


## REVIEW

## Biomarkers in functional movement disorders: a systematic review

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**ABSTRACT**

Functional movement disorders (FMD) are proposed to reflect a specific problem with voluntary control of movement, despite normal intent to move and an intact neural capacity for movement. In many cases, a positive diagnosis of FMD can be established on clinical grounds. However, the diagnosis remains challenging in certain scenarios, and there is a need for predictors of treatment response and long-term prognosis.

In this context, we performed a systematic review of biomarkers in FMD. Eighty-six studies met our predefined criteria and were included.

We found fairly reliable electroencephalography and electromyography-based diagnostic biomarkers for functional myoclonus and tremor. Promising biomarkers have also been described for functional paresis, gait and balance disorders. In contrast, there is still a lack of diagnostic biomarkers of functional dystonia and tics, where clinical diagnosis is often also more challenging. Importantly, many promising findings focus on pathophysiology and reflect group-level comparisons, but cannot differentiate on an individual basis. Some biomarkers also require access to time-consuming and resource-consuming techniques such as functional MRI. In conclusion, there are important gaps in diagnostic biomarkers in FMD in the areas of most clinical uncertainty. There is also a lack of treatment response and prognostic biomarkers to aid in the selection of patients who would benefit from rehabilitation and other forms of treatment.

**INTRODUCTION**

Functional movement disorders (FMD) are common and often disabling.<sup>1,2</sup> Their diagnosis was traditionally based on the exclusion of 'organic' conditions and on the presence of psychological trauma. However, current criteria emphasise establishing a diagnosis based on positive criteria from history and examination, such as eliciting distractibility or entrainment of functional tremor.<sup>3</sup> In addition, a 'laboratory supported' diagnostic category has been suggested, where specific investigations provide additional diagnostic certainty.<sup>4,5</sup> Recent years have seen an increasing interest in treatment of FMD, with consensus criteria published for physiotherapy treatment, and positive results from cohort and randomised trials of physiotherapy and multidisciplinary rehabilitation.<sup>6-9</sup>

However, a number of important challenges remain in diagnosis and treatment. First, diagnosis is not always straightforward, and there are particular clinical scenarios, for example, dystonic posturing,

overlay of functional symptoms on an underlying organic movement disorder, where diagnosis can be particularly difficult.<sup>10</sup> Second, treatment studies, while often positive, all show a range of treatment response with a proportion of people having no improvement. However, prediction of likely response to treatment is difficult. For example, in two studies of inpatient multidisciplinary rehabilitation for severely affected people, no reliable baseline predictors of treatment response were found.<sup>11,12</sup> This is particularly problematic given the expensive and time-consuming nature of this treatment. Third, a proportion of patients recover without treatment, while some will remain with symptoms lifelong, but there are no reliable ways of determining prognosis at first presentation. If there were, then it would be helpful for stratifying and prioritising patients for treatment. Fourth, in development of novel treatments, we do not have reliable markers of subclinical response to treatment, something that could be helpful in determining that a treatment shows promise for further development.

In other illnesses, these challenges are typically addressed through the search for biomarkers. There are different types of biomarkers depending on the purpose. The Biomarker Definitions Working Group<sup>13</sup> defines four main types of biomarkers:

1. Biomarkers used as a diagnostic tool for identifying patients with a disease or abnormal condition.
2. Biomarkers used as a tool for staging a disease or classifying the extent of disease.
3. Biomarkers used as an indicator of disease prognosis.
4. Biomarkers used for predicting and monitoring the clinical response of an intervention—response biomarkers.<sup>14</sup>

We performed a systematic review to characterise the current state of biomarker development in FMD, and to identify key gaps and challenges in order to define a roadmap of priorities for future research.

**METHOD**

For this systematic review, we first created a PubMed search term list that can be found in the online supplemental materials. A search on PubMed performed on 28 February 2019 revealed 1137 studies. We also hand searched reference lists of selected articles. The inclusion criteria were: human subjects; original studies; studies investigating the (measurable) biological correlates of abnormal movement in FMD; and literature in English. Our exclusion criteria were: sample size smaller than three participants; and studies investigating comorbidities, for



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example, abnormal emotional processing. BLCT first identified and retrieved all original studies which could be relevant, based on title and abstract. BLCT and TT then independently analysed the retrieved articles and selected studies that fulfilled the inclusion/exclusion criteria. Disagreements were discussed with MJE and resolved based on consensus. Study quality assessment was based on the size of the groups considered the sample size, inclusion of a control group and blinding. We performed a qualitative analysis and narrative synthesis per biomarker, method of measurement and movement disorder phenotype.

This study protocol was registered on PROSPERO with the registration number CRD42019127554.

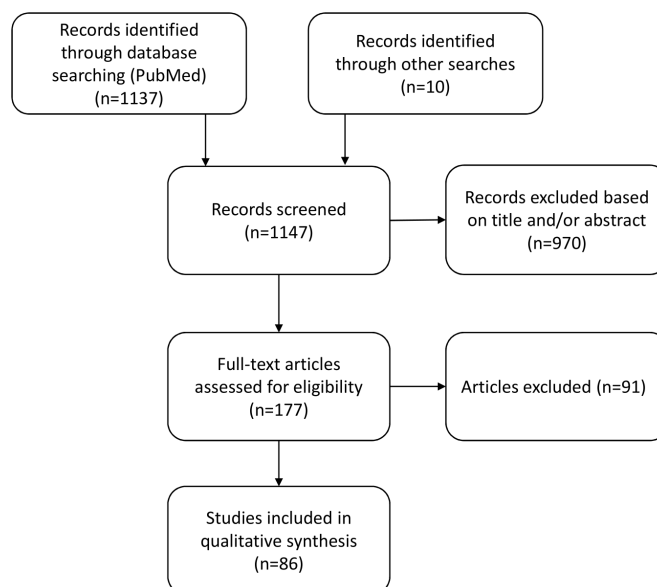
### RESULTS

Eighty-six studies were selected for the qualitative analysis (figure 1 and online supplemental table 1). The most promising diagnostic biomarkers are summarised in table 1.<sup>5 15–21</sup>

### Functional tremor

#### Neurophysiological biomarkers

Electromyography (EMG) and accelerometry have been used to define the neurophysiological characteristics of functional



**Figure 1** Flow chart of study identification. Flow diagram of the study identification and selection.

**Table 1** Potential diagnostic biomarkers in functional movement disorders

Biomarker	Technique	Group sizes	Pros	Cons	Sensitivity	Specificity	Positive predictive value
<b>Tremor</b>							
Test battery <sup>5</sup>	EMG and accelerometer recordings of upper limbs in relaxed condition, outstretched with and without weight loading, during tapping tasks and while performing ballistic movements.	FMD: 38 PD: 24 ET: 19 Dystonic tremor: 19 Other type of organic tremor: 11	High sensitivity and specificity differentiating functional and organic tremor. EMG/accelerometer are accessible techniques.	Unknown value for differentiating pure functional tremor from functional overlay; functional tremor can be diagnosed clinically with high-level confidence in most patients.	90%	96%	92%
<b>Myoclonus</b>							
Bereitschaftspotential and event-related desynchronisation <sup>15</sup>	EEG	FMD: 29 Cortical myoclonus: 16	High specificity. EEG is widely available.		76%	100%	100%
<b>Paresis</b>							
EMG activity <sup>16</sup>	EMG of the affected hand while performing finger abduction of the non-affected hand.	FMD: 10 Healthy controls: 36 Acute organic paralysis: 11	High sensitivity and specificity. EMG is widely available.		100%	100%	100%
Quantified Hoover's test <sup>17 18</sup>	Measuring force of involuntary and voluntary hip flexion in Hoover's test. 'Hoover's index'—ratio of involuntary/voluntary pressure force.	FMD: 9 Healthy controls: 9 Stroke: 9 Paresis due to pain (lumbar radiculopathy): 9	High sensitivity and specificity of 'Hoover's index' (cut-off 1.4) in differentiating functional paresis from both organic paresis and feigners.	Uncertain advantage in comparison to standard Hoover's test.	100%	100%	100%
<b>Mixed</b>							
A model of functional connectivity <sup>19</sup>	Resting state fMRI. Hyperconnected right caudate, left amygdala and bilateral postcentral gyri. Decreased functional connectivity in the right temporoparietal junction and frontal areas.	FMD: 23 Healthy controls: 25	Usable in a mixed group of FMD.	Only compared with healthy controls and not organic movement disorders. Expensive and not accessible in every hospital.	70%	68%	Diagnostic accuracy: 69% <sup>21</sup>
Body sway <sup>20</sup>	Trunk inclination in transverse plane and body angular velocity measured by accelerometers while performing distraction manoeuvre.	FMD: 12 Healthy controls: 12 MS: 12	Can differentiate FMD from both organic disease and healthy controls.	The equipment is not widely available.	100%	100%	100%

The most promising potential biomarkers for different phenotypes of functional movement disorders. EEG, electroencephalography; EMG, electromyography; FMD, functional movement disorder; fMRI, functional MRI.

tremor and also tested as a diagnostic tool.<sup>4 5 22-32</sup> Functional tremor is characterised by a large variation of tremor amplitude and frequency,<sup>24-26 28-30 32</sup> tonic discharge of antagonist muscles shortly before tremor onset<sup>4 5 30</sup> (sensitivity 46%–100%, specificity 96%–100%<sup>4 5 30</sup>), higher amplitude during loading<sup>4 5 22 24 30</sup> (sensitivity 33%–69%, specificity 75%–95%<sup>4 22 30</sup>), changes in frequency during distraction<sup>22 24 28 30</sup> (sensitivity 42%–92% and specificity of 94%<sup>22 28 30</sup>), entrainment<sup>4 5 22 24 27 29</sup> (sensitivity 39%–91%, specificity 91%–100%<sup>4 22 29</sup>), less accuracy in tapping performances<sup>4 5</sup> (sensitivity 46%, specificity 84%<sup>4</sup>), reduction of amplitude or cessation when performing ballistic movement with the opposite hand<sup>4 5 23</sup> (sensitivity 67%–100%, specificity 84%–100%<sup>4 23</sup>), significant coherence between the two hands in bilateral tremor<sup>4 5 29</sup> (sensitivity 56%, specificity 96%<sup>4</sup>), higher number of periods without significant coherence,<sup>31</sup> absence of finger tremor<sup>30</sup> (sensitivity of 100%<sup>30</sup>) and involving fewer limb segments.<sup>29</sup> Algorithms including these neurophysiological and behavioural variables have shown a sensitivity of 87%–100% and specificity of 93%–100%.<sup>4 5 26</sup>

One EMG study investigating coherence in muscle pairs (extensors and flexors) and cumulant analysis (assessing timing between EMG bursts in muscle pairs) in patients with functional tremor and different phenotypes of organic tremor found that these methods could be useful in differentiating some types of organic tremor but not for diagnosing functional tremor.<sup>25</sup> Another study observed that some patients with functional hand tremor showed tremor coherence between their hands whereas other patients showed independent oscillations. The latter might be explained by coexisting non-functional tremulous muscle activity such as clonus or enhanced physiological tremor.<sup>33</sup>

### Functional neuroimaging biomarkers

Patients with functional tremor have shown increased activity in the motor/emotion-processing circuits in the anterior cingulate/paracingulate cortex. This activation decreased in the patients who improved after cognitive-behavioural therapy.<sup>34</sup>

