Psychophysiology, *39* (2002), 166–174. Cambridge University Press. Printed in the USA.

DOI: 10.1017.S0048577201392065

Reduced sensory anticipation in migraine

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Abstract

We examined differences between migraine patients and matched healthy controls in anticipatory processes preceding a warning stimulus and preceding a response stimulus during a forewarned choice reaction time task. We manipulated stimulus preceding negativity (SPN) by inserting full response information either at the instant of the warning stimulus (cue) or at the instant of the response stimulus. In contrast to control subjects, migraineurs with aura show low anticipation towards an informative cue and high anticipation towards a noninformative cue. Migraineurs without aura showed a cortical hypoactivation during motor preparation prior to the response stimulus. We propose a functional deficiency within frontal structures or the anterior cingulate cortex in migraine. This might explain the reduced anticipation, as well as the slow responses during selective attention that we previously reported in these patients.

Descriptors: Migraine, Sensory anticipation, Attention, Stimulus preceding negativity, Contingent negative variation

Research on slow cortical brain potentials has suggested that migraine is accompanied by alterations in the contingent negative variation (CNV). The CNV (Walter, Cooper, Aldridge, McCallum, & Winter, 1964) is recorded during the foreperiod bridging a warning stimulus and an imperative stimulus, and comprises an early and a late component that become clearly visible if the foreperiod is longer than 2 s (e.g., Loveless & Sanford, 1974). Various studies have demonstrated a larger, that is, more negative, CNV amplitude in migraine patients during short foreperiods (Böcker, Timsit-Berthier, Schoenen, & Brunia, 1990; Maertens de Noordhout, Timsit-Berthier, Timsit, & Schoenen, 1987; Schoenen, Maertens de Noordhout, Timsit-Berthier, & Timsit, 1986). Studies employing longer foreperiods predominantly report a larger early wave amplitude in migraine without aura (Böcker et al., 1990; Kropp & Gerber, 1993a; 1993b; 1995), but larger late wave amplitudes have also been reported (Böcker et al., 1990). These augmented CNV amplitudes are believed to be a manifestation of cortical hyperexcitability, induced by hyperactive central catecholaminergic systems (Libet, 1979; Maertens de Noordhout et al., 1987; Nagel-Leiby, Welch, D'Andrea, Grunfeld, & Brown, 1990; Schoenen et al., 1986; Timsit-Berthier, Mantanus, Poncelet, Marissiaux, & Legros, 1986; Timsit-Berthier, Mantanus, Poncelet, et al., 1986).

In addition, the CNV appears to be sensitive to the temporal proximity of a migraine attack. The early wave increases even further during the days before an attack, but decreases to the level of healthy control subjects during an attack (Kropp & Gerber, 1995). This early wave normalization during an attack could be related to the depletion of noradrenergic activity combined with increased serotonergic transmission (Gerber & Schoenen, 1998). In the 2 to 3 days following an attack, the CNV remains at this normalized level, after which it gradually increases again (Kropp & Gerber, 1998). These dynamic changes within the migraine course emphasize that preictal or postictal effects could confound the interictal CNV, unless it is recorded in a truly interictal period. In an earlier CNV study, during a simple forewarned reaction time task recorded in a period that was free from preictal or postictal effects, we demonstrated normal CNV amplitudes in interictal migraine patients without aura (Mulder, Linssen, Passchier, & de Geus, 2001), which challenges the hypothesis of cortical hyperexcitability. Mulder, Linssen, Passchier, Orlebeke, and de Geus (1999) reported that these migraine patients, and especially migraineurs with aura, show normal error rates but increased reaction times during tasks that require sustained attention and particularly selective attention. As an alternative to cortical hyperexcitability that could explain these attentional impairments, we propose inadequate anticipation towards task-relevant stimuli. The CNV paradigm is a suitable instrument to examine different types of anticipatory processes and related deficiencies.

The CNV early wave is maximal over the frontal cortex, and is believed to be related to the orienting properties of the warning stimulus (WS) (Loveless & Sanford, 1974; Rohrbaugh & Gaillard, 1983), or to (post) stimulus processing (Simons, 1988). The late wave is most pronounced over the central cortex contralateral to the responding hand and is mainly interpreted in terms of negativity due to pure motor processes (Gaillard, 1978; Rohrbaugh & Gaillard, 1983). The idea that the CNV late wave reflects motor processes only has been challenged by the increased amplitudes taking place when subjects adequately anticipate the delivery of a response stimulus that conveys more specific response information (Van Boxtel & Brunia, 1994b; Van Boxtel, Van den Boogaart, & Brunia, 1993). The notion is that the CNV late wave comprises both motor preceding negativity, and (sensory) stimulus preceding

GlaxoWellcome (SUM9408) funding this study is acknowledged.
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negativity (Ruchkin, Sutton, Mahaffey, & Glaser, 1986) reflecting task difficulty (McCallum & Papakostopoulos, 1973), attentional demands (Tecce, 1972), and anticipation (Brunia, 1988; Van Boxtel & Brunia, 1994a, 1994b; Van Boxtel et al., 1993).

When anticipatory sensory negativity precedes a response stimulus, it theoretically precedes any task relevant stimulus, and is therefore designated "stimulus preceding negativity" (SPN; Brunia, 1988; Damen & Brunia, 1987). The presence of SPN is further strengthened by the demonstration of increased cortical negativity when: (a) stimuli are anticipated that do not require a motor response but have a cueing function and convey information about a future response (e.g., Gaillard & Van Beijsterveldt, 1991; Van Boxtel et al., 1993), and (b) subjects adequately anticipate to an informative cue compared to a noninformative cue (Van Boxtel & Brunia, 1994b). The SPN does, however, seem to reflect different anticipatory processes depending on whether it precedes an instruction or response stimulus. SPN has a frontal minimum and parietal maximum preceding a warning stimulus (Gaillard & Van Beijsterveldt, 1991; Rösler, 1991; Van Boxtel & Brunia, 1994b), which has been related to the attentional direction of anticipation (Brunia, 1988, 1993). A parietal source could reflect its involvement in the processing of spatial stimuli that prompt far-future action. The SPN prior to a response stimulus is believed to reflect a different kind of anticipation because of the involvement of a different set of dipoles (Böcker, 1994) and a different anterior–posterior scalp distribution. A frontal maximum has been frequently found preceding a motor response (e.g., Gaillard & Van Beijsterveldt, 1991; Rösler, 1991; Van Boxtel & Brunia, 1994b; Van Boxtel et al., 1993). This frontal component has been suggested to index the effortful control of task performance (see Van Boxtel, 1994) that could be related to the translation of the stimulus into near-future action.

