that post videos on the internet may be more ‘clear-cut’ or more obvious FMD cases compared to our study with patients visiting a specialized movement disorders outpatient clinic (selection bias). Another explanation for our moderate inter-rater agreement in our study could be that the study design with online videos does not resemble the ‘real-life’ hands-on diagnostic process in the outpatient clinic. Real-life diagnostic agreement might be higher, as clinicians might have access to more information in real life, such as non-verbal clues. Future studies should compare real-life
evaluation of hyperkinetic patients with video-based information to investigate if the inter-rater agreement is higher.

Along with the increase of inter-rater agreement, the degree of diagnostic certainty perceived by the experts increased with the provision of incremental diagnostics information. After the first impression the degree of diagnostic certainty was relatively low at 1.9 (SD ± 0.97) on a 5-point scale, increasing to 3.5 (SD ± 1.22) at final diagnosis (p<0.001). The addition of medical history, neurological exam and BP results significantly increased the degree of certainty, whereas psychiatric assessment did not.

Chapter 3 extends on the findings of the previous inter-rater agreement study. The aim of this study was to clarify the decision making process of expert clinicians while diagnosing FMD, myoclonus and tics. The diagnostic decision making process of experts clinicians provided valuable insight into how experts diagnose functional and hyperkinetic movement disorders. We found that experts rely on clinical assessment (first impression, history and neurological examination) in the majority (91,5%) of cases to establish a final diagnosis. Importantly, additional electrophysiological investigations (the BP) do only infrequently (8% of cases) determine the final diagnosis of the clinical experts. However, the order of presentation of the information may have influenced the findings of this study. The psychiatric evaluation was presented at the final steps of the diagnostic work-up, and earlier provision of this information might have resulted in a higher attributed diagnostic value. However, even though the psychiatric evaluation was presented as the last diagnostic step, experts were able to annotate the last diagnostic step as the most important in their diagnostic decision making, which they did not. As the consecutive order itself also induces bias, as every next diagnostic step includes information from previous steps, this bias would have tended to favor the latter steps as most important. In contrast, the findings of this study demonstrate the opposite, which implies this is not a significant bias in our study design.

Remarkably, we found that changes in differential diagnosis during the diagnostic process of experts were infrequent. The studies in chapter 2 and 3 clearly showed that FMD currently is a clinical diagnosis, but experts used different heuristics to make this diagnosis and valued steps in the diagnostic process differently. Some experts relied more on their first impression of the patients, while others rely on the neurological examination to diagnose FMD. This is in line with a previous interviews of neurologists on the diagnosis of conversion disorder.(9) Neurologists reported that “they often had an inkling that an organic explanation for the patients’ symptoms would not be found within the first few minutes of the clinical encounter”.(9) To summarize, experts predominantly rely on clinical assessment to diagnose FMD and infrequently change their diagnosis, which can be made based on the first impression. Thus, at present the Fahn and Williams diagnostic criteria for FMD and its updates did not suffice to establish good inter-rater agreement.(10, 11) Therefore, new diagnostic consensus criteria are needed, preferably incorporating the electrophysiological findings (BP) as well.
In chapter 4, we review the clinical phenomenology and electrophysiological findings in all published cases of propriospinal myoclonus (PSM). PSM was first described as an organic movement disorder which was characterized by repetitive arrhythmic muscle contractions of the trunk and limbs. Over the course of this PhD thesis, a paradigm shift has taken place and several case series, including from our own center, reported that truncal flexion jerks resembling PSM are actually FMD. This observation was the incentive to review all published cases of PSM to evaluate clinical characteristics commonly associated with FMD. Based on this review, we propose new criteria for PSM and suggest three categories: idiopathic, secondary, and functional PSM. The proposed criteria for functional propriospinal-like jerks are: 1) clinical clues; 2) involvement of facial musculature or vocalizations (incompatible with a spinal origin); 3) normal imaging findings of the spinal axis (no myelopathy); and 4) an inconsistent pattern on EMG (polymyography) or presence of a BP. After re-evaluation of all published PSM cases, we concluded that FMD should be considered as the most frequent underlying cause in the reported cases. Based on our clinical experience and the reviewed literature, we recommend to measure variability in muscle recruitment using polymyography combined with a BP recording in the diagnostic work-up of all patients with PSM-like jerks. Although structural lesions rarely underlie axial jerks, additional imaging is recommended in order not to miss this small, but important, subgroup of (treatable) secondary PSM.
In chapter 5 we approached the differentiation of jerky hyperkinetic movement disorders from a neurophysiological perspective. The aim of this study was to examine the diagnostic value of the BP in jerky movement disorders. If a BP is found to precede the jerky movement, the diagnosis FMD is more likely, but a BP can also precede tics. Consequently, we conducted measurements to determine the diagnostic value of the BP and tested if a BP was present prior to the spontaneous jerk in patients with jerky FMD, Gilles de la Tourette syndrome (GTS) or myoclonus and voluntary wrist extension. In FMD patients, significantly more BPs were found prior to the jerky movements induced by their disorder compared to patients with GTS and myoclonus. Moreover, a BP never preceded myoclonic jerks. In 86% of patients with FMD a BP was found prior to their spontaneous jerks compared to 43% of GTS patients (p=0.003) and none of the myoclonus patients (p<0.001). In patients with FMD, the BP preceding their jerks had a significantly earlier onset (median onset 1195 ms) compared to GTS patients (median onset 915 ms, p=0.020). The duration of a BP may therefore be helpful in differentiating tics from FMD. Absence of the BP prior to the spontaneous jerks may however be the case in FMD, tics and myoclonus. The absence of a BP prior to the spontaneous jerky movements therefore does, however, not differentiate FMD from myoclonus or tics.

