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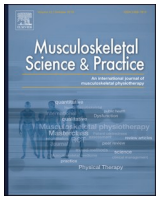

Cervical musculoskeletal impairments and pain sensitivity in migraine patients

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ABSTRACT

Introduction: Currently, examination of migraine patients relies on a clinical interview investigating symptoms characteristics. Despite this, to help identify distinct migraine subtypes and allow a personalized treatment approach, biomarkers to profile distinct migraine subtypes should be utilized in clinical and research settings. Therefore, there is a need to include physical and psychophysical examinations aimed at assessing migraine features quantitatively.

Purpose: This paper aimed to discuss if increased pressure pain sensitivity and impaired cervical musculoskeletal function could be considered 1) as quantitative features of migraine and 2) if they could be used as biomarkers to profile migraine patients in distinct subtypes.

Implication: Increased pain sensitivity and cervical musculoskeletal impairments have been suggested as quantitative biomarkers to phenotype and subgroup migraine patients in clinical and research settings.

This could provide the first step for a mechanistically-driven and personalized treatment approach according to migraine phenotypes.

1. Introduction

Migraine is a complex neurological disorder affecting around 15% of the population and is considered among the first cause of disability worldwide (Steiner et al., 2018; Vos et al., 2017). It is characterized by cyclic activation of cortical/subcortical brain areas that lead to transitory headache attacks, separated by non-headache phases (Goadsby et al., 2017). The activation of cortical and subcortical brain areas begins ~48 h before the attack (preictal phase), reaches its peak during the headache attack (ictal phase), and gradually restores to baseline levels in the ~48 h following the attack (postictal phase) (Schulte et al., 2020; Schulte & May 2016). The phase between the preictal and postictal phases is called the interictal phase. In a subgroup of patients, the ictal phase is preceded by cortical spreading depolarization lasting 5–60 min (aura) (Ferrari et al., 2022).

Cortical and subcortical brain activation leads to various symptoms in migraine patients. Headache, the main one, occurs in the ictal phase and is due to activation and sensitization of the neurovascular trigeminal complex (Ashina et al., 2019). Other symptoms include neck pain, fatigue/cognitive changes, homeostatic alterations, nausea/vomiting, and hypersensitivity to different stimuli such as somatosensory, visual, auditory, and olfactory (Al-Khazali et al., 2022; Bose et al., 2018; Calhoun et al., 2010; Karsan et al., 2018; Peng & May 2019). These symptoms follow a cyclic pattern: they begin in the preictal phase, reach their peak in the ictal phase, and gradually disappear in the postictal phase. The aura is characterized by reversible focal neurologic symptoms lasting 5–60 min.

Currently, migraine diagnosis is made primarily by a clinical interview according to symptoms characteristics. Headache should last 4–72 h and have two of the following characteristics: pulsatile in quality, unilateral, moderate/severe intensity, or aggravated by routine physical activity. Moreover, at least one associated symptom, such as nausea/vomiting or photophobia and phonophobia, is required. Different migraine phenotypes are identified according to the presence of aura (if the aura is present patients are diagnosed as having migraine with aura, if not as having migraine without aura), and according to the headache frequency (when less than 15 monthly headache days occur, migraine is called episodic (EM), when 15 or more monthly headache days occur,

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migraine is called chronic (CM)) (Olesen, 2018).

Even if the International Classification of Headache Disorders allows clinicians and researchers to correctly identify migraine patients (Olesen, 2018), its limitation is to rely only on symptoms and not on signs of migraine. The utilization of biomarkers able to assess signs of disease could help identify distinct subtypes within the same medical condition (Baron et al., 2017; Sachau et al., 2022). This could, in turn, help identify responders and non-responders to different treatments, and allow the prescription of a more personalized treatment approach (Edwards et al., 2016). Thus, to better identify different migraine phenotypes and guide migraine treatment, biomarkers able to assess signs of migraine should be included in the evaluation of these patients. Among various biomarkers, increased pain sensitivity (IPS) (Fernández-de-las-Peñas et al., 2022; Nahman-Averbuch et al., 2018) and cervical musculoskeletal impairments (CMIs) (Liang et al., 2019; Szikszay et al., 2019) have been described in the past. This paper aims to provide an overview of recent findings on quantitative biomarkers for IPS and CMIs in migraine patients. The research questions that are addressed are: 1) can IPS and CMIs be considered quantitative biomarkers for phenotyping migraine patients ? and 2) can IPS and CMIs identify distinct subtypes of migraine patients ?

