Prospective Evaluation

Subjective Cognitive Symptoms During a Migraine Attack: A Prospective Study of a Clinic-Based Sample

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-16-2015 Revised manuscript received: 06-23-2015 Accepted for publication: 07-02-2015

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Background: A migraine attack aggregates a range of different symptoms, besides pain, that contribute to attack-related disability. Cognitive dysfunction is an unacknowledged part of the migraine attack.

Objective: To provide a profile of the frequency and character of migraine attack-related cognitive symptoms occurring during the headache phase of the attack.

Study Design: Cross-sectional survey.

Setting: Clinical-based sample of episodic migraine patients.

Methods: Sequential patients were screened about the occurrence of cognitive symptoms during migraine attacks using an open-ended question followed by a self-fulfilled symptom checklist.

Results: Of 165 migraine patients (15 men, age average 37.3 ± 10.7 years), 89.7% described cognitive symptoms during the headache phase of the migraine attack. On average 2.5 ± 1.6 symptoms were reported per patient, uninfluenced by demographic or disease-related variables. The most common spontaneous symptoms related to executive functions, such as poor ability to concentrate (37%), difficulty in reasoning (25%), and thinking (23%). The pattern of responses on the symptoms checklist corroborated with those reported spontaneously and quantitative scores of the checklist were higher in patients with spontaneous symptoms.

Limitations: Open-ended questions tend to overestimate frequency; data accuracy may be influenced by the population chosen (clinical-based, some using prophylactic treatment).

Conclusions: This study detailed the frequency and characteristics of migraine attack-related subjective cognitive symptoms and found its frequency to be similar to reports of other migraine defining symptoms (ex. nausea, photophobia) in recent clinical series. Patients' reports were consistent and dominated by complaints of attention difficulties, diminished cognitive efficiency, and processing speed impairment.

Key Words: Migraine, cognitive symptoms, executive dysfunction, disease impact

Pain Physician 2016; 19:E137-E150

The 2010 Global Burden of Disease study rates migraine as the neurological disorder with the highest disability-adjusted life years (DALYs), being the seventh disabler worldwide (1,2). In this study, the estimated disability of one day with a migraine attack was 43.3% (2); loss of effectiveness while at work reported by migraine patients varies amongst studies and countries, most commonly within the range of 40 to 50% (3).

Disability assessments on migraine rely on pa-

tients' self-report of ability to function during an attack. Some instruments also measure interictal burden, including limitations of work responsibilities and career progression, disruption of social and family interactions, and ultimately health-related quality of life and comorbidities related to migraine (4).

Ictal disability is assumed to be due to the pain and its impact and has been measured using pain frequency, duration, and intensity (4-9). During a migraine attack, pain is only a part of a constellation of symptoms, and quite often patients report that their major cause of disability is not the pain itself, but other symptoms such as nausea and vomiting (6,8,10,11), photophobia (10), or cognitive impairment (12).

Cognitive symptoms occurring during migraine attacks have been described since the first century (13); in more recent clinical series of migraine, cognitive symptoms described include not being able to think or concentrate (up to 71% of patients) and being unable to carry out activities such as shopping (up to 83%), work, or taking care of children (60%) as contributing to migraine associated disability (14). However, cognitive dysfunction is far more often characterized in the premonitory (15-20) and postdromal phases (15,16,21,22) of migraine.

In a previous study we conducted structured interviews about the occurrence of cognitive symptoms during migraine attacks, aiming to generate items for the development of an instrument to quantify subjective cognitive symptoms during attacks, the Mig-SCog (12). In the present study, using a similar methodology in a qualitative research study, we aim to detail the character and frequency of migraine attack-related subjective cognitive symptoms occurring in the headache phase of the attack in a clinic-based sample of migraine patients. In addition, we want to determine if any demographic or disease related variable influenced the expression of such symptoms.

Methods

Population

Volunteers were recruited from Headache Outpatient Clinics of 2 general hospitals in Lisbon, Portugal. Inclusion criteria were a) age over 16 years old; b) at least 2 years of education (able to read and write); c) history of episodic migraine with or without typical aura, as defined by the ICDH-III (23); d) written informed consent of adult patients or of their legal guardians, in the case of patients aged 16 and 17. Because our focus was on cognitive symptomatology, we excluded patients with chronic migraine, medication overuse, and comorbid mood disorders, factors potentially able to negatively influence cognition (24,25). Non-typical auras and chronic tension-type headache were also exclusion criteria; episodic tension type-headache was allowed if the patient was able to distinguish between headache types. Previous history of alcohol or drug dependence or abuse or the presence of concomitant medical, neurologic, or psychiatric disorders with influence on cognition were also exclusion criteria, as was pregnancy. The study protocol was approved by each hospital's Institutional Review Board.