In all healthy control subjects, we found a BP prior to all types of intentionally performed movements (self-paced wrist extension and various movements of jerks of patients). Prior to our study it remained to be established if a BP could actually be correctly measured in intentionally produced jerks of the legs. The somatotopy of the primary motor cortex, with its interhemispheric located leg area deep in the sulcus, was thought to lead to false negative BP tests. On the contrary, we found a BP preceding intentional leg movements in all healthy control subjects.

An intriguing finding of our study was that in 59% of FMD cases the BP was not found prior to self-paced wrist extensions. In contrast, the BP was present in all patients (100%) with myoclonus and all but one (93%) of GTS patients. The absence of a BP prior to intentional wrist extension turned out to have a high specificity (0.98) and positive likelihood ratio of 25 for the diagnosis FMD. Hence it therefore follows that the absence of the BP prior to intentional wrist extension has the potential to differentiate FMD from other movement disorders. The absence of a BP prior to the wrist extension (task) suggests that FMD patients have automated the movements and perform the task in an automatic, rather than an intentional, fashion. Another explanation could be that the BP measurement in itself is insufficient, due to the needs to average many trials ('back averaging'). Regrettably, consensus criteria on the requirements for a reliable BP measurement and result to fulfill (for instance amplitude, amount of averaged epochs needed) are lacking. International consensus criteria for correct measurement of a BP are therefore needed. Moreover, as indicated by the diagnostic studies (chapter 2 and 3), clinical diagnostic criteria for FMD are...
needed and the role of electrophysiological testing needs to be formalized in these criteria as well. Of interest, several experts participating in the studies reported in chapter 2 and 3 indicated that if a BP is absent prior to the spontaneous jerks, the diagnosis could still be FMD. Thus, one of the key issues that needs consensus is whether the diagnosis FMD can be made in case a BP is absent prior to the jerky movements.

In chapter 5, we found that neither the BP prior to spontaneous jerky movements nor the BP prior to intentional wrist intention can differentiate reliably between FMD and tics. The value of electrophysiological testing may have been higher if in addition to the presence/absence of a BP, the burst duration had also been provided. A consistently short burst duration (<100ms) is only seen in myoclonus and may help differentiation between the phenomenology of jerky movements. Therefore, a combination of tests may provide a more reliable diagnosis. This approach of combining several tests to reach adequate sensitivity and specificity was successfully applied in functional tremor. In analogy, it would be interesting to study whether the diagnosis of ‘laboratory supported’ myoclonus-like FMD could be made more reliably with a combination of tests. Therefore, we recommend future studies to evaluate the diagnostic value of the following combination: 1) clinical clues, 2) the presence of the BP prior to the spontaneous jerks, 3) the absence of the BP prior to voluntary wrist extension, 4) EMG duration of the muscle bursts. Future studies should examine whether the diagnosis FMD is made with a higher inter-rater agreement using these combinations and should serve as an incentive for diagnostic consensus criteria.

