Neurobiology of Disease 127 (2019) 32–44

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Pathogenesis and pathophysiology of functional (psychogenic) movement disorders

José Fidel Baizabal-Carvallo[a,b,*], Mark Hallett[c], Joseph Jankovic[a]

[a] Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX, USA
[b] University of Guanajuato, Mexico
[c] Human Motor Control Section, NINDS, National Institutes of Health, Bethesda, MD, USA

ABSTRACT

Functional movement disorders (FMDs), known over time as "hysteria", "dissociative", "conversion", "somatoform", "non-organic" and "psychogenic" disorders, are characterized by having a voluntary quality, being modifiable by attention and distraction but perceived by the patient as involuntary. Although a high prevalence of depression and anxiety is observed in these patients, a definitive role of psychiatric disorders in FMDs has not been proven, and many patients do not endorse such manifestations. Stressful events, social influences and minor trauma may precede the onset of FMDs, but their pathogenic mechanisms are unclear. Patients with FMDs have several abnormalities in their neurobiology including strengthened connectivity between the limbic and motor networks. Additionally, there is altered top-down regulation of motor activities and increased activation of areas implicated in self-awareness, self-monitoring, and active motor inhibition such as the cingulate and insular cortex. Decreased activation of the supplementary motor area (SMA) and pre-SMA, implicated in motor control and preparation, is another finding. The sense of agency defined as the feeling of controlling external events through one's own action also seems to be impaired in individuals with FMDs. Correlating with this is a loss of intentional binding, a subjective time compression between intentional action and its sensory consequences. Organic and functional dystonia may be difficult to differentiate since they share diverse neurophysiological features including decreased cortical inhibition, and similar local field potentials in the globus pallidus and thalamus; although increased cortical plasticity is observed only in patients with organic dystonia. Advances in the pathogenesis and pathophysiology of FMDs may be helpful to understand the nature of these disorders and plan further treatment strategies.

1. Introduction

Functional neurological disorders represent about 6% of consultations in neurology outpatient clinics, and functional motor and sensory symptoms represent 18% of diagnoses in patients with "symptoms unexplained by organic disease" [Stone et al., 2009b; Carson and Lehn, 2016]. In one study, patients with functional or psychological diagnoses represented the second commonest category, after headache, of referrals to neurology outpatient clinics [Stone et al., 2010]. With an estimated annual incidence of 4–12 cases per 100,000 [Carson and Lehn, 2016], these disorders represent a major public health and economic problem. In one estimate, based on experience in the USA in 2005, the annual direct medical costs attributable to somatoform disorders alone were $256 billion [Barsky et al., 2005]. In another study the "cost-of-illness" was up to $5353 (in 2006 prices) per patient-year higher in patients with functional neurologic disorders compared to those without functional symptoms [Konnopka et al., 2012]. Despite their frequency and high economic burden, the pathophysiological mechanism of functional neurological disorders have been largely neglected or deemed as psychological only. New evidence suggests that functional neurological disorders also have a neurobiological basis. In this review we focus on functional movement disorders (FMDs), but also consider functional non-epileptic seizures (FNES) as they have been ranked among the top three neuropsychiatric problems by an international consensus panel [Kanemoto et al., 2017]. Moreover, the weight of evidence suggests that FMDs and FNES are more likely a continuum of functional neurological disorders [Erro et al., 2016; Kanaan et al., 2017].

The terminology used to describe these patients has evolved from the time when "hysteria" was the term in vogue to modern views (Table 1) [King, 1993; Fahn, 2005; Trimble and Reynolds, 2016; Goetz, 2016; Kanaan, 2016]. Some investigators have argued that the term "psychogenic", used in the first two international conferences on this topic, should be changed to the term "functional" and, in a compromise, the 3rd international conference used the term "functional (psychogenic)" [Edwards et al., 2014; Jankovic, 2014; Fahn and Olanow, 2014]. The DSM-5 adopted the term "Conversion Disorder or Functional Neurological Symptom Disorder" under the general category of Somatic Symptom and Related Disorders [American Psychiatric Association, 2013]. Although patients with this group of disorders have

* Corresponding author at: Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Department of Neurology, 7200 Cambridge, Suite 9A, MS: BCM 609, Houston, TX 77030-4202, USA.
E-mail address: baizabal.neuro@live.com (J.F. Baizabal-Carvallo).

https://doi.org/10.1016/j.nbd.2019.02.013
Received 6 November 2018; Received in revised form 31 January 2019; Accepted 20 February 2019
Available online 21 February 2019
0969-9961/

Table 1
Panel: History of terminology and perspectives of functional (psychogenic) disorders, through ages.

Term	Major influence	Clinical implications and psychopathology
Hysteria	Hippocrates of Kos (460–370 BCE)	The word "hysteria" is attributed to Hippocrates in the *Corpus Hippocraticum* (4th/3rd centuries BC), although whether the term was coined by Hippocrates himself is doubtful. The word hysteria was used to explain several gynecologic and other medical symptoms suspected to be linked to the womb (uterus). The concept of a "wandering womb" causing several symptoms influenced medicine for the next 500 years.
	Edward Jorden (1569–1633)	Jorden recognizes hysteria as a mental illness after centuries of view as a sign of witchcraft, following publication of the book *Malleus Maleficarium* in the late 1400s
	Thomas Willis (1621–1675)	T. Willis is one of the first authors proposing a central role of the brain in hysteria, following the influence of "vapours rising into the head from the uterus and the spleen"
Hysteria	Paul (or Pierre) Briquet (1796–1881)	Briquet in his book *Traité clinique et thérapeutique de l'Hystérie* (1859), he rejected uterine theories and influenced Charcot's work on hysteria.
	Jean-Martin Charcot (1825–1893)	J-M Charcot through clinical anatomical correlations separated organic disorders from the "neuroses" which included hysteria. His viewpoint "dynamic nervous system lesion". He emphasized the role of minor trauma triggering the hysteric symptoms. Charcot used hypnosis as an experimental method to study hysterics, separated malingering from hysteria and made detailed description of male hysteria.
Dissociative disorders	Pierre Janet (1859–1947)	Janet introduced the concept that "fixed ideas" acting in the unconscious mind, with dissociation of the conscious and unconscious mind by emotional states or hypnosis.
Conversion disorders	Sigmund Freud (1856–1939)	Freud introduced the concepts of repression of traumatic events and transformation (or conversion) of a psychological unconscious conflict into a symbolic physical manifestation.
Psychogenic Disorders	Several authors	Terminology used among neurologists and movement disorders specialists. It implies that the disorder derives from the mind, a concept recently challenged. Fahn and Williams introduced diagnostic criteria for FMDs in 1988.
Functional disorders	Several authors	An old terminology, recently reintroduced, which is gaining acceptance in the fields of neurology and psychiatry. Avoids the dualism between mind and brain, and patients may find more acceptable than "psychogenic", but it lacks specificity.

Other terms are. "non-organic", "neurologically unexplained symptoms", "psychosomatic", "somatoform". DSM: Diagnostic and Statistical Manual of Mental Disorders.

"dysfunctional" movements rather than "functional" we yield to the growing acceptance of the term "functional" and, therefore, in this review we use the term functional movement disorders (FMDs). We also use the term "organic" to refer to those disorders with a well-established neurobiological basis; but as discussed in this manuscript, recent findings have blurred the distinction between so-called "organic" and "functional" disorders. We focus on research providing insights into etiologic and pathophysiologic mechanisms of these enigmatic disorders and address some critical issues, such as why the movements are perceived by patients as involuntary and separating FMDs from malingering or factitious disorders.