Study Design

Recruitment and inclusion were carried out in a regular headache clinic visit along with standard clinical evaluation (detailed medical history, headache history, physical and neurological observation). After informed consent, a standardized data collection was performed that included checking ICDH-III criteria and registering demographic and clinical details, such as gender, age, literacy, disease duration, current attack frequency, duration and intensity, attack and aura characterization, and detailed medical and pharmacological history. Migraine impact was evaluated with the HIT-6 (26).

Data collection started with a closed question: "Do you feel any change of your mental abilities during the headache phase of your migraine attacks?" having a dichotomic (yes/no) answer. If the answer was affirmative, the researcher prompted the open-ended research question "please describe the main changes you usually feel" in order to elicit the spontaneous phrases or expressions that patients use to describe their experiences. Patients with aura were instructed to report only symptoms that occurred in attacks without aura or, if they had exclusively migraine with aura attacks, they were instructed to exclude symptoms that also started during the aura and persisted into the headache. All answers were recorded, irrespective of their content. All patients had then to complete a self-administered symptom checklist of 43 items, including subjective cognitive (executive, spatial perception, and language) and non-cognitive (mood, anxiety, and visual) symptoms (12) which was used to confirm the preceding spontaneous symptom elicitations. Each item/symptom was rated qualitatively (yes/no) and on a 3-point scale: occurring often (2 points), rarely (one point), or not occurring (0 points) during the attacks. A "don't know, don't want to answer" option was also available in or-

der to avoid blank answers; if a blank answer was spotted upon checklist return the patients was prompted to complete it.

Data and Statistical Analyses

Answers to the open-ended question about cognitive symptoms were analyzed, classified, and grouped into domains and functions by 2 authors (RGG, IPM) independently; discrepancies were resolved by consensus. Spontaneous symptoms were classified into non-cognitive and cognitive and then further classified into their specific domain (ex. executive, memory, language, and others) and grouped into different functions within each domain (ex. initiative, processing speed, etc.). The same process was applied to non-cognitive complaints that were classified as mood-related, sensorial or migraine related, and grouped into different symptoms (ex. mood, vision, phonophobia etc.). The number of different spontaneous symptoms was calculated for each domain, as was as the number of patients reporting each symptom, in order to obtain an average frequency of each symptom, in each domain. A frequency table was built including all cognitive and non-cognitive symptoms reported; the average number of symptoms per patient was calculated. Demographic and disease-related variables were compared between patients with and without spontaneous cognitive symptoms with the chi-square test for proportions and Student's t-test for means.

Analysis of the symptom checklist excluded missing answers analysis-by-analysis ("don't know, don't want to answer"). Items were scored qualitatively (having/not having the symptom) and quantitatively (0 to 3) to analyze relative impact of each symptom. Checklist symptoms frequency derived from qualitative item scores. Quantitative items scores were used to calculate scores for each domain and for the total checklist. Linear regression analysis, using the total symptom checklist score as a dependent variable, was performed to study the influence of demographic and disease-related variables.

Statistical analysis was made with SPSS v20.

Results

Population

Total population had of 172 volunteers; 7 were excluded due to medication overuse (n = 5) or chronic tension-type headache (n = 2). The study population consisted of 165 volunteers (15 men), 9 left-handed, with an age average of 37.3 ± 10.7 years (range 16 to 63 years). Average disease duration was 20.5 ± 12.2 years (range 6 months to 57 years), 25 patients had migraine with aura (15.2%) and average HIT-6 score was 61.2 ± 7.3 (range 43 to 76).

Forty-one patients (29.7%) were on migraine prophylactics, most commonly on topiramate (11), propranolol (9), amitriptyline (7), valproic acid (5), and flunarizine (2) or combinations. Attack treatment was based on triptans (33.4%), followed by analgesics (28.6%) and NSAIDs (28.5%), and ergots (9.0%). Twelve (7%) patients were taking low-dose anxiolytics or serotonin-specific reuptake inhibitors, 41 (25%) were taking the combined oral contraceptive pill and 6 (4%) were on hormone replacement therapy.

Spontaneous Cognitive Symptoms

Seventeen patients (10.3%) did not feel any change of their mental abilities during the headache phase of their migraine attacks; the remaining 148 (89.7%) patients reported on average 3.6 ± 2.0 (range 1 to 9) different spontaneous subjective symptoms. These were classified as cognitive in 144 (87.3%) patients, the average number of symptoms reported by patient being 2.5 ± 1.6 (range 1 to 9, median of 2).

The 148 patients reported the occurrence of 86 different symptoms during their headaches, using 604 different expressions to describe their symptoms. Fifty-four (62.7%) symptoms were cognitive (see Table 1).

The most frequent cognitive symptoms described related to executive dysfunction (71.4%), followed by language complains (12.5%). Non-cognitive symptoms were also frequent, mostly migraine related (50.5%) or mood changes (36.7%). Detailed description of spontaneous symptoms is presented in Tables 1 (cognitive) and 2 (non-cognitive).

