Interictal executive dysfunction in migraineurs without aura: relationship with duration and intensity of attacks

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Subjects with migraine are at increased risk of subcortical white matter lesions (WML). Reports of cognitive testing in adults with migraine have yielded inconsistent results. We performed a cross-sectional study to assess whether migraine without aura (MwA) is associated with impairment in executive functioning, a typical cognitive correlate of subcortical WML. Forty-five subjects with MwA and 90 controls, matched for age and education, underwent a cognitive battery of tests evaluating executive functions. The following migraine characteristics were collected: age at onset and length of migraine history, and frequency, duration and intensity of attacks. Subjects with MwA performed significantly lower than controls in tests evaluating complex, multifactorial executive functions. After multiple adjustments, the duration and intensity of migraine attacks significantly predicted cognitive disturbances. In the interictal phase of MwA there is evidence of mild executive dysfunction. The cumulative effects of repeated migraine attacks on prefronto-cerebellar loop probably account for our results.

Executive functions, migraine characteristics, migraine, neuropsychology

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Introduction

Migraine is a common, disabling disorder, highly prevalent in the general population (1). A complex, bidirectional relationship between migraine and ischemic stroke has been suggested (2). Subjects with migraine show a significant higher risk of periventricular white matter lesions (WML) than controls (3). Recent data suggest that migraineurs are at increased risk for subclinical strokes in the cerebellar region of the posterior circulation territory, and that the risk increases with increasing attack frequency (4). This association suggests that the presence of WML may reflect cumulative brain insults due to repeated migraine attacks (5). According to this hypothesis migraine should be considered not just as an episodic disorder but as a chronic, progressive brain disease (5). Subcortical WML have often been associated with deficits in executive functions (6), i.e. high-order cognitive processes that include planning, initiation, cognitive flexibility, decision making, regulation, judgement, and feedback utilization (7).

Cognitive deficits have been reported in migraine subjects both during and between migraine episodes (8). Neuropsychological testing has revealed impaired performance in tests of psychomotor speed (9–11), attention (9,11), language (12), verbal and visual memory (11,13,14), and executive functioning (15), particularly in subjects with migraine with aura. The existence of cognitive deficits in...
subjects with migraine without aura (MwA) remains controversial (8), and other authors have found no differences in cognitive abilities between migraineurs and controls (16–19). Methodological limitations and heterogeneity in assessing cognitive functions in subjects with migraine may explain these divergent results. Furthermore, few studies have evaluated the extent to which psychiatric disorders (e.g. anxiety and depression), often comorbid with migraine (20), might be associated with cognitive deficits in migraineurs.

It is not well known whether migraine markers of disease severity (e.g. frequency, duration and intensity of attacks) affect neuropsychological performance in subjects with migraine. Neuropsychological deficits have been observed among migraineurs with a higher frequency of attacks and a long history of migraine (11). However, these results have not been confirmed by other authors (12, 14).

Based on these conflicting results and given that subjects with migraine are at higher risk of subcortical WML, we performed a cross-sectional neuropsychological study on executive functioning in subjects with MwA. The diagnosis of migraine was carried out according to the International Classification of Headache Disorders, 2nd edition criteria (ICHD-2nd) (21), and the presence of coexisting anxiety and depressive symptoms was evaluated. The following questions were addressed: Is MwA associated with cognitive disturbances in executive functioning? Is there a relationship between specific migraine characteristics (i.e. age at onset and length of migraine history, and frequency, duration and intensity of migraine attacks) and cognitive performance?

