Prepulse inhibition of the blink reflex is abnormal in functional movement disorders

Zuzana Hanzlíková, MD,*1* Markus Kofler, MD, PD Dr,2 Matěj Slovák, MD,*1* Gabriela Věchetová, MS,*1* Anna Fečíková, MD,*1* David Kemlink, MD, PhD,*1* Tomáš Sieger, PhD, *1,3* Evžen Růžička, MD, DSc,*1* Josep Valls-Solé, MD, PhD,*4* Mark J. Edwards, MD, PhD,*5* Tereza Serranová, MD, PhD*1*

*1Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, 1st Faculty of Medicine and General University Hospital, Prague, Czech Republic*

*2Department of Neurology, Hochzirl Hospital, Hochzirl, Austria*

*3Department of Cybernetics, Faculty of Electrical Engineering, Czech Technical University in Prague, Czech Republic*

*4Neurology Service, Hospital Clíınic, Facultad de Medicina, Universitat de Barcelona, Spain*

*5Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St George’s University of London, London, United Kingdom.*

Correspondence to: Tereza Serranova, MD, PhD, Kateřinská 30, 120 00 Praha 2, Czech Republic, [tereza.serranova@vfn.cz](mailto:tereza.serranova@vfn.cz)

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**Abstract:**

**Background:** Patients with functional movement disorders (FMD) also typically have functional somatic symptoms including pain, fatigue and sensory disturbance. A potentially unifying mechanism for such symptoms is a failure in processing of sensory inputs. Prepulse inhibition is a neurophysiological method that allows for the study of pre-conscious somatosensory processing.

**Objective:** The objective of this study was to assess prepulse inhibition in patients with FMD and healthy control subjects.

**Methods:** We analysed the effect of a weak electrical stimulus to the index finger (prepulse) on the magnitude of the R2 response of the blink reflex induced by electrical stimuli delivered to the supraorbital nerve in 22 patients with clinically established FMD and 22 matched controls. Pain, depression, anxiety, and obsessive-compulsive symptoms were assessed using self-rated questionnaires. In addition, in patients we assessed motor symptom severity.

**Results:** Prepulses suppressed the R2 response of the blink reflex in both groups, by 36.4% (SD 25.6%) in patients and by 67.3% (SD 16.4%) in controls. This difference was significant (p<0.001). There was no significant correlation between motor and non-motor symptom measures and prepulse inhibition size.

**Conclusions:** Impaired prepulse inhibition of the blink reflex suggests an abnormal pre-conscious processing of somatosensory inputs, which can be interpreted within predictive coding accounts of both FMD and functional somatic syndromes. Our results, along with previous findings of a reduced prepulse inhibition in fibromyalgia syndrome, support a possible unified pathophysiology across functional neurological and somatic syndromes with noteworthy implications for diagnostic classification and development of novel biomarkers and treatments.

**Introduction**

Functional movement disorders (FMD) are commonly seen in neurological practice. Clinically, FMD are characterized by variability of signs (e.g. changes in character or fluctuation in their form of presentation), alleviation by distraction and incongruence with movement disorders caused by a known neurological disease.1 The positive diagnostic features of FMD indicate the ability for normal function to occur (e.g. cessation of functional tremor with distraction), but the apparent inability of the person to access this normal function when they wish to.

In patients who present primarily with FMD, multiple other functional somatic symptoms are almost always present, especially pain, fatigue and cognitive difficulties.2 Likewise, patients presenting primarily with chronic pain syndromes such as complex regional pain syndrome type I commonly also have functional motor symptoms.3 Patients with fibromyalgia present with high rate of motor symptoms in absence of another neurological condition.4 Recently neurobiological models of functional symptoms based on, or strongly influenced by, predictive coding accounts of perception and movement control have been proposed.5, 6 These models suggest that functional symptoms arise from the development of abnormal “priors” or predictions, the expression of which is driven by an abnormal allocation of attention. A key feature of this proposed mechanism is that the same basic computational phenomenon can account for functional symptoms across motor, sensory and interoceptive domains. It is therefore likely that there could be biomarkers of this proposed underlying dysfunction which would be common across functional motor and somatic syndromes.