NEUROPHILOSOPHICAL PERSPECTIVE

In chapter 6 we explore the relationship between free will and neuropsychiatric movement disorders from a neurophilosophical phenomenological perspective. Most people perceive that their actions arise from their own ‘free will’, commonly defined as the ability to choose how to act. Neurological disorders, such as epileptic seizures and movement disorders are often regarded as conditions in which free will is undermined. Clinically, an action is considered involuntary when it is automatically performed and cannot be controlled. In this exploratory study, we compared the perceptions of clinicians and patients on ‘free will’ and voluntariness of FMD, tics and myoclonus. We developed a custom-made questionnaire (the Symptomatology and Perceived Free Will questionnaire, SAPF), based on prerequisites of free will defined by Walter. First, to act freely one must have alternative possibilities. In philosophy this is referred to as ‘the principle of alternate possibilities’ and implies that a person must be able to act otherwise. Second, to act freely means acting or choosing for a reason. Third, free will requires that one is the originator or source of one’s actions. The SAPF questionnaire consists of 14 items related to the voluntariness of the movements as part of the patients’ disorders. The SAPF items were designed to reflect the three prerequisites of free will. Using the SAPF we measured to what extent patients with
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myoclonus, tics and FMD consider their ‘free will’ to be undermined by the movements induced by their disorder. We compared these findings with clinicians’ views of voluntariness in each of these movement disorders. Opposing views of clinicians and patients on the voluntariness of tics and FMD were found. All patients perceived their movements as involuntary. Patients with FMD perceived significantly less ownership (agency) and control compared to patients with tics and myoclonus. In contrast, some clinicians viewed FMD as a voluntary disorder. This is in line with a study by Kanaan and colleagues who performed in-depth interviews with neurologists on their understanding of conversion disorders. The interviewed neurologists revealed a wide range of views on the nature of conversion disorder, and many did not regard conversion disorder as distinct from feigning. Thus, clinicians that interpret FMD as feigning consider FMD as the ultimate form of a voluntary disorder.

Next, we combined the perceived sense of free will of patients with the findings of chapter 5 (presence or absence of the BP). The rationale for this comparison was the strong held conviction of several neuroscientists that free will is an illusion. The BP is considered as the neuroscientific objective ‘proof’ against free will. Reports of the BP preceding conscious awareness have raised questions about the ‘freedom’ of movements. The presence of specific brain activity preceding awareness of the intention is considered by some neuroscientists as a proof against conscious deliberation about our actions and freedom of choice. In chapter 6 we found that the perception of free will and voluntariness in patients was not associated with the presence or duration of the BP. Thus, we postulate that the perception of control and agency and generation of the BP may be mediated via different neural circuits, and that these neural circuits are disturbed in FMD patients. Several neuroscientific studies have investigated the neural network of intention in healthy subjects. It appears that conscious intention lags behind the start of the voluntary motor preparation. In a seminal paper, attention to intention was shown, using direct cortical simulation, to be located in the pre-SMA (supplementary motor area) and the intraparietal cortex (IPS). Several studies have confirmed that the sense of intention and self-agency are generated in the parietal cortex. Thus, based on our findings we postulate that the altered awareness of intention in patients with FMD (as reported by the SAPF questionnaire) involves a mismatch between the voluntary motor circuit and the parietal cortices. I propose the notion of a “volition paradox”, which entails the paradox between voluntary motor preparation (BP) and the lack of perceived control and self-agency. The hypothesis of a volition paradox in FMD was the incentive for the multimodal neuro-imaging study in chapter 7.
**Neuro-imaging Perspective**

