Neurophysiological and Clinical Outcomes in Episodic Migraine Without Aura: A Cross-Sectional Study

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Purpose: The aim of this study was to assess differences between people with episodic migraine and healthy controls in some neurophysiological and clinical outcomes, which, in turn, may highlight the differences in sensory processing, especially in cortical excitability, pain processing, and executive function.

Methods: A cross-sectional study was performed, including the following outcomes: pressure pain thresholds with algometry; resting motor threshold, short-interval intracortical inhibition, and intracortical facilitation with transcranial magnetic stimulation; and executive functions with the trail making test and the frontal assessment battery.

Results: Thirty adults with migraine (36 ± 10 years) and 30 healthy controls (29 ± 14 years) were included in this study. Compared with the healthy controls, participants with migraine presented lower pressure pain thresholds values in all the assessed muscles ($P < 0.001$), lower resting motor threshold (−10.5% of the stimulator output, 95% CI: −16.8 to −4.2, $P = 0.001$, Cohen $d = 0.869$) and higher short-interval intracortical inhibition motor-evoked potential's amplitude at 3 ms (0.25, 95% CI: 0.05 to 0.46, $P = 0.015$, Cohen $d = 0.662$), and worse performances both in trail making test (7.1, 95% CI: 0.9 to 13.4, $P = 0.027$, Cohen $d = 0.594$) and frontal assessment battery (−1.1, 95% CI: −1.7 to −0.5, $P = 0.001$, Cohen $d = 0.915$).

Conclusions: Participants with migraine presented significant differences in cortical excitability, executive functions, and pressure pain thresholds, compared with healthy controls.

Key Words: Migraine, Pressure pain thresholds, Transcranial magnetic stimulation, Cortical excitability, Cognitive function.

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Migraine represents one of the most common neurologic conditions, and it is associated with important consequences on the quality of life[1] due to their clinical and neurophysiological multifaceted characteristics.[2–4] Despite some conflicting results, alteration in sensory processing has been reported in people with migraine.[2,3,5,6]

Currently, some hypotheses have proposed that a migraine attack may be characterized by the following two opposing processes: lack of habituation and sensitization; lack of habituation is a reduction of inhibitory response to repeated sensory stimuli; sensitization is an augmentation of response to repeated sensory stimuli.[2,5–7] It seems that, together, they lead to alteration in sensory processing.[3,6,8] At the peripheral level, this alteration is manifested by dysfunction in response to different mechanical and thermal stimuli. At the central level, this alteration is manifested by dysfunction in cortical excitability and pain processing.[9–14] Clinically, this alteration is manifested by dysfunction in executive functions, such as working memory, shifting, and inhibition.[10,11] In fact, the cognitive impairment in migraine may be related both to the consequence of repetitive migraine attacks and to the lack of habituation that does not allow to filter out the irrelevant stimuli.[2,3,6,8] Based on these assumptions, investigating central and peripheral neurophysiological and clinical parameters in migraine might help to better describe some pathophysiological mechanisms.

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The project was approved by the Institutional Review Board (CEUR 2021-Sper-26; ID 3672).
Written informed consent was obtained from all individual participants included in the study.
Patients signed informed consent regarding publishing their data.
The research was conducted according to the principles of the Declaration of Helsinki. All participants released their informed consent for treatment of clinical data after all procedures had been fully explained. This study was approved by the Local Ethics Committee (CEUR 2021-Sper-26; ID 3672).
Anonymized data are available upon reasonable request to the corresponding author according to standard institutional procedure.
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Peripherally and centrally, algometer assessment is a well-validated and safe neurophysiological technique used to study the sensitivity of peripheral systems and, in particular, its pressure pain threshold (PPT). Reduced pressure pain threshold and increased muscle activity have been described in migraine because of peripheral and central sensitization over the trigeminal and extratrigeminal areas.[13,15–18] Centrally, transcranial magnetic stimulation (TMS) is a well-validated and safe neurophysiological technique used to study the function of the cerebral cortex and, in particular, its excitability.[9,19–21] Altered visual[22] and motor cortex[23] excitability have been described in migraine. Indeed, increased intracortical facilitation and decreased cortical inhibition have been previously reported in people with migraine, between attacks, suggesting potential alterations of intracortical circuit pathways.[23–25] Clinically, the trail making test (TMT) and the Frontal Assessment Battery (FAB) are well-validated clinical outcomes used to study executive functions.[26] Many patients with migraine presented intellectual impairment in executive functions, suggesting a correlation between cognitive dysfunction and migraine-related disability. In fact, some migraine comorbidities, such as sleep and psychiatric disorder, are associated with cognitive decline.[3,4]

The aim of this study was to assess differences between people with episodic migraine and healthy controls in some neurophysiological and clinical outcomes, which, in turn, may highlight the differences in sensory processing, especially in cortical excitability, pain processing, and executive function.

