Interictal and postictal cognitive changes in migraine

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The question whether symptom-free migraine patients show cognitive impairments compared to matched control subjects is addressed, and also whether migraine patients show transient cognitive impairments induced by an attack. The Neuropsychological Evaluation System (NES2) was administered once in an interictal period and twice within 30 h after different migraine attacks. Since cognitive impairments could be related to attack duration or severity, cognitive performance was compared during a postictal period after sumatriptan use and during a postictal period after habitual nonvasoactive medication use. Twenty migraineurs without aura, 10 migraineurs with aura, and 30 matched headache-free controls participated in the study. During a headache-free period, migraineurs without aura responded as quickly as controls, while migraineurs with aura were slower than controls during all tasks specifically requiring selective attention. These effects were not aggravated by a preceding migraine attack, irrespective of medication use and attack duration. □ *Cognitive functioning, interictal, migraine, postictal, sumatriptan*

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Neuropsychological studies have provided evidence for cognitive deficits in migraine patients, including psychomotor deficiencies (1, 2), memory deficits (2, 3), and dysfunctions in the early stages of visual processing (4, 5), especially in migraineurs with aura (3, 6, 7). However, in other studies, neither detrimental cognitive effects in migraine patients nor differences between migraineurs with and without aura have been found (8, 9). Factors that could contribute to these inconsistent results are patient selection biases, a lack of distinction between migraineurs with aura and migraineurs without aura, the absence of matched control groups, and the presence of type I errors as a result of multiple testing without adjustment of the nominal alpha level. The time interval between a migraine attack and task performance can also be an important factor.

Interictal brain functioning can be influenced by functional or structural effects of migraine on the one hand, and temporal and reversible effects of an attack on the other. Cognitive performance can be temporarily adversely affected by the physiological dynamics of a preceding or upcoming migraine attack. Post-attack effects can be pronounced, since a migraine headache is followed by transient physiological alterations remaining for up to 48 h after an attack, e.g., regional cerebral blood flow abnormalities (10), a reduction of alpha activity within the background EEG (11), and a reduction of the Contingent Negative Variation amplitude (12)—an event-related cortical potential reflecting noradrenergic arousal and dopaminergic motor control. These results, along with limited food tolerance, tiredness, altered mood state, and diuresis (13), suggest a physiological recovery phase which could also lead to an impaired cognitive performance in the post-attack period.

The present study addresses two main questions: the first whether migraine patients show cognitive impairments in an interictal period compared to matched headache-free control subjects; the second whether migraine patients show transient cognitive impairments during the post-attack period, and whether these impairments are related to the duration or the severity of the preceding attack. Cognitive performance was therefore compared during a post-attack period after sumatriptan use and during a post-attack period after habitual nonvasoactive medication use, such as aspirin or analgesics. Sumatriptan is a selective vascular $5HT_1$ receptor agonist and is more effective than a placebo or aspirin in combination with metoclopramide in the relief of migraine headache (14).

Methods

Subjects

Thirty migraine patients (20 without aura, 10 with aura) and 30 matched healthy controls participated in the study. All were students and were recruited by advertisements in university papers. Patients were diagnosed by a neurologist in accordance with the International Headache Society (IHS) criteria for

migraine (15) before being physically examined, interviewed, and included in 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. All patients had used sumatriptan at least once before participation in the laboratory sessions. Control subjects were selected from the same student population and matched to every migraine patient on the basis of gender, age, and handedness. Socioeconomic status was comparable between patients and control subjects. Controls neither suffered from migraine nor any other type of headache more than once per 2 months (e.g., due to alcohol consumption or exposure to toxic substances). Subjects were not admitted to the study if they had a history of epilepsy, possible risk of structural brain lesions, other severe medical conditions which could affect the interpretation of the results, current abuse of opiate analgesics, psychotropic drugs, ergotamine (>10 mg/week) or alcohol (>315 g/week), or a history of abuse of these substances in the previous 6 months.

