

Interictal habituation deficit of the nociceptive blink reflex: an endophenotypic marker for presymptomatic migraine?

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Habituation of the nociception-specific blink reflex (nBR) is reduced interictally in migraine patients. This could be related to the habituation deficit of evoked cortical responses, a reproducible abnormality in migraine which has a familial character, or to central trigeminal sensitization due to repeated attacks. We compared nBR habituation in healthy volunteers devoid of personal or family history of migraine (HV), in migraine without aura patients (MO) and in healthy volunteers with a family history of migraine in first degree relatives (HV-F). We elicited the nBR by stimulating the right supraorbital region with a custom-built electrode in 16 MO between attacks, 15 HV and 14 HV-F. Habituation was measured as the percentage area-under-the-curve decrease in 10 consecutive blocks of five averaged rectified responses. nBR habituation was clearly reduced in MO and HV-F compared to HV. Percentage area under the curve decreased between the 1st and the 10th block by 55.01% in HV, 25.71% in MO ($P = 0.001$) and 26.73% in HV-F ($P = 0.043$). HV-F had the most pronounced abnormality with potentiation instead of habituation in the second block. We found a positive intraindividual correlation between attack frequency and habituation in MO ($r = 0.621$; $P = 0.010$). Migraine patients have interictally a deficient habituation of the nBR which is inversely related to attack frequency, suggesting that it is not due to trigeminal sensitization. Surprisingly, the most pronounced habituation deficit is found in asymptomatic individuals with a family history of migraine. Deficient nBR habituation could thus be a trait marker for the genetic predisposition to migraine.

Keywords: sensory processing; brain circuits; migraine

Abbreviations: HV = health volunteers devoid of personal or family history of migraine; HV-F = healthy volunteers with a family history of migraine in first degree relatives; MO = migraine without aura patients; nBR = nociception-specific blink reflex

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Introduction

Lack of habituation is a reproducible abnormality found in migraineurs between attacks in evoked potential studies (Schoenen, 1996; Schoenen *et al.*, 2003). It was also recently described in migraineurs for a brainstem reflex, the nociceptive blink reflex (nBR) (Katsarava *et al.*, 2003; Di Clemente *et al.*, 2005). Contrary to the classical blink reflex which has two components (R1 and R2) and sometimes

a third one (R3), the nBR is elicited by a special stimulation electrode with high current density activating rather selectively A δ fibres and has only a R2 component (Kaube *et al.*, 2000; Katsarava *et al.*, 2002a). While the classical blink R2 reflex habituates normally in migraine patients (De Tommaso *et al.*, 2002), habituation of the nBR is reduced interictally (Katsarava *et al.*, 2003). During a migraine attack

the nBR habituates normally, a change also reported for cortical evoked responses (Afra *et al.*, 2000), while its global amplitude increases (Kaube *et al.*, 2002).

The habituation deficit of cortical evoked potentials may have a familial character and was proposed as an endophenotypic marker of migraine (Sándor *et al.*, 1999; Siniatchkin *et al.*, 2000). In migraine families it was found in asymptomatic subjects at risk of developing the disorder (Siniatchkin *et al.*, 2000).

We searched therefore for an abnormal habituation pattern of the nBR in healthy asymptomatic subjects having a first degree relative affected by migraine, and we compared them with healthy volunteers and migraine patients.

Material and methods

Subjects

Twenty-nine healthy volunteers without personal history of migraine or any other recurrent headache were recruited among students, hospital personnel and relatives of patients consulting our Headache Clinic. They were separated in two groups of comparable age and sex distribution: 15 subjects without family history of migraine (HV: mean age: 23.9 years; 10 women, 5 men) and 14 subjects (HV risk: mean age: 24.2 years; 9 women, 5 men) having at least one first degree relative who suffers from migraine and consults our clinic. These healthy volunteers were compared to 16 patients suffering from migraine without aura according to ICHD-II criteria (Headache Classification Subcommittee of the International Headache Society, 2004) (MO; ICHD-II code 1.1; mean age: 27.6 years; 11 women, 5 men). Recordings in patients were obtained interictally at least 2 days after the last and before the next migraine attack. All subjects were devoid of any other pathology, were non-smokers, and were not allowed to take drugs on a regular basis, nor caffeine or alcohol containing beverages <4 h before the recording. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki and the study protocol was approved by the local Ethics Committee.