A decrease in the activation of the right temporoparietal junction (rTPJ) during functional tremor has been reported. Reduced activation of the rTPJ might relate to patients' experience of lack of sense of agency over their movements.<sup>35</sup>

A single-photon emission CT (SPECT) study described higher relative cerebral blood flow (rCBF) in the left inferior frontal gyrus (IFG) and left insula at rest. During motor tasks, increased rCBF was observed in the cerebellum, and reduced rCBF in the medial prefrontal cortex and anterior cingulate cortex, as compared with the resting state.<sup>36</sup>

### Behavioural biomarkers

Patients with functional tremor performed a reaction time test with one hand while the other hand was either at rest or trembling. Reaction time was prolonged when the opposite hand was trembling, as compared with resting, suggesting a dual task effect in people with functional tremor that was absent in people with 'organic' tremors.<sup>37</sup> During a self-paced movement task, patients with functional tremor showed a delayed perception of their intention to move as compared with healthy controls. This was proposed to reflect a loss of sense of agency over movement.<sup>38</sup>

### Functional dystonia

#### Neurophysiological biomarkers

Contrary to patients with organic dystonia, subjects with functional mobile-type dystonia as well as those with fixed dystonia

associated with complex regional pain syndrome have shown normal sensorimotor plasticity.<sup>39-41</sup>

Functional fixed dystonia has shown fewer co-contractions on EMG as compared with fixed dystonia secondary to structural damage.<sup>42</sup> Electrophysiological measures of cortical and spinal inhibition were abnormal in both fixed and organic dystonia, but with considerable variability between individuals.<sup>43 44</sup>

### Functional neuroimaging biomarkers

A positron emission tomography (PET) study found that during a motor task, patients with functional dystonia had increased activity in the cerebellum and basal ganglia and decreased activity in primary motor cortex as compared with healthy controls and patients with organic dystonia. When comparing activity at rest and during motor tasks, increased activity was found in the dorsolateral prefrontal cortex in patients with both functional and organic dystonia. These results were proposed to reflect disturbances in motor attention in both functional and organic dystonia.<sup>45</sup>

### Structural neuroimaging biomarkers

A structural MRI study reported subtle signs of atrophy in subjects with mobile functional dystonia, involving a wide range of areas involved in sensorimotor processing, emotional and cognitive control. In addition, functional fixed dystonia was associated with a disruption of fibre architecture of white matter tracts.<sup>46</sup>

### Behavioural biomarkers

Patients with functional dystonia and primary generalised dystonia have both shown an increase in temporal discrimination thresholds as compared with healthy controls.<sup>47</sup> However, a second study failed to replicate this finding for functional dystonia.<sup>48</sup>

Mental rotation is impaired in patients with functional dystonia and organic dystonia.<sup>48</sup> Patients with functional dystonia were observed to have shorter reaction times as compared with patients with secondary dystonia, but with considerable overlap between the two groups.<sup>42</sup>

### Functional myoclonus

#### Neurophysiological biomarkers

The Bereitschaftspotential (BP), or premovement potential, is a slow-rising potential seen in the electroencephalography (EEG) starting about a second before a self-paced movement. It appears to start in the supplementary motor area (SMA), which is therefore thought to have a role in the initiation of voluntary movement.<sup>49</sup> Studies have shown that BP is present in 25%–86% of patients with functional myoclonus,<sup>15 50-54</sup> and has a specificity of 100% in differentiating functional and organic myoclonus.<sup>15 50 51</sup> Intriguingly, the *absence* of a BP prior to a *voluntary* self-paced movement had a sensitivity of 59% and a specificity of 98% to differentiate functional myoclonus from organic myoclonus and Tourette's syndrome.<sup>51</sup> The amplitude of beta and low gamma oscillations (13–45 Hz) normally reduces prior to cued and self-paced movements.<sup>55</sup> This phenomenon is called 'event related desynchronisation' and can also be measured with an EEG. The presence of event-related desynchronisation had a sensitivity of 62%–65%<sup>15 50</sup> and a specificity of 100% for diagnosing functional myoclonus.<sup>15 50 51</sup> Combined BP and event-related desynchronisation had a sensitivity of 75%–80% and a specificity of 100% in differentiating functional and organic myoclonus.<sup>15 50</sup>

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An ‘incongruent EMG’ was observed in 85% of a group of patients with functional myoclonus, and was also proposed to have diagnostic value.<sup>53 56</sup> An ‘incongruent EMG’ was defined by an inconsistent pattern of muscle involvement,<sup>56</sup> differing from the EMG findings described for propriospinal myoclonus by Brown *et al.*<sup>57</sup> In a cohort including 34 patients with functional myoclonus all showed either a BP or an incongruent EMG, suggesting a sensitivity of 100% for this combination of biomarkers.<sup>53</sup>

An EMG study investigating auditory startle responses showed increased response probability in functional myoclonus, with a more variable pattern of muscle recruitment in late startle responses.<sup>58</sup>

### Functional paresis

#### Neurophysiological biomarkers

In patients with unilateral paresis of an upper limb, finger abduction in the non-affected hand resulted in synkinetic activity detected by EMG on the affected hand in all patients with functional paresis, but none in organic paresis. This corresponds to a sensitivity and specificity of 100% in differentiating functional and organic paresis.<sup>16</sup>

Motor-evoked potentials (MEP) induced by transcranial magnetic stimulation during voluntary muscle contractions in healthy controls showed shorter latencies, increased amplitudes and a longer duration as compared with patients with functional paresis.<sup>59</sup> During a cued reaction time task, patients with functional paresis showed a larger intrasubject variation of MEP amplitudes, as compared with healthy controls and patients with amyotrophic lateral sclerosis. This parameter had high specificity for functional paresis.<sup>60</sup>

The MEP amplitude during motor imagery (subjects *imagining* performing a movement) was observed to increase by 200% in healthy controls but only by 63% in the non-paretic finger and 37% in the paretic finger of patients with functional weakness.<sup>61</sup> In healthy controls, motor imagery resulted in an increase in corticospinal excitability while patients with functional paresis showed a decrease.<sup>62 63</sup> However, during motor observation (watching a video of a person performing a movement) normal MEPs were seen, suggesting that moving focus of attention away from the patient might be a useful therapeutic approach.<sup>63</sup>

Contingent negative variation is an EEG signal detected in the waiting period between a preparation cue to move and the ‘go’ cue. In a precued reaction time task, patients with functional paresis and healthy controls feigning paresis showed similar force reductions, slowing movement and prolongation of muscle activity as compared with healthy controls instructed to move normally. However, a reduced contingent negative variation was only seen in patients and not in healthy controls feigning paresis.<sup>64</sup>

In a precued reaction time task, patients with functional weakness showed larger P3 event-related potentials when their symptomatic hands were precued as well as smaller earlier N1 potentials in comparison with feigning subjects. The authors proposed that the abnormal N1 could reflect abnormal processing of precues, and the enhancement of P3 could be related with the suppression of brain circuits involved in the attribution of agency.<sup>65</sup>

A study using a two-choice reaction task found that the event-related potentials in the anterior cingulate cortex were hyperactive during movements of the paretic arm compared with the non-affected arm.<sup>66</sup>

Using isometric measures, a large variability of torque force was seen in patients with functional paresis. Furthermore, there was a relative decrease in the torque force, which was stronger in fast as compared with slow movements.<sup>67</sup>

### Functional neuroimaging biomarkers

A functional MRI (fMRI) study reported that patients with functional paresis showed hyperactivity in the left amygdala during simultaneous emotional stimulation (pictures of sad faces) and passive movement. Furthermore, increased functional connectivity was found between the left amygdala and the (pre-)SMA and subthalamic nucleus. These results suggested a link between abnormal emotional processing and impaired motor control in functional paresis.<sup>68</sup>

fMRI during passive movement of an upper limb with functional weakness or feigned weakness showed increased activity in the IFG as compared with non-feigning healthy controls.<sup>69</sup>

Another fMRI study reported abnormal patterns of activity in the prefrontal and parietal areas, supramarginal gyrus and precuneus in patients with functional paresis as compared with feigning and non-feigning healthy controls.<sup>70</sup>

An increased functional connectivity between the dorsolateral prefrontal cortex and sensorimotor areas was observed during imagined movement of the paretic hand, as compared with the non-paretic hand.<sup>71</sup> Furthermore, there were abnormalities in the functional connectivity within the default mode network, as well as between the default mode network and other areas/networks involved in memory, emotion, self-referential processing, motor planning and execution.<sup>72</sup>

During movement, both patients with functional paresis and healthy controls feigning paresis showed smaller activation of the motor cortex contralateral to the affected limb. However, patients also showed a more widespread pattern of abnormal cortical activity.<sup>73</sup>

Motor imagery of the affected paretic upper limb was associated with an activation of the frontal cortex, superior temporal cortex and the gyrus rectus.<sup>74 75</sup> Patients with functional hemiparesis showed a reduced activity during motor imagery in the cortical hand areas contralateral to the paresis.<sup>76</sup>

Regional homogeneity is an fMRI parameter which investigates the functional network by measuring the coherence of spontaneous low-frequency signal fluctuations in the brain. The regional homogeneity was increased in the left precentral gyrus and reduced in the precuneus contralateral to the paresis. In addition, patients with functional weakness have shown a prolongation of the short-interval intracortical inhibition facilitation, which is a parameter of sensorimotor integration.<sup>77</sup>

A SPECT study demonstrated that during vibratory stimulation, patients had reduced rCBF in the thalamus and basal ganglia contralateral to the paresis. Importantly, this abnormal pattern of activity normalised after clinical recovery suggesting that it might reflect a reversible impairment of sensorimotor function.<sup>78</sup>

Finally, a PET study found a decreased rCBF in frontal regions in patients with functional hemiparesis.<sup>79</sup>

### Structural neuroimaging biomarkers

A structural MRI study reported a reduced volume of the left thalamus as compared with healthy controls. However, this relative atrophy could either be a cause or a consequence of limb paresis.<sup>80</sup> Another study found a bilateral increased grey matter thickness of the premotor cortex, but only in patients with functional hemiparesis and not in paraparesis.<sup>81</sup>

### Behavioural biomarkers

Hoover's sign is the most useful clinical manoeuvre to establish a positive diagnosis of functional paresis of the lower limb.<sup>82</sup> Two studies investigated quantitative versions of the Hoover's test, based on the measurement of isometric force of hip extension performed during direct maximal voluntary effort and contralateral hip flexion. The authors defined 'Hoover's index' as involuntary/voluntary force ratio on the affected limb as well as 'side ratios', corresponding to the *ratios* of 'involuntary/voluntary ratios' between affected and unaffected limbs. These studies reported increases in the Hoover's index of the limbs with functional weakness (sensitivity and specificity of 100% using a cut-off value of 1.4) as well as increases in the 'side ratios', as compared with healthy controls and patients with organic paresis.<sup>17 18</sup>

Patients with functional paresis have shown greater increases in muscle power during eccentric compared with static contractions as well as during encouragement (sensitivity of 100% and specificity of 67%).<sup>83</sup> Finally, functional paresis has been associated with prolonged reaction times but normal response durations, suggesting an impairment of motor initiation.<sup>84</sup>

### Mixed FMDs

Several studies included phenotypically mixed groups of patients with FMD which will be reviewed in this section. Studies of functional gait and balance disorders will also be reported here.