In chapter 7, we investigated the pathophysiology of FMD from a neuro-imaging perspective. During clinical consultation, FMD patients experience difficulty to perform a simple voluntary movement task, such as finger tapping. (16, 29) In chapter 6 we found that FMD patients reported a decreased sense of control (also known as self-agency) compared to patients with GTS. The aim of the multimodal fMRI study in chapter 7 was to understand the neural correlates involved in the volition paradox and lack of agency in FMD patients. We examined the difficulty to execute voluntary motor tasks and compared FMD patients to healthy control subjects and GTS patients (hyperkinetic control group). During finger tapping, no differences were found in activation patterns of the voluntary motor circuit (SMA, primary motor cortex, cerebellum) between the three groups. Comparing patients with FMD and GTS patients showed, decreased activation of the left DLPFC and bilateral parietal cortices (Brodmann area 31 and 7) in the FMD group. This is in line with a functional MRI study in functional tremor, in which decreased functional connectivity of the bilateral dorsolateral prefrontal cortex (DLPFC) and supplementary motor area (SMA) was found. (30) In contrast, increased activation of the DLPFC has been a consistent finding in several studies on functional sensorimotor dysfunction (both motor paralysis and somatosensory) and fixed dystonia with various experimental paradigms (see reviews (31, 32) and (33)). The increased activation of the DLPFC in ‘hypokinetic’ functional neurological disorders is explained as impairments in motor intention or disruption of motor execution. (31,32) Another explanation is that hyperactive self-monitoring, limbic processing or top-down regulation from higher order frontal regions interferes with motor execution. (30, 31, 32) Thus, the decreased activation in the left DLPFC found in our study could be a hallmark of hyperkinetic (tremor and jerky) FMD as opposed to the increased activation of the DLPFC in hypokinetic (paralysis, fixed dystonia) functional disorders.

Based on the decreased activation of the parietal cortex, we postulated that the parietal perceptual integration is decreased during voluntary task execution in FMD. This might explain the subjectively decreased sense of agency and lack of control over voluntary movements as reported by FMD patients. Moreover, the decreased activation of the parietal areas shed light on a new interpretation of the difficulty that patients perceive/experience during finger tapping, which can be described as ‘functional apraxia’. Functional apraxia resembles ideomotor apraxia in the neural activation pattern, with decreased activation of the praxis area Brodmann area 7 and the middle frontal gyrus. Upon closer investigation the difficulty that FMD patients have during finger tapping indeed clinically resembles apraxia. FMD patients use their hands as objects and therefore perceive less agency and have a similar ‘voluntary-automatic dissociation’ like patients with ideomotor apraxia. (34) The ‘voluntary-automatic dissociation’ means that patients have difficulty to perform tasks voluntarily, but can execute the same task normally in daily life as part of a routine. Our findings provide support for physiotherapeutic therapy, which was recently shown to be effective in FMD. (35) Our findings suggest that therapeutic strategies
directed to overcome this ‘voluntary-automatic’ dissociation and functional apraxia, such as physiotherapy, could help to treat FMD.

Our findings of altered activation of bilateral parietal cortex differ from previous fMRI studies, which demonstrated decreased functioning of the right temporal-parietal junction. The more extended parietal impairment as found in our study and the involvement of BA 7 and 31 (praxis areas) instead of the temporo-parietal junction might be explained by the fact that in the current study patients executed a difficult motor task. In a resting state study, in which patients do not move and hence do not require the praxis areas, decreased activations of the right temporal-parietal junction was found. The other study compared the release of functional tremor with mimicked tremor in a within patient design, and found decreased activation of the right temporal-parietal junction during functional tremor but during not mimicked tremor task.

Next, we performed a functional connectivity analysis to investigate the neural network involved in the execution of the tapping task. During finger tapping, functional connectivity was increased between the primary motor cortex and the limbic network, including the hippocampus, parahippocampal and cingulate gyrus and amygdala in FMD patients compared to both GTS patients and healthy controls (see Figure 1). Remarkably, in an imaging study using a completely opposite design, namely showing emotional faces to patients with FMD that did not have to move, the similar increased functional connectivity between the amygdala and the premotor cortex was found. These findings suggest an increased emotion-based drive to move in patients with hyperkinetic functional movement disorders, implicating a functional link between the emotional and voluntary motor network in these patients.

