

RESEARCH SUBMISSIONS

Skin wetness sensitivity across body sites commonly affected by pain in people with migraine

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Abstract

Objective: The objective of this study was to evaluate skin wetness perception and thermal sensitivity in people with migraine and similar healthy controls.

Background: Environmental triggers, such as cold and humidity, are known triggers for pain in people with migraine. Sensory inputs might be implicated in such heightened responses to cold-humid environments, such that a migraine-induced hypersensitivity to cold wetness could be present in people with migraine. However, we lack empirical evidence on skin thermal and wetness sensitivity across skin sites commonly associated with reported pain in migraine, such as the forehead.

Methods: This prospective cross-sectional observational study, conducted in a university hospital setting, evaluated skin wetness perceptions and thermal sensations to wet non-noxious warm-wet, neutral-wet, and cold-wet stimuli applied to the forehead, the posterior neck, and the index finger pad of 12 patients with migraine (mean and standard deviation for age 44.5 ± 13.2 years, 7/12 [58%] women) and 36 healthy controls (mean and standard deviation for age 39.4 ± 14.6 years, 18/36 [50%] women).

Results: On the forehead, people with migraine reported a significantly higher wetness perception than healthy controls across all thermal stimulus (15.1 mm, 95% confidence interval [CI]: 1.8 to 28.5, $p = 0.027$, corresponding to ~ 15% difference), whereas no significant differences were found on the posterior neck nor on the index finger pad. We found no differences among groups in overall thermal sensations (-8.3 mm, 95% CI: -24.0 to 7.3 , $p = 0.291$; -7.8 mm, 95% CI: -25.3 to 9.7 , $p = 0.375$; and 12.4 mm, 95% CI: -4.0 to 28.9 , $p = 0.133$; forehead, posterior neck, and index finger, respectively).

Conclusion: These findings indicate that people with migraine have a heightened sensitivity to skin wetness on the forehead area only, which is where pain attacks occur. Future studies should further explore the underlying mechanisms (e.g., TRPM8-mediated cold-wet allodynia) that lead to greater perception of wetness in people with migraine to better understand the role of environmental triggers in migraine.

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; ICHD, International Classification of Headache Disorders; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; TRPM8, transient receptor potential melastatin-8; Tsk, skin temperature; VAS, visual analog scale.

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KEYWORDS

headache, humidity, hygrosensation, pain, sensory testing

INTRODUCTION

Migraine represents one of the most common neurological conditions worldwide, and it is associated with significant morbidity and economic impact.¹ Many patients affected by migraine report a wide set of environmental triggers that contribute to the onset of an attack, including changes in weather (e.g., rain or snowstorms), exposure to bright lights, high altitude, smoke, and certain odors.^{2,3} Among environmental triggers, the weather is commonly reported to be a major contributor to migraine.²⁻⁸ Specifically, cold temperatures, high humidity, bright sunshine, and low as well as rapidly changing barometric pressure, are all weather-related parameters that have been reported to affect patients with migraine. Cold can induce intracerebral vasoconstriction,⁹ which might trigger migraine, and increased humidity can further disrupt thermal transfer. Interestingly, high humidity levels have been associated with headache in 69% of patients,¹⁰ leading to the common assumption that this weather-related parameter is an important contributing factor to migraine.^{11,12} Yet, the underlying mechanisms of action of high humidity as a trigger of a migraine attack are yet to be elucidated.

The pathophysiology of migraine has been linked to altered sensory processing.¹³ As an example, people with migraine have been shown to have cutaneous allodynia and hypersensitivity in response to noxious and non-noxious mechanical and thermal stimuli when compared with healthy controls.¹⁴⁻¹⁷ These findings could provide evidence on the potential mechanisms underlying the impact of changes in ambient temperature in triggering migraine. Specifically, it would be reasonable to hypothesize that a migraine-induced sensitization of nociceptive pathways and related decrease in thermal thresholds for discomfort and pain may result in a non-noxious change in skin temperature to be perceived as painful,¹⁸ similar to what has been hypothesized for the hypersensitivity to light.¹⁹ Applying this conceptual framework to the role of high humidity in triggering migraine, it could be proposed that a heightened skin sensitivity to humidity and wetness may underlie people with migraine's susceptibility to high ambient humidity (Figure 1). However, to the authors' knowledge, whether skin wetness sensitivity is altered in people with migraine compared with healthy controls has not been investigated empirically.

Humans are very sensitive to skin wetness and people can detect as little as 0.0002 ml/mm² of moisture on their finger pad.²⁰ Increases in skin wetness are also positively correlated with the onset of thermal discomfort.²¹ Yet, there is no evidence that our skin possesses a hygroreceptor.²² Over the past 9 years, it has been shown that healthy young adults perceive physical wetness on their skin by using cooling-related thermosensory cues induced by conductive and evaporative heat transfer in the presence of moisture on the

skin, in combination with tactile and mechanosensory cues arising from the movement of moisture across the skin.²³ Cooling cues are key for this perception, to the extent that an illusion of skin wetness can be induced in blindfolded young adults by cooling their skin with a dry-cold stimulus inducing skin cooling at a rate equivalent to that resulting from actual moisture evaporation.²⁴ Neurophysiologically, activity from cutaneous A-type afferent nerve fibers transducing cold and touch sensations is key for young adults' ability to perceive skin wetness.²⁵ Furthermore, it has been recently discovered that the cold-sensing cation channel TRPM8, expressed on A-type cold-sensing thermoreceptors, plays the dual role of cold and wetness sensor in human skin.²⁶

The literature above helps explain how, in the absence of a skin hygroreceptor, healthy young adults optimally integrate thermal and tactile cues to perceive wetness on their skin. Importantly, these physiological mechanisms could support the development of testable hypotheses for the role of humidity in migraine. Specifically, because people with migraine may have heightened thermal-tactile sensing, it would be reasonable to hypothesize that their wetness sensing may also be upregulated. Cold humid environments result in rapid drops in skin temperature as well as in an increase in condensation of moisture on surfaces (including the skin), which may in turn trigger a sensation of skin wetness, as well as colder sensations than those triggered by cold dry environments. Hence, should people with migraine perceive a greater level of skin wetness for the same moisture level, this may in turn result in greater discomfort for the same humid environment. Furthermore, because the cold and wetness sensing TRPM8 receptor is also implicated in cold allodynia,²⁷⁻²⁹ it cannot be excluded that a migraine-induced sensitization of TRPM8 may result not only in cold, but also wet-allodynia.

