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Altered Spinal Excitability in Patients with Primary Fibromyalgia: A Case-Control Study

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Background and Purpose Abnormal excitability of the central nervous system, both spinal and supraspinal, has previously been described as a pathophysiological plastic mechanism for chronic pain syndromes. Primary fibromyalgia (FM) as one extreme of this spectrum of diseases. This case-control study aimed to determine the changes in the spinal excitability by investigating the Hoffman reflex (H-reflex) in patients with FM.

Methods Thirty-eight patients with FM and 30 healthy controls participated in this case-control study. We measured the H-reflex bilaterally in the upper limbs (flexor carpi radialis) and the lower limbs (gastrocnemius and soleus). Moreover, pain-related variables were measured, including pain severity (using a visual analogue scale), pain duration, Widespread Pain Index, and the score on the Symptom Severity Scale. Various psychiatric comorbidities and quality-of-life parameters were measured for each patient, including scores on the Hamilton Depression Rating Scale, Taylor's Manifest Anxiety Scale, and the Revised Fibromyalgia Impact Questionnaire.

Results A significant increase in the ratio of the maximum baseline-to-peak amplitudes of H and M waves (H_{max}/M_{max}) but not in the H-wave minimum latency was found in patients with FM compared with healthy controls. There were no significant correlations between this ratio in both muscles and the various pain-related measures, psychiatric comorbidity, and quality of life in patients with FM. Patients with FM suffered more depression and anxiety than did the controls.

Conclusions We found increased spinal excitability in patients with FM, which was not confined to the site of maximum pain. This information may help in the diagnosis of FM and supports the hypothesis of central sensitization.

Key Words fibromyalgia, H-reflex, spinal cord, chronic pain.

INTRODUCTION

Fibromyalgia (FM) and related disorders represent a wide spectrum of syndromes that are associated with changes in the pain processing pathways of the central nervous system (CNS).[1] Those syndromes affect many systems in the body, and the associated plasticity changes in the CNS can lead to augmentation of pain transmission and processing circuits.[2,3] FM involves a diffuse musculoskeletal pain syndrome that affects females much more than males (ratio of 9:1).[4,5] The prevalence of FM in the general population is one of the highest for pain syndromes worldwide, ranging from 7.3% to 12.9% of the population.[6] The pain in patients with FM occurs as a result of a process called central sensitization (CS), which refers to increased excitability of the neurons in the dorsal horn of the spinal cord. This increased excitability is associated with increased spontaneous neuronal activity, expanded receptive fields, and enhanced responses to the impulses transmitted by both large-

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and small-fiber sensory afferents.[7]

The Hoffman reflex (H-reflex) is elicited by stimulation of type Ia afferent sensory fibers. These fibers synapse directly onto the alpha motor neurons in the anterior horn of the spinal cord, forming a monosynaptic reflex arc. Submaximal stimulation of this reflex arc elicits a compound muscle action potential (CMAP) known as the H wave. This reflex arc appears to depend on the balance between excitatory and inhibitory neurons in the spinal cord. The H-reflex is mostly recorded from the gastrocnemius and soleus (GCS) muscles, and sometimes from the flexor carpi radialis (FCR) muscle.[8] The H-reflex is often used to measure spinal excitability in various physiological and pathological states.[9-14] Since a change in spinal excitability is one of the main mechanisms underlying the hypothesis of CS in FM, measuring the H-reflex might be an easy, widely available, cheap, and objective method for assessing spinal excitability in patients with FM. However, the absolute (nonnormalized) amplitude of the H wave varies markedly among subjects.[15,16]

To the best of our knowledge, only one previous study has examined the thenar H-reflex in patients with FM.[17] That study found that eliciting an H-reflex with a shorter minimum latency of the H wave was more likely in patients with FM than in healthy controls, while there were no significant changes in the non-normalized absolute H-wave amplitude, which contradicts the CS hypothesis.

