Chapter 7
Brainstem Reflexes

Catello Vollono

Brainstem structures play a critical role in the transmission of nociceptive impulses and in descending modulation of sensory transmission. Consequently, the study of brainstem reflexes may provide valuable insights into central pain processing mechanisms.

In this field, a large number of studies explored the brainstem by using reflex recording techniques (e.g., the trigeminofacial reflex, trigeminocervical reflexes, blink reflex, etc.).

Additionally, habituation and recovery curves to paired shocks, useful methods for investigating the excitability of the relevant sensitive, sensorial, nociceptive pathways in humans, were also widely evaluated for these reflexes. Since the trigeminal system and, more generally, the brainstem are key structures in the pathogenesis of migraine, the recovery curves of the aforementioned reflexes could provide valuable information about the status of the brainstem in this chronic pain disorder.

7.1 Exteroceptive Suppression of the Temporalis Muscle Contraction

Electrical stimulation of the infraorbital and mental nerves evokes a reflex that inhibits the voluntary contraction of the temporal and masseter muscles. A brainstem reflex mediates this inhibition, which is called "exteroceptive suppression." On surface EMG recordings of jaw-closing muscles, the reflex appears as two

C. Vollono (✉)
Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Dipartimento Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy

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suppression periods (SP1 and SP2) mediated by Aβ fibers: an early period, mediated by oligosynaptic pontine pathway, named SP1 response (ES1; 10–12 ms latency), and a late period, mediated by polysynaptic chain of interneurons of the lateral reticular formation, identified as SP2 response (ES2; 40–50 ms latency). The ES2 period is modulated via peripheral and central afferents (periaqueductal gray, nucleus raphe magnus, limbic cortex, orbitofrontal cortex). Consequently, the ES2 responses constitute a neurophysiologic correlate of the brainstem's level of excitability [1].

Temporalis exteroceptive suppression (ES) has been widely studied in investigations of pain mechanisms, motor control, trigeminal nerve function, basal ganglia disorders, and brainstem lesions [2–4].

Furthermore, recording of the ES2 period of jaw-closing muscle activity is the only standardized method of studying the function of the brainstem inhibitory interneurons [2, 5].

Despite its usefulness in the assessment of pain mechanisms, only few studies investigated the ES2 duration in migraine at rest, with contradictory results.

Schoenen et al. reported reduced exteroceptive suppression of the temporalis muscle in patients with chronic tension-type headache but normal latency and duration of exteroceptive suppression in migraineurs [1].

In another study, the same author detected abnormal shortening of ES2 suppression period in patients with migraine [6].

Other authors observed low degree (the area of suppression was measured and divided by its duration) of exteroceptive suppression in 17 patients suffering from migraine without aura, while exteroceptive suppression in patients suffering from migraine with aura and cluster headache was the same as that in normative subjects [7].

The low degree of suppression might be supposed to reflect a deficiency in the endogenous pain control mechanism [8].

Unlike the previous studies, Zwart et al. observed that the durations of ES1 and ES2 periods were within normal limits in migraineurs [9].

Another study showed no statistical difference in a group of 28 migraineurs during interictal phase, considering onset latencies and duration of ES1 and ES2 periods, compared with controls. In this study, however, shorter duration of the ES2 period was evident during the attack period [10].

The mechanism governing this loss of muscle contraction control in migraineurs is still unclear. The authors of this study hypothesized that in migraine there may coexist an abnormality of control mechanisms of vascular and muscle contraction, and thus, the pain sensation of attacks might produce psychologic stress resulting in the loss of the suppressive function.

Only one study also assessed the recovery curve of the ES2 component of the temporalis muscle activity [11]. These authors reported that latencies, durations, and recovery curves of ES2 did not differ between control subjects, migraineurs, and patients with episodic and chronic tension-type headache.

In conclusion, controversial results have been reported regarding the different inhibitory and excitatory responses detected by means of exteroceptive suppression of the temporalis muscle in patients with migraine.

In many papers, there are significant abnormalities in the responses obtained during the attacks and in the intercritical phase. Scientific data pointed to the hyperactivity of contralateral aminoergic cortical-subcortical pathways, whose function is decreased between the migraine attacks [12]. Thus, unilateral trigeminal system hyperactivity has also been suggested [13, 14].

In this view, the ES2 period of exteroceptive suppression of the temporalis muscle, an anti-nociceptive reflex, may reflect a deficit in the endogenous pain control mechanisms in different types of headache. It has been suggested, however, that this response could be useful as a biologic marker in monitoring the time course of recovery from pain [15], and it is sensitive during the pain-free interval, so it can detect the persistent interictal abnormalities in migraine.

For these reasons, some authors hypothesized that the latency of ES2 period may be helpful in the differential diagnosis of peripheral and primary headache disorders and in particular to differentiate migraine and tension-type headache [16].

Moreover, it is conceivable that the exteroceptive suppression of the temporalis muscle may be used for evaluation of a drug's effect. In fact, part of the 5HT effects in migraine is related to the inhibition of the trigeminal nuclear activity, and it is probable that part of the triptans effects is also mediated at this central site [17].

