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Association between central sensitization, pain sensitivity and balance control in patients with migraine

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Abstract

Background: Balance alterations are prevalent among pain conditions, including migraine. The mechanisms explaining the association between pain and balance are unclear, as well as whether levels of pain sensitivity correlate with impaired balance. Our aim was therefore to investigate the association between balance, central sensitization symptoms and pain sensitivity in patients with migraine.

Methods: This cross-sectional study included 50 patients and demographic, clinical information, central sensitization inventory (CSI) and pain catastrophizing (PCS) scores were obtained. Patients underwent a standardized protocol evaluating balance and pain thresholds for cold (CPT), heat (HPT), mechanical (MPT) and pressure (PPT) in trigeminal (V1) and extra-trigeminal (C6) dermatomes. Data were analysed using Person's correlation, linear regression models and contrasting the presence and absence of central sensitization symptoms through *T*-tests.

Results: Mild-to-moderate correlations were observed between balance and MPT in V1 ($r=-0.24$, $p=0.046$) and C6 ($r=-0.41$, $p=0.002$), CPT in V1 ($r=0.31$, $p=0.026$), CSI scores ($r=0.27$, $p=0.029$) and migraine frequency ($r=0.25$, $p=0.040$). Balance was explained by CPT and MPT ($R^2=0.32$, $p=0.001$). The variance of CSI was explained by PCS scores and balance ($R^2=0.28$, $p=0.001$). Patients with symptoms of central sensitization presented an increased balance impairment ($p=0.044$) and higher catastrophizing levels ($p=0.001$) in contrast to patients without symptoms.

Conclusion: Balance impairment is associated with reduced pain thresholds and higher CSI scores. These results may help to elucidate the aetiology of balance alterations among chronic pain conditions.

Significance: For the first time, it has been shown that balance alterations can reflect greater pain sensitivity and signs of central sensitization in patients with migraine. This opens up perspectives for future studies to understand the mechanisms and further factors associated with balance and pain sensitivity in migraine.

1 | INTRODUCTION

According to the International Association for Study of Pain (IASP), central sensitization is defined as an augmented nociceptive responsiveness of central nervous system (CNS) neurons in the face of normal or subthreshold afferent input (International Association for the Study of Pain (IASP), 2011). In migraine, the presence of central sensitization can be observed through a range of symptoms, which mostly encompass the presence of cutaneous allodynia, primary and secondary hyperalgesia (Suzuki et al., 2022). The presence of cutaneous allodynia is related to an increased risk of migraine chronification (Bigal et al., 2008), and it is present in up to 63% of patients during attacks (Lipton et al., 2008), also often occurring between migraine episodes (Schwedt et al., 2011). Despite increased evidence of central sensitization in patients with chronic migraine, cutaneous allodynia is also reported for individuals with episodic migraine (Bigal et al., 2008), especially in migraine with aura (Ashkenazi et al., 2007).

The Quantitative Sensory Testing (QST) battery, defined by the German Research Network on Neuropathic Pain (DFNS) (Rolke et al., 2006), is considered the standard protocol to assess different pain phenotypes, including the presence of cutaneous allodynia and hyperalgesia (Nahman-Averbuch et al., 2018). Among other modalities, it includes the assessment of thresholds for heat, cold, mechanical and pressure pain (Rolke et al., 2006). Patients with migraine exhibit increased pain sensitivity to pressure and heat (Nahman-Averbuch et al., 2018). However, evidence of other modalities is inconsistent, limited by methodological heterogeneity (Nahman-Averbuch et al., 2018), and probably due to differences in patients' pain sensitivity profiles.

Further than signs and symptoms of central sensitization, patients with migraine often experience the presence of vestibular symptoms (Calhoun et al., 2011; Carvalho et al., 2017) and alterations in balance control during simple tasks such as quiet standing (Carvalho et al., 2017, 2018; Carvalho, Becnel, et al., 2022), as well as in functional activities such as walking, bypassing obstacles or sit to standing tasks (Carvalho et al., 2018). Similarly to the cutaneous allodynia phenomenon, greater alterations in balance control are reported for patients with chronic migraine and migraine with aura (Carvalho et al., 2017; Zorzin et al., 2020).

Changes in postural control may be understood as an abnormal output as a response to impaired sensory processing in the CNS. An exacerbated response of nociceptive neurons in the CNS and the presence of central sensitization can influence the processing of postural afferences and consequently change neuromuscular strategies to control balance (Nunez-Fuentes et al., 2021). Balance alterations are observed not just in migraine but also in several other chronic pain conditions such as fibromyalgia (Nunez-Fuentes et al., 2021; Peinado-Rubia et al., 2020) and chronic musculoskeletal pain (Berenshteyn et al., 2019; Lihavainen et al., 2010; Mingorance et al., 2021). The presence of psychosocial alterations is associated with dizziness and fear of falling among migraineurs (Pinheiro et al., 2022). In fibromyalgia patients, psychosocial factors are also associated with dizziness, balance performance and central sensitization levels (Peinado-Rubia et al., 2020).

The aim of this study was to assess the association between balance alterations, pain sensitivity levels and central sensitization symptoms among patients with migraine. We first hypothesize that balance is correlated with clinical and pain sensitivity outcomes; secondly, that increased pain sensitivity can explain the likelihood of presenting balance impairment and more severe levels of central sensitization symptoms. Lastly, we hypothesize that patients with central sensitization symptoms present reduced pain thresholds and greater balance impairment in contrast to patients without central sensitization symptoms, further than in comparison to a control group.

2 | METHODS

2.1 | Study design and sample

This study followed the STROBE reporting checklist for cross-sectional studies, and the recruitment took place between August and December of 2022. Patients with migraine were recruited from the community via flyers and email. The study was approved by the Ethical Committee from the University of Lübeck (process number: 21–506), and all patients received study information before providing written consent to participate in the study. The inclusion criteria were age between 18 and 65 years and a medical diagnosis of migraine with at least one attack per month within the last 3 months. Patients were excluded if they presented concomitant primary headache disorders, reported vestibular diseases or other chronic pain diseases (such as chronic back pain or fibromyalgia), had headaches on the appointment day, had systemic diseases such as uncontrolled high blood pressure and diabetes; or had any musculoskeletal conditions or neurological condition. Sixteen healthy participants without any headaches, musculoskeletal or any neurological conditions were included for comparability purposes.