The present study measured the H-reflex in the FCR in the upper limbs and the GCS in the lower limbs. The study was designed to evaluate changes in the H-reflex over a wider distribution of muscles, from its common sites of measurements in both upper and lower limbs. The aim was to obtain greater insight into various H-reflex parameters, including by using a method to measure the normalized H-wave amplitude, which the previous study[17] had found was not significantly affected in patients with FM. It was hoped that the present study would provide fundamental background knowledge about spinal excitability in FM patients that would be useful when designing specific neurorehabilitation programs to modulate the pathological changes in spinal excitability that promotes pain transmission in these patients.

METHODS

Study participants

This study involved 38 patients with FM (34 females and 4 males aged 33.6±7.4 years, mean±SD) and 30 healthy controls (27 females and 3 males aged 31.1±8.5 years). Patients with FM were diagnosed according to the 2010 American College of Rheumatology (ACR) Fibromyalgia Diagnostic Criteria (as modified in 2011). The ACR criteria included the presence of a moderate-to-high intensity of widespread musculoskeletal pain and tenderness upon digital pressure for more than the previous 3 months distributed both above and below the waist at ≥11 of 18 specific tender points. Patients were diagnosed with FM when they fulfilled the following criteria: score of ≥7 on the Widespread Pain Index (WPI) and a score of ≥5 on the Symptom Severity Scale (SSS), or a score of 3–6 on the WPI and a score of ≥9 at the SSS without evidence of another disorder that would explain the pain.[5,18]

Patients were recruited from neurology, psychiatry, and rheumatology clinics at Sohag University Hospital. Patients who are suspected of suffering or demonstrated to suffer from any autoimmune, rheumatological, or neurological disorders that could explain the pain that they experienced were excluded from the study. Patients who were already taking psychotropic drugs were excluded from the study, as were patients suffering from any disease that could affect the results and interpretation of the parameters of the H-reflex, including polyneuropathy and radiculopathy. Healthy volunteers included in the control group of the study were recruited from the medical staff and other workers in our hospital. All of the included subjects gave informed consent for their participation in the study, and the study protocol was approved by the local ethics committee of Sohag University (approval no. 2019-58).

Demographic data, psychiatric comorbidity, and quality of life in patients with FM

Demographic parameters including age, sex, marital status, body mass index (BMI), and upper and lower limb lengths were assessed in all study participants. The score on a visual analogue scale (VAS) for pain severity, the pain duration in months, and scores on the WPI and SSS were measured in patients with FM only. In addition, Arabic validated versions of the Hamilton Depression Rating Scale (HAM-D) and Taylor's Manifest Anxiety Scale (TMAS) were used to measure depression and anxiety in both patients and healthy controls.[19,20] The Arabic validated version of the Revised Fibromyalgia Impact Questionnaire (FIQR) was used[21] to measure the quality of life in patients with FM.

Measuring the H-reflex (Fig. 1)

Stimulation and recording techniques

Bipolar stimulating electrodes were used to stimulate the median nerves at the cubital and posterior tibial nerves at the popliteal fossae. The stimulation intensity was gradually increased from 0.5 mA until the maximum M wave was recorded. Stimuli of 0.2 Hz frequency and 1 ms duration were used to selectively stimulate type Ia afferent fibers. Surface