2. Phenomenology

The phenomenology of FMDs varies widely and it is beyond the scope of this review to describe the full manifestations of these disorders (Table 2) [Edwards and Bhatia, 2012; Thenganatt and Jankovic, 2015; Hallett, 2016a]. Phenomenologically, FMDs include movement disorders dominated by tremor (shaking) [Koller et al., 1989], dystonia (abnormal postures associated with muscle contractions and spasms) [Fahn and Williams, 1988], myoclonus (jerk-like movements) [Monday and Jankovic, 1993], gait and balance disorders (including astasia-abasia) [Baik and Lang, 2007], parkinsonism (slowness of movement and other parkinsonian features) [Jankovic, 2011; Thenganatt and Jankovic, 2016], tics (brief and repetitive movements and sounds) [Baizabal-Carvallo and Jankovic, 2014], hemifacial spasms (asymmetric facial contractions) [Fasano et al., 2012; Baizabal-Carvallo and Jankovic, 2017a], ocular movements (including ocular deviation, convergence spasm and dysconjugate gaze) [Fekete et al., 2012; Kaski et al., 2015; Baizabal-Carvallo and Jankovic, 2016], restless legs and moving toes [Stone and Erro, 2014], stereotypies [Baizabal-Carvallo and Jankovic, 2017b], and although FNES are not considered within the field of movement disorders; they fall within the largest category of "hyperkinetic" functional neurological disorders.

3. Predisposing, precipitating and perpetuating factors

3.1. Role of underlying adverse life events, psychiatric disorders and stress

The history of childhood psychological, sexual or physical trauma and stress on a background of a psychiatric disorder has been suggested to contribute to the pathogenesis of FMDs [Epstein et al., 2016; Roelofs and Pasman, 2016]. Patients with FMDs have been found to have higher rates of total childhood trauma (mainly emotional abuse and physical neglect), greater fear of traumatic events, and greater number of traumatic episodes than controls after controlling for depression and gender [Kranick et al., 2011]. History of sexual abuse and lower perception of parental care seem to be higher in patients with FNES compared to patients with FMDs but both groups are more affected than controls [Stone et al., 2004]. Patients with FMDs also acknowledged a higher frequency of severe life events in the preceding year compared with patients with depression and healthy controls [Nicholson et al., 2016]. However, in one study the frequency of these disorders did not differ between patients with FMDs and healthy controls or patients with focal hand dystonia, [Kranick et al., 2011]. This suggests that biased recall to previous traumatic events may underlie such differences. However, a recent meta-analysis showed that stressful life events during childhood and adulthood were considerably more common in patients with functional neurological disorders compared to controls [Ludwig et al., 2018]. Patients with FMDs have been reported to have a high frequency of lifetime anxiety disorders (61.9%), major depression (42.9%) and personality disorders (45%) [Feinstein et al., 2001]; although more recent evidence suggests that rather than a discrete diagnosis of a psychiatric or personality disorder, patients with FMDs score higher than control in depression and anxiety in validated clinical scales [Kranick et al., 2011; Ekanayabe et al., 2017]. These findings suggest that in a proportion of cases, a psychiatric disorder results from the functional neurological rather than playing an etiological role.

In addition to possible psychological stressors, there are many biological factors that play a role in the pathogenesis of functional neurological disorders. For example, increased levels of salivary cortisol and amylase reflecting hyperactivity of hypothalamo-pituitary-adrenal axis and autonomous sympathetic system, respectively, were observed in patients with functional neurological disorders compared to healthy

Table 2
Common clinical features in functional movement disorders.

Type of FMD	Clinical examination	Comments
Tremor	Variable frequency and amplitude. (Kenney et al., 2007) Positive "entrainment test" where tremor is entrained to the frequency of voluntary tapping or stops with ballistic movements (Hallett, 2010) Distractibility: movements or weakness stop when attention is draw away from the deficit Suggestibility: movements increase or appear when suggested (may be facilitated by the application of a tuning fork) Selective disability: ability to perform some functions despite what it is predicted by the manifestations Fluctuation over time; i.e. changes in the patterns of functional gait (Merello et al., 2012) Whack a mole sign: abnormal movements appear in another body part when they are externally held in the initially affected body part.	Normalization by distraction supports the integrity of the motor system
Myoclonus tics or jerks	Variability in duration, distribution and latency of myoclonus. May be stimulus-sensitive. There is usually prominent distractibility with disappearance of movements. There may be entrainment to voluntary movements For tics (motor or vocal), there is usually lack of premonitory sensation and inability to transitory suppress the tics (Baizabal-Carvallo & Jankovic 2014)	Jerks are a relative common presentation and (as other FMDs) may coexist with other phenomenology
Dystonia	Dystonia may be mobile or fixed, features such as distractibility, suggestibility may be less evident than with patients with functional tremor or jerks Less or lack co-contraction of antagonist muscles compared to organic dystonia (but with marked overlap between organic and functional dystonia)	Original diagnostic criteria by Fahn and Williams aimed to provide levels of diagnostic precision for functional dystonia
FNES	Clinical signs: eye closure during attacks, side to side head or body movements, pelvic thrusting, ictal crying, asynchronous movements, long duration events, fluctuating course, postictal stertorous breathing, absence of postictal confusion, recall of ictal events (Aybersek and Sisodiya, 2010)	No single clinical feature is accurate enough for reliable diagnosis
Parkinsonism	Clinical signs: No amplitude or speed decrement on repetitive simple motor tasks, variable muscle resistance to passive manipulation, walking is slow without freezing, pull-test may be normal or exaggerated (Jankovic, 2011)	Functional levodopa-related dyskinesia may be present. May coexist with Parkinson's disease

controls [Apazoglou et al., 2017]; and increased levels of plasma cortisol were detected in patients with FNES [Bakvis et al., 2010; Bakvis et al., 2009]; however, a normal pattern of diurnal salivary cortisol in patients with FMDs was reported in another study [Maurer et al., 2015]. Importantly, patients with functional neurological disorders had a higher subjective but dissociated biological response to stress; suggesting a hyperarousal state to external stimuli (see discussion below) [Apazoglou et al., 2017].

3.2. Role of physical trauma

Physical trauma is frequently reported preceding the onset of FMDs; the most illustrative example occurs in patients with fixed dystonia, a form of dystonia that often has a presumed functional basis [Jankovic and van der Linden, 1988; Jankovic, 2001; van Rooijen et al., 2011; Hawley and Weiner, 2011; Pirio et al., 2017]. In this type of dystonia, peripheral injury preceded the onset in 63% of cases in large series of patients with symptom duration between 0.3 and 19 years [Schrag et al., 2004]. Damage, typically mild, involves mainly soft tissue and is followed by limb overuse, fractures, or operations [Schrag et al., 2004]. In a meta-analysis aimed to assess the frequency of physical injury prior to the onset of motor and sensory conversion symptoms, 869 patients were studied in which 324 (37%) had a physical injury prior to the onset of the functional neurological disorder [Stone et al., 2009a]. A physical injury was more commonly recorded preceding weakness than movement disorders [Stone et al., 2009a]. Motor vehicle accident was the most common cause of injury, followed by falls and other minor injuries [Jankovic, 2001; Stone et al., 2009a]. In another study of 50 patients with FMDs, 40 (80%) reported a physical event within three months prior to the onset of symptoms, with about 50% of cases occurring within the first week [Pareés et al., 2014b]. Physical injury was the most common preceding event, but infections, drug reactions, and pain exacerbation were also identified; no association between the type of physical injury and the type of FMD was observed [Pareés et al., 2014b]. Unfortunately, these studies are subject to recall bias, and prospective controlled studies are difficult to carry out. Moreover, as physical trauma is also a psychologically stressful life event, making difficult to separate the role of physical and psychological consequences of trauma. Despite these limitations, evidence suggests that physical trauma often precedes or triggers FMDs. In summary, in a possible "double-hit" or "multiple hit" pathogenic mechanism, patients may be primed by several traumatic events during their lives, starting during childhood with subsequent traumatic episodes (likely during adulthood) triggering the abnormal movements.

