Chapter 9
Neurophysiology of Other Primary Headaches

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Abbreviations

CH	Cluster headache
DNICs	Diffuse noxious inhibitory controls
EMG	Electromyography
HNCS	Heterotopic noxious conditioning stimulation
LEPs	Laser evoked potentials
nBR	Nociception-specific blink reflex
PPT	Pressure pain thresholds
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TACs	Trigeminal autonomic cephalalgias
TTH	Tension-type headache
TTS	Total tenderness scores
VEPs	Visual evoked potentials

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9.1 Introduction

Primary or idiopathic headache syndromes are disorders where a temporary or permanent dysfunction of the central nervous system is present, but apparent organic lesions cannot be found. They include migraine, tension-type headache (TTH), and the trigeminal autonomic cephalalgias (TACs), among which the most common is "cluster headache" (CH). Primary headaches are highly prevalent and the most common neurological disorders among the general population. They are receiving growing attention over the years on the one hand because they affect people's quality of life and on the other hand because of their significant economic impact. The International Classification of Headache Disorders (ICHD) in its previous [1, 2] and current version [3] are the most sensitive diagnostic tool for headaches, and application of the proposed criteria greatly improved research on headaches allowing for a better comparison of clinical data between headache centers.

The large and still growing scientific knowledge on the primary headaches pathophysiological mechanisms, though scientists have not completely disentangled them, has contributed to raise interest on these neurological conditions. In fact, great advances were made during the last decades through the new research techniques. Clinical neurophysiology methods, in particular, have allowed in vivo measurements of the headache patients' cortical and peripheral responses to various sensory stimuli.

In this chapter we will review the neurophysiological studies in primary headaches other than migraine (treated elsewhere).

9.2 Tension-Type Headache

The most relevant neurophysiological abnormality in migraine is the interictal deficit of cortical habituation to repetitive stimulation. Habituation is defined as "a response decrement as a result of repeated stimulation" [4] and is a common feature of responses to any kind of sensory stimulation. In most studies this phenomenon is not present, and sometimes replaced by potentiation, in episodic migraine patients between attacks, but normalizes just before and during the headache phase. It is likely to be due to interictal cortical hyper-responsivity, which could be a possible expression of thalamocortical dysrhythmia [5]. The phenomenon of habituation has been investigated in tension-type headache as well, but there are only a few reports about it.

In episodic TTH sufferers, the habituation of the latency of P300 (a long-latency cognitive cortical evoked potential) was normal, while P300 amplitude also showed some degree of habituation, although not of statistical significance [6]. No habituation deficits were observed exploring visual evoked or event-related potentials other than P300 in episodic [7] or chronic TTH patients [7, 8]. Mismatch negativity, which is likely to reflect the automatic central processing of a novel stimulus, and

P300 habituation were significantly lower in TTH children than in healthy subjects in one study, where P300 habituation also positively correlated with behavioral symptomatology [9].

Patients affected by chronic TTH showed a normal habituation in scalp potentials evoked by CO_2 laser stimulation (LEPs) of the hand and facial skin [10].

By investigating habituation of sympathetic skin responses (SSR), a tool used to evaluate autonomic dysfunction, Ozkul and Ay found that in both episodic migraine without aura and TTH patients, there was a lack of habituation compared to normal controls [11].

The mild electrophysiological similarities in the cortical habituation behavior between the episodic forms of migraine and TTH suggest that some subgroups of TTH patients might be at the end of the migraine spectrum.

Sensitization is defined as facilitation occurring at the beginning of the stimulus presentation. The few studies in which the dynamic behavior of responses was analyzed using successive blocks of responses did not find any clear evidence for sensitization, expressed as increased amplitude of the first block, neither in episodic TTH for visual evoked potentials (VEPs) [7], visual P300 [6], laser evoked potentials (LEPs) [9], and sympathetic skin responses [11] nor in chronic TTH for visual P300 [8] and LEPs [10].

Some indirect evidence for sensitization was found in TTH, chiefly in its chronic form, with nociceptive specific reflexes and laser evoked cortical potentials, which enable to explore the cortical responses to peripheral nociceptive stimuli.

In chronic TTH patients, the amplitude, area, and latency [12–15] of the blink reflex R2 component were not different respect to values in healthy subjects, but it had a slower recovery cycle that was interpreted as a possible reduced excitability of the brainstem interneurons [14]. When a nociception-specific electrode was used, lower values of the normalized root mean square and area under the curve of the blink with control subjects were found respect to controls [16]. According to the authors, it may reflect consistent increases in eye muscle activity on the painful stimulation side.

