Functional movement disorders

New perspectives on neurophysiological markers and treatment

Dreissen, Y.E.M.

Publication date
2022

Document Version
Final published version

Functional movement disorders

new perspectives on neurophysiological markers and treatment

Yasmine Emma Maria Dreissen

Functional movement disorders

new perspectives on neurophysiological markers and treatment

Yasmine Emma Maria Dreissen

Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
Cover design: Nina Pockett & Yasmine Dreissen
Cover illustration: Nina Pockett
Layout and design: Birgit Vredenburg, persoonlijkproefschrift.nl
ISBN: 978-94-6458-041-9

This research was supported by the Prinses Beatrix Fund and Ipsen Farmaceutica BV.

The printing of this thesis was financially supported by the AMC Graduate School, the department of Neurology of the Amsterdam University Medical Center, the Nederlandse Vereniging voor Klinische Neurofysiologie (NVKNF) and the Dystonievereniging.

Dystonie vereniging

Functional movement disorders

new perspectives on neurophysiological markers and treatment

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam op gezag van de Rector Magnificus prof. dr. ir. K.I.J. Maex ten overstaan van een door het College voor Promoties ingestelde commissie, in het openbaar te verdedigen in de Agnietenkapel op vrijdag 11 februari 2022, te 10.00 uur door Yasmine Emma Maria Dreissen geboren te AMSTERDAM

PROMOTIECOMMISSIE

Promotores:	prof. dr. M.A.J. de Koning-Tijssen	Rijksuniversiteit Groningen
	prof. dr. I.N. van Schaik	AMC-UvA
Copromotores:	dr. J.H.T.M. Koelman	AMC-UvA
	dr. J.M. Dijk	AMC-UvA
Overige leden:	prof. M. Edwards	Saint George's University of London
	prof. dr. P.R. Schuurman	AMC-UvA
	prof. dr. B.R. Bloem	Radboud Universiteit Nijmegen
	prof. dr. D.C. Cath	Rijksuniversiteit Groningen
	dr. A.F. van Rootselaar	AMC-UvA
	dr. M.A. Hillen	AMC-UvA

Faculteit der Geneeskunde

TABLE OF CONTENTS

1.	General introduction	7
2.	Treatment of functional motor symptoms: a narrative review of the literature	19
3.	Botulinum NeuroToxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomized placebo-controlled trial with an open-label extension	41
4.	Long-term psychiatric outcome related to Botulinum Neurotoxin (BoNT) treatment in functional movement disorders	75
5.	Botulinum Neurotoxin (BoNT) treatment in functional movement disorders: long-term follow-up	101
6.	Exaggerated startle reactions: a narrative review of the literature	109
7.	Startle responses in functional jerky movement disorders are increased but have a normal pattern	141
8.	The auditory startle response in relation to outcome in functional movement disorders	157
9.	Summary of the thesis	173
10.	General discussion	179
11.	Case illustrations	197
12.	Dutch summary	203
13.	Appendices	209

General introduction

1

BACKGROUND

Patients with functional neurological disorders (FND) have genuine neurological symptoms, ranging from sensory changes, weakness, speech disorders, blindness, functional epileptic attacks to movement disorders which are incongruent and inconsistent with "known organic" neurological disease. Patients with FND comprise a third of the neurology population with the second most common disorder amongst newly referred outpatients in neurologic practice in the UK (1). Functional movement disorders (FMD) account for up to 25% of patients seen in movement disorder clinics (2); functional tremor and jerks are amongst the commonest phenomenology's (3-5).

A paradigm shift has taken place the last decades where less emphasis is put on the psychiatric aspects of FMD. The diagnosis forms a true challenge for the clinician at the borderland between neurology and psychiatry (6). Instead of a diagnosis of exclusion, positive clinical symptoms of incongruity and inconsistency with known neurologic disease are seen as the hallmark of the disease. The well-known diagnostic criteria of functional movement disorders by Fahn and Williams have been modified leaving out psychological disturbance, psychogenic signs or multiple somatizations as a requirement for high diagnostic certainty (5, 7-10). This has also translated in the change of the name 'psychogenic' into 'functional' neurological disorders (11) and the inclusion of "functional neurological symptom disorders" as a sub-category in the category of "conversion disorders" in the newest (5th) edition of the Diagnostic and Statistical manual of Mental disorders (DSM, the standard psychiatric classification system) (12).

The clinical signs of functional jerks and tremor, such as *distractibility* where symptoms disappear when attention is shifted or *entrainment* where the frequency of the tremor/jerks adjusts to an imposed rhythm when performing a tapping-task can be further delineated and substantiated by neurophysiological testing. Combined Electroencephalography (EEG) and Electromyography (EMG) can give insight in central processes involved in motor preparation and movement control in FMD. An example of such a neurophysiological aid is the bereitschaftspotential (BP), which is a slowly (2s) and averaged rising negative cortical deflection preceding a repeated intended movement such as wrist extension. The presence of a BP preceding jerky movements can make the diagnosis quite certain (10, 13). When the BP is combined with event-related desynchronization (ERD) in the beta-range (13-45 Hertz) prior to the jerks, even higher diagnostic certainty can be reached (14). Similarly, polymyographic EMG can aid in diagnosing functional tremor. When the presence of different features of the tremor including tap performance, entrainment, pause of the tremor with a ballistic

movement, tonic co-activation, tremor coherence and increase in tremor with loading are summarized, a sensitivity and specificity of 100% for the diagnosis of functional tremor is yielded (9).

In FMD as in FND symptoms are perceived as involuntary by the patient and should not to be mistaken for feigning or malingering, where patients deliberately simulate symptoms for primary (psychologic) or secondary (legal/economic) gain (15, 16).

This perception of patients is even more intriguing because signs as 'entrainment', distractibility and the presence of a BP strongly suggests a volitional (17-19). It has been hypothesized that abnormal disease-beliefs, attention and a lack of sense of agency play a key role in the pathophysiology (20). Although the aetiology of FMD is still elusive, impaired stress regulation is thought to play an important role (21). This is not only reflected by high rates of anxiety disorders (22), but also by a growing body of evidence suggesting aberrant functioning of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis in FND (23, 24). In the clinical setting this is reflected by hypersensitivity to external stimuli and exaggerated startling. The startle reflex is a normal physiologic phenomenon, which can be elicited by different stimuli such as a loud noise. The auditory startle (ASR) reflex which is modulated by the amygdala can be used as an objective physiological tool to assess the affective system (25-27). It consists of two responses, the first motor response (latency up to 120 ms), which involves contraction of several muscles in the body with a rostro-caudal distribution, mediated by the caudal brainstem. This component is associated with a state hyperarousal and hypervigilance and is also enlarged in anxiety disorders (28). The second response (or: the orienting response) is much more variable in pattern and associated with behavioral processing and autonomic changes (a drop in galvanic skin resistance which can be measured with sympathetic skin response (SSR) (29). The second response is much less studied but has been described to be augmented in a small case series of jerky FMD (30). Interestingly in anxiety disorders, the early ASR has been shown to serve as a physiological outcome measure in children who responded well to cognitive behavioral therapy (CBT) (31). This study also showed that a larger baseline magnitude of the early response of the ASR predicted treatment response. Pre-treatment amygdala activation is thought to play an important role in anxiety disorders, which might be similar in FMD. There is a lack in validated outcome measures in FMD and literature on biomarker-related outcome measures in FMD treatment studies is scarce. In this manner, the different components of the ASR are potential candidates to serve as outcome measure or parameters to predict treatment response.

Treatment

Treatment of FMD is based on a 'stepped care' approach. It starts with an initial consultation where the nature and mechanism of the diagnosis is explained, which might be therapeutic in itself. Many neurologists feel this is the most important step (32, 33). In a substantial part though, more specialized treatment is needed involving therapies as physiotherapy and rehabilitation therapy. FMD are seen as unconsciously learnt motor patterns, influenced by abnormal self-directed attention, often triggered by (minor) physical trauma (34). These abnormal motor programs must be 'unlearned' by distracting attention, redirecting movement and focussing on illness-beliefs and coping strategies. There have been quite promising results (improvement rates 50-75%) in this field, but randomized treatment studies in FND and more specific FMD are scarce. Therapies that have been studied are: physiotherapy, rehabilitation, disease education, psychotherapy and transcranial magnetic stimulation (TMS) (35-40). They mostly concern heterogeneous patient groups with positive (e.g. tremor, jerks, dystonia) as well as negative (paresis) motor symptoms.

In terms of more specialized treatment in FMD, Botulinum neurotoxin (BoNT) has emerged as a useful therapy for several movement disorders associated with muscle hyperactivity (41). When BoNT is injected in the muscles, the toxin produces local chemodenervation by blocking the release of acetylcholine at the neuromuscular junctions. It thereby renders the muscle (partially) unable to contract for a period of 3 to 4 months. BoNT is an effective treatment for several disorders, for example for cervical dystonia and blepharospasm, diseases for which therapeutic options previously were restricted. Organic and functional movement disorders share many similarities; in both disorders sensory motor integration may be disturbed (42). Treatment with BoNT might restore the changes in the central nervous system via normalisation of sensory feedback of movement patterns. One case series shows promising effects of BoNT injections in patients with functional axial jerks (43). Personal clinical experience in treatment of functional jerky movement disorders with BoNT clearly suggests improvement as well. Yet, large placebo-effects in this patient group have been reported, with complete recovery of symptoms following immediately after (sub-therapeutic) BoNT injections in functional (fixed) dystonia (44) and improvement of symptoms following saline injections in functional myoclonus (45). This stresses the importance of conducting a placebo-controlled double-blinded clinical trial in FMD.

Prognosis

The prognosis of functional motor symptoms (both weakness and movement disorders) is generally unfavorable (46). After a mean follow-up of 7.4 years 40% of patients showed persistent or worsened symptoms. A recent prospective cohort

study in patients with functional limb weakness, showed that 50% had persisting or worsening of symptoms after an average of 14 years follow-up (47). The prognosis of FMD is reported to be even worse with a mean of 69% of functional dystonia patients and 66% of functional tremor patients having persisting or worsening at follow-up. Patients with functional axial jerks show a similar pattern (43, 48). An important factor associated with poor outcome is longer duration of symptoms (49). Subjectively, patients often experience more distress compared to patients with organic disease who have similar disability (50). Poor quality of life and general functioning, including high rates of unemployment (43-89%) have been described in functional motor symptoms (49, 51). This is accompanied by high proportions of psychiatric co-morbidity (52). Specific for FMD (dystonia, myoclonus and tremor) rates of 50-80% for DSM IV axis I disorders (mostly mood and anxiety disorders) and between 18-45% for DSM IV axis II disorders (personality disorders) are reported (3, 22, 53-57). As a result, patients often require repeated medical attendance and not seldom hospital admission (58, 59). In all, the burden of FMD on both patients and the health care system as a whole is large.

AIM OF THE THESIS

The aim of this thesis was threefold. Firstly, we set out to describe the level of evidence of the existing therapies in functional motor symptoms. Secondly, the core of this thesis is a randomized placebo-controlled trial (RCT) on BoNT treatment in jerky and tremulous FMD. In this study secondary non-motor outcome measures are also extensively studied. We hypothesized that BoNT would interrupt and possibly restore the aberrant movement pattern by resetting the motor program, in other words 'breaking the vicious circle'. Third, our goal was to systematically assess the neurophysiological features of the early and late auditory startle reflex in FMD, specifically distinguishing between the early and the late (orienting) response. It was hypothesized that especially the late response would be augmented in FMD since it is much more influenced by behavioral processing and associated with neuropsychiatric disorders. Also, since relevant validated clinical outcome measures are scarce, we wanted to explore if the ASR could serve as a possible (objective) physiologic outcome measure or biomarker.

OUTLINE OF THE THESIS

Chapter 2 gives a narrative review on the existing therapies of FMD with the corresponding level of evidence. **Chapter 3** is dedicated to the RCT on BoNT treatment in FMD together with the results of the one year open-label treatment. The extensive

psychiatric outcome measures as well as outcome measures on pain, fatigue and stressful life events distinguishing between patients who did and did not show motor improvement after treatment during the RCT are discussed in **chapter 4**. **Chapter 5** describes the long-term (3-7 years) follow up of patients after participating the BoNT RCT. **Chapter 6** is a descriptive review of the auditory startle reflex and an overview of the different startle syndromes. In **chapter 7** the case-control study on the early and late component of the ASR in FMD compared to healthy controls is described. **Chapter 8** reports on re-testing the different components of the ASR in the same patients and controls after treatment. In **chapter 9** the results of this thesis and its implications together with future perspectives are discussed.

REFERENCES

1. Stone J, Carson A, Duncan R, Roberts R, Warlow C, Hibberd C, et al. Who is referred to neurology clinics?--the diagnoses made in 3781 new patients. ClinNeurolNeurosurg. 2010;112(9):747-51.
2. Miyasaki JM, Sa DS, Galvez-Jimenez N, Lang AE. Psychogenic movement disorders. CanJNeurolSci. 2003;30 Suppl 1:S94-100.
3. Factor SA, Podskalny GD, Molho ES. Psychogenic movement disorders: frequency, clinical profile, and characteristics. JNeurolNeurosurgPsychiatry. 1995;59(4):406-12.
4. Hinson VK, Haren WB. Psychogenic movement disorders. Lancet Neurol. 2006;5(8):695-700.
5. Shill H, Gerber P. Evaluation of clinical diagnostic criteria for psychogenic movement disorders. Movement Disorders. 2006;21(8).
6. van der Salm SM, de Haan RJ, Cath DC, van Rootselaar AF, Tijssen MA. The eye of the beholder: inter-rater agreement among experts on psychogenic jerky movement disorders. JNeurolNeurosurgPsychiatry. 2013;84(7):742-7.
7. Fahn S, Williams DT. Psychogenic dystonia. AdvNeurol. 1988;50:431-55.
8. Gupta A, Lang AE. Psychogenic movement disorders. Current Opinion in Neurology. 2009;22(4).
9. Schwingenschuh P, Katschnig P, Seiler S, Saifee TA, Aguirregomozcorta M, Cordivari C, et al. Moving toward "laboratory-supported" criteria for psychogenic tremor. Mov Disord. 2011;26(14):2509-15.
10. van der Salm SM, Tijssen MA, Koelman JH, van Rootselaar AF. The bereitschaftspotential in jerky movement disorders. JNeurolNeurosurgPsychiatry. 2012;83(12):1162-7.
11. Edwards MJ, Stone J, Lang AE. From psychogenic movement disorder to functional movement disorder: It's time to change the name. Mov Disord. 2013.
12. Association AP. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington: VA: American Psychiatric Publishing; 2013 2013.
13. Shibasaki H, Hallett M. What is the Bereitschaftspotential? Clinical Neurophysiology. 2006;117(11).
14. Beudel M, Zutt R, Meppelink AM, Little S, Elting JW, Stelten BML, et al. Improving neurophysiological biomarkers for functional myoclonic movements. Parkinsonism Relat Disord. 2018.
15. Krahn LE, Li H, O'Connor MK. Patients who strive to be ill: factitious disorder with physical symptoms. Am J Psychiatry. 2003;160(6):1163-8.
16. Bass C, Halligan P. Factitious disorders and malingering: challenges for clinical assessment and management. Lancet. 2014;383(9926):1422-32.
17. Edwards MJ, Bhatia KP. Functional (psychogenic) movement disorders: merging mind and brain. Lancet Neurol. 2012;11(3):250-60.
18. Hallett M. Physiology of psychogenic movement disorders. JClinNeurosci. 2010;17(8):959-65.

19. van der Salm SM, Cath DC, van Rootselaar AF, Koelman JH, de Haan RJ, Tijssen MA, et al. Clinician and patient perceptions of free will in movement disorders: mind the gap. J Neurol Neurosurg Psychiatry. 2017;88(6):532-3.
20. Edwards MJ, Fotopoulou A, Parees I. Neurobiology of functional (psychogenic) movement disorders. CurrOpinNeurol. 2013;26(4):442-7.
21. Baizabal-Carvallo JF, Hallett M, Jankovic J. Pathogenesis and pathophysiology of functional (psychogenic) movement disorders. Neurobiol Dis. 2019;127:32-44.
22. Feinstein A, Stergiopoulos V, Fine J, Lang AE. Psychiatric outcome in patients with a psychogenic movement disorder: a prospective study. Neuropsychiatry NeuropsycholBehavNeurol. 2001;14(3):169-76.
23. Maurer CW, Liu VD, LaFaver K, Ameli R, Wu T, Toledo R, et al. Impaired resting vagal tone in patients with functional movement disorders. Parkinsonism Relat Disord. 2016;30:18-22.
24. Apazoglou K, Mazzola V, Wegrzyk J, Polara GF, Aybek S. Biological and perceived stress in motor functional neurological disorders. Psychoneuroendocrinology. 2017;85:142-50.
25. Dreissen YE, Bakker MJ, Koelman JH, Tijssen MA. Exaggerated startle reactions. ClinNeurophysiol. 2012;123(1):34-44.
26. Angrilli A, Mauri A, Palomba D, Flor H, Birbaumer N, Sartori G, et al. Startle reflex and emotion modulation impairment after a right amygdala lesion. Brain. 1996;119 (Pt 6):1991-2000.
27. Seignourel PJ, Miller K, Kellison I, Rodriguez R, Fernandez HH, Bauer RM, et al. Abnormal affective startle modulation in individuals with psychogenic [corrected] movement disorder. Mov Disord. 2007;22(9):1265-71.
28. Bakker MJ, Tijssen MA, van der Meer JN, Koelman JH, Boer F. Increased whole-body auditory startle reflex and autonomic reactivity in children with anxiety disorders. JPsychiatry Neurosci. 2009;34(4):314-22.
29. Gogan P. The startle and orienting reactions in man. A study of their characteristics and habituation. Brain Res. 1970;18(1):117-35.
30. Thompson PD, Colebatch JG, Brown P, Rothwell JC, Day BL, Obeso JA, et al. Voluntary stimulus-sensitive jerks and jumps mimicking myoclonus or pathological startle syndromes. Movement Disorders. 1992;7(3).
31. Bakker MJ, Tijssen MA, Koelman JH, Boer F. Normalization of the auditory startle reflex after symptom reduction in children with anxiety disorders. JPsychiatr Res. 2010.
32. Espay AJ, Goldenhar LM, Voon V, Schrag A, Burton N, Lang AE. Opinions and clinical practices related to diagnosing and managing patients with psychogenic movement disorders: An international survey of movement disorder society members. Mov Disord. 2009;24(9):1366-74.
33. de Schipper LJ, Vermeulen M, Eeckhout AM, Foncke EM. Diagnosis and management of functional neurological symptoms: The Dutch experience. Clin Neurol Neurosurg. 2014;122:106-12.

34. Parees I, Kojovic M, Pires C, Rubio-Agusti I, Saifee TA, Sadnicka A, et al. Physical precipitating factors in functional movement disorders. JNeurolSci. 2014;338(1-2):174-7.
35. Nielsen G, Buszewicz M, Stevenson F, Hunter R, Holt K, Dudziec M, et al. Randomised feasibility study of physiotherapy for patients with functional motor symptoms. J Neurol Neurosurg Psychiatry. 2017;88(6):484-90.
36. Jordbru AA, Smedstad LM, Klungsoyr O, Martinsen EW. Psychogenic gait disorder: a randomized controlled trial of physical rehabilitation with one-year follow-up. J Rehabil Med. 2014;46(2):181-7.
37. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial. Neurology. 2011;77(6):564-72.
38. Kompoliti K, Wilson B, Stebbins G, Bernard B, Hinson V. Immediate vs. delayed treatment of psychogenic movement disorders with short term psychodynamic psychotherapy: randomized clinical trial. Parkinsonism Relat Disord. 2014;20(1):60-3.
39. Garcin B, Mesrati F, Hubsch C, Mauras T, Iliescu I, Naccache L, et al. Impact of Transcranial Magnetic Stimulation on Functional Movement Disorders: Cortical Modulation or a Behavioral Effect? Front Neurol. 2017;8:338.
40. Pleizier M, de Haan RJ, Vermeulen M. Management of patients with functional neurological symptoms: a single-centre randomised controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(5):430-6.
41. Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, et al. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70(19):1699-706.
42. Hallett M. Mechanism of action of botulinum neurotoxin: Unexpected consequences. Toxicon. 2017.
43. Erro R, Edwards MJ, Bhatia KP, Esposito M, Farmer SF, Cordivari C. Psychogenic axial myoclonus: clinical features and long-term outcome. ParkinsonismRelat Disord. 2014;20(6):596-9.
44. Edwards MJ, Bhatia KP, Cordivari C. Immediate response to botulinum toxin injections in patients with fixed dystonia. Mov Disord. 2011;26(5):917-8.
45. Monday K, Jankovic J. Psychogenic myoclonus. Neurology. 1993;43(2):349-52.
46. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. JNeurolNeurosurgPsychiatry. 2014;85(2):220-6.
47. Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J. The prognosis of functional limb weakness: a 14-year case-control study. Brain. 2019;142(7):2137-48.
48. van der Salm SM, Erro R, Cordivari C, Edwards MJ, Koelman JH, van den Ende T, et al. Propriospinal myoclonus: clinical reappraisal and review of literature. Neurology. 2014;83(20):1862-70.

49. Gelauff JM, Dreissen YE, Tijssen MA, Stone J. Treatment of functional motor disorders. CurrTreatOptionsNeurol. 2014;16(4):286.
50. Anderson KE, Gruber-Baldini AL, Vaughan CG, Reich SG, Fishman PS, Weiner WJ, et al. Impact of psychogenic movement disorders versus Parkinson's on disability, quality of life, and psychopathology. Mov Disord. 2007;22(15):2204-9.
51. Gelauff JM, Kingma EM, Kalkman JS, Bezemer R, van Engelen BGM, Stone J, et al. Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders. J Neurol. 2018.
52. Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. JNeurolNeurosurgPsychiatry. 2000;68(2):207-10.
53. Thomas M, Jankovic J. Psychogenic movement disorders: diagnosis and management. CNSDrugs. 2004;18(7):437-52.
54. Ertan S, Uluduz D, Ozekmekci S, Kiziltan G, Ertan T, Yalcinkaya C, et al. Clinical characteristics of 49 patients with psychogenic movement disorders in a tertiary clinic in Turkey. Mov Disord. 2009;24(5):759-62.
55. Munhoz RP, Zavala JA, Becker N, Teive HA. Cross-cultural influences on psychogenic movement disorders - a comparative review with a Brazilian series of 83 cases. Clin Neurol Neurosurg. 2011;113(2):115-8.
56. Kranick S, Ekanayake V, Martinez V, Ameli R, Hallett M, Voon V. Psychopathology and psychogenic movement disorders. Movement Disorders. 2011;26(10).
57. Tomic A, Petrovic I, Pesic D, Voncina MM, Svetel M, Miskovic ND, et al. Is there a specific psychiatric background or personality profile in functional dystonia? J Psychosom Res. 2017;97:58-62.
58. Carson A, Stone J, Hibberd C, Murray G, Duncan R, Coleman R, et al. Disability, distress and unemployment in neurology outpatients with symptoms 'unexplained by organic disease'. JNeurolNeurosurgPsychiatry. 2011;82(7):810-3.
59. Reid S, Wessely S, Crayford T, Hotopf M. Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study. BMJ. 2001;322(7289):767.

Treatment of functional motor disorders

2

Yasmine EM Dreissen*, Jeannette M Gelauff*,
Marina AJ Tijssen and Jon Stone
*Both authors contributed equally to this work

Article published in Current Treatment Options Neurology 2014 doi 10.1007/s11940-014-0286-5

OPINION STATEMENT

We recommend a three stage approach to treatment.

Firstly patients must be assessed, and given an unambiguous diagnosis with an explanation that helps them see they have a genuine disorder which has the potential for reversibility. Key ingredients are allowing the patient to describe all their symptoms and to explain their ideas about what may be wrong. The patient should explained that the diagnosis is a positive one based on the presence of typical signs (eg Hoover's sign for paralysis, entrainment test for tremor) which in themselves indicate the potential for reversibility. We suggest an approach leaving out the assumption there are psychological stressors in the patient's life that have caused the symptom. Often the symptoms themselves are the main stressor. Insisting that there must be others simply leads to a frustrated doctor and angry patient. Instead, at this first stage we encourage exploration of mechanism, e.g. triggering of symptoms by pain, injury or dissociation and a discussion about how symptoms arise as "abnormal motor programs" in the nervous system.

Secondly, further time spent exploring this diagnosis, treating comorbidity and, in the context of a multidisciplinary team, trying out altered movements and behaviours may benefit some patients without the need for more complex intervention.

Thirdly, some patients do require more complex treatment, often with a combination of physical rehabilitation and psychological treatments. Hypnosis, sedation and transcranial magnetic stimulation may have a role in selected patients.

Finally many patients do not respond to treatment, even when they have confidence in the diagnosis. Ultimately however, patients with functional motor disorder may have much greater potential for recovery than health professionals often consider.

INTRODUCTION

Functional (also known as psychogenic) motor disorders are genuine weakness or movement disorders (such as tremor, gait disorder or dystonia), but do not relate to recognised neurological disease. Symptoms are involuntary and should not be confused with feigning or malingering. The diagnosis should not be one of exclusion but rather based upon positive clinical signs that primarily indicate internal inconsistency. In some cases incongruity with recognised neurological disorder is also important but this is a lesser issue (1,2).

Functional motor disorders (FMD) have a high impact, both for individual patients as the health care system as a whole: they are the second most common functional neurological disorder seen in outpatient practice (3,4) and account for a substantial number of inpatient admission days (5). Patients with symptoms unexplained by a recognized neurological disease have similar levels of disability, and more distress than patients with symptoms explained by disease (6). Case control studies have shown levels of disability and health status comparable to Parkinson's disease (7) and multiple sclerosis (8). The prognosis of FMD is variable but generally unfavorable (9).

From a historical perspective, the range of treatments in FMD (described as hysteria or conversion disorder at the time), has reflected the many differing hypotheses regarding their origin. These include hysterectomy, hypnosis, suggestion, abreaction, electrical stimulation (of the affected limb), various forms of constrained and other physical rehabilitation, and psychotherapy including psychoanalysis (10-12). We have largely restricted ourselves to studies since 1965 whilst remaining aware that there are many important lessons to be learnt from older treatments.

In this review we summarise current evidence for treatment of FMD focusing on physiotherapy and psychological treatments (13), but also discussing other treatments such as hypnosis, transcranial magnetic stimulation, sedation and pharmacologic treatment.

Throughout we would like to emphasise our clinical experience that there is little benefit attempting to embark on treatment before a good initial consultation (1,14). A patient who has no confidence or understanding of the nature of its diagnosis rarely benefits from the treatments described below. It is our view that the neurologist or diagnosing physician is in a position to deliver the first phase of treatment and not just the diagnosis. Figure 1 shows a proposal of a 'stepped care' approach in FMD where the neurologist provides 'Step 1' of the treatment, brief therapy (most commonly

delivered by a physiotherapist for FMD) can be seen as 'Step 2' and more complex multidisciplinary care involving the full rehabilitation team and psychiatry/psychology can be seen as 'Step 3' **(see figure 1)**(15).

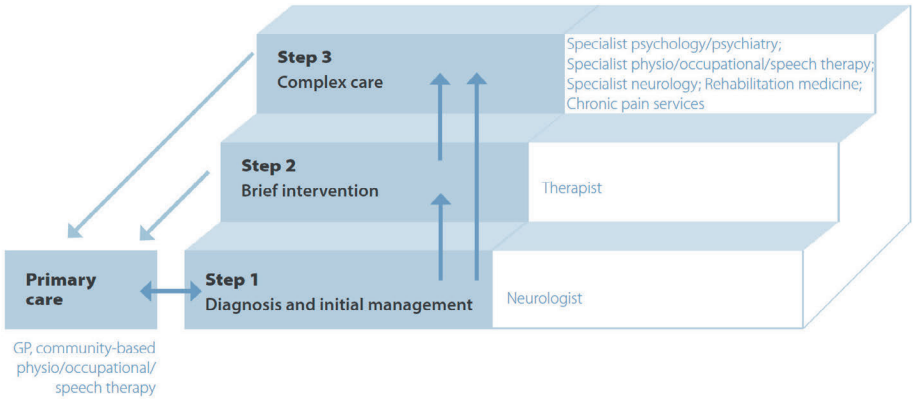

Figure 1. Stepped care approach for functional motor disorder.

TREATMENT

Physical therapy

Physiotherapy

Patients are often referred for physiotherapy after consulting a neurologist. The emerging evidence supports the idea that, regardless of psychiatric comorbidity, patients with FMD often benefit from an approach in which they are taught about the nature of their abnormal movements and how to move in a more normal way. The most successful programs appear to do this by conceptualising the problem as a problem with abnormally learnt 'motor programs' in the brain which have to be 'unlearnt' (13,16). More data is certainly required, and in particular, there is much work to be done on refining and describing techniques that may be specifically helpful for individual symptoms. Physiotherapists are surprisingly positive about treating this group of patients but feel lacking in knowledge and support from medical colleagues in doing so (17).

The first randomised controlled study of physiotherapy in 60 patients with functional gait disorder (mean duration of symptoms of 9 months), was reported recently by Jordbru et al(16). The authors compared immediate or delayed inpatient physical rehabilitation without any psychotherapy. The intervention led to a mean 7 point

change in a 15 point measure of functional mobility compared to controls waiting for the treatment and a return to normal functional independency in the active treatment group.

A retrospective study of physiotherapy compared 60 patients (mean duration of symptoms 17 months) with 60 patients who had received historical usual care (18). The one week intervention, like that of Jordbru et al. focused on physical function, with gradual progression from elementary to more complex movements, in combination with only a little psychotherapeutic element (16). Directly after treatment, 73.5% were improved according to both physician- and self-rating. At follow-up (median 25 months) 60.4% had self-rated improved symptoms and 62.4% mild or no disability level, compared to 21.9% and 43.8% respectively in the control group. The main methodological limitation of the comparison is that the control group consisted of those patients who refused to have treatment and so were intrinsically less likely to do well. Nonetheless, even as a retrospective uncontrolled series these data suggest a possible better outcome in chronic FMD than might be expected based on existing literature.

One study investigated the effect of a thrice-weekly, 12-week mild walking program on mild to moderate functional movement disorders (mean symptom duration 15 months) on 16 patients (19). Results showed an average of 70% improvement of symptoms in 10 of 16 patients. As no control group was used and symptom duration was short, the intervention effect could be attributed to several factors: there is a social element to group walking therapy since it has been shown that walking improves general wellbeing, improvement could also be attributed to natural history of the disorder, although again the improvement after a long duration is encouraging.

A systematic review of physiotherapy for FMD found a further 25 case reports and series of physiotherapy for FMD with low levels of evidence but nonetheless a trend towards positive outcome (13). In most studies a behavioral motor learning program was used: positive reinforcement with praise or rewards and privileges, while ignoring abnormal movement and maladaptive behaviors.

Inpatient rehabilitation with combined multidisciplinary treatment

In some studies inpatient treatment with a multidisciplinary approach was studied.

A recent study (20) (n=33, mean duration of symptoms 48 months) used a combination of occupational therapy, focusing on motivation and reinforcement, physiotherapy with posture exercises and massage and psycho-education. 85% of patients received CBT,

techniques included 'fostering insight and assertiveness'. Significant improvement was found in MRS scores ($p<0.001$), mobility ($p<0.001$) and ADL ($p=0.002$). No control group was studied.

A retrospective study (21) (n=26, 63% symptom duration > 3 years, all previously received failed treatment) investigated an inpatient intervention consisting of physiotherapy, occupational therapy, cognitive behavioral therapy, neuropsychiatry assessment and neurology input as required. 58% of patients reported benefit from the program on discharge and the same percentage at a mean follow-up of 7 years, but no improvement on employment rate was found. Patients were excluded if they did not accept the rationale for CBT. Thus even in a treatment resistant population, treatment is still possible, although is not suitable for those who do not accept the premise of treatment in the first place.

Contraindications, complications: Patients typically report that exercising exacerbates pain and fatigue which needs to be anticipated as part of therapy.

Cost/Cost effectiveness: No literature is available concerning the cost-effectiveness. Costs depend on treatment duration, which vary highly between studies.

Psychotherapy

The level of available evidence for psychotherapy of FMD is low (22) and much of the suggested emphasis on psychotherapy is based on historical practice or inferred from studies of similar patient populations such as patients with non-epileptic attacks or other functional somatic symptoms.

Psycho-education and explanation

To our knowledge there are no studies specifically focusing on the effectiveness of explanation and education of symptoms in this population. It is however widely believed by many specialists that education is important and can often be an effective treatment strategy (23). Studies of non-epileptic attacks have shown that around one third of patients will improve with a single consultation (24,25) and prognostic studies of both FMD and non-epileptic attacks suggest that anger with the diagnosis predicts poor outcome (14,26). Qualitative studies have also reinforced the importance of giving patients tangible diagnoses (27-29). A combined consultation and written information can be carried out with a high level of patient satisfaction (28).

Most articles on the process of giving the diagnosis of FMD and other functional neurological disorders emphasise the importance of some of the items in Table 1.

In fact these are no different to important ingredients of giving a diagnosis for any medical condition.

Element	Example
Give the patient a diagnosis	"You have a functional movement disorder"
Emphasise that symptoms are genuine (and common)	"Your symptoms are not 'imagined' or 'crazy'"
Explain on what basis the diagnosis has been made	e.g. showing patient positive features of the diagnosis such as Hoovers sign or tremor entrainment test
Emphasise potential for reversibility	"your Hoovers sign shows us that your leg has the potential to improve"
Emphasise the role of self-help / education	"Id like you to read this information (eg www.neurosymptoms.org). Its not your fault that you have this but you will need to work at it to get better"

Table 1. *Some commonly agreed initial ingredients of a successful explanation of functional neurological symptoms.*

Where authors diverge is in the name given to the condition and by default the associated explanation. Some deliberately avoid making a diagnosis (30) others emphasize re-learning normal movement (18) as part of a functional explanation. Others may use a more clear cut 'psychogenic' explanation (31). The pros and cons of different terms and models of these disorders is discussed elsewhere (32).

Explanations that rely on normal imaging or examination are generally not appreciated by patients who want to know what they have got, not what they don't have. For the same reason terms such as 'medically unexplained' tend to be regarded especially negatively.

We know something of which terms patients prefer but this is an area that would benefit from further study (33).

Cognitive behavioural therapy (CBT)

Cognitive behavioural therapy broadly describes a psychotherapy in which the patient is encouraged to challenge patterns of thinking and behaviour that are creating obstacles to symptom improvement. It focuses more on perpetuating factors than on predisposing factors. There are no trials of CBT in functional motor disorder, (22,34) although individual case studies report success (35), as do above mentioned

studies combining CBT with physical therapy (20,21). A RCT of a brief guided self-help intervention based on CBT for patients with a variety of functional neurological disorders including FMD demonstrated benefit at 3 months and 6 months in the treatment group (36).

Most studies show benefit. Even a study of CBT in 'somatisation disorder' was effective (37). Patients with FMD typically do have many other functional somatic symptoms but we should be cautious about assuming that CBT is necessarily beneficial.

Psychodynamic therapy

Psychodynamic therapy generally involves helping the patient to see their symptoms in the context of interpersonal relationships and life narrative. In a randomised trial by Kompoliti et al. (n=15) with early psychodynamic therapy versus three months of monitoring from a neurologist and after that psychodynamic therapy (38), found the same improvement in both groups. This study evolved from a case series of 10 patients of whom 8 improved (39). The study was too small to draw conclusions from although did highlight a high refusal rate for this kind of therapy in a trial setting (60% eligible patients refused).

Reuber et al. also described tailored psychodynamic therapy for 91 patients with functional neurological symptoms including at least 15 with FMD (40). 49% improved by at least one standard deviation on measures of health status.

Contraindications, complications: It is recognised that psychotherapy can sometimes temporarily worsen FMD, especially when adverse experiences are discussed for the first time.

Costs/ Cost effectiveness: Reuber et al. studied CBT in several functional neurological symptoms, amongst which 15% movement disorders and 12% problems with gait (40). They estimated a cost per "quality adjusted life year" at £5.328 based on the total study population.

Pharmacologic treatment

Antidepressants

Little has been published on pharmacological treatment of motor symptoms in FMD. No randomized or controlled studies have been conducted. Voon et al. published a series of 15 patients with functional hyperkinetic movement disorders who underwent treatment with different kinds of SSRI's (Serotonin Reuptake Inhibitors) (41). The study

was confounded by concurrent psychotherapy and does not meaningfully contribute to the evidence regarding antidepressant use.

Contra-indications and side effects, other than those that are known, of the use of an SSRI in this specific patient group are not known. Based on present literature there is no evidence to support efficacy of any pharmacological treatment for the motor symptoms of FMD. However it is reasonable to consider antidepressants for other common symptoms in FMD such as pain, insomnia, anxiety and depression.

Interventional procedures

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive method by which electromagnetic induction is used to explore cortical excitability and connectivity. Repetitive TMS (rTMS) can generate long-term potentiation or depression. TMS has been widely used in neurological and psychiatric disorders as a tool to gain insight into pathophysiology as well as a possible therapeutic treatment (42,43). Abnormalities in cortical excitability have been found in functional limb weakness (44,45) although it's unclear whether these changes are different from those found in volunteers feigning (46).

A systematic review has been conducted on the effectiveness of TMS and rTMS in FMD which explored the quality and limitations of seven studies (47). Combining this with one subsequent study means there are uncontrolled data on 119 patients who have received TMS treatment (78 weakness, 41 movement disorder) (48).

The publications are dominated by two French studies both reporting successful outcomes. Chastan and Parain's retrospectively studied the use of rTMS delivered over a single 2-3 minute period in the hemisphere contralateral to the weakness to 70 patients with functional limb weakness (49). In this highly acute and young group (44 of whom were under 20 years of age with a median duration of 5 days) there was a 89% recovery either immediately or within days. It recurred in some but repeated treatment was reported as effective. The study by Garcin et al. was from a different centre and also reported single session TMS treatment in a group of 24 with movement disorder of much longer duration (2.8 years) (48). 75% of the patients improved by more than 50% immediately after TMS with 6 patients experiencing complete resolution. The patients then received physiotherapy, psychology and neurology follow up and were assessed at a median duration of 20 months later. At that point 71% of patients were

much improved. Both studies used a stimulus sufficient to induce movement in the limb. Only one study had negative findings (50).

From a methodological perspective these studies do suggest that TMS may be a useful treatment for FMD but we should be careful to jump into too many conclusions. Patients with acute FMD may often improve anyway and the results in the patients from the Garcin study may have been influenced by subsequent therapy from an interested team (48). The only study with negative results was not published so far and included patients with chronic symptoms (50). Authors have argued that TMS can induce changes in cortical excitability (49), whereas others have pointed out that the duration of the TMS stimulus is not sufficient to induce a long lasting phsyiological change in the brain (47,48). Alternative possibilities are a placebo effect, 'relearning', regaining function with a treatment that is acceptable to the patient and/or facilitating insight in the disorder. Garcin et al. described it as a "cognitive-behavioral effect when patients see an unexpected alteration of their movement disorder. This, combined with suggestion, could be a powerful stimulus inducing change in belief about symptoms and could trigger or help recovery"(48). It certainly warrants further evaluation in controlled studies.

Contraindications, complications: TMS is considered a safe therapy, although seizures have been reported sporadically, the risk is considered very low (51).

Cost/Cost effectiveness: No literature is available on the costs or cost-effectiveness.

Transcutaneous Electrical Nerve Stimulation / Peripheral Stimulation.
Transcutaneous Electrical Nerve Stimulation (TENS) refers to a treatment concerning low-voltage electrical currents applied to the skin. Although there is no consensus on the optimal paradigm nor the mechanism of action, it is a widely used treatment in acute and chronic pain. Studies have been published with positive results using TENS in other movement disorders (52-54), little is known of its efficacy in FMD.

Literature on TENS in FMD consists of case reports or small case series (55-60); and one larger study (61) in which 19 patients with various functional movement disorders underwent a trial of TENS therapy. Electrodes were placed on the muscles most affected. All patients who considered the trial effective were offered daily TENS treatment during 30 minutes. Results showed that 15 patients (79%) chose to continue TENS after 4 months, although only 5 demonstrated a clear (>50%) effect on blindly assessed standardized videotapes, or phone assessment (42%). Shorter duration of symptoms was associated with better outcome. Because of the small population,

study design, lack of a control or use of placebo no firm conclusions can be drawn on efficacy of this treatment strategy, but like TMS it may have a place in the context of rehabilitation.

Electrical stimulation of muscles using functional electrical stimulation (which produces more of a muscle jerk than TENS) has been reported in a case report (62). Varieties of electrical stimulation were common practice as a treatment for FMD in the late 19th and early 20th century and were frequently reported to be successful. EMG feedback has also been reported successfully in four patients which may involve similar mechanism when successful (63).

Contraindications, complications: in the study by Ferrara et al. two patients temporarily got worse. TENS is generally considered a safe therapy, contra-indications include patients with an Implantable Cardioverter-defibrillator (ICD) (64).

Cost/Cost effectiveness: no literature is available on the costs or cost-effectiveness .

Abreaction and Sedation

Abreaction describes a psychiatric interview carried out while the patient is deliberately sedated. The original purpose of this was, in psychoanalytical terms, to access hidden memories, induce catharsis and thus resolve the hypothesized conflict underlying the symptom. A review summarised studies of abreaction for functional neurological disorders (33% FMD) (12). The effect was often positive, but none of the 55 included studies (mainly older case reports or case series) had a (placebo) control group.

Stone et al described the effects of sedation with the anaesthetic propofol on 11 patients with severe FMD median duration 14 months who had already accessed multidisciplinary treatment and explanation (65). The rationale here was to use sedation to demonstrate reversibility of symptoms to the patient in situations where this was not possible using the normal consultation (ie fixed dystonia, mutism). Five patients experienced rapid resolution or major improvement of their symptoms. This study is subject to the same criticism as other case series but the effect was not confounded by other new treatments and the patients largely had chronic symptoms.

Acupuncture

Although acupuncture is widely studied in other functional disorders only one case report was found in English literature (66) on a patient with longstanding functional myoclonus, who responded to acupuncture. The authors contemplate a placebo effect to explain the results. In the Chinese literature there are other reports of acupuncture

for FMD including one paper describing a 99% success rate in 1316 patients with paralysis(67).

Other therapies

Suggestion / Placebo

Placebo and suggestion cover a wide variety of potential treatments, ranging from an inert pill or infusion, to simply suggesting to the patient they may get better. The latter could be said to be a very simple form of cognitive therapy and as such is not really placebo. This may explain why placebo performs so differently among different studies.

One study with saline infusion and one case report with a placebo pill in FMD found respectively improvement in 7 of 12 patients at follow-up (duration not stated), and complete recovery (68,69).

Edwards et al report immediate resolution of symptoms of botulinum in three patients with fixed dystonia (70). As the authors discussed, had to be consistent with a placebo effect since botulinum only becomes active after 72 hours. The authors sound a note of caution about the use of this treatment but it nonetheless deserves consideration in patients where improvement by other means is not possible.

Neurologists who value transparency and honesty in diagnosis and treatment of FMD naturally object to the idea of deceptive placebo. There is a counter argument however. Placebo could be especially beneficial in functional disorders, since they may share similar pathways (71) and may be associated with similar activity of brain regions found in fMRI-studies (72). Furthermore deception is not necessary to achieve a placebo effect (73) and patients might not reject placebo use (74). Placebo response is of course an issue for many disorders in medicine and the topic is certainly an important one to consider in the design of trials.

Deliberate restriction of activity or deception by the doctor

Several earlier studies report on strategies to motivate patients recovery by restricting their activity or use of facilities (75,76). In a series of papers Shapiro and Teasell described a paradoxical rehabilitation technique in which patients were told that their symptoms would be purely psychiatric if they did not improve (77,78). The authors report improvement (71% of 23 patients improved or remitted at discharge) but we cannot endorse an approach which deliberately sets out to deceive patients and are

doubtful that it would lead to long lasting improvements. Likewise deliberate restriction of facilities or enforced disability is not compatible with modern clinical practice.

Hypnosis

Hypnosis has been used widely for FMD since the 19th century. Studies of hypnotic models of FMD have highlighted similarities to patients with clinical FMD (79,80). Hypnosis was studied in a randomised controlled trial (RCT) as an addition to standard inpatient treatment with multidisciplinary physical and psychological therapy in 92 patients with FMD (81). There was impressive symptom reduction in both groups suggesting benefit from multidisciplinary treatment but no additional benefit from hypnosis.

In another RCT the effect of ten sessions of hypnosis on 44 outpatients with long duration FMD was studied (median 3.7 years) (82). Patients improved highly significantly compared with a waiting list control group after with before treatment.

Separating out the specific effects of hypnosis from other elements of the consultation is probably impossible but the technique almost certainly has a useful role in some patients.

Complications and contraindications: Hypnosis and placebo, in common with all treatments for FMD, run the risk of nocebo, that is the possibility that the patient responds negatively to the suggestions and develops worsening symptoms.

Cost / Cost effectiveness; No literature is available on the costs, nor the cost-effectiveness of above mentioned therapies.

Emerging therapies

This review of existing studies highlights the relatively low quality of most studies and lack of randomised designs. There are particular challenges in designing treatment trials for patients with FMD. These range from how to deal with a 'placebo' arm when placebo may be an effective and desirable treatment to the difficulty of finding outcome measures that capture improvement in patients who are often polysymptomatic. Building an evidence base for a multimodal and stepped approach to treatment of FMD does remain possible. Trial registers indicate ongoing interest in TMS, psychotherapy in functional movement disorders and YD and MT are currently conducting a trial investigating botulinum-toxin injections in functional jerky movements.

Treatment of Pediatric FMD

The course of functional motor disorder in children is often thought to be benign, but data is limited and in some studies school absence, disability and morbidity is high (83). It seems likely that many of the same factors that are associated with adult FMD can be translated in to the pediatric disorder. Several small uncontrolled studies have examined the effect of a multidisciplinary approach involving neurology, psychiatry, and social work/psychology (84), with good results . All studies underline the importance of family involvement in the treatment.

Conflict of interest

The authors declare that they do not have conflict of interest.

Human and Animal Rights and Informed Consent.

This article is a review of existing literature, no human subjects or animals were enrolled.