None of the demographic variables (gender, age, literacy, disease duration, aura, previous diseases or current treatments, headache prophylaxis, attack treatment, attack frequency, intensity or duration, and disease impact, measured by the HIT-6 score) influence the likelihood of reporting cognitive difficulties during migraine attacks.

Symptom Checklist

Most of the items of the symptom checklist had less than 10% missing values ("do not know, don't want to answer"), exceptions were difficulty in drawing (59% missing), in naming famous people (19%), in mental calculus (13%), in writing (11%), and about right/left

Table 1. *Spontaneous symptoms - Descriptive analysis*

	SYMPTOMS			PATIENTS	
	Number of different symptoms	**Number of reports**	**Average reports/ symptom**	**Patients with symptoms†**	**Number of symptoms/ patient‡**
Cognitive	**54**	**416**	**7.7**	**144 (87%)**	**2.5 ± 1.6 (0-9)**
Executive	31	297	9.6	132 (80%)	1.7 ± 1.2 (0-5)
Language	9	52	5.8	42 (25%)	0.3 ± 0.6 (0-3)
Memory	5	22	4.4	18 (11%)	0.1 ± 0.4 (0-2)
Spatial perception	2	2	1	2 (1%)	0.01 ± 0.1 (0-1)
Multi-domain	7	43	6.1	39 (24%)	0.3 ± 0.5 (0-2)
Non-Cognitive	**32**	**188**	**5.9**	**97 (59%)**	**1.1 ± 1.2 (0-5)**
Mood	9	69	7.7	54 (33%)	0.4 ± 0.7 (0-3)
Sensorial	5	24	4.8	22 (13%)	0.1 ± 0.4 (0-2)
Migraine	18	95	5.3	60 (36%)	0.6 ± 0.9 (0-3)

† Number of patients reporting symptoms, N and percentage of the total (%)
‡Average of symptoms reported per patient ± standard deviation and (range)

Table 2. *Cognitive difficulties spontaneously reported during the headache phase of migraine attacks.*

Symptom Description	**N**	**%**
EXECUTIVE FUNCTION		
Low inhibitory control	7	1.7%
Lower tolerance / intolerant / grumpy	5	
Can't stand the pain / unable to stop thinking about the pain	2	
Avoidance	11	2.6%
I want to be alone/ must be alone/ I want to isolate myself/ have to be in isolation	8	
Difficulty in interaction with others / difficulty in social interaction / lower social abilities (friendliness and empathy)	3	
Difficulty in maintaining attention	72	17.2%
Difficulty or lack of attention / disperse / unable to focus or concentrate/ lower ability to concentrate/ worse concentration/ higher effort to achieve a minimum concentration level	61	
Less attention/ distracted/ difficulty in paying attention/ difficulty in maintaining attention	8	
Lose the notion of things / I feel the need to abstract from reality or not pay attention / I get abstracted / I feel lost in my thoughts	3	
Cognitive Processing Efficiency/ Reasoning	99	23.8%
Difficulty in reasoning / higher effort to reason / lower reasoning/ unable to reason / ineffective reasoning	41	
Difficulty in thinking /I can't think/ lower ability to think/ thinking is effortful / I don't feel like thinking/ I'm not able to think straight / I have a hard time thinking /thinking is bothersome/ I can't think a long period of time/ I'm not able to think the same way as usual	38	
Difficulty in making mental or intellectual effort/ intellectual laziness / mental fatigue/ I do not feel like thinking	4	
I'm not able to have complex thoughts/ lower performance/lower work efficiency/ fear of failing more complex reasoning / less efficient flow of ideas / lower ability to process information	6	
I get witless or rattle-brained / lower brain reflexes / rattle-headed/ brain blocked/ confused / incapable	10	
Stamina	27	6.5%
Tiredness/ more tired / exhausted	8	
Less strength in all my body/ difficulty in standing up / less strength	3	
Feel washed-out / I feel sluggish / without action / without energy / asthenia / globally indisposed	8	
Lose all my abilities/ just exist / do not react, like a vegetable / get diminished / it feels like being anesthetized/ less reaction / I seem to be sedated/ get alienated of what is around me	8	

Table 2 (cont.). *Cognitive difficulties spontaneously reported during the headache phase of migraine attacks.*