The aim of this investigation was to assess differences in skin wetness and thermal sensitivity between people with episodic migraine and healthy similar controls, on the principal painful body area (the forehead), on a body area which might be painful in some cases (the posterior neck), and on a neutral body area (the index finger pad). We hypothesized that people with migraine will have a greater perception of wetness for the same wet stimulus than healthy controls, and that this would be secondary to a greater cold sensitivity.

METHODS

Patients diagnosed with low-frequency (<4 severe/disabling migraine attacks/month) episodic migraine without aura attending the Headache Center of the University Hospital of Trieste were enrolled in this prospective cross-sectional observational study from April 1, 2021, to June 30, 2021. All the participants met the International

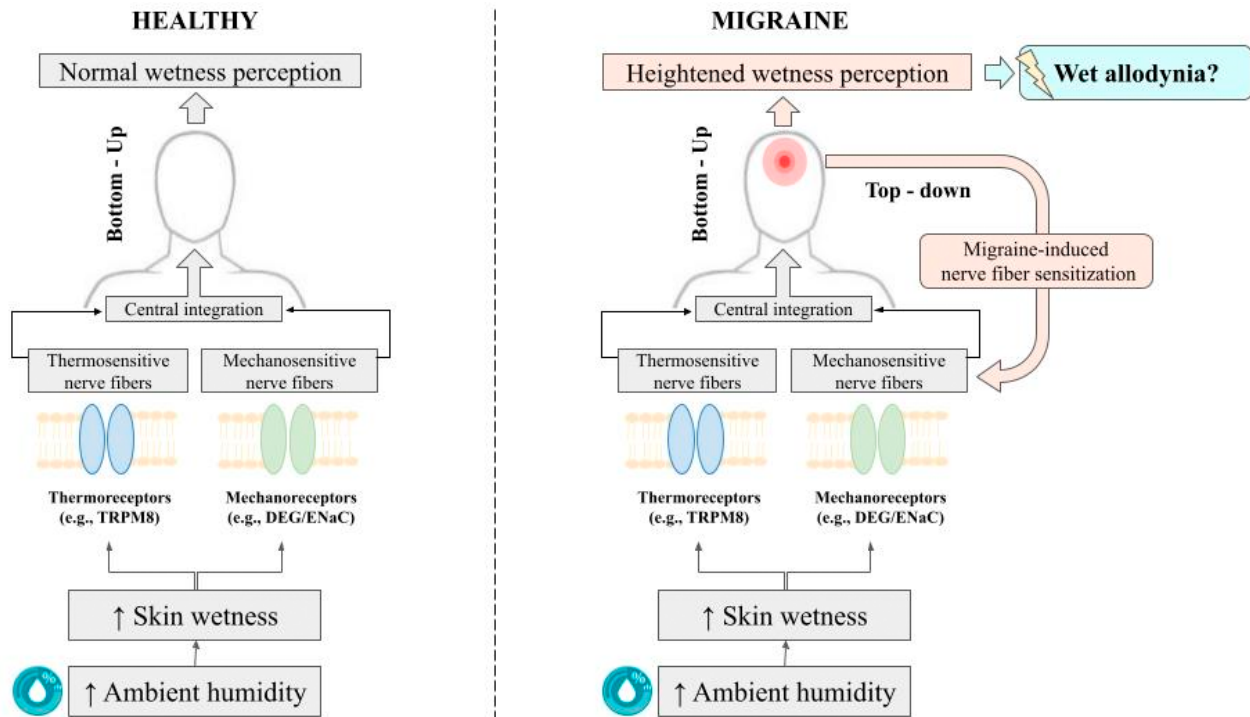


FIGURE 1 The diagram presents the physiological hypothesis of increased wetness perception and its possible role in migraine following a bottom-up and a top-down approach. Wet stimuli can be abnormally perceived by people with migraine, and this might lead to pain and the concept of wetness allodynia. Concomitantly, migraine could reduce the threshold for sensory triggering and further alter wetness perception. DEG/ENaC, degenerin/epithelial Na⁺ channel; TRPM8, transient receptor potential cation channel subfamily M (melastatin) member 8 [Color figure can be viewed at wileyonlinelibrary.com]

Classification of Headache Disorders (ICHD) criteria for migraine. Written informed consent was provided by all participants, including healthy controls. Included patients typically experienced pain in the forehead during attacks and had to have at least one subjective weather-related trigger of migraine attack among the following: hot temperatures, cold temperatures, humidity, and wind. Participants were not taking drug prophylaxis therapy or had stopped it for at least 3 months, and they were not using long half-life symptomatic drugs for migraine attacks (e.g., frovatriptan), including paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs). Participants were excluded if they presented with any comorbidity potentially influencing thermal and sensory function (e.g., diabetes, neuropathies, or Raynaud's syndrome). Patients had to be pain-free during the measurements that were performed at least 72 h before or after the cessation of a migraine attack and/or use of analgesic medications. Based on sex and age distribution, a sample of similar controls was selected from a normative dataset from healthy participants assessed with identical procedures as the ones described here, during this and other experiments conducted in our laboratories (36 individuals were selected from 40).^{30,31} To account for interindividual differences, a sample size at least three times greater than the migraine sample was selected. Specifically, we were able to devise normative values for cold-wetness, neutral-wetness, and warm-wetness sensing based on 36 for the forehead and posterior neck, and on 16 for the finger pad. Participants were instructed to refrain from: (i) performing strenuous exercise in the 48 h preceding testing; (ii) consuming caffeine or alcohol in the 24 h preceding testing; and

(iii) consuming food in the 3 h preceding testing. No statistical power calculation was conducted prior to the study, and the sample size was based on our previous experience with this design. 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, as per standard institutional procedure. This study was approved by the Local Ethics Committee Comitato Etico Unico Regionale (CEUR, FVG, Italy).