METHODS

A cross-sectional study was adopted in people with episodic migraine according to the International Classification of Headache Disorders criteria[27] (ICHD-3). This study was performed in accordance with the Declaration of Helsinki, and the institutional review board (CEUR 2021-Sper-26; ID 3672) approved the project. The privacy rights of all subjects were protected, and all subjects signed the informed consent. The first evaluation and enrolment were performed by the tertiary Headache Centre of the Clinical Unit of Neurology of University Hospital and Health Services. For patients with migraine, the following criteria of inclusion were respected: episodic migraine diagnosis and age between 18 and 65 years. While the exclusion criteria were pregnancy, contraindications for TMS, or low tolerance to TMS; other neurologic or psychiatric disorders, cranial nerves impairment, and cardiac implantable devices; current prophylactic treatment with antiepileptic drugs and/or benzodiazepines and/or other drugs that may change the cortical excitability (except symptomatic medication for the migraine attack); previous migraine prophylaxis treatment in the past three months; comorbidities such as depression, anxiety, sleep disorder; and participants who do not provide their consent to this study. Regarding the healthy control group, they were screened from teachers, students, and administrative staff of our University and from parents of patients with migraine with the following inclusion criteria: (1) age from 18 to 70 years and (2) no migraine, tension-type headache, or another primary headache form. While the exclusion criteria were headache diagnosis and the same exclusion criteria of patients with migraine (Fig. 1). All participants had to be pain-free[28] and to not take any medication that may change cortical excitability for at least 72 hours before the measurements,[29] and they were asked to refer if they had any pain attacks in the 72 hours after the measurements.

Study Design

Pressure Pain Thresholds

A hand-held pressure algometer (Somedic Sales, Hörby, Sweden) was used to assess the PPT with a higher level of reliability and validity.[15,16] In fact, the precision of the assessment of the craniofacial muscles is given by its small surface. All the evaluation was conducted in accordance with the guidelines by Andersen for PPT craniofacial muscles evaluation.[15] Five muscles over the trigeminal area were assessed bilaterally (i.e., masseter, temporalis, trapezius, suboccipitalis, and procerus), and one muscle far from this area was assessed bilaterally (i.e., tensor fascia latae). Before starting the muscle evaluation, the first trial was applied on the wrists of each subject to educate with the algometer assessment. Then, three applications were performed for each muscle with one-minute intervals. The increasing rate was approximately 30 kPa/second, and participants were asked to press the stop button of the algometer when the pressure applied felt as painful.[13,15]

Transcranial Magnetic Stimulation

The single-pulse protocol of TMS was used to test the resting motor threshold (rMT) while the paired-pulse protocol of TMS was used to assess the short-interval intracortical inhibition (SICI) and the intracortical facilitation (ICF) over the left primary motor cortex (M1), in patients with migraine and in healthy controls.[23,30,31] The MagPro magnetic stimulator (MagVenture Inc, Alpharetta, GA) was used connected to an electromyographic device (Synergy, Natus, Middleton, WI) with a figure-of-eight coil placed tangentially from the scalp to induce the electric current flowed over the left M1 in a posterior–anterior direction.

The optimal scalp position was determined by moving the coil around the area corresponding to the M1 left in 0.5 cm steps. Then, the optimal scalp position where the stimulation constantly produced the largest motor-evoked potentials (MEPs) was marked in a tight-fitting plastic swimming cap. Motor-evoked potentials were recorded from the right abductor pollicis brevis muscle in each subject with Ag/AgCl surface electrodes fixed to the skin. The electromyography signals were recorded with a bandpass of 10 to 1,000 Hz.[23,32,33]

The following TMS parameters were collected in this order:

