Interictal and Postictal Contingent Negative Variation in Migraine Without Aura

E.J.C.M. Mulder, MSc; W.H.J.P. Linssen, MD, PhD; J. Passchier, PhD; E.J.C. de Geus, PhD

Cortical hyperexcitability is thought to explain the more enhanced contingent negative variation (CNV) amplitudes and impaired CNV habituation that have been found during the interictal period in migraine without aura. These CNV characteristics have been shown to normalize to the level of healthy controls during an attack. This study aimed to replicate the interictal findings, and additionally examine whether migraineurs show reduced CNV amplitudes during the postattack period. Of 12 patients with migraine without aura and their sex- and age-matched healthy controls, CNV characteristics were recorded once in an interictal period, once during the postattack period within 30 hours after an attack that was treated with sumatriptan, and once after an attack that was treated with habitual nonvasoactive medication (counterbalanced). The present results did not confirm the enhanced CNV early and late wave amplitudes or impaired habituation, and cortical hyperexcitability that have previously been reported in the interictal period in patients with migraine without aura. During the postattack period, a decrease in CNV early and late amplitudes was found but only after sumatriptan use. This reduction in CNV amplitudes was most prominent over the frontal cortex and could reflect cortical hypoexcitability, possibly related to a suppression of central catecholaminergic activity by sumatriptan.

Key words: migraine, contingent negative variation, sumatriptan

Abbreviations: CNV contingent negative variation, WS warning stimulus, RS response signal

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Individuals with migraine have been hypothesized to be characterized by cortical hyperexcitability reflected in enhanced contingent negative variation (CNV) amplitude. The CNV is an event-related slow brain potential that is characterized by an augmenting negativity recorded on the surface of the scalp during the foreperiod that separates a warning stimulus and a response stimulus.[1] The CNV is comprised of an early and a late component that become clearly visible if the foreperiod is longer than 2 seconds.[2] These components have a different brain topography and seem to be related to different behavioral processes[2-6] such as orienting and motor preparation. The CNV is thought to be controlled by noradrenergic and dopaminergic systems within the central nervous system,[7-12] where noradrenergic pathways may have a dominant role in the early wave, and dopaminergic structures mainly contribute to the late wave.[8]

Various studies have demonstrated a more negative CNV in patients with migraine during foreperiods that are shorter than 2 seconds.[10,13,14] Studies employing longer foreperiods predominantly report a higher early wave amplitude in migraine without aura,[13,15-17] but higher late wave amplitudes have been reported as well.[13] These higher CNV amplitudes are believed to emerge as a result of the slow habituation over trials.[10,11,15,17] Research in cortical electrophysiology such as that embracing the thalamic gating model[18] or the threshold regulation theory[19] has linked the CNV to

From the Department of Biological Psychology, Vrije Universiteit (Ms. Mulder and Dr. de Geus), and the Department of Neurology, St. Lucas Andreas Hospital (Dr. Linssen), Amsterdam; the Department of Medical Psychology and Psychotherapy, Erasmus University, Rotterdam (Dr. Passchier), The Netherlands.

Address all correspondence to Dr. E.J.C.M. Mulder, Department of Biological Psychology, Vrije Universiteit, De Boelelaan 1111, 1081 HV, Amsterdam, The Netherlands.

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cortical excitability. It is assumed that slow negative brain potentials, such as the CNV, reflect the task-related tuning of cortical areas. The threshold regulation theory postulates that preparation is achieved by lowering neuronal firing thresholds in the appropriate cortical neuronal networks and by selectively increasing cortical excitability. This is ultimately reflected in an enhanced negativity in these particular cortical areas. In agreement with these ideas, migraine researchers have generally attributed these CNV findings to a hyperactivity of central catecholaminergic systems.[7-12] High catecholaminergic activity is thought to induce a state of cortical hyperexcitability and arousal that prevents normal habituation. This explanation is corroborated by transcranial magnetic stimulation studies which have linked migraine to changes in cortical excitability.[20]

In addition to larger interictal amplitude, the CNV is sensitive to the temporal proximity of a migraine attack. The early wave increases even more during the days before an attack but decreases to the level of healthy controls during the attack. Along with this normalization of CNV early wave amplitude, the impaired habituation also resolves during the attack.[17] In the 2 to 3 days following the attack, the CNV remains at this normal level after which it gradually deteriorates again.[21] This normalization during an attack has been suggested to be related to the depletion of noradrenergic activity combined with an increased serotonergic transmission.[22] These dynamic changes within the migraine course emphasize that preictal or postictal effects could confound interictal CNV results, unless it is recorded in a truly interictal period. The extent of postictal CNV changes could depend on attack severity, attack duration, and medication use. For example, aspirin decreases the CNV early wave in healthy controls.[23] These factors have not been taken into account in most interictal and postictal CNV studies.