Prepulse Inhibition (PPI) is a neurophysiological phenomenon in which a weak sensory event, subthreshold for eliciting any reflex response (prepulse), leads to reduction in magnitude of the reflex response that would be otherwise elicited by a reflex-eliciting stimulus presented 30-500 ms later. The inhibitory effect of a prepulse is considered to be related to the attentional shift towards the sensory input brought about by the prepulse.7, 8 PPI reflects an early stage of attentional processes involved in information selection processing that operates at subcortical level,9, 10 outside of conscious awareness. Reduction in PPI is one of the most robust biomarkers of schizophrenia and has also been found to be abnormal in numerous other neuropsychiatric conditions including obsessive compulsive disorder and panic disorder.12-14 In a recent study, patients with fibromyalgia syndrome, which is one of the most common causes of chronic widespread pain, showed reduced PPI, which was interpreted as indicating altered sensory perception and processing in fibromyalgia.15

Our aim was to evaluate PPI of the R2 response of the blink reflex in patients with clinically established FMD and sex-/age-matched healthy control subjects. Further, we assessed in these participants the PPI behavior and selfreported measures of pain. We also assessed the influence of factors previously associated with PPI such as anxiety and obsessive compulsive features were also assessed. 12, 13

**Subjects and methods**

We studied 22 patients (18 females, mean age 44.7 (SD 12.1) years, mean disease duration 6.5 (SD 5.7) years) with clinically definite FMD from the specialized outpatient service for FMD at the Neurology Department of *Charles University in Prague, 1st Faculty of Medicine and General University Hospital*. Twenty two unrelated sex- and age-matched control subjects (18 females, mean age 44.8 (SD 12.8) years) were recruited. The diagnosis of FMD according to Gupta and Lang criteria17 was established following detailed clinical interview and examination by an experienced movement disorders specialist (TS) based on positive signs of functional weakness and/or abnormal movements inconsistent and incongruent with known movement disorders. In all controls, a complete medical history was obtained, and full neurological examination was performed. Only controls without neurological symptoms or signs of nervous system disorder were included in the study. The study was approved by the ethics committee of *General University Hospital* (identification number 614/18S-IV) and all participants gave their written informed consent to participate in the study.

In each FMD patient, we evaluated and phenomenologically classified motor symptoms as functional weakness, tremor, dystonia/spasm, myoclonus, gait disorder, or speech disturbance. We recorded the predominant motor symptom type and all additional motor symptoms. The Simplified Functional Movement Disorders Rating Scale (s-FMDRS) was used to assess functional motor disorder severity of both abnormal movements and weakness.18 Seventeen patients reported presence of sensory symptoms (hyperesthesia or dysesthesia and or paresthesias) in some body part, however, no patient had sensory deficits (hypoesthesia) in the right upper limb where the prepulse stimulus was applied.

Exclusion criteria were the presence of comorbidities known to affect PPI such as definite or suspected diagnosis of schizophrenia-spectrum disorders, Tourette's syndrome, temporal lobe epilepsy with psychosis, obsessive-compulsive disorder (OCD),19 panic disorder,13 and administration of medication known to affect PPI, such as dopamine receptor antagonists.16, 20 Similarly, we did not include any patients with a previously diagnosed fibromyalgia or patients reporting a widespread musculoskeletal or myofascial pain suggestive of fibromyalgia.

A structured interview was completed in order to detect medical comorbidities, and to obtain family history, current medication (including hormonal contraceptives) and drugs of abuse, habits of smoking and consumption of caffeinated beverages, and handedness in all subjects. All participants were asked to refrain from smoking and drinking caffeinated beverages within 3-4 hours of the study.20 Information about menstrual cycle phase and hormonal contraceptive use was recorded in female participants.21

Four FMD and two control subjects were on serotonin reuptake inhibitors (SSRI) or on serotonin and norepinephrine reuptake inhibitors (SNRI). Six patients and four healthy volunteers were on medications not thought to effect to PPI such as blood pressure medication, statins, levothyroxine, oral antihistamines or proton pump inhibitors; one patient was on corticosteroid medication.

All subjects completed the following questionnaires: State-Trait Anxiety Inventory (STAI X-1) for assessment of anxiety; Beck Depression Inventory (BDI-II)23 to measure depressive symptomatology; PainDETECT24 for assessment of intensity of current, average, and maximal pain during the last 4 weeks preceding the examination; and Obsessive-compulsive inventory Revised (OCI-R), an 18-item self-report measure with high specificity for symptoms of OCD.