Patients filled out a questionnaire on demographic information including age, sex and body mass index (BMI), the German version of the ID Migraine (Thiele et al., 2020), years since headache onset, frequency

(headache days within the last month), intensity (NRS 0–100), the German version of the Central Sensitization Questionnaire (CSI) (Klute et al., 2021) and the German version of the Pain Catastrophizing Scale (PCS) (Meyer et al., 2008). The report of a migraine attack 48 hours before and after the appointment was also recorded.

The CSI is a screening questionnaire designed to identify symptoms associated with central sensitization (Klute et al., 2021). It consists of two parts (A and B). Part A was used in this study and includes 25 items rating the frequency of symptoms on a 5-point Likert Scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = always). The total score ranges between 0 and 100, and scores above 40 are related to clinically relevant symptoms of central sensitization (Neblett et al., 2013). This questionnaire presents high validity and reliability (ICC = 0.82) (Neblett et al., 2013). The PCS has 13 items to assess catastrophic thoughts related to pain. The scores range between 0 and 52, and scores greater than 30 indicate clinically relevant level of catastrophizing report (Sullivan et al., 1996). It presents excellent test-retest reliability (ICC = 0.94) and adequate validity (Meyer et al., 2008; Sullivan et al., 1996).

2.2 | Procedure

After filling out the questionnaires and providing demographic and clinical information, participants were assessed for their pain sensitivity and balance in a noise- and temperature-controlled room. The pain sensitivity evaluation was performed by a blinded assessor and was based on the QST protocol, established by the DFNS (Rolke et al., 2006), which included evaluation of cold and heat pain thresholds, mechanical pain thresholds and pressure pain thresholds in a fixed sequence.

Cold and heat pain thresholds were assessed with a thermal contact stimulator (TCS, QST.Lab), (TCS; André Dufour, University of Strasbourg). The probe of the TCS (T11) had a total stimulation surface of 9 cm^2 (five equal zones, each 0.74 × 0.24 cm) and a weight of 440 g. The TCS probe was able to heat or cool the skin with an initial temperature of 32°C and a temperature range from 0°C to 60°C (0.1°C steps), using temperature rise and fall rates from 0.1°C/s to a maximum of 100°C/s. Individual heat and cold pain thresholds were determined starting from an initial, with increments/decrements of 1°C/s. Patients pressed a stop button when the feeling of cold/heat first elicited pain. The probe was applied over the trigeminal area (V1) of the dominant headache side and on the ipsilateral ventral forearm in the dermatome of C6 (extratrigeminal). If no headache side could be determined in the anamnesis, a simple randomization was used to establish the evaluation site. The test was repeated 3 times for each modality (cold and heat) and each site (V1 and C6). The average of the three repetitions was used as the individual cold and heat threshold for the data analysis.

Mechanical pain thresholds were assessed using a set of weighted pin-prick stimulators (MRC Systems GmbH, Heidelberg, Germany). Five series of ascending and descending stimuli were performed in V1 as well as in C6, and patients reported which metal needle elicited pain and no pain for each one of the series. The geometric mean of the procedure was used for analysis.

Pressure pain thresholds were assessed using a mechanical pressure algometer with a 1 cm^2 rubber tip (Wagner Instruments, Greenwich, UK). A pressure increase of 500 g per second was applied at V1 and C6 and the pressure was interrupted once the patients reported the first sensation of pain. The procedure was repeated three times in each location, and the mean pressure pain threshold of C6 and V1 in kPa was used for the analysis.

Balance was assessed through the evaluation of the total head movement trajectory (cm) during standing. A marker was placed over the head of the patients, who had to stay in an upright position with bare feet for three times of 30 s with feet together on a foam surface (48 × 40 × 6 cm, 50 k/m^3) and eyes closed. The trials were recorded by a camera (iPhoneX) at a rate of 30 fps and resolution of 1080p, placed parallel and 30 cm above the head using a tripod. The head trajectory was processed using open-source software (CvMob 3.1, http://www.cvmob.ufba.br/) (Costa et al., 2017). Calibration of the CvMob was performed by using two markers separated by 2 cm, also placed over the participants' heads. After the calibration, the software extracted the antero-posterior (y) and medio-lateral (x) trajectories generated by the postural adjustments during the video. Afterwards, the total displacement trajectory area (cm) averages of each trial were obtained using Matlab R2022b (MathWorks Inc., MA). This procedure has already been used (Costa et al., 2017; Mingorance et al., 2021) and validated against the gold standard for posturography assessment (Ciria et al., 2017).

2.3 | Statistical analysis

A sample size for the regression model was defined using G*Power based on an effect size (f^2) of 0.41, an alpha of 5% and a power of 80%, resulting in a minimum of 49 patients considering 10 predictors in the multiple linear regression model. Demographic and clinical data were presented as means and standard deviations (SD). The outcomes of mechanical pain thresholds, pressure pain thresholds and balance sway presented a normal distribution after transformation to a Log_{10} scale (Shapiro-Wilk $p > 0.05$) and the Log_{10} data was used for the statistical analysis.

Pearson's correlation coefficients (r) and 95% confidence intervals (95%CI) were calculated in order to assess the association between balance, pain sensitivity and clinical outcomes. Correlation values range from −1 to 1 and weak correlation was considered when r was <0.3, moderate correlation when values were between 0.3 and 0.7, and strong correlation when values were >0.7 (Sani & Todman, 2006). Subsequently, the data were explored through two multiple linear regression models using backward elimination to explain the variability of balance sway and CSI scores. Both models included the following variables: cold and heat pain thresholds in C6 and V1, mechanical and pressure pain thresholds in C6 and V1 and PCS. In the first model, balance sway (cm) was included as an independent outcome, and in the second model, the CSI scores. The best model was determined based on R^2 values and on the absence of violation of the statistical assumptions for multiple linear regression, including absence of outliers (standardized residuals between −3.29 and +3.29), independent errors (Durbin–Watson between 1 and 3), no multicollinearity [variance inflation factor (VIF) <10 and tolerance >0.1], homoscedasticity and normal distribution of residuals, by visually assessing scatterplots and histograms of standardized residuals (Field, 2018). In order to answer the third hypothesis, patients were stratified into two groups with and without clinically relevant central sensitization symptoms based on CSI scores lower and above the cut-off of 40 points (Neblett et al., 2013). Both groups were compared using the two-tailed Students-t test for independent samples for continuous data and the Fisher's exact test for categorical data. The same tests were used to contrast C6 and V1 sites, patients with migraine with controls, and patients during the ictal and interictal phase of migraine. All data were analysed using SPSS software version 26.0 with an alpha level of 5%.

