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Lateralized nociceptive blink reflex habituation deficit in episodic cluster headache: Correlations with clinical features

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Abstract

Background: We previously observed impaired habituation mechanisms of the conventional blink reflex (BR) in patients with episodic cluster headache (ECH) during the bout, studying only the affected side. Here, we have studied the nociceptive-specific BR (nBR) both on the affected and non-affected sides, and in relation to clinical features.

Participants and methods: We recorded nBR in 18 ECH patients during the bout, and in 18 healthy volunteers (HVs). We compared pain threshold, area, and habituation of the nBR, recorded both for the affected and non-affected sides.

Results: In patients, the pain threshold on the affected side was lower than that of the non-affected side ($p = 0.009$), and lower than in HVs ($p = 0.038$). Reflex area was decreased on both sides ($p < 0.05$) compared with HVs, whereas habituation was significantly impaired only on the affected side ($p = 0.025$ vs. HVs; $p = 0.003$ vs. non-affected). The habituation slope was positively correlated with the number of days since the onset of the bout and the daily attack frequency.

Conclusions: Our data reflect lateralized pathological variations in craniofacial nociception in ECH patients over the course of the cluster period. We hypothesized that this is due to malfunctioning of mechanisms that regulate hypothalamic activity and descending aminergic controls.

Keywords

Cluster headache, blink reflex, habituation, lateralization, pain

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Introduction

In its episodic form, cluster headache (CH) is a neurological disorder characterized by excruciating pain, mediated by activation of the first division of the trigeminal nerve, and accompanied by autonomic symptoms resulting from activation of the parasympathetic component of the seventh cranial nerve (1). CH attacks usually cluster in time, lasting from seven days to a year, and are separated by remission periods lasting for months or years, with a striking circannual and circadian pattern (2). The pathophysiological facets of CH are still not comprehensively understood and provoke considerable debate. During the last few decades, great advances in the understanding of CH pathophysiology were made with the use of modern techniques for functional neuroimaging. A permissive role of the posterior hypothalamus, malfunctions in nociceptive processing, and a deficiency in the descending pain

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control system have been proposed as possible mechanisms that may contribute to CH predisposition and recurrence (3,4).

Abnormalities in pain processing have also been disclosed using electrophysiological methods, at the both the level of the brainstem and spinal cord (5). Researchers have found signs of sensitization within the trigeminal pain system. Both during and outside the bout, patients with CH had lower thresholds for pressure pain (6), electric pain of the corneal reflex (7), and increased onset latency and area under curve (AUC) ratio for the blink reflex (BR) using a nociceptive-specific surface electrode (8) on the affected side compared with the non-affected side. Similarly, researchers have detected a lower threshold for the spinal nociceptive flexion reflex (9), lateralized preferentially on the affected side rather than the unaffected side (10).

The BR is a way to indirectly assess trigeminal nucleus caudalis functional integrity. Studies involving only the affected side in CH and stimulating both tactile and nociceptive fibers by means of a standard surface electrode found a lack of habituation for both the R2 and the R3 BR components in patients compared to healthy controls (11). On the other hand, Holle et al. (2012) failed to detect altered habituation of the R2 BR in episodic and chronic CH during or outside a bout, using more preferential stimulation of facial cutaneous nociceptive fibers by means of nociceptive-specific electrodes in the territory of the supraorbital nerve. In the latter study, however, the majority of patients with CH were taking one or several prophylactic medications at the time of recording, which may have altered the course of the disease, and led to biased results (12). Therefore, further studies are needed to definitively address this issue.

Here, we have studied pain in the trigeminal system more selectively by recording the nociceptive-specific blink reflex (nBR), area, and habituation both in the affected and non-affected sides of a group of patients with untreated CH. We particularly aimed to verify whether there are fluctuations in the trigeminal responses in relation to clinical features in episodic cluster headache (ECH) during the bout, and documented lateralized pathological changes over the course of the cluster period.