The present study aims to replicate previous interictal CNV findings in a well-controlled study comparing migraineurs without aura to healthy sex- and age-matched controls. In addition, this study examines CNV amplitudes and habituation kinetics during a postattack period either after sumatriptan use or after nonvasoactive medication use. In summary, three questions will be addressed: (1) do migrainous patients show altered CNV amplitudes and habituation kinetics during an interictal period compared to matched and headache-free controls; (2) do patients with migraine show a reduction in CNV amplitude during the postattack period; and (3) is the CNV during the postattack period differently affected by vasoactive or nonvasoactive medication use?

METHODS

Subjects.—Twenty patients with migraine without aura and 20 healthy controls were recruited by advertisements in university papers. Patients were diagnosed by a neurologist in accordance with the International Headache Society criteria for migraine,[24] underwent a physical examination, and were enrolled into the study. Patients with migraine using prophylactic medication, monoamine oxidase inhibitors, β-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. All patients had used sumatriptan at least once before participation in the laboratory sessions. The controls were recruited from the same student population and matched on the basis of sex, age, and handedness. Socioeconomic status was comparable between patients and controls. Controls did not suffer from migraine and did not suffer from any other type of headache more than once per 2 months (eg, due to alcohol consumption or exposure to toxic substances). Subjects were not admitted to the study if they had a history of epilepsy or other severe medical conditions which could affect the interpretation of the results; currently abused opiate analgesics, psychotropic drugs, ergotamine (>10 mg/week), or alcohol (>315 g/week); or had a history of abuse of these substances in the previous 6 months. Prior to the study, all subjects were informed about the study and signed a consent form. The medical ethical committee of the Vrije Universiteit approved this study. Valid CNV recordings in all three sessions were obtained in 12 migraineurs and their controls.

Design.—The CNV was recorded during three different sessions in both the patients with migraine and controls. The migraineurs were tested following three different migraine attacks. The first session

took place on a headache- and symptom-free day, 4 or 5 days after the peak of a migraine attack (interictal session). If this first session was followed by a new migraine attack within 3 days, this session was considered invalid. The second and third sessions took place within 30 hours after the peak of a migraine attack (postattack sessions) and one night of sleep, after which the headache severity had to have decreased to mild, as judged on a 3-point scale (1 = mild, 2 = moderate, 3 = severe). The migraineurs treated one of these two attacks with a 100-mg sumatriptan tablet, while the other attack was treated with their habitual migraine medication, which could have been no medication. Patients using sumatriptan or ergotamine as their habitual medication were instructed to use analgesics or no medication during this attack. The interictal session was always the first session, while the order of habitual medication use or sumatriptan use was counterbalanced over the second and third session. Each laboratory session began with completion of a visual analog scale (VAS) that determined the headache severity of the preceding migraine attack on a line representing a 0 to 100 scale. The extremes of pain were "no pain" and "as bad as it could be." At the beginning of each session the number of hours that had passed after meaningful relief from the migraine and after medication intake was determined, based on the diaries that were kept during the attack. Duration of a migraine attack was determined by the question: "How many hours did your migraine attack last?" Controls were tested on three occasions. At the time of the test, they were headache-free and had not used medication on the previous 2 days. The tests occurred 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. Furthermore, the intervals between the control sessions were equivalent to the test intervals of the patient they were matching.

Contingent Negative Variation Recordings.— Subjects were in a supine position with their eyes closed in a dimly lit, sound attenuating, electrically shielded cubicle. The auditory warning stimulus (WS; 50 ms, 1000 Hz) was produced through a loudspeaker placed behind the subject. After a fixed interstimulus interval of 3000 ms, a train of flashes was presented as the response signal (RS; 18 cycles/s; maximal presentation of 1000 ms), which subjects were instructed to terminate as quickly as possible by pressing a button with the index finger of the dominant hand. If subjects exceeded the maximum response time of 1000 ms or responded prematurely, a trial was rejected. The intertrial interval was 4, 5, 6, or 7 seconds and was pseudorandomly varied with a rectangular distribution. A CNV session consisted of 52 trials during which reaction times were also recorded.

