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Assessment of Responsiveness to Everyday Non-Noxious Stimuli in Pain-Free Migraineurs With Versus Without Aura

Yelena Granovsky,*,† Merav Shor,* Alla Shifrin,*,† Elliot Sprecher,* David Yarnitsky,*,† and Tami Bar-Shalita‡,§

**Department of Neurology, Rambam Medical Center, Haifa, Israel.*
†The Rappaport Faculty of Medicine, Technion—Israel Institute of Technology, Haifa, Israel.
‡Department of Occupational Therapy, School of Health Professions, Sackler Faculty of Medicine, §Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel.

Abstract: **Migraineurs with aura (MWA) express higher interictal response to non-noxious and noxious experimental sensory stimuli compared with migraineurs without aura (MWoA), but whether these differences also prevail in response to everyday non-noxious stimuli is not yet explored. This is a cross-sectional study testing 53 female migraineurs (30 MWA; 23 MWoA) who underwent a wide battery of noxious psychophysical testing at a pain-free phase, and completed a Sensory Responsiveness Questionnaire and pain-related psychological questionnaires. The MWA group showed higher questionnaire-based sensory over-responsiveness ($P = .030$), higher magnitude of pain temporal summation ($P = .031$) as well as higher monthly attack frequency ($P = .027$) compared with the MWoA group. Overall, 45% of migraineurs described abnormal sensory (hyper- or hypo-) responsiveness; its incidence was higher among MWA (19 of 30, 63%) versus MWoA (6 of 23, 27%, $P = .012$), with an odds ratio of 3.58 for MWA. Sensory responsiveness scores were positively correlated with attack frequency ($r = .361$, $P = .008$) and temporal summation magnitude ($r = .390$, $P = .004$), both regardless of migraine type. MWA express higher everyday sensory responsiveness than MWoA, in line with higher response to experimental noxious stimuli. Abnormal scores of sensory responsiveness characterize people with sensory modulation dysfunction, suggesting possible underlying mechanisms overlap, and possibly high incidence of both clinical entities.**

Perspective: ***This article presents findings distinguishing MWA, showing enhanced pain amplification, monthly attack frequency, and over-responsiveness to everyday sensations, compared with MWoA. Further, migraine is characterized by a high incidence of abnormal responsiveness to everyday sensation, specifically sensory over-responsiveness, that was also found related to pain.***

Key words: *Headache, sensory responsiveness, pain facilitation, sensory modulatory dysfunction, sensory integration.*

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Address reprint requests to Yelena Granovsky, PhD, Department of Neurology, Rambam Health Care Campus, Haifa, Israel. E-mail: y_granovsky@rambam.health.gov.il
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Interictal increased sensitivity to nonpainful sensory stimuli in migraine was widely described in experimental studies, reflected by lower perceptual thresholds, enhanced magnitude of psychophysical and neurophysiological responses, as well as reduced adaptation and habituation to a specific sensory modality (usually visual or auditory).[21] In addition, enhanced responses to noxious stimuli has been described, pointing

at overactivation of pain facilitatory pathways, and deficient functioning of pain inhibitory pathways.[17,40,56] The underlying neurophysiological mechanisms of increased sensitivity in interictal migraine suggest alterations in the cortical circuits and neurotransmitters, which maintain the excitatory/inhibitory balance.[21,45]

Interestingly, over-responding to sensory stimuli in migraineurs was reported not only to experimental but also to various everyday stimuli. Many migraineurs report interictal discomfort to everyday stimuli such as odors, and light or sound, which may even trigger migraine attack or, if during an attack, worsen headache intensity.[10,26,47,53] This multimodal hypersensitivity (eg, visual, auditory, somatosensory, and/or olfactory stimuli), suggest abnormal multisensory integration in migraine.[47] However, despite a variety of reports, quantifying this type of everyday sensory sensitivity in migraine has not been systematically performed.