Data acquisition

The nociception-specific blink reflex was elicited according to the methods described by Kaube *et al.* (2000) and Katsarava *et al.* (2002a). Briefly, a custom-built planar concentric electrode (central cathode: 1 mm D; insert: 8 mm; anode: 23 mm OD) providing a high current density at low intensities over a $\pm 40 \text{ mm}^2$ area was used to stimulate the supraorbital region. Perception and pain thresholds were determined on both sides of the forehead with ascending and descending sequences of 0.2 mA intensity steps. For the patients' comfort and to avoid a too lengthy procedure the electrophysiological study was restricted to a unilateral right-sided stimulation. The stimulus intensity was set at 1.5 times the individual pain threshold. Monopolar square pulses of 0.3 ms of duration were delivered with pseudorandomized interstimulus intervals (ISI) of 15–17 s. With surface electrodes we recorded bilaterally over orbicularis oculi muscles 10 blocks of six rectified EMG responses with an interblock interval (IBI) of 2 min using a CEDTM 1401 signal averager

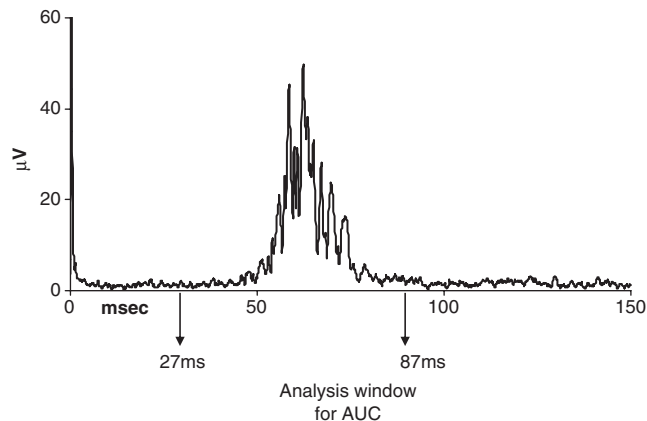


Fig. 1 Nociception blink reflex recording: one block of five rectified and averaged responses with an ISI of 15–17 s.

(Cambridge Electronic Design, Cambridge, UK). The 2-min IBI was chosen because it produces the most pronounced habituation in normal subjects (Katsarava *et al.*, 2002).

Data processing

For each sweep, 150 ms of the poststimulus period were collected and off-line filtered (1 Hz–1 kHz). Five responses were rectified and averaged for each block (Fig. 1), as the first sweep was excluded from the signal analysis to avoid contamination with startle responses (Kaube *et al.*, 2000; Katsarava *et al.*, 2002a). In order to evaluate the global EMG activity generated during the R2 reflex, we measured the area under the curve (the response area: RA) in $\mu\text{V} \times \text{ms}$.

For each averaged block, the R2 onset latency, visually determined as the take-off point from baseline, and the RA between 27 and 87 ms (Ellrich and Treede, 1998) (Fig. 1) were measured off-line by an investigator (GC or LDC) blinded to the subjects' identities. Habituation of the nBR R2 was defined as the percentage change of the R2 area between the 1st and the 10th block of recordings (IBI: 2 min). Since the study by Katsarava *et al.* (2003), showing reduced nBR habituation interictally in migraineurs was based on five responses obtained with short ISIs, we also measured the amplitude change in the five sequential responses recorded in the 1st block with an ISI of 15–17 s.