3.3. Role of social environment and influences

A role of social influence is exemplified by so-called "mass psychogenic illness" or "mass hysteria", a rare but fascinating phenomenon, implicated historically in the tragic Salem witch trials episode, where a group of individuals from a cohesive group develop similar psychogenic/functional phenomenon, such as tics [Mink, 2013]. A possible explanation is "modeling", defined as "the adoption of certain behaviors or motor patterns following the observation of close individuals displaying such manifestations" [Baizabal-Carvallo and Fekete, 2015]. This is supported by the development of the movements following observation of affected individuals and a perceived exposure to an illness-causing agent, which could be real or fake [Jones et al., 2000; Broderick et al., 2011]. A specific personality vulnerable to development of or participation in "mass hysteria" has not yet been identified [Balaratnasingam and Janca, 2006]. In a case-control study of 33 patients with FMDs a significant association between the functional movement and exposure to phenotypically congruent movement disorders was observed (odds ratio: 3.9, $P = .01$) [Pellicciari et al., 2014]. FMDs have also been described in members of the same family [Fekete and Jankovic, 2010; Stamelou et al., 2013]; however, it is unclear whether this represents a hereditary vulnerability, a restrictive form of "mass psychogenic illness" or both. It is possible that the mirror neuron system (MNS) may be involved in the development of "modeling". The MNS is composed of neuronal network located mainly in the frontal and parietal lobes and it has been implicated in cognitive-emotional processes such as action-observation, imitation and empathy

[Baird et al., 2011; Binder et al., 2017]. Secondary gain is another social factor that may contribute to FMDs and may blur the distinction between functional and factitious disorders [Jankovic, 2014]. FMDs are increasingly recognized in subjects affected by organic neurological disorders, such as Parkinson's disease [Ranawaya et al., 1990; Onofrj et al., 2010; Jankovic, 2011; Ganos et al., 2014; Djamshidian and Lees, 2014; Wissel et al., 2018]. It is not clear, however, whether the organic disorder predisposes for developing FMD or this phenomenon represents a form of "self-modeling". Thus, a current biopsychosocial model invokes the presence of one or more predisposing factor, coupled with an underlying vulnerability, influencing the onset of FMDs.

3.4. Role of genetics and epigenetics

There is a possible role of hereditary factors in predisposition to functional neurological disorders; however, few studies assessing the role of genetics have been carried out in these patients [Frodl, 2016]. A common G-allele of rs1800629 (tumor necrosis factor-α) was more common in a control group than in patients with somatoform disorders, suggesting a protective effect [Harms et al., 2013]; whereas distinct polymorphism of the enzyme tryptophan hydroxylase or catechol *O*-methyltransferase (COMT) Val158Met polymorphism have not been detected in patients with conversion and somatoform disorders [Armagan et al., 2013; Jakobi et al., 2010].

Although no specific gene has been associated with FMDs, gene-environment interactions playing a role in brain development with stable or long-lasting changes in genetic expression through epigenetic mechanisms may influence the onset of FMDs [Booij et al., 2015]. For example, a history of childhood abuse is associated with DNA methylation in the hippocampal glucocorticoid receptor and smaller hippocampal volumes [McGowan et al., 2009], moreover, high levels of childhood stress have been associated with methylation of the serotonin transporter gene SLC6A4 in monocytes and lower in vivo levels of brain serotonin in the orbitofrontal cortex and abnormal activation of the insula [Wang et al., 2012; Booij et al., 2015; Frodl et al., 2015]. It is also possible that epigenetic influences may start in utero. Pregnant women may transmit stress to the fetus through hormones crossing the placenta [Meaney et al., 2007]; leading to increased vulnerability to life stressors in the offspring [Bateson et al., 2004]. On the other hand a retrospectively perceived good maternal care during childhood was associated to larger grey matter volumes in the superior and middle frontal gyri, orbital gyrus, superior temporal gyrus and fusiform gyrus in a group of women [Kim et al., 2010]. There is little evidence of epigenetic changes in patients with FMDs, but a recent study showed increased methylation of the oxytocin receptor gene in a small series of these patients [Apazoglou et al., 2018]. Finally, although highly controversial, an association between stress-related disorders and increased risk of autoimmune diseases has been supported by a study of a large Swedish cohort followed for a mean of 10 years; but studies specifically focusing in FMDs are lacking [Song et al., 2018].

4. Neurophysiologic changes

4.1. Abnormal patterns of cerebral activation and connectivity

Since the development of functional magnetic resonance imaging (fMRI) in the 1990s, abnormal cerebral activation patterns have been recorded in patients with functional neurological disorders, including hypokinetic (i.e. weakness) and hyperkinetic movements [Marshall et al., 1997; Halligan et al., 2000; Spence et al., 2000; Burgmer et al., 2006; Stone et al., 2007]. Abnormal activation patterns in areas implicated in motor preparation and suppression of motor plans such as the supplementary motor area (SMA) and the pre-SMA has been observed in patients with FMDs [Nachev et al., 2008; Boy et al., 2010]. For example, decreased activity of the left SMA, assessed by regional cerebral blood flow (rCBF) with PET (Fig. 1A), was demonstrated in subjects with various FMDs performing a sustained grip contraction when exposed to pleasant and unpleasant stimuli [Blakemore et al., 2016], and in patients with functional fixed dystonia compared to healthy controls when averaged in the three studied tasks: leg rest, posture and movement [Schrag et al., 2013]. However, in another study, when patients with functional motor disorders were exposed to sad or fear stimuli, but not to a motor task, increased activation of the SMA was observed compared to normal controls [Vuilleumier et al., 2001; Aybek et al., 2015]. In addition to the left SMA; patients with functional dystonia tended to have decreased rCBF in the left primary motor cortex [Schrag et al., 2013].

Besides abnormal activity of the SMA, decreased activity of the right temporo-parietal junction (rTPJ) or the right middle temporal gyrus has been detected using fMRI in patients with functional tremor and dystonia (Fig. 1A and C) [Voon et al., 2010b; Maurer et al., 2016a; Espay et al., 2018a]. The rTPJ seems to monitor feedforward signaling of movements from the dlPFC, and acts as a mismatch detector by processing discrepancies between internal motor intentions and actual motor consequences, playing an important role in self-agency (see discussion below) [Decety and Lamm, 2007; Farrer et al., 2008]. The cingulate cortex is another region implicated in self-awareness, self-monitoring and active motor inhibition [Roelofs et al., 2006; de Lange et al., 2007; van Beilen et al., 2010; Aybek et al., 2015]. Increased activity of the cingulate cortex has been observed in patients with functional tremor, and functional dystonia at rest or when individual are exposed to emotional stimuli (Fig. 1B) [Hedera, 2012; Blakemore et al., 2016]. Abnormal activation patterns are also observed in areas implicated in motivational and emotional processing. The vmPFC and precuneus cortex have been found to be hyperactive in patients with conversion disorders; both areas are implicated in internal self-representations and integration of memories and imagery with affective (emotional) components (vmPFC) or sensory components (precuneus cortex) [Cojan et al., 2009; Vuilleumier, 2014]. Increased activation of the paracingulate gyrus and left Heschl's gyrus was recorded in patients with functional tremor compared with healthy controls [Espay et al., 2017]. Moreover, abnormal activation of cortical regions implicated in active inhibition of motor actions for manual and speech such as the right inferior frontal cortex (IFC) have been recognized in patients with FMDs [Kanaan et al., 2007; Xue et al., 2008; Espay et al., 2018a]; whereas increased rCBF was recorded in the left inferior frontal gyrus and the left insula in patients with functional tremor at rest [Czarnecki et al., 2011].