Approximately up to one-third of migraineurs experience aura.[32,52] The cortical disturbances in ictal and interictal periods that characterize migraineurs with aura (MWA), are associated with a reduction in the ability to prevent cortical hyperexcitation and a subsequent alteration in the processing of sensory information.[2,14,49,54] Indeed, enhanced sensory processing of experimental non-noxious stimuli during interictal periods in MWA is widely described, mainly in the neurophysiological domain,[16,18,46] whereas no quantification of sensory responsiveness to everyday stimuli were reported.

In this study, we aimed to explore the inter-relationship between self-reported sensory responsiveness to everyday sensations, experimental pain responses, and migraine clinical characteristics in MWA versus migraineurs without aura (MWoA) at the pain-free phase. We hypothesized that high incidence of self-reported abnormal sensory responsiveness will be found, whereas the sensory over-responsiveness will be associated with amplified pain responses and migraine clinical manifestations. Furthermore, this association will be more evident in MWA compared with MWoA.

Methods

The experimental protocol was approved by the Investigational Review Board of Rambam Health Care Campus, Haifa, Israel; the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all participants. This is a cross sectional study using a 2-group comparison convenience sample.

Subjects

Fifty-three episodic female migraine patients participated in this study. Patients were recruited through word of mouth and snowball sampling, starting with individuals who contacted the headache clinic at Rambam Health Care Campus. All migraine patients fulfilled the criteria set by the International Classification of Headache Disorders for the diagnosis of migraine (Beta version, 2013). The inclusion criteria were ≤15 migraine attacks per months, ages 18 to 75 years, no other pain or neurological diseases, and no use of preventive medication during the previous 3 month. Exclusion criteria were having chronic migraine (>15 days of headache per month), language barrier, or cognitive dysfunction. Patients were asked to avoid analgesics for 12 hours before the lab session. The lab session was conducted when pain-free, at least 48 hours after the last attack. All patients were screened by a neurologist who confirmed migraine diagnosis. At the consenting meeting, a headache diary was distributed to participants, who were asked to document their attacks during the month before the experimental session. This study was part of a longitudinal study that was aimed to examine the effect of preventive treatment with amitriptyline in migraine. This article presents the findings of the baseline stage.

Experimental Protocol

The study was conducted within the period between June 2014 to September 2015. All experiments were performed in the same setting by the same experimenter (M.S.) at the Technion Laboratory of Clinical Neurophysiology in Rambam Health Campus, Haifa, Israel. Subjects sat comfortably in a quiet room with an ambient room temperature of 22 to 23°C. All patients underwent 1 experimental session in the pain-free phase.

Clinical Assessment

At the beginning of the experimental session all patients completed an Excel-based questionnaire providing information about demographic data (age, family history of migraine, and origin) and migraine characteristics such as disease duration, migraine triggers, presence of aura, and time since the last attack. Because there is no established diagnosis for aura, we indicated a presence of aura if the following question was answered positively: "Do you experience vision, speech, or tactile disturbances up to half an hour before the attack?" A positive answer to this question meets the criteria B and C2,4 of the diagnostic criteria for MWA from the International Headache Society classification of the International Classification of Headache Disorders-3, version beta.

Questionnaires

After the clinical assessment, all participants completed several pain-related psychological questionnaires for assessment of pain catastrophizing (using the Pain Catastrophizing Scale (PCS)[51] and anxiety levels (with Spielberger's State-Trait Anxiety Inventory).[50]

To evaluate sensory responsiveness to everyday stimuli, all participants completed the Sensory Responsiveness Questionnaire (SRQ)-Intensity Scale[5,6] aimed at identifying abnormal patterns of sensory responsiveness. It consists of 58 items representing typical everyday scenarios. Each item involves one sensory stimulus in one modality, including auditory, visual, gustatory, olfactory, vestibular, and somatosensory stimuli, excluding pain. Participants

were asked to rate the intensity of the sensory responses to the situation, using a 5-point scale with the anchors "not at all" attached to the score of "1" and "very much" attached to the score of "5." The SRQ-Intensity Scale has been shown to have content, criterion, and construct validity, as well as internal consistency (Cronbach $\alpha = .90–.93$) and test-retest reliability ($r = .71–.84$, $P < .01–.05$).[5] The SRQ elicits 2 scores on the basis of values obtained from healthy populations: under-responsiveness, or SRQ-Hedonic (26 items), for which cutoff scores are mean (SD); 2.10 (.33), and over-responsiveness, or SRQ-Aversive score (32 items), for which cutoff scores are mean (SD); 1.87 (.26).[7] A 2-SD cutoff was applied to ensure conservative group categorization.

