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Original Research

Contingent negative variation for the periodicity of migraine attacks without aura

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Migraine is a primary neuropsychological disorder, although its etiology and pathogenesis are unknown. It has been reported that using contingent negative variation, the periodicity of migraine attacks is three days in adults. However, there is still a lack of relevant reports about the periodicity of migraine without aura in adults. Therefore, we investigated the changes of contingent negative variation in adults with migraine without aura from three to seven days after migraine attacks in order to provide the basis for exploring the circulation periodicity of migraine without aura. This prospective, observational study involved a group of 34 individuals with migraine without aura, who were screened during the three to seven days after a migraine attack without aura. A healthy group (31 individuals) was used as controls to assess the amplitudes of contingent negative variation and habituation of early contingent negative variation. Indices of the amplitudes included overall contingent negative variation, initial contingent negative variation, terminal contingent negative variation, and postoperative negative contingent variation. Differences between these indicators were analyzed. No significant difference was found between the patient and control groups for either the amplitudes of these measures of contingent negative variation or habituation of the early contingent negative variation for three to seven days after a migraine attack without aura (all $P > 0.05$). Thus, the study reported here found that the periodicity of migraine attacks without aura in adults is more than three days.

Keywords

Migraine; circulation periodicity; EEG; ERP; neuropsychology; pathophysiology

1. Introduction

Migraine is a common disabling headache disorder whose etiology and pathogenesis remain unknown. It is the third most common human disease and the seventh most disabling disease worldwide (Abajobir et al., 2017). Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms (Olesen et al., 2013). It is characterized by recurrent attacks, and there are some reports that the migrainous brain exhibits altered function between migraine episodes and that this dysfunction undergoes cyclic changes preceding initiation of an attack (Ambrosini et al., 2010). Additionally, worrying about the occurrence of the next migraine attack can seriously affect health-related quality of life during both attacks and pain-free intervals (Freitag, 2007).

The pathophysiology of migraine has been extensively studied by electrophysiological methods. One objective electrophysiological indicator, the event-related potential (ERP), refers to the change of brain response related to certain sensory, motor, or neurocognitive events (Ambrosini et al., 2010). ERPs have a high temporal resolution in the dynamic study of the characteristics of brain activity, are secure, objective and without side effects; therefore, they have been widely used in psychology, physiology, cognitive neuroscience, clinical medicine and have considerable value for both clinical and basic research. The psychophysiological stress paradigm has been applied to detect pathways through which stress can induce a migraine. Passchier (1994) concluded that the pathophysiology of migraine should form the basis for future psychophysiological research.

Contingent negative variation (CNV), an endogenous component of the ERP, is related to the process of neurocognition and is not affected by stimulating physical properties (Walter et al., 1964). CNV comprises a slow cortical event-related potential that is recorded from the scalp between two stimuli in a subject waiting for an expected second event while preparing for task performance. This potential is related to the level of cortical excitability following activation in the striatum-thalamocortical loop. It is related to the ERP, which itself indicates different stages of cognitive activity. Attention and expectancy stimulus processing are associated with early or initial CNV (iCNV), and late CNV is related to es-

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timation, preparation and motor processing (Yazawa et al., 1997). Thus, CNV provides insight into the processes of brain activity in the nervous system as an objective neural electrophysiological indicator. This may be related to the close regulation of noradrenergic and dopaminergic systems (Marczynski, 1978; Skinner, 1984) as central catechol-aminergic activity may be enhanced in migraine (Lance et al., 2010).

Moreover, migraine is a form of neurovascular headache most likely involving an ion channel in the aminergic brain stem nuclei (Tajti et al., 2012) in which neural events result in dilation of blood vessels aggravating the pain and resulting in further nerve activation. Benemei et al. (2014) underscore the possibility that transient receptor potential (TRP) channels expressed in the nerve terminals of peptidergic nociceptors contribute to the migraine mechanism. Numerous genome-wide association studies (GWAS) have implicated the transient receptor-potential M8 (TRPM8) channel in migraine (Dussor and Cao, 2016). Also, Verkest et al. (2018) supported the involvement of peripheral Acid-sensing Ion channel (ASIC)-containing channels in migraine cutaneous allodynia as well as in its chronification.

