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 pre-defined criteria and were included.

We found fairly reliable EEG and EMG-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- and resource consuming techniques such as fMRI.

In conclusion, there are important gaps in diagnostic biomarkers in FMD in the areas of most clinical uncertainty. There is also is 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.[1,2] 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.[3] In addition, a “laboratory supported” diagnostic category has been suggested, where specific investigations provide additional diagnostic certainty.[4,5] 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.[6-9]

However, a number of important challenges remain in diagnosis and treatment. First, diagnosis is not always straightforward, and there are particular clinical scenarios, e.g. dystonic posturing, overlay of functional symptoms on an underlying organic movement disorder, where diagnosis can be particularly difficult.[10] 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.[11,12] 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 life-long, 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 sub-clinical 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 biomarker depending on the purpose. The Biomarker Definitions Working Group[13] 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.[14]

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 supplementary 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; literature in English. Our exclusion criteria were: sample size smaller than three participants; studies investigating comorbidities e.g. abnormal emotional processing. BT first identified and retrieved all original studies which could be relevant, based on title and abstract. BT and TT then independently analysed the retrieved articles and selected studies that fulfilled the inclusion/exclusion criteria. Disagreements were discussed with ME 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 supplementary table 1). The most promising diagnostic biomarkers are summarised in table 1.[5,15-20]

**Table 1. Potential Diagnostic Biomarkers in Functional Movement Disorders**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Biomarker** | **Technique** | **Group sizes** | **Pros** | **Cons** | **Sensitivity** | **Specificity** | **Positive predictive** **value** |
| **Tremor** |  |  |  |  |  |  |  |
| Test battery.[5] | 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:38PD: 24ET: 19Dystonic tremor: 19Other 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 % |
| **Myoclonus** |  |  |  |  |  |  |  |
| Bereitschaftspotential and event related desynchronisation.[15] | EEG | FMD:29Cortical myoclonus: 16 | High specificity.EEG is widely available. |  | 76 % | 100 % | 100 % |
| **Paresis** |  |  |  |  |  |  |  |
| EMGactivity.[16] | EMG of the affected hand while performing finger abduction of the nonaffected hand. | FMD:10Healthy controls: 36Acute organic paralysis: 11 | High sensitivity and specificity.EMG is widely available. |  | 100 % | 100 % | 100 % |
| Quantified Hoover’s test.[17,18] | Measuring force of involuntary and voluntary hip flexion in Hoover’s test. “Hoover’s index” – ratio of involuntary/voluntary pressure force. | FMD:9Healthy controls: 9Stroke: 9Paresis due to pain (lumbal 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 % |
| **Mixed** |  |  |  |  |  |  |  |
| A model of functional connectivity.[19] | Resting-state fMRI. Hyperconnected right caudate, left amygdala and bilateral postcentral gyri. Decreased functional connectivity in the right tempoparietal junction and frontal areas. | FMD:23Healthy controls: 25 | Usable in a mixed group of FMD | Only compared to healthy controls and not organic movement disorders.Expensive and not accessible in every hospital. | 70 % | 68 % | Diagnostic accuracy: 69 %[21] |
| Body sway.[20] | Trunk inclination in transverse plane and body angular velocity measured by accelerometers while performing distraction maneuver  | FMD:12Healthy controls: 12MS: 12 | Can differentiate FMD from both organic disease and healthy controls. | The equipment is not widely available. | 100 % | 100 % | 100 % |

Legend: The most promising, potential biomarkers for different phenotypes of functional movement disorders.

**Functional Tremor**

**Neurophysiological Biomarkers**

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

One EMG study investigating coherence in muscles pairs (extensors and flexors) and cumulant analysis (assessing timing between EMG bursts in muscles 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.[25] 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.[33]

**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.[34]

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.[35]

A single-photon emission computerised tomography (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 to the resting state.[36]

**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.[37] During a self-paced movement task, patients with functional tremor showed a delayed perception of their intention to move as compared to healthy controls. This was proposed to reflect a loss of sense of agency over movement.[38]

**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.[39-41]

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

**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 to 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.[45]

**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 fiber architecture of white matter tracts.[46]

**Behavioural Biomarkers**

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

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

**Functional Myoclonus**

**Neurophysiological Biomarkers**

The Bereitschaftspotential (BP), or pre-movement 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.[49] Studies have shown that BP is present in 25-86 % of patients with functional myoclonus,[15,50-54] and has a specificity of 100 % in differentiating functional and organic myoclonus.[15,50,51] 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.[51] The amplitude of beta and low gamma oscillations (13-45 Hz) normally reduces prior to cued and self-paced movements.[55] 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 %[15,50] and a specificity of 100 % for diagnosing functional myoclonus.[15,50,51] Combined BP and event related desynchronisation had a sensitivity of 75-80 % and a specificity of 100 % in differentiating functional and organic myoclonus.[15,50]

An “incongruent EMG” was observed in 85% of a group of patients with functional myoclonus, and was also proposed to have diagnostic value.[53,56] An “incongruent EMG” was defined by an inconsistent pattern of muscle involvement,[56] differing from the EMG findings described for propriospinal myoclonus by Brown et al.[57] 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.[53]