Throughout the text we refer to "sensory responsiveness" or "sensory over-responsiveness" with regard to the SRQ-based sensory evaluation, whereas the term "increased sensitivity" is reserved for the description of migraine or psychophysics.

Psychophysical Assessment

Heat pain thresholds (HPTs) were assessed by the method of limits. The Thermal Sensory Analyzer thermode was attached to the volar aspect of the forearm. Starting at a baseline temperature of 32°C, the thermode warmed at a rate of 1.5°C/s until pain sensation was perceived. This was repeated 3 times, and results were averaged to obtain an HPT value.

Mechanical pain thresholds (MPTs) were assessed using von Frey filaments (North Coast Medical, San Jose, CA), by elevating the weight, using consecutive filaments until the patient initially reported that mild pain was perceived. Each filament was applied 3 times until the filament that evoked pain was detected in at least 2 of the 3 trials. The first filament to be detected at ≥2 of 3 times was determined as the MPT.

Mechanical temporal summation (mTS) was tested using the von Frey filament that delivers 180 g pressure (# 6.45), applied to the volar forearm. Subjects were exposed to a series of 10 stimuli, within an area of 1 cm in diameter, with an interstimulus interval of 1 second. Subjects were asked to rate the level of pinprick pain intensity using a 0 to 100 verbal numeric pain score for the first and the 10th stimulus. The difference between the 10th and the first pain scores served as the temporal summation score.

Conditioned pain modulation (CPM) was assessed using the parallel paradigm in which 2 identical test stimuli were given; stand-alone followed by the second test stimuli, simultaneously delivered with a noxious conditioning stimulus. The test stimulus was a tonic noxious contact heat stimulus applied to the volar aspect of the dominant forearm using the Thermal Sensory Analyzer. The intensity of the test stimulus was individually tailored, predetermined through the psychophysical parameter of Pain60 temperature. This parameter is determined by delivering several triplets of 7-second long stimuli of various intensities; the closest temperature that induced pain at a level of 60 on a 0 to 100 numeric pain scale was considered as the Pain60 temperature. For test stimuli, baseline temperature was 32°C, which increased at a rate of 2°C/s reaching the destination temperature, which was held for 30 seconds serving for "test stimulus," then decreased back to baseline at the same rate. Subjects were asked to rate the intensity of the "test stimulus" along the stimulus at the 10th, 20th, and 30th second. The mean pain ratings served as the pain score for the "test stimulus." After a 15-minute break, subjects were exposed to the conditioning stimulus by immersion of the nondominant hand, up to the wrist, into a hot water bath at 46.5°C (Heto CBN 8–30 Lab equipment, Allerod, Denmark) during 1 minute. Water-induced pain was rated every 10 seconds during the first 30 seconds of immersion; the mean of these 3 ratings served as the pain score for the "conditioning stimulus." During the last 30 seconds of the conditioning stimulation, an identical test stimulus was repeated, and pain ratings during test stimulus were obtained again every 10 seconds. The CPM effect was calculated as the difference between the mean pain scores of 2 test stimuli applications: the conditioned test stimulus minus the stand-alone test stimulus. More negative values indicated more efficient CPM.

All of the tests, but the hand immersion, were performed on the dominant hand. Randomization was performed for the HPT and MPT testing followed by the temporal summation assessment. The CPM assessment was always performed as the last test.