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 to 30 Hz), digitized at 250 Hz, and stored for offline processing. The EEG signals were corrected for eye movements by dynamic regression in the frequency domain.[25] All subjects were given five practice trials before the actual measurement. Reaction times and errors (premature key presses and omissions) were stored for all trials. Directly after the task, subjects completed a rating scale for mental effort.[26]

Data Reduction and Analyses.— A 500-ms pre-WS interval served as a baseline for the CNV. Trials containing values exceeding 70 μV with respect to this baseline were excluded from further analysis. The CNV was calculated over the total epoch of 4000 ms including the baseline. The early and late CNV amplitudes were calculated according to the method of Böcker et al,[13] whereby two area measures are calculated following WS (500 to 750 ms) and preceding RS (200 ms). For the determination of the habituation of these amplitudes, the 52 trials were subdivided into 8 blocks of 6 successive trials, disregarding the last 4 trials.

Repeated-measures analysis of variance (ANOVA) was performed on the duration and severity of the attack treated with sumatriptan and the attack treated with habitual migraine medication (two levels of the within-subjects factor "session"). Repeated-measures

ANOVA was also executed on early CNV amplitude, late CNV amplitude, reaction time during the CNV task, and number of errors, and the subjective amount of effort, with the within-subjects factor "session" (three levels: baseline, postattack session after sumatriptan use, postattack session after habitual medication use), and a between-subjects factor "group" (two levels: migraineurs, controls). To examine the habituation course of the early and late wave amplitude, the means of each of the eight successive trial blocks were submitted to repeated measures in ANOVA with the within-subjects factor "blocks" (mean amplitude in trial block 1 to 8), and the between-subjects factor "group" (migraineurs, controls), which was done separately within every session. Our main focus is primarily on differences between patients with migraine and controls, and only the significant group effects and session-by-group and block-by-group interactions are reported. The homogeneity assumptions for repeated measures were met, if necessary after a transformation of the dependent variable or ε-correction.

RESULTS

Demographics, Headache Severity, and Attack Duration.—The mean age of the patients with migraine was 24.3 ± 3.4 years, 78% were right-handed, and 91% were women. The mean migraine history was 7.1 ± 4.3 years. The headache severity (VAS) was not significantly different during the attacks treated with sumatriptan (75.5 ± 16.9), compared with the attacks treated with usual medication (70.4 ± 18.4). Attack duration is shortened by sumatriptan use (10.7 ± 11.3 hours), compared with usual medication use (16.3 ± 13.3 hours) ($F_{1,22} = 6.0$, $P = .023$).

Task Performance.—Figure 1 lists mean reaction times and subjectively reported mental effort, for migraineurs and controls during the three sessions. Migraineurs and controls responded with equal speed and made the same number of errors during the three sessions. A significant session-by-group interaction ($F_{1.5,59.1} = 6.4$, $P = .006$) was detected in the subjective amount of mental effort invested in performing the task indicating that, relative to controls, migraineurs reported more invested mental effort during both postattack sessions, compared with the baseline session ($F_{1,39} = 11.9$, $P = .001$).

Early and Late Wave Contingent Negative Variation Amplitudes.—Figure 2 depicts the CNV from every lead in migraineurs and controls during all sessions. At the central and parietal lead, both the early and late wave amplitudes were not significantly different between migraineurs and controls during all sessions. At the frontal lead, however, trends towards session-by-group interactions were found for the early wave ($F_{2,44} = 3.0$, $P = .078$) and late wave amplitude ($F_{2,44} = 2.9$, $P = .067$). Follow-up testing of the former effect shows that the reduced early CNV amplitude in migraineurs was more pronounced during the postattack session after sumatriptan use than after habitual medication intake ($F_{1,22} = 15.89$, $P = .001$). Follow-up testing of the latter interaction indicates that compared with the baseline session, the postattack session after sumatriptan use is accompanied by