### Neurophysiological biomarkers

Patients with FMD lacked the normal decrease in the amplitude of the sensory-evoked potentials that occurs at the onset of self-paced voluntary movement. This finding was proposed to reflect an impairment of sensory attenuation.<sup>85</sup> During a precued reaction time task, patients failed to take advantage from highly predictive cues to improve reaction times, in contrast to healthy controls. This abnormal motor performance was accompanied by an impairment of the beta desynchronisation and lateralisation during motor preparation, which was proposed to reflect abnormal attention.<sup>86</sup>

### Functional neuroimaging biomarkers

A resting state fMRI study in patients with FMD reported increased connectivity between right caudate, left amygdala and bilateral postcentral gyri as well as decreased connectivity between the rTPJ and frontal regions. A model, built from these data, to distinguish FMD from healthy controls had a sensitivity of 70%, specificity of 68% and diagnostic accuracy of 69%.<sup>19 21</sup> Another study found decreased functional connectivity between the rTPJ and the right sensorimotor cortex, cerebellar vermis, bilateral SMA and right insula.<sup>87</sup> fMRI during a motor task in a virtual reality setting where hand movements could be mimicked with high, intermediate or low accuracy showed a more restricted pattern of activation in patients with FMD (circumscribed to the right anterior insula and rTPJ), and this pattern was related with the abnormal sense of agency.<sup>88</sup>

During a two-button action selection task, patients with FMD showed hypoactivity in the left SMA in both internally and externally generated movements, which suggests a reduced top-down regulation from higher order regions. Hyperactivity of the right amygdala, left anterior insula and bilateral posterior cingulate was proposed to reflect abnormal limbic activation during motor initiation.<sup>89</sup>

During a visuomotor task consisting of drawing a straight line while the computer created deviations, subjects were asked to

rate the deviations and confidence in their responses. Healthy subjects activated the left superior precuneus and middle temporal area, which are involved in sensorimotor integration and vision, whereas patients with FMD activated the bilateral parahippocampal and amygdalohippocampal regions, which have a role in processing memory, associative processing and emotion.<sup>90</sup> fMRI performed during a motor task with emotional stimulation (exposure to pleasant and unpleasant pictures) showed increased activity in the inferior frontal cortex and pre-SMA in healthy controls but increased activity in the cerebellum, posterior cingulate cortex and hippocampus suggesting a defensive mechanism.<sup>91</sup>

### Structural neuroimaging biomarkers

Patients with FMD showed increased volume of the left amygdala, striatum, cerebellum, fusiform gyrus and bilateral thalamus as well as a decreased volume in the left sensorimotor cortex.<sup>92</sup> In addition, another study described a decreased volume of the bilateral caudate nuclei, lentiform nuclei and right thalamus.<sup>93</sup>

### Behavioural biomarkers

In a go/no-go task, patients with FMD showed an impairment of motor response inhibition.<sup>94</sup> Patients with FMD reported an auditory tone as happening earlier and the motor action as happening later compared with trials where they were only asked to report the timing of the effect (auditory tone) or action. Overall, the binding scores were lower in patients as compared with healthy controls related to a reduced experience of control.<sup>95</sup>

Patients with FMD showed a larger startle response when looking at both positive and negative pictures as compared with neutral pictures, while healthy controls only showed larger startle responses when watching negative pictures.<sup>96</sup> In patients with FMD there was a decreased force output only when looking at unpleasant pictures, while healthy controls showed a decrease for both pleasant and unpleasant pictures.<sup>91</sup>

Body sway analysis using accelerometers revealed increased trunk inclination and angular velocity in patients with FMD (sensitivity 92% and specificity 92%).<sup>20 97</sup> Body sway can also be measured by standing on a force platform. Patients with functional paresis and gait disorders showed a larger worsening of their static balance after closing their eyes.<sup>98</sup> Importantly, distraction produced a significant normalisation of the postural abnormalities in functional patients (sensitivity 100% and sensitivity 100%).<sup>20 98</sup> Finally, under a situation of mental stress, body sway was observed to decrease over time in healthy controls, but not in patients with FMD.<sup>97</sup>

## DISCUSSION

Here we have presented the results of a systematic review of biomarkers in FMD. Though over 80 studies of relevance were found, there were very few that presented biomarkers that were validated or had undergone significant development in order to assess their potential utility.

There were two areas where diagnostic biomarkers were well established and validated in several independent patient cohorts: functional myoclonus and functional tremor. In functional myoclonus the BP appears to be a robust biomarker for differentiating functional and organic myoclonus. Sensitivity was 25%–86% and the specificity was 100%.<sup>15 50–53</sup> The lack of sensitivity may reflect the technical difficulty of recording BP in people with very frequent jerks as several seconds of EMG silence are needed for the EEG to stabilise, or very infrequent

jerks where insufficient data are acquired to allow visualisation of the BP. There is the suggestion that combining the BP with assessment of event-related beta desynchronisation (another EEG measure that can be derived from the same data set, and therefore not an additional procedure for the patient) increases sensitivity.<sup>15 50</sup> Variability of EMG recruitment patterns is another potential marker of functional myoclonus.<sup>58</sup> Indeed, as is the case for functional tremor, a combination of diagnostic biomarkers may be appropriate as a standard diagnostic toolkit for functional myoclonus.

In functional tremor, a range of electrophysiological measures have been found to have good sensitivity and specificity, many of these repeated across different cohorts in different laboratories, which increases confidence in their reliability.<sup>4 5 22–32</sup> In two linked studies a battery of these tests was assembled and applied to cohorts of patients with functional tremor and organic tremor, yielding a cut-off score for diagnosis of functional tremor with a sensitivity of 100% and a specificity of 100%.<sup>4 5</sup> In the follow-up validation study these same measures were applied to a new cohort of patients, which confirmed the high sensitivity and specificity (90% and 96%, respectively).<sup>5</sup> One unanswered question from these studies is the proportion of people with tremor where such tests would actually be necessary. Clinical examination is often sufficient to diagnose functional tremor, and it is likely that these tests will only be necessary for a small number of patients. They could be useful in particular contexts, for example, in a clinical trial setting, or in cases with suspected functional overlay, particularly when invasive procedures such as deep brain stimulation or thalamotomy are being considered.

Hoover's sign is a well-established clinical sign in functional paresis. Two studies have developed quantitative versions of this manoeuvre, reporting a sensitivity and specificity of 100%.<sup>17 18</sup> One of the studies used a simple weighing scale to measure force, which makes the technique highly accessible.<sup>18</sup> However, again, it remains to be determined which patients would require this quantitative technique as opposed to simply eliciting Hoover's sign as part of physical examination. Notably, expert clinical assessment (including Hoover's sign) is the gold standard against which quantitative techniques are validated. It may be that these techniques (as well as objective techniques for diagnosing tremor) may be useful as a tool to demonstrate the diagnosis to patients as part of diagnostic explanation, potentially enhancing diagnostic understanding compared with clinical demonstration alone.<sup>99</sup>

In unilateral functional arm paresis, a presentation which is not straightforward to diagnose clinically in some cases, abduction of the non-affected fingers resulted in synkinetic activity of the affected hand measured with EMG in one study. The test showed a 100% sensitivity and specificity in differentiating functional and organic paresis, and would benefit from further validation.<sup>16</sup> In another upper limb measure using variability of movements in response to torque forces, 22 out of 25 patients performed abnormally, corresponding to a sensitivity of 88%.<sup>67</sup> However, this test requires specific equipment, limiting its clinical generalisability, at least in the form reported.

Body sway analysis could help identifying patients with functional gait and balance problems. Patients with functional gait or balance disturbance had a significantly higher angular velocity of the trunk inclination in the transverse plane which had a sensitivity and specificity of both 92%.<sup>20 97</sup> A significantly better performance during distractions had a sensitivity and specificity of 100%.<sup>20 98</sup> This finding is of interest given clinical difficulties in some patients in diagnosis of functional gait and balance problems. While the methodology of the study requires the use

of mobile accelerometers or force platforms, limiting its generalisability to clinical practice, it is possible that it could be adapted for use with more readily available devices, for example, mobile phone-based apps that are increasingly available for measurement of movement.

The clinical scenarios where diagnostic biomarkers are most needed are in functional dystonia and functional tics. There remains significant disagreement and uncertainty about the diagnosis of functional dystonia. The phenotypic qualities of organic tics (distractibility, suggestibility, suppressibility) make them complex to differentiate from functional tics, particularly in the setting of suspected functional overlay on top of Tourette's syndrome. This has important ramifications for treatment, as invasive procedures become more widely used for treatment of refractory tics. We identified no studies that specifically looked for biomarkers for functional tics; the BP does not seem to be useful as it is quite commonly recorded in people with organic tics.

In functional dystonia sensorimotor plasticity was abnormal at a group level in organic dystonia but not in functional fixed or mobile dystonia.<sup>39 41</sup> However, this measure is known to be highly variable in people with organic dystonia, and it is also not a measure that would be technically easy to implement into clinical practice.<sup>100</sup>

Functional neuroimaging techniques have mainly been used in studies focusing on pathophysiology but might also help identifying promising biomarkers. One potentially interesting diagnostic biomarker which is not linked to a specific phenotype was reported in a study of 23 patients with mixed FMD and 25 healthy controls using resting state fMRI. A model developed using the study data set to distinguish patients with FMD from healthy controls produced a sensitivity of 70% and a specificity of 68%. The model was based on hyperconnectivity in the right caudate, amygdala, prefrontal and sensorimotor regions.<sup>19</sup> There are problems of course in translating this into clinical practice methodologically, but resting state fMRI is not complex to acquire. The development of a diagnostic biomarker that is not linked to a specific phenotype is an attractive idea, and this study demonstrates that it may indeed be possible. Further work in this area would clearly be of interest.

Multiple studies have reported changes in the rTPJ and prefrontal areas which are related to sense of agency<sup>19 35 87 88</sup> and disturbances in brain regions related to motor function.<sup>35 45 68 71–79 87 88 90</sup> Increased activity has been demonstrated in the cerebellum,<sup>36 45 91</sup> basal ganglia,<sup>45 73</sup> IFG,<sup>36 69 73</sup> insula,<sup>36 73 89</sup> anterior cingulate cortex<sup>34 66</sup> and limbic structures.<sup>68 89–91</sup> However, although significant differences were found on a group level, it is not known to what extent they can differentiate at an individual patient level. These studies are also problematic for the inherent lack of generalisability of an fMRI measure to clinical practice. However, there may be certain situations where a functional neuroimaging biomarker could be used, for example, in the development of a novel medication or invasive treatment for FMD (eg, deep brain stimulation) where it is imperative to determine if there is some signal of a beneficial effect of treatment, as part of early-phase therapy development. Here, given the small number of subjects and the importance of detecting a therapeutic benefit, functional neuroimaging could be of use. However, the biomarker needed here would not be a diagnostic one, but instead a biomarker of treatment response.

Only a few studies investigated changes in biomarkers after treatment. One fMRI study described normalisation of hyperactivity in the anterior cingulate/paracingulate cortex after successful cognitive-behavioural therapy.<sup>34</sup> A SPECT study

reported normalisation of thalamic blood flow induced by peripheral vibratory stimulation after successful treatment.<sup>78</sup> Finally, we have recently reported that clinical improvement of FMD after neurophysiotherapy is associated with faster reaction times and with a normalisation of contingent negative variation during movement preparation, which was absent at baseline before treatment.<sup>101</sup>

### Limitations of available evidence

Our review discussed several other potential diagnostic biomarkers, but none had undergone sufficient testing to recommend them for current use. Most neuroimaging studies included very small sample sizes, often less than 10 subjects per group. Small sample sizes make it difficult or impossible to control for confounders. Moreover, the smaller the sample size, the larger the impact of heterogeneity among subjects with FMD in the final results. This might contribute to problems of replicability.