Sensory testing

All participants took part in one experimental session, during which the same quantitative sensory test was performed in a quiet room at $25.2 \pm 0.8^\circ\text{C}$ and relative humidity $36\% \pm 7\%$. Measurements were performed at the same time of the day, between 15:00 and 17:00. Before measurements, participants were asked to rest on a chair for 20 min to adjust to the environmental conditions. During this time, participants were familiarized with the experimental procedures, and calibrated to the visual analog scale (VAS). Calibration procedures consisted of the following. Six stimuli varying in temperature and wetness (i.e., 0.8 ml of water, or dry) were applied to the volar surface of both forearms (i.e., midpoint between the wrist and antecubital fossa) in a random order, and participants were instructed to associate each stimulus to a specific descriptor on the thermal scale. The stimuli and related descriptors were:

(i) wet stimulus, 10°C above local skin temperature—scale descriptor: very hot; (ii) wet stimulus, 5°C above local skin temperature—scale descriptor: midpoint between neutral and very hot; (iii) wet stimulus, equal temperature as local skin temperature—scale descriptor: neutral; (iv) dry stimulus, equal temperature as local skin temperature—scale descriptor: neutral; (v) wet stimulus, 5°C below local skin temperature—scale descriptor: midpoint between neutral and very cold; and (vi) wet stimulus, 10°C below local skin temperature—scale descriptor: very cold. During each of the six stimuli applications, participants were instructed to freely determine the level of wetness experienced on the wetness VAS. This procedure ensured that all participants had comparable experiences of the different stimuli and related perceptual anchor points to be used during testing. The forearm was chosen as a “neutral” calibration site to avoid any priming, given that this region was not going to be tested during the mapping protocol. Regional skin temperature (Tsk) was measured with an infrared thermal camera (FLIR Systems, Wilsonville, OR, USA) on the selected sites of measurements: on the forehead, 2 cm above the eyebrow arch, and on the posterior neck, 2 cm lateral to the C7 spinal process. The order of testing region was counter-balanced between participants and the order of stimuli (e.g., warm vs. neutral vs. cold wet) was counter-balanced between and within participants. All measurements were taken during the same day/sitting session, lasting around 40 min. Between each stimulus, a 30 s rest was allowed as a nervous refractory period. All measurements were taken on the side participants with migraine reported as the primarily affected during migraine attacks. All the participants with migraine ($n = 12$) and a subsample of healthy controls ($n = 16$) also performed the measurements on the dominant hand index finger pad to verify the absence of altered perception in body areas where differences should not be expected. The quantitative sensory test was based on an established protocol³² that consisted of participants having to report the perceived magnitude of local thermal and wetness perceptions arising from the short-duration (i.e., 5 s) static application of a warm-wet (i.e., 5°C above local Tsk), neutral-wet (i.e., equal temperature as local Tsk) and cold-wet (i.e., 5°C below local Tsk) hand-held temperature-controllable probe (surface area: 1.32 cm², water content: 0.8 ml; NTE-3, Physitemp Instruments LLC, Clifton, NJ, USA). Participants reported the magnitude of their local perceptions on two VAS for thermal sensation (length 200 mm; anchor points: 0, very cold; 100, neutral; and 200, very hot) and wetness perception (length: 100 mm; anchor points: 0, dry; 100, completely wet). All the stimulations were performed three times and the average score was automatically computed. Based on the repeated measures for each stimulus and location, the coefficient of variation ranged from 6.8% to 10.7%. The wetness VAS scale has been consistently used in our previous studies of wetness sensing, and showed very good validity in relation to the association between increasing amounts of moisture and related magnitude of perception (see Merrick et al. for relevant data on validity).²⁰

In accordance with previous studies,^{25,31,32} all participants were blinded to the nature and application of the stimuli to limit

expectation biases, and they were only informed about the location of the stimulation. The same investigator performed all testing to limit any interindividual variability arising from the procedures carried out.

Statistical analyses

All statistical analyses were performed with SPSS version 23 (IBM). This is the primary analysis of these data. Data are reported as the means, standard deviations (SDs) and 95% confidence intervals (CI), or counts and proportions (%) as appropriate. Two-tailed testing was performed. Skin temperature was compared for each body region between people with migraine and healthy controls by using an independent samples *t*-test. To account for differences between groups in thermal and wetness perception on the investigated body sites, the independent and interactive effect of health status (2 levels between subjects: people with migraine vs. healthy controls) and stimulus temperature (3 levels repeated measures: cold, neutral, and warm) was performed with a two-way mixed analysis of variance (ANOVA). These analyses established the generalized effect of migraine on wetness and thermal sensing over the different tested areas, and its interaction with stimulus temperature.³¹ In the event of statistically significant main effects or interactions, post hoc analyses were conducted with Sidak's test. Normality testing using the Shapiro–Wilk test was performed for all datasets. Significance was set for $p < 0.05$.

RESULTS

Twelve participants with migraine without aura (44.5 ± 13.2 year, 58% women) and 36 similar healthy controls (39.4 ± 14.6 year, 50% women) were included in the study. There were no missing data. Patients' clinical characteristics and weather triggers for migraine are reported in Table 1. Skin temperature before testing was found to be similar between people with migraine and healthy controls (forehead: $p = 0.198$; posterior neck: $p = 0.107$; and index finger pad: $p = 0.091$). Wetness perception and thermal sensation results on the investigated body sites are summarized in Figure 2.

Migraine effects on wetness perception and thermal sensation on the forehead

When considering wetness perception on the forehead, a significant effect for group was found ($F_{1,46} = 5.19$, $p = 0.027$), as well as for stimulus temperature ($F_{2,92} = 6.75$, $p = 0.002$), whereas no group-stimulus interaction was present ($F_{2,92} = 0.30$, $p = 0.739$). In particular, people with migraine reported an overall higher wetness perception than healthy controls across all wet stimuli (migraine vs. healthy 15.1 mm, 95% CI: 1.8 to 28.5, $p = 0.027$, corresponding to ~15% difference; Figure 3A). Both groups reported the cold stimulus

TABLE 1 Demographic and clinical characteristics of the migraine and control group

| | Migraine group (n = 12) | Control group (n = 36) |
|---------------------------------------|----------------------------|---------------------------|
| Demographics | | |
| Age, years | 44.5 ± 13.2 | 39.4 ± 14.6 |
| Sex (females), n (%) | 7 (58) | 18 (50) |
| Weight, kg | 75.0 ± 9.2 | 72.8 ± 7.7 |
| Height, m | 1.70 ± 0.08 | 1.72 ± 0.11 |
| Clinical characteristics | | |
| Time from migraine onset, years | 16.5 ± 7.9 | |
| Migraine frequency, days/month | 5 ± 4 | |
| Severe migraine frequency, days/month | 3 ± 1 | |
| Drug for attack, n (%) | | |
| Triptans | 7 (58.3) | |
| NSAIDs | 3 (25.0) | |
| Combination analgesics | 2 (16.7) | |
| Side of pain, n (%) | | |
| Forehead | 12 (100.0) | |
| Right | 5 (41.7) | |
| Left | 1 (8.3) | |
| Bilateral | 6 (50.0) | |
| Posterior neck | 3 (25.0) | |
| Weather triggers | | |
| Hot temperatures, n (%) | 1 (8.0) | |
| Cold temperatures, n (%) | 4 (33.0) | |
| Wind, n (%) | 6 (50.0) | |
| Humidity, n (%) | 7 (58.0) | |

Note: Mean ± SD and count (%), as appropriate.