REFERENCES

1. Stone J, Edwards M. Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology 2012 Jul 17;79(3):282-4.
2. Kanaan R, Armstrong D, Wessely S. Limits to truth-telling: neurologists' communication in conversion disorder. Patient Educ Couns 2009;77(2):296-301.
3. Stone J, Carson A, Duncan R, Roberts R, Warlow C, Hibberd C, et al. Who is referred to neurology clinics?--the diagnoses made in 3781 new patients. Clin Neurol Neurosurg 2010;112(9):747-51.
4. Lempert T, Dieterich M, Huppert D, Brandt T. Psychogenic disorders in neurology: Frequency and clinical spectrum. Acta Neurologica Scandinavica 82(5):335-40
5. Parry AM, Murray B, Hart Y, Bass C. Audit of resource use in patients with non-organic disorders admitted to a UK neurology unit. J Neurol Neurosurg Psychiatry 2006;77(10):1200-1.6.
6. Carson A, Stone J, Hibberd C, Murray G, Duncan R, Coleman R, et al. Disability, distress and unemployment in neurology outpatients with symptoms 'unexplained by organic disease'. J Neurol Neurosurg Psychiatry 2011;82(7):810-3.
7. Anderson KE, Gruber-Baldini AL, Vaughan CG, Reich SG, Fishman PS, Weiner WJ, et al. Impact of psychogenic movement disorders versus Parkinson's on disability, quality of life, and psychopathology. Movement Disorders 2007; 22(15):2204-9
8. Stone J, Sharpe M, Rothwell PM, Warlow CP. The 12 year prognosis of unilateral functional weakness and sensory disturbance. J Neurol Neurosurg Psychiatry 2003;74(5):591-6.
9. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry 2013 Sep 12. doi: 10.1136/jnnp-2013-305321
10. Bogousslavsky J. Hysteria after Charcot: back to the future. Front Neurol Neurosci 2011;29:137-61.
11. Splett T, Steinberg H. Treatment of hysteria in the 19th century--in which way did German psychiatrists view castration?. Fortschr Neurol Psychiatr 2003;71(1):45-52.
12. Poole NA, Wuerz A, Agrawal N. Abreaction for conversion disorder: systematic review with meta-analysis. Br J Psychiatry 2010;197(2):91-5.
13. Nielsen G, Stone J, Edwards MJ. Physiotherapy for functional (psychogenic) motor symptoms: A systematic review. Journal of Psychosomatic Research 2013;75(2): 93-102. doi: 10.1016/j.jpsychores.2013.05.006
14. Stone J, Carson AJ, Scharpe M. Psychogenic movement disorders: explaining the diagnosis. Psychogenic Movement Disorders and Other Conversion Disorders. Cambridge: Cambridge University Press; 2011. p. 254-66.
15. Health Improvement Scotland. (2012). *Stepped care for functional neurological symptoms*. HS Scotlland, Edinburgh. http://www.healthcareimprovementscotland.org/our_work/long_term_conditions/neurological_health_services/neurological_symptoms_report.aspx (accessed Dec 21 2013)

16. Jordbru AA, Smedstad LM, Klungsoyr O, Martinsen EW. Psychogenic gait disorder: A randomized controlled trial of physical rehabilitation with one-year follow-up. J Rehabil Med 2013 Nov 13. doi: 10.2340/16501977-1246
17. Edwards MJ, Stone J, Nielsen G. Physiotherapists and patients with functional (psychogenic) motor symptoms: A survey of attitudes and interest. Journal of Neurology, Neurosurgery and Psychiatry 2012;83(6):655-8
18. Czarnecki K, Thompson JM, Seime R, Geda YE, Duffy JR, Ahlskog J. Functional movement disorders: Successful treatment with a physical therapy rehabilitation protocol. Parkinsonism Relat Disord 2012;18(3):247-51
19. Dallocchio C, Arbasino C, Klersy C, Marchioni E. The effects of physical activity on psychogenic movement disorders. Movement Disorders 2010;25(4): 421-5
20. McCormack R, Moriarty J, Mellers JD, Shotbolt P, Pastena R, Landes N, et al. Specialist inpatient treatment for severe motor conversion disorder: a retrospective comparative study. J Neurol Neurosurg Psychiatry 2013 Oct 11. doi: 10.1136/jnnp-2013-305716
21. Saifee TA, Kassavetis P, Parees I, Kojovic M, Fisher L, Morton L, et al. Inpatient treatment of functional motor symptoms: A long-term follow-up study. Journal of Neurology 2012;259(9):1958-63
22. Ruddy R, House A. Psychosocial interventions for conversion disorder. Cochrane Database Syst Rev 2005;(4):CD005331.
23. Espay AJ, Goldenhar LM, Voon V, Schrag A, Burton N, Lang AE. Opinions and clinical practices related to diagnosing and managing patients with psychogenic movement disorders: An international survey of movement disorder society members. Movement Disorders 2009;24(9) :1366-74
24. McKenzie P, Oto M, Russell A, Pelosi A, Duncan R. Early outcomes and predictors in 260 patients with psychogenic nonepileptic attacks. Neurology 2010;74(1):64-9.
25. Razvi S, Mulhern S, Duncan R. Newly diagnosed psychogenic nonepileptic seizures: health care demand prior to and following diagnosis at a first seizure clinic. Epilepsy Behav 2012;23(1):7-9.
26. Carton S, Thompson PJ, Duncan JS. Non-epileptic seizures: patients' understanding and reaction to the diagnosis and impact on outcome. Seizure 2003;12(5):287-94.
27. Baxter S, Mayor R, Baird W, Brown R, Cock H, Howlett S, et al. Understanding patient perceptions following a psycho-educational intervention for psychogenic non-epileptic seizures. Epilepsy Behav 2012;23(4):487-93.
28. Hall-Patch L, Brown R, House A, Howlett S, Kemp S, Lawton G, et al. Acceptability and effectiveness of a strategy for the communication of the diagnosis of psychogenic nonepileptic seizures. Epilepsia 2010;51(1):70-8.
29. Salmon P, Peters S, Stanley I. Patients' perceptions of medical explanations for somatisation disorders: qualitative analysis. BMJ 1999;318(7180):372-6.
30. Friedman JH, LaFrance W. Psychogenic disorders: The need to speak plainly. Archives of Neurology 2010;67(6):753-5
31. Duncan R. Psychogenic nonepileptic seizures: diagnosis and initial management. Expert Rev Neurother 2010;10(12):1803-9.

32. Edwards, M. J., Stone, J., & Lang, A. (2013). From Psychogenic Movement Disorder (PMD) to Functional Movement Disorder (FMD): It's time to change the name. Movement Disorders, I2013 Jul 10. doi: 10.1002/mds.25562

33. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". BMJ 2002;325(7378):1449-50.

34. Hopp JL, LaFrance WC, Jr. Cognitive behavioral therapy for psychogenic neurological disorders. Neurologist 2012;18(6):364-72.

35. Baslet G, Hill J. Case report: Brief mindfulness-based psychotherapeutic intervention during inpatient hospitalization in a patient with conversion and dissociation. Clinical Case Studies 2011;10(2):95-109

36. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial. Neurology 2011;77(6):564-72.

37. Allen LA, Woolfolk RL, Escobar JI, Gara MA, Hamer RM. Cognitive-behavioral therapy for somatization disorder: a randomized controlled trial. Arch Intern Med 2006;166(14):1512-8.

38. Kompoliti K, Wilson B, Stebbins G, Bernard B, Hinson V. Immediate vs. delayed treatment of psychogenic movement disorders with short term psychodynamic psychotherapy: Randomized clinical trial. Parkinsonism Relat Disord 2013 Sep 22. doi: 10.1016/j.parkreldis.2013.09.018

39. Hinson VK, Weinstein S, Bernard B, Leurgans SE, Goetz CG. Single-blind clinical trial of psychotherapy for treatment of psychogenic movement disorders. Parkinsonism and Related Disorders 2006;12(3):177-80

40. Reuber M, Burness C, Howlett S, Brazier J, Grunewald R. Tailored psychotherapy for patients with functional neurological symptoms: a pilot study. J Psychosom Res 2007 Dec;63(6):625-32.

41. Voon V, Lang AE. Antidepressant treatment outcomes of psychogenic movement disorder. Journal of Clinical Psychiatry 2005;66(12):1529-34.

42. Edwards MJ, Talelli P, Rothwell JC. Clinical applications of transcranial magnetic stimulation in patients with movement disorders. Lancet Neurol 2008;7(9):827-40.

43. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010;71(7):873-84.

44. Geraldes R, Coelho M, Rosa M, Severino L, Castro J, de Carvalho M. Abnormal transcranial magnetic stimulation in a patient with presumed psychogenic paralysis. J Neurol Neurosurg Psychiatry 2008;79(12):1412-3.

45. Liepert J, Hassa T, Tuscher O, Schmidt R. Motor excitability during movement imagination and movement observation in psychogenic lower limb paresis. Journal of Psychosomatic Research 2011;70(1):59-65.

46. Liepert J, Shala J, Greiner J. Electrophysiological correlates of disobedience and feigning-like behaviour in motor imagery. Clin Neurophysiol 2013 Oct 12. doi: 10.1016/j.clinph.2013.09.013

47. Pollak TA, Nicholson TR, Edwards MJ, David AS. A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms. J Neurol Neurosurg Psychiatry 2013 Jan 8. Doi:10.1007/s13311-013-0246-x
48. Garcin B, Roze E, Mesrati F, Cognat E, Fournier E, Vidailhet M, et al. Transcranial magnetic stimulation as an efficient treatment for psychogenic movement disorders. J Neurol Neurosurg Psychiatry 2013;84(9):1043-6
49. Chastan N, Parain D. Psychogenic paralysis and recovery after motor cortex transcranial magnetic stimulation. Movement Disorders 2010;25(10):1501-4
50. Shah BB, Zurowski M, Chen R, et al. Failure of motor cortex repetitive transcranial magnetic stimulation (rTMS) combined with suggestion in the treatment of chronic psychogenic movement disorders (PMDs): a pilot study. 15th International Congress of Parkinson's Disease and Movement Disorders, Toronto, ON, Canada, 2011.
51. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008-39.
52. Toglia JU, Izzo K. Treatment of myoclonic dystonia with transcutaneous electrical nerve stimulation. Ital J Neurol Sci 1985;6(1):75-8.
53. Bending J, Cleeves L. Effect of electrical nerve stimulation on dystonic tremor. Lancet 1990;336(8727):1385-6.
54. Tinazzi M, Farina S, Bhatia K, Fiaschi A, Moretto G, Bertolasi L, et al. TENS for the treatment of writer's cramp dystonia: a randomized, placebo-controlled study. Neurology 2005;64(11):1946-8.
55. Maltete D, Verdure P, Roze E, Vidailhet M, Apartis E, Bellow F, et al. TENS for the treatment of propriospinal myoclonus. Mov Disord 2008;23(15):2256-7.
56. Foley-Nolan D, Kinirons M, Coughlan RJ, O'Connor P. Post whiplash dystonia well controlled by transcutaneous electrical nervous stimulation (TENS): case report. J Trauma 1990;30(7):909-10.
57. Withrington RH, Wynn Parry CB. Rehabilitation of conversion paralysis. J Bone Joint Surg Br 1985;67(4):635-7.
58. Atan C, Seckin U, Bodur H. Hysterical paralysis. Rheumatology International 2007; 27(9):873-4
59. Wojtecki L, Groiss S, Scherfeld D, Albrecht P, Pollok B, Elben S, et al. Transient improvement of psychogenic (proprio-)spinal-like myoclonus to electrical nerve stimulation. Movement Disorders 2009;24(13):2024-5.
60. Brierley H. The treatment of hysterical spasmodic torticollis by behaviour therapy. Behaviour research and therapy 1967;5(2):139-42.
61. Ferrara J, Stamey W, Strutt AM, Adam OR, Jankovic J. Transcutaneous electrical stimulation (TENS) for psychogenic movement disorders. The Journal of neuropsychiatry and clinical neurosciences 2011;23(2):141-8.
62. Khalil TM, Abdel-Moty E, Asfour SS, Fishbain DA, Rosomoff RS, Rosomoff HL. Functional electric stimulation in the reversal of conversion disorder paralysis. Archives of Physical Medicine and Rehabilitation 1988;69(7):545-7.

63. Fishbain DA, Goldberg M, Khalil TM, Asfour SS, Abdel-Moty E, Meagher B, et al. The utility of electromyographic biofeedback in the treatment of conversion paralysis. The American journal of psychiatry 1988;145(12):1572-5..

64. Simpson PM, Fouche PF, Thomas RE, Bendall JC. Transcutaneous electrical nerve stimulation for relieving acute pain in the prehospital setting: a systematic review and meta-analysis of randomized-controlled trials. Eur J Emerg Med 2013 Jul 7. DOI: 10.1097/MEJ.0b013e328363c9c1

65. Stone J, Hoeritzauer I, Brown K, Carson A. Therapeutic sedation for functional (psychogenic) neurological symptoms. Journal of Psychosomatic Research 2013. doi.org/10.1016/j.jpsychores.2013.10.003.

66. Van Nuenen BFL, Wohlgemuth M, Wong Chung RE, Abdo WF, Bloem BR. Acupuncture for psychogenic movement disorders: Treatment or diagnostic tool? Movement Disorders 2007;22(9):1353-5..

67. Zhang ZY, Yuan YM, Yan BW, Tian YQ, Wang W, Fan LM. An observation of 1316 cases of hysterical paralysis treated by acupuncture. J Tradit Chin Med 1987 Jun;7(2):113-5.

68. Monday K, Jankovic J. Psychogenic myoclonus. Neurology 1993;43(2):349-52.

69. Baik JS, Han SW, Park JH, Lee MS. Psychogenic paroxysmal dyskinesia: The role of placebo in the diagnosis and management. Movement Disorders 2009;24(8):1244-5.

70. Edwards MJ, Bhatia KP, Cordivari C. Immediate response to botulinum toxin injections in patients with fixed dystonia. Mov Disord. 2011 Apr;26(5):917-8

71. Shamy MCF. The treatment of psychogenic movement disorders with suggestion is ethically justified. Movement Disorders 2010;25(3):260-4.

72. Rommelfanger KS. Opinion: A role for placebo therapy in psychogenic movement disorders. Nature Reviews Neurology 2013;9(6):351-6.

73. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One 2010;5(12):e15591 doi: 10.1371/journal.pone.0015591.

74. Lynoe N, Mattsson B, Sandlund M. The attitudes of patients and physicians towards placebo treatment--a comparative study. Soc Sci Med 1993;36(6):767-74.

75. Dickes RA. Brief therapy of conversion reactions: an in-hospital technique. Am J Psychiatry 1974;131(5):584-6.

76. Trieschmann RB, Stolov WC, Montgomery ED. An approach to the treatment of abnormal ambulation resulting from conversion reaction. Arch Phys Med Rehabil 1970;51(4):198-206.

77. Shapiro AP, Teasell RW. Behavioural interventions in the rehabilitation of acute v. chronic non-organic (conversion/factitious) motor disorders. Br J Psychiatry 2004;185:140-6.

78. Teasell RW, Shapiro AP. Strategic-behavioral intervention in the treatment of chronic nonorganic motor disorders. Am J Phys Med Rehabil 1994;73(1):44-50.

79. Ward NS, Oakley DA, Frackowiak RS, Halligan PW. Differential brain activations during intentionally simulated and subjectively experienced paralysis. Cogn Neuropsychiatry 2003;8(4):295-312.

80. Bell V, Oakley DA, Halligan PW, Deeley Q. Dissociation in hysteria and hypnosis: evidence from cognitive neuroscience. J Neurol Neurosurg Psychiatry 2011;82(3):332-9.

81. Moene FC, Spinhoven P, Hoogduin KAL, Van Dyck R. A randomised controlled clinical trial on the additional effect of hypnosis in a comprehensive treatment programme for in-patients with conversion disorder of the motor type. Psychotherapy and Psychosomatics 2002;71(2):66-76..

82. Moene FC, Spinhoven P, Hoogduin KA, van DR. A randomized controlled clinical trial of a hypnosis-based treatment for patients with conversion disorder, motor type. Int J Clin Exp Hypn 2003;51(1):29-50.

83. Ferrara J, Jankovic J. Psychogenic movement disorders in children. Mov Disord 2008 Oct 15;23(13):1875-81.

84. Faust J, Soman TB. Psychogenic movement disorders in children: Characteristics and predictors of outcome. Journal of Child Neurology 2012;27(5):610-4.

Botulinum NeuroToxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomized placebo-controlled trial with an open-label extension.

3

Yasmine EM Dreissen, Joke M Dijk, Jeannette M Gelauff, Evelien Zoons, Daniel van Poppelen, Maria F Contarino, Rodi Zutt, Bart Post, Alexander G Munts, Johannes D Speelman, Danielle C Cath, Rob J de Haan, Johannes HTM Koelman & Marina AJ Tijssen

Article published in Journal of Neurology Neurosurgery and Psychiatry 2019
doi 10.1136/jnnp-2018-320071

ABSTRACT

Objective: To study the effect of BoNT treatment in jerky and tremulous FMD.

Methods: Patients with invalidating, chronic (> 1 year) symptoms were randomly assigned to two subsequent treatments with BoNT or placebo every three months with stratification according to symptom localization. Improvement on the dichotomized Clinical Global Impression-Improvement scale (CGI-I) (improvement vs. no change or worsening) at four months, assessed by investigators blinded to the allocated treatment was the primary outcome. Subsequently all patients were treated with BoNT in a ten month open-label phase.

Results: Between January 2011 and February 2015 a total of 239 patients were screened for eligibility of whom 48 patients were included. No difference was found on the primary outcome (BoNT 16 of 25 (64.0%) vs. Placebo 13 of 23 patients (56.5%); proportional difference 0.075 (95% CI -0.189 to 0.327; p = 0,77). Secondary outcomes (symptom severity, disease burden, disability, quality of life and psychiatric symptoms) showed no between-group differences. The open-label phase showed improvement on the CGI-I in 19/43 (44.2%) of remaining patients, with a total of 35/43 (81.4%) improvement compared to baseline.

Conclusions: In this double blind randomized controlled trial of BoNT for chronic jerky and tremulous FMD we found no evidence of improved outcomes compared to placebo. Motor symptoms improved in a large proportion in both groups which was sustained in the open-label phase. This study underlines the substantial potential of chronic jerky and tremulous FMD patients to recover and may stimulate further exploration of placebo-therapies in these patients.

Trial registration: Dutch Trial Registry 2478.

INTRODUCTION

Despite the fact that functional neurologic symptoms (FNS) comprise a third of the patient population of a neurologist, and disease and financial burden on the health care system is large, research on optimal treatment in this field has been very limited. In movement disorder clinics functional movement disorders (FMD) account for up to 25% of patients seen (1, 2). The diagnosis is based on positive clinical symptoms, supported by neurophysiologic tests. (2-4) Amongst FMD, jerks and tremor are frequently seen and have a relatively poor outcome at long-term follow-up (3-7 years) (5, 6). Botulinum neurotoxin (BoNT) has emerged as a useful therapy for several movement disorders associated with muscle over-activity, including dystonia, and tics (7, 8). The mechanism of action of BoNT is more extensive than blocking muscle activity alone; in dystonia for instance there is supporting evidence that BoNT induces plastic changes in the brain (9). Case reports in FMD have reported promising effects of BoNT treatment (6, 10), especially in functional dystonia in which large placebo-effects have also been described (11). This has stressed the importance of conducting a controlled clinical trial to disentangle response to an active agent versus placebo. Based on the literature, and our own experience in patients with jerky and tremulous FMD, we hypothesized that BoNT treatment enables restoring the abnormal movement pattern and therefore will be more effective than placebo. To study the long-term effects of BoNT, a subsequent open-label extension study was conducted following the randomized trial phase.

METHODS

Study design

This study was designed as a 4-month single-center, randomized, double-blind, placebo-controlled trial (RCT), followed by an open-label extension phase consisting of up to 4 treatment sessions for an additional period up to 10 months. BoNT injections were compared to injections with placebo in patients with jerky and tremulous FMD. In the follow-up period, the long-term effects of BoNT injections were assessed.

This study was performed at a tertiary referral center for movement disorders in the Amsterdam UMC, the Netherlands.

Patients

All eligible patients with jerky and tremulous FMD were consecutively seen at our outpatient clinic from 2000 or specifically referred to us for this study. Included patients had incapacitating functional jerks for at least one year, were aged between 18 and 80

years. To improve inclusion, during the study an amendment of the protocol was made adding patients with functional tremor. The diagnosis was made by two experienced movement disorder specialists (JHTMK, MAJT) and symptoms had to fulfil the criteria for "definite" or "probable" FMD (2). No change in medication was allowed in the month prior to participation. Exclusion criteria were pregnancy, coagulation disorders and insufficient knowledge of the Dutch language.

Randomization and masking

An independent trial nurse, not involved in the treatment or assessment of the outcome measures, carried out a web-based randomisation procedure (ALEA; www.aleaclinical.eu) and prepared the study medication. BoNT is available as powder for injection; after dissolving it is a colourless fluid indistinguishable from sterile saline which was used as placebo. Both BoNT and placebo were prepared in identical syringes. Patients were randomized with a ratio of 1:1 to BoNT or placebo treatment. Randomisation was stratified by localization of symptoms (extremity vs. axial), using permuted blocks with varying block sizes (2 and 4). All patients were treated by the same experienced neurophysiologist (JHTMK). The patients, treating physicians, and research group were uninformed about the allocated treatment.

Procedures

Treatment consisted of either intramuscular injections with BoNT type A (BoNT-A) or placebo. Freeze-dried BoNT-A (Dysport®, Ipsen BV, Hoofddorp, the Netherlands) was diluted to 20 units (IU) per 0.1 ml of 0.9% sterile saline and aspirated in 1-ml syringes. Placebo consisted of an equivalent volume of 0.9% sterile saline. Injections were given under simultaneous electromyogram (EMG) recordings into selected muscles using a hollow, Teflon-coated, 27-gauge needle.

During the RCT all patients were treated twice with either BoNT or placebo; at baseline and three months thereafter. The dosages of BoNT were based on the volume of the muscle(s) injected (12). Similar to a RCT in writer's cramp, the dosage was doubled at the second treatment according to the degree of response (13). After 3 months, all patients subsequently received treatment with BoNT in an open-label extension phase, resulting in a maximum of 4 open-label injections.

At baseline, patients underwent a standardized neurologic examination, video recording with a standardized protocol (**appendix 4**), and demographic characteristics were gathered. Explanation of the study including efficacy and the most common adverse events of BoNT were given (**appendix 2**). All patients underwent electrophysiologic examination (polymyography) to support FMD and to select muscles for BoNT

treatment (3). In suitable patients an electroencephalography was added to support FMD (e.g. bereitschaftspotential) (14).

Outcomes

The outcome measures were assessed at baseline, at 4 months (primary endpoint) and 4 weeks after the last treatment (end of study). Outcome indicators were: motor symptoms, motor severity, disease burden, muscle weakness, disability, quality of life, and quantitative psychiatric assessment. The primary endpoint was improvement of motor symptoms based on the video recordings rated by investigators using the Clinical Global Impression – Improvement (CGI-I) scale (a 7-point scale, ranging from 1=very much improved to 7=very much worse) (15). Improvement was defined as a CGI-I score 1, 2 or 3. Patients underwent extensive psychiatric assessment including a psychiatric interview based on the DSM-IV (MINI-plus) and several self-assessment scales including the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI).

The severity of motor symptoms was determined using the Clinical Global Impression-Severity (CGI-S) Scale (a 7-point scale, 1 = no symptoms to 7 = very severe symptoms) and the psychogenic movement disorder rating scale (PMDRS) (16). Two investigators (out of 9 assessors: JD, JG, EZ, DP, MFC, RZ, BP, AM, JDS) per subset of patients who were blinded to the allocated treatment independently assessed symptom improvement (CGI-I) and severity (CGI-S, PMDRS) based on the video recordings. Ratings of the most experienced rater were used in the final analysis. The second rater served in an inter-observer analysis.

Patients rated their perceived symptom improvement and severity using the CGI-I and CGI-S as well, combined with a 100 mm horizontal Visual Analogue Scale (VAS) measuring disease burden (0 indicating no disease burden and 100 indicating the worst possible disease burden). Muscle weakness and atrophy were examined objectively by a blinded physician (JHTMK) using the MRC scale. The AMC Linear Disability Score (ALDS) was used to measure activities of daily life. Quality of life (QL) was assessed using the 36-item Short Form Health Survey (SF-36). Quantitative questionnaires concerning psychiatric symptoms were assessed, including the Beck Depression Inventory (BDI), Montgomery Asberg Depression Rating Scale (MADRS), Beck Anxiety Inventory (BAI), Liebowitz Social Anxiety Scale (LSAS), Obsessive Compulsive Inventory (OCI) (**appendix 1**).

The most common adverse events of BoNT (pain, weakness, flu-like symptoms and any other negative effects) were actively asked for. During the trial phase, patients were

asked whether they thought they received BoNT or placebo, how much confidence they had in the treatment beforehand and whether they wanted to continue treatment.

Statistical analysis

We assumed that 30% of patients in the placebo group and 70% of the patients of the BoNT group would reach the primary endpoint. The placebo effect was hypothesized to be larger than the effect size found in a similar BoNT trial in focal dystonia (writer's cramp) (13). A two-group Chi-square test with a 0,05 two-sided significance level generated a sample size of 24 patients per arm with a power of 80%.

All analyses were done according to the intention-to-treat principle. The baseline characteristics, outcome parameters and (serious) adverse events were summarized using descriptive statistics. The CGI-I was dichotomized to improvement (score 1,2 or 3) vs. no change or worsening (score 4,5,6,7). Between-group differences in proportions (trial phase) were assessed using the x2-test or Fisher's exact test, when appropriate. Statistical uncertainty was expressed in a two-sided 95% confidence interval (CI). With regard to the primary outcome indicator, we additionally performed multivariable logistic regression with treatment groups and the stratification factor (axial vs. extremity) as independent variables. The effect size was expressed in an adjusted odds ratio.

As most continuous secondary outcome measures were non-normally distributed, all outcome measures were described in median scores, with their interquartile ranges (IQR).

The within-group median change scores (from baseline to outcome assessment) in the trial phase was calculated as the 50^{th} percentile of all individual differences. Point estimate and 95% CI of the median differences in change scores between the treatment groups was analyzed using the Hodges-Lehmann approach (17). Between-group difference in change scores was also analyzed using the Mann-Whitney U test.

The difference in within-group median scores in the open-label extension phase was analysed with the Wilcoxon signed rank test for paired data.

Interobserver agreements of the ordinal ratings on the CGI-I and CGI-S were analyzed using the average weighted Kappa (K) statistic. With regard to the interobserver agreements of the continuous PMDRS scores, we used the average Intraclass Correlation Coefficient (ICC) (**appendix 2**).

A two-sided p-value < 0.05 was considered statistically significant. Missing data were not imputed and no interim analysis was performed. All analyses were performed in IBM SPSS Statistics version 24 and STATA version 15. The pre-defined statistical analysis plan is available in **appendix 3.**

Post-hoc analyses

The primary outcome measure was analyzed setting a higher bar of improvement (CGI-I score 1-2 vs. 3-7). Possible predictors of treatment outcome on the CGI-I were analyzed using a logistic regression including: symptom duration, psychiatric co-morbidity (anxiety/depressive disorder), quantitative pain measures (subscale SF-36), pain disorder, confidence in treatment beforehand and which treatment arm patients thought they were in.

Classification of evidence

The aim of this was to provide class I evidence according to the classification of evidence from the American Academy of Neurology (18, 19) on the effect of BoNT treatment in patients with jerk-like FMD.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the local Medical Ethics Committee. All patients provided written informed consent plus separately consent for the published video-recordings. The trial is registered in the Dutch Trial Register (NTR 2478) (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2478) and was monitored by an independent monitor of the Amsterdam UMC, according to GCP guidelines. The study protocol can be found online (https://www.amc.nl/web/specialismen/neurologie-1/botulinum-neurotoxin-bont-trial.htm).

RESULTS

Between the 27th of January 2011 and the 18th of February 2015 a total of 239 patients were screened for eligibility of whom 49 patients were randomized and 48 actually received treatment **(figure 1).** For details on reasons of exclusion see **appendix 2**. Twenty-five patients were treated with BoNT and 23 patients with placebo. All patients were BoNT-naïve except for one patient who was treated ineffectively once before. He was considered to possibly benefit from treatment with better muscle selection using polymyography. All patients completed the trial phase of the study. The baseline characteristics are summarized in **table 1**. The majority of patients in both treatment arms underwent previous other sorts of treatments. Examples of included patients reflecting the clinical spectrum are shown in **videos 1-3**.

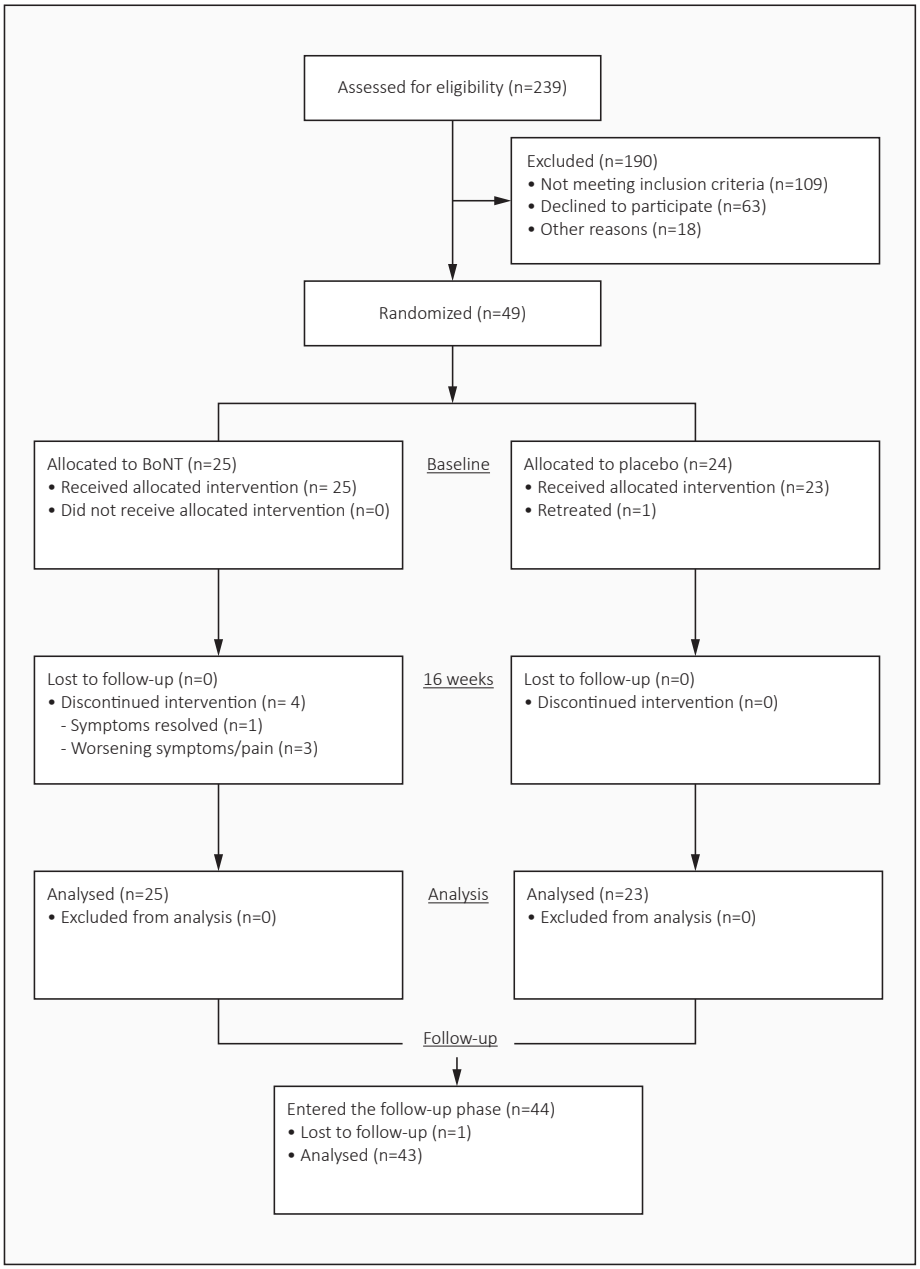

Figure 1. *Study flow-chart: enrolment, randomisation and follow-up of patients. For details on reasons why patients did not fulfill the inclusion criteria see* ***appendix 2****.*

	BoNT n=25	Placebo n=23
Age – yr (median; IQR)	50.0 (40.0; 61.5)	54.0 (37.0; 57.0)
Gender - no. (%)		
· Male	14 (56)	14 (61)
Duration of disease – yr (median; IQR)	5.0 (2.1; 13.4)	5.3 (2.2; 9.0)
Fahn and Williams diagnostic criteria - no. (%)		
· Clinically definite	18 (72.0)	16 (69.6)
· Clinically probable	7 (28.0)	7 (30.4)
Additional phenomenology based on PMDRS – no. (%)		
· Dystonia	12 (48.0)	10 (43.5)
· Tic	3 (12.0)	2 (8.7)
Distribution of jerks/tremor - no. (%)		
· Abdomen	12 (48.0)	11 (47.8)
· Extremity	13 (52.0)	12 (52.2)
Education level - no. (%)		
· Primary school	1 (4.0)	2 (8.7)
· Lower education	4 (16.0)	3 (13.0)
· Medium education/higher school	11 (44.0)	12 (52.2)
· Higher education/university	9 (36.0)	6 (26.1)
· Unemployed	17 (68.0)	13 (56.5)
· Disease-related*	13 (52.0)	11 (47.8)
Clinical neurophysiology - no. (%)**	13 (52.0)	14 (60.9)
· Pre-movement potential	11 (61.5)	11 (57.1)
Previous treatment - no. (%)***	21 (84.0)	22 (95.7)
· Rehabilitation	4 (16.0)	5 (21.7)
· Physiotherapy	8 (34.8)	9 (36.0)
· Psychotherapy	5 (20.0)	7 (30.4)
· Other****	17 (68.0)	17 (73.9)

Table 1. *Baseline characteristics of study population. IQR=Interquartile range. * Other forms of financial income included retirement (n=4 BoNT vs n=1 placebo), study (n=1 placebo). ** EEG-EMG with backaveraging could not be performed in the whole population. *** More than one category could apply per patient ****other treatment includes acupuncture, homeopathic treatment, alternative medicine, hypnosis, benzodiazepines, SSRIs, anti-epileptics, dopamine-agonists.*

Trial phase

Due to pain/worsening symptoms (n=2) and complete resolution of symptoms (n=1), 3 patients discontinued BoNT treatment after one injection. One patient discontinued the

study after two BoNT injections because of pain **(figure 1)**. In one patient, assessment of the primary endpoint was delayed to one year instead of 4 months due to personal circumstances.

In the BoNT arm the median initial dose was 240 IU (IQR 140-400) followed by 440 IU (IQR 240-705) at the second visit. The iliopsoas (n=8), rectus abdominis (n=7) and quadriceps muscle (n=6) were most frequently injected. In the placebo group patients were treated with a volume of sterile saline equivalent to a median dose of 280 IU (IQR 130-400) at the first visit, and 450 IU (IQR 240-640) at the second visit; the rectus abdominis (n=5) and iliopsoas muscle (n=5) were most frequently injected. Usually two muscles per subject were injected (range 1-6). For an extensive overview of the injected muscles and corresponding doses see **appendix 2**.

The interobserver agreement was substantial for the CGI-I and CGI-S (average weighted κ = 0.65, SD 0.16), and the PMDRS (average ICC = 0.76, SD 0.11). At the end of the trial-period 9 out of 25 (36.0%) patients in the BoNT vs. 8 out of 22 (34.8%) patients in the placebo arm thought they received BoNT. Three (12.0%) patients in the BoNT vs. 1 (4.3%) in the placebo arm could not answer the question.

Regarding the primary outcome measure; 16 of 25 (64.0%) patients in the BoNT arm showed improvement of motor symptoms (CGI-I score 1,2 or 3) compared to 13 of 23 (56.5%) in the placebo arm **(figure 2)**. This resulted in a non-significant proportional difference of 0.075 (95% CI -0.189 to 0.327; p= 0,77). Multivariable logistic regression analysis, adjusted for the stratification variable (extremity vs. axial), also did not reveal an effect of BoNT (adjusted OR 1.371; 95% CI 0.428 to 4.390; p=0,60)**.**

The CGI-I rated by patients (secondary endpoint), showed a perceived improvement (score 1,2 or 3) in 12 out of 25 (48.0%) patients of the BoNT arm compared to 12 out of 23 (52.2%) in the placebo arm resulting in a non-significant proportional difference of -0,042 (95% CI -0,300 to 0,225; p = 1,00). The other secondary outcome measures are summarized in **table 2**. There were marginal and non-significant median differences in change scores between the BoNT and placebo group.

The post-hoc analysis using a higher cut-off point for improvement on the CGI-I (score 1-2 vs. 3-7) did not alter our results (p=0,349). Also, no significant predictors for treatment response were found.

Open-label phase

After completing the trial, 44 of 48 patients participated in the open-label phase. Twenty-seven (61.4%) of 44 patients completed four treatment sessions in the open-label study (**figure 1**).

The median dose administered per visit was 350 IU (IQR 200-480). Usually two muscles were injected (ranging from 1 to 8). Due to a mistake made by the pharmacy, one patient received placebo instead of BoNT during the first session of the open-label extension study. He was called back and treated again.

Two (4.5 %) patients were treated once, 9 (20.5%) patients twice and 6 (13.6%) patients were treated 3 times. In the final analysis one patient, who refused to cooperate was lost to follow-up.

Improvement (score 1,2 or 3) of motor symptoms on the CGI-I assessed by the investigators occurred in 19 of 43 patients (44.2%) compared to the end of the randomized trial (**see figure 3**), resulting in a total of 35 out of 43 patients (81.4%) showing improvement compared to baseline.

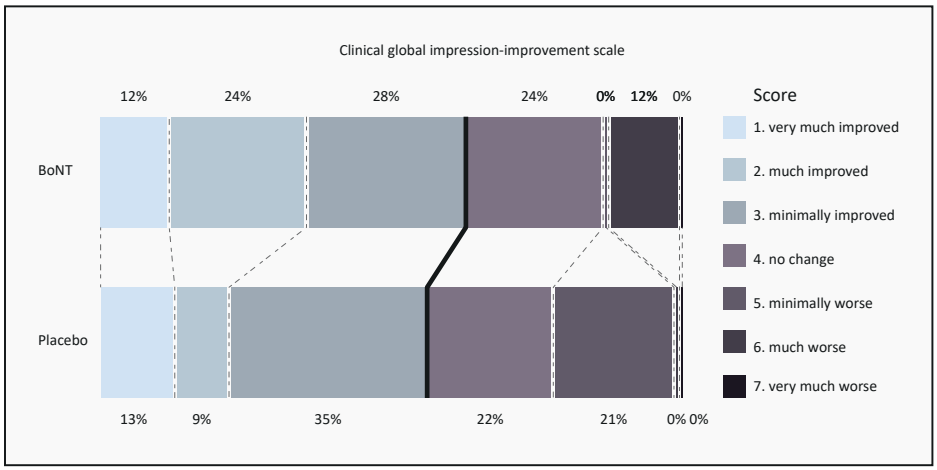

Figure 2. *Distribution of scores of the primary outcome (Clinical Global Impression-Improvement Scale). The thick black line indicates the cut-off point of improvement (score 1,2 or 3) vs. no change or worsening (score 4, 5, 6 and 7). No significant difference was found between the two treatment arms (BoNT vs. placebo; proportional difference of 0.075 (95% CI -0.189 to 0.327; p=0,77)).*

	BoNT (n=25)			Placebo (n=23)			Treatment comparison	
	Median score (IQR) at baseline	Median score (IQR) end of trial	Median score (IQR) change score	Median score (IQR) at baseline	Median score (IQR) end of trial	Median score (IQR) change score	Median difference in change scores (95% CI)	P-value*
CGI-severity investigator	3.0 (2.0; 5.0)	3.0 (2.0; 4.0)	- 1.0 (-1.0; 0.5)	4.0 (3.0; 5.0)	4.0 (2.0; 5.0)	0.0 (-1.0; 0.0)	-1.0 (-1.0 to 1.0)	0.821
CGI-severity patient	5.0 (4.0; 6.0)	4.0 (3.0; 6.0)	0.0 (-1.5; 1.0)	5.0 (4.0; 6.0)	4.0 (4.0; 5.0)	- 1.0 (-1.0; 0.0)	1.0 (-1.0 to 1.0)	0.799
VAS-disease burden patient	49.0 (30.5; 71.0)	34.0 (14.0; 78.5)	-2.0 (-27.5; 20.0)	62.0 (40.0; 86.0)	48.0 (29.0; 67.0)	-2.0 (-48.0; 12.0)	0.0 (-25.0 to 15.0)	0.613
PMDRS-motor symptoms	10.0 (5.0; 18.0)	8.0 (4.5; 15.0)	-3.0 (-6.5; 2.5)	17.0 (10.0; 21.0)	16.0 (9.0; 22.0)	0.0 (-5.0; 2.0)	-3.0 (-2.0 to 4.0)	0.438
SF-36-Physical component	37.8 (24.3; 54.4) (n=24)	36.3 (24.0; 55.1) (n=22)	-1.2 (-5.9; 4.4)	33.2 (26.7; 42.1)	32.6 (27.1; 43.0)	- 1.3 (-3.7; 2.2)	0.1 (-4.2 to 4.2)	0.964
SF-36-Mental component	50.8 (41.1; 57.9) (n=24)	52.3 (41.2; 55.4) (n=22)	0.2 (-5.6; 3.8)	52.9 (44.0; 60.3)	52.5 (40.0; 60.6)	1.0 (-2.0; 6.4)	- 0.8 (-3.6 to 5.4)	0.768
ALDS-disability	88.4 (84.2; 89.5) (n=24)	89.5 (78.8; 89.5) (n=22)	0.0 (-2.5; 0.1)	87.4 (79.0; 89.5)	86.9 (79.3; 89.2)	-0.3 (-2.1; 0.0)	0.3 (-1.3 to 1.6)	0.624

	BoNT (n=25)			Placebo (n=23)			Treatment comparison	
	Median score (IQR) at baseline	Median score (IQR) end of trial	Median score (IQR) change score	Median score (IQR) at baseline	Median score (IQR) end of trial	Median score (IQR) change score	Median difference in change scores (95% CI)	P-value*
BDI-Depressive symptoms	8.0 (4.5; 14.0) (n=24)	8.5 (4.5; 14.0) (n=22)	-1.0 (-4.0; 3.3)	9.0 (5.0; 13.0)	10.0 (3.0; 11.0)	0.0 (-3.0; 1.0)	-1.0 (-3.0 to 3.0)	0.802
MADRS-Depressive symptoms	12.0 (5.0; 15.5)	9.0 (4.0; 16.0)	0.0 (-3.0; 3.0)	13.0 (6.0; 18.0)	13.0 (8.0; 22.0)	3.00 (-4.0; 7.0)	-3.0 (-1.0 to 6.0)	0.214
BAI-Anxiety symptoms	10.0 (6.3; 15.8) (n=24)	10.0 (2.8; 15.3) (n=24)	1.0 (-1.5; 3.0)	13.0 (8.0; 18.0)	12.0 (5.0; 18.0)	0.0 (-5.0; 2.0)	1.0 (-5.0 to 1.0)	0.213
LSAS-Social anxiety	10.0 (5.3; 27.0) (n=24)	10.5 (4.8; 20.8) (n=22)	-2.5 (-6.3; 5.0)	10.0 (3.5; 17.5) *(n=22)*	9.0 (4.0; 25.0)	0.0 (-4.0; 8.3)	-2.5 (-4.0 to 10.0)	0.264
OCI-Obsessive-Compulsive symptoms	2.0 (0.3; 6.8) (n=24)	4.0 (1.0; 6.3) (n=24)	0.0 (-1.0; 3.3)	2.0 (0.0; 5.0)	4.0 (1.0; 7.0)	1.0 (0.0; 3.0)	1.0 (-1.0 to 2.0)	0.300

Table 2. *IQR = Interquartile range. 95% CI = 95% Confidence* Interval (Hodges-Lehmann approach). *CGI = Clinical Global Impression, VAS = Visual Analogue Scale, PMDRS = Psychogenic Movement Disorder Rating Scale, SF-36 = Short Form 36, ALDS = AMC Linear Disability Score, BDI = Beck Depression Inventory, MADRS = Montgomery Asberg Depression Rating Scale, BAI = Beck Anxiety Inventory, LSAS = Liebowitz Social Anxiety Scale, OCI = Obsessive Compulsive Inventory. The missing data should be noticed.*Mann-Whitney U test.*

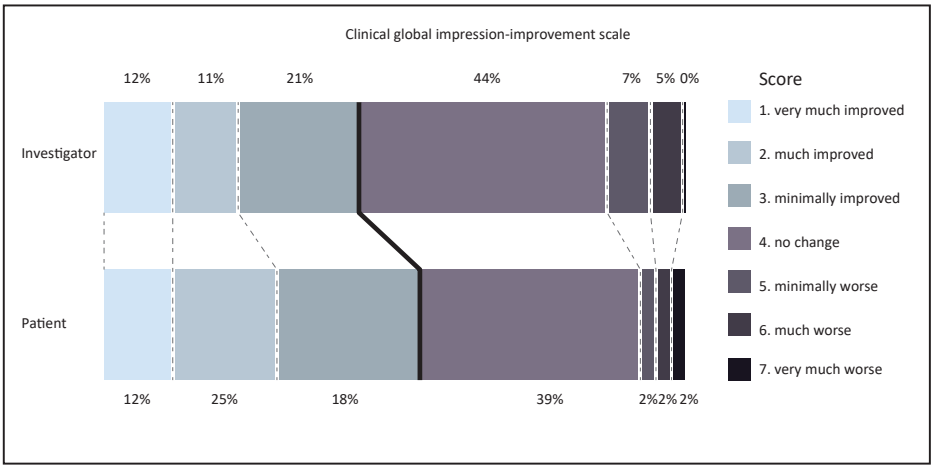

Figure 3. *Distribution of the Clinical Global Impression-Improvement Scale scores, assessing improvement of symptoms from the end of trial to the end of the open-label study, scored by the investigator and the patient.*

The CGI-I assessed by the patient revealed a perceived motor improvement in 24 of 43 patients (55.8%) compared to the end of the randomized trial (**see figure 3**), and in 29 of 43 patients (67.4%) compared to baseline (**for detailed CGI-I scores see appendix 2**). The other outcome measures are summarized in **table 3**.

Of the 44 patients who received open-label treatment, 17 (38,6%) continued treatment with BoNT after the study had ended. These were all patients with relapse of symptoms at the end of every 3 months. In 6 (13.6%) out of 44 patients symptoms diminished/ resolved and no further treatment was needed. Of the remaining patients, 15 (34.1%) did not benefit enough, 4 (9.1%) experienced too much side effects, 1 (2.3%) had worsening of symptoms and 1 (2.3%) could not continue treatment because of financial reasons.

Safety

For an overview of all adverse events during the study see **table 4**. During the trial phase equal proportions of patients per group had adverse events: BoNT 21/25 (84.0%) vs. placebo n=20/23 (87.0%). Serious adverse events occurred in 2 patients (n=1 BoNT; ketamine infusion for chronic pain vs. n=1 placebo; hospital admittance for cardial syncope). During the open-label phase serious adverse events occurred in 5 patients (lumbar disc herniation surgery (n=1), admittance rehabilitation clinic (n=2), ketamine infusion for chronic pain (n=1), surgery de Quervain's disease (n=1)). All serious adverse events were deemed not related to the study intervention and reported to the local Medical Ethics Committee.

This study provides class I evidence that BoNT treatment in jerky and tremulous FMD is not effective compared to placebo.

	Median score (IQR) at start open-label phase	Median score (IQR) end of follow-up	P-value**
CGI-severity investigator	3.0 (2.0; 4.0)	2.0 (1.0; 4.0)	**0.005**
CGI-severity patient	4.0 (4.0; 5.75)	4.0 (2.0; 5.0)	**0.044**
VAS-disease burden patient	48.0 (20.3; 71.8)	28.0 (3.0; 62.0)	**0.042**
PMDRS-motor symptoms	10.0 (5.0; 21.0)	9.0 (3.0; 17.0)	**0.010**
SF-36-Physical component*	34.4 (25.1; 48.3)	40.2 (27.4; 53.6)	0.058
SF-36-Mental component*	52.5 (41.2; 56.9)	50.0 (37.9; 55.7)	0.751
ALDS-disability*	87.8 (79.2; 89.5)	89.1 (83.5; 89.5)	0.790
BDI-Depressive symptoms*	9.0 (4.0; 12.0)	6.0 (3.0; 13.5)	0.370
MADRS-Depressive symptoms	12.0 (15.0; 18.8)	10.0 (4.0; 18.0)	0.205
BAI-Anxiety symptoms*	11.0 (3.5; 17.0)	7.0 (4.0; 16.0)	0.127
LSAS-Social anxiety*	10.0 (4.0; 21.5)	10.0 (2.0; 16.5)	0.446
OCI-Obsessive-Compulsive symptoms*	4.0 (1.0; 7.0)	3.0 (1.5; 5.0)	**0.028**

Table 3. *IQR = Interquartile range. CGI = Clinical Global Impression, VAS= Visual Analogue Scale, PMDRS = Psychogenic Movement Disorder Rating Scale, SF-36 = Short Form 36, ALDS = AMC Linear Disability Score, BDI = Beck Depression Inventory, MADRS = Montgomery Asberg Depression Rating Scale, BAI = Beck Anxiety Inventory, LSAS = Liebowitz Social Anxiety Scale, OCI = Obsessive Compulsive Inventory.*Data of n=41 patients. ** Wilcoxon signed rank test for paired data.*

	Trial-phase		Open-label phase
	BoNT n=25	**Placebo n=23**	**n=43**
Pain injection site - no. (%)	9 (36.0)	2 (8.7)	9 (20.9)
Hematoma injection site - no. (%)	2 (8.0)	2 (8.7)	2 (4.7)
Flu-like symptoms - no. (%)	2 (8.0)	4 (17.4)	4 (9.3)
Muscle weakness - no. (%)	6 (24.0)	4 (17.4)	12 (27.9)
MRC-scale – median (IQR)	5 (5; 5)	5 (5; 5)	5 (5; 5)
Worsening symptoms - no. (%)	5 (20.0)	3 (13.0)	3 (7.0)
Other* - no. (%)	9 (36.0)	10 (43.5)	19 (44.2)

Table 4. *Number of patients with adverse events; patients could fulfil more than one category. IQR=interquartile range. ⋆Other adverse events included musculoskeletal pain, planned surgery/ medical intervention, muscle cramps, infection/inflammation, nausea, stomach ache, diarrhoea, chest pain, shortness of breath, dizziness, memory problems, transient confusion, globus feeling, skin abnormalities, headache and fatigue.*

DISCUSSION

In this 4-month randomized placebo-controlled double-blinded clinical trial the effect of BoNT treatment on jerky and tremulous FMD was evaluated. Overall BoNT was safe and well-tolerated. We could not demonstrate benefit of BoNT over placebo injections in terms of symptom improvement and severity, disease burden, quality of life, disability and psychiatric symptoms. At the end of the trial phase motor symptoms of approximately 60% of patients across both treatment conditions improved; 44% of patients showed additional improvement at the end of the one year open-label study compared to the end of the trial. Eventually 81% of patients improved compared to baseline.