Design

Neuropsychological data were obtained during three sessions in patients and controls. Patients were tested following three different attacks. The first session took place on a headache and symptom-free day, at the 4th or 5th day following the peak of a migraine attack. If the first session was followed by a new migraine attack within 3 days, this session was considered invalid. The 2nd and 3rd sessions took place within 30 h after a migraine attack, but after one proper night's rest, when the headache severity had declined to, at most, mild, as judged on a three-point scale (1=mild, 2=moderate, 3=severe). During the attack directly preceding one postictal session, patients used their habitual migraine medication, which could also be no medication. During the attack preceding the other postictal session, the migraine patients used 100 mg sumatriptan tablets. The order of habitual medication and sumatriptan use was counterbalanced over the 2nd and 3rd attacks.

Mediated by test habituation and learning, repeated testing in itself will give rise to session effects. The repeated testing of the control subjects is necessary to identify postictal effects in migraineurs, because it will be confounded with the session effects. Control subjects were tested while 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. Furthermore, the intervals between the control sessions were equivalent to the test intervals of the patient they were matching.

Neuropsychological testing

Neuropsychological testing was done with the second version of the Neurobehavioural Evaluation System (NES2) (16). The NES2 has been shown to be a sensitive instrument for the detection of afflictions of the central nervous system (17). It is a self-administered test during which the subject is required to go through all the tests guided by the instructions given on the computer screen at the beginning of each task. The test battery involves three broad functional domains: cognitive, memory and learning, and psychomotor functions. Emmen et al. (18) translated and adapted the NES2 for administration in The Netherlands. The individual tasks are briefly described in Appendix 1.

Procedure

All subjects abstained from alcohol, tobacco, and caffeine during the hours prior to testing as well as during the testing procedure. Each session began with completion of a Visual Analogue Scale (VAS) to determine the headache severity of the preceding migraine attack. The extremes of pain were "no pain" and "as bad as it could be", and migraineurs marked the degree of pain on the line representing a 0–100 scale. Additionally, patients reported the current subjective impairment by answering the following question with yes or no: "Do you feel that you are still impaired by your last migraine attack at the moment (in the sense that you feel impaired in your ability to concentrate, in your alertness, clear-headedness, or to execute your daily activities)?" Furthermore, at the beginning of each session the number of hours that had passed since meaningful relief from the migraine headache was determined, as well as since medication intake, based on the diaries that were kept during the attack. Duration of the preceding migraine attack was determined by a single question: "How many hours did your migraine attack last?" Subjects were seated behind a table in a dimly lit and quiet room, facing a computer. A keyboard and joystick served as response devices. Subjects were instructed to work as quickly but as accurately as possible. The total administration time of the NES2 was about 75 min.

Data reduction and analyses

The SUMM program of the NES2 was used for a first level of data reduction. The dependent variables computed by this program mainly reflect

processing speed in the cognitive, memory and learning, and psychomotor domain. To obtain an empirical and finer level of clustering of the neuropsychological data, Principal Component Analysis (PCA) was used to cluster all variables reflecting processing speed in the baseline session from all patients and controls, after subtracting the group means and removing outliers from every task. After VARIMAX rotation, seven components were obtained explaining 73% of the variance and denoting the following domains: reasoning, reaction speed, motor functioning, selective attention, digit encoding, visual digit span, and pattern perception (see Appendix 1). In addition to processing speed, accuracy measures (e.g., the number of false-positives and false-negatives during a task) were available in some subtasks (see Appendix 1). The distributions of these individual accuracy scores were either extremely asymmetrical or showed very little variability. Therefore, the individual accuracy scores at our disposal within each PCA cluster were summed, which led to five accuracy sum-scores: reasoning (sum of correct responses in each condition), reaction speed (correct responses summed for each test in this cluster except for the simple reaction time task), selective attention (omissions and false-positive responses derived from all tasks within this cluster), digit encoding (correct responses in the horizontal addition task), and pattern perception (correct responses from both tasks in this cluster).