A major drawback of the functional MRI study was the exclusion of many participants due to motion artefact induced by the jerky movements. The exclusion of participants with the most severe jerks has implications for the interpretation of our findings and precludes drawing of firm conclusions. However, sample sizes in fMRI studies of FMD patients are usually low. These small sample sizes illustrate the difficulty of scanning FMD patients with a motion artefact sensitive imaging technique such as fMRI. To replicate our findings, future fMRI studies therefore may investigate the difficulty in the execution of voluntary tasks and the volition paradox in patients with functional paralysis. Motion artefacts are less likely to occur in patients with functional paralysis.
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Figure 1 The findings of the functional MRI study (chapter 7) in FMD patients integrated in the conceptual framework for the generation of normal volitional movement (based on (20, 21, 40-42)). During execution of the finger tapping task, decreased activation of the parietal lobe and dorsolateral prefrontal cortex (DLPFC) is found (depicted as hypoactivation in blue). We postulate that this implies decreased perceptual integration. In addition, in patients with FMD, the functional connectivity analysis showed that the drive to move originating in the limbic areas (in red) has increased functional connectivity with the primary motor cortex.
FUTURE PERSPECTIVES

The studies in this thesis shed light on the phenomenology and pathophysiology of jerky FMD and other hyperkinetic movement disorders from a clinical diagnostic, neurophysiological, neurophilosophical and neuro-imaging perspective. However, several key questions regarding the phenomenology and pathophysiology of FMD remain to be solved and will be discussed in the following sections.

PHENOMENOLOGY: FUTURE PERSPECTIVES

The diagnostic studies described in this thesis emphasize that FMD is a clinical diagnosis. In all instances, clinicians should try to establish evidence in support of the diagnosis FMD (‘positive features’). Experts in the field recommend to discuss these positive criteria with the patient and to explain why and how the diagnosis FMD is made.(43, 44)

The BP is a positive criterion and even though the clinical experts in our studies did not alter their diagnosis based on the BP results, we do recommend measurement of the BP prior to the jerky movements and intended wrist extension task. In conveying the diagnosis FMD to the patient the support of a ‘positive’ diagnostic test (instead of a ‘normal MRI’ and ‘normal laboratory results’) could help to establish an understanding of their illness in patients diagnosed with FMD.(43,45) Several clinical experts have shown that proper explanation of the diagnosis FMD can aid the recovery of these patients.(43,45) A recent study found that explanation of neurologists matters in the perception of the diagnosis of functional neurological symptoms, but repeated follow-up visits do not improve patient outcome (health-related quality of life after 12 months).(46) Thus, it is recommended to explain to the patients why the diagnosis FMD is made, for instance by showing and addressing the Hoover sign, entrainment or distractibility of the functional symptoms. We suggest that the BP results could also be used during the diagnostic explanation to patients with FMD.

The current thesis focused on a specific subtype of FMD: the jerky FMD phenotype. For the generalizability of our findings it is of interest to study the lack of self-agency, perception of free will and intentional movement generation (wrist extension, finger tapping) in patients with ‘psychogenic’ non-epileptic seizures (known as PNES), functional paralysis or other FMD subtypes, for instance functional tremor. Different subtypes of functional disorders may originate from similar pathophysiological mechanisms.

The studies in chapter 2 and 3 did not investigate the psychiatric symptoms accompanying FMD in detail. Based on a limited number of studies, psychiatric co-morbidity rates and life stressors/events appear to be low in FMD.(47) In contrast, in patients with PNES, psychiatric diagnosis rates and levels of dissociation are higher than in FMD.(48) A recent study found that qualitative instead of quantitative (Diagnostic and Statistical Manual of Mental Disorders, DSM) psychiatric testing was of value in the diagnosis of chronic FMD.(49)
Therefore, a more extensive and systematic study of psychiatric comorbidity could be of additional value. The diagnostic studies in chapter 2 and 3 suggest that clinicians do not take psychiatric co-morbidity into account during consultation in the outpatient clinic. An international survey of movement disorder specialists also indicated that psychiatric testing is regarded to be of lesser importance while diagnosing FMD. However, changing the order of the provided information would perhaps have changed the importance of a BP and psychiatric co-morbidity, as information presented early in the diagnostic process is more likely to change the differential diagnosis. Future studies should compare the order of the presented information in identical cases to elucidate whether the order of diagnostic steps biased our findings, and whether the clinician’s specialty (in these studies the majority of the clinicians were neurologists) might have influenced results. Potentially, replicating the findings with a group of psychiatrists who are experts in functional disorders may reveal different diagnostic decision-making, as previous studies demonstrated a different perspective of neurologists and psychiatrists on the diagnosis conversion disorder.