Although we assumed the placebo effect to be larger than in a similar trial in writer's cramp (13), we didn't anticipate the placebo effect to be this large (57%) as most patients had long-lasting symptoms and have had several other treatments before. Other randomized treatment studies in FNS are scarce and concern physiotherapy (20), rehabilitation (21), disease education (22, 23), psychotherapy (24) and transcranial magnetic stimulation(TMS) (25). Most are not placebo-controlled and the majority reveals significant and clinically relevant improvement in a large proportion of patients (30-70%). One study with a placebo-like control condition (25) (TMS vs. spinal cord stimulation) found large effect sizes (66%) in both the intervention and control arm, which is in line with our findings. This suggests treatment effects in FNS are largely

due to placebo-effects and the 'rituals' accompanying receiving any treatment (26, 27). The more invasive, the more effective a placebo therapy may be (28). Although it was not the purview of this study, comparing BoNT and placebo to a less invasive therapy (e.g. massage, explanation) could have given more insight in this matter.

The lack of effect of BoNT compared to placebo in jerky and tremulous FMD cannot be generalized to other forms of FMD. Organic dystonia is the movement disorder most commonly treated with BoNT. We chose jerky and tremulous FMD because these are more common than functional dystonia (1, 2) and the diagnostic process can be aided by neurophysiologic tests (4). Effective treatment of functional (fixed) dystonia in a small group with subclinical amounts of BoNT has been described (11). The immediate improvement after injections in this study suggests a placebo-effect. Further, a recent small trial (n=10) in functional dystonia showed no benefit of BoNT over placebo prior to cognitive behavioral therapy (29). In general it is still debated whether the treatment of FNS should be equalized or specialized to specific motor phenotypes (30). Based on our study and the literature definite conclusions cannot be drawn but BoNT and placebo appears to be as effective in both jerky/tremulous as dystonic FMD.

Apart from the large placebo response, an additional effect of BoNT cannot be excluded. In the open-label extension phase a large proportion of patients still improved compared to the blinded phase. Future dose and treatment duration-finding studies using larger study groups may help to pick up smaller effects. However, given the results of our study it seems more relevant to focus on placebo-like therapies.

Our study population included chronically ill patients (median symptom duration of 5 years) in whom, according to the literature, prognosis is often poor (on average 39% of patients display persistent or worsening symptoms) (5). The proportion of patients which improved is therefore a remarkable finding. Notably, this did not translate into amelioration of disability, quality of life and psychiatric symptoms. Unfortunately we could not identify any traits (e.g. pain or fatigue) of treatment-responders or non-responders in our post-hoc analyses, which should be interpreted with caution given the small study population. Ultimately, a substantial part of patients (n=17) chose to continue BoNT treatment after the study, suggesting that patients did perceive benefit of the treatment.

The amount of patients included was the result screening of a large number of eligible patients (48 (20%) of 239 patients screened). This is in line with other studies of FNS (20, 22, 23), but questions the generalizability of the results to all jerky and tremulous FMD patients. However, of the 109 excluded patients the reason was clinically relevant

as in almost half of them symptoms diminished severely or resolved, in about a quarter the symptoms were not amendable for injections, and of the remaining quarter there were other reasons including a non-functional disorder. Another interesting observation in our population was the equal number of men and women, not only in the study population, but also in the large screening pool. Axial jerks do tend to occur more often in men (6), so this might be an explanation of our population not reflecting the usual demographics of FMD with a female predominance.

Limitations

Limitations of this study include the small study population and the large number of eligible patients which had to be screened in order to reach the required amount of patients. Also, the patient who was analyzed after one year instead of 4 months was a major protocol violation.

Conclusions

In this RCT of BoNT for jerky and tremulous FMD we found no evidence of improved outcomes in patients treated with BoNT compared to placebo. The response to placebo, however, was very large. Our study underlines the potential of chronic FMD patients to improve. Despite the possible ethical issues, we advocate further exploration of placebo-like therapies in FMD.

Contributors

MAJdKT, JMD and JHTM designed the study. YEMD and JHTM collected data. YEMD, MAJdKT, JMD, JHTM and RJdH analysed and interpreted data. YEMD wrote the paper and designed the figures and tables. JMG, EZ, DvP, MFC, RZ, BP, AGM and JDS assessed the primary outcome based on video-tapes of the patients. All other authors drafted and critically revised the paper.

Disclosure statement

This study was funded by Prinses Beatrix Fund and Ipsen®. Dr Dreissen, dr Koelman and Prof Tijssen report grants from Prinses Beatrix Fund, non-financial support from Ipsen, during the conduct of the study. Dr Koelman reports grants from Ipsen, grants from Allergan, grants from Merz, outside the submitted work. Prof Tijssen reports grants from Gossweiler Foundation, grants from Phelps Stichting, grants from Stichting wetenschapsfonds dystonie vereniging, grants from Fonds NutsOhra, grants from Ipsen, Allergan, Merz, Actelion, grants from SNN Kennisontwikkeling, European funding, grants from Fonds psychische Gezondheid, outside the submitted work. All other authors have nothing to disclose.

Role of funding source

The authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. The funders (Prinses Beatrix Fund, Ipsen®) were not involved in the study design, data collection, data analysis, data interpretation or writing of the manuscript.

Data sharing statement

Individual deidentified participant data will not be shared; The study protocol is freely accessible at https://www.amc.nl/web/specialismen/neurologie-1/botulinum-neurotoxin-bont-trial.htm. The statistical analysis plan is available online as supplementary data.

Acknowledgements

This study was funded by Prinses Beatrix fund and Ipsen®. We would like to thank all the staff members of the department of Clinical Neurophysiology for their support with carrying out this study.

Legends Videos

Video 1. Male, 57 years old. Presented with jerks of the right shoulder/arm after throwing a snow ball. The video shows that the jerks are entrainable.

Video 2. Male, 66 years old. Presented with sudden onset of tremor of the right arm. The video shows attenuation/distractibility of the tremor while performing a mental task.

Video 3. Female, 74 years old. Presented with abdominal jerks after her dog died. The video shows a typical phenomenology of functional myoclonus.

REFERENCES

1. Factor SA, Podskalny GD, Molho ES. Psychogenic movement disorders: frequency, clinical profile, and characteristics. JNeurolNeurosurgPsychiatry. 1995;59(4):406-12.
2. Shill H, Gerber P. Evaluation of clinical diagnostic criteria for psychogenic movement disorders. Movement Disorders. 2006;21(8).
3. Schwingenschuh P, Saifee TA, Katschnig-Winter P, Macerollo A, Koegl-Wallner M, Culea V, et al. Validation of "laboratory-supported" criteria for functional (psychogenic) tremor. Mov Disord. 2016;31(4):555-62.
4. Beudel M, Zutt R, Meppelink AM, Little S, Elting JW, Stelten BML, et al. Improving neurophysiological biomarkers for functional myoclonic movements. Parkinsonism Relat Disord. 2018.
5. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry. 2014;85(2):220-6.
6. van der Salm SM, Erro R, Cordivari C, Edwards MJ, Koelman JH, van den Ende T, et al. Propriospinal myoclonus: clinical reappraisal and review of literature. Neurology. 2014;83(20):1862-70.
7. Cocco A, Albanese A. Recent developments in clinical trials of botulinum neurotoxins. Toxicon. 2017.
8. Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. Neurology. 2001;56(5):605-10.
9. Hallett M. Mechanism of action of botulinum neurotoxin: Unexpected consequences. Toxicon. 2017.
10. Erro R, Edwards MJ, Bhatia KP, Esposito M, Farmer SF, Cordivari C. Psychogenic axial myoclonus: clinical features and long-term outcome. Parkinsonism Relat Disord. 2014;20(6):596-9.
11. Edwards MJ, Bhatia KP, Cordivari C. Immediate response to botulinum toxin injections in patients with fixed dystonia. Mov Disord. 2011;26(5):917-8.
12. Moore AP, Naumann M. Handbook of Botulinum Toxin Treatment. 2nd ed. Oxford: Blackwell Science Ltd; 2003. 463 p.
13. Kruisdijk JJ, Koelman JH, Ongerboer de Visser BW, de Haan RJ, Speelman JD. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. J Neurol Neurosurg Psychiatry. 2007;78(3):264-70.
14. Apartis E. Clinical neurophysiology of psychogenic movement disorders: how to diagnose psychogenic tremor and myoclonus. Neurophysiol Clin. 2014;44(4):417-24.
15. W G. Clinical Global Impression. ECDEU Assessment manual for psycho-pharmacology, revised. National Institute of mental health1976.
16. Hinson VK, Cubo E, Comella CL, Goetz CG, Leurgans S. Rating scale for psychogenic movement disorders: scale development and clinimetric testing. Mov Disord. 2005;20(12):1592-7.
17. Hodges JR LE. Estimates of location based on rank tests. Annals of Mathematical Statistics. 1963;34:598-611.

18. Ashman EJ, Gronseth GS. Level of evidence reviews: three years of progress. Neurology. 2012;79(1):13-4.
19. Neurology AAo. Clinical Practice Guideline Process Manual. The American Academy of Neurology. 2011.
20. Nielsen G, Buszewicz M, Stevenson F, Hunter R, Holt K, Dudziec M, et al. Randomised feasibility study of physiotherapy for patients with functional motor symptoms. J Neurol Neurosurg Psychiatry. 2017;88(6):484-90.
21. Jordbru AA, Smedstad LM, Klungsoyr O, Martinsen EW. Psychogenic gait disorder: a randomized controlled trial of physical rehabilitation with one-year follow-up. J Rehabil Med. 2014;46(2):181-7.
22. Pleizier M, de Haan RJ, Vermeulen M. Management of patients with functional neurological symptoms: a single-centre randomised controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(5):430-6.
23. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial. Neurology. 2011;77(6):564-72.
24. Kompoliti K, Wilson B, Stebbins G, Bernard B, Hinson V. Immediate vs. delayed treatment of psychogenic movement disorders with short term psychodynamic psychotherapy: randomized clinical trial. Parkinsonism Relat Disord. 2014;20(1):60-3.
25. Garcin B, Mesrati F, Hubsch C, Mauras T, Iliescu I, Naccache L, et al. Impact of Transcranial Magnetic Stimulation on Functional Movement Disorders: Cortical Modulation or a Behavioral Effect? Front Neurol. 2017;8:338.
26. Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. Neuron. 2008;59(2):195-206.
27. Benedetti F. Placebo-induced improvements: how therapeutic rituals affect the patient's brain. J Acupunct Meridian Stud. 2012;5(3):97-103.
28. Jonas WB, Crawford C, Colloca L, Kaptchuk TJ, Moseley B, Miller FG, et al. To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with meta-analysis of randomised, sham controlled trials. BMJ Open. 2015;5(12):e009655.
29. Vizcarra JA, Lopez-Castellanos JR, Dwivedi AK, Schmerler DA, Ries S, Espay AJ. OnabotulinumtoxinA and cognitive behavioral therapy in functional dystonia: A pilot randomized clinical trial. Parkinsonism Relat Disord. 2019.
30. Espay AJ, Aybek S, Carson A, Edwards MJ, Goldstein LH, Hallett M, et al. Current Concepts in Diagnosis and Treatment of Functional Neurological Disorders. JAMA Neurol. 2018.

SUPPLEMENTARY DATA FILE

APPENDIX 1. OUTCOME MEASURES

Outcome measures

Disability was measured using the AMC Linear Disability Score (ALDS) (a generic self-assessment scale which includes instrumental activities of daily living (ADL) (1). The ALDS ranges from 0 and 100; higher scores indicate a better functional status.

Quality of life (QoL) was assessed using the 36-item Short Form Health Survey (SF-36) (2). Two dimension scores can be derived from 8 subscale scores: the Physical Component Summary and the Mental Component Summary. Both summary scores were normalized to a general Dutch population mean of 50 and a standard deviation of 10 (3). Higher scores indicate a better HRQL (4).

Psychiatric evaluation included the Mini-International-Neuropsychiatric Interview – Plus (MINI-Plus), screening for possible psychiatric co-morbidity according to DSM-IV criteria (4).

Several quantitative questionnaires concerning psychiatric symptoms were assessed too, including the Montgomery Asberg Depression Rating Scale (MADRS) (10 item interview, scores ranging from 0-60, higher scores indicating more severe symptoms) and The Beck Depression Inventory (BDI) (5) (21 item self-report scale, ranging from 0-63, higher scores indicating more severe symptoms) for depressive symptoms; the Beck Anxiety Inventory (BAI) (6) (21 item self-report scale, ranging from 0-63, higher scores indicating more severe symptoms) and Liebowitz Social Anxiety Scale (LSAS) (7) (48 item self-report scale, scores ranging from 0-144, higher scores indicating more severe symptoms) for anxiety and the Obsessive-Compulsive Inventory (OCI-R) (8) (18 item self-report, scores ranging from 0-72, higher scores indicating more severe symptoms) for obsessive-compulsive symptoms.

APPENDIX 2. ADDITIONAL INFORMATION ON METHODS AND RESULTS

Methods

Procedure

Patients were told that BoNT is a common treatment in movement disorders, but that it's efficacy is unknown in functional jerks/tremor. Tot test this half of the patients would receive BoNT and the other half placebo, which was sterile saline. After two treatment sessions, they would be enrolled in the open-label study where everybody would receive BoNT. Then we would explain how the injections would take place and what common side effects of BoNT are. Also they were instructed when to contact us (hematoma, severe weakness, severe adverse event).

Inter-observer analysis

Average weighted Kappa and ICC values of pairs of observations were considered as an overall index for concordance among observers (9). Kappa and ICC values were arbitrarily classified according to Landis and Koch (10) with values <0 indicating no agreement, 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement.

Results

Screening

Of all excluded patients, 109 patients did not fulfill the inclusion criteria. In 52 (47.8%) of the 109 patients symptoms diminished severely or resolved. In the other 57 (52,3%) reasons were diverse including: not functional (n=13), no jerks/tremor or jerks/tremor not amendable for injection (n=28), terminally ill (n=5), insufficient knowledge of Dutch language (n=2), too old or too young (n=2), previous treatment with BonT without effect (n=1), coagulation disorder (n=1), too much previous therapies (n=2), moving to other country (n=1), one amputated arm (n=1), complaints present < one year (n=1). The 18 patients who were excluded for 'other reasons' included: could not be reached (n=16), not approached because files legal complaints (n=1), death wish and died in 2012 (n=1). We don't have follow-up data on these patients unfortunately.

Selection muscles and doses used per subject

Subject	Randomisation	Axial or extremity	Muscles injected	Unilateral or bilateral	Starting dose per muscle
Pin 1	placebo	extremity	· pectoral muscle	· unilateral	100
Pin 2	botulinum	axial	· iliopsoas muscle	· bilateral	200
Pin 3	botulinum	axial	· iliopsoas muscle	· bilateral	200
Pin 4	botulinum	extremity	· trapezius muscle · teres major muscle · major pectoral muscle	· bilateral · bilateral · bilateral	50 50 50
Pin 5	placebo	axial	· paraspinal muscle Th12 · paraspinal muscle L2	· unilateral · unilateral	100 100
Pin 6	placebo	extremity	· SCM · levator scapulae muscle · trapezius muscle	· unilateral · unilateral · unilateral	60 60 120
Pin 7	placebo	axial	· iliopsoas muscle	· bilateral	200
Pin 8	botulinum	axial	· trapezius muscle · levator scapulae muscle · rectus abdominis muscle	· bilateral · bilateral · bilateral	60 60 120
Pin 9	placebo	axial	· iliopsoas muscle	· bilateral	200
Pin 10	botulinum	axial	· iliopsoas muscle	· unilateral	200
Pin 11	botulinum	extremity	· iliopsoas muscle · rectus femoris muscle · vastus medialis muscle	· unilateral · unilateral · unilateral	200 100 50
Pin 12	placebo	axial	· rectus abdominis muscle	· bilateral	120
Pin 13	botulinum	extremity	· trapezius muscle · levator scapulae muscle	· unilateral · unilateral	80 80
Pin 14	placebo	extremity	· SCM muscle · trapezius muscle · major pectoral muscle · deltoid muscle	· bilateral · bilateral · bilateral · bilateral	80 80 80 80
Pin 15	placebo	extremity	· trapezius muscle · major pectoral muscle	· bilateral · bilateral	50 100
Pin 16	placebo	axial	· paraspinal muscle Th8	· bilateral	150
Pin 17	botulinum	axial	· iliopsoas muscle · rectus abdominis muscle	· bilateral · bilateral	160 120

Subject	Randomisation	Axial or extremity	Muscles injected	Unilateral or bilateral	Starting dose per muscle
Pin 18	placebo	axial	· iliopsoas muscle · rectus femoris muscle	· unilateral · unilateral	200 200
Pin 19	botulinum	axial	· rectus abdominis muscle	· bilateral	200
Pin 20	botulinum	axial	· semispinal muscle · rectus abdominis muscle	· bilateral · bilateral	60 120
Pin 21	botulinum	extremity	· vastus medialis muscle · rectus femoris muscle	· bilateral · bilateral	100 100
Pin 22	placebo	axial	· rectus abdominis muscle	· bilateral	150
Pin 23	botulinum	extremity	· SCM muscle	· bilateral	40
Pin 24	placebo	axial	· iliopsoas muscle · rectus abdominis muscle	· bilateral · bilateral	120 120
Pin 25	placebo	extremity	· major pectoral muscle	· bilateral	60
Pin 26	placebo	extremity	· trapezius muscle · major pectoral muscle · deltoid muscle	· unilateral · unilateral · unilateral	40 80 80
Pin 27	botulinum	axial	· rectus abdominis muscle · iliopsoas muscle · vastus medialis muscle	· unilateral · unilateral · unilateral	120 120 60
Pin 28	botulinum	axial	· rectus abdominis muscle	· bilateral	120
Pin 29	botulinum	axial	· iliopsoas muscle	· bilateral	200
Pin 30	botulinum	extremity	· frontal muscle · auricularis superior muscle	· unilateral · unilateral	10 10
Pin 31	placebo	extremity	· biceps brachii muscle · deltoid muscle · extensor carpi radial muscle	· unilateral · unilateral · unilateral	120 120 40
Pin 32	botulinum	extremity	· pectoral muscle	· bilateral	80
Pin 33	botulinum	extremity	· biceps brachii muscle · flexor carpi radial muscle	· unilateral · unilateral	100 60
Pin 34	placebo	extremity	· flexor carpi radial muscle · extensor carpi radial muscle · pronator teres muscle	· unilateral · unilateral · unilateral	80 30 40
Pin 35	placebo	extremity	· abductor digiti V muscle	· unilateral	30

Subject	Randomisation	Axial or extremity	Muscles injected	Unilateral or bilateral	Starting dose per muscle
Pin 36	botulinum	extremity	· flexor carpi radial muscle · extensor carpi radial muscle	· unilateral · unilateral	120 40
Pin 37	placebo	axial	· rectus abdominis muscle · iliopsoas muscle	· bilateral · bilateral	120 100
Pin 38	placebo	extremity	· splenius capitis muscle · SCM muscle	· unilateral · unilateral	100 30
Pin 39	botulinum	extremity	· supinator teres muscle · pronator teres muscle	· unilateral · unilateral	40 80
Pin 40	placebo	axial	· rectus abdominis muscle · abdominal oblique muscle	· bilateral · bilateral	120 60
Pin 41	placebo	extremity	· extensor carpi radial muscle · flexor carpi radial muscle · triceps brachii muscle	· unilateral · unilateral · unilateral	40 80 80
Pin 42	botulinum	extremity	· quadriceps femoris muscle	· unilateral	160
Pin 43	placebo	extremity	· extensor carpi radial muscle · triceps brachii muscle	· unilateral · unilateral	40 120
Pin 44	botulinum	axial	· rectus abdominis muscle	· bilateral	120
Pin 45	placebo	axial	· paraspinal muscle Th12-L5	· bilateral	180
Pin 46	botulinum	extremity	· pterygoideus lateral muscle · depressor anguli oris muscle · platysma muscle	· unilateral · unilateral · unilateral	30 10 10
Pin 47	botulinum	axial	· major pectoral muscle	· bilateral	60
Pin 48	botulinum	axial	· iliopsoas muscle	· bilateral	160

Open-label extension

Compared to the end of the trial 19 of 43 patients (44.2%) showed improvement (score 1,2 or 3) of motor symptoms on the CGI-I assessed by the investigators (score 1 n=5 (12.0%); score 2 n=5 (11.0%); score 3 n=9 (20.9%); score 4 n=19 (44.2%); score 5 n=3 (7.0%); score 6 n=2 (4.7%); score 7 n=0) (**see figure 3**). Compared to baseline motor symptom improvement (score 1,2 or 3) occurred in 35 of 43 patients (81.4%) (score 1 n=10 (23.3%); score 2 n=10 (23.3 %); score 3 n=15 (34.9%); score 4 n=5 (11.6%); score 5 n=3 (7.0%), score 6 or 7 n=0).

The CGI-I scored by the patient revealed a perceived motor improvement compared to the end of trial in 24 of 43 patients (55.8%) (score 1 n=5 (11.5%); score 2 n=11 (25.0%); score 3 n=8 (18.2%); score 4 n=17 (38.6%); score 5 n=1 (2.3%); score 6 n=1 (2.3%); score 7 n=1 (2.3%)) (**see figure 3**). Compared to baseline perceived motor symptom improvement occurred in 29 of 43 patients (67.4%) (score 1 n=11 (25.6%); score 2 n=14 (32.6%); score 3 n=4 (9.3%); score 4 n=12 (27.9%); score 5 n=1 (2.3%); score 6 n=6 (2.3%); score 7 n=0).

REFERENCES

1. Holman R, Weisscher N, Glas CA, Dijkgraaf MG, Vermeulen M, de Haan RJ, et al. The Academic Medical Center Linear Disability Score (ALDS) item bank: item response theory analysis in a mixed patient population. Health QualLife Outcomes. 2005;3:83.
2. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
3. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998;51(11):1055-68.
4. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 4-57.
5. Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol. 1984;40(6):1365-7.
6. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56(6):893-7.
7. Heimberg RG, Horner KJ, Juster HR, Safren SA, Brown EJ, Schneier FR, et al. Psychometric properties of the Liebowitz Social Anxiety Scale. Psychol Med. 1999;29(1):199-212.
8. Foa EB, Huppert JD, Leiberg S, Langner R, Kichic R, Hajcak G, et al. The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol Assess. 2002;14(4):485-96.
9. Feinstein A. Clinimetric Perspectives. J Chron Dis. 1987;40:635-40.
10. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.

APPENDIX 3. STATISTICAL ANALYSIS PLAN

Overall principles

The data analysis will start after the 12-month follow-up data of the last included patient has been obtained, and after the study database has been cleaned and locked.

The analyses will be done by investigator (YD) supervised by the principal investigator (MAJdKT) and an independent epidemiologist/statistician of the AMC Clinical Research Unit (RdH). The statistical programming and analysis to produce all summary tables and figures will use the statistical package IBM SPSS statistics version 22.

In general, variables will be summarized using simple descriptive statistics such as means with standard deviation for continuous symmetric variables, medians and interquartile ranges for continuous skewed variables, and frequencies with percentages for categorical variables.

All analyses will be done according to the intention-to-treat principle, by analysing patients in the groups to which they were allocated by randomisation. The analyses will first be performed blind to treatment allocation, to allow for checking of the data and the proposed summaries/analyses. After the investigation and correction of any isolated or systematic data errors, treatment allocation will be unmasked.

The primary outcome will be analysed in the pre-specified subgroups below, irrespective of the presence of statistical significance in the overall analysis. Safety outcomes will be additionally analysed in the as-treated (not per-protocol) population.

Overall level of statistical significance

According to Haybittle-Peto's stopping rule, no adjustment of the p-value will be used for the final analysis. A two-sided p-value < 0.05 will be considered statistically significant. Statistical uncertainty will be expressed in a two-sided 95% CI.

Missing data

Missing baseline and outcome data will not be imputed. We will state which data are missing and calculate frequencies using the total number of patients with available data. When a patient is lost to follow-up or has withdrawn consent, we will use all available data up until withdrawal of consent or loss to follow-up. A specific section in the paper will report on missing data.

Poweranalysis

A two group Chi-square test with a 0,05 two-sided significance level will have 80% power to detect the difference between a control group proportion of 0,30 and a treatment group proportion of 0,70 (odds ratio of 5,4) when the sample size in each group is 24. As the side effects of therapy are mild and self-limiting and because only two injections are given in the trial period, we expect practically no withdrawals in this phase of the study. Assuming a withdrawal rate of 10 percent, we plan to include 27 patients per treatment arm, which means 54 patients in total.

Population

Intention-to-treat population

All randomised patients will be analysed in the treatment group to which they were originally allocated irrespective of non-adherence or deviations from protocol.

As-treated population

Patients will be analysed in groups according to treatment received. The patients will still be included in the as-treated analysis if there was a protocol violation (e.g. not receiving treatment within the described time-frame, not receiving the correct treatment, or not meeting inclusion or exclusion criteria).

List of analyses

Recruitment and retention

The trial profile and inclusion will be shown in a CONSORT flow diagram *(figure 1),* including the total number of randomised patients and then showing per treatment group the numbers receiving allocated treatment, withdrawing consent, and lost to follow up.

Baseline characteristics

Table 1: *Patient characteristics*
Treatment group vs placebo group
Age (mean of median)
Gender
Duration of symptoms (mean or median)
Site of jerks
Abdominal vs extremity
Medication usage
Presence of bereitschaftspotential

Protocol deviations and violations

All substantial protocol violations will be listed.

Adherence to allocated treatment

Adherence will be reported descriptively.

Primary outcome

An intention to treat analysis will be performed with regard to the trial results. The difference in the proportions of patients reaching the primary outcome measure (score 1,2 of 3 on CGI) between the groups treated with BoNT and with placebo will be assessed using the x2 statistic or Fisher's exact test, when appropriate. The CGI will be dichotomized to improvement (score 1,2 of 3) vs no change or worsening (score 4,5,6,7). A binary logistic regression analysis will be performed to correct for the treatment group (BoNT vs. placebo) and stratification-factor (axial vs. extremity). The effect size will be expressed in an odd's ratio.

Secondary outcomes

For the secondary outcome measures, proportional differences between the groups will be tested with the x2 statistic or Fischer's exact test when appropriate. Difference in change scores of the continuous secondary outcome measures will be calculated. The mean or median differences will be analysed with a Students t-test or Mann-Whitney (when appropriate). Statistical uncertainty will be expressed with a 95% CI.

For the long term effects, the within group change scores at t=16 months will be compared with previous assessments (end of trial and baseline) using tests for paired data (Wilcoxon Signed Rank).

Safety outcomes

Safety outcomes will be reported in the intention-to treat and as-treated populations using descriptive statistics.

Subgroup analyses

No subgroup analysis will be performed because of the small amount of patients and hence the lack of power.

APPENDIX 4. VIDEO PROTOCOL

1. Informed consent

2. Rest (sitting on research bench)

Total body	2 minutes
Focus on face	20 seconds
Reading standard text	

3. Action

Stretching out arms, palms facing downwards		30 seconds
Stretching out arms, palms facing upwards		30 seconds
Bending arms in front of chest		20 seconds
Fingertapping		10x
Bradykinesia		10x
Finger-to-nose (right and left)		5x
Stretching out leg (right and left)		20 sec
Attention task	Subtracting 100 minus 7	
	Subtracting 100 minus 13	
	Counting the months of the year backwards	
Entrainment:	tapping along with metronome: 112 en 138 bpm	
Suppressing symptoms		10 seconds

4. Leaving patient alone in the room 2 minutes

5. Standing

From four different angles	30 seconds

6. Research bench

- Testing tendon reflexes	
- Lying supine	30 seconds

7. Gait 30 seconds

Long-term psychiatric outcome related to Botulinum Neurotoxin (BoNT) treatment in functional movement disorders.

4

Yasmine EM Dreissen, Danielle C Cath, Tinka J van Trier, Evelien Zoons, Joke M Dijk, Johannes HTM Koelman & Marina AJ Tijssen

Unpublished work

ABSTRACT

Background: The aim of this study was to report on presence and course of psychiatric symptom disorders, personality traits, pain, fatigue and negative life events in patients with functional jerky and tremulous movement disorders (FJTMD) and its relation to treatment.

Methods: A randomized double-blinded placebo controlled trial (RCT) on the effect of Botulinum Neurotoxin (BoNT) in FJTMDs, followed by 10 month open-label treatment. Outcome measures were completed at baseline, end of RCT (end-RCT) and end of the open-label phase (end-open label) and compared between patients with and without motor improvement. Further associations between the severity of motor symptoms and pain, fatigue and psychiatric symptoms were assessed.

Results: Motor improvement was found in 60% (29/48) of patients at end-RCT and in 35 of the remaining 43 (81%) at end-open label. At baseline both groups showed high rates of psychiatric (72%), especially anxiety and functional pain disorders. Patients with motor improvement showed a significant decrease in anxiety disorders in the RCT-phase compared to patients without motor improvement. Further, negative life events occurred more frequently during the RCT in patients without motor improvement. Both anxiety and pain symptoms were associated with more severe motor symptoms.

Conclusions: Psychiatric co-morbidity was high in our study population. Improvement in motor symptoms after treatment was associated with improvement in anxiety disorders. Both the predictive value of anxiety and pain symptoms in treatment response and the effect of specific treatment of pathological anxiety on motor symptoms in FMD patients requires further studying.

INTRODUCTION

In movement disorder clinics, functional movement disorders (FMD) account for up to 25% of patients' diagnoses (1) amongst which jerks and tremor are commonly seen (2). Although a paradigm shift has taken place over the last decade, in which psychopathology is no longer required to reach high diagnostic certainty in FMD (3), the prevalence of psychiatric co-morbidity in FMD is high, with rates between 50-80% for DSM IV axis I disorders (mostly mood and anxiety disorders) (2, 4-8). The prognosis of chronic functional motor symptoms is poor and patients often experience more disability and distress requiring repeated medical attendance compared to organic neurologic disorders (9-11). Impaired quality of life and general functioning, including high rates (43 - 89%) of unemployment are also reported (11, 12). Further there is an overrepresentation of childhood trauma and abuse in FMD (5, 7). Although it was previously suggested that psychiatric co-morbidity is associated with poor prognosis (4), this is not well substantiated (11). A recent randomized clinical trial comparing Transcranial Magnetic Stimulation (TMS) with spinal Root Magnetic Stimulation (RMS) (13) in FMD patients failed to find a correlation between psychiatric disorders and motor improvement, which is in line with other treatment studies in FMD (14, 15).

A few studies have assessed quantitative dimensions of personality functioning to investigate potential traits that might be associated with severity of motor symptoms in FMD. These studies revealed lower levels of conscientiousness and higher levels of neuroticism compared to healthy controls (5, 7). Especially neuroticism, defined as a life-long tendency to experience events negatively, is associated with a poorer prognosis in other diseases such as depression (16).

Other important non-motor symptoms in FMD include pain and fatigue, which also negatively influence quality of life and self-rated health (12, 17). In fact, the presence of a chronic pain disorder was identified as a negative predictor of treatment response in FMD in a large retrospective cohort study (18).

Recently, we published the results of a randomized double-blinded placebo controlled trial (RCT) of Botulinum Neurotoxin (BoNT) for FMD. We found a 60% motor improvement at the end of RCT (4 months), irrespective of the treatment arm. In the following 10 months open-label phase in which all patients were treated with BoNT, a total of 80% of patients improved compared to baseline (19).

Throughout the course of the study non-motor symptoms were extensively assessed as secondary outcome measures. In the current study we aim to describe the course

of these non-motor symptoms, which encompasses psychiatric disorders/symptoms, personality traits, pain and fatigue symptoms, as well as negative life events in relation to the effect of treatment on the motor symptoms. We were interested in determining potential non-motor symptoms and factors associated with treatment response in general. In order to do so we looked at the association between the severity of motor symptoms and non-motor symptoms (i.e. psychiatric symptoms, pain and fatigue) during the study. We hypothesized that psychiatric co-morbidity, including high rates of psychiatric symptoms (depression, anxiety), and/or high rates of neuroticism, fatigue and pain would be associated with poorer treatment response.

METHODS

Procedures and study population

Included patients in this study all participated in the BoNT trial, a double-blinded RCT comparing BoNT treatment with placebo for functional jerky or tremulous movement disorders during a 4 month follow-up with an additional 10 months open label phase in which all patients were treated with BoNT. Inclusion criteria were: age between 18 and 80 years, incapacitating functional jerks or tremor, symptom duration of > 1 year and a diagnostic certainty of 'probable' or 'definite'. Pregnancy, coagulation disorders and insufficient knowledge of Dutch language were exclusion criteria (19).

At baseline several demographic characteristics were collected. Psychiatric assessment was performed by one trained investigator (YEMD) and collected during a 4-month RCT and the 10 months open-label phase. The primary endpoint of the RCT was improvement (score 1,2 or 3) of motor symptoms using the Clinical Global Impression – Improvement (CGI-I) scale (a 7-point scale, ranging from 1=very much improved to 7=very much worse), scored by the investigator based on standardized video recordings. Motor symptom severity was evaluated similarly using the Clinical Global Impression – Severity (CGI-S) scale and the Psychogenic Movement Disorder Rating Scale (PMDRS). Self-perceived motor symptom improvement and severity were evaluated by the patient using the CGI-I and CGI-S as well.

Non-motor outcome measures

All outcome measures were assessed at baseline, the end of the RCT (4 months; primary endpoint) and one month after the last open-label treatment. Qualitative psychiatric assessment was carried out with the Mini-International-Neuropsychiatric Interview – plus (MINI). This is a diagnostic interview to establish current and past DSM-IV axis 1 diagnoses, including functional pain disorders.

For quantitative psychiatric assessment, the Five Factor Inventory (FFI-NEO) self-report questionnaire was used which regards a self-administrative based scale assessing the five big personality traits i.e. neuroticism, extraversion, openness to experience, agreeableness and conscientiousness (20). Also, patients filled out a questionnaire about past negative experiences (Life threatening Events Questionnaire; LTE-Q) (21) which contained 12 categories of negative life events occurring in the past; i.e. 0-6 months ago; 6-12 months ago; 1-5 years ago and more than 5 years ago respectively. Other extensively validated self-assessment scales including the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were also used (19). For assessment of fatigue and pain, two subscales of the Short form-36 (SF-36), assessing overall vitality/fatigue (VT) and bodily pain (BP) were used. The general scores of the SF-36 were reported in our previous paper (19).

Statistical analysis

Baseline characteristics, including frequency of psychiatric diagnoses according to the MINI-interview, personality traits and past negative experiences were summarized using descriptive statistics. Median scores and interquartile ranges (IQR) were used to describe continuous outcome measures since most were not normally distributed.

Between group comparison

Between group differences in baseline characteristics, the frequency of psychiatric disorders according to the MINI-interview, personality traits, anxiety/depression, pain/fatigue and past negative experiences were determined between patients who showed motor improvement on the primary outcome measure (CGI-I) at the end of the RCT and patients who remained the same or worsened.

In order to reduce the number of statistical tests, psychiatric diagnoses were clustered into four main categories: any psychiatric disorder (psychiatric disorder total), any mood disorder (mood disorder total), any anxiety disorder (anxiety disorder total) and somatoform disorder (somatoform disorder total). In order to correct for baseline differences, a logistic regression analysis was used, in which the presence of one of the four categories of psychiatric disorders at the end of RCT was entered as dependent variable and the corresponding amount of psychiatric disorders at baseline together with the group entered as independent variables.

The continuous outcome measures (FFI-NEO, VT and BP) were analysed using the point estimate and 95% confidence interval (CI) of the median differences in change scores between patients with and without motor improvement at the end of the RCT using the Hodges-Lehmann approach (19). Past negative life events were dichotomized

into experienced vs. not experienced per category. The amount of events per category at baseline and at the end of the RCT were compared between the patients with and without motor improvement, using the Fisher's Exact test.

Relations between severity of motor symptoms psychiatric, pain and fatigue symptoms

The association between motor severity (PMDRS, dependent variable) and severity of anxiety (BAI) and depressive (BDI) symptoms and fatigue (VT) and pain (BP) symptoms (independent variables) at baseline and at the end of the RCT was explored using a multivariable linear regression analysis.

Open-label extension

The same analysis as described above was done for patients who showed motor improvement (CGI-I) at the end of the open-label study compared to baseline. We chose to put less emphasis on the open-label extension study since n=5 patients were lost to follow-up, generating possible bias.

All analyses were performed using Statistical Packaging for the Social Sciences (SPSS) version 25 and a two-sided p-value < 0.05 was considered statistically significant. The study protocol was approved by the local Medical Ethics Committee. All patients provided written informed consent. The trial was monitored by an independent monitor of the Amsterdam UMC, according to GCP guidelines and registered in the Dutch Trial Register (NTR 2478).

RESULTS

Results BoNT study

No beneficial effect of BoNT over placebo was found in the RCT; i.e. treatment effect was about 60% in both groups. In total 29 (60%) of 48 patients showed improvement on the investigator-rated CGI-I-scale (score 1-3) at the end of the RCT as opposed to 19 (40%) of 48 patients who showed the same or worsening of symptoms (score 4-7) compared to baseline. At the end of the open label phase 35 of 43 (81.4%) showed improvement on the CGI-I scale, 5 patients were lost to follow-up.

Baseline characteristics

The baseline characteristics of the patients with and without motor improvement (CGI-I) at the end of the RCT are summarized in **table 1**. There were no significant differences between groups.

	Motor improvement at end of RCT (n=29)	No motor improvement at end of RCT (n=19)
Age at baseline – year (median; IQR)	49 (31; 59)	52 (45; 58)
Gender - no. (%)		
· Male	16 (55)	12 (63)
Duration of symptoms– year (median; IQR)	5 (2; 11)	5 (2; 13)
Dominant symptom localization - no. (%)		
· Abdomen	13 (45)	10 (53)
· Extremity	16 (55)	9 (47)
Additional phenomenology based on PMDRS – no. (%)		
· Dystonia	12 (41)	10 (53)
· Tic	1 (3)	4 (21)
Education level - no. (%)		
· Primary school	2 (7)	1 (5)
· Lower education	5 (17)	2 (11)
· Medium education/higher school	11 (38)	12 (63)
· Higher education/university	11 (38)	4 (21)
· Unemployed	16 (55)	14 (74)
· Disease-related	11 (38)	13 (68)
Past psychological treatment - no. (%)	5 (17)	7 (37)

Table 1. *Baseline characteristics between patients who did and did not improve based on the CGI at end-RCT.*

Psychiatric profile, personality traits and negative life events

Table 2 shows the psychiatric profile for patients with and without motor improvement at the end of the RCT. At baseline both groups showed high rates of total psychiatric disorders, including high frequencies of anxiety disorders. In the category somatoform disorders, especially functional pain disorders were frequently present.

Between group comparison

In the patients who improved during treatment in the RCT-phase, the frequency of anxiety disorders significantly decreased during treatment (62% to 31%), while this remained stable in the patients without motor improvement (62% to 58%; p=0.04; **see table 2**). A significant reduction in vitality scores (signifying: increase in fatigue) was found in patients who improved during the RCT phase compared to patients without motor improvement (**table 3**).

	Baseline		*End of RCT (4 months)*		*Between group end-RCT vs. baseline*	*End of open-label*		*Between group end-open-label vs. baseline*
	Motor improvement n = 29	**No motor improvement n = 19**	**Motor improvement n = 29**	**No motor improvement n = 19**		**Motor improvement n=35**	**No motor improvement n=8**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**p-value**	**n (%)**	**n (%)**	**p-value**
Psychiatric disorder total	21 (72)	17 (90)	18 (62)	13 (68)	0.80	18 (51)	3 (38)	0.26
Mood disorder total	10 (35)	10 (53)	5 (17)	5 (26)	0.88	6 (17)	1 (13)	0.77
· Depression	10 (40)	9 (47)	5 (17)	5 (26)		6 (17)	1 (13)	
o Current	2 (7)	4 (21)	5 (17)	3 (16)		3 (9)	1 (13)	
· Dysthymia	0 (0)	1 (5)	-	-		-	-	
o Current	0 (0)	0 (0)						
· Hypomania	1 (3)	0 (0)	1 (3)	0 (0)		0 (0)	0 (0)	
o Current	0 (0)	0 (0)	1 (3)	0 (0)		0 (0)	0 (0)	
· Manic disorder	0 (0)	1 (5)	1 (3)	1 (5)		0 (0)	0 (0)	
o Current	0 (0)	0 (0)	1 (3)	0 (0)		0 (0)	0 (0)	
Anxiety disorder total	18 (62)	11 (58)	9 (31)	11 (58)	**0.04**	12 (34)	2 (25)	0.60
· Panic disorder	7 (24)	3 (16)	0 (0)	0 (0)		1 (3)	0 (0)	
o Current	0 (0)	1 (5)	0 (0)	0 (0)		1 (3)	0 (0)	
· Agoraphobia	7 (24)	2 (11)	1 (3)	0 (0)		0 (0)	0 (0)	
o Current	4 (67)	2 (11)	1 (3)	0 (0)		0 (0)	0 (0)	

	Baseline		*End of RCT (4 months)*		*Between group end-RCT vs. baseline*	*End of open-label*		*Between group end-open-label vs. baseline*
	Motor improvement n = 29	**No motor improvement n = 19**	**Motor improvement n = 29**	**No motor improvement n = 19**		**Motor improvement n=35**	**No motor improvement n=8**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**p-value**	**n (%)**	**n (%)**	**p-value**
· Social phobia o Current	1 (3) 1 (3)	2 (11) 2 (11)	0 (0) 0 (0)	3 (16) 3 (16)		1 (3) 1 (3)	0 (0) 0 (0)	
· Specific phobia o Current	8 (28) 8 (28)	6 (32) 5 (26)	8 (28) 8 (28)	4 (21) 4 (21)		7 (20) 7 (20)	1 (13) 1 (13)	
· Obsessive-Compulsive disorder (OCD) o Current	1 (3) 1 (3)	1 (5) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)		2 (6) 2 (6)	0 (0) 0 (0)	
· Post-traumatic stress disorder (PTSD) o Current	2 (7) 2 (7)	1 (5) 1 (5)	0 (0) 0 (0)	1 (5) 1 (5)		0 (0) 0 (0)	0 (0) 0 (0)	
· Generalized Anxiety disorder o Current	2 (7) 1 (3)	2 (11) 2 (11)	1 (3) 1 (3)	5 (26) 5 (26)		3 (9) 3 (9)	1 (13) 1 (13)	
Somatoform disorder total	9 (31)	8 (42)	7 (24)	7 (37)	0.62	7 (20)	2 (25)	0.80
· Somatization disorder	3 (10)	2 (11)	-	-		-	-	
· Hypochondria	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	

	Baseline		*End of RCT (4 months)*		*Between group end-RCT vs. baseline*	*End of open-label*		*Between group end-open-label vs. baseline*
	Motor improvement n = 29	**No motor improvement n = 19**	**Motor improvement n = 29**	**No motor improvement n = 19**		**Motor improvement n=35**	**No motor improvement n=8**	
	n (%)	**n (%)**	**n (%)**	**n (%)**	**p-value**	**n (%)**	**n (%)**	**p-value**
· Body Dysmorphic Disorder (BDD) o Current	1 (3) 1 (3)	0 (0) 0 (0)	1 (3) 1 (3)	0 (0) 0 (0)		1 (3) 1 (3)	0 (0) 0 (0)	
· Functional pain disorder o Current	7 (24) 7 (24)	7 (37) 7 (37)	6 (21) 6 (21)	7 (37) 6 (32)		6 (17) 6 (17)	2 (25) 2 (25)	
Other								
· ADHD o Current	1 (3) 1 (3)	0 (0) 0 (0)	-	-		-	-	
· Psychosis o Current	1 (3) 0 (0)	1 (5) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)		0 (0) 0 (0)	0 (0) 0 (0)	
· Alcohol dependence o Current	0 (0) 0 (0)	1 (5) 0 (0)	1 (3) 1 (3)	0 (0) 0 (0)		1 (3) 1 (3)	0 (0) 0 (0)	
· Drug dependence o Current	2 (7) 1 (5)	0 (0.0) 0 (0.0)	2 (7) 1 (5)	0 (0) 0 (0)		1 (3) 1 (3)	0 (0) 0 (0)	

Table 2. *Psychiatric profile according to the MINI-interview at baseline and end-RCT and end-open label for patients with and without motor improvement at end-RCT. Between group differences are shown for the 4 clustered psychiatric categories.*

Regarding negative life experiences, noticeable is that patients without motor improvement more often experienced negative life events in general (p=0.01), especially employment-related issues (i.e. financial problems) during the trial-period (p=0.02) (**table 4**). No between group differences were found in the FFI-NEO scores during the trial (**supplementary table 1**).

Associations between motor symptoms and pain, fatigue and psychiatric symptoms

A positive association was found between anxiety symptoms (BAI) and severity of motor symptoms (PMDRS) at baseline (p=0.01; beta=0.50, 95% CI 0.13 to 0.83) and at the end of the RCT (p=0.04; beta=0.40, 95% CI 0.01 to 0.77). Higher scores of bodily pain (signifying: lower levels of pain) were negatively associated with the severity of motor symptoms at baseline, i.e. less pain was associated with milder motor symptoms (p= 0.04; beta =-0.09, 95% CI -0.17 to -0.01). This association was no longer significant when adding anxiety symptoms (BAI), whilst a trend between anxiety symptoms and motor symptoms remained (p=0.08; beta = 0.34, 95%CI -0.04 to 0.76). No significant relation was found between fatigue (VT) and motor symptoms.

Results open-label study

The psychiatric profile at the end of the open-label study showed no between-group differences (**table 2**). No significant between group differences were found between the end of the open-label study and baseline in personality traits, fatigue, pain and negative life events (**table 3**) and FFI-NEO (**supplementary table 2**) scores during the open-label phase. The positive association between anxiety symptom severity (BAI) and motor symptom severity (PMDRS) which was found in the RCT phase, was confirmed at the end of the open-label study (p=0.03; beta=0.41, 95% CI 0.05 to 0.78). The same holds for pain which was negatively associated with motor symptom severity (meaning: less pain was associated with milder motor symptoms) (p=-0.02; beta=-0.11, 95%CI -0.20 to -0.02).

