Neurology Asia 2026; 31(2) : 649 – 654

Evaluation of auditory startle response in migraine and tension type headache

Buşra Yıldız, Baki Göksan, Meral Kızıltan

Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Neurology, Istanbul, Turkey.

Abstract

Objective: This study aimed to investigate the auditory startle response (ASR) in the ictal period of primary headache disorders. ASR may serve as a potential marker of brainstem hypersensitivity to external stimuli. *Methods:* The study included patients diagnosed with episodic migraine (EM, n=13), chronic migraine (CM, n=9), chronic tension-type headache (CTTH, n=9), and medication-overuse headache (MOH, n=8) as well as a control group of healthy individuals (n = 23). Headache diagnoses were established in accordance with the International Classification of Headache Disorders, 3rd edition (ICHD-III). ASR measurements were performed in all participants, and in patients, assessments were conducted in ictal period. ASR parameters were compared across all groups. *Results:* Total ASR probability was significantly elevated in patients with headache compared to healthy controls. In recordings from the orbicularis oculi muscle, both response duration and area under the curve (AUC) were significantly increased in patients with EM and CM. In contrast, only response duration was prolonged in individuals with CTTH and MOH. The presence of associated symptoms such as photophobia, phonophobia, osmophobia, or allodynia showed no correlation with ASR enhancement. *Conclusion:* The results demonstrate ASR hyperactivity during the ictal phase in patients with EM, CM, CTTH and MOH, with the most pronounced changes observed in EM and CM. These findings suggest that ASR alterations are associated with the pain component of headache disorders rather than with accompanying sensory symptoms.

Keywords: Auditory startle response, migraine, tension type headache, medication overuse headache

INTRODUCTION

Primary headache disorders are associated with abnormal brainstem sensitivity to both noxious and innocuous external stimuli, observed during ictal and interictal periods.[1] Among these disorders, migraine has been the most extensively studied. Sensory hypersensitivities —such as photophobia, phonophobia, osmophobia, and allodynia are common during during a migraine attack.[2] Numerous electrophysiological studies on primary headache disorders—characterized by abnormal spinal, brainstem, and cortical excitability—have utilized evoked potentials and reflex responses.[1] In particular, migraine has been shown to exhibit distinct interictal and ictal response patterns, which likely reflect dynamic alterations in brainstem circuits involved in pain modulation.

The startle reflex is an involuntary and sudden contraction of muscles in response to unexpected and intense tactile, acoustic, or vestibular stimulation and this reflex is a brainstem reflex originating from the nucleus reticularis pontis caudalis.[3-4] The ASR, a natural and stimulus-dependent reflex behavior serves as a valuable tool for investigating the integrity of motor and sensory pathways.[5] Evidence from previous studies indicates a relationship between pain and ASR. Acute painful stimuli such as foot shocks have been shown to significantly enhance ASR amplitude in rats.[6] Likewise, exposure to high-temperature stimuli has been observed to produce a similar effect in humans.[7]

In light of these findings, this study aimed to evaluate ASR parameters during the ictal phase of various primary headache disorders —including episodic migraine (EM), chronic migraine (CM), chronic tension-type headache

Address correspondence to: Buşra Yıldız, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Neurology, 34098 Fatih Istanbul, Turkey. Email: busramumay88@gmail.com

Date of Submission: 29 January 2025; Date of Acceptance: 10 February 2026

https://doi.org/10.54029/2026uak

(CTTH), and medication-overuse headache (MOH)— in comparison with healthy controls and to determine whether ASR alterations reflective of brainstem hypersensitivity are specific to migraine or present across different headache phenotypes.

METHODS

This study included 39 patients diagnosed with primary headache disorders who were followed at a tertiary headache outpatient clinic. The cohort included 13 patients with EM, 9 with CM, 9 with CTTH, 8 with MOH. Diagnoses were made in accordance with the criteria outlined in the International Classification of Headache Disorders, 3rd edition (ICHD-III).

Additionally, 23 age- and sex- matched healthy volunteers served as the control group (mean age: 37.2 ± 11.2 years in patients vs. 37.4 ± 12.2 years in controls, p=0.196). Among the patient group, 15,4% (n = 6) were male and 84.6% (n = 33) were female. The control group comprised, 26.1% male (n = 6) and 73.9% female (n = 17) participants.

The inclusion criteria for patients with headache were a diagnosis of a primary headache disorder and presentation within the first 24 hours after the onset of the pain episode, in the ictal phase. Only patients who had not taken any analgesics or triptans for the current attack were included.