The most common clinical conundrum is differentiating patients with FMD from people with other causes of neurological symptoms. However, a large proportion of studies only used healthy subjects as a control group.

There is still a major unmet need of identifying biomarkers capable of distinguishing functional neurological problems from factitious or malingering disorders in routine clinical practice. Only a few studies included control groups of healthy subjects instructed to feign, and it remains uncertain whether this constitutes an appropriate control group for this purpose.

The development of biomarkers of FMD would also not necessarily solve the problem of identifying *coexisting* non-functional causes contributing for the motor symptoms—a frequent and often a greater challenge than the detection of functional elements.

Although we reviewed studies focusing on biomarker correlates of abnormal motor phenomena and excluded studies investigating non-motor comorbidities some changes detected in neuroimaging and neurophysiology may still reflect comorbidities.

We found no biomarkers that provided information on prognosis. This is an issue of great importance in clinical practice. While there is now considerable evidence to support the use of physiotherapy and multidisciplinary rehabilitation in the treatment of FMD, all treatment studies find a proportion of people who do not benefit. This is problematic, as multidisciplinary rehabilitation is time consuming and labour intensive and will only ever be a scarce resource. It would be a great benefit to be able to determine at baseline those patients who are most likely to respond to treatment. So far, clinical measures fail to predict those who do well or poorly with such treatment.<sup>11</sup>

The gold standard used for the validation of new diagnostic biomarkers in FMD is expert opinion based on clinical assessment, and this creates a problem of ‘circularity’. In crude terms, this diagnostic strategy generates biomarkers that can only be as good as expert clinical opinion. As we improve our mechanistic understanding of FMD it may be possible to shift towards objective biomarkers in clinical practice and also in research on biomarkers and treatment.

### CONCLUSIONS

We found fairly reliable diagnostic biomarkers for functional myoclonus and to a lesser extend for tremor. However, there are major gaps in biomarker development for FMD. The most pressing clinical issues are for diagnostic biomarkers for functional dystonia and tics, and for biomarkers capable of predicting

prognosis and treatment response. Clues are available from the literature on the possible nature of these biomarkers. The potential benefits of strong diagnostic, predictive and prognostic biomarkers in FMD argue for a concerted internationally effort for biomarker development.

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“Dissociative Myoclonus”[All fields] OR “Hysterical Myoclonus”[All fields] OR “Functional Tremor”[All fields] OR “Psychogenic Tremor”[All fields] OR “Conversion Tremor”[All fields] OR “Conversive Tremor”[All fields] OR “Dissociative Tremor”[All fields] OR “Hysterical Tremor”[All fields] OR “Functional Tics”[All fields] OR “Psychogenic Tics”[All fields] OR “Conversion Tics”[All fields] OR “Conversive Tics”[All fields] OR “Dissociative Tics”[All fields] OR “Hysterical Tics”[All fields] OR “Functional Dystonia”[All fields] OR “Psychogenic Dystonia”[All fields] OR “Conversion Dystonia”[All fields] OR “Conversive Dystonia”[All fields] OR “Dissociative Dystonia”[All fields] OR “Hysterical Dystonia”[All fields] OR “Functional Posture”[All fields] OR “Psychogenic Posture”[All fields] OR “Conversion Posture”[All fields] OR “Conversive Posture”[All fields] OR “Dissociative Posture”[All fields] OR “Hysterical Posture”[All fields] OR “Functional Postures”[All fields] OR “Psychogenic Postures”[All fields] OR “Conversion Postures”[All fields] OR “Conversive Postures”[All fields] OR “Dissociative Postures”[All fields] OR “Hysterical Postures”[All fields] OR “Functional Posturing”[All fields] OR “Psychogenic Posturing”[All fields] OR “Conversion Posturing”[All fields] OR “Conversive Posturing”[All fields] OR “Dissociative Posturing”[All fields] OR “Hysterical Posturing”[All fields] OR “Functional Bradykinesia”[All fields] OR “Psychogenic Bradykinesia”[All fields] OR “Conversion Bradykinesia”[All fields] OR “Conversive Bradykinesia”[All fields] OR “Dissociative Bradykinesia”[All fields] OR “Hysterical Bradykinesia”[All fields] OR “Functional Akinesia”[All fields] OR “Psychogenic Akinesia”[All fields] OR “Conversion Akinesia”[All fields] OR “Conversive Akinesia”[All fields] OR “Dissociative Akinesia”[All fields] OR “Hysterical Akinesia”[All fields] OR “Functional Slowness”[All fields] OR “Psychogenic Slowness”[All fields] OR “Conversion Slowness”[All fields] OR “Conversive Slowness”[All fields] OR “Dissociative Slowness”[All fields] OR “Hysterical Slowness”[All fields] OR “Functional Gait”[All fields] OR “Psychogenic Gait”[All fields] OR “Conversion Gait”[All fields] OR “Conversive Gait”[All fields] OR “Dissociative Gait”[All fields] OR “Hysterical Gait”[All fields] OR “Functional Walking”[All fields] OR “Psychogenic Walking”[All fields] OR “Conversion Walking”[All fields] OR “Conversive Walking”[All fields] OR “Dissociative Walking”[All fields] OR “Hysterical Walking”[All fields]) AND (“Biomarkers”[All fields] OR “Biomarker”[All fields] OR “Magnetic Resonance Imaging”[All fields] OR “MRI”[All fields] OR “Functional magnetic resonance imaging”[All fields] OR “fMRI”[All fields] OR “Functional neuroimaging”[All fields])

OR “Positron-Emission Tomography”[All fields] OR “PET”[All fields] OR “Single-Photon Emission-Computed Tomography”[All fields] OR “Single photon emission computerized tomography”[All fields] OR “SPECT”[All fields] OR “Computed Tomography”[All fields] OR “CT”[All fields] OR “Neuroimaging”[All fields] OR “Imaging”[All fields] OR “Electroencephalography”[All fields] OR “EEG”[All fields] OR “Electromyography”[All fields] OR “EMG”[All fields] OR “Neurophysiology”[All fields] OR “Electrophysiology”[All fields] OR “Evoked potentials”[All fields] OR “Evoked potential”[All fields] OR “Movement control”[All fields] OR “Motor control”[All fields] OR “Brain activity”[All fields] OR “Transcranial magnetic stimulation”[All fields] OR “TMS”[All fields])

Supplementary table 1. Studies on Biomarkers in Functional Movement Disorders

Author	Year	Title	FMD group (N)	Control group(s) (type, N)	Main objective	Technique	Biomarker	Type of biomarker	Main findings
<b>Tremor</b>									
Schwinge nschuh[4]	2011	Moving toward "laboratory-supported" criteria for psychogenic tremor.	13	Organic tremor: 25	To develop measurable tests that can distinguish functional and organic tremor.	EMG and accelerometer measures were recorded in different states: Rest, arms outstretched to shoulder level, with 500 g mass attached to the wrists (loading), goal-directed task, tapping task, ballistic hand movements.	EMG and accelerometer data.	Diagnostic	A test battery which was calculated to a number of points (maximum 10) could differentiate functional and organic tremor. The sensitivity and sensitivity of the test battery was 100 %.
Schwinge nschuh[5]	2016	Validation of "laboratory-supported" criteria	38	PD: 24 ET: 19 Dystonic tremor: 19	To validate an electrophysiological test battery in	EMG and accelerometer.	Test battery involving recordings during relaxed condition, outstretched with	Diagnostic	Patients with FMD had a significantly higher score on the test battery compared to patients with organic tremor. The sensitivity was 90 % and the

		for functional (psychogenic) tremor.		Other type of organic tremor: 11	the diagnosis of functional tremor.		and without 500-gram loading at wrists, during tapping tasks and while performing ballistic movements.		specificity was 96 % of the test battery.
van der Stouwe [22]	2016	How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena.	50	EPT: 50 ET: 50 PD: 41 Dystonic tremor: 7 Cerebellar tremor: 8 Holmes tremor: 4	To study the sensitivity and specificity for different "typical" characteristics for five tremor phenotypes	Accelerometry, EMG and video at rest and with arm loading (500 g), entrainment, distractibility (100-7) and intention test (finger-to-nose).	Amplitude variability, entrainment and distractibility.	Diagnostic	Increased amplitude upon loading had a sensitivity of 22 % and a specificity of 92 %. Entrainment had sensitivity of 91 % and a specificity of 91 %. Distractibility had a sensitivity of 94 % and a specificity of 92 % for FMD.
Kumru [23]	2004	Transient arrest of psychogenic tremor induced by contralateral ballistic movements.	7	Healthy controls mimicking tremor: 10 PD: 11 ET: 10	To quantify the effect on ballistic movements on contralateral tremor to diagnose patients with functional tremor.	Reaction time task (ballistic movements) with one hand and with the other hand at rest or in a maintained posture. Hand oscillation mean period, amplitude, frequency, and	Data from tremor analysis	Diagnostic	The reaction time task resulted in reduction in amplitude or cessation in the contralateral hand in patients with functional tremor and healthy controls mimicking tremor but not in patients with PD or ET. The test had a sensitivity and specificity of both 100 % in differentiating healthy controls and patients with functional tremor from patients with organic tremor.

reaction time  
were measured  
using a  
movement  
transducer.

Benaderette[24]	2006	Psychogenic Parkinsonism: A Combination of Clinical, Electrophysiological, and [123I]-FP-CIT SPECT Scans Improves Diagnostic Accuracy.	9	None	To explore the concordance of clinical, electrophysiological and [123I]-FP-CIT SPECT investigations in the diagnosis of functional parkinsonism.	[123I]-FP-CIT SPECT. EMG and accelerometer recording of tremor during rest, posture and action as well as during different test: distraction, contralateral motor tasks, entrainment test, and mass loading.	Absence of dopaminergic deficiency. EMG and accelerometer data.	Diagnostic	A combination of clinical, electrophysiological and [123I]-FP-CIT SPECT investigations improved the diagnostic accuracy to differentiate between pure functional parkinsonism from a combined functional parkinsonism and Parkinson's disease and pure Parkinson's disease.
van der Stouwe [25]	2015	Usefulness of intermuscular coherence and cumulant analysis in the diagnosis of postural	21	ET: 20 PD: 19 EPT: 19	To examine the value of advanced EMG measures to distinguish different types of postural upper-limb tremor. The	EMG	Intermuscular coherence and cumulant analysis.	Diagnostic	Coherence was significantly larger in functional tremor, PD and ET patients than in EPT patients. A more synchronous pattern was predominant in PD, EPT and functional tremor compared to a predominantly alternating activity in ET. EPT patients showed significant low coherence which could

		tremor.			EMG measures were coherence and cumulant analysis of muscle pairs.				differentiate it from the other types of tremor with a sensitivity of 89% and a specificity of 80%. Frequency variability was significant in functional tremor and EPT but not in PD and ET.
Piboolnura k[26]	2005	Psychogenic Tremor Disorders Identified Using Tree-Based Statistical Algorithms and Quantitative Tremor Analysis	23	Healthy controls: 21 PD: 22 Dystonic tremor: 11 ET: 15	To demonstrate the use of a tree-based statistical algorithm derived from computerized tremor recordings to diagnose functional tremor.	EMG and accelerometer investigations at rest, with extended arms, and during finger-to-nose movements.	Data from the EMG and accelerometer investigations.	Diagnosis	A tree-based statistical algorithm based on objective data from computerized tremor recordings could differentiate functional and organic tremor. The model was based on amplitude and frequency at rest, with extended arms, and during finger-to-nose movements. The sensitivity of the test was 87 % and specificity 93 %.
McAuley [27]	2004	Identification of psychogenic, dystonic, and other organic tremors by a coherence entrainment test.	8	Healthy controls mimicking tremor: 10 Dystonic tremor: 11 ET: 2	To examine the use of coherence entrainment test to distinguish functional and organic tremor.	Accelerometer and EMG measures while performing a coherence entrainment test.	Presence of coherence	Diagnostic	The coherence entrainment test was sensitive and specific in distinguishing functional and organic tremors.