1. From single-pulse TMS and rMT: the minimum stimulation intensity required to produce a peak-to-peak MEP amplitude of ≥ 50 μV in at least 50% of five of 10 consecutive stimuli.
2. From paired-pulse TMS and SICI: evoked by delivering a subthreshold (80% rMT) conditioning stimulus, followed by a suprathreshold (130% rMT) test stimulus at interstimulus intervals (ISIs) of 3 and 5 ms. Four MEPs were recorded.
3. From paired-pulse TMS and ICF: evoked by delivering a subthreshold (80% rMT) conditioning stimulus, followed

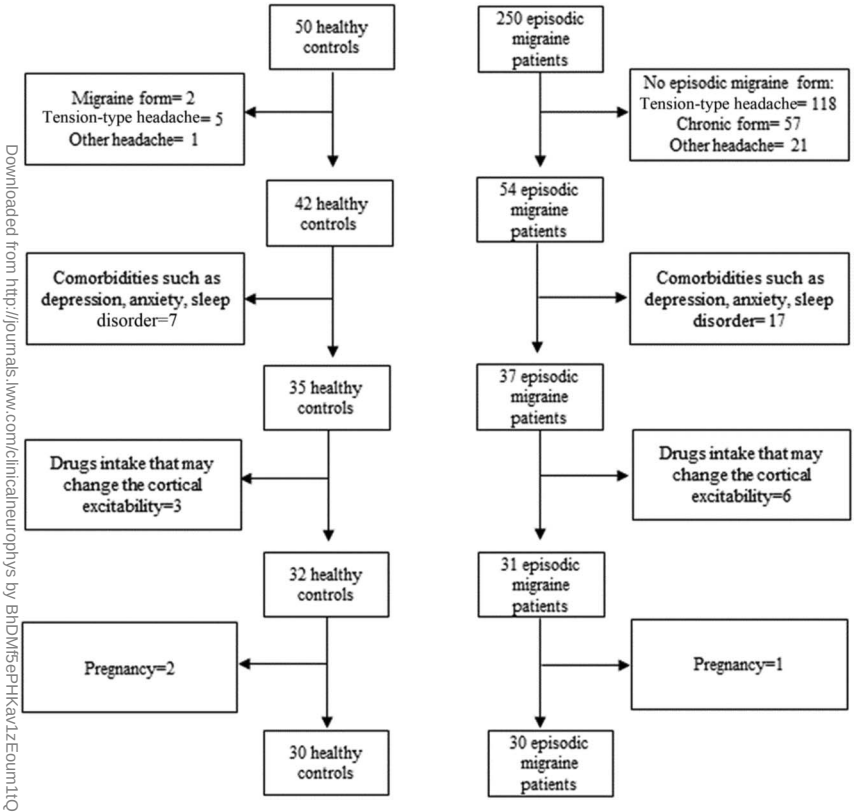

FIG. 1. Flowchart of the participants enrolment.