Exclusion criteria included evidence of structural brain pathology on magnetic resonance imaging, the use of prophylactic medications for headache, and comorbid chronic pain conditions.

The study protocol was approved by the local Ethics Committee (Approval No: 2017-166580) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical evaluation

All patients underwent a standardized clinical assessment that included headache characteristics (frequency, duration, localization, character), as well as the presence of associated symptoms including nausea, vomiting, photophobia, phonophobia, osmophobia and allodynia. Patients with MOH were evaluated during the active medication overuse phase; none of the MOH patients were assessed during the withdrawal or detoxification period.

Electrophysiological evaluation

ASR were recorded in a quiet, temperature-controlled room (22–24°C), with participants seated comfortably. To minimize variability, all recordings were conducted by the same examiner. Participants were instructed to remain awake with their eyes open throughout the procedure.

Electrophysiological recordings were performed using a Neuropack MEB550 8 system (Nihon Kohden Medical, Tokyo, Japan). Ag-AgCl surface electrodes filled with conductive paste were placed on the unilateral orbicularis oculi (O.oc), sternocleidomastoid (SCM) and biceps brachii (BB) muscles. The ground electrode was positioned on the sternum.

Auditory stimuli consisting of bilateral 105-dB, 1 kHz tone bursts were delivered through earphones at randomized intervals ranging from 1 to 3 minutes. A total of five stimuli were administered. ASR was recorded from the left orbicularis oculi muscle in all participants. Each response was recorded with a sweep duration of 500 ms, filter settings of 100 Hz to 3 kHz, and amplitude sensitivity of 200 or 500 μV/div.

Data and statistical analysis

Muscle responses were defined as valid if they exhibited deflections of ≥50 μV. Each response was evaluated based on latency (ms), amplitude (μV), duration (ms), area under-the-curve (AUC, μV × ms). Response probability was calculated as:

[Number of responses/Number of total recordings (5)] x 100.

Additionally, the presence of an orienting reaction (OR), a late response following the auditory stimulus, was assessed.[8]

Statistical analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables were analyzed using the Kruskal Wallis test, while categorical variables were compared using the the chi-squared test. Where the Kruskal-Wallis test indicated significant differences, post hoc comparisons were conducted using either the Mann–Whitney U test or independent t-test, as appropriate.

Finally, logistic regression analysis was employed to examine the associations between clinical features (e.g., photophobia, phonophobia, osmophobia, allodynia) and electrophysiological findings (e.g., presence of OR, prolonged response duration, increased AUC in the O.oc muscle). A p-value <0.05 was considered statistically significant.

RESULTS

The total ASR probability was significantly higher in the patient group compared to healthy controls (p=0.043). Specifically, the probability of responses from the sternocleidomastoid (SCM) muscle was also elevated in patients (p=0.045). Additionally, significant differences were observed in the orbicularis oculi (O. oc) responses between the two groups: response duration (p=0.022) and area under the curve (AUC) (p=0.032) were both increased in patients with headache. A summary of ASR parameters in patients and controls is provided in Table 1.

Post hoc analysis revealed that, compared to healthy controls, patients with episodic migraine (EM) demonstrated significantly prolonged O. oc response durations ($p < 0.001$) and increased AUC values (p=0.039). Similarly, in patients with CM, O. oc response duration (p=0.002) and the AUC (p=0.011) were significantly elevated. Patients with CTTH and MOH also exhibited prolonged O. oc response durations compared to controls (p=0.002), although AUC differences were not statistically significant in these subgroups. Detailed subgroup comparisons are presented in Table 2.

No statistically significant differences were observed between any patient subgroups and the control group regarding SCM and BB responses.

The OR, a late-phase auditory response, was observed in 55.6% of CM patients, 30.8% of EM patients, 44.4% of CTTH patients, 25.0% of MOH patients. Notably, OR was not detected in any of the healthy controls (p =0.002).

Regression analysis did not reveal any significant associations between sensory symptoms (photophobia, phonophobia, osmophobia, or allodynia) and electrophysiological findings such as prolonged O. oc response duration, increased O.oc AUC, or presence of OR in migraine patients.