Uncertain  
tremor:  
4

Milanov [28]	2002	Clinical and electromyographic examinations of patients with psychogenic tremor.	29	None	To explore typical clinical and electrophysiological measures in patients with functional tremor.	EMG in different positions and during distraction.	Tremor pattern, amplitude and frequency.	Diagnostic	Functional tremor was characterized by both agonistic and antagonistic muscle contractions, alternating patterns, variable amplitude and frequency, change in frequency during distractions.
O'Suilleabhain [29]	1998	Time-frequency analysis of tremors.	7	Healthy controls: 4 PD: 20 ET: 8	To test the use of electromyography in differentiate different types of tremors.	EMG while performing tapping movements with the unaffected or less affected hand at the same frequency as a metronome	Variation of frequency and muscles involved.	Diagnostic	In patients with functional tremor the tremor paused or changed frequency when tapping with the other hand. Furthermore, the tremor involved fewer limb segments, was less consistent, and the frequency of the most consistent tremor was higher than the organic types of tremor.
Deuschl [30]	1998	Diagnostic and pathophysiological aspects of psychogenic tremors.	25	PD: 8 ET: 8	To investigate clinical and quantitative characteristics of functional tremor.	Clinical examination and EMG and accelerometer measures without load, with 500 g loading and	Tremor characteristics, frequency and amplitude.	Diagnostic	Patients with functional tremor differed from patients with organic tremor by having inconsistent tremor, cease in tremor during distractions (sensitivity 86 %), and absence of finger tremor (sensitivity 100 %). The EMG and accelerometer

with 1000 g loading.

measures showed a coactivation of muscles preceding tremor (sensitivity 100 %, specificity 100 %), and increased tremor amplitude during loading (sensitivity 69 %, sensitivity 75 %). This might indicate a clonus mechanism.

Kramer [31]	2018	Wavelet coherence analysis: A new approach to distinguish organic and functional tremor types.	26	PD: 26 ET: 26 EPT: 20	To distinguish functional and organic tremor using EMG and wavelet coherence analysis.	EMG analyzed using wavelet coherence analysis.	Coherence	Diagnostic	Functional tremor could be distinguished from organic types of tremor by a higher number of periods without significant coherence.
Milanov [32]	2001	Electromyographic differentiation of tremors.	29	ET: 220 PD: 110 EPT: 120 Midbrain tremor: 24 Cerebellar tremor: 22	To investigate the potential of using electromyography to distinguish different types of tremors.	EMG	Tremor pattern, frequency, amplitude and burst duration during rest, postural, kinetic and intention tremor.	Diagnosis	Electrophysiological examination is a useful tool in the diagnosis of different types of tremor. Functional tremor was characterized by a large variation in tremor frequency and amplitude.
Raethjen [33]	2004	Two different pathogenetic	15	None	To investigate whether all types of	Accelerometer and EMG during posture.	Frequency and amplitude	Pathophysiology	Seven of 15 patients showed coherency between the two hands while 8 patients had independent oscillations.

mechanisms in psychogenic tremor.

functional tremor may be produced voluntarily.

Voluntary bilateral tremor typically results in coherence between the two hands. The absence of coherence might be due to nonvoluntary mechanism like clonus or enhanced physiologic tremor.

Canavese [102]*	2008	Polymyography in the diagnosis of childhood onset movement disorders.	6	Dystonia : 37 Tremor: 8 Subcortical myoclonus: 4 Unknown etiology: 6	To investigate the use of polymyography in the diagnosis of movement disorders in children.	EMG at rest and during distracting maneuvers (counting backwards, ballistic movements).	EMG burst amplitude, frequency, rhythm, duration, co-contraction, overflow).	Diagnostic	Polymyography was a useful tool in supporting the clinical diagnosis of FMD as well as differentiating functional and organic tremor.
Espay[34]	2019	Clinical and neural responses to cognitive behavioural therapy for functional tremor	15	Healthy controls: 25	To investigate the clinical treatment response of cognitive behavioural therapy and changes in the motor/emotional processing	fMRI during a motor task (finger tapping) and emotion face recognition task.	Brain activity	Response to treatment	Patients with functional tremor showed increased activity in anterior cingulate/paracingulate cortex during the emotion face recognition task compared to healthy controls at baseline. In patients tremor severity improved and the activity in anterior cingulate/paracingulate cortex decreased after cognitive behavioural therapy.

circuits in the anterior cingulate/pars opercularis cortex.

Voon[35]	2010	The involuntary nature of conversion disorder.	8	None	To examine the mechanisms of functional tremor being interpreted as involuntary.	fMRI during functional tremor and voluntary mimicked tremor.	Brain activity	Pathophysiology	Right temporoparietal junction hypoactivity during functional tremor compared to voluntary tremor. The right temporoparietal junction has been linked to general comparator of actions and sensory feedback.
Espay [103]*	2018	Impaired emotion processing in functional (psychogenic) tremor: A functional magnetic resonance imaging study.	27	Healthy controls: 27 ET: 16	To examine the emotional processing in functional tremor.	fMRI while performing a motor task (finger-tapping), emotion-recognition task and intense-emotion stimuli task.	Brain activity	Pathophysiology	Patients with functional tremor showed increased activity in the right cerebellum during motor task.

Czarnecki [36]	2011	SPECT perfusion patterns distinguish psychogenic from essential tremor.	5	Healthy controls: 5 ET: 5	To identify characteristic cerebral perfusion to distinguish functional tremor from essential tremor.	SPECT during rest and while performing a tremor-inducing motor task.	Brain activity	Pathophysiology	Patients with functional tremor showed increased rCBF in the left inferior frontal gyrus and left insula at rest compared to healthy controls. During the motor task rCBF was increased in the cerebellum and reduced in the left anterior cingulate cortex, and bilateral ventral medial prefrontal cortex compared to resting state. In patients with functional tremor the default mode network was deactivated during movements. A different pattern was seen in ET.
Kumru [37]	2007	Dual task interference in psychogenic tremor.	6	Healthy controls mimicking tremor: 10 PD: 9 ET: 11	To examine whether patients with functional tremor have dual task interference as seen in healthy controls to distinguish it from organic types of tremor.	Measuring simple reaction time of movements (dual task) using an accelerometer. The test was performed in a resting state while the other hand was not trembling and, in a state, where the opposite hand was trembling.	Reaction time	Diagnostic	The reaction time was significantly different between the resting state and the trembling state test in the FMD and healthy controls groups but not in the PD and ET group.

In healthy controls the tremor was mimicked.

Edwards [38]	2011	Abnormal sense of intention preceding voluntary movement in patients with psychogenic tremor.	9	Healthy controls: 9	To investigate whether patients with functional tremor have an abnormal conscious experience of voluntary movement.	Patients were performing a self-paced button press relative to a clock. They were asked to judge the timing of their intention to move.	Judgment of timing	Pathophysiology	The sense of volition preceding movement was impaired in patients with functional tremor suggesting that voluntary actions might be experienced as involuntary.
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### Dystonia

Quartarone [39]	2009	Abnormal sensorimotor plasticity in organic but not in psychogenic dystonia.	10	Healthy controls: 10 Organic dystonia: 10	To determine clinical features which can differentiate functional and organic dystonia.	TMS and MEP of the abductor pollicis brevis and first dorsal interosseus muscles.	Sensorimotor plasticity	Diagnostic	Cortical plasticity was abnormal in patients with organic dystonia but normal in patients with functional dystonia and healthy controls.
Morgante [41]	2017	Normal sensorimotor plasticity in complex regional pain	10	Healthy controls: 10	To assess sensorimotor plasticity and cortical excitability in patients	TMS and MEP recorded from the abductor pollicis brevis muscles.	Sensorimotor plasticity.	Pathophysiology	Fixed dystonia in patients with complex regional pain syndrome type 1 is not associated with abnormal sensorimotor plasticity and therefore shares pathophysiology with functional

syndrome with fixed posture of the hand.

with fixed dystonia of the hand and complex regional pain syndrome type I.

movement disorders rather than idiopathic dystonia.

Macerollo [42]	2015	Using reaction time and co-contraction to differentiate acquired (secondary) from functional 'fixed' dystonia.	9	Acquired dystonia: 9	To test the diagnostic use of reaction time and contraction analysis in patients with functional and acquired dystonia.	EMG recordings during rest and during a reaction time test in which patients should attempt to move the affected limb in the opposite direction to the habitual posture.	Reaction time and co-contraction data.	Diagnostic	Patients with acquired dystonia had a longer reaction time compared to patients with functional dystonia. Patients with functional dystonia had less co-contraction than patients with acquired dystonia. Although significant differences were found, the overlap was large which made the tests less useful for diagnostic purposes.
Avanzino [43]	2008	Cortical excitability is abnormal in patients with the "fixed dystonia" syndrome.	12	Mobile dystonia: 10 Healthy controls: 11	To evaluate cortical inhibitory mechanism.	TMS and EMG	Motor cortical excitability and sensori-motor integration.	Pathophysiology	Short intracortical inhibition was reduced and contralateral silent period was shorter in organic and functional dystonia compared to healthy controls. Abnormal cortical excitability might predispose to both organic and functional dystonia.

Espay[44]	2006	Cortical and spinal abnormalities in psychogenic dystonia.	10	Healthy controls: 12 Organic dystonia: 8	To explore if aberrant sensory input associated with abnormal posture causes abnormalities in patients with functional dystonia as seen in organic dystonia.	TMS	MEP amplitude	Pathophysiology	Cortical inhibition was reduced in both functional and organic dystonia. Cutaneous silent period was increased in functional and organic dystonia. Spinal reciprocal inhibition was reduced in only functional dystonia. Functional and organic dystonia share similar physiological abnormalities which might indicate that the findings are a result of the abnormal posture itself or that the functional and organic dystonia share some of the same predisposal factors.
Schrag [45]	2013	The functional neuroimaging correlates of psychogenic versus organic dystonia.	6	Healthy controls: 6 Organic dystonia (DYT 1): 5	To investigate the pathophysiology of right-sided functional and organic dystonia and test the role of the prefrontal cortex in these disorders.	[H <sub>2</sub> <sup>15</sup> O]-PET	Brain activity	Pathophysiology	Patients with functional dystonia had increased activity in the cerebellum and basal ganglia and decreased activity in the primary motor cortex compared to healthy controls and patients with organic dystonia during all tasks. During movement compared to rest the right dorsolateral prefrontal cortex was activated in organic and functional dystonia but not in healthy controls.