Symptom Description	**N**	**%**
Initiative	10	2.4%
I don't feel like doing anything / unwilling / reluctant to do anything	3	
Without initiative/ less predisposed to do things / lower motivation	3	
Everything is done with effort /I have a hard time doing anything	4	
Motor initiative and speed	8	1.9%
Physical movement is difficult/ I cannot move/ unwilling to move	4	
I walk slower and my movements are slower / moving is harder, slower and my body feels heavier/ slower movements, even when walking/ physically slower	4	
Processing Speed	38	9.1%
Slower thoughts/ need to think longer / slower reasoning / sluggish thinking	11	
I feel slower or slowed/ slowness/ slowing/ lower speed/ idle/ slower reactions/ slower on chores	27	
Planning	8	1.9%
I have to write down everything I'll need to do/ have to plan with notes	2	
Unable to organize daily chores/ I have a hard time organizing/ not able to program anything/ difficulty in planning ahead	6	
Decision Making	9	2.2%
Difficulty in decision taking/ difficulty in settling things/ less able to make a decision	4	
Difficulty in getting things done / cannot execute things / not able to perform any chore / lower ability to act	5	
Cognitive Flexibility	4	1.0%
Difficulty in multitasking/ less able to pay attention to several simultaneous simple stimuli	2	
Difficulty in solving practical problems/ difficulty in responding to stimuli or requests	2	
Monitoring	1	0.2%
Fear of making errors at work	1	
Calculus	3	0.7%
Difficulty in calculation or simple math's/ difficulty in sums, measurements, calculus	3	
TOTAL EXECUTIVE	297	71.4%
MEMORY		
Learning	7	1.7%
Difficulty in memorizing/ difficulty in learning new information / difficulty in retaining information in a short period of time	3	
I need more time to learn new things	1	
Studying is difficult / the study is less productive	3	
Retrieval	15	3.6%
Memory lapses/ I forget thinks/ forgetful/ I fail to remember	9	
My memory gets affected/ I get problems with my memory/ lack of memory/ damaged memory	6	
TOTAL MEMORY	22	5.3%
LANGUAGE		
Naming	2	0.5%
Difficulty in speaking out people's names	1	
I'm not able to remember simples objects names	1	
Speech Fluency	27	6.5%
Difficulty in keeping a simple conversation/ difficult to chat/ cannot organize the sentences to speak properly/ I have a hard time programming what I want to say/ I'm not able to communicate/ I find it hard to explain what I mean, while talking	8	
Difficulty talking/ not able to talk/ my speech gets stunted/ I have a hard time talking/ I feel the need to abbreviate all conversations	18	
Difficulty in articulating the speech	1	

Table 2 (cont.). *Cognitive difficulties spontaneously reported during the headache phase of migraine attacks.*

Symptom Description	N	%
Comprehension	7	1.7%
Difficulty in understanding when being spoke to / It's hard to understand verbal information	5	
Unable to pay attention to what's being asked / I'm not able to talk back when being spoke to	2	
Reading and Writing	16	3.8%
I cannot write, I forget how to write properly / I find it difficult to write/ writing takes longer than usual / I misspell more often when writing	5	
Difficulty in reading/ difficulty in understanding what's written	11	
TOTAL LANGUAGE	52	12.5%
OTHERS		
Spatial perception/ Topographic disorientation	2	0.5%
Pay less attention to normal paths or routes	1	
Difficult to calculate distances	1	
Difficulty in complex tasks (Multiple domains)	43	10.3%
I'm not able to do anything/ completely disabled/ I get disabled/ I find it hard to do anything	9	
I avoid to do any chore/ I avoid chores that have higher reasoning demands	2	
Difficulty in household chores/ difficulty in everyday chores and routine activities/ I'm not able to do household chores	8	
I can't work/ I'm not able to work properly	4	
Difficulty in cooking	2	
Difficulty in driving/ unable to drive	16	
I do everything wrong/ I no longer know how to do anything	2	
TOTAL OTHERS	45	10.8%

N – Number of patients reporting each symptom
% – Percentage of each symptom in relation to total number of cognitive symptoms reported (sum of N, 416)

orientation (10%). All the items of the symptom checklist had at least one positive answer. Positive answers were extremely frequent (> 90%) in only 3 items: attention (…do you have trouble concentrating?, 93%), stamina (… do you feel tired?, 91%), and anxiety (…do you feel irritable?, 90%). Answers were very frequent (> 80%) in items of motor initiative and processing speed (88%); attention, cognitive flexibility, cognitive processing efficiency, and motor processing speed (85%); non-cognitive very frequent answers included anxiety (84%) and visual symptoms (82%). Complete description of the symptom checklist answers are in Appendix 1

None of the demographic variables (gender, age, literacy, disease duration, aura, previous diseases or current treatments, headache prophylaxis, attack treatment, attack frequency, intensity or duration, and disease impact using HIT-6) had influence on the total score of the symptoms checklist that was used as the dependent variable in a linear regression analysis.

The most frequent cognitive symptoms identified in the symptoms checklist were executive, followed by language and spatial perception, having a distribution per domain that was comparable to that of the spontaneous symptoms (Table 3). Non-cognitive symptoms, classified in mood-related or sensorial, showed identical frequency when classified by the symptom checklist, but mood-related complaints were proportionally more frequent than sensorial symptoms when answering to the open-ended research question (Table 4).

Quantitative scores on the symptoms checklist were higher in patients spontaneously reporting symptoms in the open-ended question (Table 5).