DISCUSSION

In this study, we investigated the ASR during the ictal phase in patients with various subtypes of primary headache and compared the results with those of healthy controls. Our main findings were as follows: (i) The headache group exhibited a

Table 1: ASR in patient and control groups

	Patients (n=39)	Controls (n=23)	p
O. oc latency, ms	33.9 ± 7.9	36.5 ± 9.8	0.300
O. oc duration, ms	**97.1 ± 47.2**	**55.3 ± 16.0**	**0.022**
O. oc area under the curve	**2.7 ± 2.8**	**1.5 ± 1.3**	**0.032**
O. oc amplitude, µV	408.1 ± 289.1	289.9 ± 176.1	0.191
O. oc probability (%)	99.7 ± 1.0	96.7 ± 11.4	0.244
SCM latency, ms	76.0 ± 26.1	72.7 ± 15.6	1.000
SCM duration, ms	76.5 ± 41.8	91.7 ± 59.3	0.842
SCM area under the curve	0.9 ± 1.0	0.9 ± 0.8	1.000
SCM amplitude, µV	248.2 ± 283.1	234.2 ± 193.9	0.612
SCM probability (%)	**33.8 ± 29.2**	**19.0 ± 25.8**	**0.045**
BB latecy, ms	118.1 ± 47.4	94.8 ± 22.9	0.257
BB duration, ms	61.7 ± 53.4	42.0 ± 13.5	0.606
BB area under the curve	87.3 ± 76.7	176.2 ± 93.6	0.229
BB amplitude, µV	133.0 ± 157.1	50.0 ± 48.2	>0.99
BB probability (%)	7.0 ± 11.5	5.4 ± 11.2	0.351
Total ASR (%)	**46.6 ± 11.5**	**40.6 ± 17.9**	**0.043**

Abbreviations: ASR, auditory startle response; O. oc, orbicularis oculi; SCM, sternocleidomastoid; BB, biceps brachii

Table 2: ASR in patient subgroups and control groups

	Controls	EM		CM		CTTH		MOH	
	n=23	n=13	p	n=9	p	n=9	p	n=8	p
O. oc latency, ms	36.5 ± 9.8	34.6 ± 9.0	>0.05	29.2 ± 6.2	>0.05	36.8 ± 5.8	>0.05	35.2 ± 8.9	>0.05
O. oc duration, ms	55.3 ± 16.0	**90.2 ± 31.9**	***<0.001***	**112.4 ± 68.4**	***0.002***	**95.4 ± 45.6**	***0.002***	**99.5 ± 50.7**	***0.002***
O. oc AUC	1.3 ± 1.2	**3.3 ± 3.2**	***0.039***	**3.0 ± 1.9**	***0.011***	1.3 ± 0.9	>0.05	3.7 ± 3.9	>0.05
O. oc amplitude, µV	289.9 ± 176.1	422.9 ±299.5	>0.05	509.5 ±428.6	>0.05	275.0 ±122.3	>0.05	415.4 ±245.7	>0.05
O. oc probability (%)	96.7 ± 11.4	100	>0.05	100	>0.05	98.6 ± 4.2	>0.05	100	>0.05

Abbreviations: ASR, auidoty startle response; EM, episodic migraine; CM, chronic migraine; CTTH, chronic tension type headache; MOH, medication overuse headache; O. oc, orbicularis oculi; AUC, area under the curve

hyperactive ASR compared to healthy controls; (ii) the probability of an orienting reaction (OR) was higher in patients than in controls; and (iii) the presence of sensory hypersensitivity symptoms—such as photophobia, phonophobia, osmophobia, or allodynia— was not associated with increased ASR or OR probability.

The brainstem plays a pivotal role in the modulation of pain, and its hyperexcitability has been consistently demonstrated in primary headaches through multiple electrophysiological studies.[1,9] Previous work in this field has primarily focused on two phenomena: sensitization (enhanced response to mild stimuli) and habituation (a diminished response to repeated stimuli), often assessed through evoked potentials and reflex studies. In episodic migraine, increased sensory responsiveness during attacks and interictal habituation deficits are well documented. Notably, in the preictal phase, in CM and in MOH both sensitization and impaired habituation may coexist.[1]

In our study, we found significantly prolonged O. oc response duration and AUC values of ASR which are indicative of sensitization. Furthermore, the persistently high probability of response to repeated auditory stimuli may reflect deficient habituation. However, since the number of trials was limited, future studies employing a higher number of trials (10–20) with a regular interstimulus interval would allow a more precise assessment of habituation dynamics.

These effects were similarly observed across all headache subtypes, suggesting a common pattern of heightened brainstem excitability during headache episodes—a particularly compelling finding.

Although data on CTTH remain limited, existing electrophysiological studies generally do not demonstrate significant abnormalities in sensitization or habituation.[10-12] However, evidence from studies examining sympathetic skin responses and trigeminocervical reflexes suggests electrophysiological similarities between migraine and CTTH.[13-16] In particular, autonomic alterations, such as changes in skin resistance, may contribute to the ASR, which comprises both motor and autonomic components.[17] These findings point toward a broader dysfunction in brainstem-mediated sensory integration.