Espay [104]*	2018	Dysfunction in Emotion Processing Underlies Functional (Psychogenic) Dystonia.	12	Healthy controls: 25 Primary organic dystonia: 12	To investigate the possible abnormalities in the emotion processing in patients with functional dystonia.	fMRI while performing a motor task (finger-tapping), emotion-recognition task and intense-emotion stimuli task.	Brain activity	Pathophysiology	No difference was found in brain activity during the motor task.
Tomic[46]	2018	Are there two different forms of functional dystonia? A multimodal brain structural MRI study.	44	Healthy controls: 43	To assess structural brain alterations in functional dystonia.	Structural MRI	Cortical thickness, gray matter volume, and white matter tract integrity.	Pathophysiology	Normal cortical volumes were found in both functional dystonia groups, but atrophy of the orbitofrontal, parietal, and cingulate cortex, hippocampus, and globus pallidus was seen in patients with mobile functional dystonia compared to fixed functional dystonia. Atrophy of the basal ganglia and thalamus was found in patients with mobile functional dystonia compared to healthy controls. Severe disruption of white matter tract architecture involved with cognitive, emotional, and motor pathways was observed in fixed mobile dystonia compared to healthy controls and patients with mobile functional dystonia.

Morgante [47]	2011	Abnormal tactile temporal discrimination in psychogenic dystonia.	10	Healthy controls: 16 Primary torsion dystonia: 10	To investigate somatosensory function in patients with functional and primary torsion dystonia.	Temporal discrimination threshold testing in both hands.	Temporal discrimination threshold	Pathophysiology	Temporal discrimination threshold was higher bilaterally in patients with functional and primary torsion dystonia compared to healthy controls. In patients with unilateral affection no difference in temporal discrimination threshold was found between the two hands.
Katschnig [48]	2010	Mental rotation of body parts and sensory temporal discrimination in fixed dystonia.	11	Healthy controls: 10 Mobile dystonia: 11	To examine similarities and differences of fixed and mobile dystonia.	Mental rotation of body parts task and sensory temporal discrimination threshold test.	Mental rotation and temporal discrimination threshold	Pathophysiology	In patients with mobile dystonia abnormal mental rotation and temporal discrimination threshold were found. In patients with fixed dystonia only mental rotation was impaired compared to healthy controls. The deficits found might be due to the abnormal body posture itself, a shared predisposing pathophysiology for mobile and fixed dystonia, or a body image disturbance.
<b>Myoclonus</b>									
Meppelink [50]	2016	Event related desynchronization predicts functional	20	Organic myoclonus: 9	To determine the sensitivity and specificity	EEG and EMG	BP and ERD	Diagnostic	A significant BP was present in 25 % and a significant ERD was present in 65 % of patients with functional the propriospinal jerks. BP and ERD was absent in the healthy controls group.

		propriospi nal myoclonus.			of BP and ERD to differentiate functional and organic myoclonus.				
Beudel [15]	2018	Improving neurophysio logical bio markers for functional myoclonic movements.	29	Cortical myoclon us: 16	To investigate whether ERD and BP can be used to differentiate functional and organic myoclonus.	EEG	BP and ERD	Diagno stic	An objective BP had a sensibility of 51 % and a specificity of 100 %. ERD had a sensitivity of 62 % and a specificity of 100 %. The combination of BP and ERD had a sensitivity of 76 % and a specificity of 100 %.
van der Salm[51]	2012	The bereitschaft potential in jerky movement d isorders.	29	Healthy controls imitating jerks: 25 Tourettes syndrom e: 14 Organic myoclon us: 5	To examine the diagnostic value of BP in jerky movement disorders.	EEG	BP	Diagno stic	Patients with FMD had BP before their jerk significantly more often than healthy controls and organic myoclonus. The absence of a BP before intended movement had a sensitivity of 59 % and a specificity of 98 % for functional myoclonus.
Terada [52]	1995	Presence of Bereitschaft potential preceding p sychogenic myoclonus:	6	None	To examine if jerk- locked back averaging can be used to diagnose	EEG and EMG	BP	Diagno stic	A BP before a functional jerk was seen in five out of six patients (sensitivity 67 %). A BP before a voluntary mimicked jerk was seen in two out of six patients.

		clinical application of jerk-locked back averaging.			functional myoclonus.				
Erro[53]	2013	Clinical diagnosis of propriospinal myoclonus is unreliable: an electrophysiologic study.	65	Propriospinal myoclonus: 0	To assess the value of clinical assessment in differentiating propriospinal myoclonus from functional myoclonus.	EEG and EMG	BP and incongruent electromyographic pattern.	Diagnostic	31 patients were clinically diagnosed as propriospinal myoclonus and 34 as functional myoclonus. EEG and EMG showed that all patients had either a BP (86%) and/or an incongruent pattern on EMG (85%) and could therefore be categorized as functional myoclonus. Clinical evaluation was unreliable in differentiate propriospinal myoclonus from functional myoclonus.
Esposito [54]	2009	Idiopathic spinal myoclonus: a clinical and neurophysiological assessment of a movement disorder of uncertain origin.	20 patients with idiopathic spinal myoclonus.	None	To investigate the use of BP as a diagnostic tool to differentiate functional jerks and organic myoclonus.	EEG, EMG, and clinical evaluation by two movement disorder specialists.	BP	Diagnostic	EEG showed definite BP in 6 patients (30%), possible BP in 9 patients (45%), and an absent BP in 5 patients (25%). The two movement disorder specialists agreed 75 % of the times. The agreement between the clinical and electrophysiologic examination was 90 %.

van der Salm[56]	2010	Axial jerks: a clinical spectrum ranging from propriospinal to psychogenic myoclonus.	34	Secondary propriospinal myoclonus (ciprofloxacin induced): 1	To assess the examination of patients with possible propriospinal myoclonus.	EMG	BP	Diagnostic	Diagnosis of psychogenic axial jerks was made based on clinical clues in 8 cases, on inconsistent findings at polymyography in 15, on observations of regular eye blinking preceding jerks in 2, and on presence of a BP in 9.
Dreissen [58]	2017	Startle responses in functional jerky movement disorders are increased but have a normal pattern.	17	Healthy controls: 15	To investigate the frequency and pattern of auditory startle response in patients with functional myoclonus.	EMG recordings during auditory startle reflex provoked by 108 dB loud tones.	Size of early startle responses.	Pathophysiology	Patients with functional myoclonus showed enlarged response probability of the early and late response. The early response was enlarged, but normally patterned. The late response was more variable patterned compared to healthy controls. The high response probability corresponds to a hypersensitivity to external stimuli often linked to functional myoclonus. The enlarged response frequency of late responses indicates a behavioural component.
Zutt[105]*	2017	Myoclonus subtypes in tertiary referral center. Cortical	40	Cortical myoclonus: 29 Subcortical myoclonus	To investigate the accuracy of clinical phenotyping	EMG and EEG	BP, muscle recruitment, burst duration.	Diagnostic	Electrophysiological testing confirmed the diagnosis of myoclonus in 74% and its subtype in 78% of cases.

		myoclonus and functional jerks are common.		us: 9 Spinal myoclonus: 5 Peripheral myoclonus: 2	in patients with myoclonus. Electrophysiology was used to define the diagnosis.				
van der Salm [106]*	2017	Clinical decision-making in functional and hyperkinetic movement disorders.	60 patients in total, but the number of patients in each group is not reported.	None	To evaluate the diagnostic process in differentiating functional and organic types of hyperkinetic movement disorders (tics and myoclonus).	EMG and EEG	BP	Diagnostic	First impression of the patients was decisive in 18.5% of cases, medical history in 33.3%, neurologic examination in 39.7%, BP in 8%, and the psychiatric interview in 0.5%. Medical history resulted in a diagnostic switch in 34.5 % of cases, neurologic examination in 13.8%, BP in 7.2%, and psychiatric evaluation in 2.7%.

### Paresis

Tinazzi [16]	2008	Abduction finger sign: a new sign to detect unilateral functional paralysis of the upper	10	Healthy controls: 36 Acute organic paralysis: 11	To test whether the abduction finger sign can be used as a diagnostic tool to	EMG or the affected hand while performing abduction of the nonaffected hand.	EMG activity	Diagnostic	The test had a 100 % sensitivity and specificity.
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		limb.			differentiate acute onset functional and organic hand paralysis.				
Brum[59]	2015	Clinical Value of the Assessment of Changes in MEP Duration with Voluntary Contraction.	5	Healthy controls: 25 MS: 21 Acute stroke: 33 Hereditary spastic paraparesis: 5	To investigate how voluntary contractions, alter MEP in healthy controls and in patients with different neurological diseases.	TMS inducing MEP.	MEP with and without simultaneous voluntary motor contractions.	Diagnosis	In healthy controls voluntary contraction causes shortening of MEP latency, increasing MEP amplitude and longer MEP duration. In patients with suspected FMD no increase in MEP duration was found. This was not seen in any of the other patient groups. The phenomenon could be due to voluntary lack of alpha motor neuron activation.
Morita[60]	2008	Size variance of motor evoked potential at initiation of voluntary contraction in palsy of conversion disorder.	10	Healthy controls: 8 ALS: 9	To evaluate the diagnostic value of TMS with a cue signal to differentiate functional and organic paresis.	TMS at rest, during tonic contraction, and contraction after an audio cue signal.	MEP amplitude	Diagnosis	The MEP amplitude increased in healthy controls and patients with ALS but not obviously in some patients with FMD. A large intrasubject variance among trials were seen in the FMD group especially during the cue signal paradigm which had a high specificity in differentiating patients with FMD from healthy controls and patients with ALS.

Liepert [61]	2009	Abnormal motor excitability in patients with psychogenic paresis. A TMS study.	8	Healthy controls: 8	To investigate the mechanisms of patients with functional hemiparesis being unable to execute voluntary movements.	TMS at rest at while imagining finger movements.	Motor thresholds and MEP amplitudes.	Diagnostic	At rest the motor threshold and MEP amplitudes were almost identical in the patients and healthy controls. At motor imagery MEP amplitudes increased by 200 % in healthy controls but only by 63 % in patients imagining moving the nonaffected finger and decreased by 37 % when imagining moving the paretic finger.
Liepert [62]	2008	Electrophysiological correlates of motor conversion disorder.	4	Healthy controls: 8	To investigate if patients with functional paresis have abnormal motor excitability.	TMS during rest and during imagination of tonic index finger adductions.	Corticospinal excitability	Diagnostic	In healthy controls motor imagery resulted in an increase of corticospinal excitability while a decrease was seen in patients when imagining moving the paretic finger.
Liepert [63]	2011	Motor excitability during movement imagination and movement observation in psychogenic lower limb	10	Healthy controls: 10	To explore motor excitability during motor imagery and movement observation.	TMS	MEP	Pathophysiology and possible therapeutic approach.	During motor imagery MEPs were significantly smaller in patients compared to healthy controls. Compared to rest, motor imagery resulted in an increase of MEPs in healthy controls but a decrease in patients with functional paresis. During motor observation no significant difference was seen. Moving the focus of attention



paresis.

away from the patient could be a possible therapeutic approach.