Statistical analysis

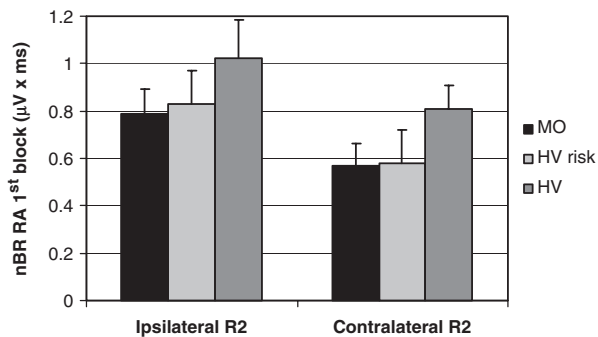
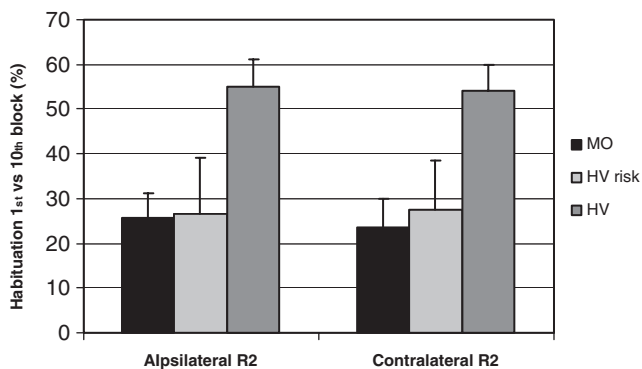
Results are presented as means \pm standard deviations except in Fig. 4 where standard errors are shown for a better visual identification of the different curves. Group differences in mean pain threshold and nBR latency were calculated with one-way analysis of variance (ANOVA). Habituation of the nBR responses was assessed by ANOVA for repetitive measurements with Scheffé's *post hoc* analysis, considering the different blocks (2 to 10) as within subject factors and the diagnostic groups (HV, MO and HV-risk) as between subject factors. Results were considered significant at $P < 0.05$.

Results

We found no significant difference in mean perception or pain threshold between the three subject groups on

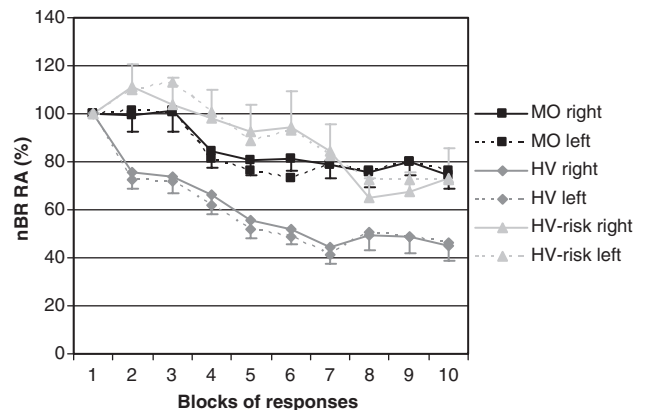
Table 1 Mean values of electrophysiological findings

| Subject groups | First block nBR RA ($\mu\text{V} \times \text{ms}$) | | Habituation 10th/1st block (%) | |
|--|---|-----------------|---------------------------------|---------------------------------|
| | Ipsilateral | Contralateral | Ipsilateral | Contralateral |
| Healthy subjects (HV; $n = 15$) | 1.02 ± 0.63 | 0.81 ± 0.54 | 55.01 ± 23.43 | 54.02 ± 22.44 |
| Healthy + 1st deg mig (HV-risk; $n = 14$) | 0.83 ± 0.52 | 0.58 ± 0.36 | $26.73 \pm 44.99^*$ | $27.36 \pm 40.76^*$ |
| Migraine without aura (MO; $n = 15$) | 0.79 ± 0.42 | 0.57 ± 0.37 | $25.71 \pm 21.27^{**}$ | $23.65 \pm 24.75^{**}$ |
| One-way ANOVA | NS | NS | * $P = 0.043$ ** $P = 0.001$ | * $P = 0.038$ ** $P = 0.001$ |

**Fig. 2** R2 response area in the first block of averaged responses ($\mu\text{V} \times \text{ms}$).**Fig. 3** Habituation of the R2 response area in the last block of averaging relative to the 1st block (%).

either side of the forehead, or between the left and right side in any group (data not shown). The mean stimulus intensities ($1.5 \times$ pain threshold) used for studying the nBR were thus similar between groups: 2.09 ± 0.44 mA for HV; 2.04 ± 0.66 mA for HV-risk and 2.15 ± 0.77 mA for MO.