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.[58]

**Functional Paresis**

**Neurophysiological Biomarkers**

In patients with unilateral paresis of an upper limb, finger abduction in the nonaffected 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.[16]

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

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 nonparetic finger and 37 % in the paretic finger of patients with functional weakness.[61] In healthy controls, motor imagery resulted in an increase in corticospinal excitability while patients with functional paresis showed a decrease.[62,63] However, during motor observation (watching a video of a person performing a movement) normal MEP were seen, suggesting that moving focus of attention away from the patient might be a useful therapeutic approach.[63]

Contingent negative variation is an EEG signal detected in the waiting period between a preparation-cue to move and the “go” cue. In a pre-cued 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 to healthy controls instructed to move normally. However, a reduced contingent negative variation was only seen in patients and not in healthy controls feigning paresis.[64]

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

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 to the non-affected arm.[66]

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 to slow movements.[67]

**Functional Neuroimaging Biomarkers**

An 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.[68]

Functional MRI 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.[69]

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.[70]

An increased functional connectivity between the dorsolateral prefrontal cortex and sensorimotor areas was observed during imagined movement of the paretic hand, as compared to the non-paretic hand.[71] 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.[72]

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.[73]

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

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.[77]

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.[78]

Finally, a PET study found a decreased rCBF in frontal regions in patients with functional hemiparesis.[79]

**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.[80] Another study found a bilateral increased grey matter thickness of the premotor cortex, but only in patients with functional hemiparesis and not in paraparesis.[81]

**Behavioural Biomarkers**

Hoover’s sign is the most useful clinical manoeuvre to establish a positive diagnosis of functional paresis of the lower limb.[82] 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 to healthy controls and patients with organic paresis.[17,18]

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

**Mixed Functional Movement Disorders**

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.[85] During a pre-cued 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.[86]

**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 %.[19,21] Another study found decreased functional connectivity between the rTPJ and the right sensorimotor cortex, cerebellar vermis, bilateral SMA, and right insula.[87]

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.[88]

During a 2-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.[89]

During a visuomotor task consisting in 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 sensory-motor integration and vision, whereas patients with FMD activated the bilateral parahippocampal and amygdalo-hippocampal regions, which have a role in processing memory, associative processing, and emotion.[90]

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.[91]

**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.[92] In addition, another study described a decreased volume of the bilateral caudate nuclei, lentiform nuclei, and right thalamus.[93]

**Behavioural Biomarkers**

In a go/no-go task, patients with FMD showed an impairment of motor response inhibition.[94] Patients with FMD reported an auditory tone as happening earlier and the motor action as happening later compared to 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 to healthy controls related to a reduced experience of control.[95]

Patients with FMD showed a larger startle response when looking at both positive and negative pictures as compared to neutral pictures, while healthy controls only showed larger startle responses when watching negative pictures.[96] 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.[91]

Body sway analysis using accelerometers revealed increased trunk inclination and angular velocity in patients with FMD (sensitivity 92 % and specificity 92 %).[20,97] 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.[98] Importantly, distraction produced a significant normalisation of the postural abnormalities in functional patients (sensitivity 100 % and sensitivity 100 %).[20,98] Finally, under a situation of mental stress, body sway was observed to decrease over time in healthy controls, but not in patients with FMD.[97]

**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 100 %.[15,50-53] 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 is 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 dataset, and therefore not an additional procedure for the patient) increases sensitivity.[15,50] Variability of EMG recruitment patterns is another potential marker of functional myoclonus.[58] Indeed, as is the case for functional tremor, a combination of diagnostic biomarkers maybe appropriate as a standard diagnostic tool-kit 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 labs, which increases confidence in their reliability.[4,5,22-32] 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%.[4,5] 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).[5] 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 %.[17,18] One of the studies used a simple weighing scale to measure force, which makes the technique highly accessible.[18] 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 to clinical demonstration alone.[99]

In unilateral functional arm paresis, a presentation which is not straightforward to diagnose clinically in some cases, abduction of the nonaffected 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.[16] 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 %.[67] 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 %.[20,97] A significantly better performance during distractions had a sensitivity and specificity of 100 %.[20,98] 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.[39,41] 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.[100]

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 dataset to distinguish FMD patients 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.[19] 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[19,35,87,88] and disturbances in brain regions related to motor function.[35,45,68,71-79,87,88,90] Increased activity has been demonstrated in the cerebellum,[36,45,91] basal ganglia,[45,73] IFG,[36,69,73] insula,[36,73,89] anterior cingulated cortex[34,66] and limbic structures.[68,89-91] 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 (e.g. 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 cingulated/paracingulate cortex after successful cognitive behavioural therapy.[34] A SPECT study reported normalisation of thalamic blood flow induced by peripheral vibratory stimulation after successful treatment.[78] 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.[101]

**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 ten 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 FMD patients 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.[11]

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.

**Figure 1. Flowchart of study identification**

Legend: Flow diagram of the study identification and selection.

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