



# Visuospatial learning is fostered in migraine: evidence by a neuropsychological study

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Received: 22 August 2018 / Accepted: 7 June 2019 / Published online: 27 June 2019  
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## Abstract

**Background** Cognitive profile in migraine patients still remains undefined. Contradictory evidence has been provided, with impairments in different cognitive domains, normal cognition, or even better performance compared to healthy controls (HC). The latter is of particular interest considering the evidence of glutamatergic upregulation in migraine, particularly in the visual cortex, and the role of the glutamatergic system in synaptic plasticity and learning. The aim of our study is to compare cognitive performance for visuospatial memory and learning (supraspan modality) between migraineurs without aura (MwoA) and HC.

**Methods** Twenty-one subjects suffering from MwoA and 21 HC were enrolled. Migraineurs during the interictal phase and HC underwent visuospatial memory test (Corsi test) and verbal memory test (Buschke Selective Reminding Test) in supraspan modality, Trial Making Test A (TMTA) and B (TMTB) as test exploring attention, and TMTB-TMTA as test of executive functioning. Depression was assessed with the Beck Depression Inventory Short Form (BDI-SF). Migraine characteristics (i.e., disease duration and frequency expressed as attacks per month) were collected.

**Results** Subjects with MwoA showed better performance than HC in test exploring both short ( $p = 0.002$ ) and long-term ( $p = 0.001$ ) visuospatial memory. No significant difference between groups was found in verbal memory, attention, executive functioning, and depression (BDI-SF). No significant association emerged between cognitive performance and migraine characteristics.

**Discussion** Subjects with MwoA had significant better performance in visuospatial memory and learning than HC. Occipitoparietal hyperexcitability (in particular in the visual cortex), which is a hallmark of the migraine brain, would probably explain these results. These data need to be confirmed in larger samples of migraineurs.

**Keywords** Migraine · Cortical excitability · Glutamate · Visuospatial memory

## Introduction

Migraine is a disabling neurological disorder, characterized by moderate to severe unilateral, pulsating headache associated with nausea or vomiting and/or photophobia and phonophobia. In about 25% of patients, headache is preceded or associated with

symptoms or signs of transitory cortical or brainstem dysfunction known as aura [1]. Even if the precise mechanism underlying the disease and more in particular the susceptibility to develop headache still remain to be clarified, relevant insights come from studies with animal models in a particular form of inherited migraine with aura, the so-called familial hemiplegic migraine (FHM) [2]. To date, three principal forms of FHM have been described, based on specific genetic defects involving neuronal membrane, which are critical for neuronal excitability:  $Ca^{2+}$  channels in FHM1 [3]; Na/K ATPase pump in FHM2 [4], and sodium channels in FHM3 [5]. All these abnormalities converge functionally on a final common pathway represented by an increase in glutamate neurotransmission with a consequent condition of neuronal hyperexcitability. Moreover, direct evidence of hyperexcitability following to glutamate upregulation is demonstrated more recently from electrophysiological studies on knock-in mouse models for genes of FHM1 and FHM2 (where

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increased susceptibility to cortical spreading depression was found) [6–8].

Evidence in favor of glutamate upregulation in migraine can also be found in humans using different experimental approaches and principally electrophysiological techniques [9]. Studies with evoked potential and non-invasive brain stimulation techniques showed a condition of abnormal cortical excitability and, more specifically, increased activity of mechanisms under the control of glutamate neurotransmission [10, 11]. However, electrophysiological studies showed also paradoxical inhibitory responses, probably due to the activation of inhibitory mechanisms of homeostatic plasticity, which cyclically changes according to migraine phases [12]. A clearly condition of cortical hyperexcitability was demonstrated by a study exploring cross-modal audiovisual illusions [13], phenomena that are more strictly dependent on visual cortical excitability [14] and less prone to mechanisms of homeostatic plasticity. The role of glutamate in migraine was recently confirmed by a spectroscopic MRI study, which showed a consistent increase of the glutamatergic neurotransmission in the visual cortex of migraineurs [15]. Glutamate is the principal facilitatory neurotransmitter of the nervous system and plays a critical role not only in maintaining cortical excitability, but also neural plasticity with relevant implications regarding higher cortical functions, including learning. Accordingly, considering the above evidence regarding glutamate upregulation in migraine (particularly in the visual cortex), better cognitive performance regarding visual-spatial memory should be hypothesized. Cognitive functioning has been diffusely explored in migraine. In particular, impaired attention in prodromal and ictal phases of the disease was described [16–18]. Subsequently, several studies evaluated the presence of cognitive impairment in migraine also in the interictal phase of the disease with the aim to better evaluate and characterize cognitive status in migraine in relationship to attack characteristics. Results were not univocal, with some author describing subtle cognitive deficits regarding executive functioning [19], verbal, visuospatial, or language processing [20], while others reporting no significant difference compared to controls [21, 22]. These contrasting findings probably account for heterogeneity due to patients' selection and disease severity, explored cognitive domains, and neuropsychological tests used. On the other hand, psychiatric comorbidity—particularly depression—may at least in part account for the variability of data obtained. Depressive states, frequently comorbid with migraine, are known to influence cognitive functioning, principally impairing memory and learning, speed of processing, executive function, and working memory [23].