On all recordings the R2 component of the blink reflex was clearly identified and there was no R1 component. Mean R2 latency was slightly shorter in migraineurs than in both groups of healthy volunteers (MO: 36.55 ± 5.66 ms; HV: 40.74 ± 7.37 ms; HV-risk: 38.81 ± 4.54 ms), but these differences were not significant [$F(1,29) = 2.919$, $P = 0.10$ versus HV; $F(1,28) = 1.162$, $P = 0.29$ versus HV-risk].

**Fig. 4** Habituation of the R2 response area of ipsi- and contralateral nBR in 10 blocks of five averagings (interstimulus interval: 15–17 ms; interblock interval: 2 min) expressed as percentage of the 1st block.

There was no significant side difference in first block nBR response area or in its habituation over 10 blocks in any of the three groups (Table 1).

The response area in the first block of stimuli was greater in healthy controls than in migraineurs or healthy volunteers with an affected first degree relative, but this difference did not reach statistical significance [$F(1,29) = 1.558$, $P = 0.22$ versus MO; $F(1,27) = 0.820$, $P = 0.37$; Table 1, Fig. 2].

There was a large interindividual variation of both first block nBR RA and habituation in the three groups of subjects (see standard errors in Fig. 4). Habituation of the nBR RA was nonetheless on average clearly different between the HV group on the one hand and the HV-risk and MO group on the other. In HV there was a strong habituation with an amplitude decrease exceeding 50% between the first and the 10th block of five averagings. This contrasted with a less than 28% habituation in the MO [$F(1,29) = 13.317$, $P = 0.001$ versus HV] and HV-risk [$F(1,27) = 4.527$, $P = 0.043$ versus HV] groups (Table 1, Fig. 3). Habituation steadily increased in successive blocks in all the three groups of subjects up to the 10th block of stimuli (Fig. 4). The difference in the degree of nBR RA habituation between healthy volunteers and the other two groups, however, was already significant in the second block

of five averagings (Fig. 4): 24.1% habituation in HV, -8.4% (i.e. potentiation) in HV-risk [$F(1,27) = 7.730$, $P = 0.010$ versus HV] and 1.5% habituation in MO [$F(1,29) = 5.145$, $P = 0.031$ versus HV].

We found a positive intraindividual correlation between attack frequency and habituation in MO ($r = 0.621$; $P = 0.010$).

Single response areas within the 1st block of stimuli and their habituation in individual subjects greatly varied. There was nonetheless a significant reduction in habituation between the first and fifth response in the HV-risk group. For instance, on the ipsilateral side the amplitude change was -36.9% (potentiation) in HV-risk, compared to $+41.5\%$ (habituation) in HV [$F(1,27) = 4.701$; $P = 0.04$]. Habituation was also lower in MO (29.7%) than in HV, but this difference was not significant [$F(1,29) = 0.751$; $P = 0.39$].