This study examines anticipation towards cue and response stimuli in migraine patients. We manipulated SPN by inserting full information regarding the motor response either at the instant of the WS or at the instant of the response stimulus (RS). In this way, we induced variations in SPN prior to both the WS and the RS, and examined their amplitudes and topographic distributions. If migraineurs show deviations in anticipation, this is expected to be expressed in an altered amplitude or topographic distribution of cortical negativity preceding task-relevant stimuli. We compared these features between interictal migraine patients (with aura and without aura) and matched healthy control subjects.

Method

Participants

CNVs were recorded in migraine patients without aura ($n = 14$), with aura ($n = 6$), and control participants ($n = 22$). All participants were recruited by advertisements in university papers. Patients were diagnosed by a neurologist in accordance with the International Headache Society (IHS) criteria for migraine (Headache Classification Committee of the International Headache Society, 1988), physically examined, and included into the study. Migraine patients using prophylactic medication, monoamine oxidase inhibitors, beta blockers, serotonin reuptake inhibitors or lithium and patients with a known hypersensitivity, intolerance, or contraindication to the use of sumatriptan were excluded from the study. Patients used analgesics, NSAIDs, or no medication as their habitual medication to treat an attack, but did not use vasoactive antimigraine medication such as ergot derivates. For reasons of comparability of socioeconomic status, control participants were recruited from the same student population and matched on the basis of sex, age, and hand preference. Controls did not suffer from migraine nor from any other type of headache more than once per 2 months (e.g., due to alcohol consumption or exposure to toxic substances). Participants were not admitted to the study if they had a history of epilepsy or other severe medical conditions that could affect the interpretation of the results, current abuse of opiate analgesics, psychotropic drugs, ergotamine (>10 mg/week), alcohol (>315 g/week), or a history of abuse of these substances in the previous 6 months. Prior to the study, all participants were informed about the study and signed a consent form. The medical ethical committee of the Vrije Universiteit approved this study.

Procedure

CNV measurement was part of a larger protocol during which neuropsychological testing took place after the EEG recordings. The CNV was measured in symptom-free migraine patients and in their matched healthy control participants . Migraine patients were tested on a headache- and symptom-free day, 4 or 5 days after the peak of a migraine attack (interictal session). If this interictal session was followed by a new migraine attack within 3 days, this session was considered invalid. For this reason, two interictal measurements were excluded from the analyses. In this way, we avoided possible preictal (Kropp & Gerber, 1995) or postictal (Kropp & Gerber, 1998) effects on CNV amplitudes in headache-free migraineurs. Control participants were tested being headache free and without having used medication during the same period of the week (beginning, middle, weekend) and at the same time during the day (morning, afternoon, evening) as the patient they were matching. All participants abstained from coffee and smoking in the hours prior to and during the measurements.

CNV Measurement

Participants were in a supine position in a dimly lit, sound attenuating, electrically shielded cubicle. A box (surface of 10×10 cm) with four response buttons ordered in a square served as the response device and was attached to the arm rest on the side of the dominant hand. The participants were instructed to place their index fingers at the intersection of the cross separating the four response buttons. They were strictly instructed to move the index finger from the intersection only at the instant of the RS, after which they immediately had to place their index finger back at the intersection again. The WS and RS were both visual stimuli presented on a monitor that was placed with in a slope of approximately 45° in front of the participants. A trial started with a fixation point presented in the middle of the monitor (1,000 ms). The WS during the "choice" condition was a bar (300 ms), and the WS in the "precued" condition was an arrow pointing (300 ms) in one of four different directions (upper left, upper right, lower left, lower right: equal probability). A fixation point was presented throughout the entire fixed interstimulus interval of 3,000 ms, after which the RS was presented. During the choice and the precued conditions, RS was an arrow pointing in one of the four possible directions. During the precued condition, WS and RS were identical arrows (see Figure 1). At the instant of RS, the participant had to respond as quickly as possible by pressing the button as indicated by the arrow. If participants exceeded the maximum response time of 800 ms, responded prematurely, or pressed the wrong button, this trial was rejected, which was indicated by an acoustic feedback stimulus (300 ms; 300 Hz) presented 200 ms after the maximum response time. The intertrial interval was 5, 6, 7, or 8 s pseudorandomly varied with a rectangular distribution.

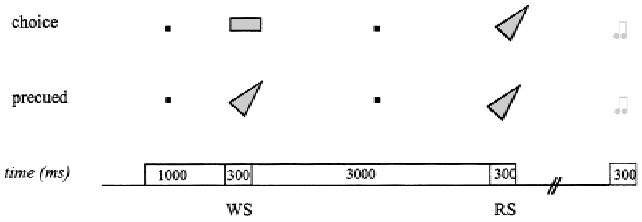

Figure 1. Trial in the choice and precued conditions of the forewarned reaction time task.

The conditions were presented in blocks, administered in a counterbalanced order, and each condition consisted of 48 trials, during which reaction times and errors (premature key presses and omissions) were stored for all trials. All participants were given practice trials before the actual measurement. Directly after each condition, participants completed a rating scale for mental effort (Zijlstra & Meijman, 1989).

The CNV was recorded using Ag/AgCl electrodes mounted in an electrocap according to the international 10-20 system positions Fz, Cz, and Pz with linked earlobes serving as the reference. A vertical bipolar derivation from the right eye and a horizontal derivation were used for the recording of the electrooculogram (EOG). The electrode resistance was below 3 KΩ for the EEG electrodes, and below 5 KΩ for the EOG electrodes. The EEG was filtered (bandpass 0.005–30 Hz), digitized at 250 Hz, and stored for off-line processing. After removing trials with excessive eye blinks (>150 μV), EEG signals were corrected for eye movements by dynamic regressive decorrelation (Brillinger, 1975).

Data Reduction and Analyses

The mean amplitude in the 500 ms preceding the fixation point was taken as the baseline for the determination of mean amplitude of CNV early wave, CNV late wave (i.e., pre-RS negativity), and pre-WS negativity. The CNV was calculated over the total epoch of 5,200 ms including the baseline. Trials containing values exceeding 70 μV with respect to this baseline were removed from further analysis. To obtain the early wave amplitude for every subject, the maximal (most negative) value at Fz was determined between 600 and 1,100 ms following WS. This point served as the middle of a 200-ms window where the mean amplitude wave was calculated for all EEG channels. The estimated negativity (SPN) prior to the WS and prior to the RS were obtained as follows: First, mean negativity was calculated in the 200-ms window preceding WS as well as in the 200 ms preceding RS (these measures will be reported on as pre-WS and CNV late wave, respectively). Second, because the pre-RS negativity is expected to be largest in the choice condition, the estimated SPN preceding RS is computed by subtracting the mean negativity in the 200-ms window in the precued condition from the pre-RS negativity in the choice condition. Likewise, the pre-WS negativity is expected to be largest in the precued condition, and the estimated SPN prior to WS is obtained by subtracting the negativity in the 200-ms window preceding the WS in the choice condition from the precued condition. This subtraction is based on the method of van Boxtel and Brunia (1994b).