Statistical Analysis

These data are initial results, representing pretreatment conditions for a drug testing study. Power analyses for the full study were on the basis of considerations for ANCOVA analyses, and no special additional power analysis was performed to determine number of cases for the statistics reported at present.

The primary interest of this study was to characterize the relationships between sensory responsiveness and migraine clinical characteristics and psychophysical pain responses in MWA versus MWoA patients. To that aim, first, a 2-tailed t-test was performed to assess the differences between MWA and MWoA for the SRQ scores, and for clinical characteristics and psychophysical pain responses. We then calculated the incidence of abnormal sensory responsiveness in our total migraine sample, as well as testing its proportions among MWoA versus MWA (Fisher exact test). Further, regression analysis tested the relationship between each of sensory responsiveness dimension (aversive and hedonic), pain and psychological characteristics, in relation to aura.

The relationship of the presence of aura to sensory over-responsiveness (SRQ-aversive score) or under-responsiveness (SRQ-hedonic score) was assessed using logistic regression. Odds ratio and 95% confidence interval for presence of aura were determined per unit increase of SRQ score. Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and JMP (SAS Institute, Cary, NC). The level of significance was set at $P < .05$. The data are presented as mean ± SD.

Table 1. Clinical Characteristics of the Migraine Patients; Whole Group and Comparison Between MWA vs MWoA (mean ± SD)

Parameters	*Whole Group*	*MWoA*	*MWA*	P
Disease duration, years	19.0 ± 13.0	17.8 ± 13.1	20.0 ± 13.1	.545
Month attacks frequency	7.6 ± 3.1	6.5 ± 3.1	8.5 ± 3.2	.025
Migraine pain intensity, NPS	84.2 ± 12.0	83.3 ± 17.8	84.8 ± 12.6	.585

Abbreviation: NPS, numerical pain scale.

Results

Patient Characteristics

Clinical characteristics of the migraine patients are presented in Table 1. Thirty of 53 patients had aura. The MWA group had higher month attacks frequency ($P = .025$; Fig 1A) but were not different from the MWoA in disease duration or migraine pain intensity. The mean age of the migraine patients was 40.3 ± 11.9 years (MWoA 40.9 ± 11.9 and MWA 39.8 ± 12.4 years, $P = .75$).

Pain Psychophysics and Sensory Responsiveness

Comparing the results of pain psychophysics among all tested parameters, the MWA patients showed higher mTS magnitude than the MWoA patients ($P = .031$). Further, the MWA group had higher SRQ over-responsiveness scores ($P = .025$; Table 2 and Figs 1B and 1C). No significant group differences were found for other pain psychophysical tests: HPT, MPT, and CPM, nor for SRQ under-responsiveness scores.

On the basis of a normative scoring of 2 SD above the SRQ mean scores, abnormal pattern of sensory responsiveness was identified in 24 of 53 patients (45%); 40% had sensory over-responsiveness, and 5% had sensory under-responsiveness. Moreover, the incidence of abnormal pattern of sensory responsiveness was higher among MWA (19 of 30, 63%) versus MWoA (6 of 23, 27%, 2-tailed Fisher exact test, $P = .012$). Furthermore, logistic regression analysis of the presence of aura depending on sensory over-responsiveness was significant, $P = .022$ (likelihood ratio test). The odds ratio was 3.575 (95% confidence interval = 1.20–12.54) for MWA per unit increase in the over-responsiveness score.

We further tested the correlation between the scores of sensory over- and under-responsiveness, with clinical and psychophysical measures. The level of sensory over-responsiveness positively correlated with attack frequency ($r = .361$, $P = .008$) and with mTS magnitude ($r = .390$, $P = .004$; Fig 2). Regression analysis indicated that this relationship was unrelated to the presence of aura neither for the parameter of attack frequency (model $P = .022$, attack frequency $P = .032$, presence of aura $P = .128$, interaction $P = .639$), nor for the mTS (model $P = .012$, mTS $P = .023$, presence of aura $P = .112$, interaction $P = .546$). As for the scores of sensory under-responsiveness, high scores were associated with higher values of HPT ($r = .286$, $P = .038$), lower mTS (trend, $r = -.259$, $P = .061$) and higher migraine pain level ($r = .351$, $P = .010$); none were related to having aura or not.