As far as concern the relationship between migraine characteristics and cognitive performance in migraineurs, the high frequency (attacks per month) and long duration of the disease have been associated with worse performance in verbal and visuospatial memory, and attention and visuomotor speed processing during headache-free interval in migraineurs compared to controls [20, 24, 25].

According to the hypothesis of dysregulated glutamate signaling in migraine, particularly in the visual cortex, the aim of our study was to explore cognitive performance regarding visuospatial memory and learning in migraine.

## Material and methods

### Subjects

Twenty-eight patients suffering from MwoA, diagnosed according to the International Classification of Headache Disorders, 3rd edition, beta version [1], were recruited at the Headache Center, Neurologic Unit of the University Hospital Paolo Giaccone of Palermo, Italy. Inclusion criteria for MwoA were as follows: history of migraine of at least 5 years; at least 12 migraine attacks in the last year and less than 4 attacks per month; normal brain magnetic resonance imaging, no other coexisting types of headache, the absence of depression (Beck Depression Inventory Short Form (BDI-SF) score < 9) [26]. Exclusion criteria were as follows: the presence of other type of headache, other neurological diseases, and consumption of psychotropic drugs, including migraine prophylactics. Seven MwoA subjects were excluded from the analysis because they suffered from clinical depression ( $n = 4$ ) and/or had high attack frequency ( $n = 3$ ), thus leaving 16 migraineurs participating in the present study. As healthy controls (HC), 21 individuals matched for age ( $\pm 2$  years), sex, and education with migraineurs were included. Exclusion criteria for the control group were the presence of first-grade relatives affected by migraine and a BDI-SF score  $\geq 9$ . All migraineur subjects were evaluated in the interictal phase (no headache attack 48 h before or after the cognitive session, assessed with a telephone call). The following migraine characteristics were collected: disease duration (years) and frequency (number of attacks per month). Demographics characteristics of the included sample are shown in Table 1. The study was approved by the Ethics Committee of the University of Palermo and

**Table 1** Demographics characteristics of HC and MwoA

	HC $n = 21$ mean (SD)	MwoA $n = 21$ mean (SD)
Age, years	27.9 (3.16)	29 (4.32)
Gender, male/female, $n$	9/12	9/12
Education, years	16.61 (1.20)	16.5 (2.10)
Disease duration, years	–	8.57 (3.69)
Frequency/ $n$ . attack $\times$ month	–	3.26 (2.70)

HC healthy controls, MwoA migraine without aura, SD standard deviation

informed consent was obtained from all participants included in the study.

### Cognitive and behavioral assessment

Subjects were evaluated at the Neuropsychological Lab of the Neurologic Unit, University Hospital Paolo Giaccone of Palermo, by experienced examiners who was blind to diagnoses and use of concurrent medications, over a 30-min time-span per interview. The cognitive and behavioral battery included the following tests:

- a) *Visuospatial memory and learning*: The nonverbal supraspan learning task measure was evaluated using the Corsi Block Tapping test [27]. Due to the low mean age and high education of the sample, the supraspan modality, considered as more sensible instrument to detect slight cognitive changes, was used. It consists of nine cubical blocks positioned on a board. The subject has to reproduce a given sequence by tapping the blocks in the same sequence showed by the examiner. The sequence is presented until the learning criterion is reached (i.e., three consecutive complete sequences or up to a maximum of 18 trials). For the current study, we slightly changed the scoring system of this task using the performance obtained in the first trial as a measure of short-term visuospatial memory, while the total score obtained in the task was used as a measure of long-term visuospatial memory [27].
- b) *Verbal, episodic memory*: Buschke Selective Reminding Test (BSRT), a measure of verbal learning and memory was administered. It consists of a list of 10 words, consecutively administered over 19 trials. During the first reading, all the 10 words from the list were verbally presented, while in the other 18 consecutive trials the examiner provided the subjects with only the words from the list that were missed on the previous trial. Also in this test, the words are presented until the participant reached three consecutive complete list. Scores reflect information acquisition, storage, and retrieval [27]. In the present study, we considered the first trial as short-term memory and the other 18 trials as long-term memory.
- c) *Selective and divided attention*: Trail Making Test Part A (TMTA) and B (TMTB) [28]. In TMTA, which evaluates selective attention and visuomotor tracking, the subject is asked to correctly connect 25 encircled numbers randomly placed on a page. In TMTB, which assesses divided attention and set-shifting, the subject is asked to join numbers and letters in an alternating, ascending sequence. In the present study, scoring is expressed for both tasks in terms of the time required (in seconds) for completion. These tests were used as internal control tasks to evaluate selective and divided attention.
- d) *Executive functions*: TMTB score minus TMTA score. This derived score is usually used to remove the speed component from the performances, thus giving a better measure of cognitive flexibility and shifting ability and executive control [28].
- e) *Depressive symptoms*: the Beck Depression Inventory Short Form (BDI-SF) using the cut off of 9 was used [26]. We excluded from the analysis 4 migraineurs due to minimal but significant BDI-SF scores to avoid the interference of depression in cognitive performance.

### Statistical analysis

Statistical analyses were performed using Statistica software (version 8.0; Dell Software, Tulsa, Oklahoma, [www.statsoft.com](http://www.statsoft.com)). Demographic and clinical characteristics were compared between the two experimental groups using Mann–Whitney *U* test. Spearman's correlation test was used to analyze the putative relationship between cognitive performance and migraine characteristics (i.e., disease duration and attack frequency). 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.

### Results

As expected, the two groups did not differ by age, sex, and education (see Table 1). The results of cognitive tests are reported in Table 2. Significant differences between MwoA and HC were found in tasks exploring both short-term ( $p = 0.002$ ) and long-term visuospatial memory ( $p = 0.001$ ). Contrarily, any difference was found in tasks evaluating verbal, episodic memory, selective and divided visual attention, and executive functioning. Lastly, MwoA and HC reported similar scores in depression scale. No significant relationship was found between migraine characteristics (i.e., illness duration, attack frequency) and cognitive performance.

### Discussion

In this study, we evaluated verbal and visuospatial memory/learning, selective and divided attention, and executive functioning in subjects with MwoA and HC. The rationale was to deepen the current knowledge related to cognitive functioning in migraine, focusing in particular on learning, a function strictly related to glutamatergic neurotransmission, which is supposed to be upregulated, particularly in the visual cortex, in subjects with migraine [15]. We checked for confounding factors (i.e., comorbid depression, ongoing drug treatment, and high migraine frequency).

**Table 2** Neuropsychological performances in HC and MWoA

	HC mean (SD)	MWoa mean (SD)	<i>p</i> value*
Visuospatial memory			
Corsi test STM	0.86 (0.40)	1.27 (0.34)	.002
Corsi test LTM	25.06 (2.77)	27.73 (2.41)	.001
Verbal memory			
STM	7.85(0.96)	8.42 (1.02)	.17
LTM	173.85 (6.48)	176.47 (2.69)	.08
Attention			
TMTA	56.57 (6.29)	53.80 (10.70)	.13
TMTB	126.09 (13.43)	121.14 (21.53)	.12
Executive functions			
TMTB-TMTA	65.23 (17.87)	69.52 (13.89)	.09
Depression			
BDI-SF	2.28 (2.17)	3.47 (1.88)	.06

HC healthy controls, MWoA migraine without aura, STM short-term memory, LTM long-term memory, TMTA Trial Making Test A, TMTB Trial Making Test B, BDI-SF Beck Depression Inventory Short Form

\*Level of significance is  $p = 0.01$ , after Bonferroni correction

As hypothesized, migraineurs performed significantly better than HC in tasks evaluating visuospatial memory and learning. This effect appears to be independent from visual attention; indeed, similar performances between migraineurs and HC were observed in TMTA and TMTB, and the latter result confirm previous data [29, 30]. Similarly, there were no differences between HC and migraineurs in tests evaluating short- and long-term verbal memory and executive functioning. Cognitive impairment, particularly deficits in memory and attention, has been frequently described in the pre-ictal and ictal phase of migraine [31]. However, cognitive dysfunction was also described in the interictal phase of migraine; but in these cases, results are controversial [19, 20]. The heterogeneity of these results is probably accounted for by difference in sample size, study design (hospital versus population based), migraine characteristics (low versus high frequency of migraine), and comorbidity (particularly anxiety and depression) [31].