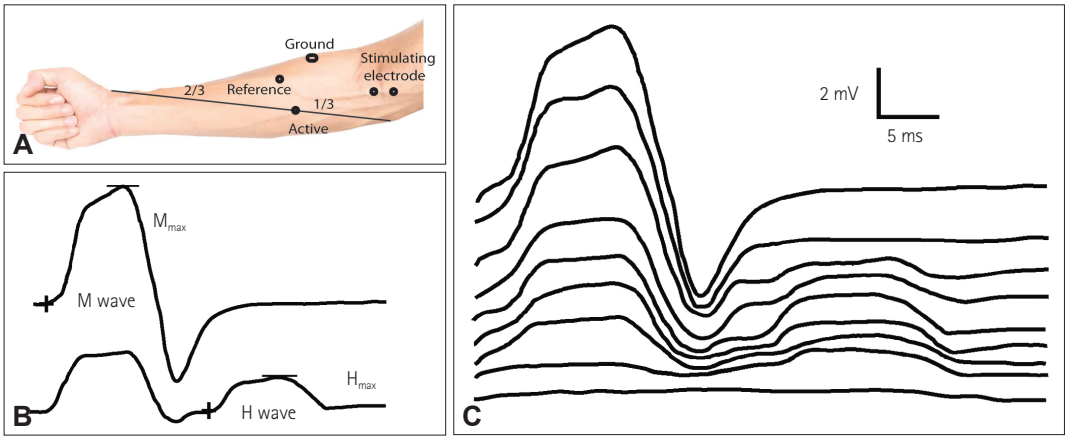

Fig. 1. Hoffman reflex (H-reflex) in the flexor carpi radialis muscle. A: Sites of stimulating, recording, and ground electrodes. B: Isolated tracing with measurement cursors for the maximum baseline-to-peak amplitude of the M wave (M_{max}) and for the maximum baseline-to-peak amplitude of the H wave (H_{max}). C: Whole tracing from one subject.

recording electrodes with an interelectrode distance of 2 cm were used for recording the CMAPs from the FCR. The recording electrodes were positioned at one-third the distance from the medial epicondyle to the radial styloid process. The FCR muscle was identified by asking the patient to flex and radially deviate the wrist while mild resistance was applied. A ground electrode was placed on the dorsum of the forearm between the recording electrodes, approximately 7.5 cm distal to the lateral epicondyle.

For measuring the GCS, a line was drawn from the popliteal fossa to the Achilles tendon and divided into eight equal divisions, and the recording electrode was placed at the fifth or sixth division. The ground electrode was placed midway between the stimulating and recording electrodes.[22]

The skin temperature was kept between 31°C and 34°C in all subjects. All electrophysiological studies were recorded using an apparatus (Neuropack MEB-2300, Nihon-Kohden, Tokyo, Japan).

Procedure

For measuring the H-reflex in the FCR, the study participants were seated in a comfortable chair with the head and neck supported. Both elbow joints were held at 135° with the forearms resting horizontally and facing upward. Since background activity in the FCR may be necessary to elicit the H-reflex,[23] subjects were asked to hold a 1-kg weight and maintain a constant background contraction.

For measuring the H-reflex in the GCS muscle, the subjects were placed in the prone position with the face downwards. The H and M waves were recorded using stimuli with stepwise increasing intensities, starting from the subthreshold intensity for eliciting the H wave up a supramaximal intensity to elicit the maximum M wave. The H-reflex was identified as a late response that was larger than the initial M wave or even present (at the appropriate delay) without an M wave, which progressively decreased until disappearing.

The minimum latency of the H wave was measured for both the FCR and GCS muscles. The maximum baseline-to-peak amplitudes of the H and M waves (H_{max} and M_{max}, respectively) were identified and measured for both FCR and GCS, and H_{max}/M_{max} ratios were calculated. All of the measurements of the H-wave minimum latencies and H_{max} and M_{max} were performed with careful manual positioning of the cursors of the machine, and the average values obtained in three trials were analyzed.

Statistical analysis

The numerical and categorical data are presented as mean±SD and number (percentage) values, respectively. The Kolmogorov-Smirnov test was used to test for the presence of normality of the numerical data. The SPSS statistical package (version 16 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The independent-samples *t*-test was used for normally distributed data, namely age, BMI, upper and lower limb lengths, and measures of psychiatric comorbidity. The chi-square and Mann-Whitney U tests were used for analyzing categorical data and various parameters of the H-reflex, since some of those parameters were not normally distributed. A p value of <0.05 was considered statistically significant.

RESULTS

There were no significant differences between patients with FM and healthy controls in age, sex, marital status, BMI, or upper and lower limb lengths. However, psychiatric comor-

bidities did differ significantly between these two groups, with patients with FM suffering more depression and anxiety compared with healthy controls according to the HAM-D and TMAS (t=8.2, $p<0.001$; and t=10.1, $p<0.001$; respectively). The demographic data for the patients and controls are presented in Table 1, while data on psychiatric comorbidity and quality of life are presented in Table 2.