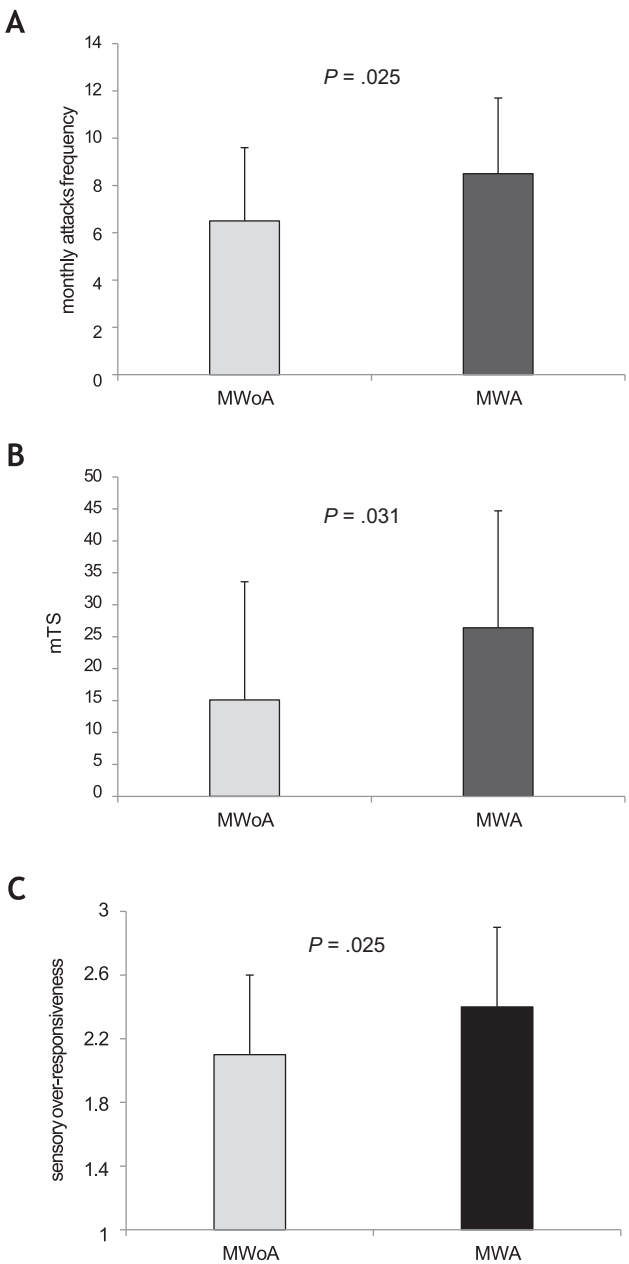

Figure 1. Patients with MWA show higher monthly attack frequency (A), higher temporal summation magnitude (B), and higher score of sensory over-responsiveness (C) compared with the MWoA patients.

Table 2. Pain Psychophysics and Sensory Responsiveness in Migraine Patients; Whole Group and MWA Versus MWoA

Parameters	Whole Group	MWoA	MWA	P
HPT, °C	44.7 ± 2.6	45.1 ± 2.2	44.4 ± 2.9	.344
MPT, g	203.5 ± 99	209.3 ± 95	199.1 ± 103.4	.714
First mechanical stimulus, NPS	17.9 ± 18.1	18.9 ± 21.7	17.2 ± 15.2	.731
Tenth mechanical stimulus, NPS	39.4 ± 25.6	34 ± 27.7	43.6 ± 23.4	.180
mTS, ΔNPS	21.5 ± 19	15.1 ± 18.5	26.4 ± 18.3	.031
Pain60, °C	44.8 ± 2.1	44.9 ± 2	44.8 ± 2.1	.912
Conditioning stimulus, NPS	74.2 ± 22.5	73.4 ± 21	74.9 ± 24	.812
Test stimulus, NPS	46.4 ± 19.9	43 ± 19	49 ± 20.6	.284
CPM, ΔNPS	–5.6 ± 21.8	–2.2 ± 17.8	–8.2 ± 24.4	.326
Sensory over-responsiveness	2.3 ± .5	2.1 ± .5	2.4 ± .5	.025
Sensory under-responsiveness	2.1 ± .5	2.1 ± .4	2.1 ± .6	.999