CNV normalization during migraine attacks has been reported. Before PMR-training, migraine patients exhibited higher amplitude iCNV and overall CNV (oCNV) than seen for healthy controls, but no differences in habituation occur (Meyer et al., 2016). Additionally, there is no significant difference in CNV amplitude or habituation in patients with migraine during an attack period when compared with a control group. Thus CNV amplitudes normalize, indicating normal habituation (Gerber and Kropp, 1994). However, Kropp and Gerber (1995) found that the total CNV amplitude in patients with migraine during pain-free intervals was significantly higher than that of healthy controls and higher than that recorded during migraine attacks, while the CNV in healthy controls and during migraine attack showed a clear habituation compared with that of patients with migraine during pain-free intervals. This indicates that the higher CNV amplitude between pain-free attacks in migraine sufferers might partly be caused by an absence of habituation. Siniatchkin et al. (2006) found that under stressful conditions, when compared with healthy controls and subjects after a migraine attack or during pain-free intervals, the amplitude of the early components of CNV, especially one to three days before a migraine attack, increased significantly and habituation was significantly reduced.

Further, Kropp and Gerber (1998) found that CNV amplitude, especially the iCNV amplitude, showed a negative upward trend one day before an attack, while the iCNV amplitude was normal for two to three days after an attack. In most situations, migraine attacks occurred when the CNV magnitude displayed its largest negativity. They also described periodic changes in the CNV, which had the highest amplitude the day before an attack and the lowest amplitude during the attack. Also, Evers et al. (2010) found that migraine sufferers with and without aura were habitually weakened and continuously increased as measured by ERPs during the migraine interval, reaching a maximum in the day before an attack and suddenly normalizing during the attack. Therefore, the neurophysiological abnormalities of adult patients with migraine appear to undergo periodic changes. This indicates that they are associated with increased brain overactivity and hypersensitivity to anticipated attacks.

For patients with migraine, the actual clinical frequency of attacks is not very high, which is inconsistent with Kropp and Gerber's three-day periodicity theory (Kropp and Gerber, 1998). This creates a challenge for the provision of clinical guidance in the prevention and treatment of migraine, and the periodicity of migraine attacks without aura needs further exploration.

Although there are many subtypes of migraine, the incidence of migraine without aura is relatively large, and symptoms are hidden. In clinical practice, migraine without aura brings greater uncertainty and harm to patients. It is also difficult to diagnose, making its prevention and treatment problematical (Ligthart et al., 2006). Therefore, the periodicity of migraine attacks without aura should be investigated to test the relevant theoretical models. As mentioned earlier, according to Kropp and Gerber's theory (Kropp and Gerber, 1998), a migraine attack occurs when the high negative amplitude of the CNV early component coincides with other precipitating factors. Regarding the amplitude changes, an underlying periodicity of approximately three days can be observed. According to this theory, the maximum negative amplitude should appear on the third to seventh day following symptom onset. It was for this reason migraine without aura in adults was selected. Using the changed amplitude of CNV on the third to the seventh day after an attack as the index, the difference between the group with migraine without aura and the healthy control group was investigated. Thus, the accuracy of the pathogenesis periodicity predicted by Kropp and Gerber's theory was evaluated, and the periodicity of migraine pathogenesis further explored.

2. Methods

2.1 Subjects

Thirty-four subjects with episodic migraine without aura diagnosed per the International Classification of Headache Disorders, 3rd edition (ICHD-3 beta) (Olesen et al., 2013), as shown in Table 1 and 31 age- and sex-matched healthy controls were recruited from hospital staff or community in the study. Subjects with migraine were diagnosed by a neurologist and instructed to return to see the doctor on the 3^{rd}, 4^{th}, 5^{th}, 6^{th} and 7^{th} day after an untreated attack to record the amplitudes of CNV and habituation of the early CNV. All patients completed a headache diary daily. They also recorded both the duration of each migraine attack which allowed CNV records to be evaluated in relation to a subsequent migraine and a headache score which represented a scoring of the most severe migraine experienced over the past year by visual analog scale, with zero representing no pain and ten the worst possible pain. No subject received prophylactic stimulation therapy, such as psychological counseling, massage, physical therapy and so on. All subjects were drug-free for at least six months before the study. Subjects with a history of analgesic drug overuse or addiction, mixed headache types, all psychiatric diseases, migraine attacks within seven to fourteen days, and subjects with other types of migraine were excluded. Subjects with migraine and other neurological disorders were also excluded. Furthermore, all participants were verified to be literate, have normal or corrected-to-normal vision and right-handed. The research protocol was approved by the Ethical Committee of Shandong Provincial Hospital Affiliated