Discussion

Our results showing that habituation of the nBR is significantly reduced interictally in migraineurs compared to healthy volunteers are in line with those reported by Katsarava *et al.* (2003). The two studies, however, differ in several aspects. While in Katsarava *et al.*'s (2003) study the habituation was assessed only on five single responses with an ISI of 15–17 s, i.e. over a maximal time span of 68 s, we measured the R2 habituation on 10 successive blocks of five averaged responses with the same ISI but with an IBI of 2 min, i.e. over a maximal period of 32 min (10th versus 1st block) or a minimal period of 256 s (2nd versus 1st block). We chose this method for two reasons. First, the habituation deficits reported in migraine for evoked and event-related potentials have been determined without exception on averaged responses and thus over long time periods reaching 30 min in some studies (Schoenen *et al.*, 2003). Second, Katsarava *et al.* (2002a) themselves have shown in healthy volunteers that habituation of the nBR2 is much more pronounced ($>75\%$) over 10 averaged blocks of five responses separated by 2 min, the IBI chosen here, than between five single responses with an ISI of 15–17 s (19–24%) (Katsarava *et al.*, 2002b). The short and long-term habituation phenomena may be related, insofar as the intrablock habituation may increase in successive blocks, but this was not mentioned in a study where two blocks of five responses were analysed (Katsarava *et al.*, 2003) and not examined in our study. To allow a better comparison of results, however, we also measured the nBR habituation over the five 1st block responses and were not able to totally confirm Katsarava *et al.*'s (2003) data. Although the intrablock habituation values were smaller in migraineurs than in healthy volunteers, this difference was not significant, possibly because standard deviations were too large and groups too small. The mechanisms underlying short and long-term habituation of the nBR may thus be partly different. The difference in nBR response area

habituation between patients and healthy volunteers is significant as early as the 2nd block of averages. It increases with repetition of stimuli and tends to become maximal in the 10th block, i.e. after 32 min of recordings, a time at which habituation was found to be maximal in normal subjects (Katsarava *et al.*, 2002a). Our stimulation method was similar to the one published by the abovementioned group (Kaube *et al.*, 2000) with the notable exception that we used a custom-built electrode with a slightly larger stimulation area. As stimuli elicited no R1 responses, it is likely that they activated chiefly A δ fibres like in Kaube *et al.*'s study. Our study was not designed to assess changes in pain perception thresholds simultaneously to the nBR habituation, as perception thresholds were measured only once at the beginning of the recording session (see Material and methods).

Although the R2 component of the classical blink reflex and the nociceptive R2 are elicited by activation of different populations of trigeminal fibres, they probably share some common features. They are both bilateral responses and involve polysynaptic neural networks comprising the spinal trigeminal nucleus, interneurons of the bulbopontine lateral reticular formation and motoneurons of the facial nucleus innervating the orbicularis oculi muscles (Holstege, 1990; Esteban, 1999). Habituation is a classical phenomenon in polysynaptic activities (Desmedt and Godaux, 1976). There are, however, striking differences between the classical and nociceptive R2 responses in migraine. For instance, the classical R2 does not habituate with IBI intervals as low as 15 s either in healthy volunteers or in migraineurs (Penders and Delwaide, 1971; de Marinis *et al.*, 2003). As mentioned, the classical R2 is essentially normal interictally, but it is less influenced by the warning of the stimulus in migraine (de Tommaso *et al.*, 2002) and, at short IBI, its habituation was found reduced in migraineurs who developed an attack within 72 h after the recording (de Marinis *et al.*, 2003). It remains to be determined if the nociceptive BR is modulated by dopamine like the classical R2. Lack of habituation of this response is a typical finding in Parkinson's disease and reversible with dopaminergic therapy (Penders and Delwaide, 1971). If so, the fact that the nBR2 habituation is decreased in migraine would not favour the hypothesis that the disorder is associated with dopaminergic hypersensitivity (see for a review Mascia *et al.*, 1998).

The rather low nBR amplitude in the first block of five averaged responses we found interictally in migraineurs contrasts with the 680% nBR RA increase reported during the migraine attack (Kaube *et al.*, 2002) which is considered to reflect ictal sensitization of spinal trigeminal nucleus neurons and not found in sinus headaches (Katsarava *et al.*, 2002b). The low nBR amplitude in our study does not favour such sensitization and rather suggests that the R2 interneurons and circuit could be hypoexcitable in between migraine attacks. This is reminiscent of our previous