Age, history, and general attack severity (see Table 1) were compared between migraineurs with aura and migraineurs without aura by submitting these variables to one-way ANOVAs using the GLM module of SPSS 7.5. These analyses included the between subjects factor Aura (migraineurs with aura, migraineurs without aura). The session characteristics listed in Table 1 were submitted to ANOVAs for repeated measures. These analyses included the within subjects factor Session (post-attack session after sumatriptan use, post-attack session after usual medication use), and the between subjects factor Aura (migraineurs with aura, migraineurs without aura). Processing speed variables and accuracy sum-scores were submitted to analyses for paired observations to increase statistical power. An individual migraine patient and the matched control were considered as one case and constitute the within subjects factor Pair (migraineurs, controls). The second within subjects factor is Session with three levels (baseline session, post-attack session after sumatriptan use, post-attack session after usual medication use). This implies that each case contained six observations. In order to group the patients in migraineurs with aura and migraineurs without aura, each case was coded by the between subjects factor Aura (migraineurs with aura, migraineurs without aura).

First, we compared migraineurs to controls in the baseline session and executed ANOVAs with the within subjects factor Pair (migraineurs, controls) and the between subjects factor Aura (migraineurs with aura, migraineurs without aura). Second, we compared the baseline session to the postictal sessions between migraineurs and controls. For this purpose, we entered all sessions to ANOVAs for repeated measures with the within subjects factors Pair (migraineurs, controls) and Session (baseline session, post-attack session after sumatriptan use, post-attack session after usual medication use), and the between subjects factor Aura (migraineurs with aura, migraineurs without aura).

We hypothesize that migraine patients are slower and make more errors than control subjects, and that migraineurs with aura are slower and make more errors than migraineurs without aura. During the postictal sessions we expect that these group differences will be smaller after sumatriptan use than after usual medication intake. Therefore, these specific effects will be tested one-tailed. Main session effects will not be reported since they reflect learning and habituation effects of equal magnitude in migraineurs and controls across the sessions. However, if postictal effects are present in migraine patients, these will be reflected in significant Pair × Session or Pair × Session × Aura interactions. One-tailed follow-up tests ensued the detection of significant interactions. The Holm method (19) was used to reduce type 1 errors by ensuring that the family wise significance level did not exceed $\alpha = 0.05$ after multiple statistical testing within each cluster of variables. This method was also used for the follow-up tests. Univariate test results are reported after Huynh-Feldt ε-tilde adjustment. Furthermore, Levene tests were executed to ensure that the assumption of homogeneity of variances between groups was met, if necessary after a transformation of the dependent variable. For this purpose, a logarithmic transformation was executed on the intervals between the sessions, a square root transformation was executed on attack duration, and two migraine patients were removed from and replaced by the group means of grammatical reasoning (these patients had correct response rates of less than 50%) and attack severity.

Results

Demographics and clinical session characteristics

Table 1 depicts the demographics and clinical session characteristics of the migraineurs with aura and the migraineurs without aura. Age and years of

Table 1. Demographics and clinical session characteristics.

		Migraineurs with aura ($n=10$)		Migraineurs without aura ($n=20$)	
Female/male		8/2		18/2	
Left/right handed		1/9		4/16	
Age		24.3	(4.9)	24.9	(2.8)
Migraine history (years)		7.1	(3.8)	6.2	(3.7)
Subjective reporting of impairment during session (% of patients)					
Sumatriptan		80		45	
Usual medication		60		55	
Interval between sessions (months)					
Baseline—sumatriptan		6.4	(7.8)	6.0	(5.2)
Baseline—usual medication		3.3	(2.0)	5.8	(5.4)
Hours between medication intake and start session					
Sumatriptan		23.1	(8.5)	21.8	(8.1)
Usual medication		26.5	(8.4)	25.8	(13.4)
Hours between meaningful relief and start session					
Sumatriptan		17.7	(9.9)	16.2	(7.7)
Usual medication		14.8	(8.1)	12.5	(7.0)
Attack duration[1] (h)	*				
Sumatriptan		7.6	(4.7)	10.7	(12.1)
Usual medication		13.4	(8.7)	17.6	(13.9)
Headache severity (VAS: 0–100)					
Attack in general	#	67	(19)	83	(11)
Sumatriptan		61	(29)	74	(17)
Usual medication		64	(21)	71	(19)