Functional neuroimaging studies have demonstrated increased activation in brainstem regions involved in pain processing in migraine attacks, including the ipsilateral locus ceruleus, dorsal raphe nucleus and periaqueductal gray matter in the ipsilateral dorsolateral pons.[18] Among these, the locus ceruleus appears to play a pivotal role. It is activated during pain, and this activation contributes to the inhibition of perceived pain. Since the final neuron in the ASR pathway is a motor neuron under noradenergic control, the startle reflex can be modulated by locus coeruleus activity.[19] In this context, experimental lesion studies have reported a decrease in ASR amplitude following damage to the locus coeruleus.[20] This finding is important as it elucidates the relationship between brainstem

pain modulation systems and the ASR. Enhanced ASR has also been observed in other pain-related conditions, such as functional abdominal pain in children.[21] Based on these observations, we propose that the elevated ASR seen in our study reflects increased brainstem excitability in response to nociceptive input during headache attacks.

Although psychological factors, including anxiety and fear-conditioning —mediated by interactions between the locus ceruleus and amygdala—can also influence ASR[22], anxiety levels were not assessed in our participants. This constitutes a limitation in interpreting the role of affective factors.

The OR, a late-phase behavioral response to sensory input, is believed to involve motor integration with emotional and attentional components.[8] In our study, OR occurence was significantly higher in headache patients than in healthy controls. Although typically discussed in the context of functional movement disorders and psychogenic non-epileptic seizures, the increased OR in our cohort may indicate heightened central sensory reactivity rather than being purely affective in nature.[23,24] Again, the lack of anxiety evaluation limits our ability to fully interpret this association.

It is well known that hypersensitivity to one sensory modality during pain (e.g., photophobia) often co-occurs with increased sensitivity to others, such as phonophobia, osmophobia and allodynia, suggesting a shared underlying hypersensitivity mechanism.[25] However, in our study, we found no significant association between the presence of these symptoms and ASR or OR measures. This suggests that ASR hyperexcitability may be more directly related to the experience of pain itself, rather than to broader sensory hypersensitivity. This distinction may indicate the involvement of a more specific brainstem circuit.

This study has several limitations. First, the relatively small sample size may reduce the generalizability of our results. Second, we did not assess anxiety or other affective parameters, which may influence both ASR and OR outcomes. Finally, we did not include interictal recordings, which would have provided a more comprehensive evaluation of habituation patterns over time.

In conclusion, our findings demonstrate that the ASR is significantly elevated during headache episodes in patients with EM, CM, CTTH, and MOH. This supports the presence of a shared mechanism of brainstem hyperexcitability across primary headache subtypes. This pattern suggests that the heightened ASR may be linked more closely to pain processing than to co-occurring sensory hypersensitivity symptoms. Future studies involving larger cohorts, including affective assessments, comparing ictal and interictal ASR responses in the same patients, and using a higher number of trials with a regular interstimulus interval for the assessment of habituation are needed for a more precise characterization of brainstem excitability dynamics and to further elucidate the clinical relevance of ASR in evaluating brainstem dysfunction in primary headaches.

DISCLOSURE

Data availability: The data that support the findings of this study are available on request from the corresponding author.

Financial support: None

Conflict of interest: None

REFERENCES

1. Coppola G, Di Lorenzo C, Schoenen J, Pierelli F. Habituation and sensitization in primary headaches. *J Headache Pain* 2013; 14(1):65. https://doi.org/10.1186/1129-2377-14-65.
2. Mathew NT, Kailasam J, Seifert T. Clinical recognition of allodynia in migraine. *Neurology* 2004;63(5):848-52. https://doi.org/10.1212/01.wnl.0000137107.27585.f7
3. Davis M, Gendelman DS, Tischler M, Gendelman PM. A primary acoustic startle circuit, lesion and stimulation studies. *J Neurosci* 1982; 2(6):791-805. https://doi.org/10.1523/JNEUROSCI.02-06-00791.1982
4. Yeomans JS, Li L, Scott BW, Frankland P. Tactile, acoustic and vestibular systems sum to elicit the startle reflex. *Neurosci Behav Rev* 2002; 26(1):1-11. https://doi.org/10.1016/s0149-7634(01)00057-4
5. Koch M. The neurobiology of startle. *Prog Neurobiol* 1999; 59(2):107-28. https://doi.org/10.1016/s0301-0082(98)00098-7
6. Krase W, Koch M, Schnitzler HU. Substance P is involved in the sensitization of the acoustic startle response by footshocks in rats. *Behav Brain Res* 1994; 63(1):81-8. https://doi.org/10.1016/0166-4328(94)90053-1
7. Crombez G, Baeyens F, Vansteenwegen D, Eelen P. Startle intensification during painful heat. *Eur J Pain* 1997; 1(2):87-94. https://doi.org/10.1016/s1090-3801(97)90066-5
8. Gogan P. The startle and orienting reactions in man. A study of their characteristics and habituation. *Brain Res* 1970; 18:117-35. https://doi.org/10.1016/0006-8993(70)90460-9