2. Increased pain sensitivity as psycophysical sign of migraine

2.1. Pain sensitivity assessments

IPS can be experimentally detected with Quantitative Sensory Testing (QST) (Arendt-Nielsen and Yarnitsky, 2009). One QST modality is to assess pain thresholds to a pressure or pinprick mechanical stimulus: the lower the mechanical pain threshold the higher the pain sensitivity. Another QST modality is to assess increased temporal summation of pain using the wind-up ratio (WUR). The increase of pain from a single painful stimulus to the pain after a series of 10 stimuli of the same force, and positive WUR is a sign of increased temporal summation (increased pain sensitivity) (Arendt-Nielsen and Yarnitsky, 2009). IPS can be assessed in different receptive fields. According to QST modalities and area tested, IPS could be considered an indirect sign of enhanced sensitization of primary neurons in the periphery, second-order spinal neurons, and third/fourth-order neurons in cortical and subcortical brain areas (Burstein, 2001). As different QST modalities are designed to test distinct peripheral nerve afferents (Walk et al., 2009), if a reduced pain threshold for one QST modality restricted to one specific area is found, IPS could be considered an indirect sign of enhanced sensitization of primary neurons in the periphery. On the other hand, when reduced pain thresholds for multiple stimuli and areas are present, IPS could be considered an indirect sign of enhanced sensitization of second-order spinal neurons, and third/fourth-order neurons in cortical and subcortical brain areas (Ji et al., 2003). On the other hand, both presynaptic and postsynaptic sensitization mechanisms could facilitate the temporal summation of pain (Herrero et al., 2000).

2.2. Increased pain sensitivity in migraine

For IPS to be considered a psychophysical sign of migraine, the following requirement needs to be fulfilled: IPS should indirectly identify cortical/subcortical alterations that characterize migraine cycle; IPS should be correlated with clinical characteristics of migraine.

In a recent paper, our research group assessed WUR, static pressure pain thresholds, and pinprick pain thresholds over the trigeminal area, static and dynamic pressure pain thresholds over the cervical area, static and dynamic pressure pain thresholds over the hand, and static pressure pain thresholds, over the leg in EM patients during the four phases of the migraine cycle and compared these results with those of healthy subjects (Di Antonio et al., 2022a; Finocchi et al., 2022). Our results support that, in all phases of the migraine cycle, EM had lower pinprick, static, and dynamic pressure pain thresholds over trigeminal and cervical areas (Di Antonio et al., 2022a; Scholten-Peeters et al., 2020; Strupf et al., 2019). As trigeminal and cervical input converges in the trigeminocervical complex (Bartsch and Goadsby, 2003), the reduced pain thresholds for multiple stimuli in the trigeminal and cervical receptive fields could be seen as an indirect sign of the increased sensitization of second-order neurons in the trigeminocervical complex that characterizes migraine (Sohn et al., 2016). Facilitation of the temporal summation of pain was observed only in the ictal phase, suggesting that the sensitization of the trigeminocervical complex is further increased and reaches its peak during this phase (Burstein et al., 2000; Katsarava et al., 2002; Kaube et al., 2002).

Moreover, in our recent paper, we found that lower pinprick and static pressure pain thresholds over the hand were present in the preictal phase (Di Antonio et al., 2022a; Sand et al., 2008). The reduced pain thresholds for multiple stimuli in the trigeminal, cervical, and hand receptive fields could be seen as an indirect sign of spreading sensitization in the cervical spinal cord or enhanced sensitization of third/-fourth order neurons in cortical and subcortical brain areas. Spreading in sensitization mechanisms in the cervical spinal cord has never been studied in migraine patients, but neurophysiological evidence suggests that enhanced sensitization of third/fourth-order neurons in cortical and subcortical brain areas begins in the preictal phase, before the headache occurs (Schulte et al., 2020; Schulte & May 2016). Finally, we found that IPS gradually increased approaching the migraine attack (Di Antonio et al., 2022a; Sand et al., 2008; Schwedt et al., 2015), showing the cyclic pattern that has been observed for increased activation of cortical/subcortical brain areas (Coppola et al., 2014; Schulte et al., 2020; Schulte & May 2016; Stankewitz et al., 2011). However, the precise duration of each migraine phase according to when modification in pain sensitivity occurs needs to be further studied. Preliminary evidence suggested that the preictal and postictal phases can last 24 h when considering changes in pain sensitivity (Sand et al., 2008; Uglem et al., 2017). This duration seems to vary between migraine patients according to migraine frequency. In a recent study, our research group showed that cyclic changes in pain sensitivity vary according to the headache frequency: the higher the frequency, the more rapid and abrupt the increase in sensitization mechanisms approaching the ictal phase (Di Antonio et al., 2023b).