Results are given as means and (standard deviations).
[1]Attack duration is determined by the number of hours between prodromina and meaningful relief.
*Significant difference between sumatriptan and usual medication use ($p<0.02$).

migraine history were equal between these patient groups. General headache severity was higher in migraineurs without aura than in migraineurs with aura [$F(1,28)=8.4$, $p<0.02$]. Headache severity was equal during the attack when sumatriptan was used compared to when usual medication was used. Attack duration was shortened by sumatriptan use compared to usual medication use [$F(1,28)=11.3$, $p<0.01$]. Furthermore, there was no significant difference in the hours that had passed between both types of medication intake and the start of the following postictal sessions. Similarly, the hours that had passed since meaningful headache relief after both types of medication at the start of the postictal sessions were not significantly different. Furthermore, the session intervals of migraineurs with aura and migraineurs without aura were similar.

Cognitive and motor speed in interictal migraineurs versus controls

Table 2 depicts the group means of the speed measures showing significant baseline effects. During the baseline session, migraine patients (migraineurs with aura and migraineurs without aura) showed equal cognitive accuracy as controls within all domains of cognitive functioning. However, they were slower compared to their controls during the pattern memory tasks within the pattern perception domain [$F(1,28)=5.6$, $p<0.03$].

Migraine patients with aura and migraine patients without aura.—Within the motor function domain, migraineurs with aura produced fewer taps than control subjects with the preferred hand [$F(1,28)=7.8$, $p<0.02$], while migraineurs without aura were equally as fast as controls. Migraine patients with aura were significantly slower compared to their controls during all tests within the selective attention domain (continuous performance with pictures: [$F(1,28)=11.4$, $p<0.02$], continuous performance with letters: [$F(1,28)=4.7$, $p<0.05$], color word task: [$F(1,28)=1.1$, $p<0.03$]), while migraine patients without aura were equally as fast as controls. During the symbol digit substitution task, migraineurs with aura were slower than their controls [$F(1,28)=18.6$, $p<0.03$], but migraine patients without aura were equally as fast as controls.

Cognitive and motor speed during interictal versus postictal sessions

Table 3 lists the significant effects and the group means of the cognitive and motor speed measures during the baseline, the post-attack session after sumatriptan use, and during the post-attack session after usual medication use. Cognitive speed and

Table 2. Cognitive and motor speed in interictal migraineurs versus controls.

		Control	Aura	No aura
Motor functioning				
Finger taps preferred	∞	179 (28)	166 (24)	174 (30)
Selective attention (ms)				
CP with pictures	∞	490 (55)	518 (53)	516 (54)
CP with letters	∞	390 (46)	393 (29)	390 (40)
Color word	∞	586 (51)	617 (47)	604 (45)
Digit encoding				
SYMDG (ms)	∞	217 (23)	250 (23)	225 (28)
Pattern perception (ms)				
Pattern memory	*	428 (87)	489 (127)	462 (101)

Data are given in means and (standard deviations) and are collected in controls ($n=30$), migraine patients without aura ($n=20$), and migraine patients with aura ($n=10$).

*Significant difference between interictal migraineurs and controls.