The H-wave minimum latencies did not differ significantly between the two groups, whereas there were significant intergroup differences in the H_{max}/M_{max} ratios (Table 3). There were no significant interside differences in either the minimum H-wave latencies or the H_{max}/M_{max} ratios among either patients with FM or healthy controls. In patients with FM, the H_{max}/M_{max} ratios for both the FCR and GCS were not significantly correlated with various pain-related variables, including the VAS score for pain severity, pain duration, SSS score, or WPI score; psychiatric comorbidity including the scores on the HAM-D and TMAS; or the FIQR score. However, there was significant positive correlation between changes in the H_{max}/M_{max} ratios in the upper and lower limbs (Pearson's correlation coefficient=0.309, $p=0.02$).

Table 1. Demographic and pain-related characteristics of patients with FM and healthy controls

	Patients with FM (*n*=38)	Healthy controls (*n*=30)
Age (yr)	33.6±7.4	31.1±8.5
Sex		
Males	4 (10.5)	3 (10)
Females	34 (89.5)	27 (90)
Marital status		
Married	31 (81.6)	24 (80)
Single	7 (18.4)	6 (20)
BMI (kg/m^2)	26.7±3.7	27.3±4.2
Upper limb length (cm)	63.2±6.2	64.3±7.6
Lower limb length (cm)	87.5±10.6	89.5±12.1
Pain duration (months)	27.1±17.6	-
VAS score for pain	6.9±2.4	-
WPI score	12.0±2.8	-
SSS score	8.7±1.3	-

Data are mean±SD values or number (%).
BMI: body mass index, FM: fibromyalgia, SSS: Symptom Severity Scale, VAS: visual analogue scale, WPI: Widespread Pain Index.

Table 2. Data on psychiatric comorbidities and quality of life for patients with FM and healthy controls

	Patients with FM	Healthy controls	*p*
HAM-D score	18.3±6.6	6.4±2.4	<0.001
TMAS score	22.4±5.3	8.6±1.9	<0.001
FIQR score	69.6±11.2	-	-

Data are mean±SD values.
FIQR: Revised Fibromyalgia Impact Questionnaire, FM: fibromyalgia, HAM-D: Hamilton Depression Rating Scale, TMAS: Taylor's Manifest Anxiety Scale

DISCUSSION

We found that the H_{max}/M_{max} ratios in the FCR and GCS were significantly higher in patients with FM than in healthy controls, and that these elevations were not confined to the site of maximum pain. These observations may support the hypothesis of hyperexcitability of the spinal cord neurons in these patients, corresponding to the phenomenon of CS. This information might be useful when designing specific neurorehabilitation programs for the management of these patients.

Patients with FM experience pain due to the process of CS. There are several lines of evidence for the hypothesis of CS, including dysregulation of the concentrations of biogenic amines and neuropeptides, and alterations of the hypothalamus-pituitary-adrenal axis.[24] CS involves increased excitability of the neurons in the dorsal horn of the spinal cord, which is associated with increased spontaneous neuronal activity, expanded receptive fields, and enhanced responses to the impulses transmitted by both large- and small-fiber sensory afferents.[7] Muscle nociceptors are more capable of inducing CS than are skin nociceptors.[25] CS occurs in many laminae of the dorsal horn of the spinal cord, including laminae I, II, V, VI, and X, which are involved in pain processing.[26] Many excitatory and inhibitory neurons in the dorsal horn of the spinal cord are involved in pain regulation. Those neurons release several neurotransmitters, including glutamate, aspartate, vasoactive intestinal peptide, substance P, and gamma-aminobutyric acid.[27,28] The second step after the spinal

Table 3. Hoffman reflex (H-reflex) parameters in patients with FM and healthy controls

Variable	Value	*p*
Minimum H-wave latency in FCR (ms)		0.171
Patients with FM	16.83±2.10	
Healthy controls	17.14±1.10	
Minimum H-wave latency in GCS (ms)		0.555
Patients with FM	31.24±2.70	
Healthy controls	31.02±1.20	
H_{max}/M_{max} ratio in FCR		<0.001
Patients with FM	0.23±0.14	
Healthy controls	0.10±0.04	
H_{max}/M_{max} ratio in GCS		<0.001
Patients with FM	0.29±0.18	
Healthy controls	0.11±0.10	