Abbreviation: NPS, numerical pain scale.
NOTE. Data are presented as mean ± SD except where otherwise noted.

Pain-Related Psychological Variables and Sensory Responsiveness

MWoA and MWA patients were neither different in the level of pain catastrophizing (total or its fractions), nor in state or trait anxiety levels. However, the SRQ over-responsive scores correlated positively with all variables: PCS total (r = .379, *P* = .007) and its subscales: rumination (r = .342, *P* = .015), magnification (r = .454, *P* = .001), and helplessness (r = .294, *P* = .038), anxiety trait (r = .402, *P* = .003), and state (r = .328, *P* = .018). Regression analysis revealed different associations between the level of anxiety trait and sensory over-responsiveness for MWoA and MWA (model *P* = .012, interaction *P* = .022) indicating positive correlation for MWA (r = .619, *P* < .001) but not for the MWoA patients (r = .027, *P* = .903).

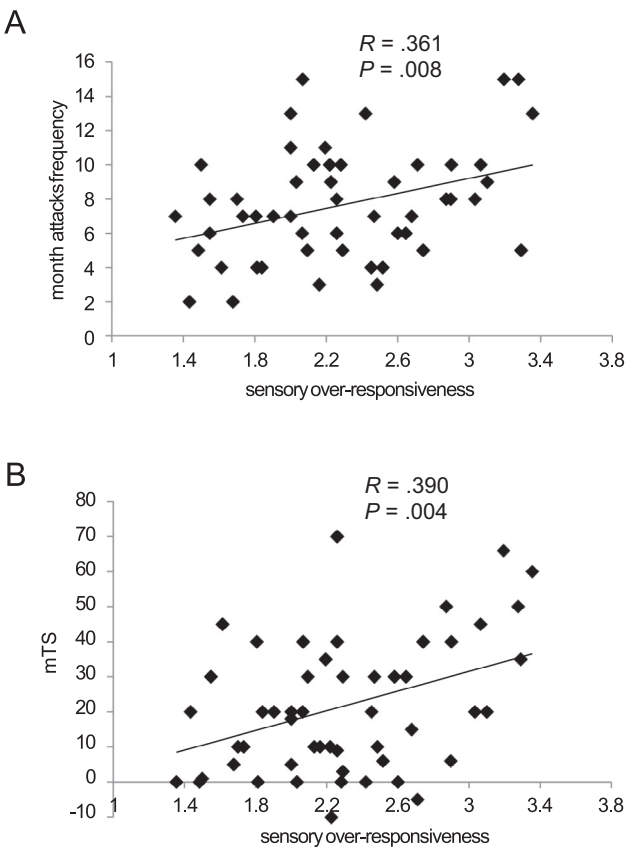

Figure 2. Sensory over-responsiveness correlates positively with the attacks frequency (A) and temporal summation magnitude (B).

Discussion

To our knowledge, this is the first study in which questionnaire-based quantification of sensory responsiveness to everyday sensations in pain-free migraine patients was performed, while also exploring whether MWA differ from MWoA in their pain and sensory sensitivity patterns. Our findings show that MWA patients were characterized by enhanced pain processing associated with amplified pain facilitation, and with higher attacks frequency. In addition, the MWA patients showed sensory over-responsiveness to everyday sensations. Furthermore, 45% of our total migraine patient sample showed abnormal (over- or under-) pattern of sensory responsiveness whereas sensory over-responsiveness was associated with enhanced activity of pain facilitatory pathways and migraine attack frequency. We therefore believe that sensory over-responsiveness in migraine, generally, might be one of the manifestations of the widely-described central neuronal excitability, being most evident in MWA.