In addition to studying the psychiatric co-morbidity in jerky FMD in more detail, also traumatic life events, for instance childhood abuse, need further study. Historically, functional neurological symptoms have been postulated to result from psychologic factors such as trauma, stress, or emotional conflict. Patients with functional neurological symptoms reported a higher incidence of physical or sexual abuse, a larger number of different types of physical abuse, sexual abuse of longer duration, and incestuous experiences more often than comparison patients. To explain the link between traumatic life events in a neurobiological manner, it was found that cortisol levels are higher in patients with PNES and paralysis. Neurobiologic stress models propose a link between major biologic stress/emotion systems (Hypothalamic-Pituitary-Adrenal (HPA) axis) and somatic symptoms. Although we have investigated the neuropsychological profile of patients with jerky FMD, we did not examine traumatic life events. In light of our fMRI findings with an increased limbic to motor functional connectivity, it would be interesting to investigate traumatic stressors and the HPA axis in our cohort of patients to provide novel pathophysiological insights and to compare hyperkinetic FMD to hypokinetic functional neurological symptoms.

The findings of our philosophical phenomenological study on the perceptions of free will and movement disorders raise questions on the discrepancy between patient and clinicians. Future studies should question patients with different neurological and psychiatric disorders, for instance epilepsy, PNES, amyotrophic lateral sclerosis, obsessive compulsive disorder and substance abuse disorders and their treating physicians, on their perceived degree of free will regarding their disorder. Understanding what it is like to have these disorders can generate novel pathophysiological hypotheses and insights into the neural network underlying self-agency, consciousness and free will.
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**Pathophysiology: Future perspectives**

The studies in this thesis provide clues to the pathophysiological network underlying FMD, and suggest involvement of the parietal cortex and limbic network that are dissociated from the voluntary motor circuit (SMA, primary motor cortex). A novel pathophysiological perspective on FMD as proposed in this thesis that requires further investigation is the voluntary-automatic dissociation in FMD and the lack of perceived control (chapter 6 and 7). Understanding the pathophysiological mechanisms involved can help to educate clinicians, as some clinicians still consider FMD a ‘voluntary’ disorder (chapter 6).

Several lines of evidence suggest that different subtypes of functional neurological symptoms have different underlying pathophysiological mechanisms. For instance, the difference in psychiatric co-morbidity is just one clue that the pathophysiological mechanism might be different. Thus, it would be interesting to study if other functional disorders (for instance functional tremor, fixed dystonia and PNES) also have decreased parietal activation during finger tapping and lack a BP prior to intended wrist extension. In addition to studying different subtypes of functional neurological symptoms, it is also of interest to study different clinical stages (acute vs. chronic vs. recovered FMD) to investigate primary deficits of FMD and factors that maintain the disease.

Studies using event related functional MRI analysis of the FMD jerks and tics need to be performed and may shed light on the pathophysiological network underlying FMD. In contrast to combined EEG-EMG studies that use jerk-locked back averaging, and therefore uses the signal *before* the onset of the jerk, MRI use the hemodynamic blood-oxygen-level dependent (BOLD) response that rises and peaks *after* the movement has occurred and is therefore heavily influenced by (head) motion artifact. This major drawback of MRI studies is illustrated in our neuro-imaging studies in which patients had to be excluded from analysis due to motion induced artefacts. Advances in MR imaging techniques, including higher spatial and temporal resolution are needed to overcome these motion induced artefacts. In our fMRI study, the time to scan one volume (whole brain, TR= 2, 5 seconds) was rather long. Other studies have chosen to only scan the areas of interest (for instance SMA) and therefore have better temporal resolution. Technical advances in off-line signal analysis are needed to better correct movement induced artefacts. This would prevent exclusion of patients with too many jerks in future fMRI studies. Moreover, in analogy to epilepsy, it would be interesting to trigger the fMRI based on the events detected by surface EMG. Starting the scan volume triggered on the onset of the jerk would still allow the imaging of the brain areas involved in the generation of the jerk, because the BOLD signal is a delayed response (by several seconds). The advantage would be that the events are aligned in time and at the start of the scan volume (common scan volume duration is 2,5 seconds).