Blakemore [64]	2015	Deficit in late-stage contingent negative variation provides evidence for disrupted movement preparation in patients with conversion paresis.	6	Healthy controls: 12 Healthy controls feigning weakness: 24	To investigate abnormal movement preparation and disrupted execution in patients with functional paresis.	EEG, EMG and kinematic measures while performing a 2-choice precued reaction time task.	Contingent negative variation (EEG measure) amplitude.	Pathophysiology	Patients with FMD and healthy controls feigning paresis showed similar reduced force, longer movement time and extended duration of muscle activity in the symptomatic limb. Patients had significantly suppressed contingent negative variation amplitude when the limb was precued which was not seen in feigning healthy controls.
Blakemore [65]	2013	Distinct modulation of event-related potentials during motor preparation in patients with motor conversion disorder.	6	Healthy controls: 12 Healthy controls feigning weakness: 12	To investigate potential EEG markers for FMD.	EEG while performing pre-cued reaction time task.	Event-related EEG potentials.	Diagnostic	When the symptomatic hand was precued, the P3 event-related potential component accompanying the precue was dramatically larger in patients with functional paresis compared to feigning healthy controls. Also, the earlier N1 event-related potential component was diminished when the precue signaled either the symptomatic or asymptomatic hand. These results might indicate a suppression of brain activity

related to self-agency.

Roelofs [66]	2006	Hyperactive action monitoring during motor-initiation in conversion paralysis: An event-related potential study	6	None	To investigate anterior cingulate cortex hyperactivity in patients with functional paresis.	EEG while performing speeded two-choice reaction task.	Event-related potentials.	Pathophysiology	Anterior cingulate cortex was hyperactive during movements initiated in the paretic compared to the non-affected arm.
Knutsson [67]	1985	Isokinetic measurements of muscle strength in hysterical paresis.	25	None	To investigate features of functional paresis using isometric measures of strength.	Torque recording during isometric flexion and extension of the knee using isokinetic measures and EMG.	Torque and force measures.	Diagnostic	Variability of torque could be seen in 22 patients. Higher torque in fast compared to slow movements was found in 8 patients. A smaller force production than expected from the weight of the leg and lever arm due to restraining activation of the quadriceps muscle was observed in 12 patients. The torque recording could support the diagnosis of functional paresis.

Hassa[68]	2017	Symptom-specific amygdala hyperactivity modulates motor control network in conversion disorder.	13	Healthy controls: 19	To investigate the neural correlates of emotion processing interacting with motor networks in patients with functional paresis.	fMRI with separate and simultaneous emotional (pictures of calm and sad faces) and sensorimotor stimulation (passive movement of one arm).	Functional connectivity.	Pathophysiology	During simultaneous emotional stimulation and passive movement of the affected hand patients with functional paresis showed hyperactivity in the left amygdala. Psychophysiological interaction revealed increased functional connectivity between the left amygdala and the (pre-)supplemental motor area and subthalamic nucleus in patients with functional paresis. These areas are involved in motor control networks.
Hassa[69]	2016	Functional networks of motor inhibition in conversion disorder patients and feigning subjects.	13	Healthy controls: 12	To investigate possible differences of patients with functional hemiparesis and feigning healthy controls.	fMRI while the paretic (patients) or feigned paretic arm (healthy controls) was passively moved. Healthy controls were also investigated in a non-feigning condition.	Brain activity (BOLD)	Pathophysiology	During passive movement of the affected arm patients with FMD showed activation of the bilateral triangular part of the inferior frontal gyri with a left side dominance compared to non-feigning controls. Feigning controls had increased activation of the right triangular part of inferior frontal gyri and a decreased activation in the medial prefrontal cortex compared to non-feigning controls. This suggests that the self-agency in patients with FMD is in between the feigning and non-feigning condition in healthy controls.

van Beilen[70]	2011	Abnormal parietal function in conversion paresis.	Right-sided functional paresis: 6 Left-sided functional paresis: 4	Healthy controls: 21 Right-sided feigning paresis: 7 Left-sided feigning paresis: 6	To identify abnormal parietal activity in patients with functional paresis.	fMRI while performing four tasks: performing flexion/extension movements in a 0.5 Hz pace of the right and left wrist separately and imagining doing it.	Brain activity	Pathophysiology	Patients with functional paresis showed abnormal parietal function. Patients also had reduced activity in the prefrontal cortex, supramarginal gyrus and precuneus.
de Lange[71]	2010	Altered connectivity between prefrontal and sensorimotor cortex in conversion paralysis.	8	None	To investigate the inter-regional coupling between prefrontal cortex and sensorimotor regions in patients with hand paresis while imagining movements.	fMRI during a motor imagery task	Functional and effective connectivity	Pathophysiology	Strong functional connectivity between the dorsolateral prefrontal cortex and several sensorimotor areas which was more pronounced when patients imagined the affected hand compared to the non-affected hand.
Monsa[72]	2018	Self-reference, emotion inhibition	7	Healthy controls: 15	To explore the pathophysiology and	Resting-state fMRI	Functional connectivity	Pathophysiology	Increased functional connectivity in default-mode network. Decreased inter-connectivity

and somatosensory disturbance: preliminary investigation of network perturbations in conversion disorder.

neuroanatomy in patients with functional unilateral paresis and hypoesthesia (pseudo-stroke).

between default-mode network and limbic/salience network, temporo-parieto-occipital junction, and medial temporal lobe and medial temporal lobe and sensorimotor network. Increased connectivity between limbic/salience network and temporo-parieto-occipital junction and between hippocampus and the default-mode network. Networks related to memory, emotion, self-referential processing, motor planning, and execution were disturbed.

Stone[73]	2007	FMRI in patients with motor conversion symptoms and controls with simulated weakness.	4	Healthy controls simulating weakness: 4	To examine neural correlates in patients with unilateral functional weakness.	fMRI during ankle flexion.	Brain activity	Pathophysiology	In both patients and healthy controls feigning paresis reduced activation of the motor cortex contralateral to the affected or simulated affected limb was seen compared to the nonaffected limb. In patients with functional paresis activation was seen in the putamen and lingual gyri bilaterally, left inferior frontal gyrus, left insula, and deactivated right middle frontal and orbitofrontal cortices. Only controls simulating weakness activated the contralateral
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supplementary  
motor area.

de Lange[74]	2008	Increased self-monitoring during imagined movements in conversion paralysis.	8	None	To investigate whether the dysfunction underlying functional paralysis is due to inhibition of the motor system or enhanced self-monitoring during motor behaviour.	fMRI while imagining moving the affected and nonaffected arm.	Brain activity	Pathophysiology	Only when imagining of moving the affected arm recruitment of the ventromedial prefrontal cortex and superior temporal cortex was seen. This might be due to heightened self-monitoring during actions in functional paralysis.
de Lange[75]	2008	Motor imagery: A window into the mechanisms and alterations of the motor system.	7	None	To examine how motor imagery can be used to investigate the pathophysiology of functional hand paresis.	fMRI during implicitly and explicitly motor imagery. The implicitly motor imaging was obtained by a motor imagery task where subjects were asked to judge the	Brain activity	Technique	Significant increased activity in dorsal parietal and premotor cortex with increasing rotation was both during implicit and explicit motor imagery. Superior and medial portions of the frontal cortex, the gyrus rectus and superior temporal cortex showed greater cerebral activity for the affected hand than the unaffected hand during implicit

laterality of the visually presented rotated hand. Explicitly motor imaging was obtained by verbal instructions.

but not explicit motor imagery.

Burgmer [76]	2006	Abnormal brain activation during movement observation in patients with conversion paralysis.	4	Healthy controls: 7	To examine if movement conceptualization is altered in patients with functional hemiparesis.	fMRI during observation and subsequent imitative execution of movements.	Brain activity	Pathophysiology	Patients with functional paresis showed decreased activation of cortical hand areas during movement observation compared to healthy controls. This effect was specific to the side of their paralysis. Brain activation compatible with movement inhibition was not observed.
Premi[77]	2017	Multimodal Brain Analysis of Functional Neurological Disorders: A Functional Stroke Mimic Case Series.	4	Healthy controls Neuroimaging: 23 TMS: 10	To identify brain abnormalities in functional stroke mimics using fMRI and TMS.	Resting state fMRI and TMS.	Regional homogeneity and short-interval intra-cortical inhibition-facilitation.	Pathophysiology	Increased regional homogeneity in the left precentral gyrus and reduced regional homogeneity in the precuneus contralateral to the hemiparetic side. Mean short-interval intra-cortical inhibition-facilitation was increased in FMD. These structures are involved in motor planning and motor execution.

Vuilleumier[78]	2001	Functional neuroanatomical correlates of hysterical sensorimotor loss.	7	None	To evaluate functional activity of the brain causing the altered experience of sensation and volition in patients with functional sensorimotor loss.	<sup>99m</sup> Tc-ECD SPECT performed at rest and during bilateral vibratory stimulation. The last scan was repeated in four cases who had recovered 2-4 months later.	Brain activity	Pathophysiology  Response to treatment	The regional cerebral blood flow during vibratory stimulation was reduced in the thalamus and the basal ganglia contralateral to the deficit. The hypoactivity resolved after recovery.
Tanaka [79]	2007	Pseudohysterical hemiparesis .	4	None	To investigate possible altered cerebral blood flow in patients with functional hemiparesis .	PET	Brain activity	Pathophysiology	Decreased cerebral blood flow was seen in cortical frontal regions corresponding to the patients' neurological deficits.
Nicholson [80]	2014	A structural MRI study of motor conversion disorder: evidence of reduction in	14	Healthy controls: 31	To explore potential abnormalities in subcortical brain structures in FMD.	Structural MRI	Volume of subcortical structures.	Pathophysiology	Patients with FMD had a significantly smaller left thalamic volume and borderline significantly smaller right thalamic volume compared to controls. This difference could be a primary disease process or a secondary effect as a result of



thalamic  
volume.

limb disuse.

Aybek[81]	2014	Grey matter changes in motor conversion disorder.	Functional hemiparesis: 9 Functional paraparesis: 6	Healthy controls: 25	To investigate potential anatomical differences in patients with FMD compared to healthy controls.	Structural MRI	Gray matter thickness	Pathophysiology	Patients with functional hemiparesis showed bilaterally increased grey matter thickness of the premotor cortex compared to healthy controls. No differences were found in the patients with paraparesis.
Ziv[17]	1998	Diagnosis of “non-organic” limb paresis by a novel objective motor assessment: the quantitative Hoover’s test	9	Healthy controls: 10 Stroke: 5 Motor neuron disease: 2	To test an objective measure of Hoover’s sign (detecting automatic contralateral contractions due to preserved anatomy in patients with functional paresis).	Measuring isometric force during involuntary and voluntary contractions measured by a strain gauge and analyzed with a computerized quantitative motor assessment system.	Force	Diagnostic	The involuntary/voluntary force ratio on the affected limb was significantly larger in patients with functional paresis compared to healthy controls and patients organic paresis. Furthermore, the ratio of involuntary/voluntary force ratio between the affected and non-affected side was more than nine times larger in functional paresis compared to the other groups.