7.2 Trigeminocervical Reflexes

The trigeminocervical reflex (TCR) is obtained from the resting sternocleidomastoid muscle, using surface electromyographic recordings. Surface electrodes are positioned in a longitudinal direction over the muscles. Electrical stimuli are applied bilaterally to the supraorbital trigeminal branch near the point of nerve exit from the skull. The intensity is modified in order to result as strong but not painful. Several consecutive responses are averaged in each trace. The onset latency (ms), duration (ms), peak-to-peak amplitude (mV), and area (mV × ms) of the reflex responses are measured [18].

The trigeminocervical reflex, utilizing connections from the face to the neck motoneurones, is used for the examination of the brainstem interneuronal activity and its central control [18]. It may be supposed that different brainstem interneurons control the trigemino-trigeminal and the trigeminocervical reflexes.

Some authors used this neurophysiologic examination to assess brainstem interneurones function in migraine.

In one of the oldest studies assessing TCR [18], on the painful side of migraine patients, the mean onset reflex latency after ipsilateral and contralateral stimulation

was strongly shortened. Conversely, there were no significant differences in the reflex duration, area, and amplitude between the painful and non-painful sides. No differences were also found between migraineurs and patients with tension-type headache [18]. The results of this study suggest a decreased activity of the brainstem inhibitory interneurons in migraine.

Other authors explored interictal and ictal phases of migraine. In particular, Nardone et al. [19] found that trigeminocervical responses are bilaterally abnormal in 17 out of 20 patients with migraine with aura (MA) and 15 out of 20 patients with migraine without aura (MO) during the headache attacks. In half of MA and MO patients, there were abnormal responses also during the interictal period. Moreover, in patients with normal trigeminocervical responses during the pain-free phase, the triptans were significantly more effective at relieving headache [19].

These findings were confirmed in another study by the same authors [20] and are consistent with the central role of the trigeminal system in the pathogenesis of migraine. The bilateral location of the abnormalities suggests a centrally located dysfunction. In particular, the trigeminocervical reflex is sensitive in disclosing a disordered brainstem activity and may be an index of neuronal activity in the human brainstem; moreover, its assessment may help as a valuable prognostic tool for predicting the efficacy of triptans therapy [20].

Partially in contrast with previous results, other authors [21] found no changes between controls and high-frequency episodic MO and MA patients in the mean values of trigemino-cervical-spinal reflexes (TCRSs) obtained at rest and during heterotopic painful stimulation (cold pressor test). Furthermore, the recovery curve of TCRs was significantly and markedly faster in migraine patients than in controls, while no differences were found in the basal trigemino-spinal reflexes (TSRs) [21]. The authors conclude that the interictal period of migraine is characterized by a hyperexcitability of the trigeminal pathways and by their anatomical and functional connections with the upper cervical cord neurons.

In conclusion, the trigemino-cervical and the trigemino-cervical-spinal reflexes may be useful for the evaluation of the impairment of the brainstem neuronal networks in migraine patients.

Overall, the more relevant findings of these studies demonstrated an abnormal hyperexcitability of trigeminal system during interictal phase, apparently not linked with supraspinal inhibitory modulation.

The “abnormality” of the supraspinal influences is probably more significant during the migraine attack and in the chronic migraine form than during the pain-free period.

TCR and TCRS studies are of little use in the diagnosis but are helpful for a better understanding of the common pain control mechanisms and the pathophysiology of migraine. In particular, the study of the recovery cycle of these reflexes appears to be a technique that can be used to make an accurate functional evaluation of the trigeminal pathways.

7.3 Blink Reflex

The mechanical or electrical stimulation of the supraorbital nerve elicits "blink reflex" responses and resembles the corneal reflex tested in clinical evaluation [22–24].

Usually, for the purpose of studying blink reflex, surface recording electrodes are located on the lower lateral side of the orbicularis oculi, reference electrodes are positioned on the lateral surface of the nose, and the ground electrode is located around the arm. The supraorbital nerve is stimulated with the cathode placed over the supraorbital foramen. Stimulation rate is 1 s^{-1}. The shortest latency is taken into account and the EMG is not rectified.

Stimulation of the supraorbital nerve elicits two temporally separate responses of the orbicularis oculi, an early (R1) component, and two temporally separate contractile late responses ipsilateral and contralateral to the stimulation (R2 and R2′, respectively). R1 is an oligosynaptic reflex response and is evoked only on the side of stimulation via a pontine pathway [22–24]. On the other hand, unilateral stimulation elicits R2 bilateral response, which is presumably relayed through a more complex route (polysynaptic), including the pons and lateral medulla [25–28].

So, the blink reflex can be an objective and useful method for studying brainstem and the trigeminal system. Blink reflex recordings provide, consequently, a quantitative analysis for functions that involve the fifth and seventh cranial nerves, the dorsolateral pons, and the lateral medulla.

Several studies compared the latencies of R1, R2, and R2′ waves in migraine patients and control subjects (Table 7.1).

In the oldest study that evaluated blink reflex in 43 migraine patients, Bánk et al. [29] obtained the same R1 latencies in migraineurs and controls but R2 latency significantly prolonged in the migraine group. These findings indicate that trigeminal afferents and/or polysynaptic pathway in brainstem may be slightly functionally altered in migraine. The reasons for this delay are uncertain, especially in a headache-free interval.

This slight functional brainstem abnormality may underline or be the basis of migraine susceptibility. On the other hand, a peripheral abnormality of the trigeminal afferents could play a part in these pathophysiologic mechanisms. Sensory deficits of the face often can cause R2 latency alteration.