Patients with FMDs also seem to have higher rCBF in the bilateral cerebellum, bilateral thalamus, left globus pallidus internus (GPi) and right caudate nucleus, compared to normal controls using a motor paradigm with the leg at rest, holding a posture and in motion [Schrag et al., 2013]. Such differences in the pattern of rCBF favoring subcortical rather than cortical motor activation were even more pronounced when patients with functional dystonia were compared with those with organic dystonia [Schrag et al., 2013]. Further evidence of increase activation of subcortical structures, comes from two recent studies showing enhanced activation of the right cerebellum in patients with functional tremor compared to patients with ET and of the bilateral cerebellum in patients with functional dystonia during a motor task using fMRI [Espay et al., 2017; Espay et al., 2018a]. Abnormal patterns of activity of the amygdala have also been observed in patients with FMDs, showing equally increased activity to positive and negative stimuli [Voon et al., 2010a]; contrasting with the greater activity observed with negative compared with positive stimuli in healthy individuals [Morris et al., 1996; Costafreda et al., 2008]. Moreover, time course analysis showed a pattern of impaired amygdala habituation in patients with FMDs, leading to prolonged activation with different stimuli (Fig. 2) [Voon et al., 2010a; Aybek et al., 2015; Hassa et al., 2017]. Other animal and human studies have shown that stress may lead to a hyperactivity of amygdala and abnormal stimulus habituation [Blakemore et al., 2016; Zhang et al., 2018]. Increased activation of the

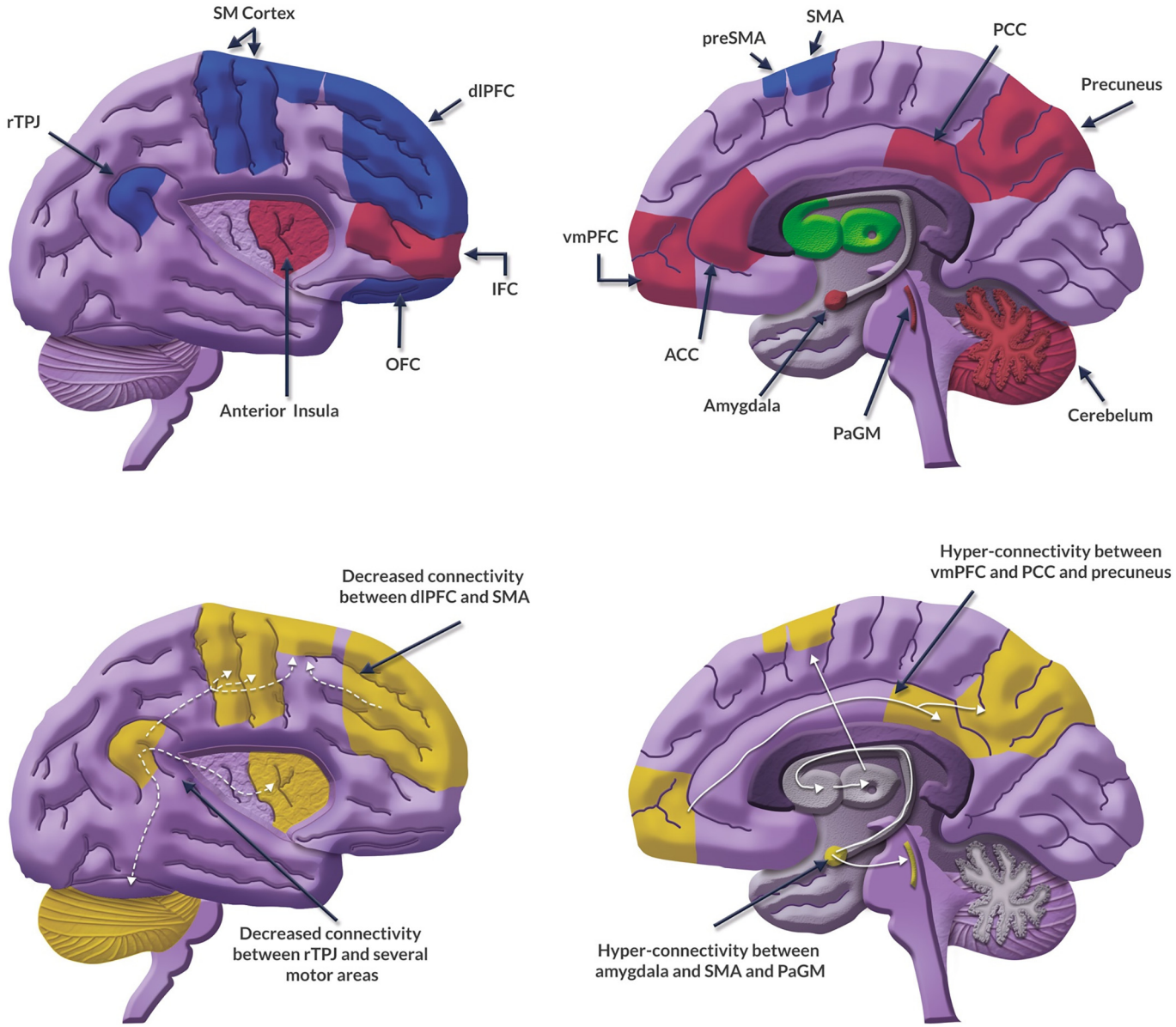

Fig. 1. A) lateral and B) medial cerebral surface showing areas of abnormal activation in patients with FMDs (red: increased; blue: decreased; green: increased in dystonia, decreased in paralysis). C) lateral and D) medial cerebral surface showing abnormal connectivity (dashed lines: decreased; straight line: increased). [Figure designed by the authors]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
ACC: anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex; IFC: inferior frontal cortex; OFC: orbitofrontal cortex; PaGM: periaqueductal grey matter; PCC: posterior cingulate cortex; r-TPJ right temporo-parietal junction; SMA: supplementary motor cortex; SM: primary sensory-motor cortex; vmPFC: ventro medial prefrontal cortex.

periaqueductal grey matter, which is involved in the freeze-response to fear is also observed in patients with FMDs (Fig. 1B), but the role of this intriguing finding in the pathogenesis of functional neurological disorders has not been clarified [Aybek et al., 2015].

Abnormal connectivity between cognitive, limbic and motor neural networks seems to occur in patients with FMDs. Increased functional connectivity between the right amygdala and the right SMA has been reported in patients with FMDs exposed to positive and negative stimuli [Voon et al., 2010a; Aybek et al., 2014b]. It has been theorized that such connection may be mediated by amygdala projections through the basal ganglia and the thalamus to the SMA, as there are no direct connections between the amygdala and the SMA (Fig. 1D) [Roy et al., 2009; Bzdok et al., 2013]. Amygdala projections to the periaqueductal grey matter and other midbrain neurons may also have an upstream effect on the SMA (Fig. 1D) [Lang and Davis, 2006]. It has been speculated that abnormal amygdala-SMA connectivity, coupled with abnormal top-down control by dlPFC, may facilitate the expression of previously learned, patterned movements [Voon et al., 2011]. This is supported by observations suggesting altered functional connectivity between the dlPFC and the SMA in patients with functional motor disorders [Voon et al., 2011].