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

being wetter than the neutral-wet (mean difference cold-wet vs. neutral-wet 19.4 mm, 95% CI: 5.9 to 33.0, $p = 0.003$, corresponding to ~19% difference) and warm-wet (mean difference cold-wet vs. warm-wet 16.0 mm, 95% CI: 2.3 to 29.6, $p = 0.017$, corresponding to ~16% difference).

When considering thermal perception on the forehead, we found a significant effect was present for stimulus temperature ($F_{2,92} = 86.88$, $p < 0.001$); yet, no significant effect for group ($F_{1,46} = 1.14$, $p = 0.291$; migraine vs. healthy -8.3 mm, 95% CI: -24.0 to 7.3), nor group-stimulus interaction was present ($F_{2,92} = 0.85$, $p = 0.430$; [Figure 3B](#)). Both groups reported the cold stimulus being colder than the neutral-wet (mean difference cold-wet vs. neutral-wet: -43.2 mm, 95% CI: -61.7 to -24.7, $p < 0.001$, corresponding to ~21% difference) and the warm stimulus being warmer than the neutral (mean difference warm-wet vs. neutral-wet 46.8 mm, 95% CI: 35.3 to 58.4, $p < 0.001$, corresponding to ~23% difference).

Forehead wetness perception and thermal sensation VAS scores are reported in [Table 2](#).

Migraine effects on wetness perception and thermal sensation on the posterior neck

When considering wetness perception on the posterior neck, a significant effect was present for stimulus temperature ($F_{2,92} = 9.10$, $p < 0.001$); yet, we found no effect of group ($F_{1,46} = 0.43$, $p = 0.515$; migraine vs. healthy 4.8 mm, 95% CI: -9.9 to 19.5), nor group-stimulus interaction ($F_{2,92} = 0.94$, $p = 0.394$; [Figure 4A](#)). Both groups reported the cold stimulus being wetter than the neutral-wet (mean difference cold-wet vs. neutral-wet 21.1 mm, 95% CI: 8.7 to 33.6, $p < 0.001$, corresponding to ~21% difference) and warm-wet (mean difference cold-wet vs. warm-wet 21.4 mm, 95% CI: 5.9 to 36.9, $p = 0.004$, corresponding to ~21% difference).

When considering thermal perception on the posterior neck, we found a significant effect was present for stimulus temperature ($F_{2,92} = 75.70$, $p < 0.001$); yet, we found no significant effect for group ($F_{1,46} = 0.80$, $p = 0.375$; migraine vs. healthy -7.8 mm, 95% CI: -25.3 to 9.7), nor group-stimulus interaction ($F_{2,92} = 0.26$, $p = 0.772$; [Figure 4B](#)). Both groups reported the cold stimulus being colder than the neutral (mean difference cold-wet vs. neutral-wet: -52.5 mm, 95% CI: -69.5 to -35.4, $p < 0.001$, corresponding to ~26% difference) and the warm stimulus being warmer than the neutral (mean difference warm-wet vs. neutral-wet: 61.5 mm, 95% CI: 36.4 to 86.6, $p < 0.001$, corresponding to ~30% difference).

Posterior neck wetness perception and thermal sensation VAS scores are reported in [Table 3](#).

Migraine effects on wetness perception and thermal sensation on the index finger pad

When considering wetness perception on the finger pad, we found a significant effect for stimulus temperature ($F_{2,52} = 30.83$, $p < 0.001$); yet, we found no significant effect for group ($F_{1,26} = 0.19$, $p = 0.666$; migraine vs. healthy -3.3 mm, 95% CI: -18.9 to 12.3), nor group-stimulus interaction ($F_{2,52} = 1.01$, $p = 0.373$; [Figure 5A](#)). Both groups reported the cold stimulus being wetter than the neutral-wet (mean difference cold-wet vs. neutral-wet: 30.7 mm, 95% CI: 19.6 to 41.8, $p = 0.001$, corresponding to ~15% difference) and warm-wet (mean difference cold-wet vs. warm-wet: 32.8 mm, 95% CI: 21.4 to 44.1, $p = 0.001$, corresponding to ~16% difference).

When considering thermal perception on the finger pad, we found a significant effect for stimulus temperature ($F_{2,52} = 34.85$, $p < 0.001$); yet, we found no significant effect for group ($F_{1,26} = 2.41$, $p = 0.133$; migraine vs. healthy 12.4 mm, 95% CI: -4.0 to 28.9), nor group-stimulus interaction ($F_{2,92} = 0.50$, $p = 0.609$; [Figure 5B](#)). Both groups reported the cold stimulus being colder than the neutral (mean difference cold-wet vs. neutral-wet: -44.4 mm, 95% CI: -60.2 to -28.5, $p < 0.001$, corresponding to ~22% difference) and