∞Significant difference between interictal migraineurs with aura and controls ($p<0.05$, ms = milliseconds; CP = continuous performance task; SYMDG = symbol digit substitution task).

accuracy were not significantly affected in the postictal sessions in migraineurs compared to the baseline session, as was indicated by the absence of Pair × Session effects. Averaged across the sessions, migraine patients produced fewer taps han controls, using the preferred hand [$F(1,28)=4.33$, $p<0.03$], the nonpreferred hand [$F(1,28)=13.84$, $p<0.01$], and alternating hands [$F(1,28)=5.0$, $p<0.02$].

Migraine patients with aura and migraine patients without aura.—When averaged over the three sessions, migraineurs with aura were slower than their control subjects during all tests of the selective attention domain (continuous performance with pictures: [$F(1,28)=8.1$, $p<0.02$], continuous performance with letters: [$F(1,28)=3.8$, $p<0.05$], color word task: [$F(1,28)=8.3$, $p<0.03$]), while migraineurs without aura were equally as fast as their control subjects. Furthermore, in congruence with the symbol digit substitution task during the baseline session, migraineurs with aura were slower than those without aura during this task across all sessions [$F(1,28)=10.6$, $p<0.03$], while migraineurs without aura were equally as fast as control subjects. During the pattern perception tasks averaged over all sessions, migraineurs with aura had two errors more than controls [$F(1,28)=4.1$, $p<0.05$]. These findings were obtained by follow-up testing of significant Pair × Aura effects.

Compared to their controls, the differences between migraine patients with aura and migraine patients without aura were equal in each of the three sessions, which was indicated by the absence of significant Pair × Session × Aura or Session × Aura interactions. One significant Pair × Session interaction was detected for the continuous performance with pictures task [$F(2,56)=3.35$, $p=0.02$]. This reflected that the prolonged reaction time present at baseline in migraineurs compared to controls was significantly reduced during the post-attack sessions [$F(1,29)=8.12$, $p<0.03$]. In addition,

Table 3. Cognitive and motor speed during interictal versus postictal sessions.

		Interictal			Sumatriptan			Usual medication		
		Control	Aura	No aura	Control	Aura	No aura	Control	Aura	No aura
Motor functioning										
Finger taps preferred	○	179 (28)	166 (24)	174 (30)	185 (27)	178 (17)	178 (26)	186 (27)	172 (42)	178 (22)
Finger taps nonpreferred	○	167 (37)	150 (26)	157 (21)	191 (37)	157 (17)	168 (24)	193 (45)	157 (31)	169 (29)
Finger taps alternating	○	223 (49)	211 (35)	191 (26)	235 (47)	211 (20)	199 (54)	231 (47)	212 (23)	203 (32)
Selective attention (ms)										
CP with pictures	#●	490 (55)	518 (53)	516 (54)	493 (71)	490 (46)	498 (44)	491 (68)	519 (78)	500 (60)
CP with letters	#	390 (46)	393 (29)	390 (40)	394 (47)	393 (46)	391 (33)	396 (46)	395 (36)	385 (35)
Color word	#	586 (51)	617 (47)	604 (45)	579 (67)	600 (29)	592 (52)	590 (62)	603 (25)	581 (52)
Digit encoding										
SYMDG (ms)	#	217 (23)	250 (23)	225 (28)	202 (27)	233 (14)	209 (26)	203 (24)	230 (7)	205 (21)

Data are given in means and (standard deviations) and are collected in controls ($n=30$), migraine patients without aura ($n=20$) and migraine patients with aura ($n=10$) during an interictal session, during a post-attack session after sumatriptan use and during a post-attack session after usual medication use. (○) Significant difference between migraineurs and controls across all sessions. (#) Significant difference between migraineurs with aura and controls across all sessions. (●) Significant Pair × Session interaction ($p<0.05$, ms = milliseconds; CP = continuous performance task; SYMDG = symbol digit substitution task).

the prolonged reaction time of migraineurs at baseline was not significantly different during the postictal session after usual medication intake but was significantly smaller after sumatriptan had been used [$F(1,29)=8.12$, $p<0.02$]. This Pair × Session interaction effect of the continuous performance task with pictures is depicted in Fig. 1.