Other authors [30] reported that there was a statistically significant extension of bilateral R2 latencies in a 40-migraineur group compared with TTH patients and control groups. These confirm that brainstem and trigeminovascular connections play an important role in migraine pathogenesis and are functionally impaired in migraineurs (trigeminal system activation, sensitization of brainstem trigeminal nucleus, abnormal synaptic transmission, suppression of brainstem interneuron region) [30].

Table 7.1 Blink reflex in migraine

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Conventional blink reflex					
Bánk et al. [29]	43	33 MO, 10 MA	31.1 (9.6)	>14 days after attack	R2 latency prolonged in migraine
Sand and Zwart [31]	11	10 MO, 5 MA	39 (12)	NA	No differences compared to controls
Avramidis et al. [38]	19	MO	37.5	Ictal	R2 amplitude reduced ictally. Sumatriptan subcutaneous increased R2 amplitude
Aktekin et al. [11]	20	MO	32.7 (8.5)	Interictal	No difference compared to controls and TTH
De Tommaso et al. [49]	35	25 MO, 10 MA	MO 33.5 (4.5) MA 37.8 (6.7)	Interictal	R3 threshold, with a normal pain threshold, in migraine patients. R2 and R3 components less influenced in patients compared with controls
De Marinis et al. [32]	30	MO	33 (8)	>72 h after attack	No baseline responses differences
Sand et al. [34]	23	13 MO, 10 MA	33.9 (12.5)	NA	No difference compared to controls
De Marinis et al. [33]	35	CM	37 (6)	>72 h after attack <3 hours before the next attack	No difference compared to controls
Yildirim et al. [30]	40	25 MO, 15 MA	33 (18–64)	Interictal	Extension of bilateral R2 latencies
Brooks and Fragoso [36]	160	CM	50.8 (18.2)	NA	No difference compared to controls
Uygunoglu et al. [35]	20	6 MO, 14 CM	37.5 (8.9)	Within 48 h after attack	No difference compared to controls
Nociception-specific blink reflex					
Kaube et al. [39]	17	MO	40 (24–56)	Interictal, <6 h, after migraine attack onset and after Zolmitriptan	Decreased R2 latencies during acute attack compared with the headache-free interval, most pronounced on the headache side
Katsarava et al. [42]	14	MO	36 (24–56)	Interictal, < 6 h, after migraine attack onset and after Zolmitriptan	Increased R2 amplitude and decreased latency on the pain side during attacks only in migraine patients

Table 7.1 (continued)

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Ayzenberg et al. [37]	45	16 MO, 29 CM	MO 37.4 (12.2) CM 40.1 (14.1)	Outside of a migraine attack	No difference between MO, CM, medication overuse headache and controls
Coppola et al. [43]	14	MO	30.7 (9.3)	Interictal, >3 days after attack <3 days before the next attack	No difference between patients and controls
Sohn et al. [44]	68	38 MO, 30 CM	MO 40.1 (10) CM 43.1 (11.1)	Interictal	Episodic migraine patients: Decreased latencies, larger amplitudes and area-under-the-curve (AUC) values for the R2 component. Chronic migraine patients: Prolonged latencies, smaller amplitudes and smaller AUC values for the R2 response
Perrotta et al. [48]	46	29 MO, 17 MA	MO 37.3 (10.6) MA 34.5 (10.9)	Interictal	No significant differences at baseline
Williams et al.	23	MO	24.32 (7.94)	Interictal	No difference of baseline nociceptive BR magnitude compared to controls
Habituation					
De Marinis et al. [32]	30	MO	33 (8)	>72 h after attack	No baseline responses differences. Blink reflex habituation markedly reduced in who had and attack within 72 h
Katsarava et al. [45]	17	MO	40 (24–56)	Interictal and within 6 h of onset of attack	Habituation deficit interictally. Difference of habituation between and during attacks Increased R2 amplitude interictally No difference between headache and non-headache sides
Di Clemente et al. [46]	15	MO	28 (10)	Interictal, > 2 days after attack <2 days before the next attack	Nociception-specific blink reflex. Decreased habituation in migraine patients

(continued)

Table 7.1 (continued)

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Di Clemente et al. [47]	16	MO	27.6	Interictal, > 2 days after attack <2 days before the next attack	Nociception-specific blink reflex. Habituation deficit in migrainepatients, inversely related to attack frequency
De Marinis et al. [33]	35	CM	33 (8)	>72 h after attack	No baseline responses differences. Significant lack of blink reflex habituation in chronic migraineurs interictally vs ictally and vs controls
Coppola et al. [43]	14	MO	30.7 (9.3)	Interictal, > 3 days after attack <3 days before the next attack	Nociception-specific blink reflex after conditioning stimulus. No basal BR difference between patients and controls. BR recovery curves were normal in MO patients compared to healthy controls
Perrotta et al. [48]	46	29 MO, 17 MA	MO 37.3 (10.6) MA 34.5 (10.9)	Interictal	Frequency-dependent deficit of habituation of nBR R2 in both MO and MA patients, less clear in MA. Positive correlation between the habituation rate and migraine frequency in MO

MO episodic migraine without aura, *MA* episodic migraine with aura, *CM* chronic migraine

Unlike previous studies, Sand and Zwart [31] reported that mean R1 and R2 latencies were no different between various headache groups and that no group differences were found for the contralateral R2 response.