9. Demarquay G, Mauguière F. Central nervous system underpinnings of sensory hypersensitivity in migraine: Insights from neuroimaging and electrophysiological studies. *Headache* 2015; 56(9):1418-38. https://doi.org/10.1111/head.12651
10. Siniatchkin M, Kropp P, Neumann M, Gerber WD, Stephani U. Intensity dependence of auditory provoked potentials in migraine families. *Pain* 2000; 85(1-2):247-54. https://doi.org/10.1016/s0304-3959(99)00271-7
11. Siniatchkin M, Kirsch E, Kropp P, Stephani U, Gerber WD. Slow cortical potentials in migraine families. *Cephalalgia* 2000; 20(10):881-92. https://doi.org/10.1046/j.1468-2982.2000.00132.x
12. Demirci S, Savaş S. The auditory event related potentials in episodic and chronic pain sufferers. *Eur J Pain* 2002; 6(3):239-44. https://doi.org/10.1053/eujp.2001.0342
13. Nardone R, Tezzon F. Short latency trigemino-sternocleidomastoid response in patients with migraine. *J Neurol* 2003; 250(6):725-32. https://doi.org/10.1053/eujp.2001.0342
14. Nardone R, Tezzon F. The trigemino-cervical reflex in tension-type headache. *Eur J Neurol* 2003; 10(3):307-12. https://doi.org/10.1046/j.1468-1331.2003.00531.x
15. Milanov I, Bogdanova D. Trigemino-cervical reflex in patients with headache. *Cephalalgia* 2003; 23(1):35-8. https://doi.org/10.1046/j.1468-2982.2003.00454.x
16. Ozkul Y, Ay H. Habituation of sympathetic skin response in migraine and tension type headache. *Auton Neurosci* 2007; 134(1-2):81-4. https://doi.org/10.1016/j.autneu.2007.02.006
17. Jansen AS, Nguyen XV, Karpitskiy V, Mettenleiter TC, Loewy AD. Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. *Science* 1995; 270(5236):644-6. https://doi.org/10.1126/science.270.5236.644
18. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann, Schankin C, Akerman S. Pathophysiology of migraine: A disorder of sensory processing. *Physiol Rev* 2017; 97(2):553-622. https://doi.org/10.1152/physrev.00034.2015
19. Heckman CJ, Mottram C, Quinlan K, Theiss R, Schuster J. Motoneuron excitability: the importance of neuromodulatory inputs. *Clin Neurophysiol* 2017; 120(2):2040-54. https://doi.org/010.1016/j.clinph.2009.08.009
20. Szabadi E. Modulation of physiological reflexes by pain: role of the locus coeruleus. *Front Integr Neurosci* 2012; 6:94. https://doi.org/10.3389/fnint.2012.00094
21. Bakker MJ, Boer F, Benninga MA, Koelman JH, Tijssen MA. Increased auditory startle reflex in children with functional abdominal pain. *J Pediatr* 2010; 156(2):285-91.e1. https://doi.org/10.1016/j.jpeds.2009.08.045
22. Fendt M, Koch M, Schnitzler HU. Amygdaloid noradrenaline is involved in the sensitization of the acoustic startle response in rats. *Pharmacol Biochem Behav* 1994; 48(2):307-14. https://doi.org/10.1016/0091-3057(94)90532-0
23. Yalçın M, Tellioğlu E, Gündüz A, *et al*. Orienting reaction may help recognition of patients with psychogenic nonepileptic seizures. *Neurophysiol Clin* 2017; 47(3):231-7. https://doi.org/10.1016/j.neucli.2017.02.005
24. Cook E, Turpin G. Differentiating orienting, startle and defense responses: the role of affect and its implications for psychopathology. In: Lang PJ, Simons RF, Balaban M, eds: Attention and orienting: sensory and motivational processes, 1st edn. Psychology Press, London. 1997: 137-66.
25. Schwedt TJ. Multisensory integration in migraine. *Curr Opin Neurol* 2013; 26(3):248-53. https://doi.org/ 10.1097/WCO.0b013e328360edb1