These results suggest that IPS can indirectly identify neurophysiological cortical/subcortical alteration that characterize the migraine cycle.

Moreover, IPS correlated with clinical characteristics of migraine. During the ictal phase, we found that a higher headache frequency and worse disability are correlated with increased WUR (Di Antonio et al., 2022a; Di Antonio et al., 2023b), suggesting that worse migraine burden is correlated with increased ictal sensitization of the trigeminocervical complex. On the other hand, we found that outside the ictal phase, increased widespread sensitization correlated with higher drugs usage and longer disease duration (Di Antonio et al., 2022a), suggesting that sensitization of higher cortical/subcortical areas can occur interictally in a subgroup of migraine patients with longer disease duration and higher drugs usage (Ferna'ndez-De-Las-Peñas et al., 2009; Perrotta et al., 2010; Sand et al., 2008).

Finally, IPS over the cervical spine seems to correlate with the presence of neck pain, one of the most common symptoms present in migraine patients (Ashina et al., 2015; Calhoun et al., 2010). When IPS over the cervical area was assessed controlling for the presence of neck pain, no differences were observed between migraine patients in the interictal or preictal phases and healthy controls. On the other hand, differences in pain sensitivity were observed between ictal migraine patients and healthy controls (Di Antonio et al., 2022b). Thus, enhanced cervical sensitization seems to be present independent of neck pain in the ictal, but not in other migraine phases. From our results, interictally and preictally IPS over the cervical spine seems to be related to the presence of neck pain (Di Antonio et al., 2022b; Di Antonio et al., 2022a). Furthermore, enhanced IPS over the cervical spine is correlated

with a higher burden due to neck pain (Di Antonio et al., 2022b).

Taken together, the results of our studies suggested that IPS can be considered a psychophysical sign of migraine.

2.2.1. Clinical implication

- IPS should be considered a psychophysical sign of migraine and should be assessed in clinical and research settings.
- When assessing IPS, attention to the phase of migraine at the time of evaluation is needed. Clinicians and researchers should consider the timing of both the previous and following headache attack to determine the phase within the migraine cycle.

2.2.2. Future research directions

- Future within-subject longitudinal studies should identify the precise duration of each migraine phase according to when modification in pain sensitivity occurs and if this duration is affected by the headache frequency.

3. Cervical muscolosheletal impairment as psycophysical sign of migraine

3.1. Cervical musculoskeletal impairments assessment

CMIs assessment can be divided into tests aimed to assess the functionality of the cervical spine (cervical musculoskeletal dysfunctions), referred pain from the head/neck region, and IPS over the cervical area (Di Antonio et al., 2022b; G. Jull and Hall, 2018; Luedtke et al., 2016). As IPS over the cervical area can be detected by assessing increased local pain sensitivity to manual palpation or with QST, cervical IPS was discussed in the previous chapter.

3.1.1. Cervical musculoskeletal dysfunctions

The functionality of the cervical spine can be investigated by assessing active mobility, passive mobility, and motor function. The Active Range of Motion (ARoM) of the cervical spine is usually assessed in sitting and can be recorded in degrees of movement with the Cervical Range of Motion Device (CROM) (Fletcher and Bandy, 2008).

Passive mobility of the cervical spine can be assessed with the Flexion Rotation Test (FRT). The patient lies in a supine position, and the therapist passively maximally flexed the cervical spine. In this flexed position, the head is passively rotated as far as possible within comfortable limits to the left and then to the right. The passive range of motion to the left and to the right can be recorded in degrees of movement with the CROM device (Hall et al., 2008, 2010).

Muscle function of the deep cervical flexor muscles can be assessed with the Cranio-Cervical Flexion Test (CCFT). The patient lies in a supine position with the neck in a neutral position. A pressure biofeedback Unit of 20–30 mmHg is placed uninflated behind the neck, adjacent to the occiput, and then is inflated to a baseline pressure of 20 mm Hg. Then, the subject performs cranio-cervical flexion in five incremental stages (22 mmHg–30 mmHg, one stage every 2 mmHg), and the mmHg value that is held for 10 s without compensation is recorded as the Activation Pressure Score (APS) (Jull et al., 2008).

3.1.2. Referred pain

The presence of headache reproduction during sustained Posterior-Anterior (PA) pressure over C-0/C-1 and C-2/C-3 vertebral segments can be assessed. The therapist applies PA pressure over the vertebral segment, which is considered positive if the pressure produced the typical migraine pain. The total number of positive vertebral segments is usually calculated (0–4) (Luedtke et al., 2018; Watson and Drummond, 2012).