Data are mean±SD values.
FCR: flexor carpi radialis, FM: fibromyalgia, GCS: gastrocnemius and soleus, H_{max}/M_{max}: ratio of the maximum baseline-to-peak amplitudes of H and M waves.

processing of pain is the transmission of nociceptive information via projection neurons to supraspinal centers, which act as a second station for CS.[29]

The H-reflex is considered to be a late response of large myelinated type Ia nerve fibers. Those afferent nerve fibers synapse with the motor neurons in the anterior horn of the spinal cord to form a monosynaptic connection. As mentioned above, the H-reflex has previously been used to measure the spinal excitability in various physiological and pathological states.[9-14] However, there have been numerous variations between studies in the measurement techniques as well as in the measured parameters. The H-wave amplitude can be influenced by various parameters, including the skin resistance, amount of subcutaneous fat, and location of the nerve relative to the stimulus. Normalization methods are necessary to control this variability and thereby allow accurate comparisons between subjects. Measuring the H_{max}/M_{max} ratio is an important method for normalizing the H-reflex.[15,16]

In comparison with the previous study of the H-reflex in patients with FM,[17] we found significant changes in the H-wave amplitude that manifested as increased H_{max}/M_{max} ratios. In contrast to our study, Azma et al.[17] did not find any change in the absolute amplitude of the H wave in patients with FM compared with healthy controls. There are two possible explanations for this discrepancy. The first one is the variability in the number of trials needed to elicit the thenar H-reflex—which is an unusual site for investigating the H-reflex—between patients and healthy controls. The amplitude of the H wave may vary with the baseline excitability of the motor neuronal pool, which itself may change between trials.[8] The second explanation is the fact that H wave amplitude is the most variable parameter in H-reflex study.

To avoid these confounding factors when measuring the H-reflex, we applied a normalization method based on the H_{max}/M_{max} ratio. M_{max} remains relatively stable for the whole motor neuronal pool excited at a supramaximal stimulation intensity, whereas H_{max} represents only the maximum portion of the motor neuronal pool that was recruited through stimulation of the Ia afferent nerve fibers. Accordingly, the H_{max}/M_{max} ratio reflects the portion of the motor neuronal pool that is recruited by afferent stimulation, which can be taken as an indirect measure of spinal excitability that is also less variable than the absolute H-wave amplitude.[15,16] Another difference between our study and that of Azma et al.[17] is in the H-wave latency, which we did not find any significant difference between the two groups. This discrepancy can be explained by the difference in the techniques used to record the H-reflex. We studied more-proximal muscles (the FCR and GCS) that have shorter reflex arcs compared with the muscles investigated by Azma et al.[17] These shorter reflex arcs might have made it too difficult to detect subtle changes in the speed of conduction along the tested pathway.

FM is one of the most mysterious chronic intractable pain syndromes that could originate from complicated mechanisms that are still largely unknown. Moreover, psychological factors may play important roles in its pathogenesis. Accordingly, the pathogenesis of FM cannot be based on a single assumption of altered spinal excitability alone, since other factors and neurological substrates may play additional roles in its pathogenesis, and hence further studies are required. On the other hand, the H-reflex has been used as an electrophysiological biomarker in a very small number of studies,[30,31] and so further studies are needed to accurately determine the sensitivity and specificity of this electrophysiological tool as a biomarker for diagnosing FM.