3 | RESULTS

From the 51 patients with migraine recruited, one was excluded because the headache did not fulfil the migraine criteria established by the ID Migraine (Figure 1). Patients with migraine were on average 27.9 (SD: 10.1) years old with a headache onset since 12.3 (SD: 8.8) years and a mean pain intensity of 59.9 (SD:18.7) (VAS: 0–100). They had a mean migraine frequency of 4.5 (SD: 3.9) days per month, with a range between 1 and 7 attacks in 82% of the sample and between 8 and 14 attacks in 18% of the sample. Up to 59% of patients presented a visual or sensory aura. Eleven patients (22%) were in regular use of prophylactic medication, which included antidepressants (Amitriptyline, Venlafaxine or Mirtazapine, $n=4$),

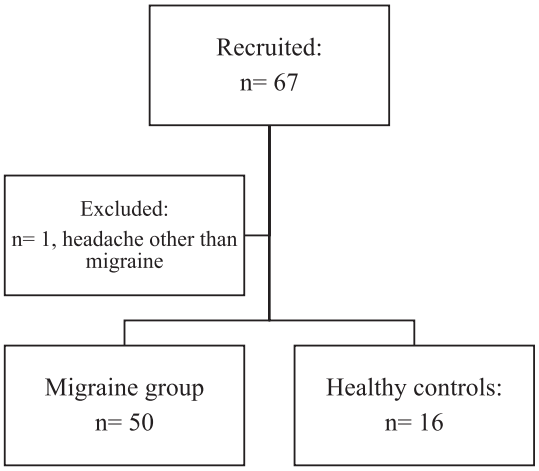

FIGURE 1 Study flow-chart.

antiepileptic drugs (Topiramate, Flunarizine, $n=3$) and anti-CGRP drugs (Erenumab, $n=3$). The mean scores of the CSI were 37.8 (SD: 10.6), indicating mild central sensitization symptoms. The PCS mean score was 23.8 (SD: 10.8), which is not considered a clinically relevant level of catastrophizing. The cold pain threshold was higher in V1 in contrast to C6 [V1: 12.9°C (SD: 7.8°C), C6: 7.73°C (SD: 7.9°C), $t=5.18$, $p<0.001$]. No differences were observed between V1 and C6 for heat pain threshold [V1: 42.6°C (SD: 4.1°C), C6: 42.2°C (SD: 4.2°C), $t=0.62$, $p=0.539$], pressure pain threshold [V1: 271.3 kPa (SD: 63.2 kPa), C6: 289.8 kPa (SD: 75.7 kPa), $t=-1.18$, $p=0.242$] or mechanical pain threshold [V1: 95.2 mN (SD: 112.0 mN), C6: 116.0 mN (SD: 141.0 mN), $t=-0.25$, $p=0.805$]. The sample characteristics can be found in Table 1. No differences were found between patients with and without a report of a migraine attack in the 48 h prior to and following the evaluation (Table S1). In contrast to migraineurs, healthy participants presented lower PCS scores ($t=3.76$, $p=0.001$), lower CSI scores ($t=6.55$, $p<0.0001$), higher pressure pain thresholds in C6 ($t=-3.40$, $p=0.002$) and V1 ($t=-2.22$, $p=0.036$), further than reduced balance sway ($t=2.38$, $p=0.021$) (Table S2).

Mild to moderate correlations were observed between balance sway and mechanical pain threshold in V1 and C6 [V1: $r=-0.24$ (95% CI: −1.00 to −0.01, $p=0.046$), C6: $r=-0.41$ (95% CI: −1.00 to −0.19, $p=0.002$)], cold pain threshold in V1 ($r=0.31$, 95% CI: 0.05 to 1.0, $p=0.026$), CSI scores ($r=0.27$, 95% CI: 0.04 to 1.0, $p=0.029$) and migraine frequency ($r=0.25$, 95% CI: 0.02 to 1.0, $p=0.040$) (Figure 2). No significant correlations were observed between balance and cold pain threshold in C6 ($r=0.16$, 95% CI: −0.08 to 1.0, $p=0.135$), heat pain threshold in V1 and C6 [V1: $r=-0.20$ (95% CI: −1.00 to 0.04, $p=0.082$), C6: $r=-0.01$ (95% CI: −1.00 to 2.22, $p=0.467$)], pressure pain threshold in V1 and C6 [V1: $r=-0.21$ (95% CI: −1.00 to 0.02, $p=0.070$), C6: $r=-0.13$ (95% CI: −1.00 to 0.11,

TABLE 1 Mean and (SD) of migraineurs' demographic and clinical characteristics.

Age (years)	27.9 (10.1)
Gender (%, *n* female)	84% (42)
Body mass index (kg/m^2)	23.8 (9.1)
Migraine onset (years)	12.3 (8.8)
Presence of aura (%, *n*)	56%, 28
Migraine frequency (days/month)	4.5 (3.9)
Migraine intensity (VAS, 0–100)	59.9 (18.7)
Use of prophylactic medication	22%, 11
Central sensitization inventory (CSI, scores)	37.8 (10.6)
Pain catastrophizing scale (PCS, scores)	23.8 (10.8)
Cold pain threshold C6 (°C)	7.7 (7.9)
Heat pain threshold C6 (°C)	42.2 (4.2)
Cold pain threshold V1 (°C)	12.9 (7.8)
Heat pain threshold V1 (°C)	42.6 (4.1)
Mechanical pain threshold C6 (mN)	116.2 (141.2)
Mechanical pain threshold V1 (mN)	95.2 (112.1)
Pressure pain threshold C6 (kPa)	271.6 (72.9)
Pressure pain threshold V1 (kPa)	261.0 (56.6)
Balance sway (cm)	79.1 (24.4)

Abbreviations: C6, extra-trigeminal area; V1, trigeminal area; VAS, visual analog scale.

$p=0.184$)], age ($r=0.08$, 95% CI: −0.15 to 1.0, $p=0.278$), BMI ($r=-0.03$, 95% CI: −0.20 to 1.0, $p=0.414$), migraine onset ($r=-0.06$, 95% CI: −0.29 to 1.0, $p=0.662$), pain intensity ($r=-0.02$, 95% CI: −0.25 to 1.0, $p=0.549$) and PCS ($r=-0.02$, 95% CI: −0.25 to 1.0, $p=0.558$).