**Neurophysiological investigation**

All neurophysiological examinations were carried out in a moderately lit and quiet room with participants sitting on a chair in a comfortable position. Subjects were thoroughly informed about the different types of stimuli they would receive, but the investigator and the equipment were out of their view, for them not to see the timing and type of stimulation. Recordings were performed with routine electrodiagnostic equipment (Synergy, CareFusion, Surrey, London). Band-pass frequency filters for EMG was 30 to 3000 Hz. The sampling rate for signal storage was 2000 Hz.

**Paradigm**

The non-rectified electromyographic activity of the orbicularis oculi muscles was recorded bilaterally with 10 mm surface gold electrodes attached to the skin using conductive electrode gel. The active electrode was placed over the middle portion of the muscle below each eye and the reference electrode 2 cm lateral to the outer canthus of each eye. Each blink reflex was evoked by an electrical stimulus (a constant current rectangular pulse of 0.5 ms duration) delivered to the right supraorbital nerve with a surface electrode, cathode over the supraorbital notch and anode 3 cm above along the course of the nerve on the forehead. We used a stimulus intensity 10 times sensory threshold, defined as the minimum intensity that subjects would perceive in at least four out of eight stimulations.

Prepulse modulation was assessed by applying a prepulse stimulus 100 ms before the supraorbital nerve stimulation. Prepulse stimuli (constant current rectangular pulses of 0.2 ms duration) were delivered through ring electrodes attached to the right index finger at the middle and distal phalanges with the cathode proximal at two times the subject’s sensory threshold intensity. Care was taken to choose a prepulse stimulus intensity subthreshold for any reflex response (about 1.5 times sensory threshold). We obtained 8 blink reflex responses for each experimental condition, i.e., a supraorbital nerve stimulus alone (baseline) or a supraorbital nerve stimulus preceded by the index finger stimulus (prepulse). Baseline and prepulse trials were intermingled at random, with always an interval of at least 10 seconds separating two consecutive trials.

**Rating of discomfort**

The level of discomfort associated with stimulation was rated with a numeric rating scale (NRS, 0= no discomfort, 10= unbearable).

**Data analysis:**

Electromyographic recordings were rectified and analysed offline. Trials containing artefacts or spontaneous blinks were excluded (approximately 1 % of trials). In each trial, we identified the early ipsilateral R1, and the late ipsilateral (R2) and the contralateral (R2c) blink reflex components.

The magnitude of the ipsilateral and contralateral R2 responses were measured as the area-under the-curve (henceforth R2 area and R2c area, respectively). The R1 component of the response was used as a marker that the afferent volley generated by prepulse stimuli had effectively reached the brainstem. 29

The R3 response 27, 28 was not included in the calculations we made since we did not plan to study this ultralate response in our planned protocol, and it was observed in some of the recordings, particularly in the initial ones, and in some patients.

To evaluate PPI we calculated the average of R2 and R2c areas as ‘blink reflex magnitude’ for each trial. For each individual, we calculated the square root of individual blink reflex magnitudes to stabilize their variances, computed the mean of the resulting values over the 8 trials obtained per condition (baseline and prepulse), and squared the means back to the original numerical scale. For normalization of data among subjects we expressed the change in the blink reflex magnitude in prepulse trials relatively to baseline trials as the percentage of the baseline trials (%PPI, %PPI = mean blink reflex magnitude in prepulse trials/mean blink reflex magnitude in baseline trials × 100). The size of the PPI effect (PPI size), which was the primary outcome, was calculated for each individual as the difference in blink reflex magnitude between the prepulse (%PPI) and the baseline trials (100%).

The statistical comparison of patient and control groups was performed using Student’s t-test for numeric outcomes and using Fisher’s exact test for categorical outcomes. A linear model was used to adjust the group comparison for BDI-II, STAI X-1, and PainDETECT scores (which were summed when entering the model to cope with their correlation and to reduce the number of covariates given the limited sample size). Holm correction for multiple comparisons was used to correct the family-wise error of the 12 inter-group tests of neurophysiological and questionnaires data, 4 within-group tests of neurophysiological and NRS data, and of 6 correlation tests. P values less than 0.05 after correction were considered significant. Uncorrected P values are reported for descriptive purposes, unless stated otherwise. Statistical analyses were performed in R statistical software.30

**Results**

FMD patients and control subjects were not significantly different in smoking habit (11 FMD patients vs. 8 control subjects, p=0.36 uncorr.) or regular caffeine intake (18 FMD patients vs. 19 control subjects, p=1.00 uncorr.).