In addition to CS, the peripheral nervous system might also play an important role in the pathogenesis of FM. Many recent studies have found consistent cutaneous and muscular changes in patients with FM, including elevated levels of substance P and other biochemical changes in their muscles.[32-36] Those changes may provide a link between peripheral tissues and pain in patients with FM. Various forms of peripheral sensitization (PS) in patients with FM including hypersensitivity of polymodal pain receptors and increased responses to mechanical nociceptive stimuli have been described.[37-40] Additionally, there is some leakage of these inflammatory mediators inside the intrafusal compartments, which might contribute to the increased excitability of the sensory afferents (Ia afferents). Also, enhanced miniature end-plate potentials and spikes derived from intrafusal end plates that also suggest an active role in alpha motor neuron efferents have been described in patients with myofascial pain.[41] Ge et al.[42] were the first authors to propose the involvement of muscle spindle afferents in the pathophysiology of latent myofascial trigger points in humans. Another recent animal study reported an evidence supporting the results of Ge et al.,[42] in finding that the H_{max}/M_{max} ratio was higher for recordings from myofascial pain trigger points than for those from myofascial nontrigger points.[43]

The H_{max}/M_{max} ratio is often used as a marker of the proportion of motor neurons recruited by the H-reflex in the motor neuronal pool, which is controlled by various supraspinal centers.[44] Accordingly, a reduction in the nociceptive thresholds of neurons in the dorsal horn of the spinal cord might be induced by the changes responsible about PS.[45-47] These observations suggest that FM is a pain condition due to CS of the CNS induced via PS.[48-50]

We found that the changes in the H-reflex in patients with FM were not confined to the site of maximum pain, since we studied both upper and lower limbs rather than only the up-

per limb. We also found that those changes were not dependent on the site or side, nor to other demographic, pain-related, psychiatric comorbidity, or quality-of-life variables. This can be explained by pain and psychiatric comorbidity being subjective sensations and feelings that are influenced by many factors including the pain threshold of each patient, and so they cannot be accurately measured using specific objective tools.

In conclusion, we found that the H_{max}/M_{max} ratio was higher in patients with FM, which implies the presence of diffuse changes in spinal excitability independently of other factors that may play a role in the pathogenesis of the disease. Diverse physical therapies are applied for FM, including manipulations, mobilizations, massage, transcutaneous electrical nerve stimulation, acupuncture, heat and cold treatments, and ultrasound. These are usually administered in combination with exercise and are used to reduce pain, so as to improve the mobility of affected patients. Further researches are needed to specifically study the effects of these different physical therapies on spinal excitability in patients with FM using H-reflex measurements, based on our findings of widespread changes in spinal excitability among these patients and the correlations of induced changes in spinal excitability with pain scores. The findings of this study may also help in diagnosing these patients using an easy, safe, widely available, cheap, and noninvasive investigative tool.

The limitations of our study include the small number of patients and the inherent variability of the techniques used for investigating the H-reflex and the interrater variability of the results among the various studies. We have therefore explained in detail the procedure used to elicit and measure the H-reflex in our study. Further studies that include larger numbers of patients are needed to clarify this issue and to construct a clear protocol that may help in the diagnosis of these patients.

Author Contributions

Conceptualization: Mohamed N. Thabit, Mohamed A. Ismael. Data curation: all authors. Formal analysis: all authors. Investigation: Mohamed N. Thabit, Ahmad Ezat, Mohamed A. Ismael. Methodology: Mohamed N.Thabit, Ahmad Ezat. Project administration: Mohamed N. Thabit. Resources: all authors. Supervision: Mohamed N. Thabit, Ahmad Ezat. Validation: Mohamed N. Thabit, Mohamed A. Ismael. Visualization: all authors. Formal analysis: all authors. Writing—original draft: all authors. Writing—review & editing: Mohamed N. Thabit.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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REFERENCES