Table 2 shows the results of the multiple linear regression to explain balance variability. The initial model did not present a significant regression equation ($F_{10,39}=2.05$, $p=0.054$) and an R^2 of 0.34. After the backward criteria for variable exclusion, the last model included three significant predictors ($F_{4,45}=5.40$, $p=0.001$) with an R^2 of 0.32 ($R=0.57$). Patients' predicted balance is influenced by cold pain threshold in V1 (0.004), the mechanical pain threshold in C6 (−0.151) and the mechanical pain threshold in V1 (−0.119). The analysis of standard residuals showed that the data contained no outliers (Standard Residual Min: −1.70, Standard Residual Max: 2.47). The remaining assumptions for linear regression were also met (Durbin-Watson: 1.48, VIF: 1.01 to 3.88, tolerance: 0.26 to 0.99, homoscedasticity and normal distribution of residuals).

Table 3 shows the results of the multiple linear regression to explain the CSI score variability. The initial model did not present a significant regression equation ($F_{10,39}=1.87$, $p=0.080$) and an R^2 of 0.32. After the backward criteria for variable exclusion, the last model included two significant predictors ($F_{2,47}=8.97$, $p=0.001$) with an R^2 of 0.28 ($R=0.53$). Patients' predicted CSI scores are influenced by pain catastrophizing scores (0.44) and by balance (27.09). The analysis of standard residuals showed that the data contained no outliers (Standard Residual Min = −2.02, Standard Residual Max = 2.84). The remaining assumptions for linear regression were also met (Durbin-Watson: 1.16, VIF: 1.00, tolerance: 1.00, homoscedasticity and normal distribution of residuals).

Patients were stratified according to the presence of clinically relevant symptoms of central sensitization based on scores greater and lower than 40 in the CSI (Table 4). Patients with scores greater or equal to 40 presented a greater balance sway and higher PCS scores ($t=3.72$, $p=0.001$) in contrast to patients with CSI scores less than 40 ($t=2.06$, $p=0.044$). No differences between both groups were observed in the remaining outcomes: age ($t=0.59$, $p=0.556$), gender ($p=0.409$), BMI ($t=-0.79$, $p=0.433$), migraine onset ($t=-0.28$, $p=0.778$), frequency ($t=0.82$, $p=0.417$), pain intensity ($t=0.83$, $p=0.412$), cold pain threshold in C6 ($t=0.54$, $p=0.593$) and in V1 ($t=1.01$, $p=0.316$), heat pain threshold in C6 ($t=-0.38$, $p=0.709$) and in V1 ($t=-1.11$, $p=0.270$), mechanical pain threshold in C6 ($t=-0.55$, $p=0.586$) and in V1 ($t=-0.40$, $p=0.688$), pressure pain threshold in C6 ($t=-0.96$, $p=0.342$) and in V1 ($t=-0.48$, $p=0.632$).

4 | DISCUSSION

This study shows for the first time the association between balance alteration, central sensitization symptoms and pain thresholds among patients with migraine, according to the a priori hypothesis. Increased balance sway was correlated with lower mechanical (C6 and V1) and cold pain thresholds (V1), greater CSI scores and greater migraine frequency. The linear regression model also demonstrated that balance can be predicted by mechanical (C6 and V1) and cold pain thresholds (V1). Similarly, the CSI scores can be predicted partially by balance and pain catastrophizing. Balance displacement and pain catrastophizing were the only outcomes with observed differences between migraine patients with and without clinically relevant symptoms of central sensitization.

Balance alterations are observed in several neurological/musculoskeletal conditions (Berenshteyn et al., 2019; Hirase et al., 2020; Mingorance et al., 2021; Nunez-Fuentes et al., 2021; Peinado-Rubia et al., 2020) and measuring balance displacement is one of the sensorimotor markers evidenced in chronic pain patients (Viseux et al., 2022). Its control is fundamental to the performance of daily activities, while its decline is associated with a loss of independence and increased fall risk (Carvalho, Luedtke, et al., 2022; Horak, 2006). Studies on experimental acute pain using saline injection, electrical stimulation or heat