Table 1. Diagnostic criteria for migraine without aura:

A	At least five attacks fulfilling criteria B–D
B	Headache attack lasting 4-72 hours (untreated or unsuccessfully treated)
	Headache has at least two of the following four characteristics:
	1. unilateral location
C	2. pulsating quality
	3. moderate or severe pain intensity
	4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
	During headache at least one of the following:
D	1. nausea and/or vomiting
	2. photophobia and phonophobia
E	Not better accounted for by another ICHD-3 diagnosis.

The International Classification of Headache Disorders, 3rd edition (ICHD-3 beta).

Table 2. Characteristics of the samples (mean ± SD)

	Migraine (n = 34)	Control (n = 31)	*P*
Sex (f/m)	18/16	17/14	
Age (years, m ± SD)	36.64 ± 9.85	35.57 ± 8.74	0.86
Education, years	14.18 ± 4.32	14.45 ± 4.08	0.79
History of migraine, Months	35.60 ± 12.20		
Duration of migraine, Hours	28.80 ± 10.60		
Migraine frequency,			
Times per month	2.54 ± 0.86		
Family history (yes/no)	10/24		

n = number of participants (n),mean (m); standard deviation (SD); Student´s *t*-test significance $P < 0.05$.

to Shandong University (Approval No. 2018-215), and written informed consent was obtained from all subjects before commencement of the test. The characteristics of the subjects are given in Table 2.

2.2 Experimental procedures

All subjects were seated eyes open in armchairs situated in an electrically shielded and soundproof room. They were asked not to close, move, or blink their eyes. During the CNV recording procedure, an auditory warning (S1) and an imperative stimulus (S2) were generated by a computer screen situated in front of the subject. The CNV recording consisted of 32 GO-trials including the S1 (duration 500 ms, 1000 Hz, 75 dB). Following an interstimulus interval (ISI) of two seconds, the S2 was presented (maximum duration 1500 ms, 2500 Hz, 75 dB). Subjects were asked to promptly react to terminate the S2 with a button press. To maintain vigilance, eight 200 Hz NO-GO trials requiring no response were randomly presented. S2 did not occur for the NO-GO-condition. Each trial (six seconds) was recorded starting two seconds before the beginning of S1 and ending two seconds after the start of S2. The period between starting and recording S1 was used as the baseline for calculations. The intertrial interval was varied randomly between six and ten seconds. The ISI between S1 and S2 had a duration of two seconds. NO-GO trials were not analyzed. All subjects were highly motivated and compliant during each CNV recording, and before each recording began, they were informed to respond as rapidly as possible. The EEG recording scheme is given in Fig. 1. The orienting pattern included a series of 20 pure sinusoidal tones of 1000 Hz, duration five seconds, 70 dB with a randomized inter-stimulus interval (mean duration 10 ± < 5 s). A red circle was generated by a function generator, and the intensity was controlled by a programmable attenuator. The stimulus was presented on a computer screen placed in front of the subject. Subjects were told they would see a simple red circle; their comfort was checked, and they were asked to sit still and remain alert.