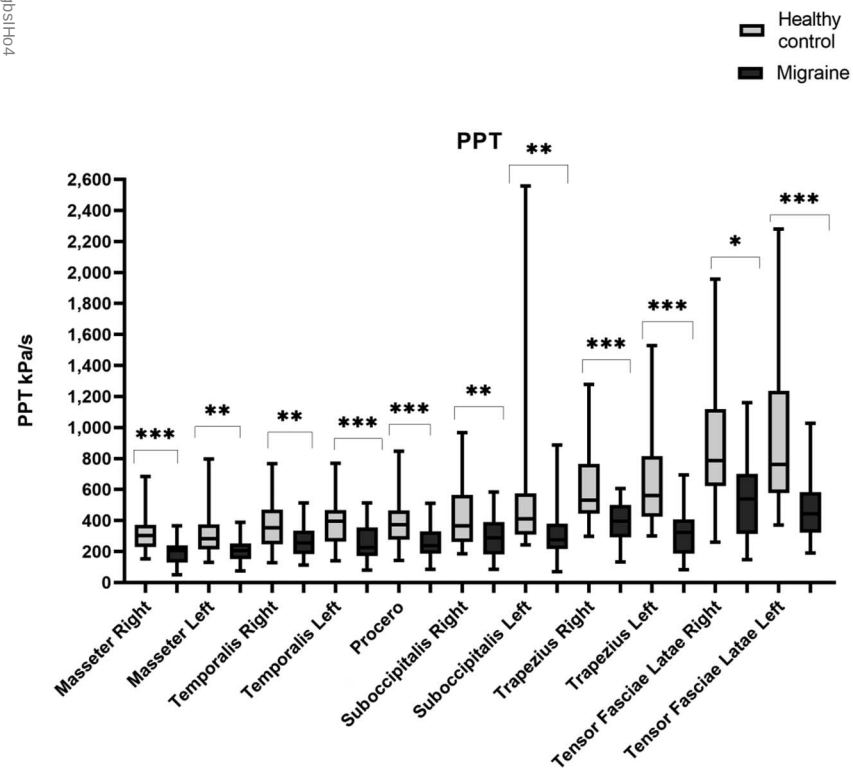

FIG. 2. Boxplots representing the difference in the PPT (kPa) on the bilateral assessed muscles of individuals with migraine ($n = 30$, black bars) and similar controls ($n = 30$, gray bars). Post hoc between groups comparison with correction for bilateral assessment. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

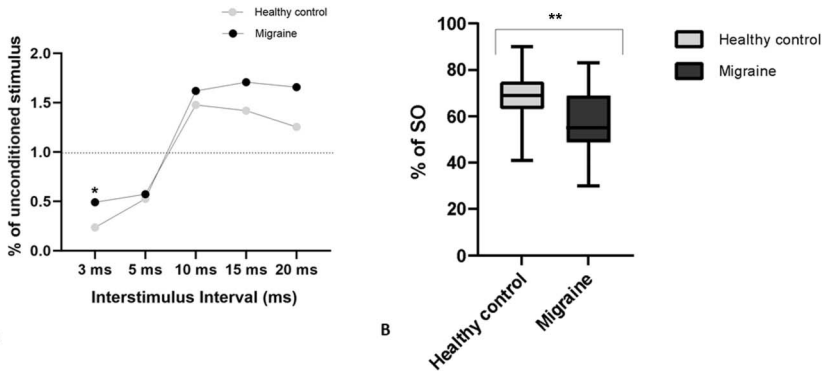

FIG. 3. **A**, TMS motor-evoked potentials at different interstimulus intervals of individuals with migraine ($n = 30$, black bars) and similar controls ($n = 30$, gray bars). Data expressed as a percentage of the unconditioned stimulus. **B**, Resting motor threshold (% of SO) of individuals with migraine ($n = 30$, gray bars) and similar controls ($n = 30$, empty bars). Post hoc between groups comparison with correction for different ISI. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. SO, stimulator output.

by a suprathreshold (130% rMT) test stimulus at ISIs of 10, 15, and 20 ms. Four MEPs were recorded.

For each assessment, the amplitude of MEPs was calculated as peak-to-peak both in the single-pulse protocol and in the paired-pulse protocol of TMS and data are reported as the percentage of the unconditioned stimulus.[33] In line with the previous TMS protocol,[33] we limited the number of stimulations in the paired-pulse protocol to four because of the migraine physiopathology.[4] All assessments were performed for each participant, both for patients with migraine and for healthy controls, between 3 and 5 PM to avoid differences due to circadian rhythmicity.

Cognitive Functions

Two neurophysiological tests were chosen from the most commonly reported to assess the executive functions in patients with migraine and in healthy controls. The trail making test is divided into two parts, TMT A and TMT B, subjects were asked to connect 25 targets in sequential order as quickly as possible.[3,26] The difference between the times of part B and those of part A (TMT B-A) was calculated and taken into consideration for each test.[34,35] The FAB battery explores the following six functions related to the frontal lobes: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.

All assessments (TMS, PPT, TMT, and FAB) were conducted during the migraine-free days such as during the interictal phase (i.e., at least three days after the latest migraine attack and they remained pain-free for at least the following three days) in all subjects.[36,37] All subjects must not have taken any drugs in the 72 hours before each assessment,[29] and the evaluation of female subjects was scheduled in the follicular phase.[38] If patients reported headaches within 72 hours of the evaluation, the evaluation was rescheduled.