These findings were completely confirmed by Aktekin and colleagues [11] in episodic migraineurs. In this population, in fact, no differences were found also considering the facial side explored.

Some other researchers found normal R1 and R2 latencies, amplitudes, and areas obtained by ipsilateral and contralateral stimulations at any time intervals, during interictal phases of migraine as well as in episodic [32] and chronic migraine [33].

Other studies confirmed that there are no differences in all blink reflex components in migraine without aura, migraine with aura patients and controls and unilateral migraine patients did not differ from patients with bilateral pain [34, 35]. No significant differences were reported in another large group of migraine patients [36] and in medication overuse headache patients [37].

Avramidis et al. [38] reported similar results during interictal phase in 19 episodic migraineurs. In particular, latencies of all components are normal in all migraineurs. Conversely, during headache phase, significantly lower values of R2

and R2′ amplitude and size were found in the migraine group compared with the healthy control group. These findings were independent from stimulation site and were altered in the symptomatic side of headache. These authors described, furthermore, that sumatriptan administration was able to normalize R2′ amplitude and size.

The interpretation of these findings is that there is a temporary dysfunction of the bulbo-pontine interneurons only during the headache phase of migraine. In particular, the brainstem interneuron, which is part of the blink reflex arc, may be diffusely suppressed in migraine, only during the headache phase. Besides, blink reflex may be an objective laboratory method to monitor the effectiveness of specific drugs proposed for the treatment of migraine.

Other authors studied the blink reflex during migraine attacks.

Kaube et al. [39] studied 17 episodic migraine patients with unilateral migraine headache. The patients were studied within 6 h of attack's onset. Blink reflexes were elicited in all patients using two different electrodes, a standard stimulating electrode (standard blink reflex) and a novel concentric stimulating "nociception-specific" electrode ("nociception-specific" blink reflex), during the acute migraine attack and after the treatment with intravenously lysine acetylsalicylate (1 g) or oral zolmitriptan (5 mg). The same protocols were used interictally. After "standard" stimulation, no differences were detected for the R1 and R2 onset latencies and areas under the curve (AUC) between the different time points and between the headache and non-headache side. "Nociception-specific" stimulation revealed, however, a significant shortening of R2 latency during the acute migraine attack compared with the headache-free interval. Drug treatment relief increased the onset latencies and reduced the AUC of R2 [39].

The authors of this study suggest a temporary sensitization of central trigeminal neurons during acute migraine attacks. In fact, the decrease of the onset latency and increase of the reflex integral (AUC) permit to hypothesize a facilitation of a spinal or medullary reflex. These findings are consistent with other experimental data [40].

These results are probably evident in this study and not in other similar studies because of a more selective stimulation ("nociception-specific") that may lead to a higher and near-maximal saturation of the afferent pathway of the blink reflex and a reduced sensitivity toward more subtle changes in central thresholds and gain in sensory trigeminal transmission [41].

Another study confirmed these findings [42]. In this study, the comparison of R2 onset latencies during pain and during pain-free period within the groups of patients with migraine and sinusitis revealed a significant decrease of R2 latencies during the migraine attack compared to pain-free period but no differences between pain phase and pain-free period in the group of patients with sinusitis. These results are consistent with the facilitation of trigeminal nociception that seems specific for migraine rather than a consequence of peripheral pain, such as frontal sinusitis [42].

Other authors assessed the "nociception-specific" blink reflex interictally. Coppola et al. [43] reported no difference between migraineurs and healthy subjects

for nociception-specific blink reflex (nBR) R2 responses in terms of stimulus intensity, pain threshold, onset latency, or AUC ipsilateral and contralateral.

Another study [44] showed that episodic migraine (EM) patients presented significantly decreased latencies and larger amplitudes and area-under-the-curve (AUC) values for the R2 component, whereas chronic migraine (CM) patients showed significantly prolonged latencies, smaller amplitudes, and AUC values for the R2 component. In the same study, the patients were assessed by means of pain-related evoked potentials (PREP) and both the EM and CM patients had decreased latencies of PREP responses with larger amplitude compared with the controls, which indicates facilitation at the cortical level. Additionally, the amplitude and AUC values of the R2 component exhibited a negative correlation, whereas the latency of the R2 component for the nBR showed a positive correlation with the frequency of headaches in migraineurs. This study provides electrophysiologic evidence that excitability of nociceptive-specific trigeminal pathways is different between EM and CM [44].

Other authors [37] assessing simultaneously nBR and PREP found "facilitation" of both trigeminal and somatic PREP, but not of nBR, indicating that the sensitization of nociceptive mechanisms mainly involved structures external to the trigeminal system and probably occurred at the supraspinal level [37].

In addition to the basal assessment of both "classical" and "nociception-specific" blink reflexes, many authors have compared the "recovery curve" and the habituation of blink reflex of migraineurs to non-migraine subjects.

Aktekin et al. reported similar R2 recovery curves in migraineurs and controls [11].

Coppola et al. confirmed these results [43] and described no difference of the nociceptive-BR R2 recovery curves between migraine patients outside of attacks and healthy volunteers.