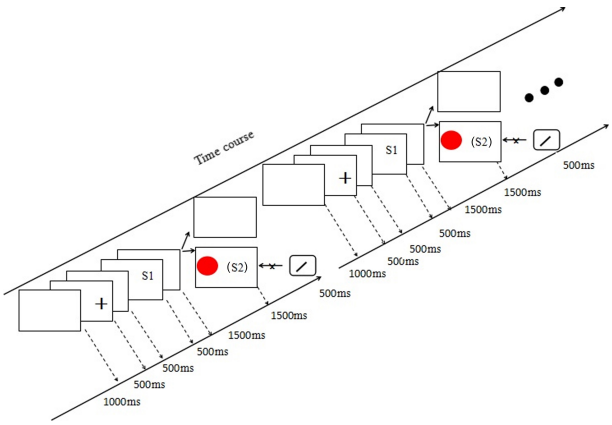

Figure 1. Schematic depiction of EEG recording. A ready warning (+), an auditory warning (S1) and an imperative stimulus (S2) were generated sequentially by a computer screen. When red circle (S2) appeared on the screen, subjects were asked to promptly react to terminate the S2 with a button press. S2 did not occur for the NO-GO-condition. Each trial (six seconds) was recorded starting two seconds before the beginning of S1 and ending two seconds after the start of S2.

2.3 Electroencephalography (EEG) recording

An EEG of each subject was recorded using Ag/AgCl electrodes over FZ, CZ, C3, and C4 according to the International 10-20 System, with a linked bilateral mastoid mean for reference as shown in Fig. 2. The signals were magnified using an EEGO EEG/ERPs 32 Channel Amplifier from ANT Neuro (Code: EE-212, Enschede, Netherlands). The sampling rate was 100 Hz, bandwidth 0-200 Hz; the electrode impedance was < 5 kΩ, which was analog-filtered using a bandpass filter of 0.05-40 Hz to extract the EEG; an independent component analysis was used to remove blink artifacts.

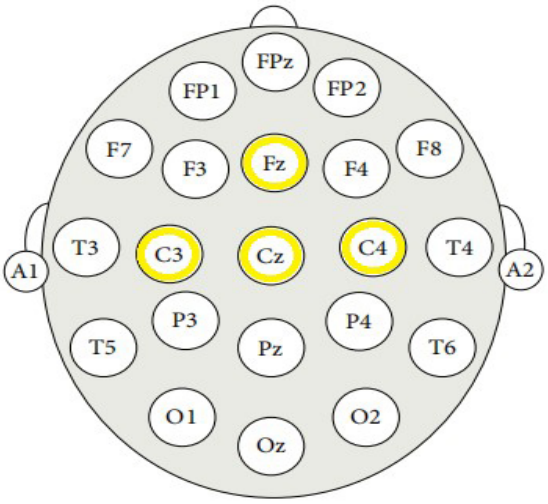

Figure 2. International 10-20 electrode placement system. The measuring electrode (FZ, CZ, C3, and C4) is as shown in yellow.

The CNV stage was completed after 40 artifact-free tests (32 GO and 8 NO-GO tests). For all subjects, the 32 GO tests of each CNV stage were grand averaged. The oCNV was calculated as the average amplitude between the starting points of S1 and S2. The iCNV was calculated following a suggestion made by Böcker et al. (2010): The maximum amplitude between 550 and 750 ms after the onset of S1 was calculated, and the latency of this maximum was used as a 200 ms window. The average amplitude of each window was defined as the iCNV. The tCNV was defined as the average amplitude in the 200 ms before the beginning of S2. The PINV was defined as the average amplitude of the CNV from 500-2000 ms following S2.

2.4 Statistical analysis

GO trials were divided into eight trial blocks, each of which included four single continuous recordings. Records of each block were then averaged. Habituation features were calculated as a tendency of the eight continuous blocks. The exact slope parameter was calculated using regression analysis, where the habituation slope "a" and intercept "b"were calculated using the linear equation $y = ax + b$ (Kropp and Gerber, 2010). SPSS 17.0 statistical software was used to process and analyze the data. All data were normally distributed (Kolmogorov-Smirnoff test) and characterized by homogeneous variances (F-test). Differences between groups were calculated by averages of the Student's t-test (one-sided). Bonferroni alpha adjustment was performed for multiple comparisons. For all calculations, the test level was $\alpha = 0.05$ for statistical significance.