Motor symptom characteristics are presented in Table 1. The majority of patients had a mixed phenotype. Mean s-FMDRS (range 0–54) was 9.0 (SD 5.1).

Results from the neurophysiological analysis are shown in Table 2. Examples of blink reflex responses without and with prepulse stimulation in a patient and a healthy control subject are shown in Figure 1. Baseline blink reflex characteristics did not differ significantly between the groups. Prepulses significantly suppressed the blink reflex magnitude in both groups of subjects (t21=-4.768, P=0.0001 corr. in FMD patients, t21=-6.13, P<0.0001 corr. in controls). The PPI was 36.4% (SD 25.6%) in FMD patients and 67.3% (SD 16.4%) in controls. This difference was significant (t35.7=4.78, P=0.0003 corr.) (Table 2; Figure 2).

No difference was found between patients and control subjects in sensory thresholds for both the supraorbital nerve stimulation (t41.0=-0.13, P=0.8960 uncorr.) and the prepulse stimulus to the index fingers (t37.9=-1.41, P=0.1668 uncorr.). Prepulses significantly reduced the level of discomfort resulting from the applied stimuli as measured on the NRS in both groups (t21=5.26, P<0.0001 corr. in FMD patients; t21=6.32, P<0.0001 corr. in control subjects). This reduction in discomfort did not differ between groups (t38.4=0.53, P=0.5984 uncorr.).

Results of self-reported measures are shown in Table 3. Patients reported a higher level of pain and depression compared to controls. The OCI-R score was missing in one patient. There was no significant between-group difference in anxiety and obsessive-compulsive symptoms. When adjusting for these factors using a linear model, the between-group difference in PPI size remained significant (F1,37=6.95, P=0.0122).

Data on menstrual cycle phase and hormonal contraceptives use are presented in the supplementary table S1. No between-group difference was found in frequencies of different menstrual cycle phases, menopause and hormonal contraceptives (Fisher’s exact test, P=0.6287).

PPI size did not correlate with the severity of depression, anxiety, pain, motor symptoms, obsessive-compulsive symptoms or disease duration (the smallest P=0.2969 uncorr.).

We performed the above presented analyses with similar results in a subgroup of subjects free of medication with known effects on the central nervous system and in a subgroup of patients who had no motor symptoms in the right upper limb where the prepulse was applied. Details are presented in Supplementary Material.

**Discussion**

Here we have explored the physiological phenomenon of PPI in FMD. We found that patients with FMD have reduced PPI compared to control subjects.

It is commonly proposed that impaired PPI reflects impaired sensory-motor gating.32 In normal environmental conditions, multiple stimuli may adopt the role of prepulse stimuli and cause PPI of undesired motor reactions, which would otherwise interfere with sensory processing of relevant inputs.10, 33 Stimulus-triggered effects in the CNS such as arousal or attention reorienting likely depend on stimulus salience.34 Internal or top-down signals guide perception through a dynamic interaction with sensory and bottom-up processes.35 The PPI may be a by-product of such processes, reflecting subcortical integration.36, 37

PPI is regulated by specific neurochemical and anatomical substrates within the prefrontal cortex, thalamus, amygdala, hippocampus, striatum, pallidum, and the pedunculopontine nucleus, with a central role of the ventral striatum/nucleus accumbens.32, 38-40 Lack of differences between FMD patients and controls in the unconditioned blink reflex suggest there is normal integrity of brainstem circuits. Abnormal top-down regulatory mechanisms mediating PPI via projections from forebrain structures to pontine reflex circuity may be the most likely network underlying abnormal PPI. Given that PPI is a subcortical automatic phenomenon and occurs before conscious perception of the stimulus37 , our results are in line with the differentiation of functional movement disorders from feigned or malingered phenomena.5

PPI is known to be modulated by higher-order cognitive processes (e.g., attentional modulation and conditional modulation).32 Volitional attentional influences seem to occur more consistently at longer interstimulus intervals, however, there is some evidence that PPI may be modulated by attentional processing even at a short interstimulus interval of 120 ms.41, 42 At early stages of sensory information processing, the level of impact of the prepulse may vary as a function of prepulse saliency.42 Therefore, reduction in PPI may reflect not only an impaired nonselective attention allocation or attention reorienting and protection of early stage processing, but also the outcome of preattentive processing in terms of an early evaluation of the significance of the prepulse. In FMD patients, functional imaging studies have shown dysfunction of the brain regions involved in the salience network including ventral striatum and amygdala.43-45 Dysfunction of the right temporoparietal junction in FMD has been linked to abnormal self-agency,46 however, this region is also associated with attention reorienting, i.e. redirecting attention from one object to another or switching between networks.35, 47 These changes could be relevant in PPI dysregulation in FMD.