Methods

Subjects

Forty-five cases fulfilling the ICHD-2nd criteria (21) for MwA were included. Patients were recruited from those attending our Adult Headache Centre. Inclusion criteria for subjects with MwA were: (a) history of migraine of ≥5 years; (b) at least 12 migraine attacks in the last year; (c) normal brain CT scan; and (d) the absence of other coexisting types of headache. Due to the fact that we were expecting a slight difference in cognitive performance between cases and controls, we included 90 controls (case:control ratio = 1:2) matched for age and education with migraineurs to increase the statistical power of data. Regarding social background, controls were selected from friends or relatives of subjects with MwA. The inclusion criteria for controls were the presence of less than three mild non-migraine headache episodes in the last year. Common inclusion criteria for cases and controls were: (a) age ≤50 years; (b) a normal neurological examination; (c) a minimal IQ value of 80; (d) normal global intellectual ability; and (e) no headache attack 48 h before or after the cognitive session. Exclusion criteria for both groups included: (a) a history of psychiatric disorders, seizures, head trauma, alcohol or drug abuse and cerebrovascular accident; and (b) consumption of psychotropic drugs at the time of testing. The study was approved by the ethics committee of the University of Palermo and all subjects gave informed consent.

Migraine characteristics

The following migraine data were collected: age at onset of migraine, length of migraine history, and frequency (numbers of attacks in the previous year), duration and intensity of attacks. Duration was calculated as the mean (in hours) of the duration of migraine attacks experienced in the previous year. Headache intensity represented the mean intensity of attacks experienced in the same period. The intensity of pain was judged on a three-point scale, as follows: 1 = mild (no reduction in activities); 2 = moderate (reduction in activities); 3 = severe (bed resting). These data were obtained by averaging those collected using a semistructured headache questionnaire, based on the ICHD-2nd criteria (21), which was administered every 3 months during outpatient visits. This questionnaire included the following specific questions: (a) How many migraine attacks have you experienced in the last three months? (b) On average, how long did the attack last in hours? (c) On average how severe was the pain of these attacks? The type of medication used for migraine attacks included non-steroidal anti-inflammatory drugs (NSAID) (66.7%, n = 30) and triptans (33.3%, n = 15).

Neuropsychological and behavioural assessment

All subjects visited our neuropsychological laboratory for a 1-day session. The participants underwent a cognitive battery of standardized tests, exploring general intellectual abilities and executive functions. These tests were administered by a neuropsychologist, who was blind to diagnoses, over a 60–90-min time-span per interview. General intellectual ability was screened by The Mini-Mental
State Examination (MMSE) (minimum score of 26/30) (22), and the Token Test (minimum score of 27/36) (23). The Test d’Intelligenza Breve (TIB) (24), an Italian version of the National Adult Reading Test (25), was used to estimate total IQ. This test, which involves pronunciation of irregular words, has been shown to be a valid measure of pre-morbid IQ in several medical conditions (26). The following tests were used to evaluate executive functioning.

Trail Making Test Part A and B. In Part A (TMTa) (27), which assesses visuomotor tracking and selective attention, the subject is asked to correctly connect 25 encircled numbers randomly arranged on a page. In Part B (TMTb) (27), which evaluates divided attention and set-shifting, the subject is asked to join numbers and letters in an alternating, ascending sequence. Scoring is expressed for both completion.

Phonemic Fluency (PF) (28). This is a word generation task based on a phonological cue, which is sensitive to frontal dysfunction (29). Scoring is expressed as the number of words generated in 1 min.

Wisconsin Card Sorting Test (64 card modality) (WCST) (30). This is a widely used test to measure cognitive flexibility, i.e. the ability to alter a behavioural response mode in the face of changing contingencies (set-shifting). On the WCST, subjects have to sort cards according to simple sorting rules (e.g. matching colour, shape and number). The correct sorting rules are unknown to the subjects and they have to be inferred from feedback on the correctness of each sort. After 10 correct sorts, the sorting rule is changed, without the subjects knowing. Scores adopted in the study included the numbers of categories achieved (WCSTc) and the number of perseverative errors (WCSTp).

In order to assess levels of depression and anxiety at the end of the cognitive session, cases and controls performed the Hamilton Depression Rating Scale (HDRS) (31) and the Hamilton Anxiety Rating Scale (HARS) (32).

Statistical analysis

First, student two-tailed $t$-test or one-way analysis of variance (ANOVA) was used to compare neuropsychological performance between cases and controls. Due to the multiple comparisons, the Bonferroni-corrected significance threshold was set at $P = 0.01$ (0.05/5) to reduce the possibility of type I errors.