Decreased functional connectivity between the rTPJ and the right sensorimotor cortex, bilateral cerebellum, bilateral SMA and right insula in patients with a variety of FMDs compared to healthy controls using resting state fMRI has been identified (Fig. 1C) [Maurer et al., 2016a]. However, increased functional connectivity between the rTPJ and the left insula was observed in individuals who had history of childhood abuse, but not in those with anxiety or depression [Maurer et al., 2016a]. Notably, the anterior insular cortex (AIC) has been associated with awareness of sensations and movement [Craig, 2009]. An

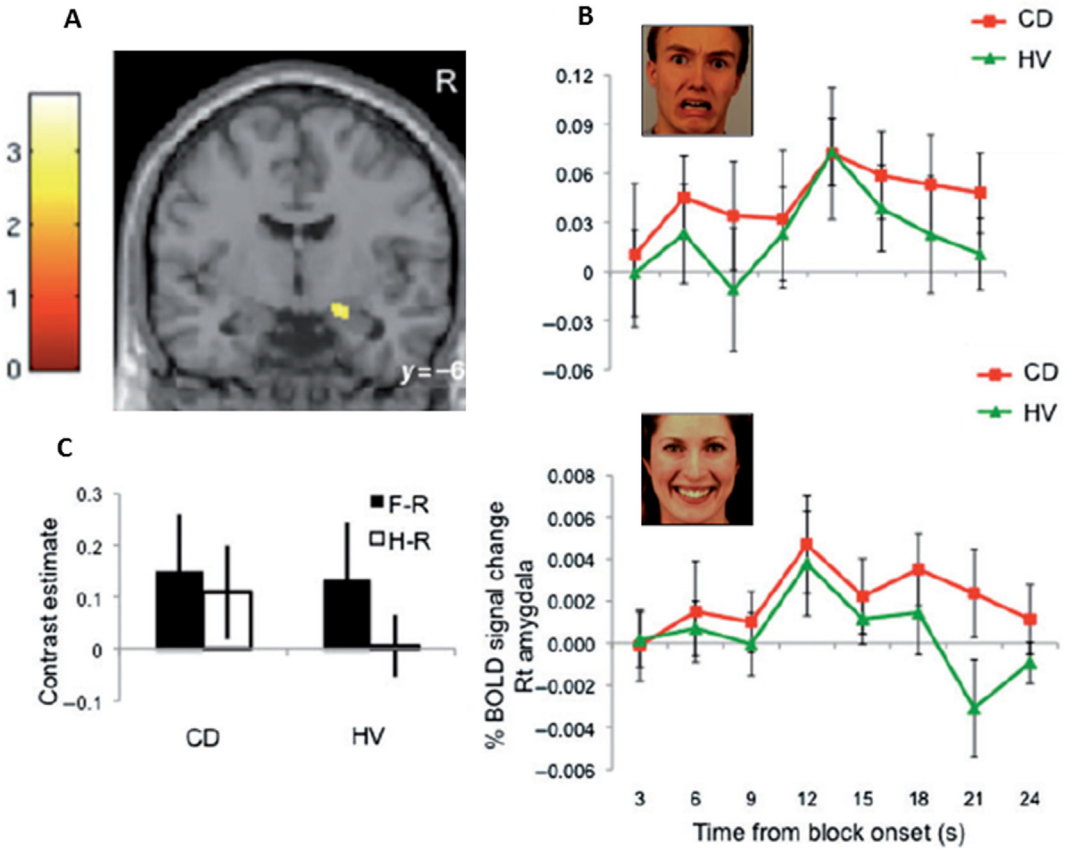

Fig. 2. A) Increased right amygdala activation in patients with motor conversion disorders. B): The area under the curve for the right amygdala time course between patients with conversion disorder and healthy volunteers for the fearful (top; t = 1.81, P = .08) and happy (bottom; t = 2.96, P = .006) conditions; C) Contrast estimates shows increased amygdala activity particularly for happy vs. rest stimulus in patients with conversion disorders [Modified from Voon et al., 2010a. Reproduced with permission of Oxford University Press].
CD: conversion disorders; HV: healthy volunteers. Fearful vs. rest (F–R) and happy vs. rest (H–R) contrasts.

inverse association has been observed between the left anterior insular volume and functional neurological disorder in women and childhood abuse burden [Perez et al., 2017a]. This evidence further supports the notion of a link between psychological trauma and functional motor disorders.

In summary, despite some inconsistencies, fMRI and PET studies in FMDs have provided evidence of decreased activity of cortical areas implicated in motor preparation, motor selection and feedforward monitoring of movements but increased activity of areas implicated in self-awareness, interoception and emotional processing has been observed with functional neuroimaging in patients with FMDs, coupled with abnormally increased connectivity between limbic and motor regions. An activity shift form cortical to subcortical structures has also been observed, but the pathogenic significance of this finding is unclear and whether activation of certain structures such as the cerebellum represents a compensatory mechanism is uncertain; however, abnormal activity of limbic/paralimbic structures may be implicated in the pathogenesis of the disorder and deserves further study.

The interpretation of the reported differences in brain activation among studies, however, is difficult to assess because the findings are confounded by inclusion of patients with diverse FMDs, use of different techniques, paradigms, and statistical analyses methods; the latter have been recently challenged [Eklund et al., 2016]. It is also unclear which is the best functional neuroimaging to study FMDs, although PET and fMRI have relatively good spatial resolution; PET has a low temporal resolution (about 30 s) limiting its ability to assess long cognitive processes; whereas fMRI is limited by movement artifacts.

4.2. Increased arousal

Arousal can be defined as a physiological and psychological state of being awake, or in a more restrictive sense, when perception occurs during stimulation of sense organs. Increased arousal in patients with FMDs compared to patients with anxiety and healthy volunteers was documented in a group of subjects with conversion disorders who failed to habituate their skin conductance to repetitive auditory stimuli [Lader and Sartorius, 1968]. Increased startle response to positive and negative stimuli in patients with FMDs compared to normal controls, has also been reported, linking arousal to reflexive motor response [Seignourel et al., 2007; Dreissen et al., 2017]. Increased mean heart rate coupled with decreased rest vagal tone and heart rate variability has been reported in patients with FMDs compared to controls [Maurer et al., 2016b]. Impaired vagal tone correlates with altered ability to adapt to environmental demands. A significant potentiation of the eyeblink response by negative pictures and slight inhibition by positive pictures compared to neutral pictures was a pattern observed in normal subjects, whereas patients with FMDs showed significantly greater startle eyeblink response to both positive and negative pictures compared to neutral ones [Terada et al., 1995]. The startle response and various autonomic functions are modulated by the amygdala; its dysfunction may be present in patients with FMDs as discussed previously [Ressler, 2010]. Overactivity of brain networks implicated in threat detection, energy regulation and action preparation have been detected in children and adolescence with functional neurological disorders [Kozlowska et al., 2018].

4.3. Readiness potential and voluntariness

The readiness potential (RP), also known as *Bereitschaftspotential*, is the cortical activation preceding self-initiated movement or volitional muscle relaxation [Shibasaki and Hallett, 2006]. The initial slow segment of the BP starts about 2 s before the movement onset in the pre-SMA and SMA, followed very shortly by activation of the lateral premotor cortex bilaterally, and eventually the contralateral primary motor cortex (M1); with increasing somatotopic specificity in the late RP [Shibasaki and Hallett, 2006]. In the early 1980s, Libet and colleagues showed that the RP begins hundreds of milliseconds earlier than the awareness of intention to move [Libet et al., 1983], suggesting that conscious will does not cause the volitional movement, challenging the traditional view of free will [Hallett, 2016b]. However, the meaning of the *Bereitschaftspotential* is not clear since it is not specific for movement preparation [Trevena and Miller, 2010] and robust RPs may occur in the absence of movement or a feeling of will [Schlegel et al., 2015; Alexander et al., 2016]. It is better to just consider it as an activation pattern of the SMA and premotor cortex.