De Marinis et al. [32] found R1 and R2 latencies, amplitudes, and areas similar in patients and control subject during basal assessment, but blink reflex habituation responses (R2 areas obtained at subsequent time intervals ranging between 10–5, 5–4, 4–3, and 3–2 s) markedly and statistically reduced in migraineurs with migraine attack within 72 h after neurophysiologic evaluation. In fact, in the comparison between groups, the R2 areas progressively decreased in control subjects, but remained high in migraine patients who experienced an attack within 72 h after testing. Also, the blink reflex habituation responses of the patients who had migraine attack after a longer time interval (from 4 to 15 days) were found reduced but did not differ significantly from those of controls. No correlations were found between blink reflex responses and age, duration of disease, and side of pain. These data are consistent with the activation of brainstem pathways involved in the blink reflex in the premonitory phase of migraine attacks, probably through mechanisms that involve dopaminergic function [32].

These findings confirmed the results of another contemporary study [45] that reported a significant defective habituation of blink reflex responses in patients

during interictal period, fully reverted and "normalized" during a migraine attack [45].

Also Di Clemente et al. [46] found significant habituation deficit of BR-R2 response area in patients with migraine without aura during interictal phase. This lack of habituation shows a positive correlation in the same patients with a cortical habituation deficit, namely, the habituation of pattern-reversal visual evoked potentials.

These authors conclude that there is a wide neurobiologic dysfunction responsible for the habituation deficit in both cortex and brainstem [46].

The same authors investigated a nociceptive BR in 16 migraine patients without aura, 15 healthy subjects, and 14 healthy subjects with family history of migraine in their first-degree relatives [47]. The most significant habituation impairment was found in healthy subjects with a family history of migraine. The second one was found in migraine patients without aura, inversely correlated with the frequency of attacks. The authors interpreted that these results are the consequence of reduced serotoninergic transmission, leading to a decreased preactivation level, and are not due to trigeminal sensitization. Finally, an insufficient nociceptive-specific BR habituation is probably a presymptomatic neurophysiologic abnormality and, in this view, a marker of genetic predisposition for migraine [47].

In another study, De Marinis et al. [33] investigated the BR habituation in 35 patients with chronic migraine, outside and during a spontaneous attack, and control subjects. The habituation responses, delivered at time intervals of 10, 5, 4, 3, 2, and 1 s, were markedly reduced in patients studied outside an attack compared with those of the same patients studied during a migraine attack and of those of control subjects. There was a significant correlation between the decreased habituation of the blink reflex and a higher frequency of attacks. The decreased BR habituation outside an attack reveals abnormal excitability in chronic migraine, which normalizes during the attacks. The authors explain these data with central sensitization mechanisms that may also cause lower detection thresholds on the side affected by headache in patients during the attacks (allodynia). The blink reflex and its habituation may help shed light on the subtle neurophysiologic changes that occur in migraine patients between and during attacks [33].

A recent study [48] has confirmed that both migraine without aura and migraine with aura subjects showed a clear frequency-dependent deficit of habituation of the nBR-R2 responses when compared to healthy volunteers. However, migraine with aura subjects showed a less marked and/or non-homogeneous significant deficit of habituation of the nBR-R2 when compared to healthy controls. Furthermore, only in migraine without aura subjects, the mean frequency of migraine attacks correlates positively with the habituation rate of the nBR-R2. Based on these slight differences in terms of habituation deficit, the authors speculate a modulating role of the migraine aura susceptibility and excitability of the nociceptive trigeminal pathways [48].

Several authors also studied the effect of preceding conditioning stimuli on a blink reflex.

De Tommaso et al. [49] described a slight increase of blink reflex responses recovery after preconditioning stimulus observed in migraine patients.

Also Coppola et al. [43] reported that the inhibition of nBR obtained by means of supraorbital or peripheral (index finger) conditioning stimulation is normal in migraineurs interictally, which does exclude the previous hypothesized persistent sensitization in the trigeminal nociceptive system and demonstrate that descending brainstem pathways on medullary R2 interneurones are normal in migraine between attacks [43].

A more recent article [35] has reported that one-third of migraine patients did not have prepulse inhibition of R2 response after conditioning stimulation of the median nerve at wrist. These authors conclude that in migraine there is a loss of sensory modulation at the level of brainstem during and immediately after the attacks.

Other authors [50] reported that migraineurs did not have a significant change in nBR magnitude during a conditioning setting (noxious counterstimulus applied by inducing forearm ischemia), suggesting impaired conditioned pain modulation and, consequently, a deficient inhibition of trigeminal nociception.

In contrast to the evident lack of habituation found in the majority of studies assessing blink reflex responses in common migraine, this deficit is not present in genetic forms of migraine.

In fact, Hansen et al. [51] found that nociceptive BR habituation increased more in familial hemiplegic migraine (FHM-1 and FHM-2) subjects than in subjects with common migraine and controls. These results indirectly suggest that hyperexcitability of cortical neurons, previously demonstrated in the animal model of the FHM-1 and FHM-2 mutations in transgenic mice [52, 53], is not per se responsible for the habituation deficit in the common forms of migraine. Alternatively, in FHM, an increase in cortical inhibitory mechanism might compensate between attacks for the genetically determined increased neuronal excitability. All these results support the concept that various pathophysiologic aspects differ between FHM and common migraine, including cortical and brainstem responsiveness.