Subsequently, to assess whether migraine affects cognitive functioning, we constructed multiple linear regression models using neuropsychological scores as outcomes. Age, gender, education, migraine characteristics and other potential confounders were used as covariates. For these analyses, a P-value ≤0.05 was considered significant. The data were analysed using SPSS statistical software, version 13.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Demographic and migraine characteristics are shown in Table 1. There were no differences in age, years of education, pre-morbid IQ and general intellectual ability between the cases and controls (Table 1). Conversely, subjects with MwA reported significantly higher levels of anxiety ($t = 5.638, P < 0.001$) and depression ($t = 4.561, P < 0.001$) as compared with controls.

Concerning executive functioning, cases showed significant lower scores than the controls on the TMTb ($t = 3.398, P = 0.001$), the WCSTc ($t = 4.167, P < 0.0001$), and the WCSTp ($t = 3.611, P = 0.001$, see Table 2).

At ANOVAs with Sheffe post-hoc comparisons, no differences were identified between test performance when cases were split according to gender or type of medication used (NSAID vs triptans). Therefore, the use of medication was not further analysed as an independent variable in the regression model.

To predict the effect of migraine characteristics on cognition in subjects with MwA, univariate followed by stepwise multivariate linear regression models were used. The outcome variables were TMTb, WCSTc and WCSTp scores. Univariate linear regression analyses verified that age at onset of migraine, length of migraine history, and duration and intensity of migraine attacks were significantly associated with the TMTb performance (see Table 3). The duration and intensity of migraine attacks were also associated with performance on the WCSTc and the WCSTp. To evaluate the possible effect of demographics and psychiatric symptoms on cognitive performance, previous analyses were repeated, including significant factors obtained from each univariate analysis and adjusting for age, gender, education and HARS and HDRS scores. Age (adjusted $R^2 = 0.266$; $F[43,1] = 16.926, P = < 0.0001$) and intensity of attacks (adjusted $R^2 = 0.366$; $F[42,1] = 5.564, P = 0.023$) significantly predicted TMTb scores. Conversely, the duration of migraine attacks significantly predicted WCSTc (adjusted $R^2 = 0.177$;
### Table 1 Demographic and clinical characteristics of cases and controls*  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Migraineurs ($n = 45$)</th>
<th>Controls ($n = 90$)</th>
<th>$P$ (t or $\chi^2$ tests)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>33.6 (8.6)</td>
<td>31.2 (8.2)</td>
<td>Ns</td>
</tr>
<tr>
<td>Education, years</td>
<td>9.9 (3.8)</td>
<td>10.1 (3.4)</td>
<td>Ns</td>
</tr>
<tr>
<td>Female sex, $n$ (%)</td>
<td>31 (68.9)</td>
<td>52 (57.8)</td>
<td>Ns</td>
</tr>
<tr>
<td>Global general cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test d’Intelligenza Breve</td>
<td>104.7 (10.1)</td>
<td>107.0 (10.8)</td>
<td>Ns</td>
</tr>
<tr>
<td>Mini Mental State Examination</td>
<td>28.4 (1.1)</td>
<td>28.8 (1.2)</td>
<td>Ns</td>
</tr>
<tr>
<td>Token Test</td>
<td>29.8 (1.9)</td>
<td>30.4 (1.8)</td>
<td>Ns</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamilton Anxiety Rating Scale</td>
<td>10.7 (7.1)</td>
<td>4.4 (3.2)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale</td>
<td>7.0 (6.1)</td>
<td>2.7 (2.8)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Migraine features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of onset of migraine, years</td>
<td>20.4 (4.9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Length of migraine history, years</td>
<td>13.3 (7.7)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Frequency of migraine attacks/year</td>
<td>34.4 (20.3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duration of attacks, hours</td>
<td>29.6 (20.9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intensity of attacks, grade</td>
<td>2.0 (0.8)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Except where indicated, data are expressed as mean (S.D.).