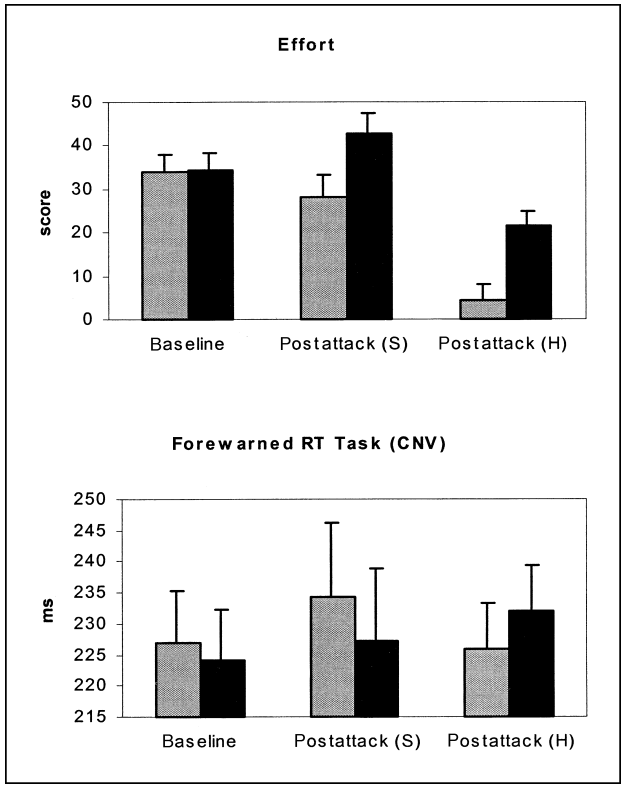

Fig 1.—Task performance in patients with migraine and controls, interictally and postictally. Means and standard errors of subjective mental effort and reaction time during the baseline session, the postattack session after sumatriptan use (postattack S), and the postattack session after habitual medication use (postattack H) in migraineurs without aura (black bars) and controls (gray bars). RT indicates reaction time; CNV, contingent negative variation.

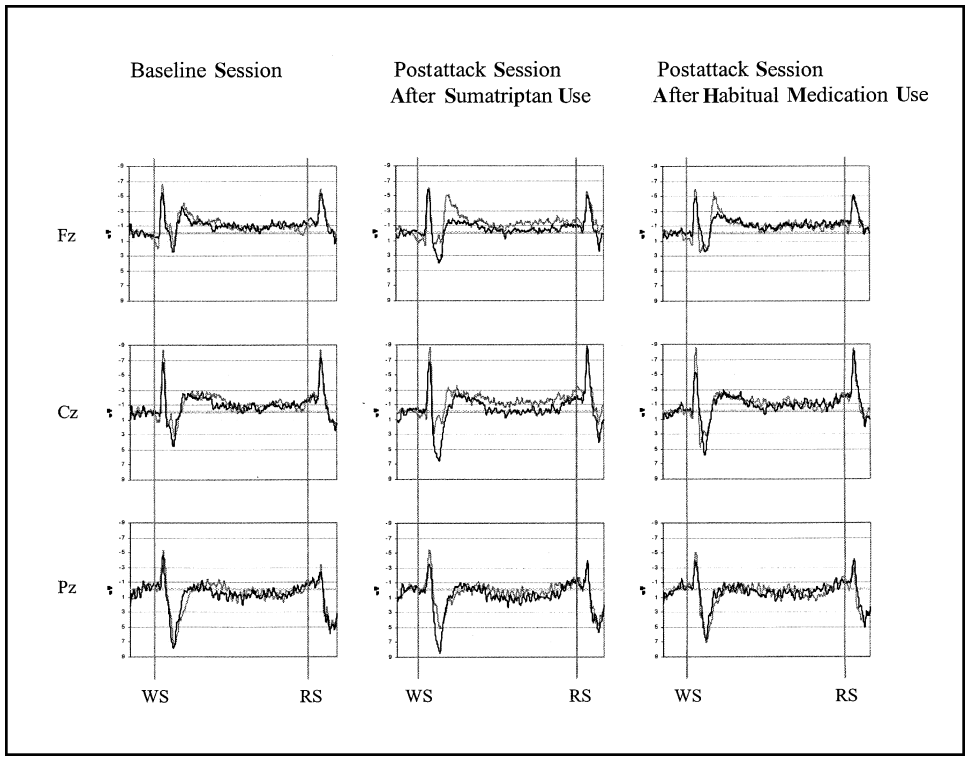

Fig. 2.—Interictal and postictal contingent negative variations in patients with migraine without aura (black lines, n = 12) and controls (gray lines, n = 12). Contingent negative variation was recorded from Fz, Cz, and Pz. WS indicates warning stimulus; RS, response stimulus.

a lower late CNV amplitude in migraineurs relative to controls ($F_{1,22} = 5.31$, $P = .031$), whereas CNV amplitudes are comparable after habitual medication intake.

Early and Late Wave Contingent Negative Variation Across Successive Blocks of Six Trials.— Nonsignificant block-by-group interactions were detected during each of the three sessions. In other words, the "habituation" course of the mean amplitude of the early CNV and late CNV was similar in migraineurs and controls during every session. Figure 3 depicts an example of the CNV habituation.