Lastly, several authors reported a clear effect (significant modification of blink reflex assessment's findings) of different substances and pharmacologic and non-pharmacologic treatment of migraine [39, 54–57].

A recent paper [58] has reported an interesting different effect of ketogenic diet on cortical and brainstem habituation responses.

Also, low-frequency short-time stimulation of the greater occipital nerve seems not to modify nociceptive blink reflex responses [59].

In conclusion, most of the studies assessing blink reflex in migraine show substantial normality of the findings obtained from basal BR recordings in patients and, in many cases, significant and sudden variations of the response patterns only in the periictal phase.

In most of the studies that evaluated habituation and/or conditioning, larger differences are evident in terms of response patterns between migraine and

non-migraine subjects. Such habituation anomalies, in almost all the studies, revert in the ictal phase.

The variability of the results in the study of blink reflex in migraine by many authors is a consequence of a series of factors: frequency of crises, proximity of the last crisis or of the next one, side predominance, stimulation modality, and prophylactic treatment.

Therefore, the blink reflex studies demonstrate the dynamic and sudden recurrent unbalance of excitability of all CNS systems (cortical, subcortical, brainstem, hypothalamus, and trigeminal structures).

This unbalance is more evident cyclically near or during a migraine attack, when the habituation deficit normalizes and sensitization of the pain pathways increases.

Finally, BR studies are a suitable tool for testing a drug's efficacy.

7.4 Auditory Evoked Potentials

Auditory stimuli elicit small electrical potentials can be distinguished into short-, middle-, and long-latency auditory evoked potentials (AEPs), based on their generators in the auditory pathways. Short-latency AEPs originate in brainstem; conversely, middle- and long-latency AEPs originate in the auditory cortex.

For clinical and research studies, a set of five recording channels is recommended, including electrodes Fz, Cz, F3, and F4 of the international 10–20 system, referenced to the linked mastoid processes, but this is rarely conceivable in clinical practice, as many evoked potential recording devices offer no more than two recording channels. Averaging should be performed after an artifact rejection and should include at least 200 responses per condition.

AEPs are a sensitive measure of central nervous system dysfunction [60, 61], particularly of the brainstem. However, the studies of these potentials in migraine has yielded contradictory results [62–64] (Table 7.2).

Studies of short-latency AEPs, that is, brainstem auditory evoked responses (BAER), provide varying and heterogeneous results in migraine. Normal latencies [62–66]; increased latencies, especially for wave V [67, 68] mostly during the attacks [62, 65]; and interaural asymmetries [67], particularly in migraine with aura [69] were reported. An inverse correlation between discomfort to stimulations of low intensity (55 dB) and wave IV–V amplitude was found in another study [66].

The rare studies of cortical long-latency auditory evoked potentials showed no significant difference between migraineurs and controls with regard to N1, P2, and N2 component latency or amplitude [68].

Another recent study has confirmed no difference in terms of latency, amplitude, and interpeak of all auditory brainstem components between a group of vestibular migraine and control subjects. The same authors, however, found increased

Table 7.2 Auditory evoked potentials in migraine

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Short latency					
Benna et al. [64]	10	MO	36 (25–46)	>8 days after attack	No abnormalities or asymmetries compared to controls
Bussone et al. [67]	20	MO	36.4 (9)	>1 week after attack	Increased and asymmetric I–V latencies in migraineurs
Yamada et al. [65]	1	MA (basilar migraine)	38 (–)	Interictal and ictal	IV and V wave latencies prolonged during headache
Podoshin et al. [62]	17	10 MO, 5 MA	36.7 (11–61)	Interictal and ictal	No interictal differences compared to controls. Prolonged interpeak latencies during headache
Battistella et al. [63]	28	23 MO, 5 MA	12 (2)	>1 week after attack	No difference compared to controls
Schlake et al. [69]	38	19 MO, 19 MA	32.4 (12.4)	Interictal	Asymmetric I, II, III and V latencies in migraineurs (especially in MA)
Drake et al. [68]	50	MO	(16–67)	NA	Prolonged I–V and III–V interpeak latencies in migraineurs compared to controls
Sand and Vingen [66]	21	15 MO, 6 MA	39.3 (9.2)	>3 days after/ before attack; 'pre-attack group': Attack within 24 h	No difference compared to controls
Takeuti et al. [70]	29	Vestibular migraine	49.7 (23.7)	Interictal	No difference in latency, amplitude and interpeak of all components compared to controls. Increased latencies of the frequency following response and lower discomfort thresholds compared to the control group
Middle latency					
Ambrosini et al. [73]	20	MO	32.5 (21–62)	3 days after the last and before the next attack	Auditory P50 response was markedly reduced in migraine patients compared to healthy volunteers
Long latency					
Drake et al. [68]	30	MO	29 (17–54)	NA	No difference compared to controls
Sand and Vingen [66]	21	15 MO, 6 MA	39.3 (9.2)	>3 days after/ before attack; 'pre-attack group': Attack within 24 h	No difference compared to controls

Table 7.2 (continued)