	RCT-phase						*Between group comparison end-RCT*	
	Motor improvement (n=29)			**No motor improvement (n=19)**				
	Median (IQR) baseline	**Median (IQR) end RCT**	**Median (IQR) change**	**Median (IQR) baseline**	**Median (IQR) end RCT**	**Median (IQR) change**	**Median difference in change (95% CI)**	**P-value**
BDI	8(3;13)	8(3;11)	-1(-3;4)	11(7;15)	11(7;16)	0(-3;1)	0(-3;2)	0.93
BAI	10(3;16)	11(3;15)	1(-3;3)	14(9;22)	13(8;22)	1(-6;3)	-1(-4;2)	0.60
Vitality	55(43;73)	50(35;69)	-5(-14;0)	48(34;60)	45(25;65)	5(-5;8)	5(0;10)	**0.04**
Bodily Pain	51(37;84)	52(41;79)	0(-8;7)	41(22;55)	41(22;57)	0(-5;11)	0(-1;10)	0.47

Table 3. *Summary of the BDI and BAI scores and vitality and bodily pain scores from the SF-36 at baseline, end-RCT and end-open label; including median change scores, between group differences in patients with and without motor improvement.*

	Open-label phase						*Between group comparison end-open-label*	
	Motor improvement (n=35)			**No motor improvement (n=8)**				
	Median (IQR) baseline	**Median (IQR) end open-label**	**Median (IQR) change**	**Median (IQR) baseline**	**Median (IQR) end open-label**	**Median (IQR) change**	**Median difference in change (95% CI)**	**P-value**
	9(5;14)	8(3;14)	-1(-3;2)	8(3;13)	3(1;4)	-5(-7;1)	-4(-7;1)	0.10
	12(6;17)	10(4;17)	0(-5;3)	11(4;21)	4(0;10)	-2(-9;2)	-2(-8;5)	0.60
	50(35;70)	48(30;70)	0(-11;10)	53(31;64)	60(40;75)	5(0;10)	5(-5;15)	0.28
	41(32;74)	53(53;84)	0(-12;9)	41(34;71)	62(22;84)	0(-12;10)	0(-12;11)	1.00

	Motor improvement						
	Baseline					**End RCT**	
Occurrence	**0-6 mos**	**6-12 mos**	**1-5 yrs**	**> 5 yrs**	**not**	**0-6 mos**	**not**
Death partner, family member or friend	2(7)	0(0)	9(31)	14(48)	4(14)	3(10)	26(90)
Severe disease of self	2(7)	2(7)	4(14)	3(10)	18(62)	2(7)	27(93)
Severe disease partner, child or other family member	4(14)	2(7)	5(17)	8(28)	10(35)	8(28)	21(72)
Accident or crime	1(3)	3(10)	3(10)	9(31)	13(45)	1(3)	28(97)
Divorce, separation	3(10)	3(10)	3(10)	11(38)	9(31)	4(14)	25(86)
Losing job, unemployment, financial trouble	4(14)	0(0)	8(28)	9(31)	8(28)	**2(7)**	27(93)
Any of above events*	29 (100)				0(0)	**14 (50)**	14 (50)

Table 4. *Negative life events at baseline compared to end-RCT and end-open label in patients with and without (%). mos=months. yrs=years.*

				No motor improvement								
	End open-label			**Baseline**					**End RCT**		**End open-label**	
	0-6 mos	**6-12 mos**	**not**	**0-6 mos**	**6-12 mos**	**1-5 yrs**	**> 5 yrs**	**not**	**0-6 mos**	**not**	**0-6 mos**	**6-12 mos**	**not**
	5(14)	4(11)	26(74)	2(11)	4(21)	5(26)	7(37)	0(0)	6(32)	13(68)	0(0)	0(0)	8(100)
	7(20)	2(6)	26(74)	2(11)	1(5)	4(21)	4(21)	8(42)	5(26)	14(74)	1(13)	1(13)	6(75)
	9(26)	3(9)	23(66)	7(37)	0(0)	3(16)	4(21)	5(26)	8(42)	11(58)	3(38)	0(0)	5(63)
	3(9)	0(0)	32(91)	1(5)	3(16)	1(5)	9(47)	5(26)	3(16)	16(84)	0(0)	0(0)	8(100)
	3(9)	4(11)	28(80)	2(11)	1(5)	5(26)	5(26)	6(32)	2(11)	17(90)	0(0)	0(0)	8(100)
	10(29)	1(3)	24(69)	5(26)	2(11)	5(26)	5(26)	2(11)	**7(37)**	12(63)	0(0)	2(25)	6(75)
	24 (71)		10 (29)	19 (100)				0(0)	**15 (88)**	2 (11)	5 (71)		2 (28)

motor improvement. ⋆Total number of events dichotomized as did or did not occur. Numbers expresses as n

DISCUSSION

This study on non-motor symptoms in FMD yielded some interesting results. First, we found high rates of anxiety disorders at baseline in the FMD study population, and patients who showed significant motor symptom improvement during treatment showed significantly larger decrease in frequency of anxiety disorders compared to patients who did not improve, regardless of treatment condition. Anxiety symptom severity showed a positive association with severity of motor symptoms at the different time points of treatment (baseline, end-RCT and end-open-label). These findings indicate a possible association between anxiety symptom and motor symptom severity that is related to treatment outcome in FMD.

The high frequency of total psychiatric disorders (79% total population) at baseline is in accordance with previous studies in FMD (2, 4). However the proportion of anxiety disorders in our patients (60% total population) was larger than in previous studies (11-25%) (2, 5, 22). Our study encompasses a population with a homogeneous phenotype (jerks and tremor), which might suggest that this is phenotype specific. However, one large cohort could not link different psychiatric profiles to a specific form of FMD (23).

Further we found an association between anxiety symptoms and the severity of motor symptoms. In general, anxiety and stress regulation are thought to play a key role in the pathophysiology of FMD. High rates of physiological symptoms of anxiety and hyperarousal, expressed in increased mean hart-rate, decreased heart rate variability/vagal tone, high levels of salivary cortisol and exaggeration of the startle reflex have been reported (24, 25). Several imaging studies have linked the amygdala, a key structure in pathological anxiety, to motor symptoms in FMD (26). Interestingly, when reviewing the quantitative anxiety scores (BAI) in our population anxiety severity was considered to be mild (19). The discrepancy between anxiety severity assessed with a self-report questionnaire (in our case the BAI) compared to an interview by a trained clinician might be explained by a frequently present phenomenon called alexithymia, where FMD patients fail to recognize and describe emotions (7, 27). In all, it would be interesting to investigate whether targeting anxiety disorders with cognitive behaviour therapy would result in improvement of motor symptoms. A recent paper regarding a 12-week cognitive behavioural therapy (CBT) in functional tremor showed a significant improvement of tremor (>75%), which was associated with changes in anterior cingulate/paracingulate activity on functional Magnetic Resonance Imaging (fMRI), an indicator of emotional dysregulation (28). This change was considered a potential marker of treatment response and was more prominent in patients with more severe depressive symptoms at baseline. Similarly, anxiety disorders might play such a role.

Noteworthy is the relatively high frequency of functional pain disorders found at baseline in the FMD group (29% total population). Pain is a well-known symptom in a functional dystonia (6) but have also been described in other FMD phenotypes (50-70%) (12, 29). The relation between functional pain disorders (according to DSM-IV criteria) and FMD has not been extensively described, although one study reports high rates (70%) in FMD and functional non-epileptic attacks, with 21% having multiple pain disorders (29). Our results showing that bodily pain is associated with more severe motor symptoms further strengthens the potential role of pain in FMD (12).

One other finding worth mentioning is that patients who did not improve at the end of the RCT, experienced more negative life events, especially financial problems (e.g. losing job) during the prior 6 months compared to patients who did improve. Potentially, this might signify that patients with motor improvement are more likely to have or maintain a job. Health-related unemployment is generally larger in patients with functional versus organic neurologic disease (10), and the receipt of health-related benefit is a known predictor of poor outcome (30).

Previous studies analysing personality traits in FMD showed lower levels of conscientiousness, and higher levels of neuroticism compared to patients with organic neurologic disorders and healthy controls (5, 7). We could not identify a certain personality trait associated with treatment response or motor severity in this study.

This study has a few limitations. First, the study is small scaled and thus relatively underpowered, and lacked a control group of healthy individuals. We also acknowledge the fact that we only used subscales of the SF-36 to measure pain and fatigue. Further we performed a relatively large amount of statistical tests in a small study population which increases the chance of generating type I errors. Considering the exploratory nature of the study, we have chosen not to correct for multiple testing, to avoid type II errors. Strengths of this study are that it consists of a prospectively collected homogeneous study population. Also, this study is unique in that we gathered extensive longitudinal psychiatric data.

CONCLUSIONS

In this study we provide longitudinal psychiatric data in a homogeneous FMD patient population who underwent treatment within the scope of an RCT. Patients who responded well to treatment (BoNT or placebo) in terms of motor symptoms, also showed improvement of anxiety disorders. Both anxiety and pain symptoms were associated with more severe motor symptoms. Although it should be noted

that these results are preliminary given the relatively small patient population. The question remains whether pain and anxiety could predispose patients to develop FMD or whether it is a consequence. In this matter it would be interesting to target anxiety disorders itself in treatment studies.

Declarations

Contributors

MAJT, JMD and JHTM designed the study. YEMD collected data. YEMD and TJT analyzed and interpreted data. YEMD wrote the paper and designed the figures and tables. All other authors drafted and critically revised the paper.

Acknowledgements

We would like to thank all the staff members of the department of Clinical Neurophysiology for their support with carrying out this study.

Conflicts of interest

This study was funded by Prinses Beatrix Fund and Ipsen®. Dr Dreissen, dr Dijk, dr Koelman and Prof Tijssen report grants from Prinses Beatrix Fund and non-financial support from Ipsen, during the conduct of the study. Dr Koelman reports grants from Ipsen, grants from Allergan, grants from Merz, outside the submitted work. Prof Tijssen reports grants from the Netherlands Organisation for Health Research and Development ZonMW Topsubsidie (91218013), the European Fund for Regional Development from the European Union (01492947) and the province of Friesland, Dystonia Medical Research Foundation, from Stichting Wetenschapsfonds Dystonie Vereniging, from Fonds Psychische Gezondheid, from Phelps Stichting, and an unrestricted grant from Actelion and from AOP Orphan Pharmaceuticals AG for a lecture. Dr Dijk reports grants from rom ZonMw (The Netherlands Organisation for Health Research and Development) and Medtronic, outside the submitted work. All other authors have nothing to disclose.

Role of funding source

The authors vouch for the accuracy and completeness of the data and for the fidelity of this report to the study protocol. The funders (Prinses Beatrix Fund, Ipsen®) were not involved in the study design, data collection, data analysis, data interpretation or writing of the manuscript.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information. Individual deidentified participant data will not be shared.

REFERENCES

1. Miyasaki JM, Sa DS, Galvez-Jimenez N, Lang AE. Psychogenic movement disorders. CanJNeurolSci. 2003;30 Suppl 1:S94-100.
2. Factor SA, Podskalny GD, Molho ES. Psychogenic movement disorders: frequency, clinical profile, and characteristics. JNeurolNeurosurgPsychiatry. 1995;59(4):406-12.
3. Gupta A, Lang AE. Psychogenic movement disorders. Current Opinion in Neurology. 2009;22(4).
4. Feinstein A, Stergiopoulos V, Fine J, Lang AE. Psychiatric outcome in patients with a psychogenic movement disorder: a prospective study. Neuropsychiatry NeuropsycholBehavNeurol. 2001;14(3):169-76.
5. Kranick S, Ekanayake V, Martinez V, Ameli R, Hallett M, Voon V. Psychopathology and psychogenic movement disorders. Movement Disorders. 2011;26(10).
6. Tomic A, Petrovic I, Pesic D, Voncina MM, Svetel M, Miskovic ND, et al. Is there a specific psychiatric background or personality profile in functional dystonia? J Psychosom Res. 2017;97:58-62.
7. Ekanayake V, Kranick S, LaFaver K, Naz A, Frank Webb A, LaFrance WC, Jr., et al. Personality traits in psychogenic nonepileptic seizures (PNES) and psychogenic movement disorder (PMD): Neuroticism and perfectionism. J Psychosom Res. 2017;97:23-9.
8. Defazio G, Pastore A, Pellicciari R, Pierri G, Gigante AF, Fabio G, et al. Personality disorders and somatization in functional and organic movement disorders. Psychiatry Res. 2017;257:227-9.
9. Reid S, Wessely S, Crayford T, Hotopf M. Medically unexplained symptoms in frequent attenders of secondary health care: retrospective cohort study. BMJ. 2001;322(7289):767.
10. Carson A, Stone J, Hibberd C, Murray G, Duncan R, Coleman R, et al. Disability, distress and unemployment in neurology outpatients with symptoms 'unexplained by organic disease'. JNeurolNeurosurgPsychiatry. 2011;82(7):810-3.
11. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry. 2014;85(2):220-6.
12. Gelauff JM, Kingma EM, Kalkman JS, Bezemer R, van Engelen BGM, Stone J, et al. Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders. J Neurol. 2018.
13. Garcin B, Mesrati F, Hubsch C, Mauras T, Iliescu I, Naccache L, et al. Impact of Transcranial Magnetic Stimulation on Functional Movement Disorders: Cortical Modulation or a Behavioral Effect? Front Neurol. 2017;8:338.
14. Jacob A, Kaelin D, Roach A, Ziegler C, LaFaver K. Motor Retraining (MoRe) for Functional Movement Disorders: Outcomes from a one-week multidisciplinary Rehabilitation Program. PM R. 2018.

15. Maggio JB, Ospina JP, Callahan J, Hunt AL, Stephen CD, Perez DL. Outpatient Physical Therapy for Functional Neurological Disorder: A Preliminary Feasibility and Naturalistic Outcome Study in a U.S. Cohort. J Neuropsychiatry Clin Neurosci. 2020;32(1):85-9.
16. Surtees PG, Wainwright NW. Fragile states of mind: neuroticism, vulnerability and the long-term outcome of depression. Br J Psychiatry. 1996;169(3):338-47.
17. Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J. The prognosis of functional limb weakness: a 14-year case-control study. Brain. 2019;142(7):2137-48.
18. Glass SP, Matin N, Williams B, Mello J, Stephen CD, Young SS, et al. Neuropsychiatric Factors Linked to Adherence and Short-Term Outcome in a U.S. Functional Neurological Disorders Clinic: A Retrospective Cohort Study. J Neuropsychiatry Clin Neurosci. 2017:appineuropsych17060117.
19. Dreissen YEM, Dijk JM, Gelauff JM, Zoons E, van Poppelen D, Contarino MF, et al. Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. J Neurol Neurosurg Psychiatry. 2019;90(11):1244-50.
20. Costa PT, Mccrae RR. The 5-Factor Model of Personality and Its Relevance to Personality-Disorders. J Pers Disord. 1992;6(4):343-59.
21. Brugha TS, Cragg D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. Acta Psychiatr Scand. 1990;82(1):77-81.
22. Munhoz RP, Zavala JA, Becker N, Teive HA. Cross-cultural influences on psychogenic movement disorders - a comparative review with a Brazilian series of 83 cases. Clin Neurol Neurosurg. 2011;113(2):115-8.
23. Gelauff JM, Rosmalen JGM, Gardien J, Stone J, Tijssen MAJ. Shared demographics and comorbidities in different functional motor disorders. Parkinsonism Relat Disord. 2020;70:1-6.
24. Dreissen YEM, Boeree T, Koelman J, Tijssen MAJ. Startle responses in functional jerky movement disorders are increased but have a normal pattern. Parkinsonism Relat Disord. 2017;40:27-32.
25. Maurer CW, Liu VD, LaFaver K, Ameli R, Wu T, Toledo R, et al. Impaired resting vagal tone in patients with functional movement disorders. Parkinsonism Relat Disord. 2016;30:18-22.
26. Voon V, Brezing C, Gallea C, Ameli R, Roelofs K, LaFrance WC, Jr., et al. Emotional stimuli and motor conversion disorder. Brain. 2010;133(Pt 5):1526-36.
27. Demartini B, Petrochilos P, Ricciardi L, Price G, Edwards MJ, Joyce E. The role of alexithymia in the development of functional motor symptoms (conversion disorder). J Neurol Neurosurg Psychiatry. 2014;85(10):1132-7.
28. Espay AJ, Ries S, Maloney T, Vannest J, Neefus E, Dwivedi AK, et al. Clinical and neural responses to cognitive behavioral therapy for functional tremor. Neurology. 2019;93(19):e1787-e98.
29. Driver-Dunckley E, Stonnington CM, Locke DE, Noe K. Comparison of psychogenic movement disorders and psychogenic nonepileptic seizures: is phenotype clinically important? Psychosomatics. 2011;52(4):337-45.

30. Sharpe M, Stone J, Hibberd C, Warlow C, Duncan R, Coleman R, et al. Neurology out-patients with symptoms unexplained by disease: illness beliefs and financial benefits predict 1-year outcome. Psychol Med. 2010;40(4):689-98.

SUPPLEMENTARY DATA FILE

1. Results RCT

	Motor improvement (n=29)			No motor improvement (n=19)			Between group comparison	
	Median score (IQR) at baseline	Median score (IQR) end of RCT	Median (IQR) change score	Median score (IQR) at baseline	Median score (IQR) end of RCT	Median (IQR) change score	Median difference in change scores (95% CI)	P-value
Neuroticism	28 (24; 34)	29 (26; 36)	0 (-5; 4)	30 (28; 36)	31 (29; 36)	1 (-1; 4)	2 (-1; 4)	0.28
Extraversion	41 (36; 44)	38 (36; 43)	-1 (-3; 2)	38 (34; 42)	38 (33; 41)	0 (-2; 2)	1 (-1; 3)	0.36
Openness	38 (34; 41)	36 (33; 38)	0 (-3; 2)	38 (36; 42)	37 (34; 42)	-1 (-4; 4)	1 (-2; 3)	0.68
Agreeableness	44 (42; 49)	47 (38; 48)	-1 (-4; 3)	44 (39; 48)	44 (41; 47)	0 (-2; 1)	1 (-2; 3)	0.75
Conscientiousness	45 (40; 49)	44 (40; 49)	-1 (-1; 1)	46 (39; 48)	44 (39; 48)	-2 (-5; 2)	-2 (-4; 1)	0.21

Supplementary Table 1. *Personality traits according to the FFI-NEO at baseline and end-RCT, including median change scores, between group differences in in patients with and without motor improvement at end-RCT.*

2. Results open-label study

	Motor improvement (n=35)			No motor improvement (n=8)			Between group comparison	
	Median score (IQR) at baseline	Median score (IQR) end of open-label	Median (IQR) change score	Median score (IQR) at baseline	Median score (IQR) end of open-label	Median (IQR) change score	Median difference in change scores (95% CI)	P-value
Neuroticism	28 (25; 35)	27 (25; 34)	1 (-4; 4)	31 (28; 35)	28 (27; 31)	-1 (-4; 3)	-1 (-5; 4)	0.72
Extraversion	40 (33; 42)	40 (34; 43)	0 (-3; 2)	38 (35; 43)	38 (34; 45)	1 (-2; 2)	0 (-3; 4)	0.85
Openness	38 (34; 41)	38 (35; 41)	0 (-2; 2)	38 (37; 39)	36 (34; 40)	0 (-3; 1)	-1 (-3; 2)	0.72
Agreeableness	44 (42; 49)	45 (40; 48)	-1 (-3; 1)	46 (39; 49)	45 (42; 46)	1 (-2; 5)	1 (-2; 5)	0.35
Conscientiousness	45 (41; 53)	45 (42; 50)	1 (-0; 3)	46 (40; 49)	43 (39; 47)	0 (-4; 1)	-2 (-6; 1)	0.14

Supplementary Table 2. *Personality traits according to the FFI-NEO at baseline and end-open label, including median change scores, between group differences in patients with and without motor improvement at end-open-label.*

Botulinum Neurotoxin (BoNT) treatment in functional movement disorders: long-term follow-up

5

Yasmine EM Dreissen*, Franka Lambert*, Joke M Dijk,
Johannes HTM Koelman & Marina AJ Tijssen
**Both authors contributed equally to this work*

Article published in Journal of Neurology Neurosurgery and Psychiatry 2020 doi 10.1136/jnnp-2020-323684

INTRODUCTION

We recently reported on a randomized controlled trial (RCT) assessing the effect of botulinum neurotoxin (BoNT) in 48 patients with chronic (>1 year) jerky and tremulous functional movement disorders (FMD) (1). The RCT showed an improvement of motor symptoms in both treatment arms (16/25, 64% BoNT vs 13/23, 57% placebo). The proportion of improved patients increased to 81% (35/43) at the end of the open-label phase. Despite symptom improvement, there was no change in quality of life and disability. In the present study our aim was to assess the long-term outcome of this study population.

METHODS

Population and study design

Included patients were aged between 18-80 years with disabling functional jerky or tremulous movement disorders with a minimum symptom duration of one year (1).

Procedures

All 48 patients who participated in the BoNT RCT were approached via letter or e-mail. Patients were interviewed by telephone (FL) and self-assessment questionnaires were sent to patients' homes. We compared the outcome measures of the current study with baseline (start RCT) and the end of the open-label phase.

Outcome measures

A selection of previous used outcome measures was used (1). Self-rated motor improvement (CGI-I) and motor severity (CGI-S), disease burden (VAS-scale), physical functioning (SF-36), depressive symptoms (Beck depression inventory (BDI)) and anxiety symptoms (Beck Anxiety Inventory (BAI)) were evaluated. Patients were questioned about their current employment status, BoNT (or other) treatment and new functional neurologic symptoms.

Medical ethical approval was obtained at the Amsterdam University Medical Center. All patients gave written informed consent.

Statistical analysis

Demographic characteristics were analysed using descriptive statistics. Patients were categorized based on CGI-I between baseline and the end of the follow-up into three groups. The first group, or 'improved' group (**group 1**), the second group, or 'no change' group (**group 2**) and a the third group, or 'worse' group **(group 3)**.

The CGI-S, VAS, BAI, BDI and SF-36 were compared between the different time points using a Wilcoxon singed rank test. Additionally, symptom improvement (CGI-I) and severity (CGI-S) were compared between patients who did and did not still receive BoNT treatment using the Fisher's exact test or Mann-Whitney U test. The threshold for statistical significance was set at a 2-sided $p < 0.05$. All analyses were performed using IBM SPSS Statistics version 24.

RESULTS

Of the 48 patients who were approached, 46 patients agreed to participate. Six patients completed the telephone interview, but did not return the questionnaires and 9 only agreed to answer a subset of questions. The follow-up duration varied between 3 and 7 years (median years (IQR 3-6)). In total CGI-I scores were available in 42 patients. The other outcome measures were available in n=46 patients.

The median age of patients at follow-up was 58 years (IQR 42-65), 54% was male. The median symptom duration was 9 years (IQR 7-18). Since the end of the open-label phase of the BoNT trial, 7 of 37 patients reported new functional symptoms. Of the 37 patients who completed the telephone interview, 2 had started working and 3 had quit work since baseline. Thirteen of these 37 patients reported that they received one or more new therapies targeting FMD. Ten out of these 13 patients reported symptom improvement attributed to these therapies, 2 remained unchanged, 1 worsened.

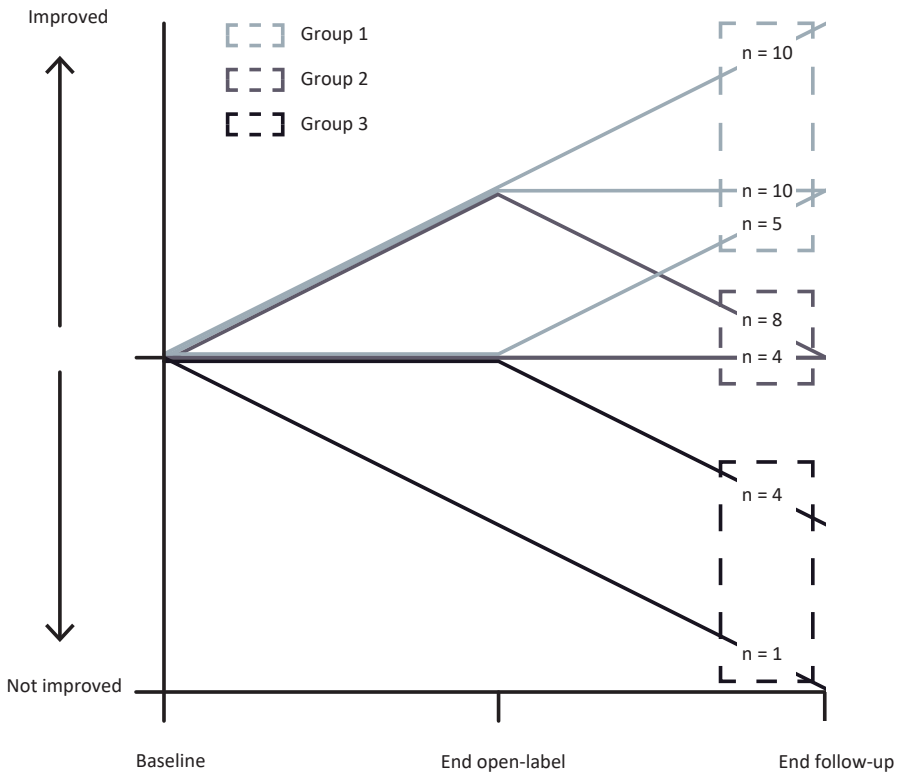

Figure 1. *Disease course in the three subgroups based on CGI-I scores at baseline, end-open label study and the end of the follow-up*

The disease course based on the CGI-I between the three time points is illustrated in **figure 1**. For the entire group (n=46) motor severity (CGI-S) improved between baseline and long-term follow-up (median 5 vs 4, p=0.00). Disease burden (VAS) improved significantly between baseline and the end of the open label phase (median 15 points; p=0.02) but returned to baseline levels at the long-term follow-up (p=1.00). Depressive symptoms improved slightly between baseline and end open-label (2 points; p=0.02) but returned to baseline levels during the long-term follow-up (for details see **supplementary data file**).

BoNT treatment

Of the 17 patients who continued BoNT treatment after the open-label phase, 10 still received BoNT at the long-term follow-up. Eight patients were stable or improved and 2 patients worsened. No differences in symptom improvement or severity were found between patients with and without BoNT treatment.

DISCUSSION

This study showed motor improvement at the end of long-term follow up in the majority of patients (25/46), although the proportion slightly diminished compared to the end of the open-label study (35/43). Still, this is more favourable than what one would expect based on current literature. Recently Gelauff et al. reported on the long-term (average 14 years) outcome of a large cohort (n=107) of patients with motor Functional Neurologic Symptoms (FNS) in which 49% had persistent or worsening of symptoms (2). This is in line with a systematic review on the prognosis of FMD (3). The natural course however of FMD is unknown. Because the number of patients in this cohort currently receiving BoNT is small, it is not possible to assess whether botulinum treatment has an additive effect. Also, 13 of 46 patients received other therapies for FMD which they largely considered effective. Regression to the mean, the natural disease course and placebo effects may play a role.

Similar to our previous study, the improvement in motor symptoms did not translate into improvement of physical functioning or disease burden. It remains a matter of speculation why there seems such a poor relation between motor and non-motor symptoms. A case-control study comparing FMD with neuromuscular disorders found that quality of life was not affected by motor symptoms (4). An important issue is the lack on validated and clinically relevant outcome measures in FNS (5), generating uncertainty in interpreting the results of the different outcome measures in this patient group.

This study has several limitations. First, the follow-up term varied in duration. We used a selection of subjective instead of objective outcome measures and data were not available in all patients.

In conclusion, this long-term follow-up study reveals a favourable motor outcome in the majority of patients with chronic FMD. The improvement may be largely due to placebo effects. It shows though that treatment studies in this difficult patient category are important and potentially rewarding.

Contributors

YEMD, MAJT and JHTM designed the study. FL collected and analyzed the data. FL and YEMD interpreted the data. FL and YEMD wrote the paper and designed the figures and tables. All other authors drafted and critically revised the paper.

Acknowledgements

We would like to thank all the staff members of the department of Clinical Neurophysiology for their support with carrying out this study.

Disclosure statement

This study was not funded. Dr Koelman reports educational grants from Ipsen, Allergan and Merz, outside the submitted work. Prof Tijssen reports grants from the Netherlands Organisation for Health Research and Development ZonMW Topsubsidie (91218013), the European Fund for Regional Development from the European Union (01492947) and the province of Friesland, Dystonia Medical Research Foundation, from Stichting Wetenschapsfonds Dystonie Vereniging, from Fonds Psychische Gezondheid, from Phelps Stichting, and an unrestricted grant from Actelion and from AOP Orphan Pharmaceuticals AG for a lecture. Dr Dijk reports grants from rom ZonMw (The Netherlands Organisation for Health Research and Development) and Medtronic, outside the submitted work. All other authors have nothing to disclose.

Role of funding source

None

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information. Individual de-identified participant data will not be shared.

REFERENCES

1. Dreissen YEM, Dijk JM, Gelauff JM, Zoons E, van Poppelen D, Contarino MF, et al. Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. J Neurol Neurosurg Psychiatry. 2019;90(11):1244-50.
2. Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J. The prognosis of functional limb weakness: a 14-year case-control study. Brain. 2019;142(7):2137-48.
3. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. J Neurol Neurosurg Psychiatry. 2014;85(2):220-6.
4. Gelauff JM, Kingma EM, Kalkman JS, Bezemer R, van Engelen BGM, Stone J, et al. Fatigue, not self-rated motor symptom severity, affects quality of life in functional motor disorders. J Neurol. 2018.
5. Nicholson TR, Carson A, Edwards MJ, Goldstein LH, Hallett M, Mildon B, et al. Outcome Measures for Functional Neurological Disorder: A Review of the Theoretical Complexities. J Neuropsychiatry Clin Neurosci. 2020;32(1):33-42.

Exaggerated startle reactions

6

Yasmine EM Dreissen, Mirte J Bakker, Johannes HTM Koelman,
Marina AJ Tijssen

Article published in Clinical Neurophysiology doi: 10.1016/j.clinph.2011.09.022

ABSTRACT

The origin of the startle reflex lies in the caudal brainstem; it can be elicited by an unexpected stimulus resulting in a bilateral activation of many muscles. Two subsequent responses can be measured during EMG recordings; after the initial motor reflex, lasting until about 150 milliseconds (ms), a second response can occur. The second response contains more emotional and voluntary behavioral responses. Clinically, syndromes with hyperstartling as common feature can be divided into three groups: hyperekplexia, stimulus-induced disorders, and neuropsychiatric disorders. Classification of startle syndromes within these three groups remains challenging. Generalized stiffness at birth, excessive startling and temporary generalized stiffness after being startled point towards hyperekplexia. Stimulus-induced disorders are distinguished by careful clinical evaluation, including video recordings. Neuropsychiatric disorders usually have additional behavioural and psychiatric symptoms. Polymyographic EMG startle recordings exhibit an exaggeration of the initial motor startle reflex in hyperekplexia, while neuropsychiatric startle syndromes demonstrate a variable response pattern and abnormal behavioural features. Neurophysiological investigation of the startle reflex can help to further delineate between the startle syndromes and unravel the aetiology of neuropsychiatric startle disorders.

INTRODUCTION

A startle reflex is a common physiological phenomenon which can be observed in healthy subjects after an unexpected stimulus. It appears at 6 weeks of age and persists for life (1-7). Clinically the startle reflex consists of a generalized myogenic flexor response with symmetrical activation of different muscles resulting in a facial grimace, abduction of the arms, flexion of the neck, trunk, elbows, hips and knees which has a classic rostro-caudal distribution. Most muscle activity is located in the face and the shoulders. The response can be elicited by visual, somatic and vestibular stimuli; however startle has mostly been described and studied in relation with auditory stimulation (8). During childhood the magnitude of the baseline startle reflex increases (2) and it is substantially reduced again with age (4).

In this review the 'startle reflex' will be discussed first in terms of its motor response evoked by sudden stimuli as well as its underlying neuronal pathways. Subsequently, three different groups of startle syndromes will be discussed namely hyperekplexia, stimulus induced disorders, and neuropsychiatric disorders such as Latah.

Normal Startle reflex

The startle reflex has been studied as early as 1926 (9). In 1929, Strauss was the first to photographically record the startle motor behavior following pistol shots (16 frames/s) (10). Landis and Hunt improved this technique by using a precision of up to 1500 frames/s (11). These recordings showed that the startle reflex was symmetrical with rostro-caudal prolongation of latencies, ending within 500 ms and that the variability of the amplitude was in proportion with the strength of the stimulus, the excitability of the subject and the unexpectedness of the stimuli. Also, Strauss mentioned a second response which quickly followed the initial reaction and contained more prolonged, complex and variable behavior, subsequently called the 'B response' by Davis and the 'orienting response' by Gogan (10, 12, 13). From 1948 more sophisticated analysis of the startle reflex was possible by the introduction of electromyography (12). Davis recorded EMG of the forearms while using a non-calibrated startling noise. After Davis, Jones and Kennedy performed a more extensive EMG study recording cranial as well as limb muscles and proved latencies to be shorter compared to the earlier photographic studies (14). Suhren et al. 1966 continued to study healthy subjects and subjects with hyperekplexia by using high-speed filming combined with EMG activity of craniocervical muscles in pistol-shot induced startle reflexes (15). Gogan (13) was the first to use calibrated auditory stimuli and Rossignol (16) (Rossignol 1975) and Fox (17) combined calibrated auditory stimuli (90-114 dB) with EMG recordings.

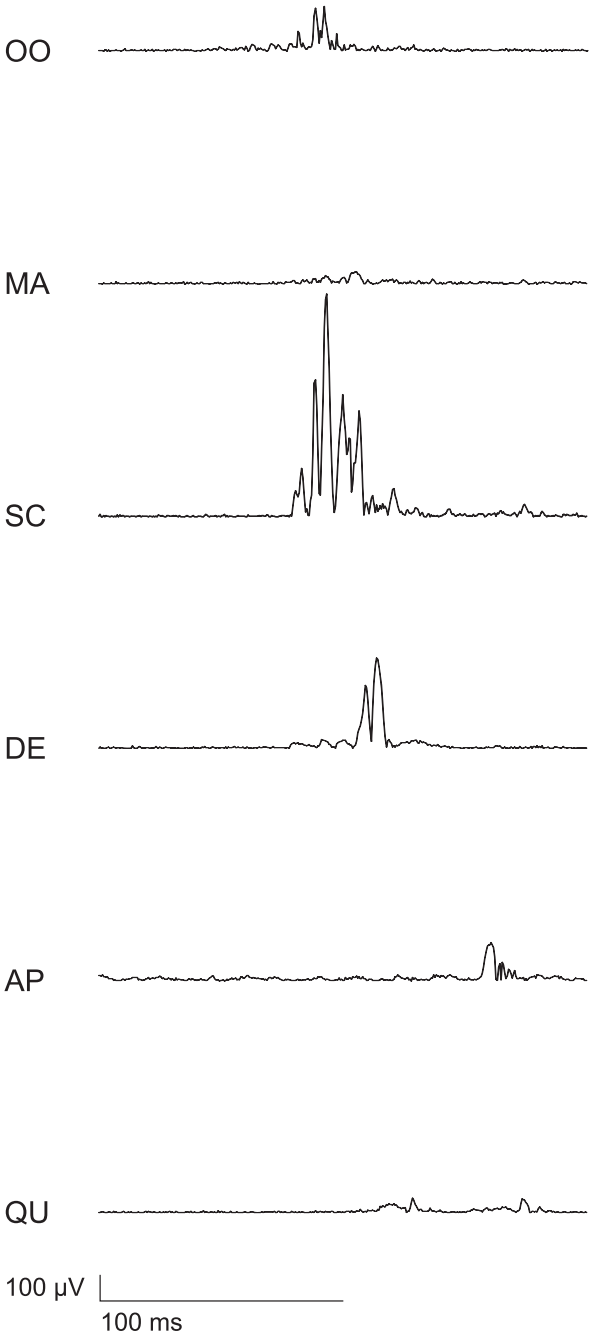

Figure 1. Rectified EMG (single trial) multiple muscle response of 13-year-old boy following 104 dB tone. OO, orbicularis oculi (latency 45 ms); MA, masseter (latency 69 ms), SC, sternocleidomastoid (latency 71 ms); DE, deltoid (latency 75 ms); AP, abductor pollicis brevis (latency 154 ms); QU, quadriceps (latency 102 ms); The latency of the AP muscle is disproportionately long

Brown et al. extended our knowledge by performing several studies on the normal startle reflex using standardized auditory tone burst with frequency of 1000 Hz, 50 ms duration and 124 dB while recording EMG activity in several muscles, including the orbicularis oculi (8).

Observing EMG muscle activity during startle responses reveals two subsequent responses. The initial patterned motor reflex, mediated by the caudal brainstem, initiates with activation of the orbicularis oculi (onset latency 20-50 ms), and spreads rostro-caudally to subsequently the sternocleidomastoid, mentalis, masseter, trunk and limb muscles **(figure 1)** (3, 8, 18). This response is roughly uniform from time to time and from individual to individual (19). This 'early' response, also known as the 'muscular tension reflex', is described by Landis and Hunt as 'an immediate reflex response which represents innate behaviour, unmodified by the various acquired patterns of behaviour' (11, 12, 20). It has been interpreted as the rapid accomplishment of a defensive stance with maximum postural stability (8, 21).

The initial motor reflex is followed by a period of decreased activity lasting for about 250 - 300 ms, after which a second response can be observed, occurring at a latency of about 400 to 450 ms, lasting from 3 to 10 seconds or more. This 'late' second response has been described as the 'what-is-it?' or 'orienting response' (10, 12, 13). This secondary response or behaviour shows more variance (3, 11, 13) and is determined by the nature of the startling stimulus and the situation in which it occurs. It contains emotional and voluntary behavioral responses in preparation of action towards the stimulus (13). It is called the orienting response because the organism is orienting towards the stimulus source including postural adjustments, as can be illustrated in the EMG. In the same time span an increase of autonomic activity, i.e. a fall in galvanic skin resistance, a rise in systolic blood pressure and acceleration of the heart rate occurs (19).The electrophysiological characteristics of the second response are not well-defined.

Different parameters can be used to quantify the auditory startle reflex, including pattern of muscle recruitment, onset latency, muscle response probability and magnitude of the EMG recordings. The blink response onset latencies are between 20 and 100 ms, followed by onset latencies ranging from 30 to 200 ms in face, neck, trunk and limb muscles for the early motor response. Onset latencies above 400 ms are described for the second response (3, 8, 13). Response probability is defined as the chance that a particular muscle responds following a stimulus. It can be calculated by dividing the amount of reflex responses in a particular muscle by the total number of traces, times 100, expressed in (%) chance (22-24). Subsequently, a combined

response probability can be calculated by averaging the response probabilities of all muscles involved. An alternative quantification of the auditory startle reflex is obtained by averaging the area-under-the-curve of the EMG signal of the different muscle responses (24). The sympathetic skin response (25, 26), also known as the skin conductance response (27) accompanies the orienting response and represents the autonomic part of the startle reflex (3, 11, 28, 29). It can be defined as the largest increase in μV 4 to 5 s from baseline in the period after the stimulus. Because of its high intra-individual variability, it is recommended to use a standardized method (24, 30, 31). Other measures of the autonomic response include heart rate, arterial blood pressure and breathing pattern (32).

An exaggeration of the startle reflex can be expressed in different features, including an excessive EMG burst duration and amplitude, a deviant activation pattern, prolonged onset latencies, a more widespread muscle activation, a lower threshold for response, impaired habituation and occurrence of a second response (33).

The brainstem origin of startle reflex in humans is supported by the persistence of the reflex in anencephalic children (34). Earlier studies in animals suggest the auditory startle reflex to originate in the lower brainstem, more specifically the bulbopontine reticular formation. A lesion of this area in rats results in diminishment of startle responses (35). Particularly, the nucleus reticularis pontis caudalis (nRPC) appears important (36). Electrical stimulation of this nucleus elicits responses resembling startle responses in rats (36). Based on these experiments, the following acoustic startle circuit has been proposed: auditory nerve, ventral cochlear nucleus, nuclei of the lateral lemniscus, nucleus reticularis pontis caudalis (nRPC), motor neurons brainstem and spinal cord. Later studies show that nRPC receive direct afferent input from the cochlear nucleus and that the lateral lemniscus is not required to elicit a startle response (37, 38). Nowadays, the auditory startle reflex is thought to be elicited by direct synaptic activation of the pontomedullary reticular formation (pmRF) through the cochlear nucleus (39-42).

Differences in latency of electromyographic (EMG) activity of the various muscles also support a brainstem origin of the startle reflex (8). Relatively slow conducting efferent impulses travel both upwards and downwards from the generator in the caudal brainstem. The latency of muscle activation thereby provides an estimate of the muscle's distance from the startle generator (8). It is however noticeable that the EMG-latencies in these particular muscles following auditory stimulation are variable but the pattern is rather fixed (3, 8, 33).

An inconsistency with the bulbospinal origin of the auditory startle reflex is the overly early response of the orbicularis oculi (3, 11, 15). Brown et al. suggested the early orbicularis oculi response is in fact an auditory blink reflex and not a true startle reflex (8). The auditory blink reflex starts as early as 20 ms after auditory stimulation, is almost invariable, not voluntary suppressible and does not habituate easily. In contrast repetitive auditory stimulation reveals rapid habituation of the responses in other muscles: after four to six stimuli the motor activity in those muscles is almost entirely extinguished (8, 11, 33, 43). Activation of the midbrain reticular formation through the neurons of the inferior colliculus are considered to mediate the initial non-habituating blink response(41, 42, 44). The second part of the activity in the orbicularis oculi muscle starts after about 50 ms and is considered part of the startle reflex. This onset latency fits well within the sequence of bulbar muscle recruitment as evidenced by other muscles (8). One consequence of this duality is that assessment of the EMG-response of the orbicularis oculi as an isolated phenomenon is not suited to study the startle reflex. The response probability of various muscles combined however represents the magnitude of the startle reflex well (22-24).

Amongst effects known to modulate the auditory startle reflex are: stimulus strength, the presence and intensity of pre-stimuli before the actual stimulus evoking the startle reaction, posture of the subject, tonic voluntary muscle activity, attentional focus, wakefulness, fluctuating cerebral states and general psychological state (3, 18, 22, 23, 45-47). Pathways of many of these modifying influences are imperfectly known. This holds in particular for cortical influences on the auditory startle reflex. For instance after cortical damage the auditory startle reflex can both decrease (48) or increase (49). Knowledge on the influence of emotion on the auditory startle reflex has been subject to many studies. In short, the emotional state or emotional stimuli presented just before a startling stimulus affect the size of the auditory startle reflex. Therefore, the auditory startle reflex can be used as a physiological and more objective tool to complement verbal reports, which are vulnerable to individual perception (18, 45, 50). Over the last decades the auditory startle reflex has become an important investigative tool to explore different affective systems. Broadly three lines of research have been conducted: baseline startle reactivity, startle during a certain emotional or motivational state and startle as an index of sensorimotor gating (pre-pulse inhibition) for more detailed information on this topic we refer to the review of Grillon and Baas (18).

Startle syndromes

An exaggeration of the physiological startle reflex is a feature which can be seen in different disorders. Clinically, startle syndromes can be divided in three groups of disorders: hyperekplexia, stimulus-induced disorders, and neuropsychiatric disorders

(51). Although all three startle syndromes are characterized by an exaggerated startle response, the features of the startle reflex and their pathophysiological mechanisms may differ. Neurophysiological examination can help discriminate between these different syndromes.

Hyperekplexia

The word 'hyperekplexia' is derived from the Greek words '*υπερ*' and '*εκ-πληοσσώ*' which together mean 'to startle excessively'. In 1958 Kirstein firstly described four members of a Swedish family with exaggerated startle reflexes and violent falls due to generalized stiffness (52). This disorder was thought to be partly psychiatric ('emotional stimuli') and partly epileptic ('drop seizures') in origin. In 1966 the term 'hyperekplexia' was introduced by Suhren *et al.* who described a large Dutch family with similar symptoms (15). The mode of inheritance was recognized as autosomal dominant and symptoms were interpreted as an exaggerated startle reaction, probably due to brainstem reticular formation dysregulation. Two clinical forms of the disorder have been described in that pedigree: the 'major' and the 'minor' form (15). The 'major' form of hyperekplexia requires the presence of three cardinal features: generalized stiffness at birth, excessive startling and temporary generalized stiffness after being startled (53). It has been identified in over 100 pedigrees (15, 43, 54-66). The occurrence of a 'minor' form of hyperekplexia with an exaggerated startle reflex as only symptom, has been reported in some families (15, 54, 67-70).

The use of the term hyperekplexia throughout history has been confusing. All diseases with a form of exaggerated startling, regardless of the cause, have been labeled hyperekplexia (55, 57, 60, 63, 67, 71-92). In our opinion it would serve clarity to solely use the term hyperekplexia (without the term 'major' or 'minor') for patients with the three cardinal features of the disease, regardless it being hereditary or sporadic. In this review we will make an effort to use the term hyperekplexia in this view. We suggest to use the term 'excessive startle reflexes' for patients who suffer from excessive startle responses without signs of stiffness.

Clinical aspects hyperekplexia

For hyperekplexia three cardinal features are required (53). The first is generalized stiffness immediately after birth, normalizing during the first years of life, which increases with handling and disappears during sleep (93).The second is an excessive startle reflex following unexpected, particularly auditory stimuli, which is present from birth throughout life. Consciousness is unaltered during startle responses. The third feature consists of generalized stiffness, lasting a few seconds following a startle reflex, during which voluntary movements are impossible (15, 54). The short-lasting

temporary generalized stiffness often causes patients to fall forwards 'as stiff as a stick' while fully conscious.

The generalized stiffness exists immediately after birth and basically permits babies to be held vertically or horizontally without any change in posture (15, 93). One important clinical sign consists of tonic neonatal cyanosis attacks (74, 90, 94). These attacks are sporadically seen in GLRA1 gene mutation positive patients (47) and can be stopped with the 'Vigevano' maneuver existing of forced flexion of the head and legs towards the trunk (95). Patients with the recently described, second hyperekplexia gene, GlyT2, suffer more frequently from these attacks of tonic neonatal cyanosis (96). The stiffness almost entirely normalizes after the first years of life, although adults with hyperekplexia often walk with a stiff-legged, mildly wide-based gait without signs of ataxia (15). Tendon reflexes and tone are normal or slightly increased, but without any signs of a pyramidal syndrome.

Apart from the essential features, there are few associated symptoms that may be present but are not essential for the diagnosis. The exaggerated head-retraction reflex (HRR) consists of a brisk, involuntary backward jerk of the head following a light tap with a hammer on the root of the nose or the middle portion of the upper lip. It is seen in neonates as well as adults with hyperekplexia and shows no habituation. Although the HRR is considered by some to be pathognomonic (61, 79, 97, 98), it has also been described in children with cerebral palsy due to severe neonatal asphyxia (99, 100). Other frequently mentioned features of hyperekplexia include periodic limb movements during sleep (PLMS) and hypnagogic myoclonus (52, 55). Associated features have occasionally been described (for overview see Bakker et al. 2006) (51). Standard tests of serum, urine and CSF, computerized tomography, electroencephalography and magnetic resonance imaging reveal no abnormalities (15, 58, 101-103).

Hyperekplexia without other family members affected, i.e.sporadic hyperekplexia, has been reported in over 120 cases (59, 63, 74, 76, 79, 87, 88, 90, 94, 104, 105). Most sporadic cases present with symptoms closely resembling hereditary hyperekplexia (74, 90, 94, 104-106). With the detection of the mainly recessive inherited GlyT2 gene, many sporadic cases appeared to have a mutation in this gene (96).

Symptomatic hyperekplexia, which has been described as an exaggerated startle reflex secondary to some form of cerebral damage is probably quite rare. Causes which have been reported include brainstem as well as cerebral damage (72, 75, 77, 78, 80, 82-84, 86, 89, 91, 92). A few symptomatic patients are reported to fall during startle, but it remained elusive whether this was actually due to stiffness or to the

extreme startle movement itself. We would prefer to label these patients as having symptomatic excessive startle reflexes.

The choice of treatment of hyperekplexia is clonazepam, which shows the most consistent effects (54, 55, 60, 107). A double-blind placebo-controlled study has shown a favorable effect of clonazepam on the magnitude of motor startle reflexes and the stiffness (107). Clonazepam has also been reported to be an effective treatment in a case of hyperekplexia due to a GlyT2 mutation, diminishing the excessive startling as well as anxiety symptoms (108). Several other drugs have been tried with contrasting results, mainly concerning case reports.

Startle reflex in hyperekplexia

The afferent and efferent system of the startle reflex in hyperekplexia is identical with that of the startle reflex in healthy subjects involving the same generator in the lower brainstem (47, 68, 109). However, a few differences distinguish the startle reflex of hyperekplexia from the normal startle reflex; the startle reflexes show abnormal short latencies (20-90 ms) (47, 109). Further, the motor responses are larger and EMG burst durations of the orbicularis oculi and sternocleidomastoid muscles are prolonged compared to control values (43, 47, 68, 85, 109). Head-retraction responses measures showed latencies of < 25 ms in cranial muscles (47) and 15-20 ms in the trapezius muscle (85). Discrepant results have been reported regarding the habituation of the startle reflex in hyperekplexia. Earlier studies describe a lack of habituation in hyperekplexia (47, 68), while Tijssen *et al.* (109) found a normal startle habituation in eight GLRA1 gene mutation positive patients. Possible explanations for this discrepancy lie in the heterogenic composition of the patient group, which in some reports included patients without the GLRA 1 gene mutation (68, 70). An alternative explanation is the definition of habituation (47).The amplitude of the psychogalvanic response, a measure of the autonomic responses, was increased in hyperekplexia, indicating that the startle reflex is not restricted to a motor response (109).

Genetics in hyperekplexia

Hyperekplexia is an inheritable disorder with mutations in different parts of the inhibitory glycine receptor (GlyR), located in the postsynaptic membrane of glycinergic and mixed GABAergic/glycinergic neurons. Glycine receptors are ligand-gated chloride channels that cause postsynaptic hyperpolarization and synaptic inhibition in the brainstem and spinal cord.