Discussion

In this study we screened for the frequency of subjective cognitive symptoms occurring during the headache phase of migraine attacks. Cognitive complaints were found to be very common in this setting; we were able to provide an extensive description of symptoms using patients' phraseologies in order to help clinicians recognize their usual pattern. The consistency of our findings supports patients' spontane-

Table 3. *Other differences (non-cognitive) of mental capacities spontaneously reported during the headache phase of migraine attacks.*

SYMPTOM DESCRIPTION	N	%
MOOD CHANGES		
Depressed Mood	7	3.7%
Lowering of mood / changes in mood / sadness / tearfulness / will cry	6	
Emotional fragility	1	
Lower interest	31	16.5%
Can't find patience to do anything / less patience /lack of patience / impatience	30	
Everything is bothersome	1	
Anxiety	28	14.9%
Irritable/ irritability	21	
Anxious/ panic/ despair/ nervous / very nervous	5	
Out of control/ upset	2	
Nervous tension	3	1.6%
Uptight/ tense	2	
Need to relax	1	
TOTAL MOOD	**69**	**36.7%**
SENSORIAL CHANGES		
Balance	5	2.7%
Disturbed by traveling	1	
Stunned / dizzy	2	
Unbalanced and dizziness / I lose my balance while walking	2	
Visual disturbances	17	9.0%
Vision impairment / foggy vision /lack of sight /different or difficult vision/ I'm unable to see properly / difficulty in seeing / out-of-focus vision/ difficulty in far seeing	17	
Sensitive disturbances	2	1.1%
Slight hand numbness/ numb hand	2	
TOTAL SENSORIAL CHANGES	**24**	**12.8%**
MIGRAINE RELATED		
Photophobia	34	18.1%
I need to get my eyes closed / difficulty in keeping the eyes open/I'm not able to open my eyes/ I cannot look at anything	8	
Difficulty in watching television/ difficulty in staring at a computer screen/ difficulty in making visual effort / I'm bothered by visual effort	11	
I need to be in the dark / I cannot stand the light/ light worsens the pain/ I get photosensitive	15	
Phonophobia	27	14.4%
I need to be in a quiet room/ it's hard for me to hear any noise/ noise disrupts my concentration	10	
I lack the patience to listen to anything/ I can't hear anything or anybody/ lower tolerance to noise/ I'm bothered by noises/ the sound of my own speech is distressful	11	
Difficulty listening/ cannot listen/ I have a hard time listening to what people say/ the sounds seem far away	6	
Kinesiophobia	19	10.1%
Difficulty walking/ I have a hard time walking	5	
My wish is to be still / I need to stay still	2	
I feel like lying down/ I have an urge to lie down/ I need to rest still/ I cannot wait to go to bed	7	
Difficulty in climbing stairs/ physical effort is difficult/ I'm not able to make any effort/ cannot pick up any weight	4	
Difficulty in turning my head	1	
Osmophobia	2	1.1%
Can't stand any smell or odor	2	

Table 3. *Other differences (non-cognitive) of mental capacities spontaneously reported during the headache phase of migraine attacks.*

SYMPTOM DESCRIPTION	N	%
Gastrointestinal upset	3	1.6%
I get nauseated / bothersome nausea	2	
I can't eat/ I get stuffed without eating	1	
Sleep disturbances	7	3.7%
Not able to sleep	2	
Sleepiness / too sleepy	5	
Others	3	1.6%
I get haggard / I get pale with dark circles around the eyes	2	
I need to squeeze my head	1	
TOTAL MIGRAINE RELATED	**95**	**50.5%**

N – Number of patients reporting each symptom
% – Percentage of each symptom in relation to total number of non-cognitive symptoms reported (sum of N, 188)

Table 4. *Spontaneous and symptom checklist symptoms per domain.*

	Spontaneous Symptoms frequency	Symptom checklist frequency		Number of spontaneous symptoms/ patient	Symptom checklist score
Total	**148 (90%)**	**165 (100%)**		**3.6 ± 2.0**	**35.9 ± 15.6**
Cognitive	144 (87%)	83 (50%)		2.5 ± 1.6	30.4 ± 13.6
Executive	132 (80%)	119 (72%)		1.7 ± 1.2	20.2 ± 7.7
Language	42 (25%)	82 (50%)		0.3 ± 0.6	8.8 ± 6.0
Spatial percep.	2 (1%)	47 (28%)		0.01 ± 0.1	1.5 ± 1.5
Non-Cognitive	97 (59%)	112 (68%)		1.1 ± 1.2	7.1 ± 3.0
Mood	54 (33%)	112 (68%)		0.4 ± 0.7	5.0 ± 2.3
Sensorial	22 (13%)	111 (68%)		0.1 ± 0.4	2.1 ± 1.3

Table 5. *Symptom checklist scores in patients with and without spontaneous symptoms.*