Using the GLM module of SPSS 10.0, we performed MANOVAs for repeated measures separately on the negativity preceding WS, the CNV early wave, and the negativity preceding RS (CNV late wave). The within-subjects factors were Condition (precued, choice), and Electrode (Fz, Cz, Pz), and the between-subjects factor was Group (control subjects, migraineurs with aura, migraineurs without aura). The analyses on the estimated SPN prior to WS and the estimated SPN prior to RS included the within-subjects factor Electrode (Fz, Cz, Pz) and the between-subjects factor Group (control subjects, migraineurs with aura, migraineurs without aura). Separate MANOVAs for repeated measures were performed on reaction time and the subjective amount of effort, where the within-subjects factor was Condition (precued, choice) and the between-subjects factor was Group (controls, migraineurs with aura, migraineurs without aura). A nonparametric test for three independent samples (Kruskall–Wallis Test) was performed on the number of errors.

We selectively specified post hoc tests following the detection of significant main or interaction effects, using the Lmatrix and Mmatrix option of the GLM module. For follow-up testing of each main or interaction effect, we used the Holm method (Aickin & Gensler, 1996) to reduce Type 1 error due to multiple testing. This method is also suitable for groups with unequal sample sizes. As an illustration for the relevance of post hoc effects, we reported some effect sizes expressed in Cohen's *d* (Cohen, 1969). Box M tests were performed for each repeated measures analysis to check the assumption that (multivariate) covariance matrices are homogenous for the levels of the within-subject factors. Levene tests were performed to check the assumption that (univariate) variances are equal between the groups (controls, migraine with aura, migraine without aura). We removed one outlier (migraine without aura) from the "CNV late wave" and "SPN to RS" because this subject deviated more than three standard deviations from the mean value of all subjects. After this, all assumptions were met. In the following, we report the multivariate (nonpooled) results.

Results

Demographics

The group of migraine patients did not differ from healthy controls in composition regarding age, hand preference, or sex (see Table 1). Migraine patients with aura and migraine patients without aura did not differ with respect to usual attack severity, migraine history, and attack frequency.

Task Performance

The number of errors are not significantly different between conditions, neither between migraine patient without aura, migraineurs with aura, and controls. Response times are longer during the choice condition than in the precued condition (Condition: $F(1,39) = 99.93$, $p = .000$). The subjective report of task-related mental effort (Figure 2) showed a trend towards a Condition × Group interaction, $F(2,39) = 1.71$, $p = .164$. This indicated that control subjects report equal amounts of mental effort during the precued and choice condition (control group only: precued minus choice: $F(1,39) = 0.01$, $p = .939$). All migraine patients (with aura and without aura) report more mental effort during the choice condition than during the precued condition (migraineurs only: precued minus choice: $F(1,39) = 6.27$, $p = .017$).

The Contingent Negative Variation

Figure 3 depicts the CNV from Fz, Cz, and Pz in symptom-free migraine patients with aura, migraine patients without aura, and matched control subjects during the choice and the precued conditions.

Table 1. *Demographics and Migraine Characteristics*

	Migraine with aura ($n = 6$)	Migraine without aura ($n = 14$)	Control subjects ($n = 22$)	
Female/male	5/1	13/1	20/2	*MWU[a] .921
Left/right handed	0/6	2/12	2/20	*MWU .921
Age	20.6 (.84)	24.8 (.82)	24.1 (.58)	*$F(1,40) = 0.43$, $p = .52$
Usual attack severity (VAS[b])	70.7 (9.5)	78.1 (9.4)		#$F(1,18) = 2.72$, $p = .12$
Migraine history (years)	8.5 (0.9)	7.9 (1.4)		#$F(1,18) = 0.09$, $p = .77$
Attack frequency				#MWU .274
1–3 attacks (per month)	$n = 4$	$n = 14$		
4–6 attacks (per month)	$n = 2$	$n = 0$		

Notes: Means and (standard errors).
[a]MWU: Mann-Whitney U Exact Significance (migraineurs with aura vs. migraineurs without aura).
[b]Visual Analogue Scale ranging from 0 (*no pain at all*) to 100 (*as bad as can be*).
*Comparison of the migraine group (with and without aura) versus controls.
#Comparison of migraine with aura versus migraine without aura.

Pre-WS negativity and estimated SPN to the WS. The significant main effect of Electrode, $F(2,38) = 3.69$, $p = .034$, indicates that pre-WS negativity has a centroparietal maximum (averaged over group and condition: Fz < Cz, $F(1,39) = 7.32$, $p = .010$; Cz = Pz, $F(1,39) = 0.19$, $p = .663$). Post hoc testing of the trend towards the Condition × Electrode × Group effect, $F(4,78) = 1.85$, $p = .128$, indicates that the parietal negativity preceding WS is unequal between the groups within each condition (precued condition only at Pz: $F(1,39) = 20.30$, $p = .000$; choice condition only at Pz, $F(1,39) = 22.49$, $p = .000$). As is shown in Figure 4, control subjects show the expected larger parietal negativity preceding the most informative WS during the precued condition, compared to the noninformative WS during the choice condition. In contrast, migraine patients (with and without aura) do not show this expected effect. Migraineurs without aura show similar negativity during the conditions, whereas migraineurs with aura show a larger negativity preceding the noninformative WS in the choice condition (Cohen's $d = .48$; medium effect size). The Condition × Electrode × Group interaction is illustrated by the anterior–posterior distribution of the estimated SPN preceding WS in the three groups (lower panel, Figure 4). Follow-up tests of the Electrode × Group interaction of this SPN, $F(4,78) = 2.64$, $p = .128$, reveal that it has a centroparietal maximum and a frontal minimum in migraineurs without aura and controls (exclusion of migraineurs with aura: Fz < Pz: $F(1,39) = 8.48$, $p = .006$), but has the reverse distribution in migraineurs with aura (exclusion of migraineurs without aura and controls: Fz > Pz: $F(1,39) = 3.21$, $p = .081$).

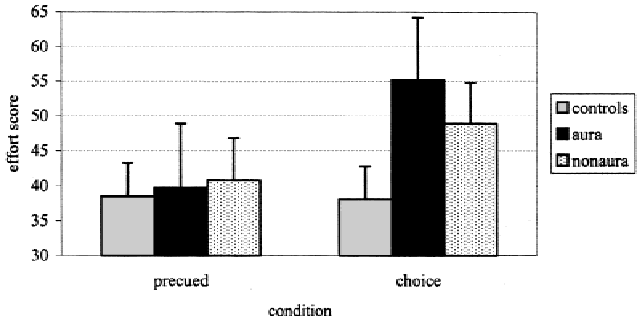

Figure 2. Subjective effort and standard errors during precued and choice conditions in migraineurs with aura, migraineurs without aura, and matched control subjects.