### Table 2 Neuropsychological differences in test assessing executive functions between cases and controls*  

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Migraineurs ($n = 45$)</th>
<th>Controls ($n = 90$)</th>
<th>$P$ ** (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail Making Test A†</td>
<td>43.1 (12.0)</td>
<td>37.1 (13.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Trail Making Test B†</td>
<td>88.7 (38.0)</td>
<td>66.2 (32.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Phonemic fluency</td>
<td>29.1 (7.2)</td>
<td>32.7 (9.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test, categories</td>
<td>2.5 (1.4)</td>
<td>3.5 (1.1)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test, perseverations</td>
<td>18.1 (7.1)</td>
<td>13.8 (5.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Data are expressed as mean (S.D.).  
**Level of significance is $P = 0.01$, after Bonferroni correction.  
†The scores are expressed as time in seconds.

### Table 3 Univariate linear regression analyses between migraine characteristics and cognitive performance in subjects with migraine without aura

<table>
<thead>
<tr>
<th>Covariates</th>
<th>TMTb $\beta$</th>
<th>SE</th>
<th>$P$</th>
<th>WCSTc $\beta$</th>
<th>SE</th>
<th>$P$</th>
<th>WCSTp $\beta$</th>
<th>SE</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset of migraine, years</td>
<td>0.292</td>
<td>0.800</td>
<td>0.052</td>
<td>-0.021</td>
<td>0.031</td>
<td>0.889</td>
<td>0.128</td>
<td>0.155</td>
<td>0.403</td>
</tr>
<tr>
<td>Length of migraine history, years</td>
<td>0.321</td>
<td>0.710</td>
<td>0.031</td>
<td>-0.067</td>
<td>0.027</td>
<td>0.660</td>
<td>0.015</td>
<td>0.140</td>
<td>0.923</td>
</tr>
<tr>
<td>Frequency of migraine attacks/year</td>
<td>0.050</td>
<td>0.285</td>
<td>0.744</td>
<td>-0.211</td>
<td>0.010</td>
<td>0.165</td>
<td>0.055</td>
<td>0.053</td>
<td>0.720</td>
</tr>
<tr>
<td>Duration of migraine attacks, hours</td>
<td>0.283</td>
<td>0.266</td>
<td>0.060</td>
<td>-0.443</td>
<td>0.009</td>
<td>0.002</td>
<td>0.441</td>
<td>0.046</td>
<td>0.002</td>
</tr>
<tr>
<td>Intensity of migraine attacks, grade</td>
<td>0.378</td>
<td>6.858</td>
<td>0.010</td>
<td>-0.282</td>
<td>0.260</td>
<td>0.060</td>
<td>0.274</td>
<td>1.327</td>
<td>0.069</td>
</tr>
</tbody>
</table>

TMTb, Trail Making Test B; WCSTc, Wisconsin Card Sorting Test, categories; WCSTp, Wisconsin Card Sorting Test, perseverations.

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Discussion

This study shows that subjects with MwA have cognitive disturbances in tasks assessing executive functions, and that impaired cognitive performance of migraineurs is related to the duration and intensity of migraine attacks.

Subjects with MwA displayed lower performance compared with controls in all tasks evaluating executive functions, but significant differences appeared only in complex, multifactorial tests such as the TMTb, the WCSTc and the WCSTp. Executive functions are multifaceted, high-order cognitive processes that require the co-ordination and goal-orientation of several subprocesses, including long-term and working memory (7). Regarding tests assessing executive functions, some have been consistently associated with selected brain regions, while others reflect a more diffuse neural network. For example, the PF has been associated with activation of the left inferior frontal gyrus (29), while the TMTa, which evaluates visuomotor selective attention, is mainly related to activation of parietal association cortices (33). Conversely, tasks that evaluate set-shifting, such as TMTb and WCST, have been associated with the wide cortico-subcortical neural network underlying executive functions (33–35). Recently, metabolic studies have clarified the distinct brain regions participating in different stages of the WCST (34, 35). Some cortical areas, such as the dorsolateral prefrontal cortex, the anterior cingulate cortex and the temporo-parietal junction, have shown increased activity during working memory and attentive operations. Furthermore, a cortico-basal-ganglia-loop, including the mid-ventrolateral prefrontal cortex, caudate nucleus, mediodorsal thalamus and the cerebellum, was found to be related to set-shifting (34, 35). Similar data have been reported for activation patterns during performance on the TMTb (33).