One of the most investigated electrophysiological tests in TTH patients is the exteroceptive suppression of the temporalis muscle contraction that is the reflex inhibition of contraction of jaw-closing muscles by electrical stimulation of the infraorbital and mental nerves. It is obtained by surface EMG recordings of contracted muscles, where two different periods of suppression can be identified (SP1 and SP2). The SP2, mediated by a polysynaptic chain of interneurons likely to belong to the bulbar reticular formation, correlates to the level of excitability of these brainstem interneurons [17]. In episodic TTH patients, it was found normal, and in chronic TTH subjects, it was shortened in some studies, but not in others [18], possibly due to methodological differences.

Trigeminocervical reflex obtained from the sternocleidomastoid muscle after electrical stimulation of the supraorbital or infraorbital nerve had reduced latencies in chronic tension-type headache patients, similarly to migraineurs [19–21]. These findings further sustain the presence of a possible dysfunction in brainstem interneuronal activity controlling the pericranial muscles.

The presence of central sensitization in chronic TTH is strongly suggested also by the results of studies on pain sensitivity in pericranial or lower limb tissues. Testing the nociceptive lower limb flexion reflex, significantly lower subjective pain thresholds and reflex threshold in chronic TTH than in controls were found [22], associated with a paradoxical facilitation of the reflex response during the cold pressor test suggesting deficient descending inhibition, an abnormality also found by others [23]. Pressure pain thresholds (PPTs) were found normal in episodic and "mixed" TTH in every studies [24–28] except one [29], but decreased in chronic TTH in almost all studies [28, 30–33] especially on the anterior part of the temporalis muscle [25, 26, 30–32, 34] and in the upper part of the trapezius muscle [35]. Only one study did not confirm these results [26]. In a follow-up study, where PPTs were tested in episodic TTH patients at baseline and retested during the following twelve years, the baseline PPTs were normal but decreased at the follow-up in patients who develop the chronic form, suggesting that it was the headache frequency to induce an increased pain sensitivity and not the opposite [36].

Another indirect measure of sensitization is the temporal summation that is the increase in pain perception to repeated noxious stimulation, obtained by an algometer and heterotopic noxious conditioning stimulation (HNCS). Chronic TTH sufferers had more pain from repeated algometer pressures, both at finger and shoulder, and it was less inhibited by conditioned HNCS compared with controls [37]. Lower pain thresholds in the muscle and skin of the cephalic region but not of the extracephalic region with higher rating to suprathreshold single and repetitive electrical stimulation were reported in patients with chronic TTH than in healthy subjects [38].

When investigating laser evoked potentials in chronic TTH patients, the heat pain threshold was not different respect to controls, at the level of both the hand and pericranial skin, but the total tenderness scores (TTS) at pericranial sites were higher in patients than in controls, which was associated to a greater amplitude of the N2a–P2 LEP complex elicited by stimulation of the pericranial zone [39].

9.3 Cluster Headache and Other Trigeminal Autonomic Cephalalgias (TACs)

Electrophysiological methods were used to investigate cognitive and nociceptive processes in trigeminal autonomic cephalalgias, particularly in cluster headache (CH).

Two visual event-related potential studies in cluster headache either during the bout or outside and in chronic paroxysmal hemicrania showed a normal cognitive habituation [8, 40]. However, intensity dependence of auditory potentials, which is supposed to be an indirect expression of deficient habituation in migraineurs [41], was found markedly increased also in cluster headache patients both during and outside the bout [42].

Formisano et al. were the first to found abnormal habituation of the blink reflex in a small number of CH patients during the attack, but in this study there was not a comparison group of control subjects [43]. Habituation of both the R2 and the R3

blink reflex components are impaired in CH patients on the affected side compared to healthy controls, and this abnormality was even more pronounced than that found in episodic migraine [44]. These results were replicated by using the nociception-specific concentric stimulating electrode: R2 reflex area and habituation were reduced on the affected CH side, and the degree of habituation deficit correlated to number of days elapsed from the beginning of the bout and the daily attack frequency [45]. Contrasting findings were obtained in another study, where the authors failed to detect altered habituation of the nBR R2 in episodic and chronic CH within or outside a bout, but the majority of CH patients investigated were taking one or several prophylactic medications at the time of recordings, which may biased the results [46].