As far as we know, this is the first study describing better performance regarding visuospatial memory and learning abilities in migraineurs with respect to controls. The latter fits well with the hypothesis of glutamate upregulation in migraine [32, 33]. In particular, results of the present study confirmed previous evidence described in FHM1 and FHM2 knock-in animal models [7–9] and by neurophysiological [12], and neuroimaging reports in migraineurs [34], which demonstrated an excessive glutamatergic neurotransmission in migraineurs, particularly in the visual cortex, supporting the hypothesis of cortical hyperexcitability in migraine [15]. Moreover, although results collected in the present study evaluate only neuropsychological functioning in migraineurs, our

results represent the first preliminary evidence concerning cognitive advantage in migraineurs. Indeed, Wen et al. [35] described better cognitive performance in a sample of middle-aged and elderly subjects with migraine, regarding global measures of cognition (i.e., Mini Mental State Examination test), and in specific domain related to executive functioning and susceptibility to interference (i.e., verbal fluency and Stroop test, respectively). Furthermore, our results highlight also the importance of accurate screening of potential confounding factors (i.e., depressive symptoms, high migraine frequency) able to affect cognition when exploring neuropsychological performance in patients with migraine.

Discrepancies between current data and previous reports describing no changes or lower performance in visuospatial memory in migraineurs compared to controls [20, 21, 25, 36–39] may probably reflect differences in methodological and statistical approaches. First, different sensitivities of instruments used to evaluate visual memory in migraineurs have to be taken into account. Indeed, the supraspan technique has not been previously used in neuropsychological studies evaluating visuospatial memory in migraine. Second, residual confounding, particularly related to comorbid depression, should be taken into account when evaluating cognitive performance in migraineurs. To this purpose, we exclude relevant comorbid depression in our sample. Depression is, in fact, considered a well-known factor affecting cognitive performance in young adults [40]. Third, differences in migraine characteristics (i.e., attack frequency) could account for discrepancies between the present study and previous finding. Indeed, severity of migraine disease has been shown to negatively affect cognition in the study by Calandre et al. [25]. These authors stratified patients according to attack frequency and found that impairment in neuropsychological performance can be related to the presence of repetitive migraine attacks. On the contrary, other authors found that the frequency of attack did not influence cognitive performance [37, 41]. Aiming to explore cognitive performance in a mild phase of disease, we excluded subjects with high frequency of attacks (> 4 attacks per month).

However, some methodological issues deserve mentioning. Caution is needed in extending these findings to the general population because the study sample was recruited in a specialized headache clinic, which might have introduced a selection bias. Although analyses were adjusted for major potential confounders, residual confounding (vascular comorbidity, drug use, etc.) cannot be excluded. Concerning the use of psychotropic drug, however, all patients included in the study were at their first assessment and were untreated. Finally, the small sample included, with a clear prevalence of female sex, may limit generalizability of the present data.

In conclusion, in the present study, better performance concerning visuospatial memory and learning was found in subjects with migraine compared to controls. These

preliminary data give further support to the glutamate hypothesis of migraine. However, further studies conducted in larger cohorts of migraineurs are needed to confirm such specific visuospatial cognitive advantage in migraineurs.

**Author's contributions** Roberta Baschi was involved in the study data collection, performed neuropsychological testing, run statistical analysis, and wrote the first draft of the manuscript. Roberto Monastero supervised statistical analysis and participated in manuscript writing and critical revision. Filippo Brighina designed the study and participated in manuscript writing and critical revision. Giuseppe Cosentino and Giuseppe Giglia participated in the study planning and were involved in the critical revision of the manuscript. Vanessa Costa and Brigida Fierro were involved in the critical revision of the manuscript.

**Compliance with ethical standards** The study was approved by the Ethics Committee of the University of Palermo and informed consent was obtained from all participants included in the study.

**Conflict of interest** The authors declare that they have no conflict of interest.

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