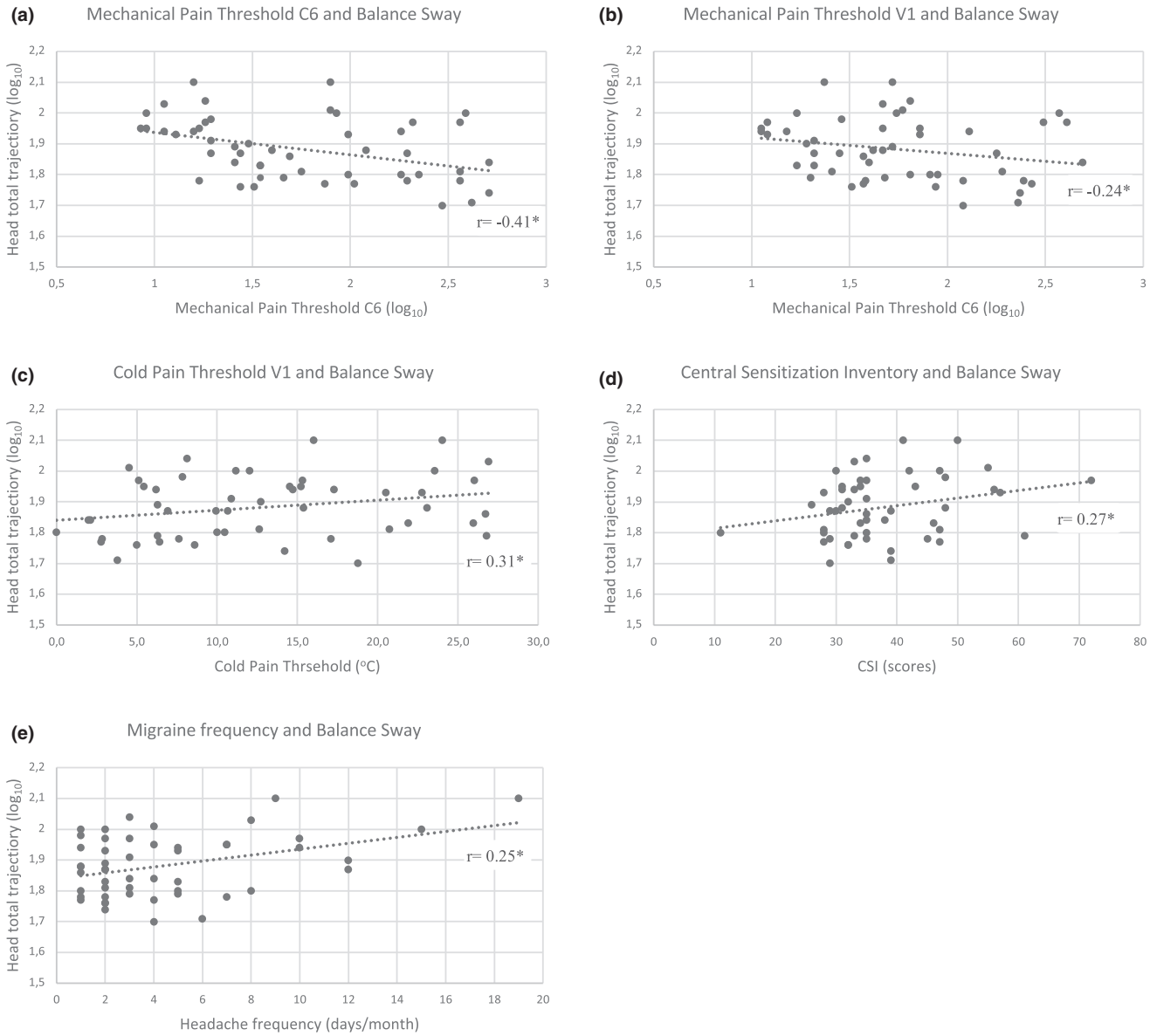

FIGURE 2 Scatter plots showing the correlation between the Balance Sway with the Mechanical Pain Threshold in C6 (a) and V1 (b), Cold Pain Threshold in V1 (c), Central Sensitization Inventory (d) and Migraine Frequency (e). V1: trigeminal area, C6: extra-trigeminal area. *$p < 0.05$.

pain demonstrated increased balance sway, suggesting that sensorimotor mechanisms are predominantly related to balance control rather than cognitive and central processes of pain (Corbeil et al., 2004; Hirata et al., 2011). These results are in line with studies on musculoskeletal pain conditions such as knee, low back and neck pain, which attribute balance alterations mainly to peripheral factors such as reduced muscular strength (Jadelis et al., 2001), trunk stiffness (Brumagne et al., 2008) and decreased proprioceptive acuity, measured through the joint position sense error (Pinsault et al., 2008; Viseux et al., 2022). These aspects are postulated to influence the body sway due to altered proprioceptive input and consequent accuracy reduction in the sensory integration process, which would lead to an imprecise estimation of the body centre of mass (Viseux et al., 2022).

However, older adults with pain present greater balance deficits in contrast to individuals without pain, even after controlling for confounders such as lower limb strength, physical activity levels and the presence of neurological and degenerative diseases (Lihavainen et al., 2010). Further than being young, patients with migraine do not exhibit alterations in the joint position sense of the neck (Meise et al., 2019). It can be speculated that central processes also play a relevant role in the balance dysfunction of patients with chronic pain. These current results support this statement by demonstrating an association between balance control and central sensitization

TABLE 2 Multiple linear regression for prediction of the balance sway based on QST outcomes, pain catastrophizing and central sensitization scores.

Models		Unstandardized coefficients		Standardized coefficients								
		B	**SE**	***β***	***t***	**Sig.**	***R***	R^2	**Adjusted R^2**	**df**	***F***	**Sig.**
1	(Constant)	1.96	0.266		7.363	0	0.59	0.34	0.17	10	2.05	0.054
	Cold pain threshold C6	0	0.002	−0.012	−0.069	0.945						
	Heat pain threshold C6	0	0.004	0.014	0.089	0.93						
	Cold pain threshold V1	0.003	0.003	0.179	0.863	0.394						
	Heat pain threshold V1	−0.004	0.006	−0.144	−0.648	0.521						
	Mechanical pain threshold C6	−0.148	0.053	−0.728	−2.812	0.008						
	Mechanical pain threshold V1	−0.124	0.067	−0.508	−1.846	0.072						
	Pressure pain threshold C6	0.144	0.211	0.142	0.682	0.499						
	Pressure pain threshold V1	−0.191	0.249	−0.158	−0.768	0.447						
	Pain catastrophizing scale	−0.001	0.002	−0.051	−0.331	0.742						
	Central sensitization inventory	0.003	0.002	0.292	1.941	0.059						
7	Constant	1.799	0.084		21.399	0	0.57	0.32	0.26	4	5.40	**0.001**
	Cold pain threshold V1	0.004	0.002	0.276	2.044	**0.047**						
	Mechanical pain threshold C6	−0.151	0.047	−0.745	−3.249	**0.002**						
	Mechanical pain threshold V1	−0.119	0.059	−0.49	−2.032	**0.048**						
	Central sensitization inventory	0.002	0.001	0.236	1.92	0.061						

Note: Bold indicates $p < 0.05$.

Abbreviations: C6, extra-trigeminal area; QST, quantitative sensory testing; V1, trigeminal area.

TABLE 3 Multiple linear regression for prediction of the central sensitization scores based on QST outcomes, balance sway and pain catastrophizing scores.

Models		Unstandardized coefficients		Standardized coefficients								
		B	SE	Beta	*t*	Sig.	*R*	R^2	Adjusted R^2	df	*F*	Sig.
1	(Constant)	−36.697	40.062		−0.916	0.365	0.57	0.32	0.15	10	1.87	0.080
	Cold pain threshold C6	0.112	0.236	0.083	0.472	0.639						
	Heat pain threshold C6	−0.361	0.415	−0.142	−0.869	0.39						
	Cold pain threshold V1	0.062	0.29	0.045	0.214	0.832						
	Heat pain threshold V1	0.508	0.583	0.196	0.872	0.388						
	Mechanical pain threshold C6	−1.023	5.675	−0.052	−0.18	0.858						
	Mechanical pain threshold V1	−1.363	6.868	−0.058	−0.199	0.844						
	Pressure pain threshold C6	−23.082	20.597	−0.234	−1.121	0.269						
	Pressure pain threshold V1	27.057	24.254	0.231	1.116	0.271						
	Pain catastrophizing scale	0.399	0.141	0.407	2.83	0.007						
	Balance sway	29.21	15.046	0.301	1.941	0.059						
9	Constant	−23.709	22.935		−1.034	0.307	0.53	0.28	0.25	4	8.97	**0.001**
	Pain catastrophizing scale	0.442	0.122	0.451	3.633	**0.001**						
	Balance sway	27.091	12.029	0.28	2.252	**0.029**						

Note: Bold indicates $p < 0.05$.

Abbreviations: C6, extra-trigeminal area; QST, quantitative sensory testing; V1, trigeminal area.

TABLE 4 Mean (SD) of balance and QST outcomes according to presence and absence of Central Sensitization according to the Central Sensitization Inventory (CSI).