Discussion

The first question addressed in the present study is whether interictal migraineurs with aura and migraineurs without aura showed cognitive impairments compared to matched and healthy control subjects. Migraine patients without aura performed as fast as control subjects on the cognitive tests. However, cognitive speed was lower in migraineurs with aura in several cognitive domains. Migraineurs with aura were slower than controls during the symbol digit substitution test, which invokes functions such as visual processing, encoding, short-term memory, and sustained attention. Since there were no other detrimental effects detected in migraineurs with aura during other tests within the digit encoding domain or during tests requiring short-term memory, the slower response during symbol digit substitution can be primarily explained by an impaired ability in visual processing or sustained attention. Since the reaction times during the pattern perception tasks were equal between migraineurs with aura and their matched controls we could not confirm the presence of visual processing deficiencies in migraineurs with aura (7). From the present results, we therefore conclude that the slower response during symbol digit substitution mainly reflects an impairment in sustained attention in migraineurs with aura.

This finding is strengthened by the results that migraine patients with aura were slower than controls during the two continuous performance tests as well as during the Stroop color word test. Besides sustained attention, performance on these tests mainly indexes selective attention on a relevant stimulus dimension, while responses to irrelevant dimensions have to be inhibited. Resistance to interference and controlling interference from both external and internal sources also play a prominent role in performance on these tests. Although some evidence of motor slowing was found in migraineurs, this cannot explain the slowed responses during selective attention, because motor slowing should then have been detrimental to the reaction speed domain also where the required motor response was similar. Since this was not the case, we conclude that when the suppression of responses to nontargets is necessary, cognitive speed is especially impaired in migraineurs with aura. The orbital prefrontal cortex participates in controlling these selective aspects of attention. Dorsolateral areas of the prefrontal cortex are involved in sustained focusing attention. The anterior cingulate gyrus in the medial prefrontal cortex is activated during concentrated attention such as the Stroop task (20). Our findings suggest that a functional disturbance may be present in prefrontal cerebral areas of migraineurs with aura.

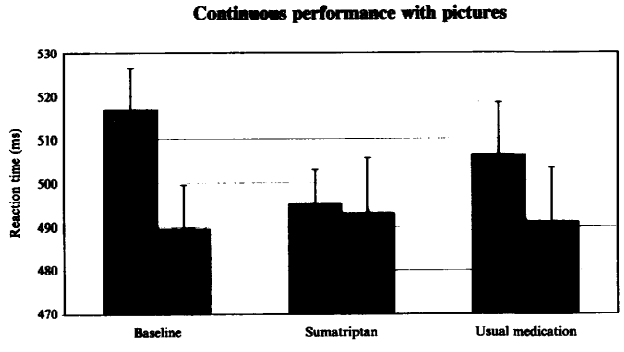

Fig. 1. Mean reaction time and standard errors of migraineurs (grey bars) and controls (black bars) in the continuous performance test with pictures at the baseline session, at the post-attack session after sumatriptan use and at the post-attack session after usual medication use.

Cognitive impairments have been suggested as being predominantly present in migraine patients with profound neurologic complaints and in patients seeking medical help (8). Since migraineurs with neurologic symptoms such as epilepsy, hemiplegia, fainting or exceptionally long and frequent attacks were excluded from the study, such a patient selection bias is unlikely to explain the attention deficit that was found in migraineurs with aura in the present study.