The alpha1 subunit of the glycine receptor (GLRA1) is the main gene for hyperekplexia. Dominant, recessive and compound heterozygote mutations are identified. This gene

is affected in about 80% of all hyperekplexia pedigrees and may be regarded the most important element of autosomal dominant hereditary hyperekplexia (15, 51, 58, 60, 98, 101, 102, 110). Recessive mutations, as well as compound heterozygosity, in the GLRA1 gene have also been found in sporadic cases and a few hyperekplexia families (57, 60, 79, 94, 102, 103, 105, 106, 111, 112).

The second most important gene which accounts for hyperekplexia in about 20% of cases is the GlyT2 (SCL6A5) encoding the presynaptic sodium- and chloride-dependent glycine transporter 2 (96). Missense, nonsense and frameshift mutations in SLC6A5 have been described. The mode of inheritance in GlyT2 patients is recessive with compound heterozygosity in the majority of cases. Only in one family a dominant mutation was identified (113).

Genetic heterogeneity has been confirmed in very rare sporadic cases of hyperekplexia with mutations affecting other postsynaptic glycinergic proteins including the GlyR subunit (*GLRB*) (112), gephyrin (*GPHN*) (114) and RhoGEF collybistin (*ARHGEF9*) (115). No genotype-phenotype correlations were found in genetically proven hyperekplexia. GlyT2 (SLC6A5) mutations could possibly give rise to a higher risk of tonic neonatal cyanosis and sudden infant death (SIDS) (47).

Taken it all together, in clinical practice, in families with an autosomal dominant inheritance pattern, the initial screening should be in the GLRA1 gene. In sporadic cases the GlyT2 and subsequently, the GLRA1 gene should be screened. If tested negative, further genetic studies as described above can be performed.

Pathophysiology of hyperekplexia

The brainstem as the origin of the abnormal startle reflex in hyperekplexia is supported by convincing evidence (51). First of all, symptomatic excessive startling usually concerns brainstem damage (73, 75, 77, 78, 80, 82, 84, 86). Second, glycine receptors are concentrated in the brainstem and spinal cord in humans (51, 116). Thirdly, the latencies of EMG responses point towards a brainstem origin: the EMG latency of the sternocleidomastoid muscle following a tap to the head or face is less than 20 ms (47, 51, 85). The minimum delay in a cortical loop is 22.8 ms, shorter latencies would require a shorter loop (51, 117). Finally, eye movement recordings showed reduced peak velocity of horizontal saccadic eye movements in hyperekplexia patients which do suggest a brainstem origin (51, 118).

Despite the evidence supporting the hypothesis that the brainstem is the generator for excessive startling, some authors suggested a primarily cortical deficit causing

hyperekplexia. An argument in favor of this hypothesis is giant evoked potentials found in a very small proportion of hyperekplexia patients (119). In a magnetic resonance spectroscopy (MRS) study concerning patients without a GLRA1 gene mutation (120) frontal dysfunction was suggested. However an MRS study showed no such abnormalities in patients with a proven mutation in the GLRA1 gene (121). Backaveraging of the EEG-activity prior to the startle reaction showed no cortical correlate, virtually ruling out the possibility that the startle response is a primary cortical response (119, 122).

Hyperekplexia 'minor' form

The hyperekplexia 'minor' form was observed in relatives of patients suffering from hyperekplexia and therefore originally considered hereditary. However, hyperekplexia 'minor' form exists solely of excessive startling, no stiffness is involved (15). The exaggerated startle responses have been reported to start during childhood (54, 120, 123) or puberty (68) or remained unclear in some cases (69, 124). In one pedigree even only the 'minor' form of hyperekplexia was reported (67). Sporadic 'minor' cases form a heterogeneous group (76, 85, 87, 104) which can be best summarized as late-onset excessive startling without other neurological signs (85) or acquired idiopathic excessive startling.

In patients with the 'minor' form of hyperekplexia a substantial difference is seen in startle reflexes to usual hyperekplexia. The startle reflexes in the 'minor' form show longer latencies and do not habituate with repetitive stimuli (125). As measured by reciprocal inhibition of H-reflexes, the spinal motor excitability, was normal in the hyperekplexia 'minor' form (126), consistent with a lack of stiffness.

Several hypotheses have been opposed to explain how it is possible that cases with the 'minor' form without an affected gene can occur in the same families with cases with a gene defect (125). The prolonged latencies in the 'minor' form can be an indication of psychological factors that might be of influence on the exaggerated startle reflex (28, 127, 128). Patients with the 'minor' form may display a learned startle reflex by being exposed to family members with organic startle attacks. Another possibility is that excessive startling like the hyperekplexia 'minor' form may be much more common than previously thought (104). A proneness to startling might be present in the form of a genetic predisposition (54, 129). In this view, the 'minor' form may represent a common variant of the startle reflex, coincidentally found in some hyperekplexia families.

In conclusion, the 'minor' form of hyperekplexia was originally considered a different expression of the same gene defect (15). Clinical, genetic and neurophysiological research proved this to be untrue. The nature of the 'minor' form seems a heterogenic category that should be labeled as excessive startling, without a genetic relation to hyperekplexia.

Stimulus-induced disorders

An excessive response other than an excessive startle reflex can be evoked by a startling stimulus. These startle-triggered syndromes are classified as stimulus-induced disorders. The main disorders include startle epilepsy, progressive myoclonus epilepsy, cortical myoclonus, reticular myoclonus, stiff-person syndrome and other rare disorders (130-141). Startle epilepsy (usually an asymmetric tonic posturing) and stiff-man syndrome represent the more prolonged tonic activations resembling the rigidity in hyperekplexia. Cortical and reticular reflex myoclonus reflect brief stimulus-induced jerks resembling the exaggerated startle reflex in hyperekplexia. Electrophysiological features can help distinguish between the different disorders.

Startle epilepsy consists of an epileptic seizure induced by an unexpected stimulus (134, 141, 142). Usually, a startling stimulus precipitates a clinically asymmetric tonic seizure with an onset latency of about 50 ms in the affected muscles. Seizures predominantly involve upper limbs, although they can involve the neck and trunk or can be generalized. EMG activity shows myoclonic (<1ms) as well as tonic activity, lasting up to 60 seconds (141). This is in contrast with the more short latency jerks existing in hyperekplexia. Patients with startle epilepsy are commonly young and experiencing infantile cerebral hemiplegia or diffuse or localized static brain encephalopathy due to different causes.

Startle-induced stiffness is mainly seen in stiff-person syndrome (143-145). Stiff-person syndrome is characterized by progressive intermittent spasms and stiffness in the legs and axial lumbar area, lasting from seconds to minutes. The spasms are mainly induced by unexpected stimuli existing of muscle stretch of the head, neck or peri-oral region with onset latencies lasting from 40-110 ms in the axial lumbar area to 70-140 ms in the lower limbs (85, 138). The combination startle-induced falls and stiffness closely resembles hyperekplexia. The stiffness in stiff-person syndrome is nearly continuous, in contrast with stiffness in adult hyperekplexia which is transient and only occurs after a startle. A study of brainstem reflexes illustrated that reflex excitation is exaggerated and inhibition is attenuated in both stiff-man syndrome and familial hyperekplexia, indicating a pathophysiological relationship (85). In stiff-person syndrome continuous EMG activity is seen in paraspinal muscles (85, 138).

Exaggerated startle reflexes have been reported (138) revealing onset latencies and muscle recruitment similar to the normal startle reflex with higher excitability in axial and leg muscles. While the classic stiff-person syndrome is characterized by widespread rigidity, painful myoclonus, spasms and long tract and brainstem signs, the rare syndrome of 'jerky stiff man syndrome' has been described in which rigidity and brainstem myoclonus are present (133). In this case auditory stimulation elicited EMG responses travelling upwards through the brainstem and downwards through the spinal cord with similar latencies as the reticular reflex myoclonus.

The differential diagnosis of stimulus-induced jerks resembling the exaggerated startle reflex in hyperekplexia includes reticular and cortical reflex myoclonus (130, 131). Cortical reflex myoclonus is often (multi)focal and more distal than proximal located, whereas reticular myoclonus is more generalized. Further, the location of the generator is given by the recruitment order of the different muscles (146). Generalized cortical myoclonus shows a rostrocaudal recruitment: from the cranial-innervated muscles (onset latency 20-40 ms) down to the upper limbs (onset latency 50-60 ms) and lower limb muscles (onset latency 60-90 ms) with a duration of 10-50 ms (131, 147). Since reticular reflex myoclonus, as the startle reflex, is generated in the reticular formation of the brainstem which lies close to the accessory nerves, the first recruited muscle is the sternocleidomastoid or trapezius muscle, after which the signal is transmitted down the spinal cord to the upper and lower limbs (40-80 ms) and up the brainstem (masseter and facial muscles), lasting from 10-30 ms (130, 147). Reticular reflex myoclonus could possibly be distinguished from the startle reflex by the EMG onset latencies of the intrinsic hand and foot muscles, which are in reticular reflex myoclonus not delayed relative to more proximal limb muscles (8). However, it should be considered that this has been described in merely one patient. Whereas hyperekplexia is characterized by stimulus-sensitivity in the mantle area and the presence of tonic spasms, cortical myoclonus is usually induced by a muscle stretch of the affected body part, while reticular myoclonus stimulus-sensitivity is usually over the limbs. In reticular reflex as well as cortical myoclonus spontaneous and action-induced jerks occur between the induced jerks (130).

In progressive myoclonus epilepsy a combination of generalized myoclonic seizures and excessive startling has been reported due to different genetic mutations, each with its characteristic clinical picture (137).

The neurophysiological features of these different stimulus-induced disorders, as described above, are summarized in **table 1**.

	Startle epilepsy	Stiff-person syndrome	Cortical reflex myoclonus	Reticular reflex myoclonus	Normal startle reflex
Muscles involved	- asymmetric - predominantly upper limbs - sometimes neck/trunk - sometimes generalized	- mainly lumbar axial and leg muscles	- focal, multifocal or generalized - often distal - rostrocaudal recruitment	- generalized - recruitment up and down from lower brainstem	- generalized - recruitment up and down from lower brainstem
Duration	ranging from myoclonic (<1 s) to tonic seizures (up to minutes)	spasms lasting from seconds to minutes	10-50 ms	10-30 ms	250–300 ms
Onset latencies following an unexpected stimulus	- ± 50 ms in affected muscles	- lumbar axial muscles: 40-110 ms - lower limb muscles: 70-140 ms	- cranial muscles: 20-40 ms - upper limb muscles: 50-60 ms - lower limb muscles: 60-90 ms	- upper limbs: ± 40 ms - lower limbs: ± 80 ms	- facial/shoulder muscles: 20-60 ms - upper limbs: 60-100 ms - lower limbs: 90-120 ms

Table 1. *Stimulus-induced disorders and the normal startle reflex with their electrophysiological characteristics*

Other stimulus-induced disorders show heterogenic symptomatology. Patients with narcolepsy can have an excessive startle reflex (148), but experience weakness and not stiffness due to the startle reflex. In paroxysmal kinesiogenic choreoathetosis, movements are induced by a sudden stimulus, but the movements concern chorea or dystonia rather than a startle reflex (139). Incidentally, startle can induce a tic, however the startle reflex is not exaggerated in these patients (149). In Creutzfeldt-Jakob's disease (150), subacute sclerosing panencephalitis (137) and paraneoplastic syndromes other clinical features are more prominent than the exaggerated startle reflex.

In summary, the phenomenology and pathophysiology of stimulus-induced disorders is diverse and not all disorders show an exaggerated startle reflex. Of course a detailed history is an important indicator to guide to the right diagnosis, including videorecordings. Additional electrophysiological examination can distinguish cortical, reticular, stiff-man syndrome from each other and from an exaggerated startle reflex in hyperekplexia.

Neuropsychiatric startle syndromes

Neuropsychiatric startle syndromes develop later in life and are accompanied by symptoms in the fields of behavioral neurology or psychiatry. Among such disorders are anxiety disorders (29), hysterical jumps (127), psychogenic startle syndromes, Gilles de la Tourette syndrome (151) and various culture-specific syndromes.

In the psychophysiological literature the startle reflex is frequently operationalized as the response of the orbicularis oculi muscle (18). In a single study in children with anxiety disorders the startle reflex was measured over multiple muscles of the body (29). In contrast to several blink response studies in anxiety disordered children (2, 152-154) this study showed an exaggeration of the auditory startle reflex (29). This illustrates that measurement over multiple muscles is a better tool to detect auditory startle reflex abnormalities in anxiety disorders. As stated, the muscle activity in the orbicularis oculi consists of a non-habituating startle-induced blink reflex followed by EMG response which habituates and shows more resemblance to the activity in other muscles of the body following a startling stimulus. A comparison of blink response studies and polymyographic studies therefore is limited. For this reason we will focus in this review on studies including a multiple-muscle auditory startle reflex measurement.

Recently, studies with detailed neurophysiological analyses in anxiety disorders, including post-traumatic stress disorder (PTSD) have been performed (28, 29, 155). Clinically, exaggerated startle reflexes are acknowledged symptoms of the hyper-

arousal criterion of post-traumatic stress disorder (PTSD) (American Psychiatric Association 1994). Classification of other anxiety disorders such as generalized anxiety disorder and panic disorder also depends in part on a hyper-arousal criterion. However, while symptoms such as insomnia and irritability are generic anxiety symptoms, hyperstartling and hyper-vigilance are more characteristic of PTSD. Evidence is conflicting regarding the question whether the auditory startle reflex is in fact increased in patients with PTSD and other anxiety disorders (18, 71). A polymyographic EMG-study in PTSD showed a normal startle reflex with delayed latencies of the early motor startle reflex in PTSD patients. Further, a frequent occurrence of second 'late' motor response has been described in these patients together with an enlargement of the psychogalvanic reflex (28). In children with anxiety disorders increased startle reflexes and an enlarged psychogalvanic reflex was described. A follow up study showed that the auditory startle reflex normalized in children in which the anxiety symptoms significantly diminished following treatment (155). It seems that neuropsychiatric startle syndromes, especially anxiety disorders can be distinguished from other startle diseases as they represent a combination of a mildly increased 'early' reflex component of the startle response (not as excessive as in hyperekplexia) combined with an exaggeration of the second or orienting component.

Stimulus-evoked psychogenic jumps or jerks can be distinguished by neurophysiological observations: a mean onset latency of more than 100 ms, variable latencies to the onset of the stimulus with repetitive stimuli, and an inconsistent pattern of EMG activity (127, 128) . They resemble more or less voluntary stimulus-induced jerks in healthy volunteers mimicking an excessive startle reflex, in which a lack of consistency in the normal pattern of rostrocaudal muscle recruitment was also detected (127).

A clinically exaggerated startle reflex has been described as part of the Gilles de la Tourette syndrome (TS). TS is known for its motor and vocal tics, in association with obsessive-compulsive behavior and stereotyping. The phenomenology of tics includes premonitory feelings or sensations preceding the tic, temporarily suppress ability, suggestibility, and an increase with stress, and wax and wane with transient remissions. Symptoms in TS typically fluctuate in severity and change character within the same person (156). Complex socially inappropriate behavior (157) and disinhibition behavior (158) have been described in TS; these were supposed to represent a more general dysfunction of impulse control (157). Anxiety is common in TS patients (159, 160). Electrophysiological studies on the startle reflexes in TS showed contrasting results with enlarged EMG amplitudes and less habituation compared to controls in one study (151) , but in other studies no significant differences were detected (161, 162). One important feature of TS is that the abnormal motor behavior is due to an

internal urge and does not require any external stimuli. Tics however, may sometimes be triggered by external stimuli and have the appearance of an exaggerated startle response (8). Several neuroanatomical substrates have been described to take part in the pathophysiology of TS. It was illustrated by activation of frontostriatal circuits that frontal involvement maintained regulatory control over the semi-voluntary tics. Frontal lobe involvement combined with basal ganglia changes have frequently been described in TS (163).

Culture-specific syndromes in all its forms are described by Simons as 'startle-matching syndromes' (164). The common feature of these disorders is non-habituating hyperstartling, evoked by loud noises or by being poked forcefully in the side. Following a startle reflex various behavioral responses may be seen, including 'forced obedience', sometimes involving violent or humiliating acts, at the detriment of themselves and others. Echolalia, echopraxia and coprolalia are frequently mentioned. Such combination of a startle response and behavioral manifestations following a loud noise may also be seen in for example TS. The propensity for such responses is enhanced by anxiety and can even be seen in normal subjects in some circumstances (165). It is thought that this link is mediated by connections between the amygdala and startle mechanisms (166). The most extensive descriptions concern the 'Jumping Frenchmen of Maine' in the USA (51, 164, 167) and Latah in Indonesia and Malaysia (164, 168). Less is known about Myriachit in Siberia and other rare entities (164).

Up till now, no detailed physiological studies documenting the nature of the startle reflexes in these culture-specific startle-matching syndromes have been published. Because of the lack of pathophysiological clues, an ongoing debate developed focusing on whether these disorders are behavioral phenomena belonging in the cultural or anthropological realm (51, 169), or whether they represent a somatic neurological disorder in which the expression is prone to local cultural influences (51, 164). The etiology of the jumping phenomenon seems to be situational because of the type of response, the peculiar circumstances of onset, and clinical evolution (51, 129). For example, the onset of abnormalities in the 'Jumping Frenchmen of Maine' often coincided with the start of work as a lumberjack (51, 129). One argument favoring a somatic explanation is found in the striking similarities between these culture-specific disorders, occurring in different cultural settings and genetic distant populations. In this view a similar neurophysiological substrate is likely to be the cause (168), suggesting that cultural aspects color the expression of an underlying common abnormality of the startle reflex. The location of this abnormality may be the brainstem, as described to be the 'startle reflex generator' in hyperekplexia (51). An alternative site is the frontal lobe,

compatible with abnormal utilization and imitation behaviour, and with an exaggerated dependency on behavioral cues from the environment.

Our group conducted a neurophysiological study in a group of Latah patients in Indonesia (170). It was found that not only the early motor startle reflexes were increased, but also the late response, considered an expression of the orienting response, and its presence implies arousal and increased alertness towards startling stimuli (13, 171).

CONCLUSION

In summary, it is still difficult to unequivocally classify startle syndromes. Progress has been made in the past years. Together with a positive family history and a positive head-retraction response, hereditary hyperekplexia is very likely, so screening for the GLRA1 gene should be undertaken. If the GLRA1 gene shows no mutation in familial and sporadic cases of hyperekplexia screening of other genes, especially GlyT2 should be considered.

Polymyographical EMG investigation of the startle reflex in hyperekplexia, stimulus-induced disorders and neuropsychiatric syndromes can help to distinguish between these groups. In hyperekplexia an evidently enlarged initial motor startle reflex can be measured. Several neurophysiological features can distinguish stimulus-induced disorders from hyperekplexia. In neuropsychiatric startle syndromes prolonged latencies of the initial reflex and a high frequency of occurrence of a second 'late' orienting response in combination with abnormal behavioral features points towards a different etiology. The exact pathophysiology of the different neuropsychiatric startle syndromes remains a subject of debate. Various internal and external influences have been suggested to explain the various symptoms, ranging from mimicking behavior through increased arousal to familial and cultural influences. Future neurophysiological investigation will help to further delineate the etiology of these syndromes.

Search strategy and selection criteria

For this review we searched Pubmed between 1969 and February 2011 and references from relevant articles. The search terms "hyperekplexia", "startle disease", "glycine receptor", "GLRA1", "GlyT2", "startle", "startle reflex", "medication", "neuropsychiatric startle", "culture-specific startle" were used. The final reference list was based on its relevance of the topic of this review.

Acknowledgements
There are no conflicts of interest. YEM Dreissen wrote this review with assistance from MJ Bakker, JHTM Koelman and MAJ Tijssen. With special thanks to IFCN who helped to pay for travel expenses.

REFERENCES

1. Anthony BJ, Graham FK. Evidence for sensory-selective set in young infants. Science. 1983;220(4598):742-4.
2. Ornitz EM, Guthrie D, Kaplan AR, Lane SJ, Norman RJ. Maturation of startle modulation. Psychophysiology. 1986;23(6):624-34.
3. Wilkins DE, Hallett M, Wess MM. Audiogenic startle reflex of man and its relationship to startle syndromes. A review. Brain. 1986;109 (Pt 3):561-73.
4. Howard R, Ford R. From the jumping Frenchmen of Maine to post-traumatic stress disorder: the startle response in neuropsychiatry. PsycholMed. 1992;22(3):695-707.
5. Grillon C, Ameli R, Goddard A, Woods SW, Davis M. Baseline and fear-potentiated startle in panic disorder patients. BiolPsychiatry. 1994;35(7):431-9.
6. Balaban MT. Affective influences on startle in five-month-old infants: reactions to facial expressions of emotions. Child Dev. 1995;66(1):28-36.
7. Grillon C, Dierker L, Merikangas KR. Startle modulation in children at risk for anxiety disorders and/or alcoholism. JAmAcadChild AdolescPsychiatry. 1997;36(7):925-32.
8. Brown P, Rothwell JC, Thompson PD, Britton TC, Day BL, Marsden CD. New observations on the normal auditory startle reflex in man. Brain. 1991;114 (Pt 4):1891-902.
9. Jacobsen E. Response to a sudden unexpected stimulus. J ExpPsychol. 1926;9(1):19-25.
10. Strauss H. Das Zusammenschrecken: experimental Kinomatographische Studie zur Physiologie und Pathofysiologie der Reaktivbewegungen. Journal für Psychologie und Neurologie. 1929;39:111-232.
11. Landis C, Hunt CA. The startle pattern. New York: Farrar and Rinehart; 1939 1939.
12. Davis R. Motor effects of strong auditory stimuli. J ExpPsychol. 1948;38:257-75.
13. Gogan P. The startle and orienting reactions in man. A study of their characteristics and habituation. Brain Res. 1970;18(1):117-35.
14. Jones FP, Kennedy JL. An electromyographic technique for recording the startle pattern. J Psychol. 1951;32:63-8.
15. Suhren O, Bruyn GW, A. T. Hyperexplexia, a hereditary startle syndrome. J Neurol Science. 1966;3:577-605.
16. Rossignol S. Startle responses recorded in the leg of man. Electroencephalogr-ClinNeurophysiol. 1975;39:389-97.
17. Fox JE. Excitatory and inhibitory components of the eyeblink responses to startle evoking stimuli, studied in the human subject. ElectroencephalogrClinNeurophysiol. 1977;44:490-501.
18. Grillon C, Baas J. A review of the modulation of the startle reflex by affective states and its application in psychiatry. ClinNeurophysiol. 2003;114(9):1557-79.
19. Pavlov I. Conditioned reflexes. London:Oxford1927 1927.
20. Davis R. The muscular tension reflex and two of its modifying conditions. Science series. 1935;3:21.

21. Sokolov. Perception and the conditioned reflex. Elmsford, NY: Pergamon press; 1963 1963.
22. Kofler M, Muller J, Reggiani L, Valls-Sole J. Influence of age on auditory startle responses in humans. NeurosciLett. 2001;307(2):65-8.
23. Kofler M, Muller J, Reggiani L, Valls-Sole J. Influence of gender on auditory startle responses. Brain Res. 2001;921(1-2):206-10.
24. Bakker MJ, Boer F, van der Meer JN, Koelman JH, Boeree T, Bour L, et al. Quantification of the auditory startle reflex in children. ClinNeurophysiol. 2009;120(2):424-30.
25. Arunodaya GR, Taly AB. Sympathetic skin response: a decade later. JNeurol Sci. 1995;129(2):81-9.
26. Claus D, Schondorf R. Sympathetic skin response. The International Federation of Clinical Neurophysiology. ElectroencephalogrClinNeurophysiolSuppl. 1999;52:277-82.
27. Fowles DC, Christie MJ, Edelberg R, Grings WW, Lykken DT, Venables PH. Committee report. Publication recommendations for electrodermal measurements. Psychophysiology. 1981;18(3):232-9.
28. Siegelaar SE, Olff M, Bour LJ, Veelo D, Zwinderman AH, van BG, et al. The auditory startle response in post-traumatic stress disorder. ExpBrain Res. 2006;174(1):1-6.
29. Bakker MJ, Tijssen MA, van der Meer JN, Koelman JH, Boer F. Increased whole-body auditory startle reflex and autonomic reactivity in children with anxiety disorders. JPsychiatry Neurosci. 2009;34(4):314-22.
30. Lykken DT, Rose R, Luther B, Maley M. Correcting psychophysiological measures for individual differences in range. PsycholBull. 1966;66(6):481-4.
31. Lykken DT. Range correction applied to heart rate and to GSR data. Psychophysiology. 1972;9(3):373-9.
32. Rogeness GA, Cepeda C, Macedo CA, Fischer C, Harris WR. Differences in heart rate and blood pressure in children with conduct disorder, major depression, and separation anxiety. Psychiatry Res. 1990;33(2):199-206.
33. Chokroverty S, Walczak T, Hening W. Human startle reflex: technique and criteria for abnormal response. ElectroencephalogrClinNeurophysiol. 1992;85(4):236-42.
34. Edinger, Fischer. Ein Mensch ohne Grosshirn. ArchfdgesPhysiol. 1913;152:535-62.
35. Leitner DS, Powers AS, Hoffman HS. The neural substrate of the startle response. Physiol Behav. 1980;25(2):291-7.
36. Davis M, Gendelman DS, Tischler MD, Gendelman PM. A primary acoustic startle circuit: lesion and stimulation studies. JNeurosci. 1982;2(6):791-805.
37. Lingenhohl K, Friauf E. Giant neurons in the rat reticular formation: a sensorimotor interface in the elementary acoustic startle circuit? JNeurosci. 1994;14(3 Pt 1):1176-94.
38. Lee Y, Lopez DE, Meloni EG, Davis M. A primary acoustic startle pathway: obligatory role of cochlear root neurons and the nucleus reticularis pontis caudalis. JNeurosci. 1996;16(11):3775-89.
39. Yeomans JS, Frankland PW. The acoustic startle reflex: neurons and connections. Brain ResBrain ResRev. 1995;21(3):301-14.

40. Davis M. Differential roles of the amygdala and bed nucleus of the stria terminalis in conditioned fear and startle enhanced by corticotropin-releasing hormone. Perception, memory and emotion. Oxford: Elsevier Ltd; 1996. p. 525-48.
41. Koch M. The neurobiology of startle. ProgNeurobiol. 1999;59(2):107-28.
42. Valls-Sole J, Kumru H, Kofler M. Interaction between startle and voluntary reactions in humans. ExpBrain Res. 2008;187(4):497-507.
43. Oguro K, Hirano K, Aiba H. Trigeminally induced startle in children with hyperekplexia. Mov Disord. 2005;20(4):484-9.
44. Hori A, Yasuhara A, Naito H, Yasuhara M. Blink reflex elicited by auditory stimulation in the rabbit. JNeurolSci. 1986;76(1):49-59.
45. Lang PJ, Bradley MM, Cuthbert BN. Emotion, attention, and the startle reflex. PsycholRev. 1990;97(3):377-95.
46. Brown P, Day BL, Rothwell JC, Thompson PD, Marsden CD. The effect of posture on the normal and pathological auditory startle reflex. JNeurolNeurosurgPsychiatry. 1991;54(10):892-7.
47. Matsumoto J, Fuhr P, Nigro M, Hallett M. Physiological abnormalities in hereditary hyperekplexia. AnnNeurol. 1992;32(1):41-50.
48. Ho KJ, Kileny P, Paccioretti D, McLean DR. Neurologic, audiologic, and electrophysiologic sequelae of bilateral temporal lobe lesions. ArchNeurol. 1987;44(9):982-7.
49. Liegeois-Chauvel C, Morin C, Musolino A, Bancaud J, Chauvel P. Evidence for a contribution of the auditory cortex to audiospinal facilitation in man. Brain. 1989;112 (Pt 2):375-91.
50. Vrana SR, Spence EL, Lang PJ. The startle probe response: a new measure of emotion? JAbnormPsychol. 1988;97(4):487-91.
51. Bakker MJ, van Dijk JG, van den Maagdenberg AM, Tijssen MA. Startle syndromes. Lancet Neurol. 2006;5(6):513-24.
52. Kirstein L, Silfverskiold B. A family with emotionally precipitated drop seizures. Acta PsychiatrNeurolScand. 1958;33(4):471-6.
53. Tijssen MA, Shiang R, van DJ, Boerman RH, Wasmuth JJ, Sandkuijl LA, et al. Molecular genetic reevaluation of the Dutch hyperekplexia family. ArchNeurol. 1995;52(6):578-82.
54. Andermann F, Keene DL, Andermann E, Quesney LF. Startle disease or hyperekplexia: further delineation of the syndrome. Brain. 1980;103(4):985-97.
55. Saenz-Lope E, Herranz-Tanarro FJ, Masdeu JC, Chacon Pena JR. Hyperekplexia: a syndrome of pathological startle responses. AnnNeurol. 1984;15(1):36-41.
56. Hayashi T, Tachibana H, Kajii T. Hyperekplexia: pedigree studies in two families. AmJMedGenet. 1991;40(2):138-43.
57. Rees MI, Andrew M, Jawad S, Owen MJ. Evidence for recessive as well as dominant forms of startle disease (hyperekplexia) caused by mutations in the alpha 1 subunit of the inhibitory glycine receptor. HumMolGenet. 1994;3(12):2175-9.

58. del Giudice EM, Coppola G, Bellini G, Cirillo G, Scuccimarra G, Pascotto A. A mutation (V260M) in the middle of the M2 pore-lining domain of the glycine receptor causes hereditary hyperekplexia. EurJHumGenet. 2001;9(11):873-6.
59. Zhou L, Chillag KL, Nigro MA. Hyperekplexia: a treatable neurogenetic disease. Brain Dev. 2002;24(7):669-74.
60. Tsai CH, Chang FC, Su YC, Tsai FJ, Lu MK, Lee CC, et al. Two novel mutations of the glycine receptor gene in a Taiwanese hyperekplexia family. Neurology. 2004;63(5):893-6.
61. Siren A, Legros B, Chahine L, Misson JP, Pandolfo M. Hyperekplexia in Kurdish families: a possible GLRA1 founder mutation. Neurology. 2006;67(1):137-9.
62. Forsyth RJ, Gika AD, Ginjaar I, Tijssen MA. A novel GLRA1 mutation in a recessive hyperekplexia pedigree. Mov Disord. 2007;22(11):1643-5.
63. Masri AT, Hamamy HA. Clinical and inheritance profiles of hyperekplexia in Jordan. JChild Neurol. 2007;22(7):895-900.
64. Doria LL, Giribaldi G, De NE, Follo R, De GE, Pintaudi M, et al. A case of major form familial hyperekplexia: prenatal diagnosis and effective treatment with clonazepam. JChild Neurol. 2007;22(6):769-72.
65. Gregory ML, Guzauskas GF, Edgar TS, Clarkson KB, Srivastava AK, Holden KR. A novel GLRA1 mutation associated with an atypical hyperekplexia phenotype. JChild Neurol. 2008;23(12):1433-8.
66. Al-Owain M, Colak D, Al-Bakheet A, Al-Hashmi N, Shuaib T, Al-Hemidan A, et al. Novel mutation in GLRB in a large family with hereditary hyperekplexia. ClinGenet. 2011;81:479-84.
67. Dooley JM, Andermann F. Startle disease or hyperekplexia: adolescent onset and response to valproate. PediatrNeurol. 1989;5(2):126-7.
68. Brown P, Rothwell JC, Thompson PD, Britton TC, Day BL, Marsden CD. The hyperekplexias and their relationship to the normal startle reflex. Brain. 1991;114 (Pt 4):1903-28.
69. Pascotto A, Coppola G. Neonatal hyperekplexia: a case report. Epilepsia. 1992;33(5):817-20.
70. Tijssen MA, Vergouwe MN, van Dijk JG, Rees M, Frants RR, Brown P. Major and minor form of hereditary hyperekplexia. Mov Disord. 2002;17(4):826-30.
71. Duensing F. Schreckreflex und schreckreaktion als hirnorganische zeichen. Arch Psychiatr Nervenkr. 1952;188:162-92.
72. Fariello RG, Schwartzman RJ, Beall SS. Hyperekplexia exacerbated by occlusion of posterior thalamic arteries. ArchNeurol. 1983;40(4):244-6.
73. Shibasaki H, Kakigi R, Oda K, Masukawa S. Somatosensory and acoustic brain stem reflex myoclonus. JNeurolNeurosurgPsychiatry. 1988;51(4):572-5.
74. Vergouwe MN, Tijssen MA, Shiang R, van Dijk JG, al SS, Ophoff RA, et al. Hyperekplexia-like syndromes without mutations in the GLRA1 gene. ClinNeurolNeurosurg. 1997;99(3):172-8.
75. Kellett MW, Humphrey PR, Tedman BM, Steiger MJ. Hyperekplexia and trismus due to brainstem encephalopathy. JNeurolNeurosurgPsychiatry. 1998;65(1):122-5.

76. Sechi G, Sotgiu S, Valenti MP, Pitzolu MG, Peterlongo P, Larizza L, et al. Beneficial effect of fluoxetine in a case of sporadic hyperekplexia. ClinNeuropharmacol. 2000;23(3):161-3.
77. Salvi F, Mascalchi M, Bortolotti C, Meletti S, Plasmati R, Rubboli G, et al. Hypertension, hyperekplexia, and pyramidal paresis due to vascular compression of the medulla. Neurology. 2000;55(9):1381-4.
78. Chaves-Vischer V, Pizzolato GP, Hanquinet S, Maret A, Bottani A, Haenggeli CA. Early fatal pontocerebellar hypoplasia in premature twin sisters. EurJPaediatrNeurol. 2000;4(4):171-6.
79. Rees MI, Lewis TM, Vafa B, Ferrie C, Corry P, Muntoni F, et al. Compound heterozygosity and nonsense mutations in the alpha(1)-subunit of the inhibitory glycine receptor in hyperekplexia. HumGenet. 2001;109(3):267-70.
80. Watson SR, Colebatch JG. Focal pathological startle following pontine infarction. Mov Disord. 2002;17(1):212-8.
81. Ruprecht K, Warmuth-Metz M, Waespe W, Gold R. Symptomatic hyperekplexia in a patient with multiple sclerosis. Neurology. 2002;58(3):503-4.
82. Goraya JS, Shah D, Poddar B. Hyperekplexia in a girl with posterior fossa malformations. JChild Neurol. 2002;17(2):147-9.
83. Zhai P, Pagan F, Statland J, Butman JA, Floeter MK. Primary lateral sclerosis: A heterogeneous disorder composed of different subtypes? Neurology. 2003;60(8):1258-65.
84. Kofler M, Muller J, Seppi K, Wenning GK. Exaggerated auditory startle responses in multiple system atrophy: a comparative study of parkinson and cerebellar subtypes. ClinNeurophysiol. 2003;114(3):541-7.
85. Khasani S, Becker K, Meinck HM. Hyperekplexia and stiff-man syndrome: abnormal brainstem reflexes suggest a physiological relationship. JNeurolNeurosurgPsychiatry. 2004;75(9):1265-9.
86. Jankelowitz SK, Colebatch JG. The acoustic startle reflex in ischemic stroke. Neurology. 2004;62(1):114-6.
87. Hamelin S, Rohr P, Kahane P, Minotti L, Vercueil L. Late onset hyperekplexia. EpilepticDisord. 2004;6(3):169-72.
88. Shahar E, Raviv R. Sporadic major hyperekplexia in neonates and infants: clinical manifestations and outcome. PediatrNeurol. 2004;31(1):30-4.
89. Gaitatzis A, Kartsounis LD, Gacinovic S, Costa DC, Harvey K, Harvey RJ, et al. Frontal lobe dysfunction in sporadic hyperekplexia--case study and literature review. JNeurol. 2004;251(1):91-8.
90. Rivera S, Villega F, de Saint-Martin A, Matis J, Escande B, Chaigne D, et al. Congenital hyperekplexia: five sporadic cases. EurJPediatr. 2006;165(2):104-7.
91. Vetrugno R, Mascalchi M, Vella A, Della NR, Guerrini L, Vattimo A, et al. Pontine hyperperfusion in sporadic hyperekplexia. JNeurolNeurosurgPsychiatry. 2007;78(9):1001-4.
92. van de Warrenburg BP, Cordivari C, Brown P, Bhatia KP. Persisting hyperekplexia after idiopathic, self-limiting brainstem encephalopathy. Mov Disord. 2007;22(7):1017-20.

93. Koning-Tijssen MA, Brouwer OF. Hyperekplexia in the first year of life. Mov Disord. 2000;15(6):1293-6.

94. Miraglia del GE, Coppola G, Bellini G, Ledaal P, Hertz JM, Pascotto A. A novel mutation (R218Q) at the boundary between the N-terminal and the first transmembrane domain of the glycine receptor in a case of sporadic hyperekplexia. JMedGenet. 2003;40(5):e71.

95. Vigevano F, Di CM, Dalla BB. Startle disease: an avoidable cause of sudden infant death. Lancet. 1989;1(8631):216.

96. Rees MI, Harvey K, Pearce BR, Chung SK, Duguid IC, Thomas P, et al. Mutations in the gene encoding GlyT2 (SLC6A5) define a presynaptic component of human startle disease. NatGenet. 2006;38(7):801-6.

97. Shahar E, Brand N, Uziel Y, Barak Y. Nose tapping test inducing a generalized flexor spasm: a hallmark of hyperexplexia. Acta PaediatrScand. 1991;80(11):1073-7.

98. Bernasconi A, Cendes F, Shoubridge EA, Andermann E, Li LM, Arnold DL, et al. Spectroscopic imaging of frontal neuronal dysfunction in hyperekplexia. Brain. 1998;121 (Pt 8):1507-12.

99. Shimamura M. New developments in electromyography and clinical neurophysiology. Basel: Karger1973 1973.

100. Oguro K, Aiba H, Hojo H. Different responses to auditory and somaesthetic stimulation in patients with an excessive startle: a report of pediatric experience. ClinNeurophysiol. 2001;112(7):1266-72.

101. Ryan SG, Sherman SL, Terry JC, Sparkes RS, Torres MC, Mackey RW. Startle disease, or hyperekplexia: response to clonazepam and assignment of the gene (STHE) to chromosome 5q by linkage analysis. AnnNeurol. 1992;31(6):663-8.

102. Vergouwe MN, Tijssen MA, Peters AC, Wielaard R, Frants RR. Hyperekplexia phenotype due to compound heterozygosity for GLRA1 gene mutations. AnnNeurol. 1999;46(4):634-8.

103. Coto E, Armenta D, Espinosa R, Argente J, Castro MG, Alvarez V. Recessive hyperekplexia due to a new mutation (R100H) in the GLRA1 gene. Mov Disord. 2005;20(12):1626-9.

104. Gastaut H, Villeneuve A. The startle disease or hyperekplexia. Pathological surprise reaction. JNeurolSci. 1967;5(3):523-42.

105. Brune W, Weber RG, Saul B, von Knebel DM, Grond-Ginsbach C, Kellerman K, et al. A GLRA1 null mutation in recessive hyperekplexia challenges the functional role of glycine receptors. AmJHumGenet. 1996;58(5):989-97.

106. Kwok JB, Raskin S, Morgan G, Antoniuk SA, Bruk I, Schofield PR. Mutations in the glycine receptor alpha1 subunit (GLRA1) gene in hereditary hyperekplexia pedigrees: evidence for non-penetrance of mutation Y279C. JMedGenet. 2001;38(6):E17.

107. Tijssen MA, Schoemaker HC, Edelbroek PJ, Roos RA, Cohen AF, van Dijk JG. The effects of clonazepam and vigabatrin in hyperekplexia. JNeurolSci. 1997;149(1):63-7.

108. Bakker MJ, Peeters EA, Tijssen MA. Clonazepam is an effective treatment for hyperekplexia due to a SLC6A5 (GlyT2) mutation. Mov Disord. 2009;24(12):1852-4.

109. Tijssen MA, Voorkamp LM, Padberg GW, van Dijk JG. Startle responses in hereditary hyperekplexia. ArchNeurol. 1997;54(4):388-93.

110. Davies JS, Chung SK, Thomas RH, Robinson A, Hammond CL, Mullins JG, et al. The glycinergic system in human startle disease: a genetic screening approach. Front MolNeurosci. 2010;3:8.

111. Humeny A, Bonk T, Becker K, Jafari-Boroujerdi M, Stephani U, Reuter K, et al. A novel recessive hyperekplexia allele GLRA1 (S231R): genotyping by MALDI-TOF mass spectrometry and functional characterisation as a determinant of cellular glycine receptor trafficking. EurJHumGenet. 2002;10(3):188-96.

112. Rees MI, Lewis TM, Kwok JB, Mortier GR, Govaert P, Snell RG, et al. Hyperekplexia associated with compound heterozygote mutations in the beta-subunit of the human inhibitory glycine receptor (GLRB). HumMolGenet. 2002;11(7):853-60.

113. Harvey RJ, Topf M, Harvey K, Rees MI. The genetics of hyperekplexia: more than startle! Trends Genet. 2008;24(9):439-47.

114. Rees MI, Harvey K, Ward H, White JH, Evans L, Duguid IC, et al. Isoform heterogeneity of the human gephyrin gene (GPHN), binding domains to the glycine receptor, and mutation analysis in hyperekplexia. JBiolChem. 2003;278(27):24688-96.

115. Harvey K, Duguid IC, Alldred MJ, Beatty SE, Ward H, Keep NH, et al. The GDP-GTP exchange factor collybistin: an essential determinant of neuronal gephyrin clustering. JNeurosci. 2004;24(25):5816-26.

116. Shiang R, Ryan SG, Zhu YZ, Fielder TJ, Allen RJ, Fryer A, et al. Mutational analysis of familial and sporadic hyperekplexia. AnnNeurol. 1995;38(1):85-91.

117. Brown P. Neurophysiology of the startle syndrome and hyperekplexia. AdvNeurol. 2002;89:153-9.

118. Tijssen MA, Bollen E, van EE, van Dijk JG. Saccadic eye movements in hyperekplexia. Mov Disord. 1995;10(6):749-53.

119. Markand ON, Garg BP, Weaver DD. Familial startle disease (hyperexplexia). Electrophysiologic studies. ArchNeurol. 1984;41(1):71-4.

120. Bernasconi A, Regli F, Schorderet DF, Pescia G. [Familial hyperekplexia: startle disease. Clinical, electrophysiological and genetic study of a family]. RevNeurol(Paris). 1996;152(6-7):447-50.

121. Tijssen MA, Brown P, MacManus D, McLean MA, Davie C. Magnetic resonance spectroscopy of cerebral cortex is normal in hereditary hyperekplexia due to mutations in the GLRA1 gene. Mov Disord. 2003;18(12):1538-41.

122. Morley DJ, Weaver DD, Garg BP, Markand O. Hyperexplexia: an inherited disorder of the startle response. ClinGenet. 1982;21(6):388-96.

123. Milani N, Dalpra L, del PA, Zanini R, Larizza L. A novel mutation (Gln266-->His) in the alpha 1 subunit of the inhibitory glycine-receptor gene (GLRA1) in hereditary hyperekplexia. AmJHumGenet. 1996;58(2):420-2.

124. Saul B, Kuner T, Sobetzko D, Brune W, Hanefeld F, Meinck HM, et al. Novel GLRA1 missense mutation (P250T) in dominant hyperekplexia defines an intracellular determinant of glycine receptor channel gating. JNeurosci. 1999;19(3):869-77.

125. Tijssen MA, Padberg GW, van Dijk JG. The startle pattern in the minor form of hyperekplexia. ArchNeurol. 1996;53(7):608-13.

126. Crone C, Nielsen J, Petersen N, Tijssen MA, van Dijk JG. Patients with the major and minor form of hyperekplexia differ with regards to disynaptic reciprocal inhibition between ankle flexor and extensor muscles. ExpBrain Res. 2001;140(2):190-7.

127. Thompson PD, Colebatch JG, Brown P, Rothwell JC, Day BL, Obeso JA, et al. Voluntary stimulus-sensitive jerks and jumps mimicking myoclonus or pathological startle syndromes. Movement Disorders. 1992;7(3).

128. Brown P, Thompson PD. Electrophysiological aids to the diagnosis of psychogenic jerks, spasms, and tremor. Mov Disord. 2001;16(4):595-9.

129. Saint-Hilaire MH, Saint-Hilaire JM. Jumping Frenchmen of Maine. Mov Disord. 2001;16(3):530.

130. Hallett M, Chadwick D, Adam J, Marsden CD. Reticular reflex myoclonus: a physiological type of human post-hypoxic myoclonus. JNeurol NeurosurgPsychiatry. 1977;40(3):253-64.

131. Hallett M, Chadwick D, Marsden CD. Cortical reflex myoclonus. Neurology. 1979;29(8):1107-25.

132. Alfrey D, Rauscher L. Tetanus: a review. Crit Care Med. 1979;7:176-81.

133. Leigh PN, Rothwell JC, Traub M, Marsden CD. A patient with reflex myoclonus and muscle rigidity: "jerking stiff-man syndrome". JNeurol NeurosurgPsychiatry. 1980;43(12):1125-31.

134. Saenz L, Herranz F., J. M. Startle epilepsy: a clinical study. AnnNeurol. 1984(16):78-81.

135. Goutieres F, Aicardi J. Atypical presentations of pyridoxine-dependent seizures: a treatable cause of intractable epilepsy in infants. AnnNeurol. 1985;17(2):117-20.

136. Tohier C, Roze JC, David A, Veccierini MF, Renaud P, Mouzard A. Hyperexplexia or stiff baby syndrome. Arch DisChild. 1991;66(4):460-1.

137. Aicardi J. Diseases of the nervous system in childhood. Suffolk: the Lavenham Press Ltd.1992 1992.

138. Matsumoto JY, Caviness JN, McEvoy KM. The acoustic startle reflex in stiff-man syndrome. Neurology. 1994;44(10):1952-5.

139. Bhatia KP. The paroxysmal dyskinesias. JNeurol. 1999;246(3):149-55.

140. Valls-Sole J, Rothwell JC, Goulart F, Cossu G, Munoz E. Patterned ballistic movements triggered by a startle in healthy humans. JPhysiol. 1999;516 (Pt 3):931-8.

141. Tibussek D, Wohlrab G, Boltshauser E, Schmitt B. Proven startle-provoked epileptic seizures in childhood: semiologic and electrophysiologic variability. Epilepsia. 2006;47(6):1050-8.

142. Yang Z, Liu X, Qin J, Zhang Y, Bao X, Wang S, et al. Clinical and electrophysiological characteristics of startle epilepsy in childhood. ClinNeurophysiol. 2010;121(5):658-64.

143. Gordon EE, Januszko DM, Kaufman L. A critical survey of stiff-man syndrome. AmJMed. 1967;42(4):582-99.

144. Lorish TR, Thorsteinsson G, Howard FM, Jr. Stiff-man syndrome updated. Mayo ClinProc. 1989;64(6):629-36.

145. Brown P, Marsden CD. The stiff man and stiff man plus syndromes. JNeurol. 1999;246(8):648-52.

146. Cassim F, Houdayer E. Neurophysiology of myoclonus. NeurophysiolClin. 2006;36(5-6):281-91.

147. Brown P, Thompson PD, Rothwell JC, Day BL, Marsden CD. A case of postanoxic encephalopathy with cortical action and brainstem reticular reflex myoclonus. Mov Disord. 1991;6(2):139-44.

148. Lammers GJ, Overeem S, Tijssen MA, van Dijk JG. Effects of startle and laughter in cataplectic subjects: a neurophysiological study between attacks. ClinNeurophysiol. 2000;111(7):1276-81.

149. Tijssen MA, Brown P, Morris HR, Lees A. Late onset startle induced tics. JNeurolNeurosurgPsychiatry. 1999;67(6):782-4.

150. Matthews W. Recent advances in clinical neurology. Edinburgh: Churchill Livingstone1982 1982.

151. Gironell A, Rodriguez-Fornells A, Kulisevsky J, Pascual B, Riba J, Barbanoj M, et al. Abnormalities of the acoustic startle reflex and reaction time in gilles de la tourette syndrome. ClinNeurophysiol. 2000;111(8):1366-71.

152. Schmidt LA, Fox NA, Schulkin J, Gold PW. Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. DevPsychobiol. 1999;35(2):119-35.

153. Lipschitz DS, Mayes LM, Rasmusson AM, Anyan W, Billingslea E, Gueorguieva R, et al. Baseline and modulated acoustic startle responses in adolescent girls with posttraumatic stress disorder. JAmAcadChild AdolescPsychiatry. 2005;44(8):807-14.

154. Waters AM, Craske MG, Bergman RL, Naliboff BD, Negoro H, Ornitz EM. Developmental changes in startle reactivity in school-age children at risk for and with actual anxiety disorder. IntJPsychophysiol. 2008;70(3):158-64.