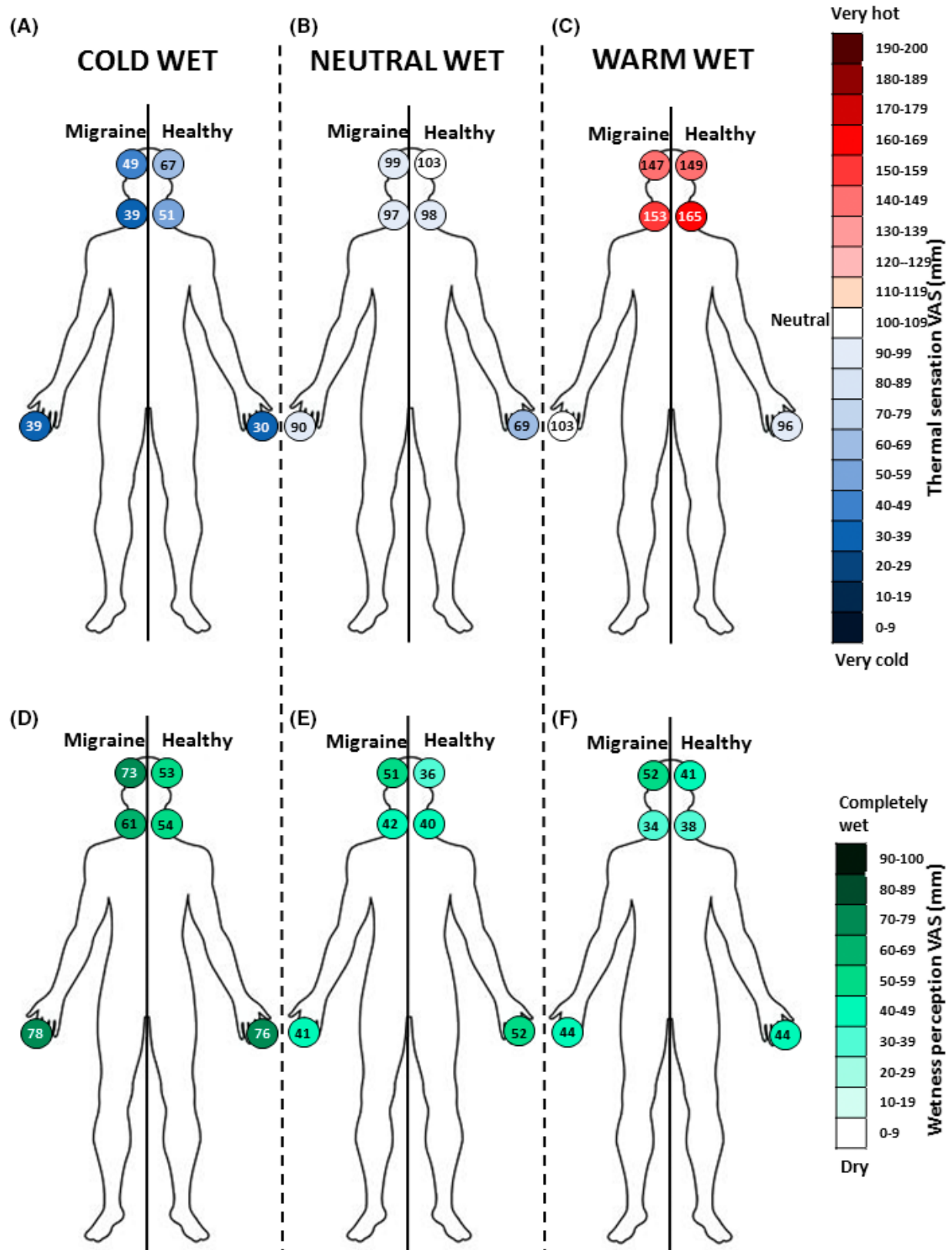


FIGURE 2 Body maps of thermal sensations and wetness perceptions in people with migraine ($n = 12$) and healthy similar controls ($n = 36$), resulting from the application of the cold-wet (A and D), neutral-wet (B and E), and warm-wet stimuli (C and F). Numerical data represent group means. [Color figure can be viewed at wileyonlinelibrary.com]

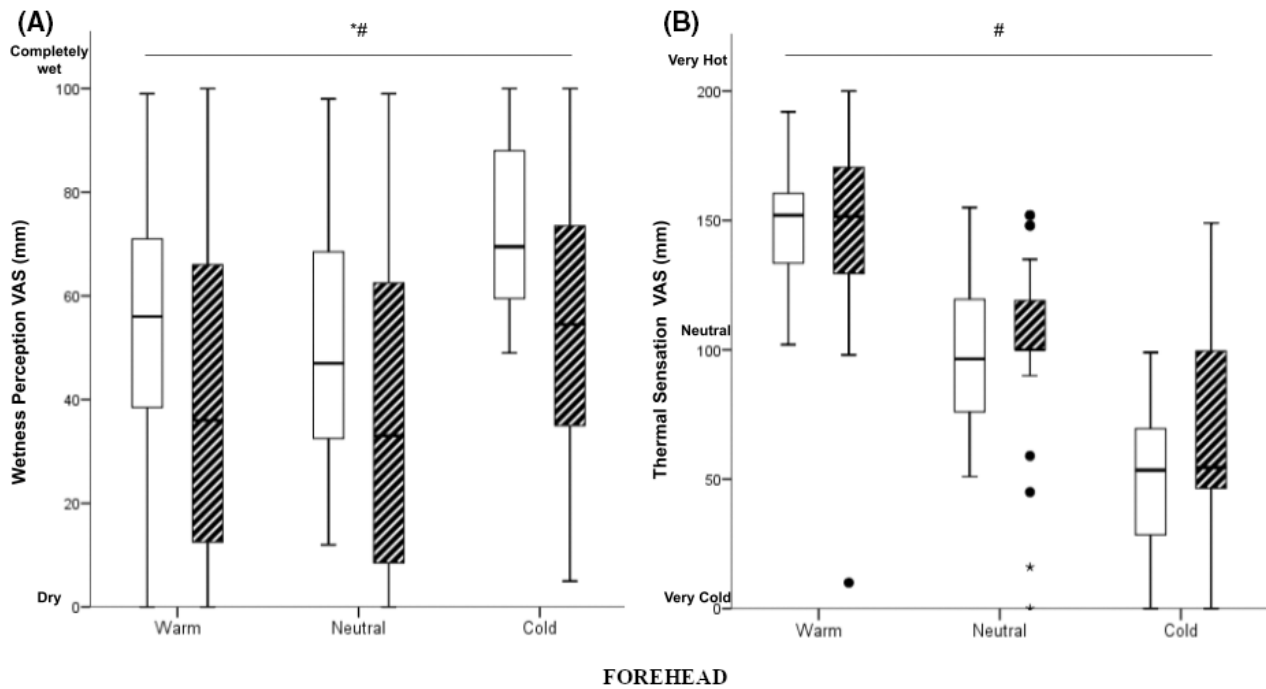


FIGURE 3 Boxplots representing the difference in wetness perception (A) and thermal sensation (B) on the forehead of individuals with migraine ($n = 12$, empty bars) and similar controls ($n = 36$, dashed bars) for the three stimuli temperature conditions (warm-wet, neutral-wet, and cold-wet). For wetness perception overall significant group ($*p = 0.027$) and temperature stimulus effect ($\#p = 0.002$). For thermal sensation only significant temperature stimulus effect ($\#p < 0.001$). VAS, visual analog scale