Abnormal PPI is one of the most robust and reproducible markers of schizophrenia and is considered to be a highly heritable phenotypic measure.48 In patients with schizophrenia the loss of PPI has been related to the “abnormal salience” theory of schizophrenia.49, 50 This relates to a fundamental difficulty in filtering salient information from the environment, which in turn is thought to drive abnormal perceptual inferences and therefore hallucinations and delusions.51

In patients with schizophrenia, the inability to detect salient events was demonstrated by abnormal mismatch negativity (MMN), a neurophysiological event-related potential that is recorded when an unexpected event occurs.51, 52 In schizophrenia, one could hypothesise that unconstrained sensory input prevents differentiation of salient events such as the prepulse stimulus from other stimuli, and hence it fails to influence other sensorimotor activity such as the blink reflex (abnormal somatosensory gating).

Pathophysiological theories of schizophrenia and functional symptoms are fundamentally different, making it appear difficult to reconcile the presence of abnormal PPI in both disorders. In contrast to abnormal salience, it has been proposed that in FMD there is relative insensitivity to exteroceptive and interoceptive input due to abnormally strong high-level priors. However, this abnormality would also be predicted to cause abnormal PPI as the resulting insensitivity to salient events occurring in the sensorium would be predicted to lead to down-weighting of the influence of the prepulse on other sensorimotor activity (e.g. the blink reflex). Comparative studies between FMD, “organic” movement disorders and schizophrenia would be useful to provide further evidence for these hypothesized mechanisms of impaired PPI and other inhibitory mechanisms.

There are findings from imaging, electrophysiological and psychophysical studies in FMD which align with this proposal. We have previously reported abnormal sensory attenuation in patients with functional movement disorders.53, 54 This phenomenon has also been reported in patients with schizophrenia, but as with our finding of reduced PPI we have proposed that the mechanism for abnormal sensory attenuation in schizophrenia is likely to be different than in patients with functional symptoms.55

Beside schizophrenia,48 PPI disturbances are associated with a wide range of neuropsychiatric disorders with an established dysfunction of cortico-basal ganglia circuits including movement disorders such as Huntington’s disease,62 Parkinson’s disease,63 and dystonia.64 However, a reduced PPIdoes not necessarily indicate circuit or clinical dysfunction as documented byawide range of basal levels of PPI in healthy subjects and studies on sex differences and menstrual cyclicity of PPI in healthy humans.65, 21 Importantly, an intact PPI was found in other serious brain disorders such as bipolar disorder 66 or major depressive disorder.67

While previous studies across many different clinical entities including functional dystonia revealed reducedshortinterval intracortical inhibition suggestive of impairment inGABA-mediated cortical-inhibition,68, 69reduced PPI indicates impairment in a subcortical inhibitory mechanism at the pre-attentive stage. These findings challenge the categoric distinction between functional and “non-functional”/”organic” disorders. Rather, there may well be many routes to the development of abnormal PPI, given the range of disorders affecting movement, mental state and pain sensation that are associated with abnormal PPI.

The lack of a definite correlation between magnitude of PPI and motor symptom severity or disease duration does not allow us to conclude that it plays a mechanistic role in generation of motor symptoms in FMD.Interestingly, in organic dystonia patients with sensory trick PPI was less impaired. It was suggested that a dysfunction in the processing of sensory input contributes to the maintenance of dystonic spasms.64 Relationship of PPI size to motor symptom persistency should be possibly studied in FMD. Abnormal PPI may represent a premorbid trait rendering patients more susceptible to disease (as suggested in schizophrenia)48 or it may be a consequence of or a compensatory phenomenon related to the disease.