Statistical Analyses

All statistical analyses were performed with SPSS version 23 (IBM). This is the primary analysis of these data. Data are

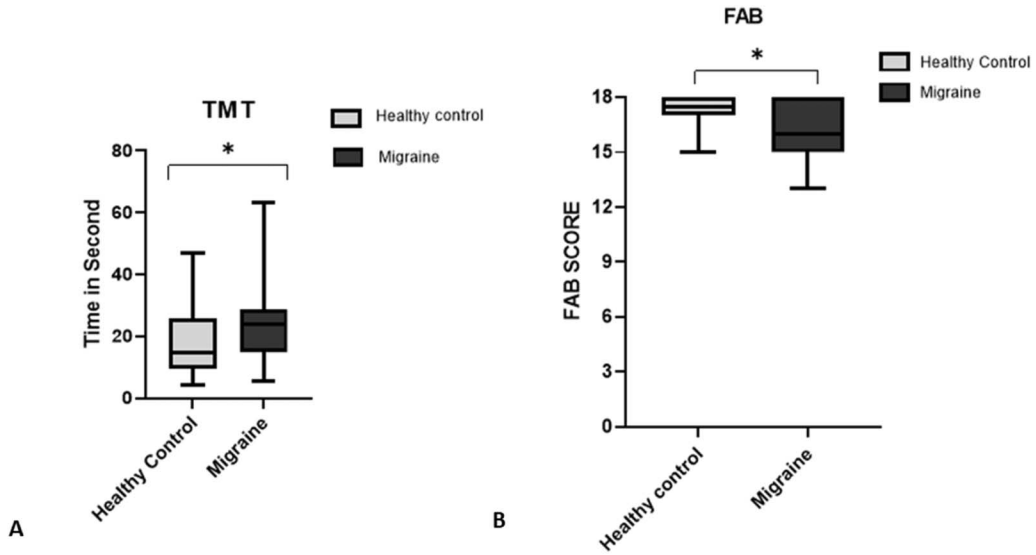

FIG. 4. **A**, Boxplots representing the difference in the TMT (B-A, seconds) of individuals with migraine ($n = 30$, black bars) and similar controls ($n = 30$, gray bars). **B**, Boxplots represent the difference in the FAB (score) of individuals with migraine ($n = 30$, gray bars) and similar controls ($n = 30$, empty bars). Independent samples t test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

TABLE 1. Demographical Data of the Participants

	Migraine ($n = 30$)	Healthy Controls ($n = 30$)
Age	38 (24.2–43.5)	24 (22–26)
Sex	11 M/19 F	11 M/19 F
Year of studies	8 (8–11)	8 (8–11)
BMI	23.4 (22.5–24.1)	23.5 (22.3–24.2)

Significance for between-groups analysis with independent sample *t* test.
BMI, body mass index.

reported as the means, SDs, and 95% confidence intervals (CIs) or counts and proportions (%) as appropriate. Two-tailed testing was performed. An independent samples *t* test was used to assess differences between people with migraine and healthy controls. To account for differences between groups in PPT on the investigated bilateral body sites, the independent and interactive effect of health status (two levels between subjects: people with migraine vs. healthy controls) and side of the body (two levels repeated measures: right and left side) was performed with a two-way mixed analysis of variance. These analyses established the generalized effect of migraine PPT over the different tested areas, and its interaction with the side of the body, and have been applied in other body sensory testing protocols. To account for differences between groups in SICI and ICF considering the different ISI applied, the independent and interactive effect of health status (two levels between subjects: people with migraine vs. healthy controls) and ISI (2 levels repeated measures for SICI: 3 and 5 ms; three levels repeated measures for ICF: 10, 15, and 20 ms) was performed with a two-way mixed analysis of variance. These analyses established the generalized effect of migraine MEPs over the different paired-pulse protocols (different ISI) and their interaction. In the event of statistically significant main effects or interactions, post hoc analyses were conducted with the Sidak test. Normality testing using the Shapiro–Wilk test was performed for all data sets. Significance was set for $P < 0.05$.

RESULTS

Thirty adults with migraine (11 M and 19 F, 38 years from 22 to 52 years) and 30 healthy controls (11 M and 19 F, 24 years from 19 to 62 years) with similar sex distribution ($P = 1.000$) and age ($P = 0.074$) were included in this study and performed all the measurements. Moreover, no differences were found in body mass index ($P = 0.740$) nor in years of study ($P = 0.840$) between patients with migraine and healthy controls. Regarding patients with migraine, they present the following clinical characteristics: frequency of migraine 9 ± 4 days per month, duration of attacks 75.5 ± 52.2 hours per month, and pain intensity 25.5 ± 39.5 severe hours of migraine per month (Table 1).