155. Bakker MJ, Tijssen MA, Koelman JH, Boer F. Normalization of the auditory startle reflex after symptom reduction in children with anxiety disorders. JPsychiatr Res. 2010.

156. Robertson MM. Tourette syndrome, associated conditions and the complexities of treatment. Brain. 2000;123 Pt 3:425-62.

157. Kurlan R, Daragjati C, Como PG, McDermott MP, Trinidad KS, Roddy S, et al. Non-obscene complex socially inappropriate behavior in Tourette's syndrome. JNeuropsychiatry ClinNeurosci. 1996;8(3):311-7.

158. Cohen AJ, Leckman JF. Sensory phenomena associated with Gilles de la Tourette's syndrome. JClinPsychiatry. 1992;53(9):319-23.

159. Robertson MM. Annotation: Gilles de la Tourette syndrome--an update. JChild PsycholPsychiatry. 1994;35(4):597-611.

160. Robertson MM, Stern JS. The Gilles de la Tourette syndrome. Crit RevNeurobiol. 1997;11(1):1-19.

161. Stell R, Thickbroom GW, Mastaglia FL. The audiogenic startle response in Tourette's syndrome. Mov Disord. 1995;10(6):723-30.

162. Sachdev PS, Chee KY, Aniss AM. The audiogenic startle reflex in Tourette's syndrome. BiolPsychiatry. 1997;41(7):796-803.

163. Mazzone L, Yu S, Blair C, Gunter BC, Wang Z, Marsh R, et al. An FMRI study of frontostriatal circuits during the inhibition of eye blinking in persons with Tourette syndrome. AmJPsychiatry. 2010;167(3):341-9.

164. Simons R. Boo! culture, experience and the startle reflex. Oxford (UK): University press; 1996 1996.

165. Thompson PD. The Phenomenology of Startle, Latah, and Related Conditions. Psychogenic Movement Disorders. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 48-52.

166. Hitchcock JM, Davis M. Efferent pathway of the amygdala involved in conditioned fear as measured with the fear-potentiated startle paradigm. BehavNeurosci. 1991;105(6):826-42.

167. Saint-Hilaire MH, Saint-Hilaire JM, Granger L. Jumping Frenchmen of Maine. Neurology. 1986;36(9):1269-71.

168. Tanner CM, Chamberland J. Latah in Jakarta, Indonesia. Mov Disord. 2001;16(3):526-9.

169. Bartholomew RE. Disease, disorder, or deception? Latah as habit in a Malay extended family. JNervMentDis. 1994;182(6):331-8.

170. Bakker MJ, van Dijk JG, Pramono A, Sutarni S, Tijssen MA. Latah: an Indonesian startle syndrome. Mov Disord. 2013;28(3):370-9.

171. Orr SP, Metzger LJ, Pitman RK. Psychophysiology of post-traumatic stress disorder. Psychiatr ClinNorth Am. 2002;25(2):271-93.

Startle responses in functional jerky movement disorders are increased but have a normal pattern

7

Yasmine EM Dreissen, Thijs Boeree, Johannes HTM Koelman & Marina AJ Tijssen

Article published in Parkinsonism and related disorders 2017 doi: 10.1016/j.parkreldis.2017.04.001

ABSTRACT

Background: Exaggerated startle reactions have been frequently described in patients with functional movement disorders (FMD). An inconsistent recruitment pattern and long onset latencies are thought to be a hallmark. Differentiation of the early (motor) and late (orienting) components of the startle reflex have not been systematically addressed.

Objectives: Assessing the size and pattern of the early and late component of the auditory startle response in patients with functional jerky movement disorders.

Methods: A case-control design was used to study 17 patients with functional jerky movement disorders and 15 healthy gender- and age-matched control subjects. The auditory startle reflex was elicited by 108 dB loud tones and assessed with electromyography in multiple muscles.

Results: Response probability of the early and the late response were significantly enlarged in patients with FMD. The early response showed a normal muscle recruitment pattern whereas the late response revealed a more variable pattern compared to controls. Both early and late responses showed a normal habituation pattern in both groups. Remarkably, a high response rate of the abdominal muscle was noted especially in patients suffering from abdominal jerks.

Conclusions: This study shows that FMD patients reveal enlarged, but normally patterned early startle responses. The variable recruitment pattern of the late response found in these patients is compatible with the behavioral component of this orienting phase and has been described in other neuropsychiatric startle syndromes. Hypersensitivity to external stimuli, often noted in FMD is supported by the enlargement of both components of the startle response.

INTRODUCTION

Functional (psychogenic) movement disorders (FMD) refer to a heterogeneous category of movement disorders not caused by a known underlying neurological disease (1). They are commonly seen in daily neurological practice and jerky movements are one of the most prevalent (15%) phenomenologies (2, 3).

The cause of FMD is largely unknown. There appears to be a discrepancy between perception of the movements as involuntary by the patient, while the clinical and neurophysiologic characteristics, such as distractibility, entrainment, and the readiness potential, suggest volitional control. In the clinical setting, abnormal sensory processing is reflected by hypersensitivity to external stimuli and exaggerated startle reactions (4).

The auditory startle reflex (ASR) can be used as an objective neurophysiological measure of the affective system (5). It is one of the fastest responses of the fear system and consists of two parts. The first motor response involves generalized muscle activation with short onset latencies (<100-120 milliseconds (ms)) and a fixed recruitment pattern (6). This early part is the motor startle reflex. It is mediated by the caudal brainstem (7). In patients with hyperekplexia and anxiety disorders this response is enlarged (8). The second part of the startle response - also called the 'orienting response' - occurs with longer onset latencies (± 400 ms) and is characterized by posture adjustment and orientation towards the startling stimulus, accompanied by autonomic changes (9). This second response is influenced by psychological and behavioral processing and is much more variable in pattern and size (10).

So far, only one small electrophysiological study on the startle response in five FMD patients has been conducted (11). It showed long and variable onset latencies.

The aim of the present study was to systematically assess the ASR in patients with functional jerks. The ASR has never been systematically in patients with FMD and no clear distinction has been made between the early and late component of the ASR. We studied different parameters of the ASR, including the response rate, onset latencies, recruitment pattern and habituation. We hypothesized that patients would reveal predominantly second responses with long and variable onset latencies. Analyzing the startle reflex in a systematic manner, distinguishing the early and late phase, might help further delineate the origin and substrate of hypersensitivity and exaggerated startle which is often mentioned as clinical feature in FMD.

METHODS

Participants

The study was performed in patients with either focal or generalized jerks, consecutively included from the outpatient clinic (n=17). Two movement disorders specialists (MT or JK) evaluated the patients. Only patients who met Fahn and Williams criteria of 'clinically probable, established, or documented FMD' were included. To support the diagnosis patients underwent EEG-EMG co-registration to demonstrate the presence of a Bereitschaftspotential (BP) (12). Furthermore, all subjects were screened for co-morbid psychiatric disorders based on the DSM-IV using the Mini International Neuropsychiatric Interview - PLUS (MINI-PLUS) (13). In total 15 healthy age- and gender-matched controls participated. Control subjects who used psychiatric medication, or had neurologic or psychiatric disorders were excluded. Further, patients and controls with a hearing defect were excluded. The local Medical Ethics Committee of the AMC approved this study and all participants gave written informed consent.

Study procedure

Subjects were instructed to sit in an upright position on a bed and were asked to sit quietly and relaxed and keep their eyes open. They were instructed to listen to a series of beeps through headphones.

Paradigm

The ASR was recorded with 16 bipolar active cutaneous Ag-AgCl EMG electrodes (Active One System; Biosemi, Amsterdam, The Netherlands) over the right orbicularis oculi, masseter, sternocleidomastoid, deltoideus, abductor pollicis brevis, rectus abdominis and quadriceps muscle. The psychogalvanic reflex (PGR) was recorded as the difference in potential between the palm and the dorsum of the right hand. The impedance of all electrodes was checked to be below 10 kΩ. For further details on data acquisition we refer to a previous study conducted by our research group (5). Headphones were used to present 8 consecutive binaural auditory stimuli of 200 Hz with a duration of 55 ms and loudness of 110 dB. Stimuli were presented with a varying interval of 1.5 to 3 minutes, using the same order in all subjects.

Data processing

Data analysis was performed off-line using Brain Vision Analyzer version 2.0 (Brain Products GmbH). For a detailed description of data preprocessing see Bakker et al. 2009 (5). We specifically distinguished between the first and second response of the ASR by quantifying different parameters of the ASR for two different time windows (14). A time window of 1-100 ms and 100-1000 ms for the orbicularis oculi, masseter

and sternocleidomastoid muscle and 1-120 ms and 120-1000 ms in the remaining muscles was used to discriminate the early and late components. One researcher (YD) visually inspected and marked response occurrence at a constant scale sensitivity (200 uV) for all subjects. EMG criteria for a response were pre-defined as an increase in EMG activity of a minimal duration of 30 ms and amplitude of 30 uV. Unreliable EMG segments (caused by ECG or other artefacts) were not included in the analysis. Response probabilities and onset latencies were determined for all muscles. Further, a total response probability was calculated using the average response probabilities of all muscles.

To be able to quantify the PGR channels were re-segmented (-100 ms before and 8000 ms after stimulus) and baseline corrected (0-900 ms). The PGR, defined as the largest increase in amplitude from baseline after stimulation within 4-5 s, was calculated and standardized to the intra-individual maximum (0%-100%)(5, 15).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (IBM SPSS version 20). A Student's T-test or Mann-Whitney U test (where applicable) was used in order to test for differences in onset latencies and response probabilities of individual muscles. Differences in onset latencies were only tested when there was a sufficient response rate. A level of $p<0.05$ was considered significant. Response probability revealed a positively skewed overdispersed distribution, therefore a negative binomial regression model was used to analyze the group differences and habituation effects (General Estimation Equation method type III Wald chi-square statistics with robust estimator as covariance matrix). A repeated measures analysis was performed to analyze group differences (patients vs controls) and habituation difference between the groups (group * stimulus) PGR (Linear mixed model with fixed effects). Possible confounding factors, i.e. medication use and co-morbid anxiety disorders, were added to the different models to assess their influence on the different startle parameters.

RESULTS

Patient characteristics

Baseline characteristics are summarized in **table 1**. Age and gender in patients and controls was not significantly different. Three patients (18%) had a current anxiety and three (18%) a current depressive disorder. The median FMD disease duration of patients was 36 months with a range between 2 and 372 months. All patients but one had a disease duration of at least one year. Within the patient group 9 patients (53%) had abdominal and 6 (35%) limb jerks, 2 (12%) had both. The history of 2 patients

stated increased startle responses, accompanied by non-verbal vocalizations in one of them. Twelve subjects (71%) in the patient group were on medication with influence on the central nervous system **(table 1)**. In 8/17 patients (47%) a BP preceding the jerks was found. In 6 other patients (24%) other polymyographic characteristics supported FMD, such as disappearance of jerks with distraction and variability in muscle jerk recruitment pattern. In one patient a BP could not be recorded due to infrequency of the jerks. Finally, in 2 patients both the BP preceding the jerks as well as the voluntary movement, was lacking. This has been reported in FMD patients before (16).

	Patients (n=17)	Controls (n=15)
Male (n;%)	11 (65)	10 (67)
Age years (median;range)	56 (21-69)	54 (24-63)
Medication* (n;%)	12 (71)	0 (0)
Disease duration months (median;range)	36 (2-372)	-
Current anxiety disorder (n;%)	3 (18)	0 (0)
Current depressive disorder (n;%)	3 (18)	0 (0)
BAI score (median;range)**	12 (0-23)	-
BDI score (median;range)**	9 (0-23)	-

Table 1. *Baseline characteristics of patients and control subjects. *Medication included: sulpiride, levomepromazine, paroxetine, fluoxetine, fluvoxamine, mirtazepine, amitriptyline, clonazepam, temazepam, alprazolam, flurazepam, tramadol.**Assessed in 15 patients.*

Early auditory startle response (onset latency 0-120 ms)

Results of the different startle parameters for the early motor startle response are shown in **table 2**. As was expected the orbicularis oculi muscle most often showed a response in both groups (53% in patients and 51% in controls). The sternocleidomastoid (21% in patients and 3% in controls), masseter (13% in patients and 6% in controls) and deltoid (13% in patients and 0% in controls) muscle showed a response less frequent. The rectus abdominis muscle responded remarkably often in patients (14%) opposed to controls (2%). All patients with responses in the rectus abdominis muscle suffered from abdominal jerks.

Onset latencies in the orbicularis oculi did not differ between groups ($p>0.05$). The other muscles responded too infrequent to perform statistical testing.

Onset latencies of the muscles showed a recruitment pattern congruent with the normal startle reflex.

Patients showed significantly larger (chisquare=8.8, p=<0.01) total response probability (patients mean=17.1%; SD=18.6 vs. controls mean=8.9%; SD=7.5) compared to controls. Moreover the group as a whole revealed a significant habituation effect (stimulus) of the response probability (chisquare=7.4, p<0.01) **(figure 1)**.There was no difference in habituation between groups (chisquare=2.2, p>0.05).

	Patients		***Controls***	
	Latency (ms) (median; range)	**Response %**	**Latency (ms) (median; range)**	**Response %**
Orbicularis oculi	39(8-89)	53(SD 37)	45(16-64)	51(SD 41)
Masseter	55(11-91)	13(SD 25)	48(29-50)	6(SD 23)
Sternocleidomastoid	56(6-97)	21(SD 29)	57(39-83)	3(SD 7)
Deltoid	99(59-119)	13(SD 22)	-	-
Abductor pollicis brevis	49(15-110)	4(SD 27)	60(32-87)	2(SD 4)
Rectus abdominis	91(39-118)	14(SD 27)	103(-)	2(SD 4)
Quadriceps	104 (62-116)	3(SD 5)	-	-
Total		*17.1(SD 18.6)*		*8.9(SD 7.5)*

Table 2. *Onset latencies (ms), response probabilities (%)with an onset from 0-100 ms for the orbicularis oculi, masseter and sternocleidomastoid muscles and an onset of 0-120 ms for the remaining muscles. SD=standard deviation. *=p<0.05, **=p<0.01.*

Late response (onset latency 100-1000 ms)

Late response probability (chisquare=6.8, p<0.01) (patients 21.6% (SD 17.9) vs. controls 5.5% (SD 6.1)) was significantly larger in patients compared to controls. Patients and controls together revealed significant habituation (stimulus) of the response probability (chisquare=13.3, p=<0.01) **(figure 2).** No difference in habituation pattern was found between patients and controls.

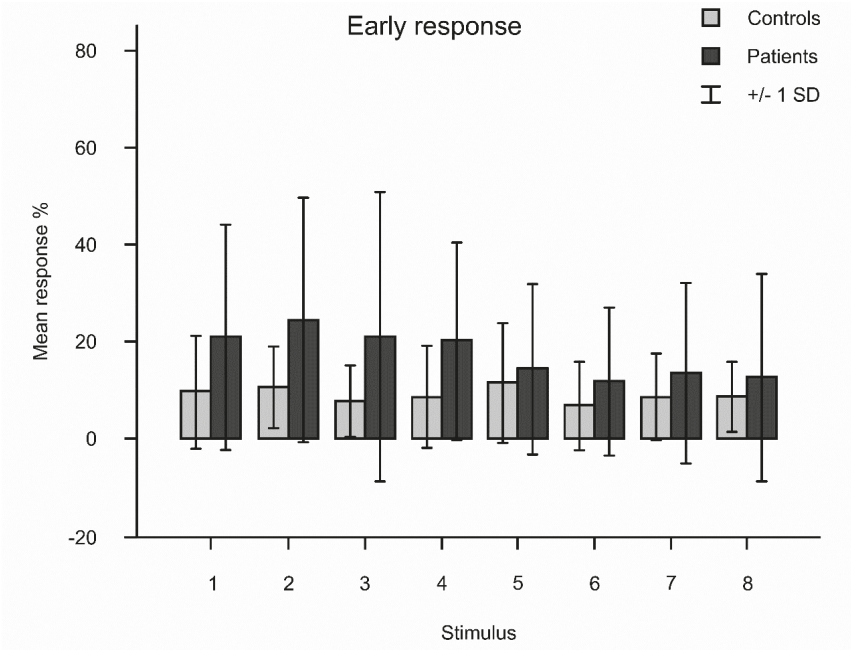

Figure 1. *Mean response probability (%) early response in patients and controls. SD=standard deviation.*

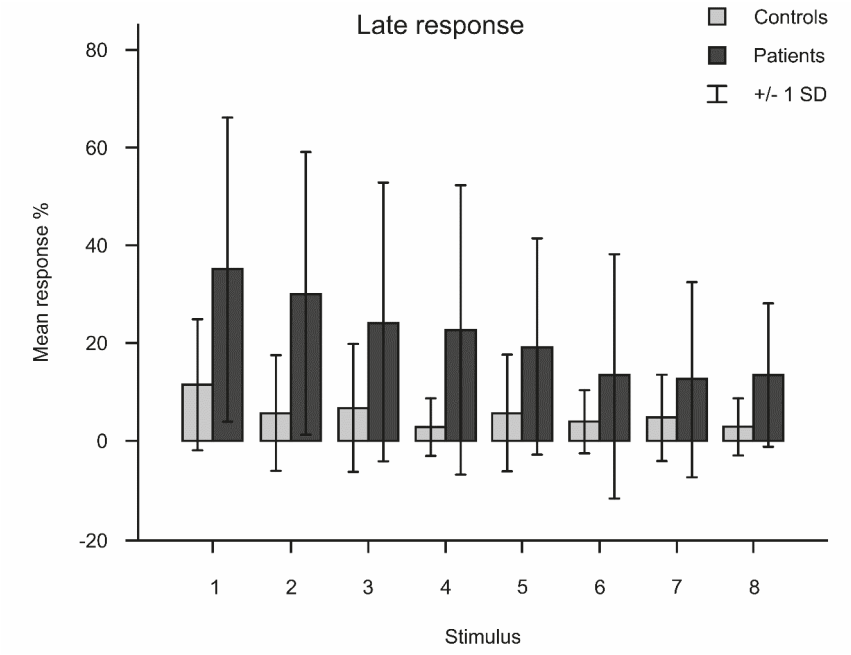

Figure 2. *Mean response probability (%) late response in patients and controls. SD=standard deviation.*

The different startle parameters of the late response are shown in **table 3**. As was seen in the early response, the orbicularis oculi muscle also most often showed a late response (36% in patients vs. 21% in controls). Late responses in different muscles were more frequent in patients compared to controls: sternocleidomastoid (30% vs. 7%), masseter (23% vs. 7%) and deltoid muscles (13% vs. 1%). Notable again is the frequent late response in the rectus abdominis muscle in patients (25%) compared to controls (1%) and the quadriceps muscle (14% vs. 0%).

Onset latencies were much more variable with a wider range compared to the early response, especially in patients. There was no difference in onset latency in the orbicularis oculi muscle between groups (p>0.05). The other muscles responded too infrequent to compare onset latencies or statistically analyze the recruitment pattern of the responses between patients and controls. In five patients the frequency of responses were sufficient on an individual level to show a variable recruitment pattern with variable latencies and response frequencies.

	Patients		***Controls***	
	Latency (ms) (median; range)	**Response %**	**Latency (ms) (median; range)**	**Response %**
Orbicularis oculi	218(107-896)	36(SD 25)	246(123-915)	21(SD 25)
Masseter	166(106-714)	23(SD 29)	288(112-759)	7(SD 13)
Sternocleidomastoid	182(102-545)	30(SD 27)	236 (117-438)	7(SD 18)
Deltoid	192(129-685)	13(SD 20)	259 (-)	1(SD 3)
Abductor pollicis brevis	183.5(127-740)	10(SD 17)	163(160-825)	3(SD 7)
Rectus abdominis	186(123-509)	25(SD 25)	414 (-)	1(SD 3)
Quadriceps	177(120-691)	14(SD 22)	-	-
Total		*21.6(SD 17.9)***		*5.5(SD 6.1)*

Table 3. *Onset latencies (ms) and response probabilities (%) with an onset from 101-1000 ms for the orbicularis oculi, masseter and sternocleidomastoid muscles and an onset of 121-1000 ms for the remaining muscles. SD=standard deviation. *=p<0.05, **=p<0.01.*

Sympathetic skin response (PGR)

No significant difference in PGR was detected between groups (F=3.2, P>0.05). Habituation pattern was similar in both groups (F=3.6, P>0.05).

Medication use and co-morbid anxiety disorders

Medication use did not influence the results significantly. Because of the low prevalence of anxiety disorders in patients, testing of its influence on the different startle parameters would generate statistically unreliable results, therefore it was omitted.

DISCUSSION

This study shows that the early motor phase of the auditory startle reflex generated in the brainstem is enlarged in FMD patients, but show normal response latencies and a normal recruitment pattern. The second orienting phase of the startle reflex, reflecting a more behavioral component, was also found to be enlarged and showed variable recruitment pattern.

Increased early motor startle responses have been found in hereditary hyperekplexia (17), but also in pathological anxiety (8). Anxiety disorders, characterized by a state of hyperarousal and increased vigilance, are highly influenced by the amygdala, a part of the brain's arousal circuit and involved in rapid orientation towards potential threat without involvement of the cortex (18-21). The role of the amygdala in FMD has become a topic of interest over the last couple of years. Functional Magnetic Resonance Imaging study in patients with FMD showed abnormal activity and reduced inhibition of the amygdala in response to arousing stimuli (22). Moreover, increased connectivity of the amygdala and the supplementary motor area (motor planning) has been found, explaining a possible neural mechanism between emotion and motor symptoms. A general state of hyperarousal in FMD may explain the enlarged early motor startle reflex found in the present study.

Not only the brainstem mediated early motor response, but also the late(orienting) response of the ASR was enlarged in FMD patients in our study. Few systematic studies have been conducted separating the first and second phase of the startle response (10). In post-traumatic stress disorder (PTSD) enlargement of the late (orienting) response has been reported (23). In Latah, an Indonesian culture-specific startle syndrome (14) both early and late components of the startle response are also enlarged with a variable pattern of the second response. This similarity with Latah, a neuropsychiatric disorder, strengthens the idea that the second response is a more stereotyped response, influenced by behaviour. In Latah phenomena such as echolalia, palylalia and coprolalia are part of the clinical picture revealing both tic and functional characteristics (14). Altogether, the enlargement of the second response with variable pattern of muscle recruitment supports a neuropsychiatric background in FMD.

Thompson et al. (11) performed an electrophysiological study of the startle reflex on patients with stimulus-induced focal or generalized jerks initially clinically classified as either reflex myoclonus or a form of a pathological startle. The electrophysiologically measured startle reflex in these five patients, revealed long (>100 ms) and variable onset latencies, incompatible with brainstem myoclonus or pathological startle. Therefore, a 'voluntary' origin of the jerks was supposed. In contrast to our study no distinction between the early and late component of the startle reflex was made. We suggest that the variable and long latencies in the study by Thompson may reflect the late orienting response of the startle reflex.

Interestingly, we found a relatively high response probability in the rectus abdominis muscle in patients suffering from abdominal functional jerks compared to controls. This might reflect a start-react reaction where a cortically prepared and stored movement is released at faster latencies due to an involuntary subcortical trigger evoked by the startle reflex (24). This phenomenon is well known in sprinters, where the loud start signal decreases the reaction time of the athletes (25, 26). We hypothesize that in patients with functional abdominal jerks the constantly subconsciously 'preparing' (BP) of their upcoming jerk, is released by the startling stimulus (27).

Decreased habituation of the psychogalvanic response to auditory stimuli in patients with mixed functional neurological symptoms has been shown in the past (28, 29). We failed to find any differences between FMD and controls. In line with this, a recent study in patients with FMD, failed to reveal a difference in cortisol levels, a biomarker for stress, compared to healthy controls (30). The role of the autonomic nervous system and stress circuitry in FMD remains a topic of debate.

LIMITATIONS

Response rates were low in the distal muscles of patients and especially control subjects, limiting the possibility of comparison of latencies, habituation and pattern. It may be helpful to use different startle modalities (e.g. tactile stimulation) to increase response rates. However, our results are similar to those in previous studies in Latah and anxiety patients and therefore appear reliable. Although infrequently present anxiety in patients may have confounded the results to some extent. Another limitation is the relatively small study sample.

CONCLUSION

Both the early and late (orienting) phase of the startle reflex are enlarged in FMD patients compared to controls. In contrast to what was found in earlier studies, the recruitment pattern is consistent with the normal startle reflex. The late response revealed more variable onset latencies but is known to be behaviourally influenced. The higher frequency and pattern of the late orienting response in patients is in line with what has been found in other neuropsychiatric disorders. This is the first study systematically assessing the startle reflex in a homogeneous group of patients with jerky FMD. Distinguishing the early and late response has gained insight in the origin of the increased startle sensitivity often mentioned as clinical feature in patients with FMD.

Author contribution:
Y.E.M.D., J.H.T.M.K. and M.A.J.T. designed the study. T.B. provided technical equipment and performed data acquisition. Y.E.M.D. performed statistical analysis and drafted the manuscript. J.H.T.M.K. and M.A.J.T. revised the manuscript. All authors approved the final version to be submitted.

Study funding
This study was part of a larger study project which was funded by the Prinses Beatrix Fund.

Competing interests
None

Patient consent
Obtained

Ethical approval
The ethics approval was provided by the Medical Ethical Committee of the Academic Medical Centre, University of Amsterdam.

Disclosures
Y. Dreissen and T. Boeree report no disclosures relevant to the manuscript. J. Koelman received educational grants from Allergan and Ipsen and a research grant from Ipsen and funding by STW Technology Society–NeuroSIPE and Prinses Beatrix Fonds. M. Tijssen is funded by STW Technology Society–NeuroSIPE, Netherlands Organization for Scientific Research–NWO Medium, Fonds Nuts-Ohra, Prinses Beatrix Fonds,

Gossweiler Foundation, Stichting Wetenschapsfonds Dystonie Vereniging, and educational grants from Ipsen, Allergan, and Medtronic.

REFERENCES

1. Edwards MJ, Bhatia KP. Functional (psychogenic) movement disorders: merging mind and brain. Lancet Neurol. 2012;11(3):250-60.
2. Lang A. General overview of psychogenic movement disorders: epidemiology, diagnosis and prognosis. Psychogenic movement disorders-neurology and neuropsychiatry. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 35-41.
3. Stone J, Carson A, Duncan R, Coleman R, Roberts R, Warlow C, et al. Symptoms 'unexplained by organic disease' in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? Brain. 2009;132(Pt 10):2878-88.
4. Ganos C, Aguirregomozcorta M, Batla A, Stamelou M, Schwingenschuh P, Munchau A, et al. Psychogenic paroxysmal movement disorders--clinical features and diagnostic clues. ParkinsonismRelat Disord. 2014;20(1):41-6.
5. Bakker MJ, Boer F, van der Meer JN, Koelman JH, Boeree T, Bour L, et al. Quantification of the auditory startle reflex in children. ClinNeurophysiol. 2009;120(2):424-30.
6. Brown P, Rothwell JC, Thompson PD, Britton TC, Day BL, Marsden CD. New observations on the normal auditory startle reflex in man. Brain. 1991;114 (Pt 4):1891-902.
7. Davis M. The role of the amygdala in fear and anxiety. AnnuRevNeurosci. 1992;15:353-75.
8. Bakker MJ, Tijssen MA, van der Meer JN, Koelman JH, Boer F. Increased whole-body auditory startle reflex and autonomic reactivity in children with anxiety disorders. JPsychiatry Neurosci. 2009;34(4):314-22.
9. Gogan P. The startle and orienting reactions in man. A study of their characteristics and habituation. Brain Res. 1970;18(1):117-35.
10. Bakker MJ, van Dijk JG, van den Maagdenberg AM, Tijssen MA. Startle syndromes. Lancet Neurol. 2006;5(6):513-24.
11. Thompson PD, Colebatch JG, Brown P, Rothwell JC, Day BL, Obeso JA, et al. Voluntary stimulus-sensitive jerks and jumps mimicking myoclonus or pathological startle syndromes. Movement Disorders. 1992;7(3).
12. Brown P, Thompson PD. Electrophysiological aids to the diagnosis of psychogenic jerks, spasms, and tremor. Mov Disord. 2001;16(4):595-9.
13. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. JClinPsychiatry. 1998;59 Suppl 20:22-33.
14. Bakker MJ, van Dijk JG, Pramono A, Sutarni S, Tijssen MA. Latah: an Indonesian startle syndrome. Mov Disord. 2013;28(3):370-9.
15. Lykken DT, Rose R, Luther B, Maley M. Correcting psychophysiological measures for individual differences in range. PsycholBull. 1966;66(6):481-4.
16. van der Salm SM, Tijssen MA, Koelman JH, van Rootselaar AF. The bereitschaftspotential in jerky movement disorders. JNeurolNeurosurgPsychiatry. 2012;83(12):1162-7.

17. Dreissen YE, Bakker MJ, Koelman JH, Tijssen MA. Exaggerated startle reactions. ClinNeurophysiol. 2012;123(1):34-44.
18. Ohman A. The role of the amygdala in human fear: automatic detection of threat. Psychoneuroendocrinology. 2005;30(10):953-8.
19. Davis M. Fear-potentiated startle in rats. CurrProtocNeurosci. 2001;Chapter 8:Unit.
20. Liddell BJ, Brown KJ, Kemp AH, Barton MJ, Das P, Peduto A, et al. A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. Neuroimage. 2005;24(1):235-43.
21. Schmitz A, Grillon C. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). NatProtoc. 2012;7(3):527-32.
22. Voon V, Brezing C, Gallea C, Ameli R, Roelofs K, LaFrance WC, Jr., et al. Emotional stimuli and motor conversion disorder. Brain. 2010;133(Pt 5):1526-36.
23. Siegelaar SE, Olff M, Bour LJ, Veelo D, Zwinderman AH, van BG, et al. The auditory startle response in post-traumatic stress disorder. ExpBrain Res. 2006;174(1):1-6.
24. Stevenson AJ, Chiu C, Maslovat D, Chua R, Gick B, Blouin JS, et al. Cortical involvement in the StartReact effect. Neuroscience. 2014;269:21-34.
25. Pain MT, Hibbs A. Sprint starts and the minimum auditory reaction time. J Sports Sci. 2007;25(1):79-86.
26. Valls-Sole J, Rothwell JC, Goulart F, Cossu G, Munoz E. Patterned ballistic movements triggered by a startle in healthy humans. JPhysiol. 1999;516 (Pt 3):931-8.
27. Valls-Sole J, Kofler M, Kumru H, Castellote JM, Sanegre MT. Startle-induced reaction time shortening is not modified by prepulse inhibition. ExpBrain Res. 2005;165(4):541-8.
28. Lader M, Sartorius N. Anxiety in patients with hysterical conversion symptoms. JNeurolNeurosurgPsychiatry. 1968;31(5):490-5.
29. Horvath T, Friedman J, Meares R. Attention in hysteria: a study of Janet's hypothesis by means of habituation and arousal measures. AmJPsychiatry. 1980;137(2):217-20.
30. Maurer CW, LaFaver K, Ameli R, Toledo R, Hallett M. A biological measure of stress levels in patients with functional movement disorders. Parkinsonism Relat Disord. 2015;21(9):1072-5.

The auditory startle response in relation to outcome in functional movement disorders

8

Yasmine EM Dreissen, Johannes HTM Koelman & Marina AJ Tijssen

Article published in Parkinsonism and related disorders 2021 doi: 10.1016/j.parkreldis.2021.07.012

ABSTRACT

Background: The auditory startle reflex (ASR) is enlarged in patients with functional movement disorders (FMD).

Objectives: To study whether the ASR relates to symptom reduction in FMD patients, who participated in a placebo controlled double blind treatment trial with Botulinum Neurotoxin (BoNT).

Methods: Response to treatment in the BoNT study was assessed using the Clinical Global Impression – Improvement scale (CGI-I). The electromyography (EMG) muscle activity of 7 muscles following 110 dB tones was measured in 14 FMD patients before and after one-year treatment and compared to 11 matched controls. The early and a late (behaviorally affected) component of the ASR and the sympathetic skin response (SSR) were assessed.

Results: 10 of 14 patients (71.4%) showed symptom improvement, which was believed to be mainly caused by placebo effects. The early total response probability of the ASR at baseline tended to be larger in patients compared to controls ($p=0.08$), but normalized at follow-up ($p=0.84$). The late total response probability was larger in patients vs. controls at baseline ($p< 0.05$), a trend that still was present at follow-up ($p=0.08$). The SSR was higher in patients vs. controls at baseline ($p< 0.01$), and normalized at follow-up ($p=0.71$).

Conclusions: On a group level 71.4% of the patients showed clinical symptom improvement after treatment. The early part of the ASR, most likely reflecting anxiety and hyperarousal, normalized in line with the clinical improvement. Interestingly, the augmented late component of the ASR remained enlarged suggesting persistent altered behavioral processing in functional patients despite motor improvement.

INTRODUCTION

In recent years the research focus in functional movement disorders (FMD) has shifted from a psychological towards a neurobiological basis. Although the etiology and pathophysiology of FMD is unknown, impaired stress regulation is thought to play an important role (1).

In an earlier study we found an augmented early and late response of the auditory startle reflex (ASR) in patients with jerky and tremulous FMD compared to healthy controls (2). The early component of the ASR is the fastest response of the fear system. It has a fixed rostro-caudal recruitment pattern mediated by the caudal brainstem with onset latencies between 20-120 milliseconds (ms) (3). It is modulated by the amygdala and enlarged in anxiety disorders (4, 5). The enlarged early response of the ASR in FMD patients is accompanied by an increase in autonomic activity, measured with the sympathetic skin response (SSR) (6). The late component with an onset latency of 100-120 ms, also referred to as the 'orienting response' (7) has a more variable pattern and is associated with behavioral processing. It is less studied and enlarged in culture-specific startle syndromes as Latah (8).

Now, we studied the startle reflex over time in a group of FMD patients who participated in a randomized controlled trial of treatment with botulinum neurotoxin (BoNT) (9). In this study, a 60% motor improvement was seen in the 4-month RCT-phase in both the BoNT and placebo group, which increased to 80% after one year open-label treatment. As the effect of BoNT was largely considered a placebo effect, we hypothesize there is no specific effect of BoNT on the startle reflex. We suppose that the effects on the ASR reflect hyperarousal and behavioral aspects in relation to the course of FMD symptoms in the studied patients.

METHODS

Study population

Included patients participated in the a BoNT treatment study (**table 1**) (9). They were diagnosed by two experienced movement disorder neurologists (JHTMK, MAJT) and fulfilled diagnostic criteria of 'definite' or 'probable' FMD. Healthy gender- and age-matched subjects without neurologic/psychiatric deficit and without usage of central nervous system(cns)-acting medication served as a control group. Both patients and controls with a hearing defect were excluded.

Treatment

The treatment intervention consisted of two sessions of either BoNT or placebo during the RCT-phase. (9) The injection site was based on clinical examination in combination with polymyographic electromyography (poly-EMG) (**table 1**). If there was no effect, the dosage was doubled at the second treatment session. After the RCT-phase, all patients received BoNT treatment in the one year open-label phase.

Study procedure and outcome assessment

The ASR was recorded twice in patients and control subjects, at baseline and at follow-up after one year. Outcome measures were assessed at these occasions. The primary outcome of the BoNT study was the Clinical Global Impression – Improvement (CGI-I), a 7 point Likert Scale ranging from 1 (very much improved) to 7 (very much worse), which was dichotomized to symptom improvement (score 1-3) vs. same or worse (score 4-7). Motor symptoms were assessed using the Psychogenic Movement Disorder Rating Scale (PMDRS). Both of these outcome measures were rated based on video recordings, by two independent researchers who were blinded to the allocated treatment (9). Patients also underwent a psychiatric interview by one researcher (YEMD) based on the DSM-IV using the Mini-International Neuropsychiatric Interview - PLUS (MINI-PLUS). Self-assessment scales included the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI). Controls were only screened for a current depressive or anxiety disorder based on the DSM-IV using the relevant part of the MINI-PLUS.

ASR and SSR assessment

During ASR assessment, subjects were seated on a bed with a headphone and instructed to sit quietly and listen to a series of beeps. After skin preparation, the ASR was recorded using bipolar active cutaneous Ag-AgCl EMG electrodes (Active One System; Biosemi, Amsterdam, The Netherlands) in the following seven muscles: orbicularis oculi (OO), masseter (Mass), sternocleidomastoid (SCM), deltoid (Delt), abductor pollicis brevis (APB), rectus abdominis (RA) and the quadriceps (Quad) muscle. The response in the OO muscle usually contains of two EMG responses, the early eye-protective blink response and a second response which is part of the ASR. Because of the overlap between the two responses, distinguishing them is almost impossible. (6) The SSR was recorded on the palm of the hand with the reference electrode on the dorsum. Eight consecutive 200 Hertz (Hz) auditory stimuli of 110 dB sound pressure level and duration of 55 milliseconds (ms) with a varying interval of 1.5 and 3 minutes were used to elicit the ASR. This paradigm was identical to our previous study (2), in accordance with the paradigm previous used by our group (6) and with guidelines on the startle reflex by the Psychophysiology committee (10). All

participants gave written informed consent and this study was approved by the local Medical Ethical Committee.

Data processing

Data analysis was performed off-line using Brain Vision Analyzer version 2.0 (Brain Products GmbH). The different parameters of the ASR were quantified distinguishing between the early component with onset latency of 0 - 100 ms for the OO and Mass and 0 - 120 ms for the remaining muscles and the late component with onset latencies of 100 – 1000 ms for the OO and Mass and 120 – 1000 ms for the remaining muscles. (2) Predefined criteria for classifying a response were used, i.e. a clear increase from baseline with a minimal duration of 30 ms and amplitude of 30 microVolt (μV). All responses were manually marked by one investigator (YEMD) at the same scale sensitivity (200 μV). The response probabilities were assessed for all the muscles separately by dividing the total amount of responses per muscle by the total amount of trials and multiplying this by 100. The total response probability was calculated as the average response probability of all muscles together. The SSR, which was defined as the largest increase in amplitude from baseline after stimulation within 5 s, was calculated and standardized to the intra-individual maximum (0%-100%).

Statistical analysis

Baseline characteristics were summarized using descriptive statistics. Possible differences in gender between patients and controls were tested with a Fisher's exact test. A Mann-Whitney U test was used to test for differences in age between groups. In the patient group the difference in motor symptoms (PMDRS) between baseline and after treatment was tested using a Wilcoxon signed rank test. A repeated measures analysis (general linear mixed model with fixed effects) was used to assess the effect of group (patients vs. controls) and the repeated stimuli, which is a measure of habituation, on the total response probability for the two different time points (baseline and follow-up) separately. In order to correct for the possible confounding factors cns-acting medication and anxiety disorders, a second model was built in which these factors were added. The same model was also used to determine whether there was a change in ASR between baseline and follow-up (effect of timing of measurement) for patients vs. controls. All tests were two-sided and a p-value of < 0.05 was considered statistically significant. The analyses were performed with Statistical Packaging for Social Sciences (SPSS) version 25.

RESULTS

Population characteristics

Fourteen patients and 11 control subjects were included in this study. The majority of both groups was male (n=9; 64% patients vs. n= 8; 73% controls). The groups did not differ in terms of age, with a median age of 58 (interquartile range (iqr) 46 – 60) in patients compared to a median of 56 (iqr 46 – 62) in the control group. Eight (57%) of patients were using cns-acting medication (including amitriptyline, clonazepam, temazepam, diazepam, tramadol and pramipexol).

Response to BoNT treatment

In total 10 of 14 patients (71.4%) showed motor improvement at follow-up on the CGI-I. A significant improvement of PMDRS-scores was found in patients between baseline and follow-up (median 15 (iqr 9 – 23) to median 9 (iqr 2 – 19); p=0.01). There was no significant change in anxiety symptoms between baseline (BAI median score 12; iqr 5-17) and follow-up (BAI median score 11; iqr 3-19) in the patient group (p=0.95) nor in the amount of anxiety disorders (baseline (n=3 (21%) vs. follow-up (n=3 (21%); p=1.00).

ASR and SSR at baseline

A trend towards a larger early total response probability was found in patients compared to controls (17% vs. 7%; estimate -0.11; 95% CI -0.23 to 0.01; p=0.08). The total response probability of the late response was significantly larger in patients compared to controls at baseline (16% vs. 7%; estimate -0.24; 95% CI -0.41 to -0.07; p< 0.05). The early (estimate -0.02; 95% CI -0.02 to -0.01; p< 0.01) as well as the late response showed a significant habituation effect in both groups (estimate -0.03; 95% CI -0.05 to -0.01; p<0.01). The SSR was enlarged in patients (median 0.63; iqr 0.45 to 0.90) compared to controls (median 0.57; iqr 0.36 to 0.81) at baseline (estimate -0.23; 95% CI -0.38 to -0.09; p< 0.01) with a significant habituation effect (estimate -0.07; 95% CI -0.09 to -0.04; p<0.01). Adding the factors anxiety disorder and cns-acting medication to the different models did not alter the results. However the presence of an anxiety disorder was a significant contributor to the early total response probability, but not the late. For details on response probabilities per muscle for the early and late responses see **table 2 and 3 of the supplementary data file**.

ASR at follow-up and difference between baseline and follow-up

Early response

Compared to baseline, at follow-up no difference in total early response probability was found between patients and controls (16% vs. 8%; estimate 0.01; 95% CI -0.09 to 0.10; p=0.84). The early total response probability showed significant habituation per stimulus in both groups (estimate -0.01; 95% CI -0.01 to 0.00; p<0.05). Also, there was a significant habituation with a decrease between baseline and follow-up in the whole group (estimate -0.05; 95% CI -0.09 to -0.00; p<0.05). A trend was seen towards a decrease in total response probability between baseline and follow-up in patients (estimate -0.05; 95% CI -0.10 to 0.00; p=0.06), which was not present in controls (estimate -0.03; 95% CI -0,08 to 0.02; p=0.22).

Late response

At follow-up a trend was still seen towards a larger total response probability of the late response in patients compared to controls (22% vs. 6%; estimate - 0.09; 95% CI -0.19 to 0.01; p=0.08). No habituation effect was found of the stimulus, nor was there a habituation found between baseline and follow-up. The late response did not change between baseline and follow-up in patients (estimate -0.04; 95%CI -0.19 to 0.11; p=0.54), but a trend was seen towards a decrease in controls (estimate -0.03; 95% CI -0.06 to 0.00; p=0.06). **Figure 1** shows an example of the startle response before and after treatment in a patient nr 12 (**table 1**).

SSR

No difference in SSR was detected between patients and controls at follow-up. Also, no change between baseline and follow-up was found in controls as well as patients.

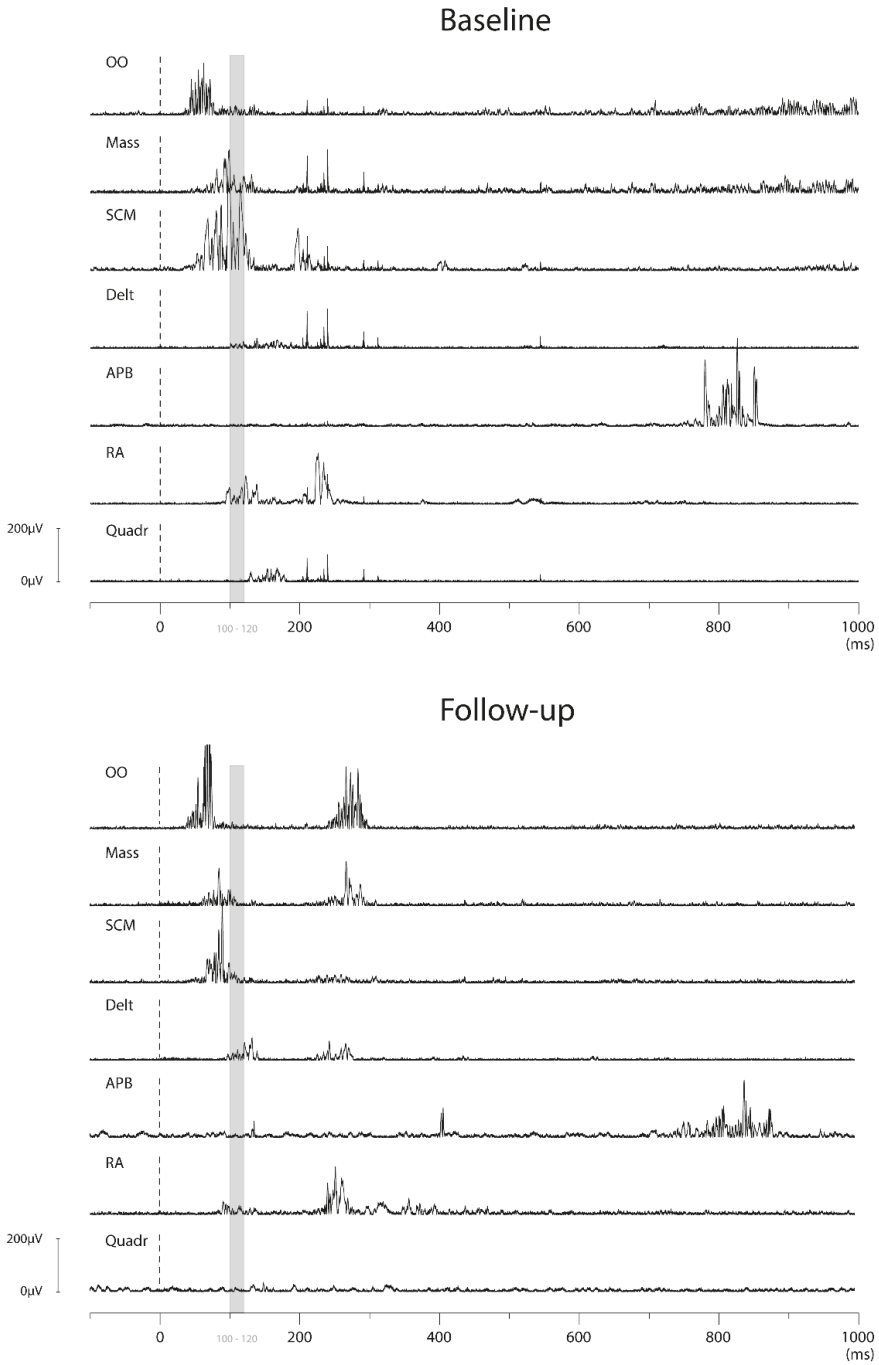

Figure 1. *An example of the ASR before (above) and after treatment in patient nr 12 (see table 1). The gray bar marks the beginning of the late response. Especially the late response, remains prominent after treatment.*

Patients	Phenomenology	Muscle(s) treated	CGI-I follow-up	PMDRS baseline	PMDRS follow-up	Current anxiety disorder baseline	Current anxiety disorder follow-up	BAI-scores baseline	BAI-scores follow-up
1	jerks abdomen and legs	iliopsoas	1	12	11	no	no	16	18
2	jerks both legs	iliopsoas	1	10	1	no	no	0	0
3	jerks one leg	iliopsoas rectus femoris vastus medialis	1	27	6	no	no	17	11
4	jerks abdomen	rectus abdominis	5	22	22	yes	no	15	6
5	jerks one shoulder	trapezius levator scapulae	4	18	0	no	no	9	0
6	jerks both shoulders	SCM trapezius major pectoral deltoid	4	25	25	no	no	3	4
7	jerks both shoulders	trapezius major pectoral	1	10	9	no	yes	11	15
8	jerks back	paraspinal	3	5	2	yes	no	4	0
9	jerks abdomen	iliopsoas rectus abdominis	3	23	19	no	no	12	20
10	jerks one leg	iliopsoas rectus femoris	3	24	20	no	no	9	6
11	jerks abdomen	rectus abdominis	3	6	3	no	yes	15	22

Patients	Phenomenology	Muscle(s) treated	CGI-I follow-up	PMDRS baseline	PMDRS follow-up	Current anxiety disorder baseline	Current anxiety disorder follow-up	BAI-scores baseline	BAI-scores follow-up
12	jerks abdomen and shoulder	semispinal rectus abdominis	2	5	0	no	no	16	10
13	jerks one leg	vastus medialis rectus femoris	3	18	9	no	no	5	11
14	jerks abdomen	rectus abdominis	5	11	13	yes	yes	23	31

Table 1*. Clinical characteristics of patients before and after treatment. PMDRS = Psychogenic Movement Disorder Rating Scale. BAI = Beck Anxiety Inventory. SCM=sternocleidomastoid. Botulinum Neurotoxin (BoNT) starting dose per muscle (iliopsoas: 160-200 International Units (IU); rectus femoris 100 -200 IU; vastus medialis 50 IU; rectus abdominis 120-200 IE; trapezius 50-80 IU; levator scapulae 60-80 IU; SCM 40-80 IU; pectoral major 80-100 IU; deltoid 80 IU; paraspinal 150 IU; semispinal 60 IU).*

DISCUSSION

In this study we report on the ASR in relation to outcome in FMD patients and found a tendency for the early component of the ASR to normalize with clinical improvement, whereas the late, behavorially affected component remained enlarged in patients compared to controls.