There were no between-group differences in sensory thresholds nor in the effect of the prepulse on the intensity of discomfort resulting from the application of the electrical stimuli. This contrasts with the finding of a reduced effect of prepulses on pain in fibromyalgia patients compared to control subjects. In line with previous studies, patients with FMD reported higher levels of depression and pain than control subjects.70 However, these factors do not seem to systematically affect the impairment in PPI in FMD patients: when adjusting for these factors the difference in PPI size remained highly significant.

In accordance to findings in larger cohorts of FMD patients,73, 74 functional weakness and hyperkinetic phenotypes coexisted in a large proportion of our patients and deficits in PPI were present regardless of motor symptom type. Such observations favour lumping these clinical populations together in future studies on FMD biomarkers.

Reduced PPI has been previously demonstrated in patients with fibromyalgia syndrome and interstitial cystitis/bladder pain syndrome.15, 75 In our sample of FMD patients, the magnitude of PPI was not related to the reported severity of pain and nor was it linked to a specific motor phenotype. The unified mechanism of functional symptoms presenting in motor, sensory, interoceptive or cognitive domains proposed by neurobiological models is in line with clinical overlap of symptom domains and of risk factors such as trauma and recent health events.76-78 However, diagnostic classification systems have persistently sought to create a diagnostic divide between (often polysymptomatic) people with predominant pain and fatigue from those with typical “conversion disorder”. This distinction has been maintained in the latest edition of DSM with separate categories of conversion disorder/functional neurological symptom disorder (which would include people with FMD) and somatic symptom disorder (which would include people with functional pain and fatigue syndromes). The PPI finding we report is therefore another piece of evidence that this diagnostic distinction is not likely to be correct. Further research in this area should systematically test whether there are indeed trans-syndromic biomarkers in those with functional symptoms, taking care of course to deal with the potentially confounding effects of shared co-morbidities such as depression and anxiety. Finally, theutility and treatment consequences of a diagnostic category that includes both functional neurological disorders and somatic symptom disorder criteria (i.e. the somatization disorder diagnosis from DSM-IV with updated "rule in" criteria for functional neurological disorders components of the diagnosis) could be assessed, although this would require a reassessment of the necessity or otherwise of including psychological and/or behavioural factors as of diagnostic importance which were dropped from DSM-5 criteria for functional neurological disorders.

Our study has limitations. It is not known if there is an interference of voluntary or functional movements on PPI. However, an electrical stimulus to a tremulous index finger may have a gating effect over the sensory stimulus coming from the moving finger. We did not find difference in PPI size with prepulses applied to the right upper limb with and without abnormal movements. However a possible interaction between the site of motor symptom and PPI which might provide important insights into the sensorimotor gating and the pathophysiology of FMD might not have been detected due to a small sample size. Another limitation of the study is that we did not perform a structured psychiatric interview for psychiatric comorbidities which may be more sensitive to the detection of abnormalities compared to our questionnaire methods. Additionally, the relationship between deficits in PPI and attentional and cognitive factors should be analysed in the future.

In conclusion, this is the first study demonstrating abnormal PPI in patients with FMD. Integration of this novel finding with previous PPI data in people with chronic pain and previous pathophysiological findings in FMD gives support for a trans-syndromic view of functional symptoms. Here, a common abnormality in prior expectancies and attentional allocation to these priors could produce perceptual and /or motor control distortions, which could be reflected in markers of sensorimotor integration such as PPI. This has implications for the structure of our current diagnostic criteria and for the search for biomarkers and novel therapies in these common and disabling disorders.

**Figure Legends**

Figure 1. Representative example of blink reflex responses without (upper two traces) and with prepulse stimulation (lower two traces, thin arrow indicates prepulse stimulus to the right index finger; thick arrow indicates stimulus to the supraorbital nerve) in an FMD patient (left) and a control subject (right). Each trace represents two superimposed single rectified recordings. Early ipsilateral R1, late ipsilateral (R2), and late contralateral (R2c) blink reflex components are labelled. Note that the R2 and R2c area-under-the-curve suppression (i.e., prepulse inhibition) was smaller in the patient than in the control subject.