Materials and methods

Participants

Eighteen patients with ECH (code 3.1.1, Table 1) with strictly unilateral pain (eight right side, 10 left side) were recruited from among those who attended our headache center. Other types of primary or secondary headaches were excluded by clinical and/or instrumental evaluation, as appropriate. We collected information on various patient clinical characteristics at the time of either the screening visit or the day of the recording session: daily attacks frequency, attacks duration, and days elapsed from the beginning of the bout. Moreover, we were able to collect information on duration of history of ECH and total number of bouts experienced so far in 14 out of 18 patients, and the number of hours elapsed from the last attack in 10 out of 18 patients (Table 1). Exclusion criteria included any serious systemic or neurological disease or psychiatric disorder. Patients with ECH with a family history of migraine (first-degree relatives) were excluded. All patients were observed during a bout, but outside the attacks. No preventive drugs were permitted during the three months preceding observations. For comparison, 18 healthy volunteers (HVs) of comparable age and gender distribution (Table 1) were recruited from among medical students and health care professionals. They had to be devoid of any overt medical condition,

Table 1. Details of the enrolled participant demographic and clinical characteristics.

	HVs ($N = 18$)	ECH ($N = 18$)
Age (minimum/maximum)	39.5 ± 10.1 (26–60)	40.0 ± 8.7 (27–52)
Gender (M/F)	(15/3)	(16/2)
Duration of history of ECH (years)		8.57 ± 7.57
Bouts experienced so far *(N)*		8.28 ± 7.47
Attacks frequency (*N*/day)		2.38 ± 2.14
Attacks duration (minutes)		47.66 ± 34.56
Days from the beginning of the bout *(N)*		22.16 ± 23.57
Hours elapsed from the last attack (*N*)		13.66 ± 9.15
Usual cluster side (right/left)		(8/10)

HVs: healthy volunteers; ECH: episodic cluster headache; M: male; F: female.

personal or family history of migraine or epilepsy, and regular drug intake.

None of the enrolled participants had sleep deprivation or alcohol ingestion the day preceding the recordings. Caffeinated beverages were not allowed on the day of recordings. All individuals gave their written informed consent to participate in the study, which had the approval of the local ethics committee. The study complied with the terms of the Helsinki Declaration on human experimentation.

Procedure

The participants were comfortably settled in an armchair in a quiet room, and were asked to sit back and relax, keeping their eyes open. During the entire duration of the recording session, we checked at regular intervals that their level of attention and vigilance remained normal. All recording sessions were performed in the morning (9:00–11:00 a.m.) by two expert neurophysiologists (M.B. and D.D.L.).

Percutaneous electrical stimulation of the innervation territory of the supraorbital nerve (SON) was obtained by means of a specific (nociceptive) concentric surface electrode. The concentric electrode was constructed according to the physical characteristics described by Kaube et al. (13). Our group has validated the technique in a previous study by eliciting another brainstem reflex, the trigeminocervical reflex (14).

Individual sensory (ST) and pain (PT) perception thresholds were defined as the minimum stimulation intensity perceived as tactile and painful, respectively, over three series of ascending and descending stimuli.

A train of electrical stimuli composed of three pulses, each of 0.1-ms duration (interpulse interval, 5 ms) (15), was delivered at pseudorandom 30- to 35-second interstimulus intervals, at a fixed intensity of $1.2 \times PT$, via a stimulating electrode applied to the supraorbital notch. Recording electrodes were placed infraorbitally (active) over the orbicularis oculi muscle and latero-orbitally (reference) on both sides. A ground electrode was placed on the left arm. We recorded two blocks of six rectified electromyogram (EMG) responses with an interblock interval of two minutes, bilaterally over the orbicularis oculi muscles using a Digitimer D360 amplifier (band-pass 0.05–2000 Hz, Gain 1000) and CED^{TM} power 1401 digital-to-analog converter (Cambridge Electronic Design Ltd, Cambridge, UK). All recordings were averaged off-line using the Signal^{TM} software package, version 4.10 (CED Ltd). For each sweep, the post-stimulus period was recorded for 150 ms and subsequently, off-line filtered (high-pass 10 Hz). The procedure was conducted on both affected and non-affected sides in ECH patients, on the right side in HV. In patients, the two experimental sessions (affected and non-affected side stimulation) were performed in a random order at $\geq$15-minute intervals. Five responses were rectified and averaged for each block (Figure 1), as the first