Although recent neuroimaging studies question the presence of cerebral atrophy or neuronal damage in migraine patients (21), the long-term exposure to migraine attacks might eventually lead to cerebral damage (22, 23). The attack duration and severity, the length of the migraine history and age are factors that have implicitly been assumed to influence the extent of this damage and cognitive dysfunctions. However, these factors cannot explain why, exclusively, migraineurs with aura showed cognitive impairments in the present study because (i) attack duration was equal between migraineurs with aura and migraineurs without aura, (ii) migraineurs with aura rated their general attack severity to be even lower than patients without aura, and (iii) the length of migraine history and age were equal between migraineurs with and without aura. In addition, it should be noted that the patients in the present study are young compared to other studies where similar cognitive impairments were found (2, 3). The present study,

along with other studies suggesting that cognitive impairment is unrelated to the length of migraine history (2, 3, 8), does not support the notion that cognitive dysfunctioning is a consequence of the cumulative effects of repeated migraine attacks.

Alternatively, the impaired cognitive functioning in migraineurs with aura can be due to a predisposition to migraine with aura rather than a consequence of repeated attacks. What kind of underlying factors could predispose subjects to migraine with aura and could affect attention as well? Ophoff (24) found a genetic factor in familial hemiplegic migraine, expressed in a structural disturbance in the calcium channels of cortical neurons that are involved in the signal transmission. These findings apply to hemiplegic migraine, but similar results may be found in other types of migraine as well. Ophoff (24) suggests that such a genetic predisposition could evoke a heightened susceptibility to the generation of a spreading cortical neuronal depression which may underlie the aura symptoms of migraine. Peroutka et al. (25) have found the frequency of the dopamine DRD2-C allele of the *Nco*I polymorphism to be selectively increased in migraine patients with aura. Since dopamine receptors play a role in cognitive functioning, the impaired sustained attention in migraineurs with aura may stem from a disturbed dopamine sensitivity. Another predisposing factor for the cognitive impairment in migraineurs with aura could be a hyperactive central catecholamine system, which has been associated with migraine (26). A hyperactive catecholamine system has been reported in migraineurs without aura and was found to normalize during an attack (12). If this system plays a role in cognitive functioning, this may result in an improved cognitive performance during the postictal period compared to the interictal period. However, the present study did not provide substantial evidence for such an improvement, except for the continuous performance task with pictures.

The second question addressed in the present study was whether there are transient negative effects of a migraine attack on cognitive functioning. The majority of the migraineurs with aura subjectively reported impairments during the postictal period, especially after sumatriptan use. This could be due to side effects such as malaise, fatigue, and dizziness, all of which are frequently experienced after sumatriptan use (14). However, this subjective impairment was not reflected in the neuropsychological test results. There were no aggravations detected in the existing interictal impairments of symbol digit substitution and the three tests of selective attention in the postictal period. In addition, an attack did not introduce new detrimental effects, irrespective of attack duration or the type of medication that was used. On the contrary, the prolonged reaction time of the total group of interictal migraineurs compared to controls during the continuous performance test with pictures was reduced in the post-attack period, specifically after sumatriptan use.

In conclusion, migraineurs with aura were slower than controls during the symbol digit substitution task and during all tests specifically requiring selective attention. These effects were not aggravated by a preceding migraine attack irrespective of medication use and attack duration. In spite of physiological studies suggesting a migraine recovery phase up to 48 h after an attack (10–12), the present study did not support the idea that a migraine attack induces neuronal alterations that affect cognitive functioning during the postictal period.

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Appendix 1. Description of NES2 tasks

Reasoning

Reasoning: This is a verbal grammatical reasoning task in which the subject must verify if an instance ("AB" or "BA") is concordant with a statement (e.g., "A follows B") by pressing the "Yes" or "No" button as quickly as possible. The stimuli vary on the following dimensions; the verb ("precedes vs follows"), active–passive, positive–negative, whether the first letter is "A" or "B" and whether the statement is true or false. The average response latency on the active, passive, positive and negative condition is used as well as the number of correct answers in each condition.

Reaction speed

Simple reaction time: Subjects are required to press a button as quickly as possible if a large square appears on the screen. Reaction times are used for analysis.