Classical blink reflex studies did not disclose any sign of sensitization in CH [47, 48]. In episodic CH patients within a bout, a significantly faster R2 blink reflex recovery curve on the symptomatic side was found after paired supraorbital stimuli, likely to indirectly reflect sensitization within the spinal trigeminal nucleus. Furthermore, when the supraorbital stimulus was preconditioned by a peripheral stimulation of the index finger, the R2 recovery curve was faster on both affected and unaffected sides in CH patients than in controls. Naloxone injection transiently reverted this bilateral R2 sensitization, suggesting that the faster R2 recovery may reflect hypoactivity of reticular nuclei, due to reduced descending opiatergic inhibition [49], a mechanism that was recently supported by functional neuroimaging studies [50, 51].

Cluster headache patients had lower thresholds for pressure pain [52], electric pain, and nociceptive flexion reflex [53] on the affected than on the unaffected side both in the episodic (in and outside of a bout) and in the chronic type [54]. A phase shift of the normal circadian rhythmic variations in nociceptive flexion reflex threshold in episodic bouts of CH with respect to the remission period and absence of circadian rhythmicity of the nociceptive flexion reflex threshold in chronic CH patients have already been described [54]. The functional activity of the descending diffuse noxious inhibitory controls (DNIC) (or conditioned pain modulation system) was also investigated in a group of episodic CH patients during active and remission phases compared to healthy controls, by measuring the influence of a cold pressor test on the nociceptive withdrawal reflex [55]. Cluster headache patients had a significant facilitation in temporal processing of pain at spinal level during the active phase of the disease, and a facilitation in pain processing reverted during the remission phase of the disease. The cold pressor test activating the DNIC did not induce any significant inhibitory effect on the neurophysiological responses during the active phase of the disease, but was able to induce a clear inhibition during the remission phase. It was thus hypothesized that cluster headache sufferers have a dysfunction of the supraspinal control of pain, which changes according to the clinical activity of the disease and leads to facilitation of pain processing.

Procacci et al. (1989) found cutaneous and deep hyperalgesia to mechanical and electrical stimuli with earlier appearance of pain after an ischemic test in the upper limbs on the affected side of the body in episodic CH patients [56], but when using quantitative sensory testing, perception of warmth, cold, and pressure, the sensation

of pain was reduced on the affected side as compared with the contralateral asymptomatic side in episodic and chronic CH patients [57, 58].

Unfortunately, the literature concerning neurophysiological tests in trigeminal autonomic cephalalgias other than cluster headache is really poor. In one study, pain pressure threshold, subjective pain perception after sural nerve stimulation, and nociceptive flexion reflex threshold were tested in patients with chronic paroxysmal hemicrania and with hemicrania continua, and they appeared reduced mostly on the affected side, compared to healthy subjects [59]. Corneal reflex thresholds were significantly reduced on both sides only in chronic paroxysmal hemicrania patients, though there were no abnormalities in the blink reflex. In patients affected by the idiopathic form of another rare type of TACs, "short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing" (SUNCT) trigeminal reflexes and laser evoked potentials did not show any abnormalities [60].

9.4 Discussion

Neurophysiological studies have disclosed some abnormalities of the spinal, brainstem, and cortical responsivity to external innocuous or noxious stimuli not only in migraine but also, at a lesser extent, in other primary headaches. These abnormalities can be summarized as follows:

- In subgroups of tension-type headache sufferers, some evidence of deficient habituation chiefly with cognitive potentials (mismatch negativity and P300) and sympathetic skin responses have been found. Indirect evidence for sensitization has been disclosed in chronic TTH patients with nociceptive specific reflexes and grand-averaged evoked potentials. These studies suggest for the subjects chronically affected the presence of generalized increased sensitivity to pain and a dysfunction in supraspinal conditioned pain modulation, which may contribute to the development and/or maintenance of central sensitization in this disorder.
- Habituation deficit of the blink reflex was found in episodic cluster headache patients and more pronounced than in interictal migraineurs, suggesting that additional dysfunctional neurobiological factors are implicated in CH, though CH and migraine probably share some pathophysiological mechanisms, as suggested also by the marked increase of intensity dependence of auditory potentials found in CH [42]. A sensitization of pain processing was observed only during the bout, but not outside. Several causes could be at the basis of this observation: a dysfunctioning descending aminergic, especially dopaminergic, control [61, 62], a malfunctioning hypothalamo-trigeminal control [63], and an altered descending opiatergic pain control system [50, 51]. Future electrophysiological works should aim to understand the role of the descending monoamine and opioid systems in the mechanism of sensitization and lateralization of pain and to unravel the mechanisms of CH periodicity and of its chronification.

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