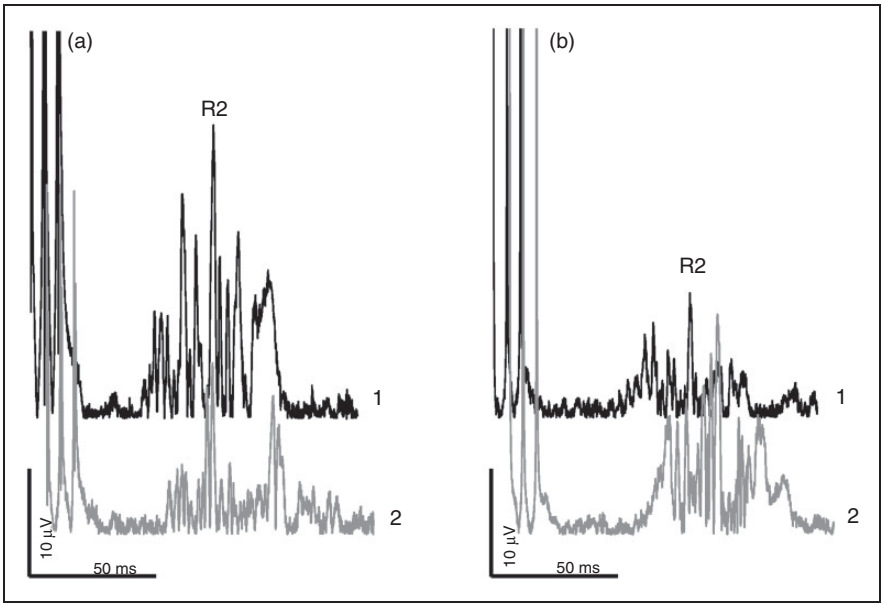

Figure 1. Representative traces of nociceptive blink reflex recordings: Two blocks of five rectified and averaged responses in a healthy volunteer (a) and a patient with episodic cluster headache (b).

sweep was excluded from the signal analysis to avoid contamination with startle responses. For each averaged block, the R2 component of the AUC ($\mu V \times ms$) calculated between 27 and 87 ms (16,17) were measured off-line by an investigator (M.B.) who was blinded to the participants' identities. Habituation of the nBR R2 was defined as the slope of the linear regression of the R2 area between the first and the second blocks of recordings.

Statistical analysis

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0. The normal distribution of data for each group of individuals was tested using the Shapiro-Wilk test. Because all the considered variables (ST, nBR blocks area and slope) but one (PT) showed a non-Gaussian distribution, all the variables were compared using the non-parametric Mann-Whitney *U*-test (HVs vs. ECH-affected; HVs vs. ECH non-affected side) and the Wilcoxon test (ECH-affected vs. ECH non-affected side). Because of normal distribution, pain threshold was then tested using the independent-samples *t*-test (HVs vs. ECH-affected; HVs vs. ECH non-affected side) and the paired sample *t*-test (ECH-affected vs. ECH non-affected side). Regression analysis was used to disclose linear trends in the R2 component of the AUC across blocks (slope) group. Spearman's rho correlation test was used to search for correlations among the neurophysiological parameters and clinical variables. Values of $p < 0.05$ were considered statistically significant.

Results

Examples of nBR recordings obtained from an HV and an ECH patient are shown in Figure 1.

Perception thresholds were not different between subject groups (HVs vs. ECH-affected $U = 109.0$, $p = 0.091$; HVs vs. ECH non-affected $U = 105.5$, $p = 0.073$; ECH-affected vs. ECH non-affected $Z = -1.332$, $p = 0.183$), whereas PT was significantly lower on the affected side in patients with ECH compared both with the HVs ($t = 2.162$, $p = 0.038$), and the non-affected side ($t = 2.958$, $p = 0.009$) (Figure 2). Onset latency of the R2 nBR component was not significantly different between groups ($p > 0.05$).

The R2 component of the nBR AUC in blocks 1 and 2 was significantly lower both on the affected and non-affected sides in patients with ECH than in HVs (all $p < 0.05$, Figure 3). Habituation, as reflected by the slope of the linear regression of nBR AUCs from block 1 to block 2, was positive on the affected side in patients with ECH ($+0.08 \pm 0.39$; $U = 91.0$, $p = 0.025$ vs. HVs, and $Z = 2.940$, $p = 0.003$ vs. non-affected side), and negative on the non-affected side in patients with ECH (-0.22 ± 0.34, $U = 158.5$, $p = 0.912$ vs. HVs) and in HVs (-0.26 ± 0.52; Figure 4).