The presence of headache reproduction during stimulation of Myofascial Trigger Points (MTrPs) can also be assessed. MTrPs are defined as hypersensitive spots in a taut band in the muscle belly that resulted in referred pain. MTrPs can be considered active (referred pain is recognized by the patient as the usual headache) or latent (referred pain is not recognized by the patient as the usual headache (Fernández-de-las-Peñas & Dommerholt, 2018). In migraine patients, the presence of MTrPs is usually assessed bilaterally in the temporal muscles, masseter muscle, sternocleidomastoid muscle, suboccipital muscles, splenius muscles, and trapezius muscle. The total number of active and latent trigger points is recorded (Fernández-De-Las-Peñas et al., 2006; Mayoral del Moral et al., 2018).

3.2. Cervical musculoskeletal impairment in migraine

Although CMIs have been widely studied in migraine patients, due to the high prevalence of neck pain (Ashina et al., 2015; Calhoun et al., 2010), the mechanisms underly the presence of CMIs in the migraine population are still unclear. On the one hand, CMIs could be considered a psychophysical sign of migraine being present independent of neck pain (Jull and Hall, 2018). On the other hand, CMIs could be considered comorbidity, a sign of concomitant neck pain, and a musculoskeletal-related headache that could be misdiagnosed as migraine (Blumenfeld and Siavoshi, 2018).

Thus, for CMIs to be considered a psychophysical sign of migraine, the following requirement needs to be fulfilled: CMIs should be present during the migraine cycle independently of neck pain and should correlate with cortical/subcortical alterations that characterize the migraine cycle; CMIs should be correlated with clinical characteristics of migraine.

In a recent paper, our research group assessed cervical ARoM, FRT, APS, headache reproduction following PA over C1/C2 vertebral segments, and MTrPs in head/neck muscles in EM patients during the four phases of the migraine cycle. These results were compared with those of healthy subjects controlling for the presence of neck pain (Di Antonio et al., 2022b).

In all phases of the migraine cycle, EM showed a reduction in FRT, APS, and higher myofascial and articular areas that reproduced headaches independently of neck pain. On the other hand, a reduction in ARoM was present only during the ictal phase. Our interpretation of these results was that the migraine attack could act as a trigger to affect cervical mechanical behavior and impair cervical ARoM (Arendt-Nielsen et al., 2008; Nijs et al., 2012). This transient impaired cervical musculoskeletal function during the ictal phase could be due to two mechanisms. On the one hand, as the migraine attack is aggravated by routine physical activity (Olesen, 2018), cervical ARoM could enhance headache, leading patients to avoid this movement. On the other hand, the acute pain and the enhanced sensitization that characterized the migraine attack could lead to neurophysiological alteration of the cortical-motor pathway (Cortese et al., 2017; Cosentino et al., 2014), leading to an impairment of cervical mechanical behavior. Even if ARoM impairment was transitory and restored to baseline level after the headache attack, this change in mechanical behavior could cause long-term mechanical consequences, such as increased muscle stiffness and reduced movement variability (Hodges and Tucker, 2011). Thus, the reduction in FRT and APS present outside the ictal phase could be considered a long-term consequence of ictal changes in mechanical behaviors. Interestingly, outside the headache attack, a reduction in ARoM was correlated with higher disability due to neck pain and enhanced widespread sensitization. These results suggest that the transitory reduction in ARoM could become a permanent impairment in a subgroup of migraine patients with worse neck-related disability and enhanced sensitization (Di Antonio et al., 2022b). Finally, a higher number of myofascial and articular areas correlated with worse headache characteristics, suggesting the presence of referred pain could be a biomarker able to identify a migraine subgroup worse affected by the disease (Di Antonio et al., 2022b).

Taken together our findings suggest that CMIs are present during the

migraine cycle independent of neck pain, correlate with cortical/subcortical alterations that characterized the migraine cycle, and with clinical characteristics of migraine. Thus, CMIs can be considered psychophysical signs of migraine.

3.2.1. Clinical implication

- CMIs should be considered a psychophysical sign of migraine and should be assessed in clinical and research setting independent of the presence of neck pain.
- When assessing CMIs, particular attention should be paid to the phase of migraine cycle during which CMIs evaluation is performed.

3.2.2. Future research directions

- The link existing between a migraine attack and cervical mechanical behaviour should be further investigated. Future within-subjects studies should assess the effect of a migraine attack on cervical active and passive mobility or muscle function (both clinical migraine attacks and experimentally induced migraine attacks can be used).