Pressure Pain Thresholds

The measurements of the PPT did not show any significant side effect in none of the muscles: masseter ($F_{1,58} = 0.001$, $P = 0.976$, $\eta^2_P = 0.000$), suboccipital ($F_{1,58} = 2.863$, $P = 0.096$, $\eta^2_P = 0.047$), temporalis ($F_{1,58} = 0.254$, $P = 0.616$, $\eta^2_P = 0.004$), trapezius ($F_{1,58} = 2.502$, $P = 0.119$, $\eta^2_P = 0.041$), and tensor fasciae latae (TFL) ($F_{1,58} = 0.815$, $P = 0.370$, $\eta^2_P = 0.014$). In addition, regarding the side x group effect, no significance differences were found in the masseter ($F_{1,58} = 2.592$, $P = 0.113$, $\eta^2_P = 0.043$), suboccipital ($F_{1,58} = 2.067$, $P = 0.156$, $\eta^2_P = 0.034$), temporalis ($F_{1,58} = 1.209$, $P = 0.276$, $\eta^2_P = 0.020$), trapezius ($F_{1,58} = 5.398$, $P = 0.024$, $\eta^2_P = 0.085$), and TFL ($F_{1,58} = 0.124$, $P = 0.726$, $\eta^2_P = 0.002$). By contrast, significantly lower PPT values were found in the migraine group compared with healthy controls in all the assessed muscle. Indeed, a significant group effect in the masseter (−111.3 kPa, 95% CI: −163.8 to −58.8, $F_{1,58} = 18.016$, $P < 0.001$, $\eta^2_P =$

TABLE 2. Pressure Pain Threshold (PPT) in People With Migraine and Healthy Controls

PPT	Migraine ($n = 30$)	Healthy Controls ($n = 30$)	Significance
Temporalis (kPa)			**<0.001**
Left	235.8 (176.3–335.4)	339.37 (430.9–821.5)	**<0.001**
Right	263.9 (188.6–318.5)	263.9 (188.6–318.5)	**0.002**
Suboccipitalis (kPa)			**0.001**
Left	286.8 (218–375.9)	412.9 (317.4–587)	**0.005**
Right	290 (187.2–378.4)	372.4 (273.7–574.3)	**0.005**
Masseter (kPa)			**<0.001**
Left	205.3 (153.6–249.1)	286.5 (217.2–375.2)	**0.001**
Right	203.2 (133.4–238.6)	304.4 (230.4–377.7)	**<0.001**
Trapezius (kPa)			**<0.001**
Left	321.4 (195.3–404.7)	561.1 (430.9–821.5)	**<0.001**
Right	385.5 (312.8–488.9)	536.3 (468.6–778.8)	**<0.001**
Procerus (kPa)	246.9 (189.8–319)	386.7 (281.9–474.9)	**<0.001**
TFL (kPa)			**<0.001**
Left	462.5 (328.7–579.8)	796.3 (608.9–1,238.9)	**<0.001**
Right	528 (332.5–694.7)	788.6 (651.6–1,119.8)	**0.015**

Significance for between-groups analysis with independent sample *t* test and mixed factors analysis of variance, bold for $P < 0.05$. Data are shown as the median and interquartile range.
TFL, tensor fasciae latae.

TABLE 3. TMS Single-Pulse and Paired-Pulse Outcomes in People With Migraine and Healthy Controls

TMS	Migraine ($n = 30$)	Healthy Controls ($n = 30$)	Significance
rMT (% of SO)	69 (64–75)	55 (49–68)	**0.001**
SICI			
3 ms	0.4 (0.1–0.7)	0.1 (0.05–0.4)	**0.015**
5 ms	0.5 (0.2–1)	0.2 (0.1–0.7)	0.750
ICF			
10 ms	1.0 (0.5–1.8)	1.6 (1–2.1)	0.641
15 ms	1.0 (0.5–1.4)	1.6 (1.2–2.4)	0.338
20 ms	1.0 (0.6–1.9)	1.4 (0.8–2.1)	0.135

For SICI and ICF, data expressed as a percentage of the unconditioned stimulus. Significance for between-groups analysis with independent sample *t* test and mixed factors analysis of variance, bold for $P < 0.05$. Data are shown as median and interquartile range.

ICF, intracortical facilitation; rMT, resting motor threshold; SICI, short-interval intracortical inhibition; SO, stimulator output.