	CSI ≥40 ($n = 16$)	CSI < 40 ($n = 34$)	Statistic
Age (years)	29.1 (12.3)	27.3 (9.1)	$t = 0.59$, $p = 0.556$
Gender (%, *n* female)	35.7% (15)	64.3% (27)	$p = 0.409$[a]
Body mass index (kg/m^2)	22.4 (3.7)	24.5 (10.6)	$t = -0.79$, $p = 0.433$
Migraine onset (years)	11.7 (10.7)	12.5 (8.1)	$t = -0.28$, $p = 0.778$
Migraine frequency (days/month)	5.2 (5.2)	4.2 (3.2)	$t = 0.82$, $p = 0.417$
Migraine intensity (VAS, 0–100)	63.1 (18.2)	58.3 (19.0)	$t = 0.83$, $p = 0.412$
Pain catastrophizing scale (PCS, scores)	31.1 (8.8)	20.3 (9.9)	$\mathbf{t = 3.72, p = 0.001}$
Cold pain threshold C6 (°C)	8.6 (6.7)	7.3 (8.5)	$t = 0.54$, $p = 0.593$
Heat pain threshold C6 (°C)	41.9 (2.9)	42.4 (4.7)	$t = -0.38$, $p = 0.709$
Cold pain threshold V1 (°C)	14.5 (7.9)	12.2 (7.6)	$t = 1.01$, $p = 0.316$
Heat pain threshold V1 (°C)	41.6 (3.5)	43.0 (4.3)	$t = -1.11$, $p = 0.270$
Mechanical pain threshold C6 (mN)	90.3 (116.5)	128.3 (151.5)	$t = -0.55$, $p = 0.586$
Mechanical pain threshold V1 (mN)	95.0 (130.0)	95.3 (104.7)	$t = -0.40$, $p = 0.688$
Pressure pain threshold C6 (kPa)	254.2 (43.7)	279.9 (82.5)	$t = -0.96$, $p = 0.342$
Pressure pain threshold V1 (kPa)	254.6 (50.4)	264.0 (59.7)	$t = -0.48$, $p = 0.632$
Balance sway (cm)	89.3 (35.3)	74.3 (15.7)	$\mathbf{t = 2.06, p = 0.044}$

Note: Bold indicates $p < 0.05$.

Abbreviations: C6, extra-trigeminal area; CSI, central sensitization inventory; QST, quantitative sensory testing; V1, trigeminal area.

[a]Fisher's exact test.

symptoms, when the latter is considered a determining factor for the risk and perpetuation of chronic pain (Suzuki et al., 2022).

Nonetheless, the central mechanisms involved in the balance control alterations in patients with migraine remain unclear. An adequate balance control demands not just the input of proprioceptive afferences regarding the different body segment positions into the CNS but also its integration with the visual and vestibular sensory systems, considering their relationship to one another and to the surroundings (Horak, 2006). Since migraine has a greater prevalence of vestibular symptoms, one may speculate that alterations in the vestibular system are directly associated with balance disorders. However, studies failed to demonstrate an influence of vestibular symptoms or vestibular dysfunction on the postural sway of migraineurs (Carvalho, Luedtke, et al., 2022; Casani et al., 2009; Zorzin et al., 2020).

On the other hand, some specific areas related to pain processing may influence balance. The extensive brain network responsible for nociceptive processing—well known as the salience network or cerebral signature of pain (Tracey & Mantyh, 2007)—consists of several brain structures, including the spinoreticular tract, which, among others, processes autonomic responses, affective and cognitive dimensions of pain. The spinoreticular tract plays a role in motor control due to its projections into the lateral reticular formation (Viseux et al., 2022). Furthermore, chronic pain and its severity are often associated with cortical reorganization not just in the sensory but also in the motor cortex (Flor, 2003), with cortical change restoration after pain treatment and remission (Maihofner et al., 2004).

The presence of cutaneous allodynia, a marker for central sensitization in migraine, is well known to be related to poorer clinical outcomes such as increased depression levels, higher disability, lower quality of life, medication overuse and pain intensity (Dodick et al., 2019; Seo & Park, 2019). Nonetheless, it also predicts a poor response to acute pain treatment (Burstein et al., 2004), and it is considered a critical factor for suicidality, along with the presence of osmophobia (Park et al., 2015). Are balance changes also a manifestation of central sensitization? Although further mechanisms remain to be elucidated, these current results indicate that among all measures of pain sensitivity from various modalities, just balance and pain catastrophizing showed differences between patients with and without symptoms of central sensitization.

Although pain sensitivity levels did not differ among patients with and without symptoms of central sensitization, the mechanical pain thresholds in trigeminal and extra-trigeminal areas, in association with the cold pain threshold in local areas, were considered predictors of poorer balance control. Since migraine is a chronic disease with episodic manifestations, one can suggest that QST measurements, in contrast to balance sway, cannot recognize clinically relevant symptoms of central sensitization among migraineurs with similar headache features. In fact, while increased pain sensitivity to pressure and heat in migraine was reported by a previous meta-analysis when comparing migraine with healthy controls, the evidence for sensory changes is inconsistent in migraine and highly influenced by patients' heterogeneity (Nahman-Averbuch et al., 2018) and by the migraine phase (Peng & May, 2018; Scholten-Peeters et al., 2020). Furthermore, our results can be generalized to a comparable migraine population, and future studies should consider testing the association between pain sensitivity and balance among healthy participants.

This study presents some limitations. First, the patients were recruited in the community and had an average of 4.5 migraine attacks per month. Although all of them have received a migraine diagnosis and fulfilled the migraine ID criteria, it can be that this current sample does not represent a group of patients with a greater impairment of migraine and a higher frequency of attacks. Albeit significant, the correlations between balance and pain outcomes were low-to-moderate, while the linear regression models predicted 34% and 28% of the balance and CSI score variability, respectively. In this way, it can be suggested that other factors not considered in this study may additionally contribute to the balance sway and CSI scores in migraine. In this way, larger sample sizes should be considered in further studies to explore comprehensively this issue, as well as the mechanisms related to it. Although patients with migraine reported no other symptom than headache and no comorbidities, they were screened based on their clinical history and not based on neurophysiological examination. In this way, it is possible that other factors could have influenced the study outcomes. Lastly, the comparison among patients with and without symptoms of central sensitization may present generalizability restrictions due to power limitations. Despite these limitations, this is the first study to demonstrate a relationship between balance, pain sensitivity and central sensitization, highlighting aspects of migraine that are common to other chronic pain conditions and opening perspectives for future studies to understand the mechanisms and further factors associated with balance and pain sensitivity in migraine. As already suggested by previous authors (Viseux et al., 2022), advancing knowledge on the influence of pain on balance can contribute to the development of therapeutic strategies in patients with chronic pain, including migraine disorders.