RP often, but not always, precedes psychogenic jerks, but it is always absent in subjects with organic myoclonus [Terada et al., 1995; Colebatch, 2007; van der Salm et al., 2012]. Although RP has been considered a neurophysiological marker for "voluntariness", this is not correct as patients with FMDs perceive their unwanted movements as "involuntary" even when RP is recorded prior to the movement. Interestingly, absence of RP was reported in a high proportion of patients suffering FMDs when asked to perform voluntary wrist extension, contrasting with the presence of RP in patients with Tourette syndrome and organic myoclonus when executing the same task [van der Salm et al., 2012]. The interpretation of this finding is unclear, but the level of intention, motivation, attention, preparatory state, movement selection, and movement complexity can influence the amplitude and course of RP [Terada et al., 1995].

4.4. Abnormal sense of agency and movement intentions

There is a substantial body of clinical and neurophysiological evidence indicating that functional disorders of movement are recruited by neural pathways implicated in volitional motor control (Tables 2 and 3) [Reuber et al., 2002; Aybersek and Sisodiya, 2010; Hallett, 2010; van der Salm et al., 2010; Schwingenschuh et al., 2011; Merello et al., 2012; Erro et al., 2013; Baizabal-Carvallo and Fekete, 2015; Schwingenschuh et al., 2016]. However, one intriguing and central question is why a movement which is seemingly under volitional control is perceived by patients with FMDs as involuntary. Voluntary movements are associated with a conscious experience, including two basic components: 1) the sense of one's intention to move or willing, and 2) the sense of agency, which refers to the feeling of controlling an external event through one's own action [Haggard, 2008; Chambon et al., 2014]. These are separate phenomena, although agency requires willing or intention; the latter can occur without agency, for example in individuals with paresis who can will, but nothing will happen.

The "intentional binding effect" defined as the subjective compression of the temporal interval between an intentional action and its sensory consequences, is an implicit measure of the sense of agency [Haggard et al., 2002; Moore and Obhi, 2012]. The more this time is compressed, the more the sense of agency is reinforced. The binding effect is partially based on a retrospective inference between intentions and sensory consequences [Moore and Obhi, 2012]. Intentional binding is likely related to an appropriate function of several motor and sensory structures. Inhibition with theta burst stimulation of the pre-SMA by transcranial magnetic stimulation (TMS) leads to a significant reduction of intentional binding [Moore et al., 2010]. The SMA has also been implicated in the sense of agency, through self-initiated actions, and non-conscious motor inhibition [Nachev et al., 2008] as well as in the physiology of free will [Hallett, 2016b].

An abnormal experience in the intention to move has been observed when a normal voluntary movement is executed by patients with functional tremor compared with healthy controls [Kenney et al., 2007; Edwards et al., 2011]. Patients with functional motor disorders had lower binding scores, compared with normal age and sex-matched controls (i.e. patients perceived the action-effect interval significantly larger), consistent with reduced sense of agency [Kranick et al., 2013]. In this experiment, exposure to happy and neutral faces influenced the total binding in healthy volunteers, but not in patients with FMDs. This contrasts with what has been observed in patients with schizophrenia

Table 3
Neurophysiology and clinical neuroimaging of different functional movement disorders.

Type of FMD	Neurophysiology, neuroimaging	Comments
Tremor	Coherence analysis (accelerometer or EMG): tremor has the same frequency and is in phase in different limbs, contrasting with what is usually observed in organic tremors (except in orthostatic tremor) EMG: Co-activation sign: simultaneous tonic contraction of antagonist muscles at the beginning of tremor; the resulting stiffness increases the resonant frequency of a joint	Single features have low sensitivity and specificity to diagnose functional tremor, but combination of features may yield high accuracy (Schwingenschuh et al., 2016)
Myoclonus	EMG burst length is longer (> 30–50 ms) than epileptic myoclonus, but there is marked overlap with other forms of myoclonus. A normal readiness potential is observed in functional myoclonus (Hallett, 2010)	None of these tests has enough sensitivity or specificity
Reflex myoclonus	C-reflex: Latencies are never faster than the fastest voluntary reaction time (100 ms) (Hallett, 2010)	
Propriospinal myoclonus	Jerk-locked EEG. Present of readiness potential. Polymyography: incongruous pattern (Erro et al., 2013, van der Salm et al., 2010)	
Dystonia	R2 of blink reflex: disinhibited in "organic" blepharospasm, but it is normal in FMDs patients and normal controls (Schwingenschuh et al., 2011) Transcranial Magnetic Stimulation: Trend for reduction of short and long intracortical inhibition Reduced cortical silent period Reduced reciprocal inhibition of the H reflex "Normal plasticity" with the paired-associative stimulation technique	A normal blink reflex (R2) recovery cycle indicates normal brainstem interneuron excitability
FNES	EEG does not show epileptic activity during spells (when assessed by video-EEG)	A high rate of interictal abnormalities is observed in EEGs of FNES patients (Reuber et al., 2002)
Parkinsonism	DAT SPECT or ^{18}F-Dopa PET: normal dopaminergic innervation	Dopaminergic denervation observed when coexists with Parkinson's disease

FNES: Functional non-epileptic seizures; RP: readiness potential.

who seem to show increased binding, despite the fact that they also report an abnormal sense of agency [Voss et al., 2010]. Although these studies only verified the binding effect in normal voluntary movements and not in abnormal movements, they suggest the presence of an underlying pathological trait affecting volition.

Current evidence suggests that prediction of self-motor action also contributes to the intentional binding effect [Moore and Haggard, 2008; Chambon et al., 2013]. The angular gyrus (AG) in the TPJ monitors signals related to the feedforward signaling of action selection from the dorsolateral prefrontal cortex (dlPFC), prospectively informing oneself the subjective judgments of motor control over the action outcomes in normal individuals [Farrer et al., 2008; Chambon et al., 2013; Khalighinejad and Haggard, 2015]. Disruption of perceived motor control at the point of action selection has been shown using TMS over the left inferior parietal cortex in normal individuals [Chambon et al., 2015]. Furthermore, as stated above, decreased activity of the rTPJ, and its interactions with the sensorimotor cortex, as well as lower connectivity with areas involved in motor preparation and execution, seem to be implicated in discrepancies perceived between motor intentions and motor consequences, influencing self-agency [Voon et al., 2010a, 2010b; Decety and Lamm, 2007; Farrer et al., 2008; Maurer et al., 2016a]. Using fMRI, altered responsiveness in areas believed to be critically involved in the sense of agency (i.e. dlPFC, pre-SMA) has been noted in patients with FMDs but not in healthy controls [Voon et al., 2010a, 2010b; Nahab et al., 2011; Nahab et al., 2017]. Increased activity of the limbic system and abnormalities in agency, implicated in feedforward signaling of motor control, are emerging paradigms in the pathogenesis of FMDs. There is less evidence for abnormal feedback, but current data suggest that an abnormality in sensory processing is present in at least some patients with FMDs, as discussed in the following section (Fig. 3) [Patel et al., 2014].