0.237), suboccipital (−196.4 kPa, 95% CI: −310.2 to −82.6, $F_{1,58} = 11.928$, $P = 0.001$, $\eta^2_P = 0.171$), temporalis (−129.1 kPa, 95% CI: −197.9 to −60.3, $F_{1,58} = 14.107$, $P < 0.001$, $\eta^2_P = 0.196$), trapezius (−309.0 kPa, 95% CI: −428.9 to 189.1, $F_{1,58} = 26.628$, $P < 0.001$, $\eta^2_P = 0.315$), and TFL (−508.8 kPa, 95% CI: −764.7 to −252.9, $F_{1,58} = 15.841$, $P < 0.001$, $\eta^2_P = 0.215$) (Table 2 and Fig. 2). Moreover, Procero's PPT was found to be significantly lower in the migraine group compared with the healthy group (−139.8 kPa, 95% CI: −211.3 to −68.3, $P < 0.001$, Cohen $d = 1.010$).

Transcranial Magnetic Stimulation

The resting motor threshold was significantly lower in people with migraine compared with healthy controls (−10.5% of the stimulator output, 95% CI: −16.8 to −4.2, $P = 0.001$, Cohen $d = 0.869$). During the SICI assessment, a significant ISI x group was found ($F_{1,58} = 4.069$, $P = 0.048$, $\eta^2_P = 0.066$). Indeed, when considering the two different ISIs between the two groups, a significant difference was only found at 3 ms, suggesting higher MEP values in the migraine group (0.25, 95% CI: 0.05 to 0.46, $P = 0.015$, Cohen $d = 0.662$) suggesting reduced inhibition compared with healthy controls. Regarding ICF, no significant ISI effect ($F_{2,116} = 0.368$, $P = 0.693$, $\eta^2_P = 0.006$), ISI x group effect ($F_{2,116} = 0.481$, $P = 0.619$, $\eta^2_P = 0.008$), and group effect ($F_{1,58} = 1.302$, $P = 0.258$, $\eta^2_P = 0.022$) were found (Table 3 and Fig. 3).

Cognitive Functions

People with migraine were characterized by significantly worse performances both in the FAB (−1.1, 95% CI: −1.7 to −0.5, $P = 0.001$, Cohen $d = 0.915$) and TMT (7.1, 95% CI: 0.9 to 13.4, $P = 0.027$, Cohen $d = 0.594$) when compared with similar healthy controls (Table 4 and Fig. 4).

DISCUSSION

Extensive research has shown that migraine pathophysiology is characterized by alteration in sensory processing.[2,3,6,10] Our study found statistically significant differences in some neurophysiological and clinical outcomes in healthy controls. First, participants with migraine reported a significantly lower PPT both in the trigeminal and extratrigeminal areas compared with healthy subjects. Second, participants with migraine obtained significantly lower scores in the TMT and FAB. Third, participants with migraine presented a significantly lower rMT and cortical inhibition compared with the healthy controls.

Pressure pain threshold quantifies the mechanical sensitivity of the evaluated musculature. In our study, participants with episodic migraine presented a decreased PPT in the muscles over the trigeminal and extratrigeminal areas. This result agrees with the literature, and in fact, some studies have already shown a correlation between increased craniofacial muscle tenderness and a reduction in PPT in patients with migraine because of sensitization of the trigeminal nociceptive pathway.[13,15,18] Despite no differences were found among the muscles assessed in the migraine group, masseter, temporalis, and suboccipitalis were the most sensitive. These three muscles seem to play a pivotal role in migraine because of their anatomic connection: the temporalis and the masseter muscles are directly innervated by the trigeminal nerve; the suboccipitalis muscles are innervated by the greater occipital nerve and have an anatomic connection with the dura mater, which in turn is innervated by the ophthalmic division of the trigeminal nerve and the greater occipital nerve.[2,39] The results confirm the presence of local hyperalgesia due to peripheral sensitization over the trigeminal–cervical area. Conversely, the result of PPT in the extratrigeminal area, in particular in the TFL, suggests the presence of widespread pain due to central sensitization in participants with

TABLE 4. Cognitive Assessment in People With Migraine and Healthy Controls

	Migraine ($n = 30$)	Healthy Controls ($n = 30$)	Significance
TMT	23.7 (16.4–27.9)	14.8 (9.0–25.0)	**0.027**
FAB	16.0 (15.0–17.7)	17.5 (17.0–18.0)	**0.001**

Significance for between-groups analysis with independent sample *t* test, bold for $P < 0.05$.