Spearman's test disclosed correlations between nBR parameters and clinical variables. In the ECH patient group, the slope was positively correlated with the number of days elapsed from the beginning of the bout ($rho = 0.575$, $p = 0.05$) and the daily attack frequency ($rho = 0.537$, $p = 0.032$), but only when the affected side was stimulated. In a subgroup of patients from whom we had collected this clinical information

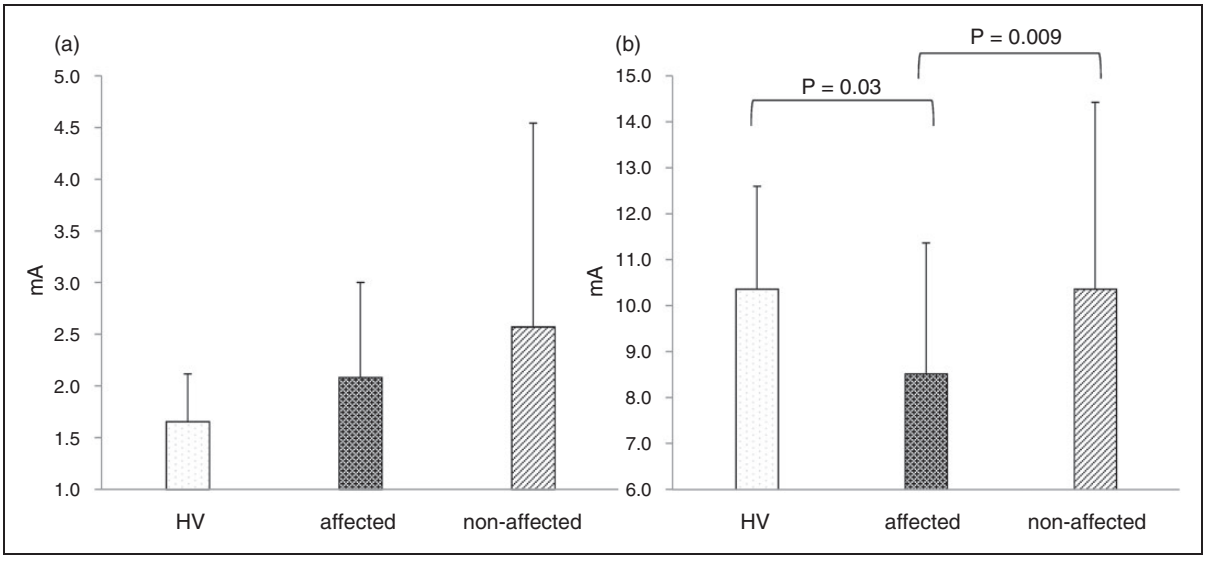

Figure 2. Perception (a) and pain (b) thresholds in healthy volunteers (HVs) and in patients with episodic cluster headache (ECH) on the headache-affected and non-affected sides.

there was no significant correlation between each neurophysiological parameter and duration of history of ECH, total number of bouts experienced so far, and hours elapsed from the last attack.

Discussion

The main finding of the present study was that patients with ECH had lateralized BR abnormalities. In fact, the PT was lower and habituation was deficient only when the affected side was stimulated, compared with the non-affected side and with HVs. The slope representing the degree of habituation was strongly related to the cluster clinical features because it was positively correlated with the number of days elapsed from the beginning of the bout and the daily attack frequency.

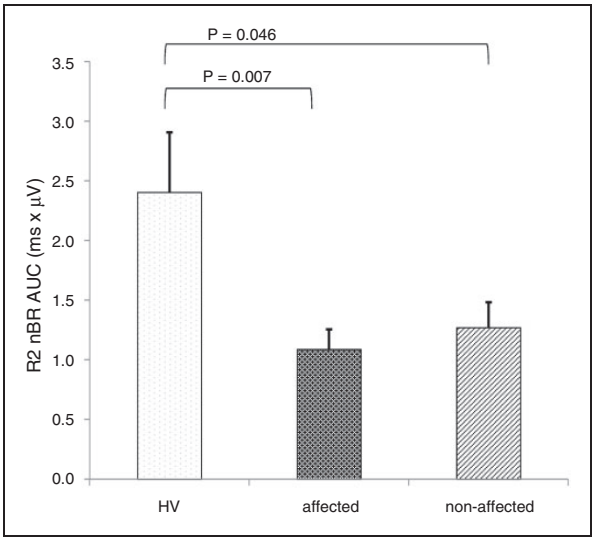

Figure 3. R2 response area under the curve (AUC) in the first block of averaged responses.