4.5. Abnormal somatosensory processing

Sensory attenuation (SA) is a normal phenomenon, consistent with awareness of identical stimuli, perceived differently whether they are self-generated or externally generated [Blakemore et al., 1998]. An illustrative example is the different perception tickling oneself compared with tickle by others [Blakemore et al., 2000]. SA is translated into a reduction in the amplitude of sensory evoked potentials when the stimulus is self-generated, for example in self-paced movements. Experimental studies have shown that patients with FMDs consistently show a lack of SA compared to normal controls [Pareés et al., 2014a; Macerollo et al., 2015]. This lack of SA (lack of decreased amplitude of somatosensory potential) may be interpreted by the subject with FMDs as a stimulus (movement) externally generated rather than internally generated, leading to a reduction in the sense of agency [Macerollo et al., 2015]. Normal SA has been associated with less activation of the somatosensory area, ACC and cerebellum, areas that have been found hyperactive in patients with FMDs [Blakemore et al., 1999; Blakemore et al., 2000].

Several other alterations in sensory processing have been reported in patients with FMDs, including altered position of the ankle in patients with fixed dystonia [Stone et al., 2012], abnormal mental rotation of body parts [Katschnig et al., 2010], disorientation of limb position, increased perception of limb size, and hostility toward an affected limb. The latter has been reported in subjects with complex regional pain syndrome, a disorder with possible functional basis, often

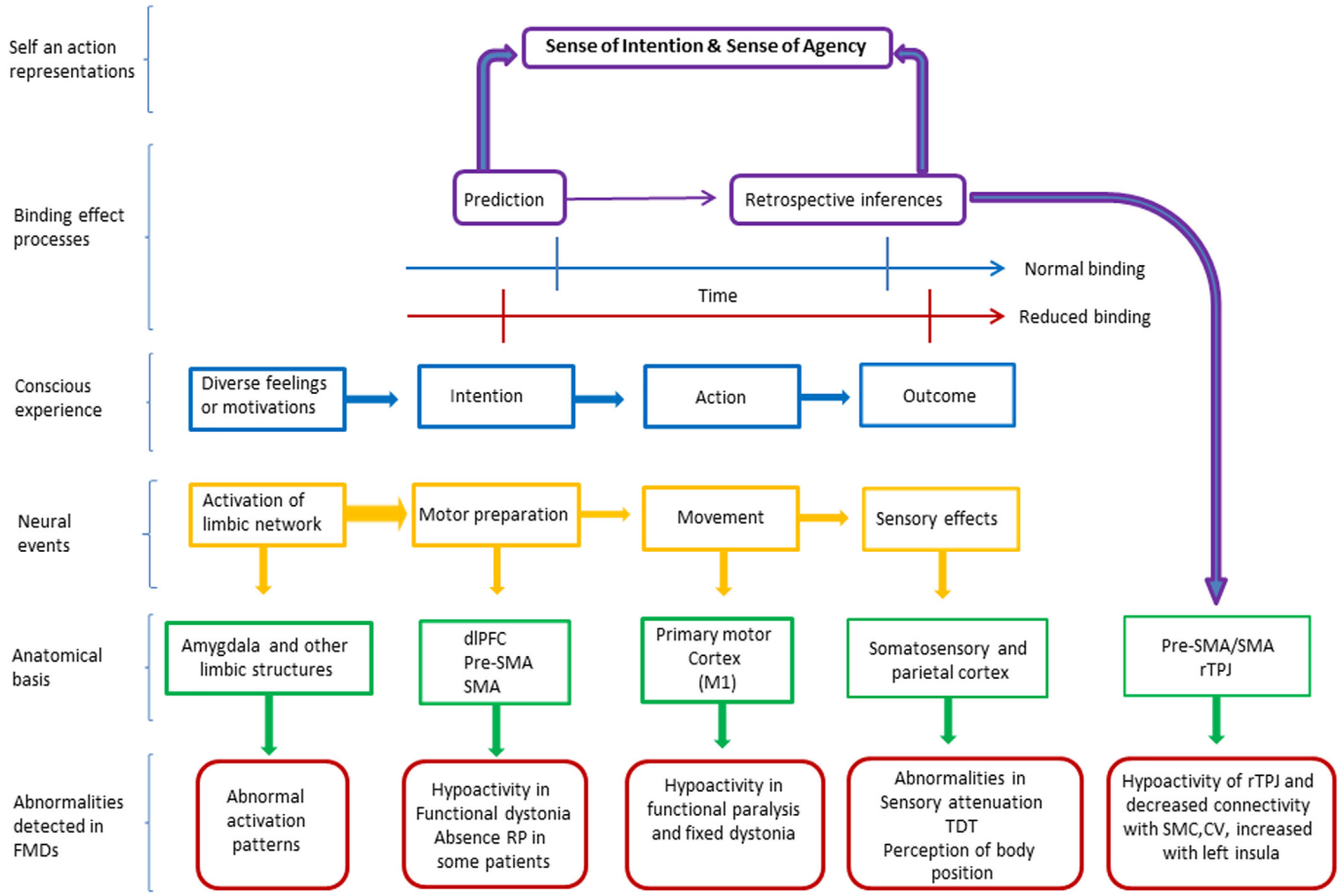

Fig. 3. A model of neural processes underlying the experience of voluntary action and abnormalities recorded in patients with FMDs (red color). [Modified from Haggard, 2008]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

coexisting with functional dystonia [Schrag et al., 2004; van Rooijen et al., 2011; Stone et al., 2012; Popkirov et al., 2018]. Temporal discrimination threshold (TDT) is the interval of time required for subjects to recognize two stimuli as separate. TDT was found to be longer in patients with functional and organic dystonia compared with normal controls [Molloy et al., 2003; Morgante et al., 2011]. Interestingly, the abnormally long TDT did not differ between the affected and unaffected limbs in patients with both types of dystonia [Morgante et al., 2011]. Examiner maneuvers frequently influence FMDs, whether this represents abnormal somatosensory processing, suggestibility or both is unclear [Baizabal-Carvallo and Jankovic, 2017c].

Abnormalities in sensory processing in unaffected limbs suggest they are a trait predisposing individuals to develop FMDs rather than the result from persistent abnormal movements. Moreover, abnormalities in somatosensory processing may influence the sense of intention and agency as both components are based in somatic experience.

4.6. Abnormal cognitive processing

Abnormalities in higher order cognitive processing are also observed in patients with FMDs. Distractibility is one of the most characteristic features of FMDs and patients with functional tremor showed increased visual attention toward the trembling limb when performing a motor task compared to patients with organic tremors [van Poppelen et al., 2011]. Abnormal beliefs and emotions may also influence the sense of agency and intentional binding [Edwards et al., 2012; Yoshie and Haggard, 2013]. Patients with FMDs may experience a distorted perception of their “involuntary” (functional) movements. In a study assessing the time the patients perceived tremor during the waking day; wristwatch-like accelerometer recordings coupled with self-reporting diaries were analyzed in patients with functional and organic tremor [Pareés et al., 2012b]. Although both groups overestimated the amount of daytime with tremor; functional patients reported 65% more tremor than the one registered by actigraphy, compared to 28% excess for patients with organic tremor [Pareés et al., 2012b]. Abnormalities in probabilistic reasoning and motor response inhibition have been observed in patients with FMDs suggesting a disturbed capability to process novel sensory and cognitive data [Pareés et al., 2012a; Voon et al., 2013]. Furthermore, patients with FMDs reported excessive cognitive complaints compared to normal controls in one study, despite the lack of impairment in neuropsychological evaluations [Heintz et al., 2013].