Switching attention (SA): This is a test measuring the ability to switch rapidly between different types of response requirements indicated by two-choice visual discriminations. There are three different testing conditions. In the first condition ("side"), the subject must respond to each of a series of rectangles presented in succession on the monitor. The rectangle appears on either the left or the right side of the screen. The subject has to press the button on the corresponding side. In the second condition ("direction"), an arrow, pointing to either the left or the right, is presented in the middle of the screen. The corresponding button has to be pressed as swiftly as possible. The third condition ("switching"), the words "side" or "direction", serving as a response instruction, appear directly preceding each reaction stimulus. These stimuli are arrows pointing to either the left or the right and are presented either on the left or on the right side of the screen. Measures are mean response latencies in each condition.

Motor functioning

Finger taps: This is a test of motor speed and accuracy, requiring key tapping with the index finger of the preferred, nonpreferred and both hands in alternation. The measure is the number of taps generated within a 30 s interval in these three conditions.

Hand–eye coordination (HEC): This test of dexterity and visuomotor coordination is executed with the dominant hand. A series of three sawtooth and four sinuses are presented on the monitor. The subject controls the vertical location of a cursor, the horizontal movement of which is preprogrammed, in order to keep it synchronous with the pattern on the screen. The measure is log root square error of the two best trials.

Selective attention

Continuous performance (CP) with pictures: Visual attention is measured by this task in which reaction speed is recorded in response to a target stimulus (cat) semi-randomly embedded in a series of images of animal silhouettes. Stimuli are presented without intervals. The measures are mean response latency and number of false-positive and nonresponses.

Continuous performance (CP) with letters: This test measures sustained visual attention. Reaction speed is recorded in response to a target letter semi-

randomly embedded in a series of five single letters, sequentially presented. The measures are mean response latency and the number of false-positive and nonresponses.

Color word: This is an equivalent of the Stroop test. The words "red", "blue", "green", and "yellow" are presented for 1500 ms one at a time in the center of the screen with an interval of 700 ms. In addition, the words are printed in one of these four colors. Only when color and word are congruent are the subjects required to press a button. The measures are number of false-positive and nonresponses and the response latencies for correct responses.

Digit encoding

Serial digits: A sequence of eight digits is briefly presented. A maximum of eight trials is presented repeatedly until the subject recalls the whole sequence. The learning criterion is two successive correct trials. The measure is a weighted score reflecting the number of errors on each trial.

Symbol digit substitution (SYMDG): The subject is required to enter the digit associated with each symbol from the keyboard. The pairing of symbols and digits changes randomly on each trial. Errors must be corrected before proceeding. The measure is the average mean latency per digit for the two fastest trials.

Horizontal addition: This test measures not only basic arithmetic ability but also aspects of mental manipulation. A row of three one-digit numbers is presented and the subject must enter each two-digit answer from left to right. The measure is the response latency and number of correct responses.

Visual digit span

Visual digit span: A sequence of digits is presented one at a time, after which the subject is required to enter the sequence on the computer keyboard. Increasingly longer digit spans are presented until two errors are made at a span length. After these two errors a second condition is initiated in which the backward digit span is established. At each span length, the span is increased by one if the subject answers correctly. If the subject responds incorrectly, a second trial with a different sequence but identical span length is administered. Testing ends if two successive trials are incorrect. The measure is the maximum correct span length.

Pattern perception

Pattern comparison: A pattern comparison task in which three arrays consisting of 100 black and white blocks (10×10) are presented. Two of the arrays are identical and the third contains four pseudo-randomly chosen blocks that differ in color. The subject is asked to choose the pattern that differs from the other two. The measures are mean response latency on correct trials and number of correct responses.

Pattern memory: A single array consisting of 100 black and white blocks (10×10) is presented for 4000 ms. After a 3 s interval, three arrays are presented simultaneously. On each of the 25 trials the subject has to choose which one matches the original array. The nontargets are different from the target with respect to five blocks within the array. The measure is the mean response latency on correct trials and number of correct responses.