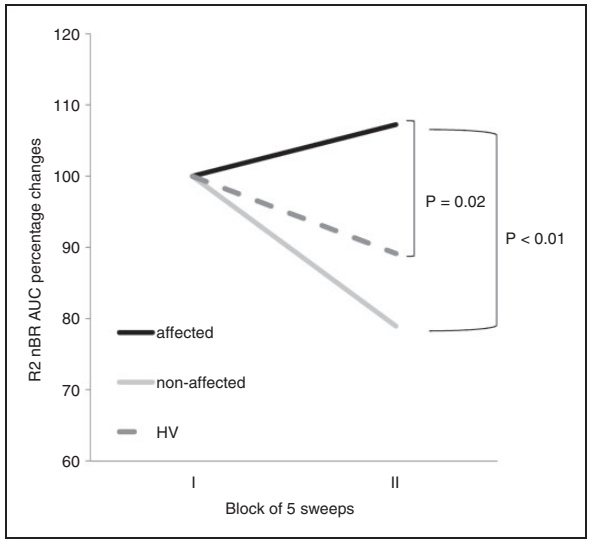

Figure 4. Habituation of the R2 response area on the affected and non-affected cluster side, compared with healthy volunteers (HVs), in two blocks of five averaged responses expressed as a percentage of the first block.

In a previous paper, Holle and colleagues (2012) did not detect altered habituation of the R2 BR in ECH and chronic CH during or outside a bout, also using nociceptive-specific electrode and stimulating both headache sides. This contrasts with our data and may be related to the differences in patients' selection criteria and/or stimulus protocol. In Holle et al. the majority of patients were taking prophylactic medications (verapamil, lithium, topiramate) at the time of recording, which may have altered the spontaneous course of the disease, and biased the results (12). Additionally, they acquired one block of 15 stimuli delivered at pseudorandom 12- to 18-s interstimulus intervals, which is a faster stimulation protocol than our two blocks of six stimuli delivered at pseudorandom 30- to 35-s interstimulus intervals with and intra-blocks interval of two minutes. Whether the degree of R2 nBR component habituation assessed with the nociceptive electrode varies with the frequency of stimulus repetition, as happened by using the standard electrode in CH (11), remains to be determined in a properly designed study.

Evoking the BR using a standard electrode, we have previously observed deficient habituation both of the polysynaptic R2 and the R3 BR components in the affected side in patients with episodic CH when compared with HVs (11). Our limitations were: having studied only the side usually affected; and not having minimized the non-nociceptive component of reflex blinking, because a standard electrode elicits a reflex response comprising a summation both of tactile and nociceptive fiber activation (16,18). The present data thus extend and complement our previous findings, because we have stimulated both the affected and non-affected sides. We discovered that the lack of BR habituation was present only when the affected side was stimulated, and using a nociceptive electrode. This electrode is able to depolarize the superficial, nociceptive fiber-containing layer of the dermis without reaching the deeper one because of its peculiar physical characteristics, namely concentric shape and small anode-cathode distance and a high current density at low stimulation intensity. This may allow depolarization of the nociceptive afferent fibers present in the superficial layer with negligible involvement of the tactile nociceptors present in the deeper layers. This peculiarity has permitted us to detect a

lower PT compared with HVs only when the affected side is stimulated, a datum that was not observed in our previous work (11). A possible explanation for this may lie in the more efficacious activation of the nociceptive Aδ fibers with lower electrical intensity stimulation by the concentric electrode. Similarly, Sandrini and colleagues (1991) elicited another trigeminofacial reflex namely the corneal reflex, mediated predominantly by unmyelinated fibers, in a mixed group of patients with episodic and observed a reduced PT on the affected side although perception was normal (7). The latter, together with our lowed PT, seems to provide strong evidence for the presence of sensitization over the first division of the trigeminal nerve in CH during the bout outside an attack. On the contrary, the fact that the amplitude of the corneal reflex was normal and the area of nBR in our patients was reduced overall instead of showing an increase, seems to suggest otherwise. Additional dysfunctional neurobiological factors could be at work in patients with CH, and these would otherwise normally act as mechanisms for nociceptive pathway sensitization.