TABLE 2 Wetness perception and thermal sensation on the forehead, in people with migraine and healthy controls

| Forehead | Migraine ($n = 12$) | Healthy controls ($n = 36$) |
|------------------------|-----------------------|-------------------------------|
| Warm-wet stimulus | | |
| Wetness perception, mm | 52.3 ± 30.2 | 41.3 ± 30.3 |
| Thermal sensation, mm | 146.9 ± 25.8 | 149.1 ± 37.5 |
| Neutral-wet stimulus | | |
| Wetness perception, mm | 50.7 ± 24.6 | 36.0 ± 30.1 |
| Thermal sensation, mm | 99.1 ± 30.7 | 103.3 ± 32.2 |
| Cold-wet stimulus | | |
| Wetness perception, mm | 72.7 ± 17.6 | 52.9 ± 25.4 |
| Thermal sensation, mm | 48.7 ± 31.3 | 67.3 ± 33.0 |

Notes: Visual analog scale scoring (mm) for wetness perception (0 dry–100 wet) and thermal sensation (0 cold–100 neutral–200 hot) during a warm-wet stimulus ($+5^{\circ}\text{C}$ and 0.8 ml), neutral-wet stimulus (temperature equal to the skin and 0.8 ml), and cold-wet stimulus (-5°C and 0.8 ml).

Mean \pm standard deviation.

the warm stimulus being warmer, although not significantly, than the neutral (mean difference warm-wet vs. neutral-wet: 20.3 mm, 95% CI: -1.1 to 41.8, $p = 0.067$, corresponding to $\sim 10\%$ difference).

Index finger pad wetness perception and thermal sensation VAS scores are reported in [Table 4](#).

DISCUSSION

The aim of this investigation was to study the independent effect of migraine on skin wetness and thermal sensitivity across a principal painful body area (the forehead), a body area that might be painful in some cases (the posterior neck), and a neutral body area (the index finger pad). Our cohort of people with migraine reported wetness perceptions from the application of wet stimuli to the forehead that were $\sim 15\%$ more intense than those reported by the healthy control group; yet, no differences in wetness perception were observed between groups during the stimulation of the posterior neck and the index finger pad. In contrast, we found that, whereas both groups were able to discriminate thermal sensations arising from cold, neutral, and warm stimuli, the magnitude of those sensations did not differ between the groups on any of the tested body sites. Finally, both groups perceived the cold-wet stimulus as “wetter” compared with the neutral and warm-wet stimuli, despite that the same quantity of water (0.8 ml) was applied to the probe during each stimulation. Taken together, these findings provide preliminary evidence that people with migraine may have a heightened perception of skin wetness in response to non-noxious temperature stimuli spanning warm and cold temperatures, which is specific to a principal painful body area (i.e., the forehead). Furthermore, our study indicates that, whereas people with migraine may experience sensitization to wet stimuli, they maintain similar central integratory mechanisms for wetness sensing to healthy individuals (i.e., integration of cold-sensing and mechano-sensing afferent inputs).^{23,25,32,33} We believe

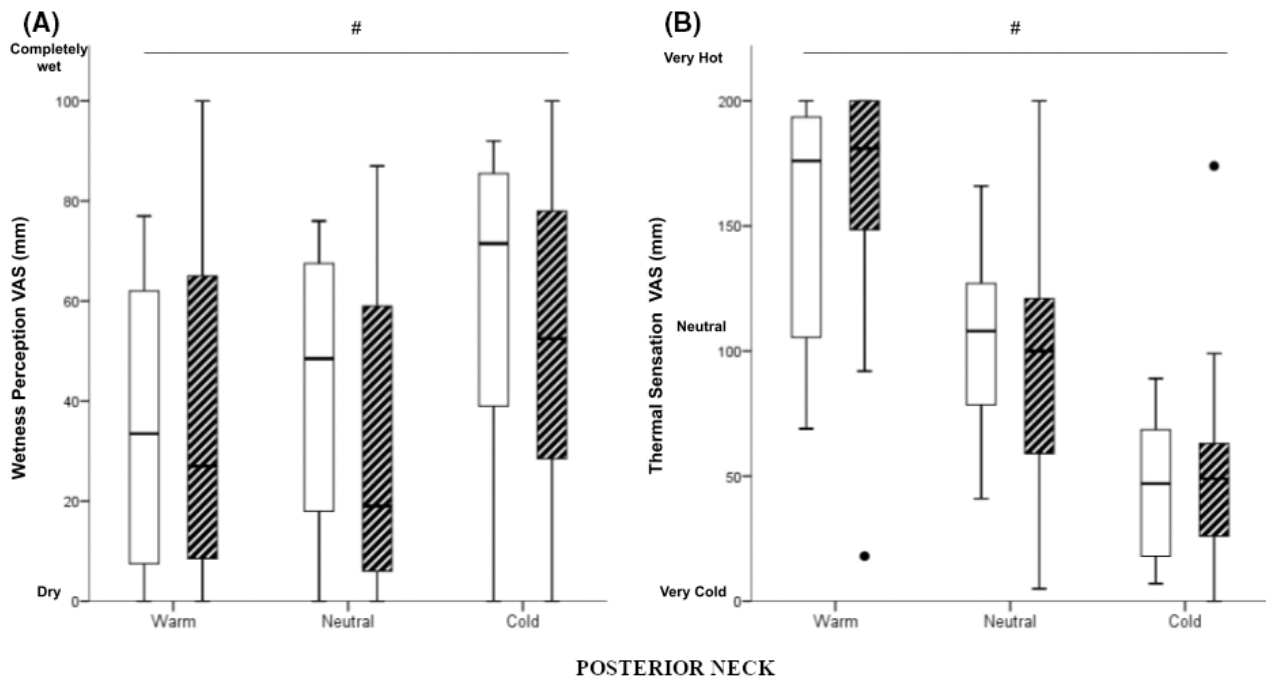


FIGURE 4 Boxplots representing the difference in wetness perception (A) and thermal sensation (B) on the posterior neck of individuals with migraine ($n = 12$, empty bars) and similar controls ($n = 36$, dashed bars) for the three stimuli temperature conditions (warm-wet, neutral-wet, and cold-wet). For wetness perception, only significant temperature stimulus effect ($\#p < 0.001$). For thermal sensation, only significant temperature effect ($\#p < 0.001$). VAS, visual analog scale