CNV early wave. The amplitude of the CNV early wave is not significantly different between the groups, but is more negative in the precued than in the choice condition (main effect of Condition: $F(1,39) = 6.29$, $p = .016$). Post hoc testing of the significant main effect of Electrode, $F(2,38) = 20.58$, $p = .000$, shows that the early wave has a frontocentral maximum (averaged over group and condition: Fz ≤ Cz: $F(1,39) = 4.21$, $p = .047$; Cz > Pz: $F(1,39) = 38.58$, $p = .000$).

CNV late wave and estimated SPN to the RS. As can be seen from Figure 5, the CNV late wave is larger in the precued than in the choice condition (main effect Condition: $F(1,38) = 15.72$, $p = .000$). Post hoc testing of the main effect of Electrode, $F(2,37) = 9.07$, $p = .001$, shows that the late wave reaches maximal negativity over central areas (averaged over group and condition: Fz < Cz: $F(1,38) = 13.73$, $p = .001$; Cz > Pz: $F(1,38) = 9.62$, $p = .004$; Fz ≤ Pz: $F(1,38) = 2.89$, $p = .097$). The follow up test of the trend towards the main effect of Group, $F(2,38) = 2.54$, $p = .092$, shows that migraineurs without aura have a lower CNV late wave than controls, $F(1,38) = 4.96$, $p = .032$, Cohen's $d = .63$; medium to large effect size. At the central as well as at the frontal electrode, the groups differ in amplitude (averaged over condition: Cz only: $F(1,38) = 35.86$, $p = .000$; Fz only: $F(1,38) = 35.86$, $p = .000$); however, these groups' differences change over Fz and Cz. As is depicted in Figure 5, migraineurs without aura have the smallest amplitude over Cz, whereas migraineurs with aura have the smallest amplitudes over Fz (Cohen's $d = .62$; medium to large effect size). The anterior–posterior distribution of the sensory SPN prior to RS (lower panel, Figure 5) is similar between the three groups (Electrode × Group: $F(4,78) = 1.21$, $p = .314$). Follow-up testing of the significant main effect of Electrode, $F(2,37) = 14.15$, $p = .000$, indicates that all groups show the expected frontal maximum of the SPN (averaged over groups: Fz > (Cz + Pz/2): $F(1,38) = 23.73$, $p = .000$). The SPN amplitude is different over the groups at Cz, $F(1,38) = 18.49$, $p = .000$, at which migraineurs without aura have the largest sensory negativity.

Association between subjective effort rating and SPN prior to response stimulus. The Pearson correlations between the pre-RS

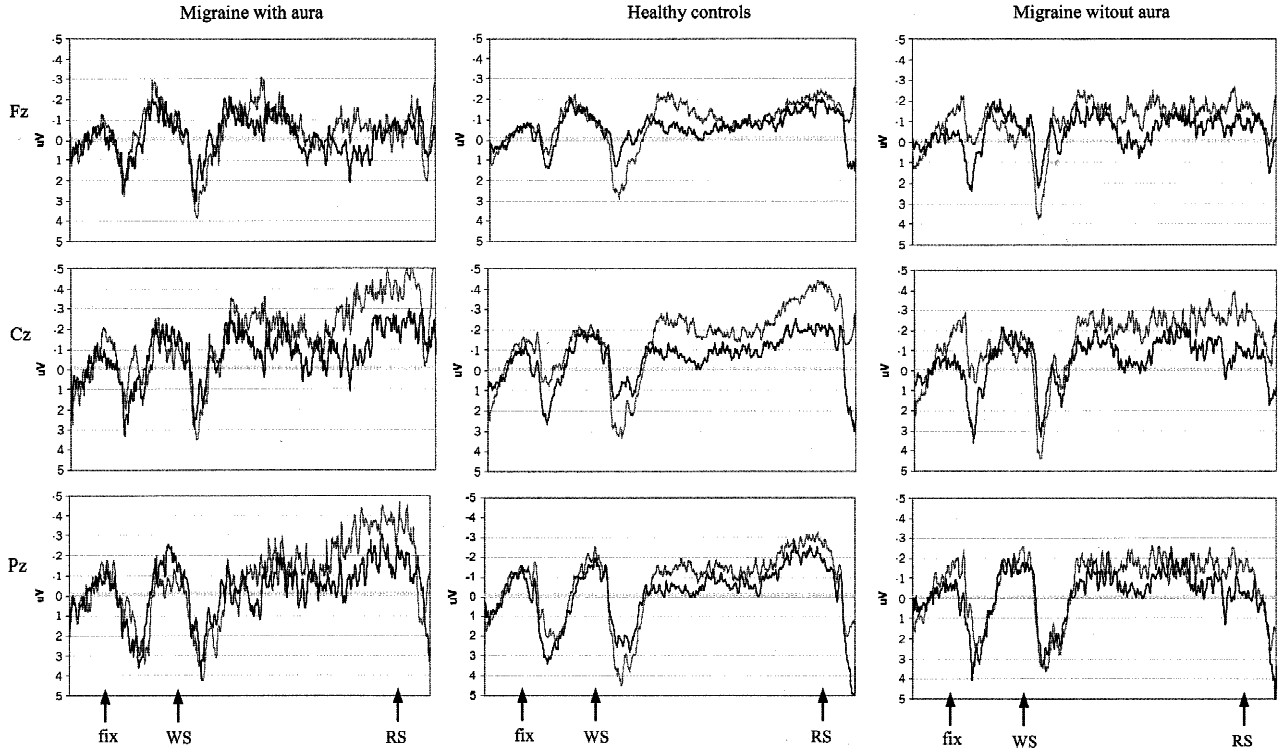

Figure 3. CNV during the precued (gray lines) and choice (black lines) conditions, recorded from Fz, Cz, and Pz (from upper to lower rows) in migraine patients with aura ($n = 6$; left column), migraine patients without aura ($n = 14$; right column), and healthy control subjects ($n = 22$; middle column). Fix: fixation dot; WS: warning stimulus; RS: response stimulus.

SPN amplitude and subjective mental effort (during choice minus precued condition) is .31 ($p = .046$) over the Fz electrode, whereas this association is not significant at Cz (.10) and Pz (.09).