In patients, the early motor total response probability showed a trend to be enlarged at baseline, which normalized at follow-up. A similar study showed that the ASR decreased in children with anxiety disorders who responded well to Cognitive Behavioral Therapy (CBT) (11). Imaging studies have shown that the magnitude of pre-treatment amygdala activation in general predicts better treatment response (12). In line with this, the early motor ASR could potentially serve as an outcome measure and/or biomarker in patients with FMD. The stable findings in controls indicate that the test-retest reliability is high.

At baseline the late response was enlarged in patients compared to controls which tended to remain enlarged at follow-up despite motor improvement in a large proportion of patients. The lack of normalization of the late response might reflect a persisting general disorder in the regulation of behavioral aspects which is thought to play a key role in FMD.

Other related neurophysiological studies have shown impaired prepulse inhibition of the blink reflex in FMD (13), suggesting abnormal preconscious processing of somatosensory inputs, which may also play a role in our results on the ASR given the pathophysiology of FMD.

Regarding limitations, the patient group was too small to compare patients with and without motor improvement. Further, the ASR is determined by a large number of factors including cns-active medication and anxiety disorders which could influence results, despite correction. Lastly, habituation could have influenced the results of the ASR at follow-up.

CONCLUSIONS

This is the first study to assess the ASR in relation to treatment outcome in FMD. The early response appears to relate to motor improvement after treatment. The abnormalities in the behavioral (late) component of the ASR persisted despite clinical

improvement, and may indicate a more general disorder in the regulation of behavioral aspects in FMD.

Contributors
YEMD, MAJT and JHTM designed the study. YEMD collected, analyzed. YEMD, MAJT and JHTM interpreted the data. YEMD wrote the paper and designed the figures and tables. MAJT and JHTM drafted and critically revised the paper.

Acknowledgements
We would like to thank all the staff members, especially T. Boeree of the department of Clinical Neurophysiology for their support with carrying out this study.

Disclosure statement
This study was part of a larger study project which was funded by the Prinses Beatrix Fund. Dr Koelman reports educational grants from Ipsen, Allergan and Merz, outside the submitted work. Prof Tijssen reports grants from the Netherlands Organisation for Health Research and Development ZonMW Topsubsidie (91218013), the European Fund for Regional Development from the European Union (01492947) and the province of Friesland, Dystonia Medical Research Foundation, from Stichting Wetenschapsfonds Dystonie Vereniging, from Fonds Psychische Gezondheid, from Phelps Stichting, and an unrestricted grant from Actelion and from AOP Orphan Pharmaceuticals AG for a lecture. Dr Dijk reports grants from rom ZonMw (The Netherlands Organisation for Health Research and Development) and Medtronic, outside the submitted work. All other authors have nothing to disclose.

Role of funding source
None

Data sharing statement
All data relevant to the study are included in the article or uploaded as supplementary information. Individual de-identified participant data will not be shared.

REFERENCES

1. Baizabal-Carvallo JF, Hallett M, Jankovic J. Pathogenesis and pathophysiology of functional (psychogenic) movement disorders. Neurobiol Dis. 2019;127:32-44.
2. Dreissen YEM, Boeree T, Koelman J, Tijssen MAJ. Startle responses in functional jerky movement disorders are increased but have a normal pattern. Parkinsonism Relat Disord. 2017;40:27-32.
3. Dreissen YE, Bakker MJ, Koelman JH, Tijssen MA. Exaggerated startle reactions. ClinNeurophysiol. 2012;123(1):34-44.
4. Bakker MJ, Tijssen MA, van der Meer JN, Koelman JH, Boer F. Increased whole-body auditory startle reflex and autonomic reactivity in children with anxiety disorders. JPsychiatry Neurosci. 2009;34(4):314-22.
5. Angrilli A, Mauri A, Palomba D, Flor H, Birbaumer N, Sartori G, et al. Startle reflex and emotion modulation impairment after a right amygdala lesion. Brain. 1996;119 (Pt 6):1991-2000.
6. Bakker MJ, Boer F, van der Meer JN, Koelman JH, Boeree T, Bour L, et al. Quantification of the auditory startle reflex in children. ClinNeurophysiol. 2009;120(2):424-30.
7. Gogan P. The startle and orienting reactions in man. A study of their characteristics and habituation. Brain Res. 1970;18(1):117-35.
8. Bakker MJ, van Dijk JG, Pramono A, Sutarni S, Tijssen MA. Latah: an Indonesian startle syndrome. Mov Disord. 2013;28(3):370-9.
9. Dreissen YEM, Dijk JM, Gelauff JM, Zoons E, van Poppelen D, Contarino MF, et al. Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. J Neurol Neurosurg Psychiatry. 2019;90(11):1244-50.
10. Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp OV, van Boxtel A. Committee report: Guidelines for human startle eyeblink electromyographic studies. Psychophysiology. 2005;42(1):1-15.
11. Bakker MJ, Tijssen MA, Koelman JH, Boer F. Normalization of the auditory startle reflex after symptom reduction in children with anxiety disorders. J Psychiatr Res. 2011;45(6):796-802.
12. Klumpp H, Fitzgerald JM. Neuroimaging Predictors and Mechanisms of Treatment Response in Social Anxiety Disorder: an Overview of the Amygdala. Curr Psychiatry Rep. 2018;20(10):89.
13. Hanzlikova Z, Kofler M, Slovak M, Vechetova G, Fecikova A, Kemlink D, et al. Prepulse inhibition of the blink reflex is abnormal in functional movement disorders. Mov Disord. 2019;34(7):1022-30.

SUPPLEMENTARY DATA

	Patients (n=14)		Controls (n=11)	
	Baseline	Follow-up	Baseline	Follow-up
	Response % (SD)	Response% (SD)	Response% (SD)	Response% (SD)
OO	52 (38)	42 (SD 43)	58 (SD 38)	42 (SD 44)
Mass	11 (23)	7 (SD 27)	8 (SD 26)	3 (SD 8)
SCM	18 (30)	13 (SD 25)	3 (SD 8)	6 (SD 10)
Deltoid	10 (16)	6 (SD 23)	0 (SD 0)	1 (SD 4)
APB	3 (5)	2 (SD 7)	2 (SD 5)	0 (SD 0)
RA	10 (21)	4 (SD 10)	2 (SD 5)	3 (SD 11)
Quad	4 (6)	0 (SD 0)	0 (SD 0)	0 (SD 0)
Total	**15 (17)**	**10 (SD 16)**	**10 (SD 7)**	**8 (SD 8)**

Table 2. *Early mean response probabilities per group at baseline and at follow-up per muscle and of all muscles combined. OO=Orbicularis Oculi, Mass=Masseter, SCM=Sternocleidomastoid, APB=Abductor Pollicis Brevis, RA=Rectus Abdominis, Quad=Quadriceps. SD=standard deviation.*

	Patients (n=14)		Controls (n=11)	
	Baseline	Follow-up	Baseline	Follow-up
	Response % (SD)	Response% (SD)	Response% (SD)	Response% (SD)
OO	32 (SD 25)	13 (SD 25)	20 (SD 22)	9 (SD 18)
Mass	17 (SD 22)	13 (SD 24)	7 (SD 15)	5 (SD 15)
SCM	23 (SD 25)	22 (SD 31)	9 (SD 20)	3 (SD 11)
Deltoid	10 (SD 20)	10 (SD 26)	1 (SD 4)	2 (SD 5)
APB	3 (SD 5)	9 (SD 20)	2 (SD 5)	0 (SD 0)
RA	18 (SD 18)	14 (SD 26)	1 (SD 4)	0 (SD 0)
Quad	1 (SD 24)	11 (SD 24)	0 (SD 0)	2 (SD 8)
Total	**17 (SD 16)**	**13 (SD 22)**	**6 (SD 7)**	**3 (SD 6)**

Table 3. *Late mean response probabilities per group at baseline and at follow-up per muscle and of all muscles combined. OO=Orbicularis Oculi, Mass=Masseter, SCM=Sternocleidomastoid, APB=Abductor Pollicis Brevis, RA=Rectus Abdominis, Quad=Quadriceps. SD=standard deviation.*

Summary of the thesis

9

1. Treatment of functional movement disorders and the BoNT trial

Chapter 2 presents an overview on functional neurologic disorders. In recent years, the name 'functional' disorder has largely replaced 'psychogenic', which is considered least offensive to patients and supports an underlying biopsychosocial mechanism instead of a dualistic etiology (1). The diagnosis of FMD should be based on 'positive' clinical signs, such as for instance entrainment and distractibility. These features are also seen in voluntary movements and thus suggest some degree of volitional control. However, patients perceive their symptoms as involuntary. Showing patients these features during the physical examination can be therapeutic in itself (2). If clinical examination is not conclusive, neurophysiologic testing such as EEG-EMG with jerk-locked backaveraging in order to demonstrate a bereitschaftspotential (BP) preceding the jerky movements, can be used as a helpful aid to the diagnosis. If there are additional psychiatric symptoms, referral to a psychiatrist may be necessary, but it should not be standard care. In general, the prognosis is regarded poor: in more than one third of patients symptoms persist or worsen at long-term follow-up, especially when symptoms are chronic (> 1 year) (3). These poor prognostic numbers are often based on patients treated in movement disorder clinics and not in primary care facilities. It is expected that the group visiting a movement disorders clinic probably comprises patients with more severe and longer lasting symptoms which would require more specialized therapy. However, there is a lack of evidence-based therapies for FMD and there is no 'one-size-fits-all' approach since symptoms are heterogeneous.

Botulinum Neurotoxin (BoNT) has emerged as useful therapy in some specific movement disorders, especially in dystonia in which it has shown not only to temporarily block neuromuscular transmission, but also induces plastic changes in the brain (4). Hence, BoNT could not only potentially decrease motor symptoms in FMD by a direct neuromuscular action but may also restore normal brain function. To investigate the effect of BoNT in FMD, a randomized placebo-controlled trial was conducted. **Chapter 3** describes the results of this RCT on BoNT treatment in jerky and tremulous FMD. In total 48 patients were randomized to either BoNT or placebo during 4 months, followed by a one-year open-label follow-up. In the RCT-phase 64% of patients treated with BoNT showed motor improvement on the primary outcome (Clinical Global Impression-Improvement Scale; CGI-I) compared to 57% of the placebo group, a non-significant difference. No between group differences in secondary outcome measures (symptom severity, quality of life, disability, psychiatric symptoms) were found. In the open-label phase, beneficial motor response increased to 81%, which however, did not translate into improvement of quality of life and disability. **Chapter 4** of this thesis discusses the psychiatric profile and non-motor outcome of the patients who participated in the BoNT trial in more depth, distinguishing between

the patients who did and did not show motor improvement (based on CGI-I). Overall, at baseline patients showed high rates of psychiatric disorders (72%), with high rates of anxiety disorders and functional pain disorders. An association between the severity of motor symptoms and anxiety and pain symptoms was shown. Patients with motor improvement after treatment showed a significant decrease in anxiety disorders, which was not seen in patients without motor improvement, showing a possible link between anxiety and motor symptoms. **Chapter 5** elaborates on the results of the long-term follow-up (3-7 years) of the majority (n=46) of patients who participated in the BoNT trial. In 17 patients who continued BoNT treatment at the end of the RCT, 10 still received BoNT treatment. Despite the long symptom-duration at follow-up (median 9 years), the majority of patients showed a sustained response or further improvement of motor symptoms at the end of the long-term follow-up compared to baseline. Again, quality of life and disability did not improve and only two patients had resumed work.

2. Functional movement disorders and the auditory startle reflex

Hypersensitivity to external stimuli and/or exaggerated startle reactions are often described as clinical phenomenon in FMD, especially in functional jerks (5, 6). In some patients the jerks can be elicited when or even before the hammer hits the knee when checking reflexes. **Chapter 6** describes the ASR and classifies different startle syndromes into three categories: hyperekplexia, stimulus-induced disorders and neuropsychiatric startling. Abnormal stress regulation and increased arousal are thought to play an important role in the pathophysiology of FMD. To assess this possible pathophysiological mechanism with a neurophysiologic tool the ASR was used. A study on the ASR in FMD (n=17) vs. healthy age- and gender-matched control subjects (n=15) was conducted **(chapter 7).** In this study we distinguished between the early motor response (latency 1-100/120 ms), representing the characteristic fast brainstem response meant to prepare for possible danger and the late motor response (latency 100/120-1000 ms), representing a slower response meant to orientate towards the source, hence the 'orienting response'. Results were corrected for central nervous system (cns)-active medication and current anxiety disorders. We found a normal patterned but increased early and late ASR compared to controls. There was a relatively high response frequency of rectus abdominis muscle activity. Both a state of hyperarousal (first response) and behavioral components may play a role in the increased startle responses. Results of re-assessment of the ASR after BoNT treatment are described in **chapter 8**. The same patients and control subjects were used as in our first study on the ASR. The early startle response, representing a state of hyperarousal, normalised in combination with motor improvement. The late startle response however remained enlarged at follow-up, suggesting persistent abnormal behavioral processing.

REFERENCES

1. Edwards MJ, Stone J, Lang AE. From psychogenic movement disorder to functional movement disorder: It's time to change the name. Mov Disord. 2013.
2. Stone J, Edwards M. Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology. 2012;79(3):282-4.
3. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. JNeurolNeurosurgPsychiatry. 2014;85(2):220-6.
4. Hallett M. Mechanism of action of botulinum neurotoxin: Unexpected consequences. Toxicon. 2017.
5. Ganos C, Aguirregomozcorta M, Batla A, Stamelou M, Schwingenschuh P, Munchau A, et al. Psychogenic paroxysmal movement disorders--clinical features and diagnostic clues. ParkinsonismRelat Disord. 2014;20(1):41-6.
6. Thenganatt MA, Jankovic J. Psychogenic (Functional) Movement Disorders. Continuum (Minneap Minn). 2019;25(4):1121-40.

General discussion

10

FMD patients may suffer from long-lasting invalidating symptoms with poor quality of life and general functioning. Although there is a growing interest in these disorders, randomized studies on treatment are lacking and the pathophysiology remains largely elusive. In this chapter the most important findings of this thesis will be summarized and put into perspective.

1. Conclusions and implications BoNT trial

Effect on motor symptoms

The inspiration to perform the BoNT trial, came from the observation that patients who eventually were diagnosed to have a functional disorder, had a beneficial response to botulinum toxin injections. In literature similar results have been reported in functional jerks and fixed dystonia, (1, 2). In writer's cramp the corticomotor representation has been shown to be temporarily reversed in patients when treated with BoNT (3). A mechanism which can also be potentially beneficial in FMD. On the other hand FMD are traditionally known to show remarkable placebo responses including dramatic and immediate responses to sub-therapeutic dosages or placebo (sterile saline) (1, 4, 5). In fact, resolution of symptoms after administration of a placebo is 'prove' of the diagnosis according to widely used diagnostic criteria (6). The BoNT trial is the first to confirm the large placebo response in FMD in a double-blinded manner, with an equal benefit (60%) on motor symptoms in the BoNT and the placebo arm (7). An effect which was sustained and increased (80% motor response) in the open-label follow-up study. Because we found an unexpected high placebo effect, we will start by further elaborating on the placebo effect and its underlying neural mechanisms after which we will relate it to the pathophysiology of FMD and will discuss the different aspects of the BoNT RCT, including the possibility of an effect of BoNT.

The pathophysiology of the placebo effect

The definition of a placebo is the psychobiological reaction in the brain of the patient following administration of an inert substances (8). It is largely dependent on the psychosocial context (i.e. the words and ritual) it is given in. The placebo effect is based on two key mechanisms: expectation and learning. Positive expectations often lead to anxiety reduction which is associated with clinical improvement. Vice versa negative expectations may lead to worsening of symptoms or adverse reactions (nocebo effect). Learning effects concern for example a previous experience that a treatment was effective creating powerful placebo responses. The two underlying neural pathways most often studied in this field are the opioid system and the dopaminergic system. Evidence that the placebo effect can act on different neural pathways, is that the analgesic effect of placebo can be mediated by the mu-opioid receptor as well as the

CB1 cannabinoid receptor, dependent on whether patients were previously treated with opioid-acting (9) or cannabinoid-acting medication respectively (10). Likewise, dopamine receptors in the striatum are activated after placebo administration in patients with Parkinson's disease. There are intra-operative single-neuron recordings during deep brain stimulation (DBS) showing a disappearance of pathological bursting activity in the subthalamic nucleus as part of the response to placebo (11, 12). The power of expectation is illustrated by the fact that telling a patient he/she is injected with a pain killer (which is actually sterile saline), is equivalent to a hidden administration of 6-8 mg of morphine (13, 14). This is strengthened by the observation that patients with cognitive impairment, especially with disturbed prefrontal functioning, experience smaller placebo responses (15).

The placebo response in relation to the pathophysiology of FMD

Very little is known about the neurobiological underpinnings of the placebo response in FMD. Although the exact etiology of FMD remains elusive, it is hypothesized that the pathophysiology of FMD is strongly dependent on pathological prior beliefs and expectations (16). These priors may be altered by the patients expectations of treatment. As such it is understandable that FMD patients are especially sensitive in this matter. In this context, in our RCT we studied a link between the expectations of patients beforehand and the effect of treatment on motor symptoms. Post-hoc analyses did not reveal a significant effect of the patients 'belief' in whether they received placebo or BoNT, nor did it show an effect of the 'belief' at baseline whether the treatment would be a success. Brain regions involved in the pathophysiology of FMD (amygdala-frontal connections) (17) overlap with that of the placebo response, suggesting an underlying neural basis. Anxiety symptoms frequently improved after intervention in our BonT study population. In a Positron Emission Tomography (PET) – study on Selective Serotonin Reuptake Inhibitors (SSRI's) in patients with social anxiety disorders, a change in cerebral blood flow in amygdala-frontal projections and cingulate cortices pre-and post-placebo treatment could distinguish between treatment responders and non-responders (18, 19). There was no difference in cerebral blood flow between the placebo and the SSRI-group, which suggests that SSRI's as well as placebo act on the same neural pathways involving the amygdala.

Interestingly, placebo's have also been linked to physical performance in a sense that they can decrease muscle fatigue and enhance endurance in healthy subjects (20). This even started an ethical discussion whether placebo-use in athletes would be considered 'doping'-use (21). When starting an exercise, a motor program is commenced to recruit the correct muscles which is influenced by emotion, motivation and prior experiences in performing the task. This has many similarities with FMD in

the context of expectations and prior beliefs as mentioned before (16). In summary, the underlying neural pathways of the placebo response and motor preparation seem to be intertwined and highly affected by prior expectations, which is supposed to be at the core of FMD.

Considerations on performing RCT's in FMD

In terms of the treatment effect in the BoNT study we found 60% improvement in the RCT-phase and 80% in the open-label phase. Other randomized treatment studies in FMD are not placebo-controlled, but do reveal significant and clinically relevant improvement in a large proportion of patients (30-70%), often with chronic symptoms (> 1 year) with a considerable follow-up duration of 3-12 months (22-28). This raises questions on the supposed poor prognosis in FMD. It should be noted though that these studies concern heterogeneous patient groups using different therapies (disease education, physical/rehabilitation therapy, disease education and transcranial magnetic stimulation). It is likely, given the sensitivity of FMD patients for placebo effects, these effects also play an important role in these studies. However, none of these studies are placebo-controlled and the placebo response has never been studied in a double-blinded manner in FMD before. Since this information was lacking, the power calculation of the BoNT RCT was based on a similar RCT in focal hand dystonia (placebo response: 30%). Placebo responses vary between different disorders, Parkinson's disease with response rates between 16-55% (29), pain disorders (e.g. migraine) with responses of about 30% (30) and 50% in depressive disorders (31). With hindsight, the placebo-response was underestimated in our trial and one could argue that we should have predicted it to be larger than in other movement disorder such as focal hand dystonia.

Another methodological issue concerns the possibility that spontaneous remission of symptoms may have occurred. In this matter it would have been insightful to have added a third or fourth treatment arm consisting of a less invasive therapy (e.g. massage) or standard care. In future trials the current study could help estimating the placebo-effect in power-analyses. Moreover the large proportion of patients that showed improvement is encouraging.

Concerning feasibility of this RCT, taking into account a larger placebo response would have required a much larger patient population. Collecting a larger patient population, would have been challenging given the large number of patients who had to be screened (n=239) to reach our target (n=48). This stresses one of the difficulties in conducting clinical trials in this patient group. Despite the fact that our center specializes in (jerky and tremulous) FMD and neurologists throughout the country

were asked to refer all possible cases, we had to make a large effort and extend the inclusion criteria from jerks to including functional tremor as well to reach our target. Pleizier et al. (25), who conducted a trial on disease education in FND also reported a large number of patients who had to be screened to include their target population (20% of screened patients were included, which is comparable with our numbers). Further, the majority of patients did not return questionnaires in the follow up study indicating a possible poor willingness to participate.

In our study the majority of patients screened did not fulfill inclusion criteria. The most common reason (50%) was that complaints diminished or even resolved in some cases. These patients were recruited from a database in which patients were consecutively collected over a longer time period (years), which might explain the spontaneous remissions, which is a well-known feature of FMD. However, the high rate of remissions (50%) is a remarkable finding. It could mean that the prognosis or natural history in FMD is much more favorable than expected based on current literature (32). This also emphasizes that the patients who did participate in our RCT were chronically affected, which makes the results of our study even more notable.

In the introduction of this thesis the hypothesis was formulated that BoNT treatment would 'break the vicious cycle' implicating that potentially a small number of treatment sessions would be enough to restore the abnormal movements. This was found to be partially true. At the end of the open-label study, 17 of 44 patients (39%) continued treatment. These were all patients in whom symptoms relapsed every 3 months. In 14% of the initially treated patients, symptoms improved or resolved, and therefore did not require treatment anymore. These results are comparable to a trial in Transcranial Magnetic Stimulation (TMS) of Garcin et al., where 12 of 33 (36%) relapsed after 12 months and were offered additional TMS (24). Similar to our study, placebo effects played an important role in this study, where both TMS (active treatment) and spinal root magnetic stimulation (RMS) (inactive treatment) were found to be equally beneficial.

Apart from a large placebo response, there may be an underestimation of the effect of BoNT. A small sample size increases the risk of uneven distribution of baseline characteristics during randomization. Because of the relatively small sample size, patients in the placebo arm seemed to have worse symptoms at baseline (higher scores on the PMDRS, CGI-S and self-rated VAS scale), which could potentially generate a phenomenon called 'regression towards the mean', where extremer values tend to get closer to the average at a second measurement. The non-dichotomized CGI-I assessed by the investigator does show a larger proportion of patients with a

score 1 ('very much improved') and 2 'much better' (36,0% BoNT vs. 21,7% placebo) in the BoNT compared to the placebo group. This idea is strengthened by the results of the open-label study where a large proportion improved (81,4% on the CGI-I scored by investigator and 67,4% scored by the patients). However, the large placebo response found in the RCT-phase remains.

Effect on non-motor symptoms and quality of life

Despite the promising effect of treatment found on motor symptoms, the lack of effect on quality of life, disability and general functioning (e.g. returning to work) is disappointing. This could be due to several reasons. There is a lack in validated outcome measures for FMD. A task force has been established to tackle this problem (33). Other studies in FMD, such as Nielsen et al. (22) (physical therapy) and Pleizier et al. (25) (disease education) did find improvement on Quality-of-life measures (SF-36). The RCT of Pleizier et al. assessed patients with a short symptom duration (< 1 year), who in general have a more favorable prognosis. In the trial of Nielsen et al. patients with functional motor symptoms were treated with a specialized 5-day physiotherapy program which was compared to standard care. Patients with severe anxiety, depression, pain, fatigue or disability were excluded though. Another possible explanation for the lack of effect on non-motor symptoms, could be that there is a difference in prognosis and quality of life in different subgroups of FMD. There is some evidence that functional (axial) jerks and tremor have a relatively poor prognosis compared to other forms of FMD (2, 32), although physical functioning, work and social adjustment have been found to be less affected in jerks/tremor compared to gait disorders (34). All in all, it would be helpful to neurologists and patients to have some insight beforehand which patients would respond well to treatment and which patients would not. When performing the RCT, our impression was that patients with severe pain responded worse to treatment. Although this could not be identified as a negative treatment predictor, pain symptoms were associated with worse motor symptoms.

Long-term follow-up

The majority of patients (n=46) was re-assessed after 3-7 years. Of the 17 patients who continued BoNT at the end of the open-label study, 10 patients still received BoNT treatment. Interestingly, only a small proportion of patients relapsed in terms of motor symptoms and most were stable or even had further improved. Although this was based on self-assessment scales, and 13 of 46 patients received other treatments, outcome is better than what one would expect based on literature.

2. Conclusions and implications auditory startle reflex in FMD

To our knowledge, our study was the first to assess the ASR systematically in FMD and to distinguish between the early and late part of the startle response. Before our study, the study of Thompson et al. representing a case-control study of 5 patients with stimulus-sensitive jerks compared to healthy controls was the only study available assessing the startle reflex in FMD (35). In this study long latencies (> 100 ms) and a variable recruitment pattern are described argumentative of the diagnosis FMD. Our results instead show an exaggerated but normal patterned early brainstem mediated startle reflex compared to healthy controls. The high frequency of responses in the rectus abdominis muscle in terms of recruitment pattern was remarkable, and was solely observed in patients with functional abdominal jerks. We previously speculated that this could be a 'start-react' phenomenon, a well-known symptom in athletes who perform with faster reaction-times after being startled by a loud start signal. In our patients this means that involuntary but cortically prepared (bereitschaftspotential) jerky movements are released at faster latencies, elicited by a startle reflex.

In line with our presumption, the second behaviorally influenced response was enlarged in patients compared to controls and did show much more variation in onset latencies, recruitment pattern and duration of EMG-activation. Based on our study we assume that the results found by Thompson et al. mainly reflect the second responses. Without distinguishing between the early and late responses, the first uniform brainstem mediated motor responses might be overlooked.

In terms of pathophysiological implications, it is assumed that the enlarged early ASR reflects a state of hyperarousal (36). There is a growing body of evidence revealing signs of stress related features including impaired habituation of sympathetic skin conductance (37), increased mean heart rate/decreased rest vagal tone and heart rate variability (38) and increased activation of brain networks involved in threat detection (39). Moreover, patients with FMD show signs of abnormal sensory processing expressed as abnormal sensory sensitivity (e.g. loud noises, pain) which may trigger or amplify symptoms (40). Also, FMD patients tend to be hyperfocused on sensory experiences, creating a state of hypervigilance and hyperarousal. In the study of Ranford et al. sensory processing patterns were assessed using a self-report questionnaire (Adolescent/Adult Sensory Profile) in a retrospective cross-sectional cohort of patients with a Functional Neurological Disorder (FND). Interestingly multivariate regression analysis showed that the presence of an anxiety disorder independently predicted sensory processing abnormalities in this study, which is in accordance with the high rate of anxiety disorders found in our population. The authors of this study suggest abnormal sensory processing to be a vulnerability trait for developing FND (40).

One of the key structures involved in stress regulation and affective processing is the amygdala (41), which also modulates the startle reflex (42, 43). Imaging studies have made the link between the affective processing mediated by the amygdala and motor symptoms in FMD, revealing a possible underlying neural mechanism (17, 44-46). Although it was previously thought that the adult nervous system was a fixed structure, recent insights have shown that physiological and structural change can occur under the influence of environmental factors and epigenetic regulation (47). The old idea of Charcot that functional disorders (previously called conversion disorders), since he defined them as a neurologic disorder, have a hereditary origin is being revived. The biopsychosocial model still applies here, where genetic *predisposing* factors make individuals more prone to develop functional symptoms under the influence of *precipitating* (e.g. physical trauma) and *perpetuating* (chronic stress/pain) factors. Childhood trauma and maltreatment, which are highly prevalent in FMD, are also risk factors for developing mental disorders such as depression (48), post-traumatic stress disorders (49) and anxiety disorders (50). Childhood trauma is linked to chronic stress which induces changes in the hypothalamic-pituitary-adrenal axis and inflammatory pathways which causes damage to the developing brain (51). Several forms of childhood abuse are associated with smaller hippocampal volumes (52). Not only childhood maltreatment, but also recent stressors are associated through inflammatory-mediated pathways with lower levels of brain-derived neurotrophic factor (BDNF), increased cortisol levels and smaller left hippocampal volumes (53). This links trauma and stress to structural brain changes through epigenetic mechanisms. Although there is still no literature on FMD and genetic factors, there are some studies linking the A-allele in tumor necrosis factor to be a risk factor for somatoform disorders (54), but there are also several negative studies exploring the COMT gene (55) and the serotonergic pathway (56).

Much less is known of the less studied late (orienting) response of the ASR. Enlargement of the late response has been described in patients with a post-traumatic stress disorder (PTSD) (57). It also has been systematically assessed by our group in Latah, an Indonesian culture-specific neuropsychiatric startle syndrome (58) which is characterized by stereotyped repetitive behavior elicited by loud noises. This behavior typically involves 'forced obedience' (involuntary immediate obedience of commands), coprolalia (involuntary swearing) and echolalia/echopraxia (copying words or actions). Its etiology is still debated since it encompasses both neurologic as well as psychiatric features. As in FMD, in Latah the late response has been found to be enlarged including long-lasting stereotyped motor responses and vocal. This concerned patients who revealed a history of excessive startling. However, although there are some similarities as suggestibility, other factors supporting a functional origin in Latah are lacking. In all,

the pathophysiology of the late response and its relation to different neuropsychiatric startle disorders remains to be elucidated.

Effect of treatment on early and late startle response

Results of our study show that the early response of the ASR normalized after treatment with BoNT. Interestingly, in a separate study we found that anxiety disorders significantly decreased in combination with motor improvement after treatment, together with a significant association between anxiety symptoms and the severity of motor symptoms. The abnormal state of hyperarousal, which is hypothesized to be part of the underlying pathophysiological mechanism of FMD, could be linked to anxiety as well as motor symptoms which is expressed in enlargement of the early ASR. Vice versa, it is possible that improvement of motor symptoms may also lead to improvement of abnormal stress regulation and anxiety symptoms. This is further strengthened by the SSR, a physiological measure of the autonomic nervous system, which was enlarged in FMD compared to controls at baseline and normalized after treatment.

In contrast to the early response, the late response remained enlarged in FMD patients after one-year treatment with BoNT. This strengthens the idea that the second response of the ASR is more specific for FMD and is influenced by behavior. No difference between patients who responded well to treatment and those who did not could be identified, probably due to the small sample size. However, the late response could possibly serve as neurophysiological aid to the diagnosis.

Future research

It would be interesting to conduct RCT's comparing different treatment arms, running from care-as-usual to invasive therapies in order to explore and quantify the placebo response. This may also give insight if certain treatment regimens have more effect on motor symptoms or on non-motor symptoms. Exploring the nature of the placebo-effect was not the aim of this thesis. However, given the large placebo-effect found and the historical intertwining of placebo with FMD, it seems to be a logic step to conduct studies to discover the underpinnings of the placebo response in this patient group. Studies involving neuro-imaging such as fMRI and PET, but also neurophysiologic measures of motor preparation should be considered.

Placebo-therapy in FMD

Our study also suggests that placebo therapies may be beneficial and may be used more often in FMD. Still, its use is controversial due to ethical issues. A recent survey amongst movement disorder specialists showed that placebo use has increased in

the past decade (59). In the US 50% of physicians have used placebo for a variety of disorders including gastro-intestinal, immune and neurologic disorders (60, 61). Despite its wide use, evolving knowledge on the mechanisms and the fact that placebo's can produce clinically meaningful improvement in variable conditions, the moral objections remain rigid. In this view it is important to distinguish between the use of placebo in diagnosing or in treating FMD. The former should be used with caution, given the large placebo responses which can occur in other movement disorders as well, such as Parkinson's disease which might lead to a misdiagnosis (62). The main concern here is not the placebo use itself, but the hidden nature of using a placebo, which might endanger the physician-patient alliance. However, studies in neurologists and psychiatrists treating patients with functional seizures and FMD have shown that placebo therapy can be used to build a relationship with a patient by following and monitoring symptoms, eventually leading to acceptance of the diagnosis by the patient, which may help to recover (63). The 'deceptive' nature of placebo-use and the reason that for instance the American Medical Association advices against its use, is its supposed 'inert' nature. In other words, it is unethical as a physician to administer something which has no beneficial effect on the condition of patients. However, with our current knowledge the 'inert' nature of placebo's is no longer scientifically substantiated. Another concern is the possible iatrogenic harm, caused especially by 'active' placebo's, for instance medication registered for a different condition which is of course an important issue to be looked after. Placebo has been shown to help in avoiding iatrogenic harm in 'real' medication. This is nicely shown in a study on children with ADHD who were set on an optimal medication regime, after which the dose was reduced with 50% for one month (Sandler et al. 2010). Half of the group was given placebo to enhance the dose which was told to the parents and the children. The effect in the placebo group was equal to the 100% dose and more effective than the 50% dose alone. This study also shows that deceiving patients is not necessary in order for placebo therapy to work (64). In our own experience when carrying out the RCT, patients did not mind the use of placebo and would consider using it as a therapy if it would help them. This is strengthened by several studies showing that patients are more open-minded and positive about placebo use, than physicians (65-67). In all, one might ask themselves the following question: "Is it ethical to withhold placebo therapy from patients with FMD, knowing that it could possibly alleviate suffering?". Therefore, we would like to argue to explore the use of placebo-therapy both in the consultation room as for research purposes in FMD patients. Off course this should always be carried out, keeping in mind the medical-ethical considerations and putting the interest of the patient first.

N=1 trial

Although the difference between BoNT and placebo was very small (64% BoNT vs. 58% placebo), a possible effect of BoNT cannot be ruled out. At the end of the follow-up n=10 patients still received BoNT injections. It would be interesting to perform a n=1 trial in these patients to further delineate whether BoNT or placebo causes symptom improvement.

Outcome measures in FMD

As mentioned before, one of the challenges in performing RCT's in FMD is the lack of validated outcome measures. Our primary outcome measure (CGI-I) was based on standardized video recordings assessed by a movement disorder specialist. This off course, only reflects a brief moment which is problematic given the paroxysmal and variable nature of FMD. This issue was partly resolved by the outcome measures used who were assessed by the patient. In a future trial, it would be interesting to use an ambulatory outcome measure to record symptoms for a longer period of time in a patient's home setting, using for instance an actigraph in combination with a symptom diary. Also, there is a desperate need for research on outcome measures in FMD. Based on our experience a tailored approach should be followed based on the specifics of the outcome measure and the symptoms.

Homogeneous or heterogeneous patient groups

It is still a matter of debate if treatment studies should address mixed FMD groups or specific phenotypes, in other words 'to lump or to split'. Advantages of splitting is that the patient group is as uniform as possible, removing possible bias based on symptom characteristics. It is possible that specific therapies are less effective in certain patient groups, for instance it is possible that BoNT (or placebo) injections wouldn't work in patients with functional gait disorders or functional limb weakness. However, this might not be true in therapies targeting symptoms in a more general manner, as for instance disease education, physical therapy or Cognitive behavioral Therapy (CBT). Also, underlying pathophysiological mechanisms which might be different in different FMD symptoms might be missed or overlooked. A disadvantage of the 'splitting principle' is that it comes at the cost of generalizability to other forms of FMD. However, one could also reason otherwise, that if a treatment is found effective in a mixed group of FMD, it also applies for a single phenotype. We advocate a tailored approach where the pros and cons are taken into account when designing a study and that the aim of the study should determine whether to 'lump' or to 'split'.

Future studies on the ASR

Lastly, the ASR is a relatively simple neurophysiological tool, which can be easily assessed and give information on the autonomic and affective system. For future studies, we recommend to use additional modalities (e.g. tactile stimulation) next to auditory stimuli to increase the response rate. Also, since we are the first group to discriminate between the first and second response, it would be interesting to further explore the second response and whether the enlargement is specific to FMD. In order to do so we suggest comparing different patient groups, both neurologic (organic myoclonus, tics) and for instance psychiatric disorders (anxiety disorders). Further, it would be interesting to use the ASR in treatment studies in larger groups to explore it's feasability as outcome measures and as marker for treatment response.

Fortunately, during the past decades there is a growing interest in the pathophysiology and treatment of FMD, contributing to better research and understanding of the disease which leads to better patient care. However, as illustrated by the suggestions of future research above, there is still a lot to gain.

REFERENCES

1. Ganos C, Aguirregomozcorta M, Batla A, Stamelou M, Schwingenschuh P, Munchau A, et al. Psychogenic paroxysmal movement disorders--clinical features and diagnostic clues. ParkinsonismRelat Disord. 2014;20(1):41-6.
2. van der Salm SM, Erro R, Cordivari C, Edwards MJ, Koelman JH, van den Ende T, et al. Propriospinal myoclonus: clinical reappraisal and review of literature. Neurology. 2014;83(20):1862-70.
3. Byrnes ML, Thickbroom GW, Wilson SA, Sacco P, Shipman JM, Stell R, et al. The corticomotor representation of upper limb muscles in writer's cramp and changes following botulinum toxin injection. Brain. 1998;121 (Pt 5):977-88.
4. Edwards MJ, Bhatia KP, Cordivari C. Immediate response to botulinum toxin injections in patients with fixed dystonia. Mov Disord. 2011;26(5):917-8.
5. Monday K, Jankovic J. Psychogenic myoclonus. Neurology. 1993;43(2):349-52.
6. Gupta A, Lang AE. Psychogenic movement disorders. Current Opinion in Neurology. 2009;22(4).
7. Dreissen YEM, Dijk JM, Gelauff JM, Zoons E, van Poppelen D, Contarino MF, et al. Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. J Neurol Neurosurg Psychiatry. 2019;90(11):1244-50.
8. Carlino E, Piedimonte A, Benedetti F. Nature of the placebo and nocebo effect in relation to functional neurologic disorders. Handb Clin Neurol. 2016;139:597-606.
9. Zhang W, Guo J, Zhang J, Luo J. Neural mechanism of placebo effects and cognitive reappraisal in emotion regulation. Prog Neuropsychopharmacol Biol Psychiatry. 2013;40:364-73.
10. Benedetti F, Amanzio M, Rosato R, Blanchard C. Nonopioid placebo analgesia is mediated by CB1 cannabinoid receptors. Nat Med. 2011;17(10):1228-30.
11. Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, Pesare M, et al. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. Nat Neurosci. 2004;7(6):587-8.
12. Benedetti F, Lanotte M, Colloca L, Ducati A, Zibetti M, Lopiano L. Electrophysiological properties of thalamic, subthalamic and nigral neurons during the anti-parkinsonian placebo response. J Physiol. 2009;587(Pt 15):3869-83.
13. Levine JD, Gordon NC, Smith R, Fields HL. Analgesic responses to morphine and placebo in individuals with postoperative pain. Pain. 1981;10(3):379-89.
14. Levine JD, Gordon NC. Influence of the method of drug administration on analgesic response. Nature. 1984;312(5996):755-6.
15. Benedetti F. Placebo analgesia. Neurol Sci. 2006;27 Suppl 2:S100-2.
16. Edwards MJ, Adams RA, Brown H, Parees I, Friston KJ. A Bayesian account of 'hysteria'. Brain. 2012;135(Pt 11):3495-512.
17. Voon V, Brezing C, Gallea C, Ameli R, Roelofs K, LaFrance WC, Jr., et al. Emotional stimuli and motor conversion disorder. Brain. 2010;133(Pt 5):1526-36.

18. Faria V, Appel L, Ahs F, Linnman C, Pissiota A, Frans O, et al. Amygdala subregions tied to SSRI and placebo response in patients with social anxiety disorder. Neuropsychopharmacology. 2012;37(10):2222-32.
19. Faria V, Ahs F, Appel L, Linnman C, Bani M, Bettica P, et al. Amygdala-frontal couplings characterizing SSRI and placebo response in social anxiety disorder. Int J Neuropsychopharmacol. 2014;17(8):1149-57.
20. Pollo A, Carlino E, Benedetti F. Placebo mechanisms across different conditions: from the clinical setting to physical performance. Philos Trans R Soc Lond B Biol Sci. 2011;366(1572):1790-8.
21. Piedimonte A, Benedetti F, Carlino E. Placebo-induced decrease in fatigue: evidence for a central action on the preparatory phase of movement. Eur J Neurosci. 2015;41(4):492-7.
22. Nielsen G, Buszewicz M, Stevenson F, Hunter R, Holt K, Dudziec M, et al. Randomised feasibility study of physiotherapy for patients with functional motor symptoms. J Neurol Neurosurg Psychiatry. 2017;88(6):484-90.
23. Jordbru AA, Smedstad LM, Klungsoyr O, Martinsen EW. Psychogenic gait disorder: a randomized controlled trial of physical rehabilitation with one-year follow-up. J Rehabil Med. 2014;46(2):181-7.
24. Garcin B, Mesrati F, Hubsch C, Mauras T, Iliescu I, Naccache L, et al. Impact of Transcranial Magnetic Stimulation on Functional Movement Disorders: Cortical Modulation or a Behavioral Effect? Front Neurol. 2017;8:338.
25. Pleizier M, de Haan RJ, Vermeulen M. Management of patients with functional neurological symptoms: a single-centre randomised controlled trial. J Neurol Neurosurg Psychiatry. 2017;88(5):430-6.
26. Sharpe M, Walker J, Williams C, Stone J, Cavanagh J, Murray G, et al. Guided self-help for functional (psychogenic) symptoms: a randomized controlled efficacy trial. Neurology. 2011;77(6):564-72.
27. Kompoliti K, Wilson B, Stebbins G, Bernard B, Hinson V. Immediate vs. delayed treatment of psychogenic movement disorders with short term psychodynamic psychotherapy: randomized clinical trial. Parkinsonism Relat Disord. 2014;20(1):60-3.
28. Vizcarra JA, Lopez-Castellanos JR, Dwivedi AK, Schmerler DA, Ries S, Espay AJ. OnabotulinumtoxinA and cognitive behavioral therapy in functional dystonia: A pilot randomized clinical trial. Parkinsonism Relat Disord. 2019.
29. Goetz CG, Wuu J, McDermott MP, Adler CH, Fahn S, Freed CR, et al. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. Mov Disord. 2008;23(5):690-9.
30. Bendtsen L, Mattsson P, Zwart JA, Lipton RB. Placebo response in clinical randomized trials of analgesics in migraine. Cephalalgia. 2003;23(7):487-90.
31. Dworkin RH, Katz J, Gitlin MJ. Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain. Neurology. 2005;65(12 Suppl 4):S7-19.
32. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. JNeurolNeurosurgPsychiatry. 2014;85(2):220-6.

33. Nicholson TR, Carson A, Edwards MJ, Goldstein LH, Hallett M, Mildon B, et al. Outcome Measures for Functional Neurological Disorder: A Review of the Theoretical Complexities. J Neuropsychiatry Clin Neurosci. 2020;32(1):33-42.
34. Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J. The prognosis of functional limb weakness: a 14-year case-control study. Brain. 2019;142(7):2137-48.
35. Thompson PD, Colebatch JG, Brown P, Rothwell JC, Day BL, Obeso JA, et al. Voluntary stimulus-sensitive jerks and jumps mimicking myoclonus or pathological startle syndromes. Movement Disorders. 1992;7(3).
36. Baizabal-Carvallo JF, Hallett M, Jankovic J. Pathogenesis and pathophysiology of functional (psychogenic) movement disorders. Neurobiol Dis. 2019;127:32-44.
37. Lader M, Sartorius N. Anxiety in patients with hysterical conversion symptoms. JNeurolNeurosurgPsychiatry. 1968;31(5):490-5.
38. Maurer CW, Liu VD, LaFaver K, Ameli R, Wu T, Toledo R, et al. Impaired resting vagal tone in patients with functional movement disorders. Parkinsonism Relat Disord. 2016;30:18-22.
39. Kozlowska K, Spooner CJ, Palmer DM, Harris A, Korgaonkar MS, Scher S, et al. "Motoring in idle": The default mode and somatomotor networks are overactive in children and adolescents with functional neurological symptoms. Neuroimage Clin. 2018;18:730-43.
40. Ranford J, MacLean J, Alluri PR, Comeau O, Godena E, LaFrance WC, Jr., et al. Sensory Processing Difficulties in Functional Neurological Disorder: A Possible Predisposing Vulnerability? Psychosomatics. 2020;61(4):343-52.
41. Liddell BJ, Brown KJ, Kemp AH, Barton MJ, Das P, Peduto A, et al. A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. Neuroimage. 2005;24(1):235-43.
42. Angrilli A, Mauri A, Palomba D, Flor H, Birbaumer N, Sartori G, et al. Startle reflex and emotion modulation impairment after a right amygdala lesion. Brain. 1996;119 (Pt 6):1991-2000.
43. Seignourel PJ, Miller K, Kellison I, Rodriguez R, Fernandez HH, Bauer RM, et al. Abnormal affective startle modulation in individuals with psychogenic [corrected] movement disorder. Mov Disord. 2007;22(9):1265-71.
44. Voon V, Brezing C, Gallea C, Hallett M. Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. Mov Disord. 2011;26(13):2396-403.
45. Aybek S, Nicholson TR, Zelaya F, O'Daly OG, Craig TJ, David AS, et al. Neural correlates of recall of life events in conversion disorder. JAMA Psychiatry. 2014;71(1):52-60.
46. Aybek S, Nicholson TR, O'Daly O, Zelaya F, Kanaan RA, David AS. Emotion-motion interactions in conversion disorder: an FMRI study. PLoS One. 2015;10(4):e0123273.
47. Frodl T. Do (epi)genetics impact the brain in functional neurologic disorders? Handb Clin Neurol. 2016;139:157-65.
48. Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol. 1997;48:191-214.

49. Bonne O, Vythilingam M, Inagaki M, Wood S, Neumeister A, Nugent AC, et al. Reduced posterior hippocampal volume in posttraumatic stress disorder. J Clin Psychiatry. 2008;69(7):1087-91.
50. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001;49(12):1023-39.
51. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008;455(7215):894-902.
52. Frodl T, Reinhold E, Koutsouleris N, Reiser M, Meisenzahl EM. Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. J Psychiatr Res. 2010;44(13):799-807.
53. Mondelli V, Cattaneo A, Murri MB, Di Forti M, Handley R, Hepgul N, et al. Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: a pathway to smaller hippocampal volume. J Clin Psychiatry. 2011;72(12):1677-84.
54. Gil FP, Giegling I, Reisch N, Hartmann AM, Konte B, Schwarz MJ, et al. Association of somatoform disorder symptoms with genetic variants potentially involved in the modulation of nociception. Psychiatr Genet. 2011;21(1):50.
55. Jakobi J, Bernateck M, Tran AT, Holm L, Volkmann L, Buers D, et al. Catechol-O-methyltransferase gene polymorphisms are not associated with multisomatoform disorder in a group of German multisomatoform disorder patients and healthy controls. Genet Test Mol Biomarkers. 2010;14(3):293-7.
56. Koh KB, Choi EH, Lee YJ, Han M. Serotonin-related gene pathways associated with undifferentiated somatoform disorder. Psychiatry Res. 2011;189(2):246-50.
57. Siegelaar SE, Olff M, Bour LJ, Veelo D, Zwinderman AH, van BG, et al. The auditory startle response in post-traumatic stress disorder. ExpBrain Res. 2006;174(1):1-6.
58. Bakker MJ, van Dijk JG, Pramono A, Sutarni S, Tijssen MA. Latah: an Indonesian startle syndrome. Mov Disord. 2013;28(3):370-9.
59. LaFaver K, Lang AE, Stone J, Morgante F, Edwards M, Lidstone S, et al. Opinions and clinical practices related to diagnosing and managing functional (psychogenic) movement disorders: changes in the last decade. Eur J Neurol. 2020;27(6):975-84.
60. Sherman R, Hickner J. Academic physicians use placebos in clinical practice and believe in the mind-body connection. J Gen Intern Med. 2008;23(1):7-10.
61. van Tilburg MA, Palsson OS, Levy RL, Feld AD, Turner MJ, Drossman DA, et al. Complementary and alternative medicine use and cost in functional bowel disorders: a six month prospective study in a large HMO. BMC Complement Altern Med. 2008;8:46.
62. Baik JS, Han SW, Park JH, Lee MS. Psychogenic paroxysmal dyskinesia: the role of placebo in the diagnosis and management. Mov Disord. 2009;24(8):1244-5.
63. Rommelfanger KS. Opinion: A role for placebo therapy in psychogenic movement disorders. NatRevNeurol. 2013;9(6):351-6.

64. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One. 2010;5(12):e15591.

65. Lynoe N, Mattsson B, Sandlund M. The attitudes of patients and physicians towards placebo treatment--a comparative study. Soc Sci Med. 1993;36(6):767-74.

66. Hull SC, Colloca L, Avins A, Gordon NP, Somkin CP, Kaptchuk TJ, et al. Patients' attitudes about the use of placebo treatments: telephone survey. BMJ. 2013;347:f3757.

67. Bishop FL, Howick J, Heneghan C, Stevens S, Hobbs FD, Lewith G. Placebo use in the UK: a qualitative study exploring GPs' views on placebo effects in clinical practice. Fam Pract. 2014;31(3):357-63.

Case illustrations

11

While working on this thesis, we often thought that it was a shame that the stories of the patients who participated remained untold since they were so remarkable. In the next paragraphs a few illustrative patients are described.

Patient 1 represents a 56-year-old woman. She suffered from jerky movements of the left leg and dystonic posturing with inward positioning of the ankle and foot, which predominantly occurred when she was sitting. Her symptoms had started after an arthroscopy of the left knee where she felt that the local anesthetic of the femoral nerve went 'wrong'. Touching the left leg and checking reflexes would elicit the movements. The patient could resolve the dystonic posturing by tapping the upper leg at a certain spot. EMG of the femoral nerve was normal. One year after these complaints started, the patient suffered from a psychosis and was admitted for several months at a psychiatric ward of a general hospital. She recovered with anti-psychotic medication. One year later the patient also experienced an exaggerated startle reaction after someone made a loud noise by slapping his hand on a table. This led to a generalized attack with uncontrollable non-synchronous movements of the arms and legs with vocal utterings and hyperventilation while consciousness was preserved. The patient was admitted to a neurology ward for several days, where an ictal EEG was made without signs of epilepsy. She was discharged from hospital but she remained sensitive to loud noises. We assessed the ASR which revealed an extreme startle reaction with long-lasting (minutes) stereotyped movements, vocal utterings and pre-dominantly second responses (> latencies 100 ms). BoNT treatment of the left leg evidently improved symptoms and the ASR normalized one year after treatment.

Patient 2 is a 41-year-old male, who presented with axial jerks consisting of a short-lasting slight retroflexion of the spine and retraction of the shoulders. These jerks would occur spontaneously, especially in a seating position. He could sense when the symptoms would occur by a preceding sensation of tension building up in his body. He was able to suppress the symptoms, but this would induce temporarily worsening (rebound effect). Further, the symptoms could be elicited by touching a specific point between his shoulder blades. The movements started at a meeting of charismatic Christians, during which people were making ritual movements that were similar to the jerks the patient developed. Symptoms had been present for about 20 years, waxing and waning, but showed worsening in the year prior to visiting the outpatient clinic for this problem. The patient mentioned to have had a lot of stress lately in his personal life because of his partner who suffered from Post-Traumatic Stress Disorder (PTSD) and a dissociative identity disorder. The patient was still able to perform his work as a high school physics and math teacher but found the symptoms to be very

bothersome. An MRI of the spine showed no abnormalities and EEG-EMG with jerk-locked backaveraging showed a bereitschaftspotential (BP) preceding the jerks. He was treated with BoNT several times at the specific location between the shoulder blades but unfortunately did not improve.

Patient 3 is a man aged 52, with a history of Bechterew's disease. He developed jerks of the abdomen and legs, which predominantly occurred in the supine position and which started after a period of severe lower back pain. Especially in the evening before falling asleep, symptoms would occur in episodes which could last for hours with jerks occurring every few seconds. The symptoms waxed and waned for years but worsened again in the past year. Due to these symptoms, the patient was heavily incapacitated and declared unfit to work. It also led to a social isolation which took a toll on his family as well. An MRI scan of the spine was normal, and EEG-EMG with jerk-locked backaveraging showed that the jerks were preceded by a BP. The patient was treated with BoNT in the rectus abdominis muscle once; hereafter the symptoms completely resolved one week after treatment. We made a 'shared decision' not to treat the patient again. At one year follow-up, the symptoms of the patients had returned to baseline severity. The patient refused another injection because of pain during the first treatment session.

Patient 4 is a man of 52 years with an unremarkable medical history. He presented with complaints of involuntary jerks of the left leg for three years. Symptoms would occur mostly in the supine position and were preceded by cramp in the left hip/pelvis region. The symptoms had started with pain in the left hip, which was always a sore spot since he had an infection on this side as a child. Stressful situations but also loud startling noises would elicit symptoms. The patient also experienced hypersensitivity and an itchy feeling of the skin of the whole body. Five years before symptoms started, the patient had a traumatic experience when he saw a child die due to a car accident in front of his house. Because of the symptoms the patient was severely incapacitated and was unfit to perform his work as a gardener. An MRI of the lumbar spine did not show any abnormalities and the jerks were preceded by a BP. Motor symptoms as well as pain reduced significantly with BoNT in the left iliopsoas and rectus femoris muscle and we decided to continue treatment after cessation of the study.

Of course, all these cases encompass clinical signs supportive of a functional origin such as sudden symptom onset, a waxing and waning disease course, suggestibility, entrainment and psychiatric co-morbidity. However, we would like to address a few clinical signs which are similar and nicely illustrated by the abovementioned cases. First there seems to be a clear *physical trigger* in all cases preceding the symptoms.

In some cases, this is a short-lasting event, such as knee surgery (**patient 1**), pain in the hip (**patient 4**). In other cases, there were physical symptoms that slowly emerged, as the musculo-skeletal pain accompanying Bechterew's disease in **patient 3**. Additionally, worsening of symptoms could also be elicited by a specific event, i.e. vitamin B12 injections and an episode of extreme lower back pain. In the second case a physical trigger was missing, although the beginning of the symptoms was clearly linked to this Christian meeting, where movements similar to his motor symptoms were made. Also, the problems in his current relationship triggered the worsening of symptoms in the year prior to consultation. This is in accordance with recent literature, that functional symptoms are often preceded by (minor) physical injuries (1). It is also noteworthy that symptoms occurred near the *location* of the trigger: so the leg after knee operation/hip pain, the abdomen after gastro-intestinal problems and lower back pain. Patients in our study would often tell that they felt that their involuntary movement originated from one spot.

Another similarity of these cases is that they all seem to have some form of *hypersensitivity* to tactile or startling stimuli. In some cases, this was very specific, where touching a specific spot between the shoulder blades would elicit symptoms (**patient 2**), or touching the leg would resolve the symptoms (**patient 1**). In case 4 there was a more generalized sensitivity to tactile stimuli. Other cases (**patient 1, 4**) show hypersensitivity to loud noises and exaggerated startle reactions, together with signs of pathological anxiety in case 1 and 5 (claustrophobia, hyperventilation) which strengthens the hypothesis that an underlying state of *hyperarousal* is part of the pathophysiology of FMD.

In the end, careful observation and taking a good history is the most important tool we have as a physician. History shows that a lot is learned from single case observations (2). It helps to recognize specific symptoms and syndromes which helps to generate hypotheses on pathophysiology and possible treatments. In all, listening to a patient with attention and care, is an important part of the therapy we give.

REFERENCES

1. Parees I, Kojovic M, Pires C, Rubio-Agusti I, Saifee TA, Sadnicka A, et al. Physical precipitating factors in functional movement disorders. JNeurolSci. 2014;338(1-2):174-7.
2. Bloem BR, Monje MHG, Obeso JA. Understanding motor control in health and disease: classic single (n = 1) observations. Exp Brain Res. 2020;238(7-8):1593-600.

Nederlandse samenvatting

12

1. Behandeling van functionele bewegingsstoornissen en de BoNT studie

In **hoofdstuk 2** wordt een overzicht gegeven van functionele neurologische stoornissen. De term 'functioneel' heeft in de afgelopen jaren de meer beladen term 'psychogeen' vervangen. Uit onderzoek blijkt dat de term 'functioneel' voor patiënten het minste weerstand oproept, bovendien ondersteunt het de denkwijze over de pathofysiologie van functionele bewegingsstoornissen (FBS) waarbij het biopsychosociale model wordt aangehouden in plaats van het verouderde dualistisch denken (1). De diagnose FBS is gebaseerd op 'positieve' klinische symptomen zoals afleidbaarheid en het fenomeen "entrainment", waarbij de tremor of spierschokken van de patiënt een van buiten opgelegd ritme aannemen. Deze fenomenen kunnen ook worden gezien als mensen een vrijwillige/geplande beweging maken, waarbij de suggestie wordt gewekt dat functionele symptomen door patiënten bewust te beïnvloeden zijn. Echter patiënten ervaren hun symptomen als onvrijwillig en hebben hier weinig tot geen controle over. Het laten zien van deze fenomenen aan patiënten, kan soms al tot verbetering van symptomen leiden (2). Indien er bij anamnese en lichamelijk onderzoek nog twijfel bestaat over de diagnose, kunnen aanvullende neurofysiologische tests inclusief een simultaan EEG-EMG met "jerk-locked backaveraging" om een bereitschaftspotentiaal (BP) aan te tonen een waardevolle ondersteuning zijn. Als er sprake is van bijkomende psychiatrische stoornissen, kan de patiënt worden verwezen naar een psychiater, echter dit is geen deel van de standaard behandeling. De prognose van functionele neurologische stoornissen is ongunstig: een tot twee derde van de patiënten behouden symptomen of verslechteren op de lange termijn. Dit geldt vooral voor patiënten met chronische klachten (>1 jaar) (3). Een kanttekening hierbij is dat deze cijfers veelal gebaseerd zijn tertiaire verwijscentra. Dit betreft logischerwijs dus patiënten die langdurigere en ernstigere symptomen hebben, waarbij meer gespecialiseerde therapieën nodig zijn.

Er is een gebrek aan wetenschappelijk gefundeerde therapie in FBS. Botuline NeuroToxine (BoNT) heeft zich bewezen als effectieve behandelmethode in verschillende bewegingsstoornissen zoals dystonie. Ook is inmiddels bekend dat BoNT niet alleen de neuromusculaire overgang tijdelijk blokkeert, maar dat het ook veranderingen kan induceren in de hersenen zelf (4). Met andere woorden, BoNT kan dus ook zorgen voor het herstel van hersenfuncties. Om het effect van BoNT bij functionele bewegingsstoornissen te onderzoeken, hebben we een gerandomiseerde placebo-gecontroleerde trial (RCT) opgezet, de resultaten hiervan worden besproken in **hoofdstuk 3**. In deze studie werden er in totaal 48 patiënten met functionele tremor of schokken ingesloten. Er werd gerandomiseerd tussen de behandeling met BoNT of placebo, welke werd gecontinueerd gedurende 4 maanden. Hierna werden alle patiënten gedurende een jaar behandeld met BoNT. In de RCT-fase werd

aangetoond dat 64% van de patiënten verbetering van motorische symptomen liet zien op de primaire uitkomstmaat (Clinical Global Impression – Improvement Scale) na behandeling met BoNT, vergeleken met 57% in de placebogroep. Dit verschil was niet statistisch significant. Er bleken tevens geen verschillen in de secundaire uitkomstmaten (ernst symptomen, kwaliteit van leven, mate van invaliditeit, psychiatrische symptomen) tussen de twee behandelarmen. In de niet-geblindeerde fase van de studie nam de verbetering van motorische symptomen toe naar 81%. **Hoofdstuk 4** beschrijft het psychiatrisch profiel en de uitkomst van de BoNT studie op het gebied van niet-motorische symptomen. Hierbij werd onderscheid gemaakt tussen patiënten die wel en geen motorische verbetering lieten zien op de primaire uitkomstmaat (CGI-I). Aan het begin van de studie bleek 72% van de patiënten te voldoen aan een psychiatrische diagnose, waarbij angststoornissen en functionele pijnstoornissen het vaakst voorkwamen. Verder werd er een associatie aangetoond tussen de ernst van de motorische symptomen en angst- en pijnsymptomen. Ook werd bij patiënten met motorische verbetering na behandeling een verbetering van angststoornissen geobserveerd. **Hoofdstuk 5** geeft de lange termijn (3-7 jaar) uitkomst van de patiënten die hebben meegedaan aan de BoNT studie. Ondanks dat patiënten op het moment van deze studie langdurige symptomen hadden (mediane duur 9 jaar), liet de meerderheid een aanhoudende motorische verbetering dan wel verdere verbetering zien vergeleken met het begin van de BoNT studie. Dit vertaalde zich opnieuw niet in verbetering op de secundaire uitkomstmaten, zoals kwaliteit van leven en slechts twee patiënten konden hun dagelijkse werkzaamheden hervatten.

2. Functionele bewegingsstoornissen en de schrikreflex

Overgevoeligheid voor externe stimuli en/of overmatige schrikreacties worden vaak beschreven als klinische fenomenen bij FBS (5, 6). Een bekend voorbeeld hiervan is dat de spierschokken van patiënten kunnen worden opgewekt bij het slaan van spierrekkingsreflexen, waarbij het opvallend is dat de spierschokken vaak al optreden voordat de reflexhamer de patiënt raakt. **Hoofdstuk 6** behandelt de auditieve schrikreflex (ASR) en verdeelt de verschillende schriksyndromen in 3 categorieën: hyperekplexie, stimulus-geïnduceerde stoornissen en neuropsychiatrische schriksyndromen. Gestoorde stress regulatie en een verhoogde staat van alertheid (Engelse woord: *arousal*) spelen een belangrijke rol in de pathofysiologie van FBS. Om dit pathofysiologisch fenomeen te onderzoeken, werd de ASR onderzocht in 17 patiënten met FBS en vergeleken met 15 gezonde vrijwilligers met een overeenkomstig geslacht en een overeenkomstige leeftijd (**hoofdstuk 7**). In deze studie werd onderscheid gemaakt tussen de vroege respons (latentietijd 1-100/120 ms), een zeer snelle respons die zijn oorsprong vindt in de hersenstam en bedoeld is ter voorbereiding op eventueel gevaar, en de late respons (latentietijd 100/120-1000 ms),

ook wel de 'oriënterende' respons, een tragere respons waarbij de aandacht wordt gericht op de bron van het gevaar. De resultaten in deze studie werden gecorrigeerd voor medicatie met invloed op het centraal zenuwstelsel en de aanwezigheid van een eventuele angststoornis. De uitkomsten lieten een verhoogd aantal zowel vroege als late responsen zien bij patiënten met FBS, vergeleken met de gezonde vrijwilligers. Het patroon van de responsen was echter niet afwijkend. Wel opvallend was dat de musculus rectus abdominis vaak deel was van de respons bij patiënten. Zowel een verhoogde staat van alertheid (eerste respons) als een gedragsmatige component (tweede respons) werden geacht een rol te spelen in de gevonden resultaten. Na behandeling met BoNT werd de ASR opnieuw onderzocht in dezelfde groep patiënten en controles (**hoofdstuk 8**). Hieruit bleek dat de vroege respons, geassocieerd met abnormale stress regulatie, normaliseerde in combinatie met het verbeteren van motorische symptomen. De late respons echter bleef verhoogd in patiënten vergeleken met controles ondanks behandeling, passend bij het persisteren van de afwijkende gedragsmatige component.

REFERENCES

1. Edwards MJ, Stone J, Lang AE. From psychogenic movement disorder to functional movement disorder: It's time to change the name. Mov Disord. 2013.
2. Stone J, Edwards M. Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology. 2012;79(3):282-4.
3. Gelauff J, Stone J, Edwards M, Carson A. The prognosis of functional (psychogenic) motor symptoms: a systematic review. JNeurolNeurosurgPsychiatry. 2014;85(2):220-6.
4. Hallett M. Mechanism of action of botulinum neurotoxin: Unexpected consequences. Toxicon. 2017.
5. Ganos C, Aguirregomozcorta M, Batla A, Stamelou M, Schwingenschuh P, Munchau A, et al. Psychogenic paroxysmal movement disorders--clinical features and diagnostic clues. ParkinsonismRelat Disord. 2014;20(1):41-6.
6. Thenganatt MA, Jankovic J. Psychogenic (Functional) Movement Disorders. Continuum (Minneap Minn). 2019;25(4):1121-40.

List of publications
List of contributing authors
Portfolio
Dankwoord
Curriculum Vitae

Appendices

LIST OF PUBLICATIONS

In this thesis

- Dreissen YE, Bakker MJ, Koelman JH, Tijssen MA. Exaggerated startle reactions. *Clin Neurophysiol.* 2012;123(1):34-44.
- Gelauff JM, Dreissen YE, Tijssen MA, Stone J. Treatment of functional motor disorders. *Curr Treat Options Neurol.* 2014;16(4):286.
- Dreissen YEM, Boeree T, Koelman J, Tijssen MAJ. Startle responses in functional jerky movement disorders are increased but have a normal pattern. *Parkinsonism Relat Disord.* 2017;40:27-32.
- Dreissen YEM, Dijk JM, Gelauff JM, et al. Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. *J Neurol Neurosurg Psychiatry.* 2019.
- Dreissen YE, Lambert F, Dijk JM, Koelman JH, Tijssen MA. Botulinum neurotoxin (BoNT) treatment in functional movement disorders: long-term follow-up. *J Neurol Neurosurg Psychiatry.* 2020;91(10):1120-1121.
- Dreissen YEM, Koelman JHTM, Tijssen MAJ. The auditory startle response in relation to outcome in functional movement disorders. *Parkinsonism Relat Disord.* 2021;89:113-117.

Other

- van Tricht MJ, Dreissen YE, Cath D, et al. Cognition and psychopathology in myoclonus-dystonia. *J Neurol Neurosurg Psychiatry.* 2012;83(8):814-820.
- Dreissen YE, Tijssen MA. The startle syndromes: physiology and treatment. *Epilepsia.* 2012;53 Suppl 7:3-11.
- Dreissen YE, Cath DC, Tijssen MA. Functional jerks, tics, and paroxysmal movement disorders. *Handb Clin Neurol.* 2016;139:247-258.
- Peall KJ, Dijk JM, Saunders-Pullman R, et al. Psychiatric disorders, myoclonus dystonia and SGCE: an international study. *Ann Clin Transl Neurol.* 2016;3(1):4-11.
- Zutt R, Dijk JM, Peall KJ, et al. Distribution and Coexistence of Myoclonus and Dystonia as Clinical Predictors of SGCE Mutation Status: A Pilot Study. *Front Neurol.* 2016;7:72.
- Zoons E, Tijssen MAJ, Dreissen YEM, Speelman JD, Smit M, Booij J. The relationship between the dopaminergic system and depressive symptoms in cervical dystonia. *Eur J Nucl Med Mol Imaging.* 2017;44(8):1375-1382.
- Zoons E, Booij J, Speelman JD, Dreissen YEM, Smit M, Tijssen MAJ. Lower serotonin transporter binding in patients with cervical dystonia is associated with psychiatric symptoms. *EJNMMI Res.* 2017;7(1):87.

- Marapin RS, van der Stouwe AMM, de Jong BM, et al. The chronnectome as a model for Charcot's 'dynamic lesion' in functional movement disorders. *Neuroimage Clin.* 2020;28:102381.
- Zoons E, Tijssen MAJ, Dreissen YEM, Smit M, Booij J. The Effect of Escitalopram on Central Serotonergic and Dopaminergic Systems in Patients with Cervical Dystonia, and Its Relationship with Clinical Treatment Effects: A Double-Blind Placebo-Controlled Trial. *Biomolecules.* 2020;10(6).

LIST OF CONTRIBUTING AUTHORS

Johannes HTM Koelman, Mirte J Bakker, Thijs Boeree
Department of Clinical Neurophysiology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

Marina AJ Tijssen, Franka Lambert
Department of Neurology and Expertise Center Movement Disorders, University Medical Center Groningen, Groningen, The Netherlands

Jeannette M Gelauff, Joke M Dijk, Daniel van Poppelen, Johannes D Speelman, Tinka van Trier
Department of Neurology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

Rob J de Haan
Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

Jon Stone
Department of Clinical Neurosciences, Center for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom

Evelien Zoons
Department of Neurology, Zaans Medisch Centrum, Zaandam, the Netherlands

Maria F Contarino
Department of Neurology, Haga Teaching Hospital, The Hague, the Netherlands; Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands

Rodi Zutt
Department of Neurology, Haga Teaching Hospital, the Hague, the Netherlands

Bart Post
Department of Neurology, Radboud University Medical Center, Nijmege, the Netherlands

Alexander G Munts
Department of neurology, Excellent klinieken, Dordrecht, the Netherlands

Danielle C Cath
Department of Psychiatry, University Medical Center Groningen, Rijks Universiteit Groningen, GGZ Drenthe Mental Health Institution, Groningen, the Netherlands

PORTFOLIO

Name PhD student: Yasmine EM Dreissen
PhD period: 2010-2020
Names of PhD supervisor(s) & co-supervisor(s): Prof. dr. M.A.J. de Koning-Tijsen, Prof. dr. I.N. van Schaik, dr. J.H.T.M. Koelman, dr. J.M. Dijk

1. PhD training

General courses	Year	ECTS
- AMC World of Science – AMC Graduate School	2010	0.8
- BROK cursus – AMC Graduate School	2011	1
- Cursus Practical Biostatistics – AMC Graduate School	2011	1
- Cursus Clinical Epidemiology – AMC Graduate School	2011	0.8
- Cursus Pubmed – AMC Graduate School	2011	0.5
- Cursus clinical Epidemiology: Randomized Clinical Trials – AMC Graduate School	2014	0.5
Specific courses		
- Data-analyse Matlab – AMC Graduate School	2014	1
- Cursus functional neuro-anatomy – ONWAR graduate school	2014	1
- Cursus fMRI – ONWAR Graduate School	2015	1
Seminars, workshops and master classes		
- Masterclass bewegingsstoornissen – Groningen	2011	0.5
- COST dystonia training school - Groningen	2015	0.5
Presentations		
'Anxiety in myoclonus-dystonia' (poster) - *15th International Congress of Parkinson's Disease and Movement disorders – Toronto*	2011	0.2
'Botulinum toxin as new treatment modality for jerky functional movement disorders : an ongoing randomized clinical trial' (poster) - *17th International Congress of Parkinson's Disease and Movement disorders – Sydney*	2013	0.2
'Botuline toxine als nieuwe behandeling bij patienten met functionele bewegingsstoornissen'(oral) – *Wetenschappelijke avond Noordelijke Neurologenvereniging UMCG - Groningen*	2013	0.3
'Altered auditory startle reflex pattern in functional movement disorders: a new diagnostic tool?' (poster) – 30th *International Congress of Clinical Neurophysiology (ICCN) of the IFCN Berlin & 18th International Congress of Parkinson's Disease and Movement disorders- Stockholm*	2014	0.2
Patientencasus multipele mononeuropathie op basis van neuroborreliose (oral) – *Amsterdamsche Neurologen Vereeniging (AMC)*	2015	0.3
Patientencasus Delayed post-hypoxic leukencephalopathy (oral) - *Amsterdamsche Neurologen Vereeniging (AMC)*	2016	0.3

'Botulinum Neurotoxin (BoNT) for treatment of functional (psychogenic) jerky movement disorders: a randomized placebo-controlled clinical trial' (poster) - *International Congress of Parkinson's disease and other movement disorders - Vancouver*	2017	0.2
'Botulinum Neurotoxin (BoNT) for treatment of functional (psychogenic) jerky movement disorders: a randomized placebo-controlled clinical trial' (oral) – *European Academy of Neurology - Amsterdam*	2017	0.3
Botuline toxine als nieuwe behandeling bij functionele bewegingsstoornissen: een gerandomiseerde placebo-gecontroleerde studie (oral)- *Wetenschappelijke avond Amsterdamsche Neurologen Vereeniging AMC*	2018	0.3
'Botulinum Neurotoxin (BoNT) for treatment of functional (psychogenic) jerky movement disorders: a randomized placebo-controlled clinical trial' (poster) – *3rd International Conference on Functional Neurological Disorders - Edinburgh*	2017	0.2
(Inter)national conferences		
- 5th International Dystonia symposium - Barcelona	2011	0.8
- 15th International Congress of Parkinson's Disease and Movement disorders – Toronto	2011	0.8
- 16th International Congress of Parkinson's Disease and Movement disorders – Dublin	2012	0.8
- 17th International Congress of Parkinson's Disease and Movement disorders – Sydney	2013	0.8
- 18th International Congress of Parkinson's Disease and Movement disorders – Stockholm	2014	0.8
- 30th International Congress of Clinical Neurophysiology (ICCN) of the IFCN - Berlin	2014	0.8
- 20th International Congress of Parkinson's Disease and Movement disorders – Berlin	2016	0.8
- 21th International Congress of Parkinson's Disease and Movement disorders – Vancouver	2017	0.8
- 3rd International Conference on Functional Neurological Disorders – Edinburgh	2017	0.5

2. Teaching

	Year	**ECTS**
Supervising		6
- Studenten medisch wetenschappelijke stage Tinka van Trier en Franka Lambert	2015, 2018	

3. Parameters of Esteem

	Year
Grants	
- IFCN Fellowship 30th International Congress of Clinical Neurophysiology	2014
- AUF Amsterdams Universiteitsfonds	2014
- Travel Grant International Conference of Parkinson's Disease and other Movement Disorders 2017, Vancouver	2017
- Bursary of Participation, European Academy of Neurology 2017	2017

4. Publications

Peer reviewed

- Dreissen YE, Bakker MJ, Koelman JH, Tijssen MA. Exaggerated startle reactions. *Clin Neurophysiol.* 2012;123(1):34-44.
- Dreissen YE, Tijssen MA. The startle syndromes: physiology and treatment. *Epilepsia.* 2012;53 Suppl 7:3-11.
- van Tricht MJ, Dreissen YE, Cath D, et al. Cognition and psychopathology in myoclonus-dystonia. *J Neurol Neurosurg Psychiatry.* 2012;83(8):814-820.
- Gelauff JM, Dreissen YE, Tijssen MA, Stone J. Treatment of functional motor disorders. *Curr Treat Options Neurol.* 2014;16(4):286.
- Dreissen YE, Cath DC, Tijssen MA. Functional jerks, tics, and paroxysmal movement disorders. *Handb Clin Neurol.* 2016;139:247-258.
- Peall KJ, Dijk JM, Saunders-Pullman R, et al. Psychiatric disorders, myoclonus dystonia and SGCE: an international study. *Ann Clin Transl Neurol.* 2016;3(1):4-11.
- Zutt R, Dijk JM, Peall KJ, et al. Distribution and Coexistence of Myoclonus and Dystonia as Clinical Predictors of SGCE Mutation Status: A Pilot Study. *Front Neurol.* 2016;7:72.
- Dreissen YEM, Boeree T, Koelman J, Tijssen MAJ. Startle responses in functional jerky movement disorders are increased but have a normal pattern. *Parkinsonism Relat Disord.* 2017;40:27-32.
- Zoons E, Tijssen MAJ, Dreissen YEM, Speelman JD, Smit M, Booij J. The relationship between the dopaminergic system and depressive symptoms in cervical dystonia. *Eur J Nucl Med Mol Imaging.* 2017;44(8):1375-1382.
- Zoons E, Booij J, Speelman JD, Dreissen YEM, Smit M, Tijssen MAJ. Lower serotonin transporter binding in patients with cervical dystonia is associated with psychiatric symptoms. *EJNMMI Res.* 2017;7(1):87.
- Dreissen YEM, Dijk JM, Gelauff JM, et al. Botulinum neurotoxin treatment in jerky and tremulous functional movement disorders: a double-blind, randomised placebo-controlled trial with an open-label extension. *J Neurol Neurosurg Psychiatry.* 2019.
- Marapin RS, van der Stouwe AMM, de Jong BM, et al. The chronnectome as a model for Charcot's 'dynamic lesion' in functional movement disorders. *Neuroimage Clin.* 2020;28:102381.
- Dreissen YE, Lambert F, Dijk JM, Koelman JH, Tijssen MA. Botulinum neurotoxin (BoNT) treatment in functional movement disorders: long-term follow-up. *J Neurol Neurosurg Psychiatry.* 2020;91(10):1120-1121.
- Zoons E, Tijssen MAJ, Dreissen YEM, Smit M, Booij J. The Effect of Escitalopram on Central Serotonergic and Dopaminergic Systems in Patients with Cervical Dystonia, and Its Relationship with Clinical Treatment Effects: A Double-Blind Placebo-Controlled Trial. *Biomolecules.* 2020;10(6).
- Dreissen YEM, Koelman JHTM, Tijssen MAJ. The auditory startle response in relation to outcome in functional movement disorders. *Parkinsonism Relat Disord.* 2021;89:113-117.

DANKWOORD

Na lange tijd is er dan toch een einde gekomen aan mijn promotietraject. Maar zoals bij alles in het leven, gaat dit niet zonder hulp. Op deze plek wil ik graag even stilstaan en mijn dank betuigen.

Allereerst aan de patiënten en gezonde vrijwilligers, die bereid zijn geweest deel te nemen. Zonder hen was er geen proefschrift geweest.

Dan aan mijn promotores, prof. dr. M.A.J. de Koning-Tijssen en prof. dr. I.N. van Schaik.

Marina, ik leerde je kennen als medisch student tijdens mijn wetenschappelijke stage. Meteen voelde het werken bij jou als 'een warm bad'. Om jou heen formeerde je een gevarieerde, enthousiaste (vaak eigengereide) groep mensen, waar ik me altijd heb thuis gevoeld. Alhoewel de start van dit geheel begon met een kleine dosis 'koudwatervrees', wist je me op de voor jou kenmerkende directe en overtuigende wijze weer het rechte pad te krijgen. Jouw vertrek naar Groningen viel me zwaar, maar ik ben er bovenop gekomen en zo kwam het dan toch nog allemaal goed. Ik wil je niet alleen bedanken voor je goede begeleiding maar vooral ook voor alle leuke en mooie herinneringen, waaronder de vele congressen naar het buitenland, die ik dankzij jou aan mijn promotietijd heb. Samen met Hans vormde je een prachtig onderzoeks-echtpaar en ik ken weinig mensen die zo kunnen inspireren en enthousiasmeren. Hoewel ik nu een ander pad in ben geslagen, hoop ik dat we op wat voor manier dan ook verbonden blijven.

Ivo, ook jou wil ik bedanken voor je begeleiding. Hoewel minder op de inhoud, heb ik je aansturing op de vorm enorm gewaardeerd. Jij maakt ingewikkelde dingen simpel en je pragmatische houding heb ik altijd als zeer geruststellend ervaren. Ook ken ik je als neuroloog en zeer prettige achterwacht tijdens de diensten gedurende de neurologie opleiding. Door je heldere manier van denken, heb je me bovendien veel bijgebracht wat betreft het lokaliseren en klinisch redeneren.

Evenzo aan mijn co-promotores, dr. J.H.T.M. Koelman en dr. J.M. Dijk

Hans, je bent een baken van rust, een rots in de branding. Toen Marina naar Groningen vertrok, heb je het achterblijvend kroost met verve opgevangen. Gedurende mijn gehele promotietijd heb ik ongestoord bij je kunnen binnen lopen om gedachten te wisselen over onderwerpen als 'de vrije wil' en die 'toch wel hele bijzondere patiënten!'. We hebben elke patiënt in de trial samen behandeld en ik weet zeker dat jouw ervaren en

geruststellende stem heeft bijgedragen aan het grote placebo-effect dat we vonden. Tijdens congressen waren jij en Marina ook nooit te beroerd om mee te gaan met de jeugd, waarbij je je in enigszins bedenkelijke etablissementen hebt begeven zoals de nodige karaoke-bars en Berlijnse nachtclubs genaamd 'the suicide circus'. Ik wil je hierbij bedanken voor je uitstekende begeleiding, je hebt naast alle praktische inspanning denk ik nooit langer dan een week gedaan over het retourneren van mijn artikel, aan jou heeft het dan ook zeker niet gelegen! Een klein beetje pijn in het hart deed het wel, dat ik een andere weg in ben geslagen, maar uit het oog is voor mij zeker niet uit het hart.

Joke, ook jou heb ik leren kennen als de begeleider van mijn wetenschappelijke stage. Je vormde een mooi vrouwelijk duo samen met Marina, waarbij jouw kritische blik en genuanceerde bijdrage aan de details van absolute meerwaarde was. Bovendien heb je me de grondbeginselen van de statistiek en epidemiologie bijgebracht, iets waar ik nog steeds profijt van heb. Je achtte mij geschikt en in staat tot het in goede banen leiden en afronden van dit onderzoek. Ik heb dit vertrouwen altijd gevoeld en daar ben ik je enorm dankbaar voor.

Dan wil ik graag de leden van de promotiecommissie, Prof. dr. M. Edwards, Prof. dr. P.R. Schuurman, Prof. dr. B.R. Bloem, Prof. dr. D.C. Cath, dr. A.F. van Rootselaar en dr. M. A. Hillen hartelijk danken dat ze de tijd hebben genomen om in de commissie deel te nemen en mijn proefschrift van kundig commentaar te voorzien. Ik zie uit naar de verdediging!

Niettemin wil ik ook alle co-auteurs bedanken voor hun waardevolle bijdragen aan de verschillende manuscripten. In het bijzonder wil ik hier noemen, Jeannette Gelauff, en hele fijne collega met wie ik bovendien altijd heb kunnen sparren over functionele stoornissen. Rob de Haan, die betrokken was bij de opzet en statistische analyse van de botuline trial. Mirte Bakker, die haar kennis van de schrikreflex met me heeft gedeeld en heeft bijgedragen aan verschillende artikelen. Evelien Zoons en Daan van Poppelen, die in mijn afwezigheid mijn taken hebben waargenomen. En alle beoordelaars van de video's van de patiënten, te weten Fiorella Contarino, Bart Post, Rodi Zutt, Alexander Munts en Hans Speelman, dit was zeker geen klein klusje! Ook wil ik medisch studenten Tinka van Trier en Franka Lamberts bedanken voor hun bijdrage.

En dan, mijn steun en toeverlaat tijdens mijn promotie-tijd: Bas, Sarvi, Rens, Arthur en Joost. Zonder jullie had het leven destijds een stuk minder kleur gehad. Zowel op onze kamer D2-136, het oude Gasthuis, als op de vele plekken in de wereld inclusief Berlijn, Sydney, Dublin, Stockholm en Toronto hebben we ons uitstekend vermaakt.

Ik weet niet of iedereen onze running gags en morbide humor inclusief 'pompert-schalen', dolfijn-spellen, geiten en vreemde uitspraken kon volgen, maar wij hadden het in ieder geval leuk.

Bas, ook wel B. Waar moet ik beginnen. Vanaf het eerste moment hadden wij echt 'een klik'. Ik geloof dat je jouw dankwoord aan mij ook zo begon. We hebben wat meegemaakt samen, waarbij onze vriendschap naast hoge pieken ook wel kleine dalen heeft gekend. Het zal onze Amsterdamse inslag met het hart op de tong wel zijn, maar ach, 'you need friends who beat you'. Ook na onze gezamenlijke onderzoekstijd en gedeelde tijd als ANIOS en AIOS, hebben we contact gehouden. En al zien we elkaar een tijdje niet, het voelt altijd meteen weer vertrouwd. Ik weet zeker dat dit altijd zo zal blijven, op een levenslange vriendschap.

Sarvi, ook wel woman. Jij was de eerste die na mij aansloot op de KNF. Ik weet nog dat Marina jouw naam niet helemaal wist te spellen en dat ik dacht dat Twente in de achterhoek lag (dat denk ik nog steeds eigenlijk). Niet de beste eerste indruk van mijn kant, maar al snel waren we echte maatjes. Ik heb zoveel herinneringen met jou, waaronder die uren-durende gesprekken op onze kamer, de congressen waar we ons vaak 'heel slecht' voelden, jouw wekker-melodietje en onze mooie reis samen door Australië. Ik kan met geen onderzoekstijd zonder jou voorstellen en niet voor niets ben jij mijn paranimf. Ook jij bent bijna klaar en dan is er een einde gekomen aan een KNF-tijdperk. Ik weet zeker dat we elkaar zullen blijven zien als collega en daarbuiten!

Rens, ook wel captain Philips. Je kwam iets later bij de groep, maar dat heb je ruimschoots ingehaald. Met je flegmatieke Brabantse inslag bracht je weer wat nieuws in de groep. Gelukkig hebben Bas en ik je al snel de nodige dosis Hazes verschaft en ben je inmiddels overtuigd dat Ajax de beste club is van Nederland. Vice versa, hebben ik en Bas carnaval leren vieren in Eindhoven, zo is het geven en nemen in een relatie. Ook na onze promotietijd bleven we elkaar zien, waarbij onze vakanties en avonden in de Twee Zwaantjes onvergetelijk zijn. Hopelijk doen we daar snel weer een biertje!

Arthur, ook wel Atje. We kennen elkaar eigenlijk al van de basisschool, de Wielewaal. Je was de eerste van ons die promoveerde en dat kenmerkt jou als mens. Op congres was jij altijd degene die de dingen regelde, van nachtclubs in Berlijn (die Badstube oid) tot aan rooftop-hotels in Sydney. In dat kleine campertje slapen met 5 collega's was misschien een iets minder goed idee, maar achteraf wel een mooi verhaal natuurlijk. Je hebt een aanstekelijk enthousiasme en ik word altijd vrolijk als ik je zie. Laten we snel weer eens een reünietje doen.

Joost, ook wel Joostje. Jij kwam van H2 gevlucht naar de veilige haven van de KNF. Ondanks dat we je soms een beetje pestten als fysiotherapeut (of acupuncturist?), hebben we je vanaf het begin in ons hart gesloten. Je kenmerkt je door je nuchtere houding, en vooral doordat je niet zo goed tegen gezeur kan, door jou vaak benoemd als 'gepijpzeik'. Dit was vooral met Bas soms een lastige combinatie. Ik bewonder hoe gemakkelijk je je beweegt op verschillende plekken in het ziekenhuis en internationale congressen, zo kom je altijd en overal op je pootjes terecht.

Dan wil ik ook nog de overige onderzoekers van de bewegingsstoornissengroep door de jaren heen bedanken: Sandra van der Salm, Katja Ritz, Richard Beukers, Jeroen van der Meer, Mirjam van Tricht, Justus Groen, Constant Verschuur, Sven Suwijn, Daan Velseboer en Vincent Odekerken.

Mijn enorme dank gaat ook uit naar Dorien, voor betrokkenheid en ondersteuning bij de opzet van het onderzoek. Miranda, voor het kundig randomiseren en oplossen van de botuline-toxine. Stefanie en Janny, voor het lopende houden van het onderzoek toen ik niet aanwezig was. Zonder jullie was dit boekje er niet gekomen!

Dan kom ik bij alle overige leden van de KNF-familie. Bedankt dat deze geweldige plek tijdelijk mijn thuis mocht zijn en bedankt voor het mogelijk maken van alle onderzoeken en botuline- behandelingen. In willekeurige volgorde wil ik hierbij bedanken: Fleur, Camiel, Jose, Hannah, Marijke, Erik, Edwin, Dwar, Lo, Netty en Wouter. En dan nog een bijzonder dankjewel aan Thijs. Dude, ik ben je zeer dankbaar voor je hulp tijdens de metingen, het maken van figuren voor artikelen en alle ander mogelijke ondersteuning die je door de jaren heen hebt geboden. Als ik een probleem had, dan loste jij het op (dat doe je overigens voor iedereen). Maar vooral wil ik je bedanken voor je humor en ons oeverloze geouwehoer over niks. Hopelijk snel weer eens een avondje doorzakken op de Zeedijk.

Ook wil ik bedanken de staf, de assistenten en onderzoekers van de afdeling neurologie. Dit is waar ik vandaan kom en waar ik de basis van het vak op een gedegen manier heb kunnen leren en dat is een groot compliment aan de opleiding. Daarnaast heb ik me altijd zeer vermaakt op alle assistentenweekenden en Babinski's. Ik kan niet iedereen apart noemen, maar in het bijzonder wil ik Yvo Roos bedanken voor het creëren van een veilig en prettig opleidingsklimaat. Ik heb me altijd gesteund gevoeld, ook toen mijn keus op de neurochirurgie viel.

Van de neurologie, beland ik bij de neurochirurgie, mijn huidige thuis. Wat een geweldig leuke en diverse groep hebben we, waar ook vaak, ondanks de ernst van het

vak, smakelijk kan worden gelachen. Hierbij wil ik in het bijzonder Peter Vandertop bedanken, die mijn enthousiasme voor de overstap meteen deelde en bij wie ik altijd vertrouwen voel. De opleiding wordt uiteraard gevormd door alle stafleden, van wie ik op verschillende manieren verschillende (en ook dezelfde) dingen leer. Ik zou over iedereen wel iets individueels willen zeggen, maar dat gaat niet, dus Rick, Pepijn, Michiel, Bert, René, Maarten, Roos, Mariam, Dennis, Friso, Gert Joan, Jantien, Ellen, Ronald, Saskia, Hans, David, Ricardo, Philip en Sander, bedankt!

Dan de AIOS. Hisse, bedankt voor je vermakelijke taalgebruik en Brabantse wijsheden, je bent de grondlegger van onze lijfspreuk: 'only the strong survive'. Paul, onze start was wat hobbelig, maar dat is inmiddels ruimschoots gladgestreken, bedankt voor je humor, jij kan van een avond een feestje maken. Steven, de trepaneerbeer, je lijkt soms wat Noordelijk en nors, maar hebt een klein hartje, bedankt dat je alles altijd zo goed regelt. Ivar, ook wel bekend bandlid, bedankt voor je muzikale begeleiding. Lucas, poes, bedankt dat je alles niet zo serieus neemt, en dat je met me meegaat op cursus! Anil, waar moet ik beginnen, ik zou deze opleiding niet overleven zonder jou, bedankt dat ik altijd eindeloos tegen je aan mag praten over alles wat ons overkomt. En tot slot bedankt en welkom aan de jongerejaars Myron, Victoria, Nadine en Rens.

Verder wil ik dan ook alle ANIOS en onderzoekers van de neurochirurgie bedanken.

Zonder ontspanning, creativiteit en kunst, zou ik mijn werk niet zo kunnen uitvoeren. Daarom wil ik alle leden van de opera-groep, Pieter-Paul, Nicole, Isabelle, Hester, Lea, Stephanie en Meija, met wie we jarenlang prachtige voorstellingen hebben gemaakt, bedanken. Ook wil ik Marieke bedanken, die jaar in jaar uit op dinsdagavond dansles gaf en van wie we prachtige danscreaties hebben geleerd. Daarnaast bedank ik alle dansmariekes die altijd trouw naar de les kwamen. Tot slot wil ik mijn dank betuigen aan alle leden van (v)Rauw en Glansloos, dit jaar gaan we weer samenkomen!

Ook wil ik uiteraard mijn vrienden en familie bedanken.

Sophie, we leerden elkaar kennen op muziekles en deelden dezelfde middelbare school. Mijn vriendschap met jou is voor mij nooit een vraag. Bedankt voor je bewondering en vertrouwen dat ik dit proefschrift zou gaan afronden.

Rosalie, onze vriendschap begon in de zandbak en kenmerkte zich vroeger vooral door de slappe lach. Wij zijn elkaar heel wat jaren uit het oog verloren, maar toen we elkaar weer tegen kwamen was het alsof er niets veranderd was. Ik weet zeker dat we dit gaan voorzetten en ben dankbaar dat we elkaar hervonden hebben.

Emma, bedankt dat jij jezelf bent met al je enthousiasme en gekke ideeën. Je daagt me altijd uit om anders na te denken, onze vriendschap is een verrijking van mijn leven.

Susanne, ik vind het nog steeds zo bijzonder dat we elkaar leerde kennen op een congres en nadien moeiteloos weken met elkaar op vakantie zijn gegaan. Met jou verveel ik me nooit en kan ik altijd mezelf zijn, bedankt hiervoor, op naar de volgende vakantie!

Lisanne, je bent de fijnste huisgenoot die ik ooit heb gehad. Ik vind het nog steeds jammer dat we elkaar zo weinig zien, ondanks dat Parijs niet het einde van de wereld is. A bientot mon amie!

Liesbeth, ik wil je bedanken voor alles wat je de afgelopen jaren voor me hebt gedaan. Je bent een enorme steun geweest in een zeer lastige periode en kon complexe problematiek altijd haarfijn analyseren. Bovendien liet je me de sterke kant van mezelf zien, ook toen ik die zelf niet zag en dat begon al in de tijd met André. Hopelijk kunnen we onze etentjes in Djago binnenkort weer voortzetten.

Dan aan de kleinsten in dit gezelschap, Matthias, Zosia, Caiza, Aenea, Julian en Saga. Wat gaan jullie fantastische mensen worden. Ik ben dankbaar dat ik jullie (soort-van) tante mag zijn.

Michaja, gedurende onze jeugd waren we onafscheidelijk. Zo hadden we weken waarin we elkaar dagelijks zagen. Logischerwijs drijft dit met de jaren wat uiteen en zijn wij ieder onze eigen weg in geslagen. Ik zal nooit vergeten dat ik gedurende een lastige periode in mijn leven in jouw kamer heb mogen wonen. Voor mij ben jij familie en dat zal nooit veranderen.

Thomas (de Gee), bedankt dat je zo'n goede vader bent voor Julian en Saga en bedankt dat je voor Michaja zorgt.

Nina, vanaf het eerste moment dat ik je leerde kennen als de vriendin van Thomas was het goed. Je bent een baken van rust, altijd loyaal en bovendien heb je de prachtige kaft van dit proefschrift gecreëerd!

Thomas, van alle mensen die dichtbij me staan, heb ik met jou wel een hele bijzondere band. Er zijn weinig mensen die me zo goed kennen. Ooit mijn vriendje, nu mijn beste vriend en niet voor niets mijn paranimf. Ik bewonder je als vader, als vriend, in je baan en als mens. We dagen elkaar uit en hopelijk blijven we dat altijd doen.

Opa, je wordt nog vaak genoemd in de wandelgangen. Ik ben dankbaar dat ik je kleindochter ben. Sophie, bedankt dat je er voor opa bent.

Laura, mijn zusje. Het is goed je weer te zien. Je bent een volwassen vrouw geworden en ik ben trots op wat je bereikt hebt. Hopelijk kunnen we hier de komende jaren op voortbouwen.

Papa en mama, ik ben blij dat we zo ver zijn gekomen en dat jullie op mijn promotie aanwezig zijn. Jullie zijn waar ik vandaan kom, en daar ben ik dankbaar voor. Ik hou van jullie.

En dan tot slot, Walter en Hildeke. Vanaf mijn jeugd al kind aan huis, en dat was niet voor niets. Jullie representeren een wereld die ik nergens anders vond. In de afgelopen jaren hebben jullie me op alle mogelijke manieren gesteund en vertrouwen gegeven in wie ik ben. Mijn dank aan jullie is eindeloos.

CURRICULUM VITAE

Yasmine Dreissen was born on the 8th of September 1986 in Amsterdam, the Netherlands. In 2004 she completed secondary school (Vossius Gymnasium), after which she studied biomedical sciences for one year. In 2005 she began to study medicine at the University of Amsterdam. During her study she became interested in neurology, especially due to the lectures of prof. dr. J. Stam and prof. dr. M. Vermeulen. This led to a scientific internship concerning neurological movement disorders under the supervision of prof. dr. M.A.J. de Koning-Tijssen and dr. J.M. Dijk. The results of this study became her first scientific publication (*Cognition and psychopathology in myoclonus-dystonia*). In 2010 she became a PhD-student concerning functional movement disorders which ultimately resulted in this thesis (supervisors: prof. dr. M.A.J. de Koning-Tijssen, prof. dr. I.N. van Schaik, dr. J.H.T.M. Koelman and dr. J.M. Dijk). While combining research and medical internships, Yasmine graduated from medical school in 2013. She worked as a neurological resident at the Onze Lieve Vrouwe Gasthuis from 2015 to 2016 (supervisors: prof. dr. P. Portegies and dr. V.I.H. Kwa), and began her training to become a neurologist in 2016 at the Amsterdam University Medical Center AMC (supervisors: prof. Y.B.W.E.M. Roos, prof. dr. I.N. van Schaik, dr. J.H.T.M. Koelman and dr. V.J.J Odekerken). However, during her neurosurgical internship in 2018 she became captivated by this specialty and decided to change her career path. She started her training as a neurosurgical resident in 2019 at the Neurosurgical Center Amsterdam and the Onze Lieve Vrouwe Gasthuis (supervisors: prof. dr. W.P. Vandertop, prof. dr. S.M. Peerdeman, drs. J.C. Baaijen and drs. M.B. Lequin) and plans to complete it in 2024.