4. Identification of different migraine phenotypes according to clinical and psychophysical characteristics

Currently, migraine patients are subgrouped according to two clinical biomarkers, headache frequency and presence of aura (Olesen, 2018). As IPS and CMIs can be considered psychophysical biomarkers relevant to migraine pathophysiology, in a recent paper our group suggested that migraine patients can be subgrouped according to clinical and psychophysical characteristics that can be used in a clinical setting (Di Antonio et al., 2023a). EM and CM patients were assessed in the ictal/pericrtal phase and interictal phase, and distinct migraine subgroups were identified using simple clinical and psychophysical bed-side tools: headache frequency and disability, cervical ARoM, pressure pain threshold over temporalis, C1 and C4 vertebral segments, hand, and leg. We found two different clusters in the ictal/pericrtal phase, with one group showing No Psychophysical Impairment (NPI) (Cluster-1.1, NPI, 19% of the population) and one showing Increased Pain Sensitivity (IPS) and Cervical Musculoskeletal Dysfunctions (CMD), as well as higher disability (Cluster-1.2, IPS–CMD, 81%). In the interictal phase, three distinct clusters were identified, with one group showing no psychophysical impairment (Cluster-2.1, NPI, 18%), one increased pain sensitivity (Cluster-2.2, IPS, 45%), and one increased pain sensitivity and cervical musculoskeletal dysfunctions, as well as higher headache frequency, disability, and longer duration of the disease (Cluster-2.3, IPS-CMD, 37%). In a secondary analysis, in data yet to be published, we investigated the clinical validity of these distinct migraine clusters. We assessed differences in clinical characteristics through multiple questionnaires and quantitative differences in somatosensory function and cervical musculoskeletal impairments using comprehensive QST and cervical musculoskeletal assessment. We also compared the results with healthy controls matched for sex and age. The results confirmed that the distinct migraine subgroups identified using simple clinical and psychophysical bed-side tools were differently affected by the disease and can be considered distinct migraine phenotypes.

When migraine patients were assessed during the ictal/pericrtal phase, Cluster-1.2 (IPS-CMD) showed worse clinical and psychophysical characteristics assessed through multiple questionnaires, comprehensive QST, and cervical musculoskeletal assessment compared to Cluster-1.1 (NPI). Compared to healthy subjects, Cluster-1.2 (IPS-CMD) showed IPS and worse CMIs, while Cluster-1.1 (NPI) reduced pain sensitivity (hypoalgesia) and subtle CMIs, as reduced APS, FRT, and increased myofascial and articular areas that reproduced headache (Table 1).

When migraine patients were assessed interictally, Cluster-2.2 (IPS) showed worse clinical characteristics and higher pain sensitivity, while Cluster-2.3 (IPS-CMD) worse clinical and psychophysical characteristics assessed through multiple questionnaires, comprehensive QST, and cervical musculoskeletal assessment compared Cluster-2.1 (NPI). Cluster-2.3 IPS-CMD had worse CMIs, and clinical characteristics also compared to Cluster-2.2 (IPS). Compared to healthy subjects, Cluster-2.3 (IPS-CMD) showed IPS and worse CMIs; Cluster-2.2 (IPS) had IPS and subtle CMIs (reduced APS, FRT, and increased myofascial area that reproduced referred pain); Cluster-2.1 (NPI) had reduced APS, FRT,

Table 1
Difference in general, clinical, and psychophysical characteristics across M patients.

a. ictal/pericrtal M (Cohort 1)

	Cluster 1.2 IPS-CMD vs Cluster 1.1 NPI
Years lived with headache	=
Headache frequency	=
Headache intensity	↑
Headache duration	=
Use of drugs	=
Prevalence of neck pain	↑
Questionnaires	
HDI-P*	=
HDI-E*	↑↑
NDI*	↑↑
NDI-physical*	↑↑
NDI-mental*	↑
SF-36, physical #	↓↓
SF-36 mental #	=
CSI*	↑↑
HADS-A*	↑↑
HADS-D*	↑↑

b. interictal M (Cohort 2)

	Cluster 2.3 IPS-CMD vs Cluster 2.2 IPS	Cluster 2.3 IPS-CMD vs Cluster 2.1 NPI	Cluster 2.2 IPS vs Cluster 2.1 NPI
Years lived with headache	↑↑	=	=
Headache frequency	↑↑	=	=
Headache intensity	=	=	=
Headache duration	=	=	=
Use of drugs	↑↑	=	=
Prevalence of neck pain	=	=	=
Questionnaires			
HDI-P*	↑↑	=	=
HDI-E*	↑↑↑	↑	=
NDI*	=	=	=
NDI-physical*	=	↑↑	=
NDI-mental*	=	=	=
SF-36, physical #	=	=	=
SF-36 mental #	=	=	=
CSI*	=	↑	=
HADS-A*	=	=	=
HADS-D*	↑	=	=