5 | CONCLUSION

Mechanical and cold pain thresholds are correlated and can predict postural balance sway. Higher severity of symptoms related to central sensitization are associated with balance control changes and catastrophizing, but not with pain thresholds, among patients with migraine.

AUTHOR CONTRIBUTIONS

G. F. Carvalho, T. M. Szikszay and K. Luedtke conceived the study idea. A. Sennholz, G. F. Carvalho drafted the manuscript. A. Sennholz, T. Marusich and G. F. Carvalho organized and/or conducted data collection. All authors were involved in data interpretation, write-up of results and finalizing the manuscript.

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This data has not been presented in any form previously.

CONFLICT OF INTEREST STATEMENT

The Author(s) declare(s) that there is no conflict of interest.

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REFERENCES

Ashkenazi, A., Sholtzow, M., Shaw, J. W., Burstein, R., & Young, W. B. (2007). Identifying cutaneous allodynia in chronic migraine using a practical clinical method. *Cephalalgia*, *27*, 111–117.

Berenshteyn, Y., Gibson, K., Hackett, G. C., Trem, A. B., & Wilhelm, M. (2019). Is standing balance altered in individuals with chronic low back pain? A systematic review. *Disability and Rehabilitation*, *41*, 1514–1523.

Bigal, M. E., Ashina, S., Burstein, R., Reed, M. L., Buse, D., Serrano, D., Lipton, R. B., & Group A. (2008). Prevalence and characteristics of allodynia in headache sufferers: A population study. *Neurology*, *70*, 1525–1533.

Brumagne, S., Janssens, L., Knapen, S., Claeys, K., & Suuden-Johanson, E. (2008). Persons with recurrent low back pain exhibit a rigid postural control strategy. *European Spine Journal*, *17*, 1177–1184.

Burstein, R., Collins, B., & Jakubowski, M. (2004). Defeating migraine pain with triptans: A race against the development of cutaneous allodynia. *Annals of Neurology*, *55*, 19–26.

Calhoun, A. H., Ford, S., Pruitt, A. P., & Fisher, K. G. (2011). The point prevalence of dizziness or vertigo in migraine and factors that influence presentation. *Headache*, *51*, 1388–1392.

Carvalho, G. F., Becnel, A. R., Miske, C., Szikszay, T. M., Adamczyk, W. M., & Luedtke, K. (2022). Postural control impairment in patients with headaches—A systematic review and meta-analysis. *Headache*, *62*, 241–270.

Carvalho, G. F., Bonato, P., Florencio, L. L., Pinheiro, C. F., Dach, F., Bigal, M. E., & Bevilaqua-Grossi, D. (2017). Balance impairments in different subgroups of patients with migraine. *Headache*, *57*, 363–374.

Carvalho, G. F., Florencio, L. L., Pinheiro, C. F., Dach, F., Bigal, M. E., & Bevilaqua-Grossi, D. (2018). Functional balance deterioration on daily activities in patients with migraine: A controlled study. *American Journal of Physical Medicine & Rehabilitation*, *97*, 90–95.

Carvalho, G. F., Luedtke, K., Pinheiro, C. F., Moraes, R., Lemos, T. W., Carneiro, C. G., Bigal, M. E., Dach, F., & Bevilaqua-Grossi, D. (2022). Migraine and balance impairment: Influence of subdiagnosis, otoneurological function, falls, and psychosocial factors. *Headache*, *62*, 548–557.

Casani, A. P., Sellari-Franceschini, S., Napolitano, A., Muscatello, L., & Dallan, I. (2009). Otoneurologic dysfunctions in migraine patients with or without vertigo. *Otology & Neurotology*, *30*, 961–967.

Ciria, L. F., Munoz, M. A., Gea, J., Pena, N., Miranda, J. G. V., Montoya, P., & Vila, J. (2017). Head movement measurement: An alternative method for posturography studies. *Gait & Posture*, *52*, 100–106.

Corbeil, P., Blouin, J. S., & Teasdale, N. (2004). Effects of intensity and locus of painful stimulation on postural stability. *Pain*, *108*, 43–50.

Costa, I. D., Gamundi, A., Miranda, J. G., Franca, L. G., De Santana, C. N., & Montoya, P. (2017). Altered functional performance in patients with fibromyalgia. *Frontiers in Human Neuroscience*, *11*, 14.

Dodick, D. W., Reed, M. L., Fanning, K. M., Munjal, S., Alam, A., Buse, D. C., Schwedt, T. J., & Lipton, R. B. (2019). Predictors of allodynia in persons with migraine: Results from the migraine in America symptoms and treatment (MAST) study. *Cephalalgia*, *39*, 873–882.

Field, A. P. (2018). *Discovering statistics using IBM SPSS statistics* (5th ed., North American edition). Sage Publications Inc.

Flor, H. (2003). Cortical reorganisation and chronic pain: Implications for rehabilitation. *Journal of Rehabilitation Medicine*, *35*, 66–72.

Hirase, T., Okubo, Y., Sturnieks, D. L., & Lord, S. R. (2020). Pain is associated with poor balance in community-dwelling older adults: A systematic review and meta-analysis. *Journal of the American Medical Directors Association*, *21*, 597–603.e8.

Hirata, R. P., Ervilha, U. F., Arendt-Nielsen, L., & Graven-Nielsen, T. (2011). Experimental muscle pain challenges the postural stability during quiet stance and unexpected posture perturbation. *The Journal of Pain*, *12*, 911–919.

Horak, F. B. (2006). Postural orientation and equilibrium: What do we need to know about neural control of balance to prevent falls? *Age and Ageing*, *35*(Suppl 2), ii7–ii11.

International Association for the Study of Pain (IASP). (2011). Pain terms and definitions. https://www.iasp-pain.org/resources/terminology/

Jadelis, K., Miller, M. E., Ettinger, W. H., Jr., & Messier, S. P. (2001). Strength, balance, and the modifying effects of obesity and knee pain: Results from the observational arthritis study in seniors (oasis). *Journal of the American Geriatrics Society*, *49*, 884–891.

Klute, M., Laekeman, M., Kuss, K., Petzke, F., Dieterich, A., Leha, A., Neblett, R., Ehrhardt, S., Ulma, J., & Schafer, A. (2021). Cross-cultural adaptation and validation of the German central sensitization inventory (CSI-GE). *BMC Musculoskeletal Disorders*, *22*, 708.