Diukova [18]	2013	Simple quantitative analysis of Hoover's test in patients with psychogenic and organic limb pareses	9	Healthy controls: 9 Stroke: 9 Paresis due to pain (lumbal radiculopathy): 9	To examine an objective Hoover's sign test.	Measuring involuntary and voluntary pressure force using routine weighing scales.	Force	Diagnostic	The involuntary/voluntary force ratio on the affected limb and the ratio of the involuntary/voluntary force ratio of the two sides were significantly larger in patients with functional paresis compared to healthy controls and patients with stroke and paresis due to pain. The test had a sensitivity and specificity of both 100 %.
van der Ploeg[83]	1991	The 'make/break test' as a diagnostic tool in functional weakness	20	Healthy controls: 20 Neuromuscular disease: 20 Diagnoses blinded for the examiner : 20		Maximum voluntary contractions measured using a myometer during a "make test" (static contraction) and a "break test" (muscle force is overcome). The tests were performed with and without encouragement from the examiner.	Force	Diagnostic	In healthy controls there was only a small increase (3 %) in motor contraction in the "break" compared to "make" test. The difference was slightly larger (6 %) in patients with organic paresis and considerably larger (68 %) in patients with functional paresis. Patients with functional paresis had a larger effect of encouragement compared to the other groups and showed an increasing force during the tests. Based on the data a cut off value of 20 % improvement of force during "break" compared to "make" and during encouragement was used to test the patients with a blinded diagnosis. Three patients had

									organic paresis and 17 had functional paresis. In 19 out of 20 patients the diagnosis was confirmed using these criteria. One patient with organic paresis fulfilled the criteria for functional paresis. This corresponds to a sensitivity of 100 % and a specificity of 67 %.
Roelofs [84]	2002	Motor initiation and execution in patients with conversion paralysis.	4	None	To explore the hypothesis that the motor initiation and not the response duration is affected in patients with functional paresis.	Verbal reaction time tasks: Simple choice reaction time-task, a mental letter rotation task, and an implicit and explicit mental hand rotation task.	Reaction time	Pathophysiology	Reaction time but not response duration was impaired suggesting that the motor initiation was affected.

**Mixed**

Macerollo [85]	2015	Sensory Attenuation Assessed by Sensory Evoked Potentials in Functional	17	Healthy controls: 17	To explore sense of agency in patients with FMD.	SEP at rest and while performing self-generated movement with simultaneous	SEP amplitude and onset of movement.	Pathophysiology	Patients with FMD lacked attenuation of SEPs at the onset of movement whereas healthy controls showed reduction in amplitude of SEPs. This may indicate that patients have an impaired sense of agency for
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		Movement Disorders.				EEG and EMG recording.			movement.
Teodoro [86]	2018	Abnormal beta power is a hallmark of explicit movement control in functional movement disorders.	21	Healthy controls: 13	To investigate whether sensorimotor beta-frequency oscillatory power is raised during motor preparation in patients FMD.	EEG while performing a reaction time test with varying cue validity.	Beta power	Pathophysiology	Opposite healthy controls, patients with FMD did not improve in reaction time with highly predictive cues and showed impairment of beta desynchronization and lateralization before movement. This may reflect attention towards the movement itself rather than the goal resulting in abnormal movement.
Wegrzyk [19]	2018	Identifying motor functional neurological disorder using resting-state functional connectivity .	23	Healthy controls: 25	To explore whether resting-state fMRI can distinguish patients with FMD from healthy controls.	Resting-state fMRI.	Functional connectivity.	Diagnostic	Patients with FMD had hyperconnected right caudate, left amygdala and bilateral postcentral gyri. Decreased functional connectivity was found in the right temporoparietal junction and frontal areas. A model was made to distinguish FMD and healthy controls. The model had an accuracy, specificity and sensitivity all above 68 %.

Maurer [87]	2016	Impaired self-agency in functional movement disorders: A resting-state fMRI study.	35	Healthy controls: 35	To explore the neural mechanism of impaired self-agency in patients with fMRI.	Resting-state fMRI.	Functional connectivity.	Pathophysiology	Patients with FMD had decreased functional connectivity between the right temporoparietal junction and the right sensorimotor cortex, cerebellar vermis, bilateral supplementary motor area and right insula compared to healthy controls. Temporoparietal junction is involved in self-agency and the results might explain why patients of FMD experience their movements as involuntary.
Nahab[88]	2017	Impaired sense of agency in functional movement disorders: An fMRI study.	14 with MRI 21 with behavioural testing	Healthy controls: 20	To study alterations in sense of agency in patients with FMD.	fMRI while performing finger movements tasks with their right hand in a virtual reality where subjects could see the hand movement on a screen. Sometimes the hand on the screen would mimic the movements completely, not at all, or	Brain activity (BOLD signal)	Pathophysiology	The dorsolateral prefrontal cortex and the pre-supplementary motor area on the right did not respond differently to the loss of movement control indicating a dysfunction of the sense of agency neural network.

intermediate.

Voon[89]	2011	Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder.	11	Healthy controls: 11	To investigate the motor initiation in patients with FMD.	fMRI while performing either an internally or externally generated 2-button action selection task.	Brain activity	Pathophysiology	Both during internally and externally generated movements FMD patients had lower activity in left supplementary motor area (implicated in motor initiation) and higher activity in right amygdala, left anterior insula, and bilateral posterior cingulate.
Begue[90]	2018	Metacognition of visuomotor decisions in conversion disorder.	10	Healthy controls: 10	To study metacognitive function in FMD patients.	fMRI while performing visuomotor task.	Brain activity	Pathophysiology	When subjects rated the deviation and confidence of their response healthy controls engaged the left superior precuneus and middle temporal region which are involved in sensory-motor integration and vision whereas FMD patients recruited bilateral parahippocampal and amygdalo-hippocampal regions which are related to memory, emotions, and contextual associative processing.

Blakemore [91]	2016	Aversive stimuli exacerbate defensive motor behaviour in motor conversion disorder.	10	Healthy controls: 10	To examine whether negative affect (unpleasant emotional images) worsens alterations of motor control (isometric precision-grip) and corresponding brain activity in patients with FMD.	fMRI during motor task and exposure to pleasant or unpleasant pictures.	Behavioural effect and brain activity.	Pathophysiology	The force output decayed for healthy controls when looking at both pleasant and unpleasant pictures while the patients FMD showed decayed force when looking at pleasant pictures but maintained the force when looking at unpleasant pictures indicating a pronounced effect of negative effect on force output. When looking at unpleasant pictures healthy controls had increased activity in the inferior frontal cortex and pre-supplementary motor area whereas patients with FMD had increased activity in the cerebellum, posterior cingulate cortex and hippocampus. This might indicate that psychological stressors result in defensive behavior in patients with FMD.
Yažići [107]*	1998	Cerebral blood flow changes in patients with conversion disorder.	5	None	To examine the regional cerebral blood flow in patients with functional astasia-abasia.	<sup>99m</sup> Tc HMPAO SPECT and sensory evoked potentials.	Brain activity	Pathophysiology	Decreased perfusion was seen in the left temporal lobe in two patients, in the bilateral temporal lobes in one patient, in the left parietal lobe in one patient, and in the left temporal and parietal lobe in one patient. The left hemisphere was dominant in all patients.

Maurer [92]	2018	Gray matter differences in patients with FMD.	48	Healthy controls: 55	To investigate alterations in gray matter volume in patients with FMD.	Structural MRI	Gray matter volume	Pathophysiology	Increased volume of the left amygdala, left striatum, left cerebellum, left fusiform gyrus, and bilateral thalamus, and decreased volume of the left sensorimotor cortex in FMD. These structures are involved with limbic and sensorimotor circuitry.
Atmaca [93]	2006	Volumetric investigation of brain regions in patients with conversion disorder.	10	Healthy controls: 10	To investigate possible volumetric differences in patients with FMD compared to healthy controls.	Structural MRI	Volumes of brain structures	Pathophysiology	Patients had significantly smaller volumes of the bilateral caudate nuclei, lentiform nuclei, and right thalamus compared to healthy controls. Age at disease onset showed a significant relation with left caudate volume.
Voon[94]	2013	Response inhibition in motor conversion disorder.	30	Healthy controls: 30	To examine the motor response inhibition in patients with FMD.	Go/No-go task	Motor response inhibition.	Pathophysiology	The motor response inhibition in patients with FMD was impaired compared to healthy controls. The result remained significant after controlling for attention, sustained attention, depression, and anxiety.
Kranick [95]	2013	Action-effect binding is decreased in motor conversion	20	Healthy controls: 20	To examine the sense of agency with voluntary movements in patients	Motor task was performed (action) followed by an auditory tone (effect) after	Action-effect binding	Pathophysiology	An effect following a voluntary action was perceived as happening earlier and the action later compared to tests of only motor action or tones. Patients with FMD had reduced action-



disorder:  
implications  
for sense of  
agency.

with FMD.

completing  
where high,  
medium and  
low tones were  
coupled to  
pictures of  
happy, fearful  
and neutral  
faces. Subjects  
should judge  
either the time  
action and  
effect – action-  
effect binding.

effect binding scores compared  
to healthy controls. The  
emotional stimuli did not have  
any effect.

Seignourel [96]	2007	Abnormal affective startle modulation in individuals with psychogenic [corrected] movement disorder.	12	Healthy controls: 12	To evaluate how emotional functioning and responsiveness to stress are related to FMD.	Recordings of eyeblink responses to white noise bursts while watching positive, neutral, and negative pictures.	Affective startle response	Pathophysiology and diagnostic.	Healthy controls showed significant potentiation of startle responses by negative pictures and a tendency of inhibition by positive pictures. In patients with FMD both negative and positive pictures resulted in a larger startle response compared to neutral pictures. Depression and anxiety did not correlate with the startle response. The abnormal startle response modulation might be useful in differentiating FMD and malingering.
Wolfsegger [21]	2013	Objectification of psychogenic postural	12	Healthy controls: 12 MS: 12	To test the value of biomechanical balance	Trunk inclination in transverse plane and	Trunk sway	Diagnostic	FMD patients had increased values of trunk angular velocity compared to MS patients and healthy controls which had a

instability by trunk sway analysis.

analysis to identify functional balance and gait disorders. corresponding body angular velocity measured by accelerometers while performing distraction maneuver (numbers written on their back).

sensitivity of 92 % and a specificity of 92 %. Furthermore, a significant effect of distractibility was found which had a 100 % sensitivity and 100 % specificity. This test can be used to confirm a positive diagnose of FMD.

Zito[97]	2018	Abnormal postural behavior in patients with functional movement disorders during exposure to stress	9	Healthy controls: 13	To investigate abnormal motor responses when exposed to stress in patients with functional paresis, tremor and myoclonus.	Body sway measured with accelerometers and gyroscopes attached to thorax during Trier Social Stress Test (imitating performing a speech for a job interview and a mathematical test).	Body sway	Pathophysiology	Patients with FMD showed larger body sway compared to healthy controls. In healthy controls, body sway decreased over time during exposure to stress whereas it was stable in patients with FMD. Complexity of movement pattern over time was lower in patients in FMD compared to healthy controls.
Stins[98]	2015	Attention and postural control in patients with	12	Healthy controls: 12	To examine whether attention can alter the motor	Maintaining static balance standing on a stabilometric platform with	Body sway	Pathophysiology and possible	Compared to healthy controls, patients with FMD showed a larger decrease of static balance when eyes were closed compared to opened. Cognitive

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conversion paresis	performanc e in patients with functional paresis or gait disorder.	eyes open and closed and while performing an attention demanding task.	therape utic approac h.	distractions improved static balance in patients with FMD but decreased balance in healthy controls.
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Legend: Abbreviations: *FMD* functional movement disorder, *MRI* magnetic resonance imaging, *fMRI* functional magnetic resonance imaging, *PET* positron emission tomography, *SPECT* single-photon emission computed tomography, *BOLD* blood oxygenation level dependent, *rCBF* relative cerebral blood flow, *EEG* electroencephalography, *EMG* electromyography, *ERD* event related desynchronization, *BP* Bereitschaftspotential, *PD* Parkinson's disease, *ET* essential tremor, *EPT* enhanced physiologic tremor, *MS* multiple sclerosis, *ALS* amyotrophic lateral sclerosis, *TMS* transcranial magnetic stimulation, *MEP* motor evoked potential, *SEP* sensory evoked potential.

\*Not included in the narrative review.

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