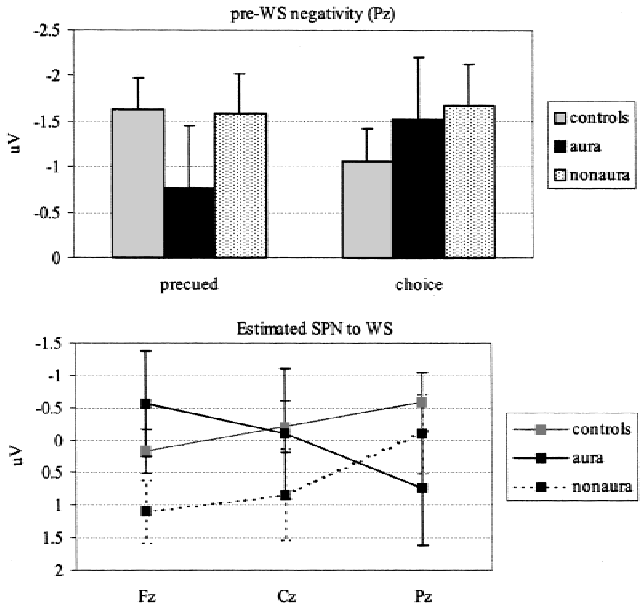

Figure 4. Cortical negativity (Pz) and estimated SPN with standard errors preceding the warning stimulus (WS). SPN to the WS = pre-WS negativity during precued minus choice conditions.

Discussion

We examined whether migraineurs show deviant CNV early and late wave amplitudes compared to healthy matched controls, and whether migraineurs show deviant sensory anticipation as indexed by the SPN to instruction (cueing) stimuli or response stimuli. The latter might explain the slowed cognitive speed that we showed in the same migraine population during tasks that require sustained and particularly selective attention (Mulder et al., 1999). We manipulated sensory anticipation within a CNV paradigm by inserting all task-relevant response information either at the instant of the warning stimulus or at the instant of the response stimulus. In correspondence with our findings during a classic CNV paradigm in a forewarned simple reaction time task (Mulder et al., 2001), we did not find any evidence for the larger interictal CNV early and late wave amplitudes that are often reported for migraineurs without aura (e.g., Böcker et al., 1990; Kropp & Gerber, 1993a, 1993b, 1995). In fact, we even found a smaller CNV late wave in migraineurs without aura than in healthy matched controls. This disparity with other studies could be due to our relatively young, homogenous, nonclinic sample of migraineurs having a relatively short migraine history compared to studies reporting large CNV amplitudes. In addition, we matched control subjects quite rigorously (i.e., for age, sex, dominant hand, and time of measurement) compared to other studies.

In line with similar studies to the present one (see Van Boxtel, 1994), we showed that the early wave is larger after a warning stimulus that transmits full information about the future motor response, compared to a warning stimulus that does not contain specific response information. Simons (1988) refuted the classical

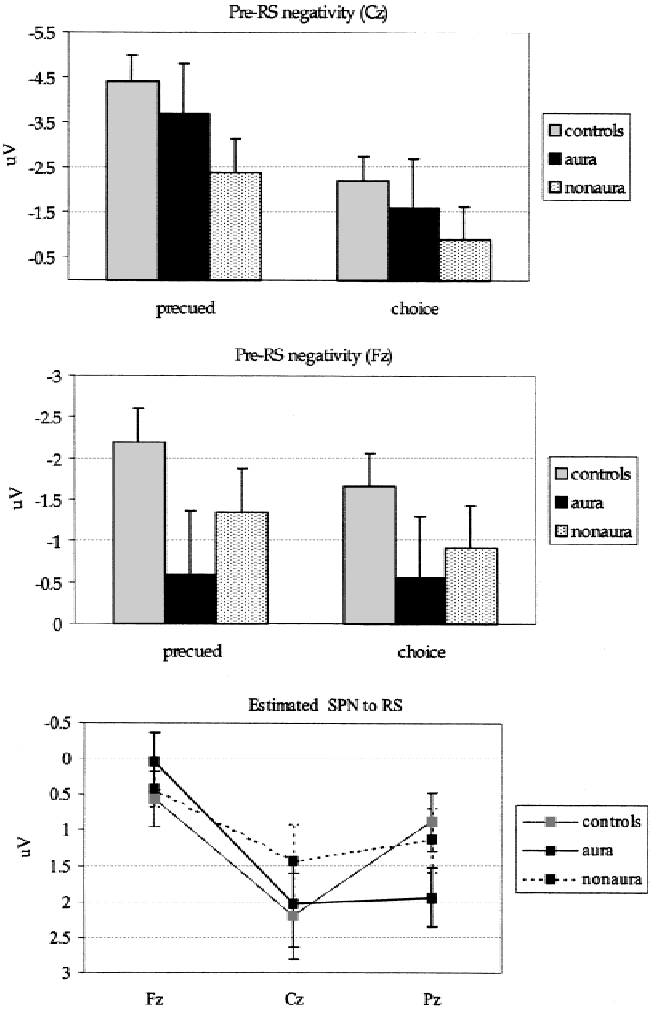

Figure 5. Cortical negativity (Cz, Fz) and estimated SPN with standard errors preceding the response stimulus (RS). SPN to the RS = pre-RS negativity during choice minus precued condition.

notion that the CNV early wave reflects Sokolov's orientation reflex, and suggested that the early wave reflects poststimulus processing. The similar CNV early wave amplitudes in migraineurs and controls suggests that migraineurs with aura and migraineurs without aura show normal poststimulus processing.

The warning stimulus during the precued condition is highly informative and conveys full information about the future response, whereas the warning stimulus in the choice condition does not transmit specific response requirements. The warning stimulus in the precued condition was, therefore, expected to be preceded by a larger anticipatory negativity compared to the choice condition (Van Boxtel & Brunia, 1994b). The present study showed that control subjects indeed exhibit this larger negativity prior to the warning stimulus in the precued condition compared to the choice condition, but migraine patients without aura show equally high anticipation during both conditions (Figure 4). In contrast, migraineurs with aura show high anticipatory negativity prior to a noninformative stimulus and a low negativity prior to an informative stimulus. We confirmed the expected frontal minimum and parietal maximum of the SPN prior to the warning stimulus (Gaillard & Van Beijsterveldt, 1991; Rösler, 1991; Van Boxtel & Brunia, 1994b) in healthy control subjects and migraineurs without aura, but migraineurs with aura exhibit the reverse anterior–posterior distribution. These results suggest that migraine patients with aura show deficiencies in adequately anticipating task-relevant instruction stimuli.