1. Bolay H, Moskowitz MA. Mechanisms of pain modulation in chronic syndromes. *Neurology* 2002;59:S2-S7.
2. Clauw DJ. Fibromyalgia: a clinical review. *JAMA* 2014;311:1547-1555.
3. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience* 2016;338:114-129.
4. Staud R. Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome. *Arthritis Res Ther* 2006;8:208.
5. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. *J Rheumatol* 2011;38:1113-1122.
6. Neumann L, Buskila D. Epidemiology of fibromyalgia. *Curr Pain Headache Rep* 2003;7:362-368.
7. Li J, Simone DA, Larson AA. Windup leads to characteristics of central sensitization. *Pain* 1999;79:75-82.
8. Knikou M. The H-reflex as a probe: pathways and pitfalls. *J Neurosci Methods* 2008;171:1-12.
9. Knikou M, Murray LM. Repeated transspinal stimulation decreases soleus H-reflex excitability and restores spinal inhibition in human spinal cord injury. *PLoS One* 2019;14:e0223135.
10. Kumru H, Albu S, Valls-Sole J, Murillo N, Tormos JM, Vidal J. Influence of spinal cord lesion level and severity on H-reflex excitability and recovery curve. *Muscle Nerve* 2015;52:616-622.
11. Grosprêtre S, Martin A. H reflex and spinal excitability: methodological considerations. *J Neurophysiol* 2012;107:1649-1654.
12. Knikou M, Schmit BD, Chaudhuri D, Kay E, Rymer WZ. Soleus H-reflex excitability changes in response to sinusoidal hip stretches in the injured human spinal cord. *Neurosci Lett* 2007;423:18-23.
13. Kumar S, Dereddy NR, Bhatia BD, Prakash U. Spinal motor neuron excitability in newborns following fetal distress: sub-clinical depression revealed by soleus H-reflex. *Clin Neurophysiol* 2005;116:2342-2347.
14. Hasbroucq T, Akamatsu M, Burle B, Bonnet M, Possamaï CA. Changes in spinal excitability during choice reaction time: the H reflex as a probe of information transmission. *Psychophysiology* 2000;37:385-393.
15. Palmieri RM, Ingersoll CD, Hoffman MA. The hoffmann reflex: methodologic considerations and applications for use in sports medicine and athletic training research. *J Athl Train* 2004;39:268-277.
16. Crone C, Hultborn H, Mazières L, Morin C, Nielsen J, Pierrot-Deseilligny E. Sensitivity of monosynaptic test reflexes to facilitation and inhibition as a function of the test reflex size: a study in man and the cat. *Exp Brain Res* 1990;81:35-45.
17. Azma K, Raeissadat SA, Hosseini A, Mahmoudi H, Sepehrian M, Salehi Z. Thenar muscles H reflex in patients with fibromyalgia: a case control study. *Acta Reumatol Port* 2016;41:145-150.
18. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 2010;62:600-610.
19. Alhadi AN, Alarabi MA, Alshomrani AT, Shuqdar RM, Alsuwaidan MT, McIntyre RS. Arabic translation, validation and cultural adaptation of the 7-item Hamilton Depression Rating Scale in two community samples. *Sultan Qaboos Univ Med J* 2018;18:e167-e172.
20. Fahmi M, Ghali M, Meleka K. Arabic version of the personality scale of manifest anxiety. *Egypt J Psychiatry* 1997;11:119-126.
21. Abu-Dahab S, AbuRuz SM, Mustafa K, Sarhan Y. Validation of the Arabic version of the revised Fibromyalgia Impact Questionnaire (FIQR_A) on Jordanian females with fibromyalgia. *Clin Rheumatol* 2014;33:391-