Lihavainen, K., Sipila, S., Rantanen, T., Sihvonen, S., Sulkava, R., & Hartikainen, S. (2010). Contribution of musculoskeletal pain to postural balance in community-dwelling people aged 75 years and older. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *65*, 990–996.

Lipton, R. B., Bigal, M. E., Ashina, S., Burstein, R., Silberstein, S., Reed, M. L., Serrano, D., Stewart, W. F., & American Migraine Prevalence Prevention Advisory G. (2008). Cutaneous allodynia in the migraine population. *Annals of Neurology*, *63*, 148–158.

Maihofner, C., Handwerker, H. O., Neundorfer, B., & Birklein, F. (2004). Cortical reorganization during recovery from complex regional pain syndrome. *Neurology*, *63*, 693–701.

Meise, R., Ludtke, K., Probst, A., Stude, P., & Schottker-Koniger, T. (2019). Joint position error in patients with headache: Systematic review of the literature and experimental data for patients with chronic migraine. *Schmerz*, *33*, 204–211.

Meyer, K., Sprott, H., & Mannion, A. F. (2008). Cross-cultural adaptation, reliability, and validity of the German version of the pain catastrophizing scale. *Journal of Psychosomatic Research*, *64*, 469–478.

Mingorance, J. A., Montoya, P., Miranda, J. G. V., & Riquelme, I. (2021). An observational study comparing fibromyalgia and chronic low back pain in somatosensory sensitivity, motor function and balance. *Healthcare (Basel)*, *9*, 9.

Nahman-Averbuch, H., Shefi, T., Schneider, V. J., 2nd, Li, D., Ding, L., King, C. D., & Coghill, R. C. (2018). Quantitative sensory testing in patients with migraine: A systematic review and meta-analysis. *Pain*, *159*, 1202–1223.

Neblett, R., Cohen, H., Choi, Y., Hartzell, M. M., Williams, M., Mayer, T. G., & Gatchel, R. J. (2013). The central sensitization inventory (CSI): Establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *The Journal of Pain*, *14*, 438–445.

Nunez-Fuentes, D., Obrero-Gaitan, E., Zagalaz-Anula, N., Ibanez-Vera, A. J., Achalandabaso-Ochoa, A., Lopez-Ruiz, M. D. C., Rodriguez-Almagro, D., & Lomas-Vega, R. (2021). Alteration of postural balance in patients with fibromyalgia syndrome—A systematic review and meta-analysis. *Diagnostics (Basel)*, *11*, 11.

Park, S. P., Seo, J. G., & Lee, W. K. (2015). Osmophobia and allodynia are critical factors for suicidality in patients with migraine. *The Journal of Headache and Pain*, *16*, 529.

Peinado-Rubia, A., Osuna-Perez, M. C., Rodriguez-Almagro, D., Zagalaz-Anula, N., Lopez-Ruiz, M. C., & Lomas-Vega, R. (2020). Impaired balance in patients with fibromyalgia syndrome: Predictors of the impact of this disorder and balance confidence. *International Journal of Environmental Research and Public Health*, *17*, 17.

Peng, K. P., & May, A. (2018). Quantitative sensory testing in migraine patients must be phase-specific. *Pain*, *159*, 2414–2416.

Pinheiro, C. F., Bevilaqua-Grossi, D., Florencio, L. L., Bragatto, M. M., Benatto, M. T., Dach, F., Bigal, M. E., & Carvalho, G. F. (2022). Is kinesiophobia related to fear of falling, dizziness disability, and migraine disability in patients with migraine? *Physiotherapy Theory and Practice*, *38*, 2727–2735.

Pinsault, N., Vuillerme, N., & Pavan, P. (2008). Cervicocephalic relocation test to the neutral head position: Assessment in bilateral labyrinthine-defective and chronic, nontraumatic neck pain patients. *Archives of Physical Medicine and Rehabilitation*, *89*, 2375–2378.

Rolke, R., Baron, R., Maier, C., Tolle, T. R., Treede, D. R., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Botefur, I. C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G. B., Magerl, W., Maihofner, C., Rolko, C., Schaub, C., ... Wasserka, B. (2006). Quantitative sensory testing in the German research network on neuropathic pain (DFNS): Standardized protocol and reference values. *Pain*, *123*, 231–243.

Sani, F., & Todman, J. (2006). *Experimental design and statistics for psychology: A first course*. Oxford.

Scholten-Peeters, G. G. M., Coppieters, M. W., Durge, T. S. C., & Castien, R. F. (2020). Fluctuations in local and widespread mechanical sensitivity throughout the migraine cycle: A prospective longitudinal study. *The Journal of Headache and Pain*, *21*, 16.

Schwedt, T. J., Krauss, M. J., Frey, K., & Gereau, R. W. (2011). Episodic and chronic migraineurs are hypersensitive to thermal stimuli between migraine attacks. *Cephalalgia*, *31*, 6–12.

Seo, J. G., & Park, S. P. (2019). Clinical significance of sensory hypersensitivities in migraine patients: Does allodynia have a priority on it? *Neurological Sciences*, *40*, 393–398.

Sullivan, M. J. L., Bishop, S., & Pivik, J. (1996). The pain catastrophizing scale: Development and validation. *Psychological Assessment*, *7*, 524–532.

Suzuki, K., Suzuki, S., Shiina, T., Kobayashi, S., & Hirata, K. (2022). Central sensitization in migraine: A narrative review. *Journal of Pain Research*, *15*, 2673–2682.

Thiele, A., Strauß, S., Angermaier, A., Kronenbuerger, M., & Fleischmann, R. (2020). Translation and validation of an extended German version of ID migraine™ as a migraine screening tool. *Cephalalgia Reports*, *3*. https://doi.org/10.1177/2515816320962773

Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron*, *55*, 377–391.

Viseux, F. J. F., Simoneau, M., & Billot, M. (2022). A comprehensive review of pain interference on postural control: From experimental to chronic pain. *Medicina (Kaunas)*, *58*(6), 812. https://doi.org/10.3390/medicina58060812

Zorzin, L., Carvalho, G. F., Kreitewolf, J., Teggi, R., Pinheiro, C. F., Moreira, J. R., Dach, F., & Bevilaqua-Grossi, D. (2020). Subdiagnosis, but not presence of vestibular symptoms, predicts balance impairment in migraine patients—A cross sectional study. *The Journal of Headache and Pain*, *21*, 56.

SUPPORTING INFORMATION

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