Involvement of the hypothalamus in the pathogenesis of CH has been widely demonstrated both at functional and biochemical levels (1). Hypothalamic hyperactivity ipsilateral to the affected side in CH has been observed during the attacks, as reported by almost all the neuroimaging studies (3,19). However, hypothalamic activation does not seem to be disease specific, since it has been observed during other trigeminal autonomic cephalalgia attacks (20,21) and even during spontaneous attacks of migraine without aura (22). It could still be a factor that contributes towards a central permissive state that allows activation of the trigeminal system, mediating pain, and of the parasympathetic reflex, producing the autonomic symptoms (1,3). We have previously hypothesized that the hypothalamus could also be involved in the habituation deficit observed in our patients with CH (11). In fact, the hypothalamus is known to have a modulatory effect on the trigeminovascular nociceptive system and on autonomic pathways (23,24). In transgenic mice overexpressing corticotrophin-releasing hormone resulting in chronic hypothalamus-pituitary-adrenal axis hyperactivity, reduced magnitude and response habituation of the startle reflex was observed by Dirks et al. (2002), which is comparable to our findings (i.e. reduced area and habituation of BR) in patients with ECH (25). However, this pattern of reduced reactivity and plasticity of the trigeminal system does not seem to be due to a general deficit in attentional processes, since these patients have not shown reduced amplitude and habituation, as reflected by using event-related potentials (26,27).

Our finding of hypothalamic involvement in the lateralized neurophysiological abnormalities is also supported by the observation that there are variations in the degree of deficit in BR habituation depending on the severity of clinical features. In other words, the steepness of the habituation slope increases with the number of days elapsed from the beginning of the bout and the daily attack frequency. Interestingly, it is well known that the frequency of attacks usually tends to increase during the course of the active phase in CH (28,29), but the proximity of the last CH attack does not change trigeminofacial measurements (7), as also confirmed by us in subgroup analysis. These findings, together with our present results, indicate that the overall performance of the trigeminal system strongly depends on the evolution of clinical features during the active period rather than the manifestations of single attacks. Moreover, the observation that, at least in a subgroup of patients, nBR habituation deficit did not correlate both with the history of ECH and number of bouts experienced so far points against bout repetition and long-lasting induced effects.

Additional dysfunctional neurobiological factors could be at work in determining lack of BR habituation in patients with CH. We recently described the case of a patient with chronic CH whose condition improved with the administration of transdermal rotigotine, a dopamine agonist. In addition to clinical improvements, a normalization of the habituation deficit of the R2 nBR component, and a normal decreasing response to repeated stimulation, was observed during rotigotine administration (30). The latter indirectly suggests a malfunction in descending aminergic (especially dopaminergic) control in CH during the bout (30,31). In fact, in an experimental model, dopamine could directly inhibit the activation of trigeminocervical neurons in response to middle meningeal artery stimulation (32). Moreover, it has also been shown that the dopaminergic control pathways can modulate BR excitability via serotoninergic transmission by the nucleus raphe magnus that, in turn, inhibits the spinal trigeminal nucleus (33). Deficiency in descending aminergic control in CH was recently confirmed by our observation that the tonic supraspinal control of pain evoked by the cold pressor test had no effect on nociceptive flexion, reflex temporal summation, and reflex area only during the bout (but not outside) (4).

In conclusion, taking into account the recent advances in the understanding of CH pathophysiology, we have hypothesized that dysfunctional hypothalamic trigeminal and descending aminergic control, as well as sensitization phenomena occurring at the level of the nucleus trigeminal caudalis, could be the underlying

causes of the lateralized abnormal trigeminal processing observed in our patients showing ECH, during the cluster period. A full explanation for the lack of habituation in ECH during the bout outside an attack will depend on the understanding of interrelationships between the mechanisms that regulate hypothalamic activity, descending aminergic controls, and the trigeminal system.

Clinical implications

- We have studied pain in the trigeminal system more selectively by recording the nociceptive-specific blink reflex (nBR), area, and habituation both in the affected and non-affected sides of a group of patients with untreated cluster headache (CH).
- Reflex area was decreased on both sides, whereas pain threshold was lower and habituation slope was steeper only on the affected side.
- The habituation slope was positively correlated with the number of days since the onset of the bout and the daily attack frequency.
- We hypothesized that our results are due to malfunctioning of mechanisms that regulate hypothalamic activity and descending aminergic controls.

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Conflict of interest

None declared.

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