interictal findings with evoked cortical potentials where low 1st block amplitude and lack of habituation are found in concert (Schoenen *et al.*, 2003). We have provided indirect evidence (Bohotin *et al.*, 2002; Coppola *et al.*, 2005) that both abnormalities might be a consequence of reduced serotonergic transmission (Wang *et al.*, 1996; Juckel *et al.*, 1997) leading to a decreased preactivation level. Interestingly, it has been shown in cat that the serotonergic raphe magnus nucleus is a pivotal relay between the basal ganglia and the trigeminal neurons mediating the blink reflex; the loss of dopaminergic neurons in Parkinson's disease is thought to disinhibit the blink reflex by causing a lack of activation of raphe magnus neurons (Basso and Evinger, 1996). The habituation deficit might thus represent a trait marker for migraine patients and their low serotonin disposition (Ferrari *et al.*, 1989), and play a role in its pathomechanisms (Schoenen, 1998). It does not seem to be a consequence of repeated attacks and persistent attack-related sensitization (Kaube *et al.*, 2002), as in this case one would expect a more pronounced deficit in patients with frequent attacks. As a matter of fact, we find the opposite in our study: nBR habituation increases, rather than decreases, with increasing attack frequency, which confirms our previous results (Di Clemente *et al.*, 2005). Few correlations have been found between neurophysiological results and attack frequency in migraine. In a study of laser-evoked cortical responses, the habituation deficit found interictally in migraineurs was positively correlated with attack frequency (de Tommaso *et al.*, 2005) and in a magnetoencephalographic recording of somatosensory evoked potentials the N20m amplitude increase in migraineurs was linked to the frequency of attacks (Lang *et al.*, 2004). We have therefore no satisfactory explanation for our finding of a negative correlation between the habituation deficit on the nBR and attack frequency. It could, however, be related to the fact that nBR short-term habituation (Katsarava *et al.*, 2003), akin to habituation of evoked cortical potentials (Schoenen *et al.*, 2003), normalizes during the attack period. One might thus speculate that patients with high-attack frequencies were at greater risk of being recorded in closer vicinity to an attack.

Our most striking finding is that asymptomatic subjects with a first degree migrainous relative present the same nBR abnormalities as patients with full-blown migraine between attacks. Compared to healthy volunteers without a family history of migraine, they tend to have smaller first block nBR response areas and, more significantly, reduced nBR habituation. Their degree of habituation is intermediate between that of healthy controls who habituate more and that of migraineurs who habituate less, but the difference is significant respective to the former, but not to the latter. Healthy subjects at risk also have a significant reduction of habituation within the 1st block of five responses, which differs from the findings in migraineurs. The possible relation between intra- and

interblock habituation remains to be determined. Whatever it may be, our finding raises the possibility that subjects with a familial predisposition for migraine may present a presymptomatic neurophysiological abnormality in response habituation. A similar suggestion was made for increased amplitudes and lack of habituation of contingent negative variation, an event-related potential (Siniatchkin *et al.*, 2000). Although certain rare migraine subtypes such as familial hemiplegic migraine are monogenic diseases, there is increased evidence that the common forms of migraine are polygenic multifactorial diseases, where the genotype determines a migraine threshold which is modulated by internal (e.g. hormonal) and environmental factors (Montagna, 2000; Sandor *et al.*, 2002; Haan *et al.*, 2005). It seems evident from the previous studies and from our results that not all subjects with a first degree relative having migraine have abnormal CNV or nBR patterns, as likely not all of these subjects are genetically predisposed to migraine. This may explain why standard deviations and variance for nBR habituation values are largest in the HV-risk group. One may hypothesize, however, that subjects who show the same habituation deficit as migraine patients are at risk of developing migraine. To verify this hypothesis it seems worthwhile to conduct a longitudinal follow-up study of healthy subjects at high risk and to compare the genotypes, and, if ethically acceptable, the sensitivity to glyceryl trinitrate administration (Olesen *et al.*, 1993) between those who have a normal habituation pattern and those who have not. It would be of even greater interest to determine which factors such as personality traits, life events, environment or comorbidity can protect subjects with a family history of migraine against developing migraine.

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