CSI: Central sensitization inventory; HADS-A: Hospital Anxiety and Depression Scale Anxiety; HADS-D: Hospital Anxiety and Depression Scale Depression; HDI-E: Headache disability index emotional; HDI-P: Headache disability index physical; IPS-CMD: increased pain sensitivity and cervical musculoskeletal impairment IPS: increased pain sensitivity; NDI: Neck disability index; NPI: no psychophysical impairments; NPRS: numeric pain rating scale; SF-36: Medical Outcomes Study Short Form 36.
* Higher the results, higher the disability.
# Lower the results, lower the disability.
=no differences ($p > 0.05$).
↑ = higher ($p < 0.05$); ↓ = lower ($p < 0.05$).
↑↑ = higher ($p < 0.01$); ↓↓ = lower ($p < 0.01$).
↑↑↑ = higher ($p < 0.001$); ↓↓↓ = lower ($p < 0.001$).

increased myofascial area that reproduced referred pain, and reduced pain sensitivity (Table 2).

Our results suggested that a subgroup of patients, accounting for 20% of the total migraine population, showed reduced pain sensitivity and signs of subtle CMIs. The remaining 80% of migraine patients (Cluster-1.2 IPS-CMD), who are worse affected by the disease, showed IPS and worse CMIs during the headache attack. In those patients, IPS persisted also following the headache phase. On the other hand, reduction in ARoM was a transitory phenomenon in 45% of the sample who had a reduction in CMIs after the headache attack (Cluster-2.2 IPS). In the remaining 35% of the sample (Cluster-2.3 IPS-CMD), reduction in ARoM became a permanent impairment. As Cluster-2.3 (IPS-CMD) showed longer disease duration and were worse affected by the disease than Cluster-2.2 (IPS), our hypothesis is that these two subgroups represent the two extremities in terms of disease progression of a single group (Cluster-1.2 IPS-CMD). Cluster-2.2 (IPS) represents the lower extremity, while Cluster-2.3 (IPS-CMD) the higher extremity (Fig. 1a and b). However, this hypothesis needs to be confirmed by longitudinal studies that assess the same patients across different migraine phases.

Interestingly, even if in different proportions, all subgroups had migraine patients with neck pain. These results suggested the existence of different phenotypes of neck pain in migraine patients driven by distinct mechanisms. In migraine patients without psychophysical impairments (Cluster-1.1 NPI ictal/peritcal, Cluster-2.1 NPI interictal), where only CMIs were present, neck pain is likely to be driven by peripheral mechanisms. On the other hand, in migraine patients with both

Table 2
Difference in Cervical musculoskeletal impairments and Quantitative sensory testing across M patients and healthy controls.

a. Ictal/peritcal M (Cohort 1)

	Cluster 1.2 IPS-CMD vs Controls	Cluster 1.2 IPS-CMD vs Cluster 1.1 NPI	Cluster 1.1 NPI vs Controls
Cervical musculoskeletal impairments			
ARoM Flexion	↓↓↓	↓↓↓	=
ARoM Extension	↓↓↓	=	=
ARoM Right lateral flexion	↓↓	↓↓↓	=
ARoM Left lateral flexion	↓	↓	=
ARoM Right rotation	↓↓	=	=
ARoM Left rotation	↓↓	=	=
Flexion rotation test	↓↓↓	=	=
Cranio-cervical flexion test (APS)	↓↓↓	=	↓↓↓
Total MTrPs	↑↑↑	↑	↑↑
Cervical vertebral segments positive to PA pressure	↑↑↑	↑	↑↑↑
Quantitative sensory testing			
WUR temporalis	↑	=	↑
MPT temporalis	↓↓↓	=	=
sPPT temporalis	↓↓↓	↓↓↓	↑
sPPT upper cervical spine	↓↓↓	↓↓↓	↑
sPPT lower cervical spine	↓↓↓	↓↓↓	=
dPPT cervical spine	↓↓↓	↓↓↓	=
sPPT second metacarpophalangeal joint	↓↓↓	↓↓↓	=
MPT thenar eminence	↓↓↓	=	=
sPPT tibialis muscle	↓↓↓	↓↓↓	↑↑

b. Interictal M (Cohort 2)