The presence of anticipatory (nonmotor) negativity embedded in the CNV late wave is indicated by the fact that the conditions prompt unequal late wave amplitudes. We showed that the CNV late wave is larger in the precued than the choice condition, which is in line with other studies (Macar, Vidal, & Bonnet, 1990; MacKay & Bonnet, 1990; Vidal, 1993), although others find the opposite (e.g., McCallum & Curry, 1981; Rohrbaugh, Syndulko, & Lindsley, 1976; Van Boxtel & Brunia 1994a, 1994b; van Boxtel et al., 1993). The higher CNV late wave amplitude during the precued condition might be explained by the fact that subjects are enabled to preprogram a specific response during the foreperiod, which is not possible during the choice condition, where response requirements are not transmitted until the response stimulus. The shorter reaction times during the precued compared to the choice condition support this idea of facilitating preparation. The CNV late wave is lowest in migraineurs without aura, suggesting cortical hypoactivation during motor preparation. Negativity related to nonmotor anticipation (SPN) showed a clear frontal maximum and parietal minimum in controls as well as in both migraine groups. This is also found by others during similar conditions in healthy subjects (Van Boxtel & Brunia, 1994a; Van Boxtel et al., 1993). A frontal maximum of the SPN prior to a response stimulus is possibly related to the involvement of the frontal cortex in the effortful control of task performance (Van Boxtel, 1994). We support this idea by the positive correlation between the subjective effort rating and the frontal SPN amplitude. We found a relative hypoactivation of frontal cortical areas in migraineurs with aura during motor preparation (Figure 5), which might reflect deficiencies regarding effortful attentional control.

In short, migraine patients with aura show deficiencies in directing anticipation towards cueing stimuli prompting far-future action, whereas when near-future action is required, they show a frontal hypoactivation that might be related to problems in effortful control of task performance. Migraineurs without aura show a cortical hypoactivation during motor preparation. These differences between migraineurs with aura and migraineurs without aura call for future research addressing whether these types of migraine reflect different pathogenic entities or different grades of severity on a single continuum.

Inadequate anticipation to instruction stimuli in migraineurs with aura may lead to a slow detection of target stimuli in early processing stages, whereas inadequate motor preparation in migraineurs without aura might lead to slowing of later stages. These deficiencies might explain the longer reaction times during selective attention in a previous migraine study (Mulder et al., 1999). In a larger group of interictal migraineurs, especially in those with aura, we found normal response speed during various simple and choice reaction time tasks, digit span, and grammatical reasoning, whereas responses were significantly slowed when the suppression of responses to nontargets is necessary. It is as yet unclear how these attentional problems relate to migraine.

The provision of top-down support for task relevant stimulus–response mapping involves both parietal and frontal areas. PET studies performed during shifting attention, especially between spatial locations, have confirmed the importance of the posterior parietal lobe (Corbetta, Miezin, Shulman, & Petersen, 1993) as well as the pulvinar and frontal areas (Corbetta, Shulman, Miezin,

& Petersen, 1995). The posterior parietal cortex mainly processes information for the purpose of planning actions, and may also play a role in changing movement intentions. Both sensory-related and intention-related activities have been shown in the posterior parietal cortex, which is consistent with its proposed role in sensory-motor transformations and integration (Snyder, Batista, & Andersen, 2000). Single-cell recordings in animals have demonstrated that the parietal cortex is involved in stimulus processing, especially if that stimulus cues a response (Seal, Hasbroucq, Mouret, Akamatsu, & Kornblum, 1991). Within the frontal component of the attentional network, the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) have complementary functions in the dynamic regulation of cognitive control. The DLPFC serves the implementation of control by keeping task-relevant representations active such as instructions and appropriate actions. The ACC is likely to be involved in evaluation processes such as error and response conflict monitoring, and in indicating when control needs to be more strongly engaged (MacDonald, Cohen, Stenger, & Carter, 2000).

We speculate that a functional disturbance is present in frontal cerebral areas of migraineurs, especially those with aura, and we propose the involvement of the ACC in particular. On the basis of cytoarchitecture, patterns of projections as well as function, the ACC can be subdivided into an anterior "cognitive/executive" region and a posterior "affective/evaluative" region that interact in unidentified ways (Bush, Luu, & Posner, 2000). Various imaging studies showed that the cognitive division of the ACC (BA 24/32) is activated during attention-demanding tasks (see Hsieh, Belfrage, Stone-Elander, Hansson, & Ingvar, 1995; Picard and Strick, 1996). Based on PET imaging and lesion studies, Posner and Raichle (1994) refer to this brain area as the executive area for attention. ACC activation could be related to response inhibition or executive functioning as such, or to the higher levels of anticipation or effortful control these types of tasks require. Functional MRI studies suggest that ACC activation during attention-demanding tasks merely depends on anticipatory state rather than the attentional properties of the task itself (Davis, Taylor, Crawley, Wood, & Mikulis, 1997; Murtha, Chertkow, Beauregard, Dixon, & Evans, 1996). The ACC is presumably more activated when attentional control needs to be more strongly engaged, which could especially be the case during selective attention and response inhibition. This could imply that ACC dysfunctioning yields impairments in selective attention. A future fMRI study would have to confirm whether migraineurs indeed show a deviant ACC activation relative to controls during selective attention tasks. Besides the role of the ACC in anticipatory state and attention, it is of significant importance in pain perception (Davis et al., 1997; Vogt, Sikes, & Vogt, 1993), which further enforces its possible involvement in migraine. This idea is strengthened by the changes that occur in this structure after a migraine attack has been initiated. Weiller et al. (1995) demonstrated with PET that during a spontaneous migraine attack without aura, activation takes place in the auditory and visual association cortices, the brain stem, and the ACC. After an injection with sumatriptan, an antimigraine serotonin receptor agonist, had induced complete relief from headache, photophobia, and phonophobia, the ACC activation disappeared. It is unclear whether these proposed functional changes in frontal cerebral areas would reflect a (genetic) predisposition or a consequence of the repeated and prolonged exposure to severe headache, yielding inadequate stimulus anticipation and impairments in selective attention.

We hypothesize that migraine is related to a functional disturbance of frontal cerebral areas that may involve the serotonergic system. Migraine is characterized by low serotonergic activity between attacks attack (Ferrari & Saxena, 1993). In a postattack period after the use of sumatriptan, these patients showed improvements in selective attention (Mulder et al., 1999), and a decrease in the early and late CNV that is confined to the frontal areas during a simple forewarned reaction time task (Mulder et al., 2001). The CNV is thought to be controlled by noradrenergic and dopaminergic systems within the central nervous system (Libet, 1979; Maertens de Noordhout, Timsit-Berthier, Timsit & Schoenen, 1986; Nagel-Leiby et al., 1990; Schoenen et al., 1986; Timsit-Berthier, Mantanus, Poncelet, et al., 1986; Timsit-Berthier, Mantanus, Marissiaux, et al., 1986), where noradrenergic pathways are believed to have a dominant role in the early wave, and dopaminergic structures mainly contribute to the late wave (Timsit-Berthier, Mantanus, Marissiaux, et al., 1986). The serotonergic system might influence frontal attentional mechanisms through its effects on these central catecholaminergic systems. The serotonergic system inhibits dopaminergic function at the level of the midbrain as well as at the level of terminal dopaminergic fields in the forebrain (Kapur & Remington, 1996). Interactions between serotonergic and dopaminergic systems within the frontal cortex have been shown to play an important role in the modulation of sustained attention and response control (Puumala & Sirviö, 1998). Noradrenergic frontal activity normally functions to preserve attentional selectivity under arousing circumstances (Everitt, Robbins, & Selden, 1990), and could have a role in effortful processing while leaving automatic processing largely unchanged (Cole & Robbins, 1992). These noradrenergic fibers projecting from the locus coeruleus are shown to be especially dense in the frontal cortex and the cingulate gyrus (Descarries & Lapierre, 1973). These findings suggest a catecholaminergic influence of frontal attentional processes that can be modulated by the serotonergic system. Considering the fact that migraine is a condition with serotonergic dysfunction, we speculate that the anticipatory deficiencies as reflected in the deviant SPNs, as well as the lower reaction speed during selective attention, especially in migraine with aura, are related to low levels of serotonin within the frontal cortex or the anterior cingulate cortex.