SYMPTOM CHECKLIST	Spontaneous Symptoms (all)		*P*	Spontaneous Symptoms (cognitive)		*P*
	No	Yes		No	Yes	
	17	148	--	21	144	--
Total	22.7 ± 15.0	39.2 ± 14.8	< 0.0001	24.1 ± 14.3	39.5 ± 14.8	< 0.0001
Cognitive	18.0 ± 12.8	31.9 ± 13.1	< 0.0001	19.0 ± 12.4	32.1 ± 13.1	< 0.0001
Executive	12.4 ± 7.4	21.1 ± 7.2	< 0.0001	13.0 ± 7.1	21.2 ± 7.2	< 0.0001
Language	4.7 ± 4.6	9.2 ± 6.0	0.001	4.8 ± 4.7	9.3 ± 6.0	0.001
Spatial percep.	0.9 ± 1.3	1.5 ± 1.5	0.119	1.1 ± 1.2	1.5 ± 1.6	0.206
Non-Cognitive	4.6 ± 3.3	7.3 ± 2.9	< 0.0001	5.1 ± 3.4	7.3 ± 2.9	0.002
Mood	3.5 ± 2.2	5.2 ± 2.2	0.004	3.8 ± 2.3	5.2 ± 2.2	0.011
Sensorial	1.2 ± 1.2	2.2 ± 1.2	0.002	1.3 ± 1.3	2.2 ± 1.2	0.004

ous claims of cognitive impairment during attacks. These symptoms probably contribute to the self-perceived decrease of 64% in work efficiency during attacks (9) and to migraine related disability and burden; their identification allows improvement in the perception of patients' impairment and the adequacy of treatment strategies.

The majority (87.3%) of episodic migraine patients report cognitive symptoms during attacks, a percentage comparable to reports of nausea (52 – 86%), photophobia (55 – 80%), phonophobia (47 to 100%), and pain aggravation by physical effort (53 – 70%) in large clinical series of migraine (27-30), supporting that cognitive symptoms are an intrinsic part of the attack (12). Analysis of prodromal and postdromal cognitive symptoms' incidence is around 20 and 30%, respectively, comparable to reports of photophobia (21 and 18%), phonophobia (21 and 15%), and nausea (23 and 11%) in the same attack phases (15,16,18,19,22,31).

Non-cognitive symptoms included in the answers to our study question were either attack-related (such as photophobia, phonophobia, gastrointestinal upset, etc.), accompanying mood changes (anxiety, depressed mood, etc.), or sensorial complaints (balance, visual and sensitive disturbances), all described in clinical series of migraine patients (29,32,33). These were unanticipated answers, as often occurs with open-ended questions. To our purpose of surveying the maximum variety of spontaneous cognitive symptoms without influencing or leading the answers, an open-ended question was more likely to provide in-depth information, while assuming the risk of over-interpretation of the term "mental abilities." The fact that all non-cognitive symptoms reported were migraine-related can be valued as a concurrent validity measure, implying that patients' answers were strictly referring to phenomena occurring during migraine attacks.

On average, 2.5 cognitive symptoms were reported spontaneously by each patient, which can be explained either by the high frequency of different symptoms but most likely by the difficulty in describing the symptomatology; 92% of patients reported one to 4 symptoms. Cognitive difficulties are often vague and difficult to define either because its experience may not be universal or it may be influenced by performance of complex tasks involving several cognitive domains. To support this view, 24% of patients reported difficulties in complex tasks, such as cooking, driving, or everyday tasks, being unable to define what the specific difficulties of task execution were.

We were unable to find a relation between the presence of cognitive symptoms during attacks and any of the demographic or migraine-related variables, nor to migraine impact.

Variables that were expected to influence the report of subjective cognitive complaints include psychological disturbances (depression, chronic stress/exhaustion, and sleeping problems [34]), the female gender (especially during pregnancy [35] or menopause [36]), medication (including migraine prophylactics, antidepressants, and hormones) (37-39), and age (40).

Our study design limited the influence of some of these variables, as we excluded co-morbid mood disorders and pregnancy. We were unable to find any effect of age in the frequency of spontaneous symptoms or in the score of the symptoms checklist, probably reflecting the young age average of our population, typical of migraine patients. Our sample had a low percentage of patients on prophylactic treatment (under one third), 42% of which were using topiramate, a drug that influences cognitive functioning (37). We were unable to find a relationship between topiramate use and the number of spontaneous cognitive symptoms nor to the score of the symptoms checklist. Around 7% of our patients were taking low-dose anxiolytics or serotonin-specific reuptake inhibitors and 4% were post-menopausal women on hormone replacement therapy; however, our data did not allow us to determine any effect of these variables.

The lack of association of cognitive symptoms to migraine disease duration or impact suggests that cognitive dysfunction in episodic migraine is mainly an attack-related phenomena and perception of cognitive decline is not a consequence of migraine, by itself (41). This assumption requires confirmation in further studies powered to answer this question.