Interictal migraine is characterized by a pronociceptive pattern of response manifested as low pain threshold,[25,48] reduced habituation,[28,34] high pain facilitation,[24,27,56] along with some reports on less efficient endogenous pain inhibition[17,40] compared with healthy subjects. However, to date research on pain processing in MWA versus MWoA is scarce. To the best of our knowledge, the evidence is limited to only one study describing the pronociceptive pattern of interictal pain processing in MWA associated with lack of pain habituation, and increased amplitude of pain-evoked potentials compared with MWoA or control subjects.[34] The results of our study are in line with these findings and revealed enhanced pain temporal summation in MWA evoked by repeated application of mechanical pricking stimuli, with no group difference in the CPM response. Thus, our current study provides

additional evidence, revealing different patterns of pain processing in MWA versus MWoA, that are related to enhanced activity of pain facilitatory pathways rather than to deficient pain inhibition, and are associated with sensory over-responsiveness.

The described relationship between presence of aura, higher level of sensory over-responsiveness, increased sensitivity to psychophysical parameters, and clinical migraine pain characteristics is in line with the reports on central neuronal hyperexcitability in MWA. The cortical excitability is reflected by enhanced sensory brain activation, impaired cortical inhibition and abnormal excitation/inhibition balance,[16,18,41] associated with impaired GABA-ergic[35] and enhanced glutamatergic transmission[15] which differentiates MWA from MWoA. A proposed imbalance between centrally mediated excitatory and inhibitory processes is also assumed to underlie sensory modulation dysfunction (SMD)—a neurodevelopmental condition associated with general multisensory over-responsiveness to everyday nonpainful stimuli that are perceived as abnormally irritating, unpleasant,[31,57] or painful.[6,7]

SMD is a type of sensory processing disorder, impacts single or multiple sensory systems, affecting the capacity to regulate responses to sensory input in a graded and adaptive manner,[31,38,44,57] greatly limiting and interfering with quality of life, work performance, and participation in everyday routines.[4,22] SMD is reported in approximately 10% (range 5–16%) of the pain-free otherwise healthy pediatric and adult populations.[1,4,9] Importantly, in line with our findings on 45% of our migraine patients who were diagnosed with SMD, higher prevalence is reported in other neurodevelopmental syndromes (eg, 40–70% in attention-deficit/hyperactivity disorder[43]; 70% in autistic spectrum disorder[33]). These findings indicate amplification of experimental pain, adaptation deficiency, and facilitation of physiological responses to a combination of sensory modalities (eg, abnormal multisensory integration) in SMD, similar to those that characterize migraine,[6,7,11,12] suggestive of a posible overlap between the underlying mechanisms of SMD as well as migraine. Furthermore, on the basis of the published normative SRQ data (Bar-Shalita et al[3,4]), the definition of SMD (2 SD higher than the normal mean) was made for 63% of MWA more than twice the incidence in MWoA, indicating clinical significance of abnormal sensory responsiveness specifically in MWA.

The association between sensory responsiveness, pain processing, and clinical migraine characteristics might be related to the central integration of sensory and pain transmitting pathways in migraine.[47] Indeed, it is reported that experimental trigeminal pain further enhances the lack of habituation and cortical hyperexcitability to light in migraineurs.[11] This phenomenon can be related to the anatomical integration of pain and visual processing in thalamic nuclei,[42] projecting to cortical areas involved in the processing of pain and visual perception. The same thalamic areas are activated in patients undergoing a migraine attack with extracephalic allodynia.[13,36] A possible pathophysiological mechanism underlies this high-level multisensory interaction in interictal migraine, which may also involve amplification of low-frequency thalamocortical oscillations and cortico-cortical connections.[29,30] The alteration in somatosensory and auditory integration in time course as well as location,[12] along with deficiency in filtering out repeated auditory stimuli,[19] and lingering and intense processing,[20] were evident also in nonmigraine individuals with sensory over-responsiveness. Because of scarce basic science evidence on abnormal multisensory integration in SMD, we can only propose a central neuroanatomical integration alteration in sensory and pain-transmitting pathways similar to that described in migraine.