COMMENTS

The present study assessed the early and late CNV waves in patients with migraine without aura during an interictal measurement and during two postattack measurements, either after sumatriptan use or after habitual nonvasoactive medication use. Early and late CNV amplitudes in interictal migraineurs were comparable to those of matched and healthy controls. Habituation of the CNV components, or the course of the mean amplitudes across successive blocks of trials, was also similar in patients with migraine and controls. These results contrast with previous findings of large early wave amplitudes in migraineurs without aura[13,15,16,17,21] and late wave amplitudes[13] that have been attributed to slow habituation.[10,11,15,17] Based

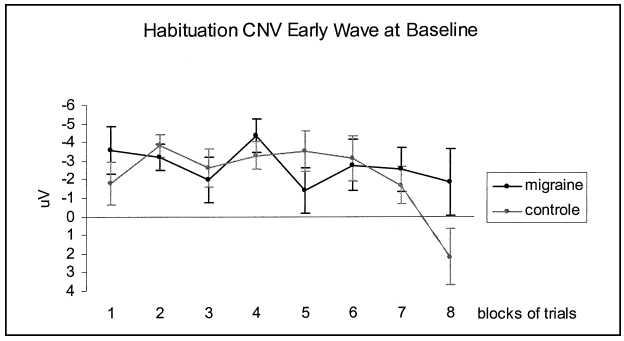

Fig 3.—Habituation course of the contingent negative variation early wave (Fz) over blocks of trials.

on evidence linking the CNV to cortical excitability,[18,19] we conclude that in the present study, the patients with migraine without aura did not exhibit deviations in cortical excitability during the interictal period.

A number of reasons might explain why the present study, in contrast to previous studies, did not find enhanced CNV amplitudes. First, the CNV early wave amplitude is sensitive to WS characteristics such as duration[27] and intensity.[28] The studies on CNV and its habituation in migraineurs[15,17] used a 100-ms auditory warning signal and a 1500-ms auditory RS, while we used a 50-ms WS and a train of flashes as an RS comparable with other studies.[11,13,29] Second, medication use, as demonstrated for some types of medication,[10,23] length of migraine history, migraine severity, and age might have contributed to the previously found enlarged CNV in migraineurs. We examined a relatively young and homogeneous group of patients with migraine (students, aged 24 years) with a short migraine history (7 years), who did not use prophylactic medication or ergot derivates, and who were recruited in a nonclinical setting. Böcker et al[13] did not report medication use and enrolled migraineurs without aura ranging from 22 to 55 years old from a clinical setting. The patients in the studies of Kropp and Gerber[15,17] averaged 35 years of age and had a migraine history of 18 years. The recruitment procedure was not reported. Third, in the present study, we made a point of ensuring that the interictal session took place 4 to 5 days after a migraine attack to eliminate the possibility of preictal and postictal changes to confound our interictal results. Finally, controls were matched to patients with migraine with regard to age, sex, and time of measurement (day of week, time of day) and also participated in three sessions. Under these methodological constraints, we found normal CNV early and late amplitudes in interictal migraineurs without aura.

The present study showed that patients with migraine subjectively report investing more mental effort in task performance during both postattack periods than between attacks. This could be associated with feelings of fatigue and weakness that are characteristic of the postattack period.[30] The increased subjective effort was not reflected in prolonged reaction times or an increase in errors during the CNV task. Previous research showed that the enhanced early CNV in patients with migraine without aura normalizes during a migraine attack[17] and remains at this normalized level during the 2 to 3 days following an attack.[21] The reduced CNV amplitude has been suggested to reflect reduced catecholaminergic or an increased serotonergic activity.[22] Our study showed an interictal to postictal reduction of both CNV components. However, this was mostly found only over the frontal electrode and most prominently after treating an attack with sumatriptan. This suggests that previous findings of CNV normalization during and after an attack may, at least in part, have reflected the effects of vasoactive medication.

We conclude that interictal migraineurs without aura show normal cortical excitability, based on the normal CNV early and late wave amplitudes and normal habituation kinetics. During the postattack period, we demonstrated lower CNV early and late wave amplitudes over the frontal cortex in migraineurs without aura compared with controls, suggesting postattack hypoexcitability of the frontal cortex. Hypoexcitability was greatest after sumatriptan use, suggesting suppression of central catecholaminergic activity by this serotonergic agent.

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