3. Results

3.1 Behavioral performance

The reaction time (RT) at FZ, C3, CZ, and C4 is given in Table 3. There were no significant differences between migraineurs and control groups of oCNV, iCNV, tCNV, PIN. This means that the RT of subjects did not influence CNV measurement.

3.2 Contingent negative variation amplitudes and habituation

The CNV amplitudes and habituation slope "a" and intercept "b" of the migraineurs and healthy control groups at the electrodes of FZ, CZ, C3 and C4 are given in Tables 4, 5, 6 and 7, respectively. A positive value of slope "a" indicates a lack of or deficient habituation, while habituation is indicated by negative slope values. Neither the slopes nor the y-intercept of the migraineurs and control groups were significantly different.

The average CNV amplitudes and habituation between migraineurs and control groups were used by linear maps, respectively, as shown in Fig. 3. Compared with control groups, there were no significant differences in migraineurs for the amplitudes of oCNV, iCNV, tCNV, PINV, and the habituation of early CNV.

4. Discussion

CNV changes in adults with migraine without aura from three to seven days after migraine attacks were studied to provide a basis for exploring the circulation periodicity of migraine without aura. Results showed there to be no difference in RT, so the effect of RT on CNV was excluded. There were no significant differences in the amplitudes of iCNV, tCNV, oCNV, and PINV in the three to seven days after a migraine attack without aura and the healthy controls. There also were no differences in the habituation slope "a" and intercept "b" of the migraine and control groups, indicating normal habituation. This suggests that CNV amplitude and early habituation tend to normalize in adult rats within three to seven days after a migraine without aura. No maximum negative amplitude was found. According to the three-day periodicity theory of migraine occurrence suggested by Kropp and Gerber (1998), the maximum negative amplitude should appear within three to seven days after a migraine. Thus, the periodicity of migraine attacks without aura may be greater than three days.

The average frequency of migraine attacks is about one to four times per month; therefore, additional precipitating factors should be involved, and it is only when the predisposing factors conform with a high CNV amplitude that the rhythm can induce migraine. Previously, Elbert and Rockstroh (1987) showed that the CNV amplitude is greatest before a migraine attack, which may indicate regulation of hyperactive levels of intrinsic brain activity. However, Kropp and Gerber (1998) believed that the amplitude tended to normalize after a migraine attack, indicating less hyperactivity which might be caused by a refractory period following an attack. The study reported here showed no significant difference in amplitude three to five days after a migraine attack without aura for adults and healthy controls. This is consistent with the conclusion

Table 3. Migraineur and control group RT at FZ, nC3, nCZ, nC4 (mean ± SD)

		Migraineurs n = 34	Control n = 31	df	*t*-score	*P*
FZ	iCNV	0.070 ± 0.036	0.699 ± 0.037	44	0.008	0.994
	tCNV	1.885 ± 0.052	1.913 ± 0.067	44	-1.55	0.128
	pCNV	2.336 ± 0.047	2.357 ± 0.145	44	-0.662	0.511
	oCNV	0.451 ± 0.398	0.447 ± 0.447	44	0.031	0.976
C3	iCNV	0.690 ± 0.047	0.648 ± 0.066	41.5	0.485	0.117
	tCNV	1.885 ± 0.052	1.895 ± 0.056	44	-0.047	0.147
	pCNV	2.331 ±0.087	2.316 ± 0.116	44	0.499	0.62
	oCNV	0.705 ± 0.506	0.382 ± 0.273	42.717	2.006	0.055
CZ	iCNV	0.671 ± 0.065	0.689 ± 0.046	44	-1.11	0.273
	tCNV	1.887 ± 0.053	1.905 ± 0.071	44	-0.982	0.331
	pCNV	2.345 ± 0.107	2.309 ± 0.112	44	1.109	0.274
	oCNV	0.289 ± 0.189	0.387 ± 0.283	40.393	-1.388	0.173
C4	iCNV	0.676 ± 0.056	0.669 ± 0.057	44	0.371	0.712
	tCNV	1.896 ± 0.052	1.909 ± 0.065	44	-0.756	0.454
	pCNV	2.352 ± 0.099	2.356 ± 0.129	44	-0.108	0.914

Response time (RT), mean (m); standard deviation (SD); degree of freedom (df), Student's *t*-test significance $P < 0.05$.