Testing pain perception in everyday life contexts among pain-free individuals indicated that SMD co-occurs with daily pain sensitivity.[4] Further, individuals with SMD have also shown alterations in responses to pain psychophysical tests such as hyperalgesia and pain-lingering sensations (pain after-sensation), suggestive of impaired endogenous pain modulation.[6,7,55] Co-occurrence of enhanced pain sensitivity and SMD may be because of brain regions activation, commonly considered the "pain matrix," that are equally involved in processing nociceptive and nonnociceptive stimuli.[39] Therefore, we suggest that the sensory over-responsiveness that characterizes SMD, coexists with pain mechanism alterations, and may also share mechanisms with migraine. This assertion can be further supported by: 1) the results of our brief telephone survey of randomly chosen SMD individuals (unpublished data), in which 50% of subjects with SMD reported having chronic headaches, and 75% had family history of severe headaches, 2) findings that SMD has a predictive role in developing of complex regional pain syndrome (CRPS), a chronic pain syndrome associated with enhanced central neuronal excitability. We found, using logistic regression modeling, that the risk for developing CRPS for a person with sensory under- or over-responsiveness was 8.21 and 2.68 times higher, respectively, compared with a person with sensory normoresponsiveness. Thus, probably being nonspecific only to migraine, abnormal sensory modulation can characterize or even underlie the development of chronic pain conditions.

The level of sensory over-responsiveness in our migraine patients correlated positively with the PCS and its subscale scores, and with the state and trait anxiety level. Positive associations with PCS were reported for pain-free individuals with SMD but not for non-SMD subjects,[4] further emphasizing shared central mechanisms between SMD and migraine. An interesting positive association between sensory over-responsiveness and anxiety trait in MWA is in line with such associations described in adults[3,23] and in children with SMD.[8] In the latter study, anxiety level was found as a mediating factor between sensory responsiveness and ritual behaviors. Following this line, we may assume, that anxiety trait is a psychological parameter contributing to abnormal sensory modulation and higher pain sensitivity in MWA.

The positive association between sensory under-responsiveness (hedonic SRQ scores), migraine pain intensity, and antinociceptive psychophysical responses (high HPTs, low magnitude of temporal pain summa-

tion) is curious. Interestingly, the hedonic SRQ scores better predicted the odds to develop CRPS, compared with the aversive SRQ scores. We can hypothesize that prolonged suffering from strong pain diminishes preexisting perceptual aversive value of senses other than pain, and even modifies it to being plausible, probably as a part of a behavioral coping strategy needed to manage strong chronic pain.[37]

Our study has several possible limitations. One relates to the recruitment process. The patients were recruited via 2 main approaches—word of mouth between our hospital employees and their relatives, and among the migraine patients treated in the hospital headache clinics. This nonrandom sampling method could lead to a potential community bias, explaining also the relatively high incidence of aura among our patients. In addition, the definition of aura was on the basis of a single question response: "Do you experience vision, speech, or tactile disturbances up to half an hour before the attack?" rather than specific questions for presence or absence of each of the aura characteristics mentioned in the International Classification of Headache Disorders-3 beta definition. Finally, our findings were not corrected for multiple comparisons. Because this was the first study of its kind on this patient group, we chose to maximize sensitivity to identify possible parameters of interest for this and future studies, accepting the risk of increased type I error.

Conclusions

Migraine patients with aura are characterized by amplified pain facilitation, higher attacks frequency, and abnormal everyday non-noxious sensory responsiveness. The association between sensory over-responsiveness and migraine clinical and experimental pain characteristics suggests similar underlying mechanisms for SMD and migraine in general, and particularly for the MWA type. Further research is warranted to explore SMD as a risk factor for MWA.

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