	Cluster 2.3 IPS-CMD vs Controls	Cluster 2.3 IPS-CMD vs Cluster 2.2 IPS	Cluster 2.3 IPS-CMD vs Cluster 2.1 NPI	Cluster 2.2 IPS vs Controls	Cluster 2.2 IPS vs Cluster 2.1 NPI	Cluster 2.1 NPS vs Controls
Cervical musculoskeletal impairments						
ARoM Flexion	↓↓↓	↓↓↓	↓↓	=	=	=
ARoM Extension	↓↓↓	↓↓	=	=	=	=
ARoM Right lateral flexion	↓↓↓	↓↓↓	↓↓↓	=	=	=
ARoM Left lateral flexion	↓↓↓	↓↓↓	↓↓↓	=	=	=
ARoM Right rotation	↓↓↓	↓↓↓	↓↓↓	=	=	=
ARoM Left rotation	↓↓↓	↓↓↓	↓	=	=	=
Flexion rotation test	↓↓↓	↓↓↓	↓	↓↓	=	↓↓
Cranio-cervical flexion test (APS)	↓↓↓	↓↓↓	↓↓↓	↓↓↓	=	↓↓
Total MTrPs	↑↑↑	=	=	↑↑↑	=	↑↑
Cervical vertebral segments positive to PA pressure	↑↑↑	=	=	↑↑↑	=	↑↑↑
Quantitative sensory testing						
WUR temporalis	=	=	=	=	=	=
MPT temporalis	↓	=	=	↓↓	=	↓↓
sPPT temporalis	↓↓	=	↓↓↓	↓↓↓	↓↓↓	=
sPPT upper cervical spine	↓↓	=	↓↓↓	↓↓↓	↓↓↓	=
sPPT lower cervical spine	↓↓	=	↓↓	↓↓↓	↓↓↓	=
dPPT cervical spine	↓↓↓	=	=	↓↓↓	↓	=
sPPT second metacarpophalangeal joint	↓↓	=	↓↓↓	↓↓	↓↓↓	↑
MPT thenar eminence	↓↓	=	=	↓	=	=
sPPT tibialis muscle	=	=	↓↓↓	=	↓↓↓	↑↑

APS: activation pressure score; AROM: active range of motion; dPPT: dynamic pressure pain threshold FRT: Flexion rotation test; MCP: metacarpophalangeal joint; MPT: Mechanical pain threshold; MTrPs: Myofascial Trigger Points; PAI: posterior-anterior; sPPT: Static pressure pain threshold; WUR: wind-up ratio.
=no differences ($p > 0.05$).
↑ = higher ($p < 0.05$); ↓ = lower ($p < 0.05$).
↑↑ = higher ($p < 0.01$); ↓↓ = lower ($p < 0.01$).
↑↑↑ = higher ($p < 0.001$); ↓↓↓ = lower ($p < 0.001$).