396.
22. Preston D, Shapiro B. Late responses. In: *Electromyography and Neuromuscular Disorders*. 3rd ed. London: W.B. Saunders, 2013;36-46.
23. Bodofsky EB. Contraction-induced upper extremity H reflexes: normative values. *Arch Phys Med Rehabil* 1999;80:562-565.
24. Neeck G. Neuroendocrine and hormonal perturbations and relations to the serotonergic system in fibromyalgia patients. *Scand J Rheumatol Suppl* 2000;113:8-12.
25. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J Physiol* 1984;356:443-458.
26. Mense S. Nociception from skeletal muscle in relation to clinical muscle pain. *Pain* 1993;54:241-289.
27. Coggeshall RE, Carlton SM. Receptor localization in the mammalian dorsal horn and primary afferent neurons. *Brain Res Brain Res Rev* 1997;24:28-66.
28. Malcangio M, Bowery NG. GABA and its receptors in the spinal cord. *Trends Pharmacol Sci* 1996;17:457-462.
29. Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: pathogenetic role. *Curr Pain Headache Rep* 2002;6:259-266.
30. Rudge P, Jaunmuktane Z, Hyare H, Ellis M, Koltzenburg M, Collinge J, et al. Early neurophysiological biomarkers and spinal cord pathology in inherited prion disease. *Brain* 2019;142:760-770.
31. Lee-Kubli C, Marshall AG, Malik RA, Calcutt NA. The H-reflex as a biomarker for spinal disinhibition in painful diabetic neuropathy. *Curr Diab Rep* 2018;18:1.
32. Sprott H, Bradley LA, Oh SJ, Wintersberger W, Alarcón GS, Mussell HG, et al. Immunohistochemical and molecular studies of serotonin, substance P, galanin, pituitary adenylyl cyclase-activating polypeptide, and secretoneurin in fibromyalgic muscle tissue. *Arthritis Rheum* 1998;41:1689-1694.
33. Sprott H, Salemi S, Gay RE, Bradley LA, Alarcón GS, Oh SJ, et al. Increased DNA fragmentation and ultrastructural changes in fibromyalgic muscle fibres. *Ann Rheum Dis* 2004;63:245-251.
34. Salemi S, Rethage J, Wollina U, Michel BA, Gay RE, Gay S, et al. Detection of interleukin 1beta (IL-1beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. *J Rheumatol* 2003;30:146-150.
35. Graven-Nielsen T, Arendt-Nielsen L. Is there a relation between intramuscular hypoperfusion and chronic muscle pain? *J Pain* 2002;3:261-263.
36. Elvin A, Siösteen AK, Nilsson A, Kosek E. Decreased muscle blood flow in fibromyalgia patients during standardised muscle exercise: a contrast media enhanced colour Doppler study. *Eur J Pain* 2006;10:137-144.
37. Graven-Nielsen T, Arendt-Nielsen L. Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. *Curr Rheumatol Rep* 2002;4:313-321.
38. Granot M, Buskila D, Granovsky Y, Sprecher E, Neumann L, Yarnitsky D. Simultaneous recording of late and ultra-late pain evoked potentials in fibromyalgia. *Clin Neurophysiol* 2001;112:1881-1887.
39. Kosek E, Ekholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. *Pain* 1996;68:375-383.
40. Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ Jr. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. *Pain* 2003;102:87-95.
41. Partanen JV, Ojala TA, Arokoski JP. Myofascial syndrome and pain: a neurophysiological approach. *Pathophysiology* 2010;17:19-28.
42. Ge HY, Serrao M, Andersen OK, Graven-Nielsen T, Arendt-Nielsen L. Increased H-reflex response induced by intramuscular electrical stimulation of latent myofascial trigger points. *Acupunct Med* 2009;27:150-154.
43. Liu L, Huang QM, Liu QG, Nguyen TT, Yan JQ, Bo CZ. Relationship between muscle spindles and myofascial trigger spots according to Hoffmann reflex pathway and tissue morphology characteristics in a rat model. *Acupunct Med* 2020;38:109-116.
44. de Oliveira Silva D, Magalhães FH, Faria NC, Pazzinatto MF, Ferrari D, Pappas E, et al. Lower amplitude of the Hoffmann reflex in women with patellofemoral pain: thinking beyond proximal, local, and distal factors. *Arch Phys Med Rehabil* 2016;97:1115-1120.
45. Arendt-Nielsen L, Graven-Nielsen T. Central sensitization in fibromyalgia and other musculoskeletal disorders. *Curr Pain Headache Rep* 2003;7:355-361.
46. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum* 2003;48:1420-1429.
47. Staud R. New evidence for central sensitization in patients with fibromyalgia. *Curr Rheumatol Rep* 2004;6:259.
48. Hudson JI, Arnold LM, Keck PE Jr, Auchenbach MB, Pope HG Jr. Family study of fibromyalgia and affective spectrum disorder. *Biol Psychiatry* 2004;56:884-891.
49. Arnold LM, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, et al. Family study of fibromyalgia. *Arthritis Rheum* 2004;50:944-952.
50. Thieme K, Turk DC, Flor H. Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. *Psychosom Med* 2004;66:837-844.