Authors	*N*	Diagnosis	Mean age (SD/range)	Timing of recording	Significant findings
Intensity dependence AEPs					
Wang et al [77]	26	MO	28.8 (6.4)	>1 week after attack	Enhanced intensity dependence of N1-P2 in migraineurs
Judit et al. [76]	77	69 MO, 8 MA	34	1 day before attack, during attack, 1 and 2 days after attack, interictal	Enhanced intensity dependence of auditory evoked potential interictally and dramatic reduction just before and during the attack
Siniatchkin et al. [79]	16	MO	10.6 (7–13)	NA	IDAP parameters enhanced in migraine
Sándor et al [78]	26	24 MO, 2 MA	30.9 (14.4)	3 days after the last and before the next attack	IDAP parameters enhanced in migraine
Ambrosini et al. [80]	328	232 MO, 96 MA	35.3–34.4	3 days after the last and before the next attack	Intensity dependence of auditory evoked cortical potentials is increased during interictal phase of migraine
Habituation					
Wang et al. [71]	35	25 MO, 10 MA	36–37	>1 week after attack <5 days befor attack	Potentiation of N1–P2 amplitude only at high stimulus intensities
Sand and Vingen [66]	21	15 MO, 6 MA	39.3 (9.2)	>3 days after/ before attack; 'pre-attack group': Attack within 24 h	No difference compared to controls
Ambrosini et al. [72]	14	MO	31.2 (19–62)	3 days after the last and before the next attack	Potentiation in migraineurs, greater for high- than for low-intensity stimulations

MO episodic migraine without aura, *MA* episodic migraine with aura

latencies of the frequency following response and lower discomfort thresholds in migraineurs compared to the control group [70].

Only few studies have explored the habituation of cortical AEPs.

The first one reported "potentiation" of N1-P2 amplitude only at high stimulus intensities in migraineurs, contrasting with physiologic habituation in healthy volunteers [71]. This result was not confirmed in another report [66], probably because of methodological differences.

In a successive study [72], the intensity dependence of auditory N1-P2 and habituation for each stimulation intensities was measured and potentiation was found in migraineurs, greater for high-intensity stimulations than for low-intensity stimulations, as opposed to the habituation or absence of amplitude change for all stimulation intensities in controls.

In addition to the study of habituation, another method of dynamic study of auditory evoked potentials consists of the study of sensory "gating." Gating of sensory input is another characteristic of central processing of incoming information. A typical example of this phenomenon is the suppression of the cortical response to a test stimulus delivered after an identical preceding conditioning stimulus.

The middle-latency P50 component of the auditory evoked cortical potential is very sensitive to gating. Gating of the auditory P50 response was markedly reduced in migraine patients compared to healthy volunteers [73], which was considered an expression of reduced short-term habituation [74].

Another method suitable to assess physiologic CNS responses by means of AEPs is the intensity dependence of AEPs (IDAP), which assesses the amplitude increase of auditory evoked cortical responses with increasing stimulation intensities.

IDAP amplitude was found suddenly increased in migraine between attacks with increasing stimulus intensity [71], reflecting a pronounced intensity dependence of auditory evoked potentials (IDAP), which is likely to reflect reduced central serotonin neurotransmission [75].

The increased IDAP normalizes during the migraine attack [76], as well as during other dynamic changes of CNS excitability.

IDAP abnormalities correlate with personality profiles [77], and some authors interpret this finding with lower serotonergic transmission in migraine, but not in posttraumatic headache [77].

Two independent studies [78, 79] found evidence for a familial effect on IDAP in migraineurs, indicative of a genetic background; however, up to now no direct genetic link has been identified.

These hypotheses are fully confirmed in a recent multicentric study [80]. In this large study, in fact, the intensity dependence of auditory evoked cortical potentials is significantly increased during the interictal phase of migraine [80]. The underlying mechanism of these findings is still under debate and might involve lower preactivation levels of sensory cortices, due to thalamo-cortical dysrhythmia, and low serotonergic tone. Nevertheless, the peculiar abnormalities of both visual and auditory cortical potentials, together, have a high sensitivity and specificity to be considered as an endophenotypic biomarker of migraine.

The results of a previous study by Afra et al. [81], which do not report correlations between PR-VEP and IDAP amplitude-stimulus function slopes in patients with migraine, are partially against these hypothesis.

In conclusion, the studies of basal AEPs in migraine have produced divergent results. However, the dynamic assessment (habituation, gating, and IDAP) widely detects a deficit of habituation or potentiation, with evidence for a genetic-phenotypic correlation.

IDAP is not useful for diagnostic purposes, because of its limited repeatability in pathophysiologic studies [82]. This may be related to the fact that the major part of the IDAP increase in migraine could be due to the AEP habituation deficit at high-intensity stimulations [72].

Recent evidence, however, underlines that, if associated with other neurophysiologic methods, they can become more sensitive and specific in order to distinguish different types of headache [80].

On the other hand, IDAP is certainly suitable in longitudinal (to assess the same subjects at different time points) and pharmacologic studies [83].

7.5 Other Brainstem Reflexes: Nociceptive Flexion Reflex, Corneal Reflex, Jaw-Stretch Reflex, Others

7.5.1 Jaw-Stretch Reflex

Up to now, no study has explored jaw-stretch reflex in migraine.