With the aim of identifying potential predictors of executive dysfunction in subjects with MwA, we evaluated the association between cognitive performance and migraine characteristics. Due to the fact that demographics and psychiatric symptoms are factors often affecting cognitive performance, all analyses were adjusted for these covariates. We found that intensity and duration of migraine attacks significantly predicted TMTb, WCSTc and WCSTp performance, thereby suggesting that more severe and longer migraine attacks may cause some subtle but significant changes in cognition.

Cognitive dysfunction in migraine may be a consequence of the cumulative effects of repeated migraine attacks leading to subcortical WML (3). The positive association between longer duration and intensity of attacks and poorer cognitive performance strengthens this hypothesis. Deficits in executive functioning may be also related to subclinical strokes in the cerebellar region of the posterior circulation territory (4). Indeed, recent data suggest that disorders of the cerebellum, in particular those involving cerebral hemispheres and dentate nuclei, are associated with disturbances of executive functions (36). According to this data, the coexistence of normal brain CT scans in our MwA subjects with significant deficits of executive functioning suggests a mild functional dysfunction in the prefronto-cerebellar loop (37).

Several studies have evaluated cognition in subjects with migraine. Cognitive deficits in tests assessing psychomotor speed (9–11), attention (9, 11), verbal and visual memory (11, 13, 14), and verbal comprehension (12), have been reported in subjects with migraine. However, only recently executive disturbances have been demonstrated in migraineurs. Mongini et al. (15) found impaired performance in subjects with chronic migraine in the Tower of Hanoi and the Object Alternation Test, two tasks related to the same neural network that is associated with brain activation during TMTb and WCST performance (38, 39). In contrast to these and our results, other studies have not identified any differences in cognitive abilities between migraineurs and controls (16–19).

Few studies to date have assessed factors affecting cognitive performance in migraine. Calandre et al. (11) have reported neuropsychological deficits among migraineurs with a higher frequency of attacks and a long history of migraine. Again, these results have not been confirmed by others (12, 14, 17).

The variability in data concerning the presence, type and predictors of cognitive deficits in subjects with migraine largely reflects inclusion and selection biases. Further factors that may contribute to these conflicting data are: the lack of specific statistical procedures (i.e. correction for multiple comparisons) and differences in neuropsychological methodologies, used in conducting cognitive assessments. Finally, the influence on cognitive functioning of coexisting anxiety and depressive symptoms was hardly evaluated.
To overcome these shortcomings, we conducted a cross-sectional study, matching subjects for age and education. All subjects were evaluated with standardized tests, migraine diagnoses were performed according to the ICHD-2nd criteria (21), and the data obtained were corrected for multiple comparisons. We used multiple regression models, adjusting for demographics and psychiatric comorbidity. Despite the rigorous statistical approach and case selection adopted, some potential limitations of this study deserve mention. First, migraine patients did not undergo brain MRI, the most sensitive technique for evaluating WML in adults (40). Thus, we can only hypothesize that covert subcortical lesions account for deficit in executive functioning observed in migraineurs. Secondly, as subjects who participated in this study were from a specialized clinical setting, caution is necessary in generalizing our results. Thirdly, we acknowledge that, with the aim of increasing the statistical power of our study, we would have doubled the number of subjects with migraine rather than the controls. Unfortunately, the strict inclusion criteria adopted for migraineurs suggested doubling the size of the control group. However, we carried out separate analyses, adopting a 1:1 case:control proportion, and the results were similar to those reported in Table 2 (data not shown).

In conclusion, our study shows that there is evidence of executive dysfunction in the interictal phase of MwA. The association between executive disturbances and the duration and intensity of migraine attacks suggests that prolonged exposure to migraine might cause a mild cognitive dysfunction. Due to the responsiveness of migraine to specific preventive treatments (1), our findings may have relevant therapeutic implications. Prospective studies coupling brain functional imaging with cognitive testing are required to confirm these results.

References

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