There were 3 symptoms very consistently described by patients using a very similar phraseology, the first being a lower ability to concentrate (14.7% of symptoms, reported by 37% of patients), followed by difficulty in reasoning (9.8% of symptoms, 25% patients), and being "less able" to think (9.1% of symptoms, 23% patients), reflecting attention and cognitive processing efficiency problems. Symptoms that could be attributed to executive domains comprised about 2/3 of spontaneous complaints, probably relating to their relevance in daily functioning compared to other domains (e.g., impaired drawing ability). The symptom checklist also screened infrequent cognitive activities; difficulties in determining some symptoms' occurrence were re-

flected in high percentages of missing answers of some items – 59% of patients were unable to say if they had drawing difficulties, 19% did not know if it was hard to recognize famous personalities, and 13% if their mental calculus was appropriate, during attacks. Average scores on the symptom checklist were lower in patients without spontaneous symptoms. The differences between spontaneous or cued reporting can be due to lower impact of these symptoms or to differences in metacognition abilities of some individuals.

The pattern of spontaneous cognitive symptoms identified is consistent with previous descriptions of difficulties during attacks (13,14,42), with descriptions of prodromal and postdromal symptoms (15,16,18,19,22,31) and to objective impairment, as identified by neuropsychological testing during attacks (43,44) most consistently in domains of attention, processing speed, working memory, and learning. Language-related symptoms were also frequent, while memory complaints were not as usual.

It remains speculative why this specific pattern emerges during attacks, and even putting aside the discussion, if these subjective symptoms relate to clinically relevant brain dysfunction, their consistency supports that these brain functions are modified during migraine attacks. Attention, processing speed, and working memory have some common characteristics, namely (1) being basic executive functions, related to pre-frontal activity; (2) representing brain processes that subserve other higher-order cognitive domains; and (3) depend on subcortical circuitry.

Attention may be viewed as brain network function involving 3 subsystems – alertness or arousal (thalamic function), orienting or selection (parietal function), and executive or conflict resolution (anterior cingulated function) that might interact or function independently (45). Processing speed is influenced by subcortical white matter (46) and/or cortical structures (47). Working memory is a prefrontal cortex function that involves different areas according to the specific task required; recent evidence suggests that dorsal prefrontal cortex plays a more prominent role in encoding information while retrieval may be mediated either by the ventral or the dorsal prefrontal cortex (48).

The participation of cortical brain areas in migraine attacks has been documented in the insula, temporal lobe (49), and cingulated and pre-frontal cortex (50). Subcortical structures, such as the raphe nuclei with its cortical serotoninergic projections (ex. orbitofrontal cortex, precentral gyrus, temporal pole, insula, and somatosensory area) (51) and the thalamus, are also activated during attacks in humans (50) and may represent the anatomical substrate explaining this symptomatology. Improving the knowledge about cognitive dysfunction during migraine attacks can provide clues to the brain processes occurring within the attack and help in determining the sequence of brain events resulting in the episodic dysfunction of migraine patients.

We acknowledge that the frequency of cognitive symptoms occurrence is probably overestimated in our study, as the research question was open-ended and interview based, which may incite the patient to respond affirmatively. We could have chosen to use a standard research method in issue exploration, such as the modified Delphi technique, that would have had the advantage of improving the consensus over which symptoms would be relevant in this context and increase the accuracy of the results. However, it has several potential disadvantages such as higher work load, the potential of low response rates and for molding opinions by investigators, and the risk of reducing variability (52). Our priority was to be as inclusive as possible, to identify the maximum variety of spontaneous cognitive symptoms without influencing or leading the answers and we wished to provide clinicians the expressions most often used by patients.

We chose a clinic-based population with episodic migraine, excluding severe co-morbid mood disorders, chronic migraine, and medication overuse because we wanted to focus on the attack and avoid potential confounding factors on cognition (24,25). As a consequence, our results cannot be extrapolated for the general population, but are probably useful in neurology and headache clinics. Medication use is an important potential confounder not controlled for and acknowledged as a limitation of this study.

Conclusion

We conclude that reversible subjective cognitive symptoms are consistently described in the headache phase of the migraine attack. The pattern most often reported (either by its frequency or by its relevance on functional ability) is of attention, cognitive efficiency, and speed impairment, probably relating to pre-frontal or, most likely, subcortical brain networking dysfunction. Migraine attacks are the hallmark of migraine as a disease; further knowledge about brain function during these events may help to identify new therapeutic targets or developing therapeutic agents in which

efficiency would not be restricted to the control of pain, but also to attack-related reversible cognitive symptoms.

Conflicts of Interest & Funding

The authors have no conflicts of interest regarding this study. This study was not funded.

Appendix – Scores of the symptom checklist, per item

During your headache...