TABLE 3 Wetness perception and thermal sensation on the posterior neck, in people with migraine and healthy controls

| Posterior neck | Migraine ($n = 12$) | Healthy controls ($n = 36$) |
|------------------------|--------------------------|-------------------------------------|
| Warm-wet stimulus | | |
| Wetness perception, mm | 34.1 ± 29.2 | 38.0 ± 31.6 |
| Thermal sensation, mm | 152.9 ± 48.6 | 165.0 ± 43.3 |
| Neutral-wet stimulus | | |
| Wetness perception, mm | 42.0 ± 27.7 | 39.6 ± 28.9 |
| Thermal sensation, mm | 97.4 ± 39.8 | 97.5 ± 47.7 |
| Cold-wet stimulus | | |
| Wetness perception, mm | 60.9 ± 28.9 | 53.9 ± 29.3 |
| Thermal sensation, mm | 39.4 ± 27.4 | 50.6 ± 33.6 |

Notes: Visual analog scale scoring (mm) for wetness perception (0 dry–100 wet) and thermal sensation (0 cold–100 neutral–200 hot) during a warm-wet stimulus (+5°C and 0.8 ml), neutral-wet stimulus (temperature equal to the skin and 0.8 ml), and cold-wet stimulus (−5°C and 0.8 ml).

Mean \pm standard deviation.

that these findings are novel and carry clinical implications for the understanding of the link between high humidity and greater susceptibility to the onset of a migraine episode.

Transient receptor potential cation channel subfamily M (me-lastatin) member 8 (TRPM8) can be triggered by moisture, chemicals, and even cold-dry stimuli, resulting in a series of functions not

immediately related to each other in human sensitivity.^{26,34} The relative importance of thermal sensing compared to tactile sensing depends on the wet stimulus temperature, as neutral-wet and warm-wet perception might rely more on tactile than on thermal cues, whereas a higher contribution of the cold-sensing receptors might be expected for cold-wet perception.³² Thermal perception did not show a significant group effect, with a preserved capacity to discriminate among the three stimuli conditions in both groups. As such, we could speculate that there were minimal peripheral thermal (including cold) sensing differences between the two groups, and this might have a minor impact on the altered wetness perception. Nevertheless, the thermal stimuli were above the pain threshold and therefore these findings should be considered as indicative of non-noxious thermal sensations. Previous findings indicated that during the interictal period, people with episodic and chronic migraine can be more sensitive to thermal stimulation than non-migraine controls.¹⁵ The non-noxious experimental model used in this study can help to discriminate the relative contribution of thermal versus tactile cues in wetness sensing. Specifically, wetness perceptions reported during the neutral-wet stimulus compared with those reported during the cold-wet and warm-wet ones can suggest the contribution of tactile cues, which depends on the mechanical adhesion of the wet surface to the skin in the absence of thermal cues,³⁵ to the perception of wetness. Although it did not reach statistical significance, people with migraine reported a slightly higher wet perception on the forehead also during the neutral-wet stimulus. Taken together, these findings do not provide a clear indication of the principal contributor

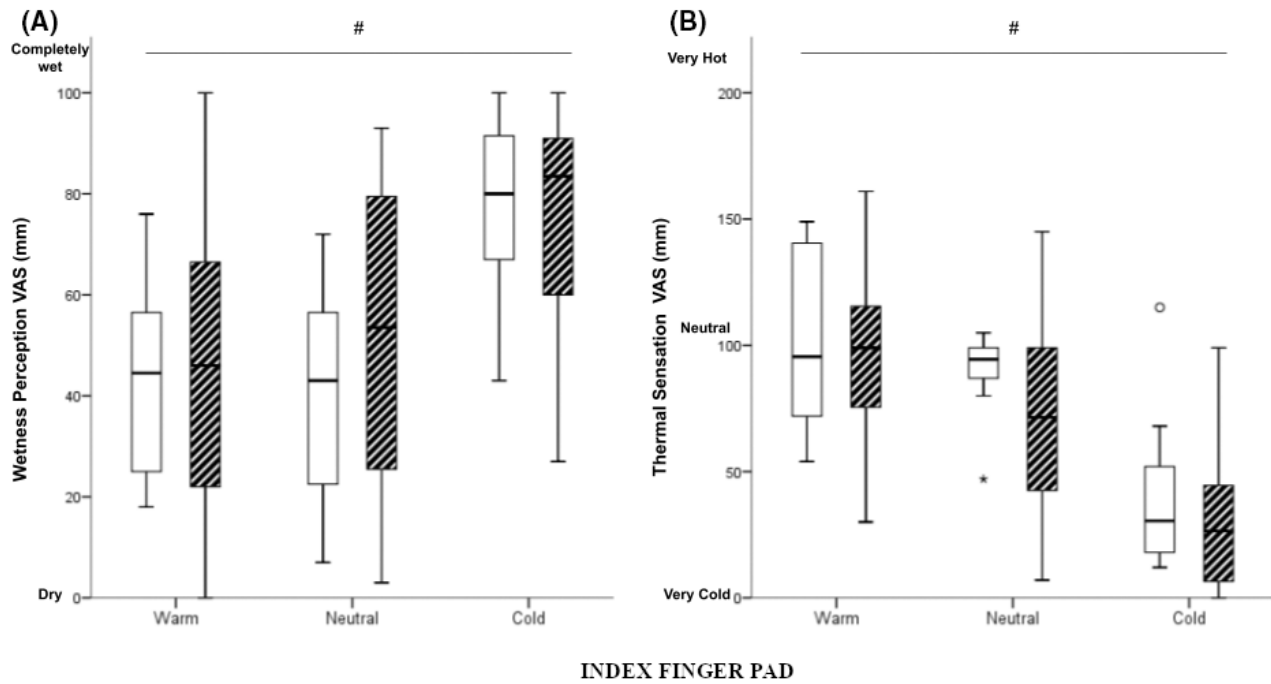


FIGURE 5 Boxplots representing the difference in wetness perception (A) and thermal sensation (B) on the index finger pad of individuals with migraine ($n = 12$, empty bars) and similar controls ($n = 16$, dashed bars) for the three stimuli temperature conditions (warm-wet, neutral-wet, and cold-wet). For wetness perception, only significant temperature stimulus effect ($^{\#}p < 0.001$). For thermal sensation, only significant temperature effect ($^{\#}p < 0.001$). VAS, visual analog scale