REFERENCES

Aickin, M., & Gensler, H. (1996). Adjusting for multiple testing when reporting research results: The Bonferroni vs. Holm methods. *American Journal of Public Health, 86,* 726–728.

Böcker, K. B. E., Timsit-Berthier, M., Schoenen, J., Brunia, C. H. M. (1990). Contingent negative variation in migraine. *Headache, 30,* 604–609.

Böcker, K. B. E. (1994). *Spatiotemporal dipole models of slow cortical potentials*. Ph.D. thesis. University of Tilburg, The Netherlands.

Brillinger, D. (1975). *Time series: Data analyses and theory*. London: Holt, Rinehart and Winston Inc.

Brunia, C. H. M. (1988). Movement and stimulus preceding negativity. *Biological Psychology, 26,* 165–178.

Brunia, C. H. M. (1993). Waiting in readiness: Gating in attention and motor preparation. *Psychophysiology, 30,* 327–339.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences, 4,* 215–222.

Cohen, J. (1969). *Statistical power analyses for the behavioral sciences*. Orlando, FL: Academic Press.

Cole, B. J., Robbins, T. W. (1992). Forebrain norepinephrine: Role in

controlled information processing in the rat. *Neuropsychopharmacology*, *7*, 129–142.

Corbetta, M., Miezin, F. M., Shulman, G. L., & Petersen, S. E. (1993). A PET study of visuospatial attention. *Journal of Neuroscience*, *13*, 1202–1226.

Corbetta, M., Shulman, G. L., Miezin, F. M., & Petersen, S. E. (1995). Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science*, *270*, 802–805.

Damen, E. J. P., Brunia, C. H. M. (1987). Changes in heart rate and slow brain potentials related to motor preparation and stimulus anticipation in a time estimation task. *Psychophysiology*, *24*, 700–713.

Davis, K. D., Taylor, S. J., Crawley, A. P., Wood, M. L., & Mikulis, D. J. (1997). Functional MRI of pain- and attention-related activations in the human cingulate cortex. *Journal of Neurophysiology*, *77*, 3370–3380.

Descarries, L., & Lapierre, Y. (1973). Norepinephrine and axon terminals in the cerebral cortex of the rat. *Brain Research*, *51*, 141–160.

Everitt, B. J., Robbins, T. W., & Selden, N. R. W. (1990). Functions of the coeruleus noradrenergic system: A neurobiological and behavioural synthesis. In D. J. Heal & C. A. Marsden (Eds.), *Pharmacology of noradrenaline* (pp. 349–378). Oxford: Oxford University Press.

Ferrari, M. D., & Saxena, P. R. (1993). On serotonin and migraine: A clinical and pharmacological review. *Cephalalgia*, *13*, 151–165.

Gaillard, A. W. K. (1978). S*low brain potentials preceding task performance*. Amsterdam: Academic Press.

Gaillard, A. W. K., & Van Beijsterveldt, C. E. M. (1991). Slow brain potentials elicited by a cue signal. *Journal of Psychophysiology*, *5*, 337–347.

Gerber, W. D., & Schoenen, J. (1998). Biobehavioral correlates in migraine: The role of hypersensitivity and information-processing dysfunction. *Cephalalgia*, *18*, Suppl. 21, 5–11.

Headache Classification Committee of the International Headache Society. (1988). Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. *Cephalalgia*, *8*, Suppl. 7, 1–96.

Hsieh, J. C., Belfrage, M., Stone-Elander, S., Hansson, P., Ingvar, M. (1995). Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. *Pain*, *63*, 225–226.

Kapur, S., Remington, G. (1996). Serotonin-dopamine interaction and its relevance to schizophrenia. *American Journal of Psychiatry*, *153*, 466–476.

Kropp, P., & Gerber, W. D. (1993a). Is increased amplitude of the contingent negative variation in migraine due to cortical hyperactivity or to reduced habituation? *Cephalalgia*, *13*, 37–41.

Kropp, P., & Gerber, W. D. (1993b). Contingent negative variation: Findings and perspectives in migraine. *Cephalalgia*, *13*, 33–36.

Kropp, P., & Gerber, W. D. (1995). Contingent negative variation during migraine attack and interval: Evidence for normalisation of slow cortical potentials during the attack. *Cephalalgia*, *15*, 123–128.

Kropp, P., & Gerber, W. D. (1998). Prediction of migraine attacks using a slow cortical potential, the contingent negative variation. *Neuroscience Letters*, *257*, 73–76.

Libet, B. (1979). Slow post-synaptic actions in ganglionic function. In M. C. Broos, K. Koizumi, & A. Sato (Eds.), *Integrative functions of the autonomic nervous system* (pp. 197–222). North Holland: Elsevier Biomedical Press.

Loveless, N. E., & Sanford, A. J. (1974). Slow potential correlation of preparatory set. *Biological Psychology*, *1*, 303–314.

Macar, F., Vidal, F., & Bonnet, M. (1990). Laplacian derivations of CNV in time programming. In C. H. M. Brunia, A. W. K. Gaillard, & A. Kok (Eds.), *Psychophysiological brain research* (pp. 69–76). Tilburg: Tilburg University Press.

MacDonald, A. W., III, Cohen, J. C., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, *288*, 1835–1838.

MacKay, W. A., Bonnet, M. (1990). CNV stretch reflex and reaction time correlates of preparation for movement direction and force. *Electroencephalography and Clinical Neurophysiology*, *76*, 47–62.

Maertens de Noordhout, A., Timsit-Berthier, M., Timsit, M., & Schoenen, J. (1986). Contingent negative variation in headache. *Annual Neurology*, *19*, 78–80.