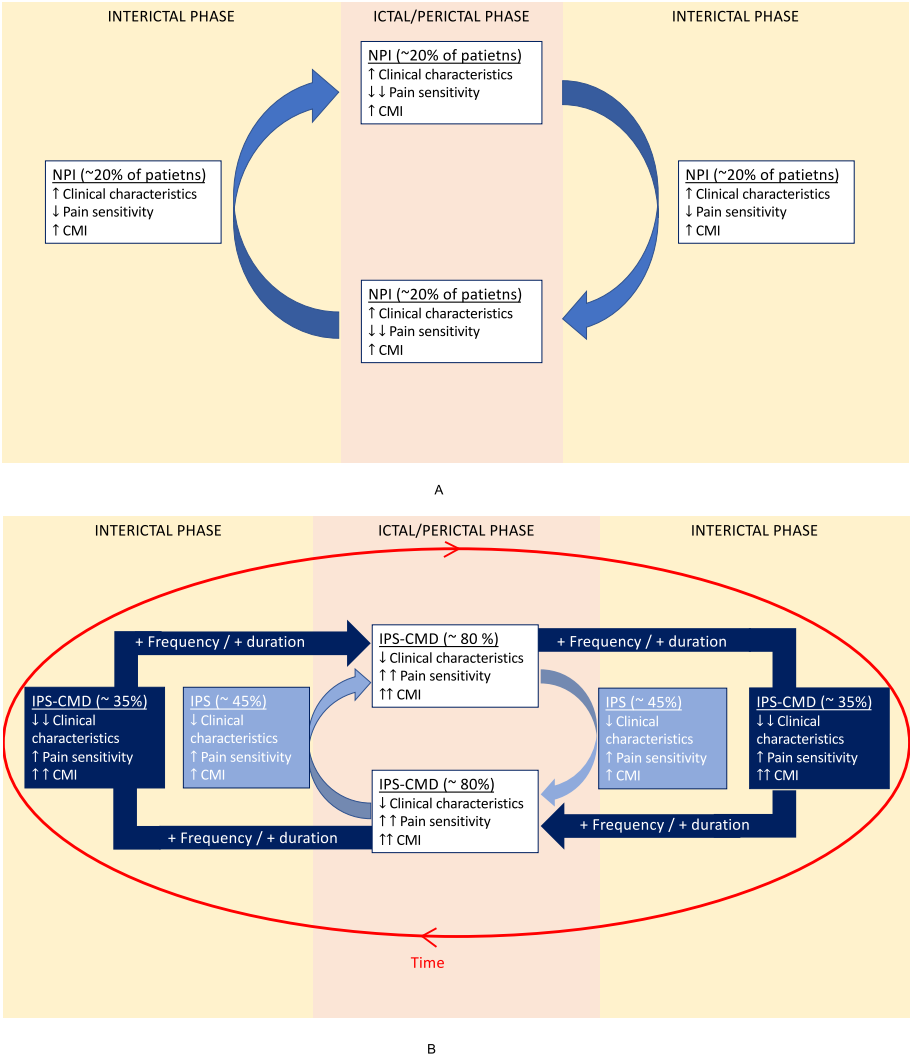

Fig. 1. a Migraine patient without psychophysical impairments across the migraine cycle
b Migraine patients with psychophysical impairments across the migraine cycle
CMI cervical musculoskeletal impairment; IPS: increased pain sensitivity; IPS-CMD: increased pain sensitivity – cervical musculoskeletal dysfunctions; NPI: no psychophysical impairment.

IPS and CMIs, both peripheral and central sensitization mechanisms could exist. These results outline the necessity to combine the investigations of neck pain as a symptom with a physical examination aimed to assess CMIs and IPS. In this way, according to CMIs and IPS results, the driver mechanisms underlining neck pain can be identified.

4.1. Clinical implication

According to our findings, the assessment of migraine patients should include clinical and psychophysical characteristics and should be aimed at identifying different migraine phenotypes.

This could help to:

Identify responders and non-responders to a given pharmacological treatment approach and help in developing a more personalized treatment approach.

- Migraine patients with IPS seem to have a worse response to treatment whose main effect is in the peripheral nervous system (Ashina et al., 2023; Peng et al., 2022; Schwarz et al., 2021)
- Migraine patients with IPS seem to have a better response to treatment whose main effect is in the central nervous system when only EM patients were considered (Kisler et al., 2019), and a worse response when only CM patients were considered (Pan et al., 2022)
- Migraine patients with worse CMIs seem to have a worse response to treatment which main effect is in the peripheral nervous system (Schwarz et al., 2021)

Including other non-pharmacological treatment approaches aimed to reduce IPS and CMIs in those patients with these impairments.

Treatment aimed to reduce IPS:

- Physiotherapy treatment modalities such as manual therapy techniques can reduce pain sensitivity (Coronado et al., 2012; Falsiroli Maistrello et al., 2019; Geri et al., 2022; Maistrello et al., 2018; Rist et al., 2019; Rodríguez-Sanz et al., 2020; Watson and Drummond, 2014) by initiating a cascade of neurophysiological responses from the nervous system with a pain modulatory effect (Bialosky et al., 2009).
- Dynamic resistance or isometric contraction exercises in the cervical spine or aerobic exercise (i.e., bicycling, running) can reduce pain sensitivity in migraine patients (Lemmens et al., 2019; Sluka et al., 2018; Vaegter and Jones, 2020; Woldeamanuel and Oliveira, 2022).
- To enhance its clinical effect and further reduced pain sensitivity, physiotherapy intervention should be coupled with pain neuroscience education (Dolphens et al., 2014; Kindelan-Calvo et al., 2014; Meise et al., 2023; Minen et al., 2021)

Treatment aimed to reduce CMIs:

- Physiotherapy intervention, such as manual therapy techniques and specific exercise, can also restore CMIs (Blomgren et al., 2018; Buyukturan et al., 2018; Cho et al., 2017; Eckner et al., 2018; Jull et al., 2009; Sheikhhoseini et al., 2018)
- To avoid that ictal transitory reduction in cervical ARoM could become permanent, clinicians should include preventive treatments aimed to maintain ARoM also in those patients without interictal/pericTal ARoM impairments.

4.2. Future research directions

- The presence of distinct migraine phenotypes in different migraine phases should be further investigated, and our results should be replicated by independent research groups.
- Future studies assessing the presence of distinct migraine phenotypes should consider including bed-side tools with cut-off values that can be used to predict the inclusion in a particular subgroup (Sachau et al., 2022).
- Future studies should assess if being included in a particular migraine subgroup can predict the response to different treatment modalities and help to develop a more individualized treatment approach.

Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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