Figure 1. Representative examples of blink reflexes without (upper two traces) and with prepulse stimulation (lower two traces) in a patient with functional movement disorder (FMD patient, left) and in a healthy control subject (right). Each trace represents two superimposed rectified recordings. Thick arrows indicate stimuli applied to the right supraorbital nerve; thin arrows indicate prepulse stimuli delivered to the right index finger. Early ipsilateral R1, late ipsilateral (R2), and late contralateral (R2c) blink reflex components are labelled. Note in the lower two traces that the suppression of R2 and R2c area-under-the-curve (i.e., prepulse inhibition) was smaller in the patient than in the control subject.

Figure 2. PPI size in FMD patients and control subjects. The prepulse inhibition (PPI) size (i.e. the difference between mean blink reflex magnitude in baseline trials and in trials with prepulse, expressed in %) was smaller in functional movement disorders (FMD) patients as compared to control subjects (P=0.0003 corr.)

\*\*\* denote P <0.001.

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**Authors´ Roles:**

1. Research project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript: A. Writing of the first draft, B. Review and Critique;

4. Funding: A. Obtaining.

Zuzana Hanzlíková: 1BC, 2C, 3AB.

Markus Kofler: 2BC, 3AB.

Matěj Slovák: 1C, 2C, 3B.

Gabriela Věchetová: 1C, 2C, 3B.

Anna Fečíková: 1C, 2C, 3B.

David Kemlink: 2ABC, 3AB.

Tomáš Sieger: 2ABC, 3AB.

Evžen Růžička: 1C, 2C, 3B, 4A.

Josep Valls-Solé: 2C, 3AB.

Mark J. Edwards: 2C, 3AB.

Tereza Serranová: 1ABC, 2AC, 3AB, 4A.

**Financial Disclosures of all authors (for the preceding 12 months):**

**Zuzana Hanzlíková**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

**Partnerships:** None

**Contracts:** None

**Honoraria:** None

**Royalties:** None

**Grants:** None

**Other:** None

**Markus Kofler**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** Department of Neurology, Hochzirl Hospital, Hochzirl, Austria

**Partnerships:** none

**Contracts:** none

**Honoraria:** Medtronic

**Royalties:** none

**Grants:** none

**Other:** none

**Matěj Slovák**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

**Partnerships:** None

**Contracts:** None

**Honoraria:** None

**Royalties:** None

**Grants:** Ministry of Health of the Czech Republic, Charles University in Prague

**Other:** Owner of Rebox Therapy Ltd.

**Gabriela Věchetová**

**Stock Ownership in medically-related fields**: None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic; National Institute of Mental Health, Klecany, Czech Republic

**Partnerships:** None

**Contracts:** Independent Contractor Agreement (independent rater in clinical trial), ProPhase, LLC

**Honoraria:** None

**Royalties:** None

**Grants:** Ministry of Health of the Czech Republic, Charles University in Prague, Czech Science Foundation

**Other:** None

**Anna Fečíková**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

**Partnerships:** None

**Contracts:** None

**Honoraria:** None

**Royalties:** None

**Grants:** Czech Science Foundation

**Other:** None

**David Kemlink**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

**Partnerships:** None

**Contracts:** None

**Honoraria:** None

**Royalties:** None

**Grants:** Ministry of Health of the Czech Republic, Ministry of Education of the Czech Republic

**Other:** None

**Tomáš Sieger**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic, Dept. of Cybernetics, Faculty of Electrical Engineering, Czech Technical University in Prague

**Partnerships:** None

**Contracts:** None

**Honoraria:** None

**Royalties:** None

**Grants:** Ministry of Health of the Czech Republic

**Other:** None

**Evžen Růžička**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic

**Partnerships:** None

**Contracts:** None

**Honoraria:** None

**Royalties:** None

**Grants**: Ministry of Health of the Czech Republic

**Other:** None

**Josep Valls-Solé**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: None

**Advisory Boards:** None

**Employment:** Universitat de Barcelona, Spain

**Partnerships:** None

**Contracts:** None

**Honoraria:** None

**Royalties:** None

**Grants:** None

**Other:** None

**Mark Edwards**

**Stock Ownership in medically-related fields:** None

**Intellectual Property Rights:** None

**Consultancies:** None Expert Testimony: I provide testimony in medico legal cases

**Advisory Boards:** Merz pharma

**Employment:** St George's University of London

**Partnerships:** None

**Contracts:** None

**Honoraria:** Merz Pharma, UCB

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**Tereza Serranová**

**Stock Ownership in medically-related fields**: None

**Intellectual Property Rights:** None

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