episodic migraine. Such evidence could therefore suggest the importance of a combined pharmacological and nonpharmacological treatment, which seems to give greater results in increasing PPT in participants with migraine.[13,18] In addition, the nonpharmacological approach including manual therapy and active exercise should target not only the trigeminal–cervical area but also the spine.[13,16,18,40]

Regarding TMS outcomes, first, the rMT from single-pulse TMS assesses cortical excitability: i.e., low rMT reflects high cortical excitability, whereas high rMT reflects low cortical excitability.[23] Our study found a significantly lower rMT in migraine compared with healthy controls. Second, SICI and ICF, as determined by different ISIs during the paired-pulse TMS protocol, evaluate both the inhibitory circuits mediated by GABAergic (γ-aminobutyric acid) neurotransmission (SICI) and excitatory mediated by glutamatergic neurotransmission GLX (combined glutamate and glutamine) (ICF).[23–25,30,41] In line with previous neurophysiological studies, our results confirm that patients with migraine presented a significant reduction in the SICI (in the pain-free days) than healthy controls.[23,25,42,43] The results of rMT and SICI may highlight the lack of habituation during stimulus repetition and the dysregulation between excitatory–inhibitory transmission GABA/GLX that characterized the brain of people with migraine in the pain-free days.[2,6] From the neurophysiological aspect, on one side, the lack of habituation could be manifested by an increase in rMT, which, in turn, may reflect an abnormal thalamocortical activity called "thalamocortical dysrhythmia."[2,6,8,43] The thalamus is the relay center of the cortex for the central processing and integration of sensory information; habituation is a form of learning that lead to process, selecting, and filtering sensory information. Lack of habituation and thalamocortical dysrhythmia in the premonitory phase of migraine reduce the ability of the cortex to filter and inhibit irrelevant stimuli and, as a consequence, this led to cortical hyperresponsivity to sensory stimuli.[2,6,8,42–44] On the other side, the dysregulation between excitatory–inhibitory transmission GABA/GLX could be manifested by a reduction in SICI, which, in turn, may reflect the predisposition for a migraine attack.[25,41]

The results from this study suggest a possible worse cognitive function in people with migraine. In particular, both TMT and FAB were found significantly impaired by ∼39% and ∼9%, respectively, compared with similar healthy controls. Such findings are in line with previous results observed in people with migraine without aura, compared with healthy controls.[26] Among the symptoms of migraine, cognitive impairment is often considered one of the most impacting and invalidating after pain, and it can occur in all phases of a migraine attack.[45] Executive functions seem to be the most affected by migraine, and both neuroimaging and neuropsychological investigations have identified frontal lobe–related brain abnormalities and cognitive impairment.[46] A possible neurobiological mechanism underlying cognitive deficits in migraine could be a pain-related reorganization of intrinsic connectivity networks.[3,47] As such, it might be hypothesized that habituation and sensitization mechanisms can participate in the reorganization of the central nervous system and therefore affect cognitive functions and, in particular, executive function.

Limitation and Future Perspective

Regarding the limitations of the present work, the most relevant is the absence of sex stratification. Sex plays a pivotal role in pain modulation, in particular in the context of migraine pathology and pathophysiology.[38] Despite the sample size did not allow a statistical interpretation of gender variability, the same number of female and male subjects was assigned in the migraine group and in healthy controls and all the assessments in female subjects were scheduled in the follicular phase. However, the strength of this study is the evaluation of cortical excitability, pain perception, and cognitive function in the same sample and during the same preictal phase. In perspective, the efficacy of migraine treatments could be evaluated concerning not only clinical outcomes, such as headache parameters, but also these neurophysiological outcomes. Therapies and treatments that may reduce pressure pain threshold[13,48] could be integrated with treatments that may reduce cortical excitability and responsivity[49–51] to enhance their efficacy in migraine treatment.

CONCLUSION

To summarize, individuals with episodic migraine presented significant differences in some neurophysiological and clinical outcomes compared with healthy controls. Although neurophysiological measurements in migraine present variability, reduction in pressure pain threshold, in cortical inhibition, in resting motor threshold, and in executive functions seems to characterize migraine. These outcomes could be used to evaluate the effects of pharmacological, nonpharmacological treatments, and their association. In fact, understanding how different treatments could modulate the neurophysiological characteristics of these habituation and sensitization outcomes could lead to a better clinical management of this complex multifactorial disorder.

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