Table 4. CNV amplitudes (μV) and habituation parameters in migraineurs and control groups at FZ (mean ± SD)

	Migraineurs (n = 34)	Control (n = 31)	df	*t*-score	*P*
OCNV	-5.39 ± 2.08	-5.54 ± 3.10	43	0.191	0.85
iCNV	-2.45 ± 1.49	-2.69 ± 2.08	43	0.443	0.66
tCNV	-1.33 ± 2.16	-1.83 ± 2.69	43	0.698	0.489
PINV	-7.19 ± 5.16	-9.38 ± 4.57	43	1.494	0.143
Habituation "*a*"	-8.03 ± 9.27	-8.79 ± 7.71	44	0.296	0.769
y-intercept "*b*"	-4.55 ± 6.58	-5.62 ± 5.26	43	0.925	0.556

SD: Standard deviation (SD). Habituation characteristics "*a*" and intercept "*b*" refer to iCNV amplitudes. overall CNV (oCNV), initial CNV (iCNV), terminal CNV (tCNV), postoperative negative variation (PINV), degree of freedom (df), Student's *t*-test significance $P < 0.05$.

Table 5. CNV amplitudes (μV) and habituation parameters in migraineurs and control groups at CZ (mean ± SD)

	Migraineurs (n = 34)	Control (n = 31)	df	*t*-score	*P*
oCNV	-5.81 ± 3.03	-6.37 ± 3.42	43	0.584	0.562
iCNV	-2.67 ± 1.78	- 3.14 ± 1.84	43	0.873	0.387
tCNV	-0.63 ± 2.09	-1.95 ± 4.05	29	1.341	0.19
PINV	-9.01 ± 5.38	-11.79 ± 6.80	43	1.531	0.133
Habituation "*a*"	-7.44 ± 11.85	-9.57 ± 12.25	44	0.598	0.553
y-intercept "*b*"	-4.26 ± 8.05	-6.24 ± 8.14	44	-0.826	0.414

SD: Standard deviation (SD). Habituation characteristics "*a*" and intercept "*b*" refer to iCNV amplitudes. overall CNV (oCNV), initial CNV (iCNV), terminal CNV (tCNV), postimperative negative variation (PINV), degree of freedom (df), Student's *t*-test significance, $P < 0.05$.

Table 6. CNV amplitudes (μV) and habituation parameters in migraineurs and control groups at C3 (mean $\pm$ SD)

	Migraineurs (n = 34)	Control (n = 31)	df	*t*-score	*P*
OCNV	-5.65 $\pm$ 2.63	-5.83 $\pm$ 2.76	43	0.224	0.824
iCNV	-2.22 $\pm$ 1.58	-2.83 $\pm$ 2.15	43	1.086	0.284
tCNV	-0.88 $\pm$ 1.83	-2.43 $\pm$ 3.14	41.3	2.369	0.124
PINV	-7.98 $\pm$ 5.09	-10.06 $\pm$ 5.65	43	1.303	0.199
Habituation "*a*"	-7.23 $\pm$ 10.60	-9.27 $\pm$ 6.83	41.44	0.787	0.436
y-intercept "*b*"	-4.45 $\pm$ 7.34	-6.12 $\pm$ 4.56	40.79	-0.941	0.352

Standard deviation (SD). Habituation characteristics "*a*" and intercept "*b*" refer to iCNV amplitudes. overall CNV (oCNV), initial CNV (iCNV), terminal CNV (tCNV), postimperative negative variation (PINV), degree of freedom (df), Student's *t*-test significance $P < 0.05$.