7.5.2 Nociceptive Flexion Reflex

The stimulation of the sural nerve by means of a pair of surface electrodes, placed on the skin at the retro-malleolar site, evokes muscular response (RIII reflex—nociception flexion reflex) recorded electromyographically from the ipsilateral biceps femoris muscle (capitis brevis). The nociceptive flexion reflex (NFR) is a reliable and objective tool for exploring pain control systems in humans [84]. The threshold and amplitude of the RIII reflex are strictly linked to the threshold and amplitude of the concomitant pain evoked by the electrical stimulus, and the RIII reflex has been reported to be significantly inhibited by the activation of diffuse noxious inhibitory control (DNIC) [84–86].

In the older study assessing NFR [87], Sandrini et al. reported a decrease of RIII reflex threshold in severe and evolutive form of migraine and hypothesized, in this clinical condition, an impairment of the serotoninergic antinociceptive system.

In the same way, with an elegant and more recent study, the same authors [88] assessed, in migraine patients, the effects of heterotopic noxious conditioning stimulation (HNCS), in the form of the cold pressor test (CPT), on the NFR. The major finding of this study is that migraine patients showed no inhibition, but there was facilitation of the RIII reflex during the HNCS. The authors conclude that in migraine there is an impairment of supraspinal pain modulation systems that may contribute to the central sensitization.

Other authors [89] described significant fluctuations in the threshold of the nociceptive flexion reflex between the third week of active estrogen treatment and during the hormone-free interval. These fluctuations are more pronounced in women with migraine compared to non-migraineurs (without statistical significance). This "increased sensitivity," mediated by estrogen withdrawal, was interpreted as the trigger of migraine attacks during the hormone-free interval.

7.5.3 Corneal Reflex

Electrical stimulation by means of a thin cotton thread connected to the cathode of a constant current stimulator, air puff, or direct touch to the cornea elicits a contraction of the orbicularis oculi muscle, defined *corneal reflex* (CR), similar to the blink reflex response. The muscular response is recorded from the orbicularis oculi using an electrode placed on each side of the inferior lid. In contrast to the BR, the CR has no early ipsilateral R1, but only a late bilateral R2 response [90]. The corneal reflex (CR) is a naturally protective brainstem reflex and allows the investigation of peripheral trigeminal nerve structures.

Few studies evaluated the corneal reflex in migraine.

One study [91] detected a reduction in the CR threshold and an increased sensitivity to tactile and painful stimulation in patients with migraine during the interictal phase, more marked on the symptomatic side. These findings were interpreted as an impairment of the afferent pathways and/or changes in excitability of the trigeminal pain pathway in migraine patients leading to cortical and subcortical hyperexcitability of sensory pathways.

Another study [92] reported no differences in baseline response areas under the curve (AUC) and latencies of the R2 components of CR between patients and controls, or any significant differences concerning the headache side and no significant influence of oral triptans. The authors conclude that there is no facilitation of the trigeminal system in the headache-free interval and that there is no effect of sumatriptan on this facilitation.

7.5.4 Others

Isolated studies used other less-validated methods in order to assess brainstem reflexes. In one of these studies, Duncko et al. [93] found that migraine is associated with a higher acoustic startle responsiveness that is already present in children at risk of developing the disorder.

7.6 Conclusions

Large varieties of neurophysiologic tools and different protocols have been used with the aim of studying the function of the brainstem in migraine.

None of the studies of the brainstem reflexes reveal completely repeatable and exhaustive results in terms of normality or alteration of the responses of migraineurs compared to those obtained from non-migraine subjects.

Therefore, none of these neurophysiologic methods have such a high sensitivity and specificity that they can be considered able to definitively differentiate migraine from other forms of primary or secondary headaches.

Results that are much more homogeneous have been obtained using protocols for the study of the habituation and recovery curves to paired shocks of such reflexes.

Since the brainstem plays a crucial role in the pathogenesis of migraine, the habituation and recovery of curves of brainstem reflexes could provide valuable information about the status of the brainstem in such disorder.

Overall, interictally migraineurs with and without aura show a time-dependent amplitude increase of evoked potentials and reflexes to repeated stereotyped stimuli compared to normal subjects. This phenomenon was called "deficient habituation" or "lack of habituation" and was seen only during the interictal period for almost all sensory modalities. In this view, this phenomenon is considered a neurophysiologic biomarker of migraine.

Nevertheless, the habituation is a dynamic phenomenon, as it changes when incoming an attack, during the attack and when episodic migraine evolves to chronic migraine. Chronic migraine is a complication of migraine where sensitization makes its appearance and change profoundly the response pattern to incoming inputs.

The interictal dysexcitability may be of subcortical (thalamo-cortical) origin or correspond to a primary cortical dysfunction (impaired inhibition due to disrupted excitatory glutamatergic neurotransmission), or can represent the result of coexistence of both phenomena and can occur in variable degrees depending on patients and on the migraine phases (time from the previous or the next attack and frequency of migraine) [94].

As a result, neurophysiologic methods have had and continue to have considerable importance in the study of the pathophysiologic mechanisms underlying migraine, in particular of the neurobiologic mechanisms modulating the processing of information at different levels, above all with regard to the cyclical and sudden variations of excitability of the CNS in critical phase.

The incomplete repeatability of the different study methods, anyway, does not exclude that these methods may be useful in longitudinal studies, that is, in the same subjects during ictal and interictal phase or at different timings of the illness natural history.

Finally, the different ways of studying brainstem reflexes represent an interesting tool useful to test a drug's efficacy.

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