TABLE 4 Wetness perception and thermal sensation on the index finger pad, in people with migraine and healthy controls

| Index finger pad | Migraine ($n = 12$) | Healthy controls ($n = 16$) |
|------------------------|--------------------------|-------------------------------------|
| Warm-wet stimulus | | |
| Wetness perception, mm | 43.9 ± 20.6 | 44.4 ± 29.3 |
| Thermal sensation, mm | 103.0 ± 35.4 | 96.1 ± 34.1 |
| Neutral-wet stimulus | | |
| Wetness perception, mm | 40.8 ± 22.7 | 51.6 ± 29.5 |
| Thermal sensation, mm | 90.0 ± 15.2 | 68.5 ± 38.8 |
| Cold-wet stimulus | | |
| Wetness perception, mm | 77.7 ± 16.6 | 76.2 ± 21.5 |
| Thermal sensation, mm | 39.3 ± 30.0 | 30.4 ± 29.2 |

Notes: Visual analog scale scoring (mm) for wetness perception (0 dry–100 wet) and thermal sensation (0 cold–100 neutral–200 hot) during a warm-wet stimulus ($+5^{\circ}\text{C}$ and 0.8 ml), neutral-wet stimulus (temperature equal to the skin and 0.8 ml), and cold-wet stimulus (-5°C and 0.8 ml).

Mean \pm standard deviation.

to altered forehead wetness perception in people with migraine (i.e., thermal vs. tactile sensing), but it might be speculated that it depends on their combination. Indeed, the altered thermal pain threshold reported in other studies could suggest a primary role of these sensory pathways in the development of pain,¹⁵ although increased mechanical sensitivity has been also reported in people with migraine.³⁶

According to this study, some potential mechanisms could be discussed related to the higher wetness perception reported by people with migraine and its relationship with weather-induced pain attacks. Despite three patients reporting that their migraine-related pain originated also in the posterior neck area, the forehead was the common body area related to migraine attacks. Previous studies have shown that TRPM-8 receptors are highly expressed in trigeminal and dorsal root ganglia, particularly in a subpopulation of small-diameter nonmyelinated neurons which may exert both a thermoceptive and a nociceptive function.³⁷ The aforementioned circuitries are eminently involved in migraine and in neuronal pain and, in confirmation of this, a reduced level of genetic expression of TRPM-8 receptors entails a diminished risk to develop migraine attacks.³⁸ Therefore, a rationale might exist behind the reciprocal inter-relation between moisture sensitivity and migrainous diathesis. Unfortunately, the absence of a significantly higher thermal sensitivity to cold stimulus does not allow speculation on the expression and activity of these receptors in people with migraine, and, in particular, on the forehead, trigeminal nerve territory,³⁹ and in comparison to control subjects and to the posterior neck surface, occipital nerve territory.⁴⁰ However, by the use of a validated experimental protocol to evaluate wetness and thermal perception, it was possible to show an association with the clinical observation that some patients with migraine, in contrast to unaffected people, can particularly experience atmospheric events, and, in particular, cold and humid conditions. As described in the work by Burstein et al.,¹⁴ the 79% of enrolled people with migraine had cutaneous allodynia, variably spreading but always engaging the referred area

of pain onset. We have additionally found that in correspondence with the most involved site of pain (invariably the forehead in our sample) an increased sensitivity to cold wetness seems also to exist, even without evoking pain.

Limitations and future perspectives

This study was conducted on a small sample of people with migraine, which might represent a limitation to interpreting the findings. Indeed, although the selection criteria attempted to include a sample of patients with similar clinical characteristics (including migraine frequency), some differences might be present among the patients and might have influenced the results. In addition, due to the variable nature of the symptoms and the variability in pain side (some patients reported bilateral pain or alternating sides), it was not possible to perform a comparison between the affected and unaffected sides of the body. Future studies in larger populations should consider potential differences based on the side of pain. All measurements were performed during a pain-free period, and all the participants were asked to avoid analgesics during the 72 h prior to the experiments; nonetheless, it is not possible to determine if the medication's long-term effects might have influenced the rating. Skin biophysical characteristics (as skin hydration) might influence skin and thermal wetness perception³¹; in this study, we were not able to collect such data, although any effect of migraine on such characteristics should not be expected. The involvement of TRPM-8 receptors should be further investigated, given their already elucidated role in the disposition to migraine and the modulation of skin wetness sensation. In perspective, a more extensive application of sensory testing procedures could help clinicians to identify the subpopulation of people with migraine who are more susceptible to develop headaches in relation to specific environmental conditions. These patients might be recommended to avoid these trigger factors to reduce the incidence of attacks and could also be selected as possible better responders to eventual future therapies directed against TRPM-8 receptors.⁴¹

CONCLUSIONS

In conclusion, this study used an accurate and reproducible experimental procedure to evaluate skin wetness and thermal perception in people with low-frequency episodic migraine and sensitivity to environmental triggers. Compared with similar healthy controls, higher wetness sensitivity (especially to cold-wet stimulus) was found coinciding with the forehead. These findings provide a preliminary pathophysiological rationale behind the association between environmental conditions and migraine attacks.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: Alex Buoite Stella, Davide Filingeri, Giovanni Furlanis, Antonio Granato, Paolo Manganotti. *Acquisition of data:* Alex Buoite Stella, Gabriele Garascia, Davide Filingeri, Laura D'Acunto. *Analysis and interpretation of data:* Alex Buoite Stella, Davide Filingeri, Paolo Manganotti. *Drafting of the manuscript:* Alex Buoite Stella, Davide Filingeri, Gabriele Garascia, Laura D'Acunto. *Revising it for intellectual content:* Giovanni Furlanis, Antonio Granato, Paolo Manganotti. *Final approval of the completed manuscript:* Alex Buoite Stella, Davide Filingeri, Gabriele Garascia, Laura D'Acunto, Giovanni Furlanis, Antonio Granato, Paolo Manganotti.

DATA AVAILABILITY STATEMENT

Anonymized data are available upon reasonable request to the corresponding author according to standard institutional procedure.

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