Table 7. CNV amplitudes (μV) and habituation parameters in migraineurs and control groups at C4 (mean $\pm$ SD)

	Migraineurs (n = 34)	Control (n = 31)	df	*t*-score	*P*
OCNV	-5.1 $\pm$ 1.88	-5.58 $\pm$ 2.19	43	0.793	0.432
iCNV	-2.41 $\pm$ 1.50	-2.21 $\pm$ 2.27	43	-0.358	0.722
tCNV	-0.32 $\pm$ 1.99	-2.26 $\pm$ 3.93	28.8	2.041	0.051
PINV	-8.37 $\pm$ 5.61	-9.52 $\pm$ 5.29	43	0.701	0.487
Habituation "*a*"	-3.27 $\pm$ 9.88	-4.77 $\pm$ 9.45	44	0.523	0.604
y-intercept "*b*"	-1.81 $\pm$ 6.78	-3.80 $\pm$ 6 .37	43	-1.007	0.320

Standard deviation (SD). Habituation characteristics "*a*" and intercept "*b*" refer to iCNV amplitudes. overall CNV (oCNV), initial CNV (iCNV), terminal CNV (tCNV), postimperative negative variation (PINV), degree of freedom (df), Student's *t*-test significance $P < 0.05$.

that the CNV amplitude is normal for several days after an attack (Gerber and Kropp, 1994) which might result from decreased levels of post-paroxysm activity during the refractory period. The refractory period is possibly still within the periodicity of the given migraine attack, which suggests that the periodicity of migraine attack without aura might be more than three days, differing from the three-day periodicity proposed by Kropp and Gerber (1998).

The inconsistency with Kropp and Gerber's findings might be explained by the fact that: Firstly, their subjects did not distinguish between migraine subtypes. Because of the complexity of the causes of migraines and the unclear origin of the nerve affected, it may be a combination of multiple symptoms or different subtypes. According to the phenotype of migraine, it includes at least: a) Migraine without aura; b) Migraine with aura; c) Chronic migraine; d) Complications of migraine; e) Probable migraine; and f) Episodic syndromes that may be associated with migraine (Olesen et al., 2013). Kropp and Gerber (1998) were concerned about migraine in general; however, the present study only focused on the migraine without aura subtype, which might explain the inconsistencies. Migraine either with or without aura are the two main subtypes of migraine, and previous studies have shown there is a difference in CNV between these subject groups. For example, when studying subjects with migraine with and without aura, it was found that increased CNV amplitudes were more common in subjects without aura than in those with aura (Böcker et al., 2010) Clinical differences indicated that migraine with and without aura are distinct entities (Russell et al., 2010). Even the headache phase between the two entities differ, according to studies on clinical differences between the International Headache Society defined migraine and migraine without aura. It is worthwhile distinguishing between migraine with and without aura, perhaps even looking for the genes that underly these more common forms of migraine (Kallela et al., 2010).

Moreover, their different pathogeneses have been demonstrated. Domitrz et al. (2015) found a higher level of histidine in subjects with migraine without and with aura and a lower level of valine and leucine in subjects with migraine without aura. Higher plasma glutamine and aspartic acid levels have also been found in patients with migraine (notably with aura) between attacks (Ferrari et al., 1990). Also, mutations in three different ion channels genes, CACNA1A, ATP1A2, and SCN1A can be causal. Functional studies of these mutations have shown that they can result in defective regulation of glutamatergic neurotransmission and the excitatory/inhibitory balance in the brain, which lowers the threshold for cortical spreading depression, a wave of cortical depolarization thought to be involved in headache initiation mechanisms (Sutherland and Griffiths, 2017). KATP channels are also connected to several key molecules in migraine pathogenesis, particularly nitric oxide, CGRP, PACAP and PGI2 known to provoke migraine attacks (Al-Karagholi et al., 2017). Human experimental models have demonstrated that the activation of the cAMP and cGMP pathways can trigger headache in healthy volunteers and migraine attacks in migraine sufferers (Ashina et al., 2013). Therefore, these factors complicate the interpretation of our research into migraine and could account for contradictory findings. Along with previous studies, this study has revealed different aspects of the complexity of migraine symptoms and their influencing factors.