4.7. Changes in neural physiology

Functional dystonia is one of the most intensely studied FMDs, as it is one of the most common FMDs encountered in movement disorders centers. In one landmark study reduced cortical inhibition was observed using TMS in organic and psychogenic dystonia compared to healthy controls (supplementary table) [Espay et al., 2006; Avanzino et al., 2008]. However, only patients with organic dystonia seem to have increased sensorimotor plasticity, even in patients with complex regional pain syndrome type I and fixed dystonia, plasticity has been reported as normal [Quartarone et al., 2009; Morgante et al., 2017]. It is not clear whether the observed abnormalities represent an underlying neurophysiological trait to develop FMDs or are the result of persistent abnormal movements. However, abnormalities in cortical excitability were observed bilaterally in patients with unilateral dystonia suggesting that they may represent a trait rather than a secondary effect from the muscle contractions [Avanzino et al., 2008]. Interestingly, no differences were found in local field potentials of the GPi and thalamus in three patients with functional dystonia (thought to have organic dystonia) compared to patients with genetic dystonia with intraoperative microelectrode recording during deep brain stimulation surgery [Kobayashi et al., 2011; Ramos et al., 2015]. These findings suggest that functional and organic dystonia share some pathophysiological features and, except for a disinhibited blink-reflex in organic dystonia [Schwingenschuh et al., 2011], there is no neurophysiological marker that reliably differentiates between the two disorders.

4.8. Abnormalities in cerebral volume

Structural imaging investigations showed increased grey matter volume in subcortical motor (basal ganglia), cerebellum, thalamus and limbic/paralimbic cortical structures; mostly on the left side and decreased volume in the left precentral and postcentral gyri [Atmaca et al., 2006; Perez et al., 2017a; Perez et al., 2017b; Maurer et al., 2018]. The subcortical altered morphology mirrors some findings in functional neuroimaging showing increased activity in the basal ganglia and cerebellum in patients with FMDs (Schrag et al., 2013). On the other hand, increased cortical volume in the SMA, superior temporal gyrus and dorsomedial prefrontal cortex was observed in children and adolescents with functional neurological disorders compared with healthy controls [Aybek et al., 2014a; Kozlowska et al., 2017]. Such cortical regions have also been implicated in abnormal motor planning and execution in patients with FMDs. These volumetric alterations did not correlate with duration of anxiety and depressive symptoms, or use of CNS-acting medications in the largest study to date (Maurer et al., 2018). However, impaired self-reported mental health and increased anxiety correlated with increased right amygdala volume in another cohort [Perez et al., 2017b]; and inverse correlation between post-traumatic stress disorder severity and childhood abuse burden with anterior cingulate cortex and anterior left insula volume respectively were observed in another cohort [Perez et al., 2017a]. Such findings suggest that volumetric alterations in patients with FMDs are common, but it is still unclear which of these changes are specific for FMDs and which are specific for comorbid psychological trauma. It is also unknown whether these abnormalities antedate or are the result of abnormal activation and connectivity patterns observed in these patients; it is possible that function and morphology have bidirectional interactivity during the course of the disease, resulting in the observed abnormalities. The changes in cortical thickness and cortical surface area are dynamic events observed through an individual's life; they have been attributed to modifications in dendritic length, but also to glial and vascular changes (Schnack et al., 2015). Cortical thickness in motor areas is reported to be increased in normal individuals undergoing motor training and in patients with hereditary dystonia, but is decreased after a period of immobilization [Granert et al., 2011], suggesting that the cortical volume reflects motor activity. Different patterns of abnormal cortical volume are observed in patients with mobile compared to fixed functional dystonia [Tomic et al., 2018]. It is unclear, however, why patients with hyperkinetic neurological disorders have decreased primary motor cortex volume rather than increased [Labate et al., 2012; Nicholson et al., 2014; Maurer et al., 2018].

5. Treatment

It is beyond the scope of this article to discuss management of patients with FMDs, and the reader is referred a comprehensive treatise on FMDs [Hallett et al., 2016]. Trials of psychotherapy aimed at gaining insight into potential psychodynamic factors have been associated with improved clinical outcome [Hinson et al., 2006; Kompoliti et al., 2014; Nielsen et al., 2015; Hallett, 2018]; physical therapy used with the rationale of motor retraining are two of the main treatments used for FMDs [Czarnecki et al., 2012; Jordbru et al., 2014; Matthews et al., 2016; Nielsen et al., 2017; Jacob et al., 2018; Espay et al., 2018b]. Showing patients their physical signs may be helpful to make them understand the nature of the disorder [Stone and Edwards, 2012]. Improvement with these therapies and placebos [Rommelfanger, 2013] supports at least a partial reversibility of the underlying neural abnormalities. These therapies aim mainly to reinforce the top-down regulation of the movements; however, attempts to modify directly cortical excitability by means of large field repetitive TMS has been

used with promising results in some [Garcin et al., 2013; Parain and Chastan, 2014], but not in all studies [McWhirter et al., 2016]. It is possible that the observed improvement represents a cognitive-behavioral effect, rather than neuromodulation [Shah et al., 2015; Garcin et al., 2017; Schönfeldt-Lecuona et al., 2006; Pollak et al., 2014; Parain and Chastan, 2014]. The role of placebos for provocative diagnosis and in treatment of FMD is being re-evaluated in view of new findings that placebos may not be as "inert" as previously thought and their use may be ethically justified in some circumstances [Rommelfanger, 2016]. Although some of these therapies have proven effective, it is unclear how they would modify the morphological and neurophysiological changes reported in patients with FMDs. In addition to these interventions, judicious pharmacologic management of associated neuropsychiatric co-morbidities such as depression, anxiety, pain and fatigue [Voon and Lang, 2005; Barton et al., 2017; Gelauff et al., 2018] along with psychotherapy, is usually warranted and may facilitate symptomatic improvement. Despite many interventions, a proportion of patients do not show a desirable improvement; whether this represents enduring physiological changes in the nervous system or insufficient/incorrect treatment strategies is unclear.

6. Conclusions

Several neurobiological abnormalities have been identified in patients with FMDs including abnormal patterns of cerebral activation along with abnormal connectivity between the limbic and motor networks in patients with various functional neurological disorders.

FMDs may be viewed as disorders of networks implicated in volition, emotion, and motor control. The movements appear to arise from the influence of the limbic system on movement generation, perhaps facilitated by attention. The perception that the movements are involuntary is related to an altered sense of agency, originating in a mismatch between internal predictions from the abnormal movement genesis and feedback from the executed movement. The internal predictions are also modified by prior information (the Bayesian "prior") of the subject's belief system regarding motor control. These processes primarily involve the frontal and parietal cortex (Figs. 1 and 3). We propose that in this complex scenario, multiple life-events resulting in psychological and physical trauma may have an additive effect which eventually reshapes network connectivity until a specific threshold is reached when an adverse life event acts as a precipitating factor in an already vulnerable brain. The role of genetic and epigenetic influences and changes in grey and white matter morphology warrants further research. The body of evidence supporting a biological role in the pathogenesis of functional disorders, along with requirement of positive clinical signs in the neurological examination and abandonment of recent stress and comorbid psychiatric disorders for diagnostic purpose in the DSM-5, has led to functional disorders being categorized under the neurology section of the International Classification of Diseases (ICD-11) [Stone et al., 2014]. Since functional disorders are viewed as biopsychosocial disorders they require multidisciplinary evaluation and treatment strategies for the most optimal long-term outcome.

Financial disclosure/conflict of interest concerning the research related to the manuscript

Funding

None for all authors.

Acknowledgement

We thank Ian Osuna for help designing figure 1.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2019.02.013.

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