Maertens de Noordhout, A., Timsit-Berthier, M., Timsit, M., & Schoenen, J. (1987). Effects of beta-blockade on contingent negative variation in migraine. *Annual Neurology*, *21*, 111–112.

McCallum, W.C., & Curry, S. H. (1981). Late slow wave components of auditory evoked potentials: Their cognitive significance and interaction. *Electroencephalography and Clinical Neurophysiology*, *51*, 123–137.

McCallum, W. C., & Papakostopoulos, D. (1973). The CNV and reaction time in situations of increasing complexity. In W. C. McCallum & J. R. Knott (Eds.), *Event related slow potentials of the brain: their relations to behavior* (pp. 179–185). Amsterdam: Elsevier.

Mulder, E. J. C. M., Linssen, W. H. J. P., Passchier, J., & de Geus, E. J. C. (2001). Interictal and postictal contingent negative variation in migraine without aura. *Headache*, *41*, 72–78.

Mulder, E. J. C. M., Linssen, W. H. J. P., Passchier, J., Orlebeke, J. F., & de Geus, E. J. C. (1999). Interictal and postictal cognitive changes in migraine. *Cephalalgia*, *19*, 557–565.

Murtha, S., Chertkow, H., Beauregard, M., Dixon, R., & Evans, A. (1996). Anticipation causes increase of blood flow to the anterior cingulate cortex. *Human Brain Mapping*, *4*, 103–112.

Nagel-Leiby, S., Welch, K. M. A., D'Andrea, G., Grunfeld, S., Brown, E. (1990). Event-related slow potentials and associated catecholamine function in migraine. *Cephalalgia*, *10*, 147–152.

Picard, N., & Strick, P. L. (1996). Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex*, *6*, 342–353.

Posner, M. I., & Raichle, M. E. (1994). *Images of mind*. New York: Scientific American Library.

Puumala, T., & Sirviö, J. (1998). Changes in activities of dopamine and serotonin systems in the frontal cortex underlie poor choice accuracy and impulsivity of rats in an attention task. *Neuroscience*, *83*, 489–499.

Rohrbaugh, J. W., & Gaillard, A. W. K. (1983). Sensory and motor aspects of the contingent negative variation. In A. W. K. Gaillard & W. Ritter (Eds.), *Tutorials in ERP research: Endogenous components* (pp. 269–310). Amsterdam: North-Holland Publishing Company.

Rohrbaugh, J. W., Syndulko, K., & Lindsley, D. B. (1976). Brainwave components of the contingent negative variation in humans. *Science*, *191*, 1055–1057.

Rösler, F. (1991). Perception or action: Some comments on preparatory negative potentials. In C. H. M. Brunia, G. Mulder, & M. N. Verbaten (Eds.), *Event-related brain research* (pp. 116–192). Amsterdam: Elsevier.

Ruchkin, D. S., Sutton, S., Mahaffey, D., & Glaser, J. (1986). Terminal CNV in the absence of motor response. *Electroencephalography and Clinical Neurophysiology*, *49*, 445–463.

Schoenen, J., Maertens de Noordhout, A., Timsit-Berthier, M., & Timsit, M. (1986). Contingent negative variation and efficacy of beta-blocking agents in migraine. *Cephalalgia*, *6*, 229–233.

Seal, J., Hasbroucq, T., Mouret, I., Akamatsu, M., & Kornblum, S. (1991). Possible neural correlates for the mechanism of stimulus-response association in the monkey. In J. Requin, G. E. Stelmack (Eds.), *Tutorials in motor neuroscience* (pp. 29–39). Dordrecht: Kluwer.

Simons, R. F. (1988). Event-related slow brain potentials: A perspective from ANS psychophysiology. In P. K. Ackles, J. R. Jennings, & M. G. H. Coles (Eds.), *Advances in psychophysiology* (vol. 3, pp. 223–267). Greenwich: JAI Press.

Snyder, L. H., Batista, A. P., & Andersen, R. A. (2000). Intention-related activity in the posterior parietal cortex: A review. *Vision Research*, *40*, 1433–1441.

Tecce, J. J. (1972). Contingent negative variation (CNV) and psychological processes in man. *Psychological Bulletin*, *77*, 73–108.

Timsit-Berthier, M., Mantanus, H., Marissiaux, P., Ansseau M., Doumont, A., Geenen, V., & Legros, J.-J. (1986). CNV and dopamine receptor reactivity: Correlations with the apomorphine test. *Electroencephalography and Clinical Neurophysiology*, *38*, 403–405.

Timsit-Berthier, M., Mantanus, H., Poncelet, M., Marissiaux, P., & Legros, J.-J. (1986). Contingent negative variation as a new method to assess the catecholaminergic systems. In V. Gallai (Ed.), *Maturation of the CNS and evoked potentials* (pp. 260–268). Amsterdam: Elsevier Science Publishers.

Van Boxtel, G. J. M. (1994). *Non-motor components of slow brain potentials*. Ph.D. thesis. University of Tilburg, The Netherlands.

Van Boxtel, G. J. M., Boogaart, van den, B., & Brunia, C. H. M. (1993). The contingent negative variation in a choice reaction time task. *Journal of Psychophysiology*, *7*, 11–23.

Van Boxtel, G. J. M., & Brunia, C. H. M. (1994a). Motor and non-motor components of the contingent negative variation. *International Journal of Psychophysiology*, *17*, 269–279.

Van Boxtel, G. J. M., & Brunia, C. H. M. (1994b). Motor and non-motor aspects of slow brain potentials. *Biological Psychology*, *38*, 37–51.

Vidal, F. (1993). Programmation de la durée d'une résponse motrice. Etude chronometrique et electroencephalograpphique chez l'homme. Ph.D. Thesis. Marseille: CNRS-LNC.

Vogt, B., Sikes, R. W., & Vogt, L. R. (1993). Anterior cingulate cortex and the medial pain system. In B. A. Vogt, & M. Gabriel (Eds.), *Neurobiology of cingulate cortex and limbic thalamus: A comprehensive handbook* (pp. 313–344). Boston, MA: Birkhäuser.

Walter, W. G., Cooper, R., Aldridge, V. J., McCallum, W. C., & Winter, A. L. (1964). Contingent negative variation: An electrical sign of sensori-motor association and expectancy in the human brain. *Nature, 203,* 380–384.

Weiller, C., May, A., Limmroth, V., Jüptner, M., Kaube, H., van Schayck, R., Coenen, H. H., & Diener, H. C. (1995). Brain stem activation in spontaneous human migraine attacks. *Nature Medicine, 1,* 658–660.

Zijlstra, F., & Meijman, T. (1989). Het meten van mentale inspanning met behulp van een subjectieve methode. In T. Meijman (Ed.), *Mentale belasting en werkstress* (pp. 42–61). Assen: van Gorcum.

(Received June 12, 2000; Accepted August 29, 2001)