		Yes	M	% (%)	Av ± SD
EXECUTIVE FUNCTION	Attention	132		80%	
	…do you have trouble concentrating?	154	0	93%	1.5 ± 0.6
	…do you find it difficult to follow or maintain attention when being spoken to?	140	0	85%	1.2 ± 0.7
	…are you easily distracted?	103	7	62 (65)%	1.0 ± 0.8
	Stamina	150		91%	
	…do you feel tired?	150	1	91 (91)%	1.5 ± 0.6
	Initiative	94		57%	
	…do you have trouble starting an activity ?	128	8	78 (81)%	1.2 ± 0.7
	…do you have trouble in taking initiative?	118	6	72 (74)%	1.0 ± 0.7
	…do you forget to take your pain-killers?	36	3	22 (22)%	0.3 ± 0.6
	Motor initiative and speed	146		88%	
	… do you have trouble performing tasks at your normal speed?	146	1	88 (89)%	1.4 ± 0.7
	Planning	112		68%	
	… do you have trouble in remembering about things you need to do (ex E.g. paying bills, making phone calls etc.)?	105	6	64 (66)%	1.0 ± 0.8
	… do you find it hard to plan your routine chores (ex E.g. cooking, shopping etc.) and compromises?	120	11	73 (78)%	1.1 ± 0.7
	Cognitive Flexibility	118		72%	
	… are you able to deal with several stimuli at the same time (ex to be able to drive)?	141	5	85 (88)%	1.0 ± 0.8
	… do you find it difficult to change your activity?	95	12	58 (62)%	0.8 ± 0.8
	Monitoring	53		32%	
	… do you lose the correct notion of time?	53	7	32 (34)%	0.4 ± 0.6
	Cognitive processing efficiency / Reasoning	124		75%	
	… do you have trouble thinking?	125	1	76 (76)%	1.1 ± 0.8
	… do you have trouble maintaining the tread of your thoughts?	141	2	85 (86)%	1.3 ± 0.7
	...do you feel confused?	107	2	65 (66)%	0.8 ± 0.7
	Processing speed	143		87%	
	… do you find it difficult to think at your normal speed?	146	1	88 (89)%	1.4 ± 0.7
	… do you find it difficult to react at your normal speed?	140	5	85 (88)%	1.4 ± 0.7
	Calculus	118		72%	
	… do you find it difficult to do mental calculation?	118	21	72 (82)%	1.2 ± 0.7

LANGUAGE	Naming	57		35%	
	… do you have trouble speaking out other people's names?	78	1	47 (48)%	0.6 ± 0.8
	… do you have trouble in remembering objects names?	65	2	39 (40)%	0.5 ± 0.7
	… do you have trouble in memorizing people's names?	68	9	41 (44)%	0.6 ± 0.8
	… do you have trouble recognizing famous people?	16	32	10 (12)%	0.2 ± 0.4
	Comprehension	87		53%	
	… do you have trouble in understanding when being spoke to?	87	2	53 (53)%	0.8 ± 0.8
	Speech Fluency	83		50%	
	… do you have trouble in organizing your ideas in order to speak correctly?	97	5	59 (61)%	0.8 ± 0.8
	… do you speak with a lot of interruptions or brakes?	108	4	65 (67)%	1.0 ± 0.8
	… do you switch the words you want to speak by others?	71	7	43 (45)%	0.6 ± 0.7
	… do you switch the sounds or syllables within words ?	50	10	30 (32)%	0.4 ± 0.7
	… is your voice slurred when speaking?	71	9	43 (46)%	0.6 ± 0.8
	… do you have difficulty in organizing a sentence or a conversation?	99	1	60 (60)%	0.9 ± 0.8
	Reading and Writing	102		62%	
	… do you have trouble writing?	82	18	50 (56)%	0.8 ± 0.8
	… do you find it difficult to read?	121	11	73 (79)%	1.3 ± 0.8

OTHER	Spatial Perception	47		28%	
	… do you fell disoriented in a familiar place?	48	1	29 (29)%	0.4 ± 0.6
	… do you find it difficult to draw?	29	98	18 (43)%	0.6 ± 0.7
	… do you confuse left with right?	26	16	16 (17)%	0.2 ± 0.6
	… do you have trouble following a route (by driving or walking)?	85	3	52 (52)%	0.7 ± 0.7

NON-COGNTIVE	Mood Changes	82		50%	
	… do you feel like crying?	104	2	63 (64)%	1.0 ± 0.8
	… do you feel sad?	130	4	79 (81)%	1.2 ± 0.8
	… do you feel euphoric or pleased?	11	9	7 (7)%	0.1 ± 0.3
	Anxiety	143		87%	
	… do you feel irritable?	148	0	90%	1.4 ± 0.7
	… do you feel nervous or anxious ?	138	2	84 (85)%	1.3 ± 0.7
	Visual Symptoms	111		67%	
	… do you have staring?	136	3	82 (84)%	1.4 ± 0.8
	… does your vision feels foggy?	87	1	53 (53)%	0.7 ± 0.8

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