Technical advances in neurophysiology that provide alternative analysis methods for voluntary motor preparation are needed. A drawback of jerk-locked back averaging (BP) is
The studies in this thesis provide clues to the pathophysiological network underlying FMD, and suggest involvement of the parietal cortex and limbic network that are dissociated from the voluntary motor circuit (SMA, primary motor cortex). A novel pathophysiological perspective on FMD as proposed in this thesis that requires further investigation is the voluntary-automatic dissociation in FMD and the lack of perceived control (chapter 6 and 7). Understanding the pathophysiological mechanisms involved can help to educate clinicians, as some clinicians still consider FMD a 'voluntary' disorder (chapter 6).

Several lines of evidence suggest that different subtypes of functional neurological symptoms have different underlying pathophysiological mechanisms. For instance, the difference in psychiatric comorbidity is just one clue that the pathophysiological mechanism might be different. (47) Thus, it would be interesting to study if other functional disorders (for instance functional tremor, fixed dystonia and PNES) also have decreased parietal activation during finger tapping and lack a BP prior to intended wrist extension. In addition to studying different subtypes of functional neurological symptoms, it is also of interest to study different clinical stages (acute vs. chronic vs. recovered FMD) to investigate primary deficits of FMD and factors that maintain the disease.

Studies using event-related functional MRI analysis of the FMD jerks and tics need to be performed and may shed light on the pathophysiological network underlying FMD. In contrast to combined EEG-EMG studies that use jerk-locked back averaging, and therefore use the signal before the onset of the jerk, MRI uses the hemodynamic blood-oxygen-level dependent (BOLD) response that rises and peaks after the movement has occurred and is therefore heavily influenced by (head) motion artifact. This major drawback of MRI studies is illustrated in our neuro-imaging studies in which patients had to be excluded from analysis due to motion induced artefacts. Advances in MR imaging techniques, including higher spatial and temporal resolution are needed to overcome these motion induced artefacts. In our fMRI study, the time to scan one volume (whole brain, TR= 2.5 seconds) was rather long. Other studies have chosen to only scan the areas of interest (for instance SMA) and therefore have better temporal resolution. Technical advances in offline signal analysis are needed to better correct movement induced artefacts. This would prevent exclusion of patients with too many jerks in future fMRI studies. Moreover, in analogy to epilepsy, it would be interesting to trigger the fMRI based on the events detected by surface EMG. Starting the scan volume triggered on the onset of the jerk would still allow the imaging of the brain areas involved in the generation of the jerk, because the BOLD signal is a delayed response (by several seconds). The advantage would be that the events are aligned in time and at the start of the scan volume (common scan volume duration is 2.5 seconds).

Technical advances in neurophysiology that provide alternative analysis methods for voluntary motor preparation are needed. A drawback of jerk-locked back averaging (BP) is the requirement to average many epochs (events), which precludes analysis in FMD patients with few jerks unless the EEG recordings are of long duration. This limits the diagnostic value of the BP as a routine diagnostic test. Future studies using EEG and EMG should investigate alternative analysis methods for jerk-locked back averaging, such as event-related desynchronization or non-linear analysis methods (for instance entropy measures). (59)

Treatment of FMD is notoriously difficult.(60) Therapy usually consists of psychotherapy and physiotherapy and one study advocated the use of antidepressants.(35, 61-64) Therapeutic strategies were not studied in this thesis, but the pathophysiological findings of this thesis provide several clues in support of psychotherapy and physiotherapy. Future studies should focus on overcoming functional apraxia and the voluntary-automatic dissociation. This may be accomplished either by cognitive behavioral therapy, which requires mental effort of the patient, or physiotherapy, which requires physical effort, or ideally both.(61) Future studies should evaluate the efficacy of these treatment options, since FMD patients can potentially recover fully.

CONCLUSIONS
To summarize, the studies in this thesis provided multifaceted insights on the phenomenology, diagnostic process and pathophysiology of FMD. Using clinical observation, neurophysiological investigations and functional MRI, FMD is deconstructed as a neural network disorder with a volition paradox. This paradox appears to be based on a mismatch between voluntary motor preparation, perceived free will, self-agency and self-directed attention.
REFERENCES