Secondly, during the interictal period, the CNV amplitude increased significantly when compared with healthy subjects due to elevated cortical arousal and decreased habituation in subjects

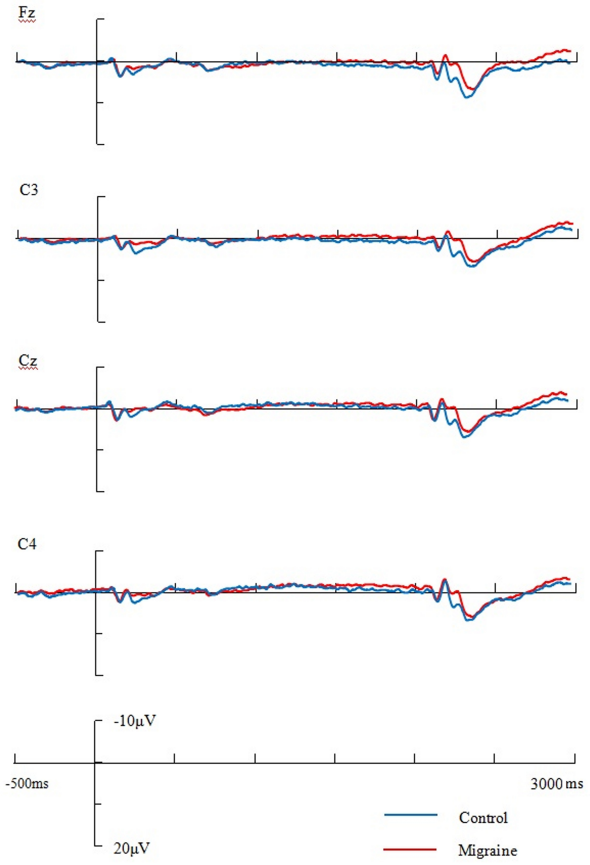

Figure 3. The grand averaged CNVs waveforms in migraine patients and healthy controls, respectively. The sites include scalp electrodes, FZ, C3, Cz, and C4. Redline represents migraine patients and blue line healthy controls.

with migraine. This manifested as changes in cortical excitability (Kropp and Gerber, 2010; Nordhout et al., 2010). Additionally, deficient habituation can be considered a neurophysiological marker for pre-symptomatic migraine (Di et al., 2007; Siniatchkin et al., 2001). It has been proposed that the absence of habituation in migraine is related to low cortical activation caused by low serotoninergic activity and cortical hyperexcitability (Schoenen et al., 1996). This may be one cause of migraines.

Further, abnormal habituation might explain the periodic variation of physiological parameters during the pain-free interval. However, the aberrant habituation of early CNV in migraine is related to increased directional activity found in the central component during alpha-blocking of the directional reaction (Siniatchkin et al., 2010). Whatever the final explanation, it is important to consider that habituation deficits are not invariable in patients with migraine. The degree of habituation can change not only interictally and preictally, but also during the pain-free period between the previous or subsequent attack (Coppola et al., 2013).

Thirdly, as far as is known, there is no single satisfactory explanation for the periodic nature of episodic migraine. For instance, clinical observations of migraine precursors and current published electrophysiological research propose that cortical information processing might change at the time of an attack. The normalization of cortical responses before and during an attack might reflect increased cortical preactivation levels as a result of increased activity in raphe-cortical serotonergic pathways (Judit et al., 2010) and metabolic factors (Paemeleire and Schoenen, 2013); the biological rhythms of hypothalamic activity (Maniyar et al., 2014); or the actual trigger of attacks may be the functional variation in hypothalamic-brainstem connections (Schulte and May, 2016); or periodicity of brain activity in neurophysiology may be related to psychophysiology, genetic (SÃndor et al., 1999; Siniatchkin et al., 2001); Moreover, psychophysiological pathways have become the basis of migraine research. Through the study of ERP, the results show that patients suffering from migraine without aura between attacks display a higher level of arousal and more superficial attention, but require more time for automatic and/or voluntary processes (Wang et al., 1995).

Thus, migraine periodicity may be the result of several interacting biological periodicities and might not arise from a single determining factor, but rather from a complex interaction between intrinsic cerebral, hormonal and external environmental elements that act on a genetically susceptible nervous system. In the study of specific groups (adult migraine without aura) and periods (three to seven days after a migraine attack) results indicated that this period is not be only three days. The problem of inconsistency between experimental findings and the long periods between migraine attacks in a clinical setting was discussed.

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Conflict of interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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