EFFECTS OF EMOTIONAL CONTENT ON DECLARATIVE MEMORY: TWO STUDIES CONDUCTED ON HEALTHY SUBJECTS AND CEPHALALGIC PATIENTS

EFECTOS DEL CONTENIDO EMOCIONAL SOBRE LA MEMORIA DECLARATIVA: DOS ESTUDIOS EFECTUADOS EN SUJETOS SANOS Y PACIENTES CEFALÁLGICOS.

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Abstract

Several studies suggest that emotional arousal can promote memory storage. We report two studies evaluating the effects of emotional content on declarative memory, conducted with healthy subjects and cephalgic patients. We utilized an adaptation of two versions of the same story, with different arousing properties (neutral or emotional), which have been already employed in experiments involving the enhancing effects of emotions on memory retention. In the first study, conducted on healthy students, we used event related potentials (ERP) to evaluate whether there is a sex-related hemispheric lateralization of electrical potentials elicited by the emotional content of a story. We compared left and right hemisphere P300 waves, recorded in P3 and P4 electrode sites, in response to emotional or neutral stimuli in men and women. In the left hemisphere, emotional stimuli elicited a stronger P300 in women, compared to men, as indexed by both amplitude and latency measures; moreover, the emotional content of the story elicited a stronger P300 in the right hemisphere in men than in women. The better memory for the arousal material may be related to the differential P300 at encoding. These data indicate that both sex and cerebral hemisphere constitute important, interacting influences on neural correlates of emotion, and of emotionally influenced memory.

In the second study we evaluated the influence of the same emotional stimuli, utilized in the first study, on declarative memory on cephalalgic patients, suffering from migraine headache, divided in 2 groups: migraineurs without any treatment and migraineurs treated with the antidepressant amitriptyline. No ERP analysis was performed in this part of research. The findings of the present experiments suggest that chronic migraine is associated with memory impairment. Taking into account that migraine is associated with major depression, in the present research the effect of the antidepressant amitriptyline was also evaluated. Our results showed that amitriptyline has an impairment effect on memory. In fact, in our study the untreated migraineurs recalled the most emotional phase of the arousal story significantly better compared to migraineurs treated with amitriptyline. Then, our data suggest that amitriptyline prevents the enhancing effects of emotional content on memory processes.

Key words: emotional memory, event related potentials, P300 wave, migraine, amitriptyline.

Resumen

Varios estudios sugieren que el despertar emocional puede promover el almacenamiento de información en la memoria. Nosotros reportamos dos estudios evaluando los efectos del contenido emocional sobre la memoria declarativa, efectuados con sujetos sanos y pacientes cefalálgicos. Utilizamos una adaptación de dos versiones del mismo relato, con diferentes propiedades (neutral o emocional), la cual ha sido previamente empleada en experimentos que abordan los efectos de mejoría sobre la retención de la

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memoria causados por las emociones. En el primer estudio, efectuado en estudiantes sanos, empleamos potenciales relacionados a eventos (PRE) para evaluar si existe una lateralización hemisférica relacionada al sexo, de los potenciales eléctricos producidos por el contenido emocional de un relato. Comparamos las ondas P300 de los hemisferios izquierdo y derecho, registrados en los sitios correspondientes a los electrodos P3 y P4, en respuesta a estímulos neutrales o emocionales en hombres y mujeres. Los estímulos emocionales produjeron un P300 mayor, medido tanto por la amplitud como por la latencia del potencial, en el hemisferio izquierdo de mujeres comparado con el de los hombres, sin embargo, produjeron un P300 mayor en el hemisferio derecho en los hombres comparado con el de las mujeres. La mejoría en la memoria, originada por el contenido emocional de la información, puede estar relacionada con el diferencial del componente P300 durante la codificación. Estos datos indican que tanto el sexo como la lateralización hemisférica constituyen importantes factores que interactúan para influenciar tanto a los correlatos neurales de las emociones como a la memoria influenciada emocionalmente.

En el segundo estudio evaluamos la influencia del mismo estímulo emocional, utilizado en el primer estudio, sobre la memoria declarativa de pacientes cefalálgicos, que padecen migraña, divididos en dos grupos: migrañosos sin ningún tratamiento y migrañosos tratados con el antidepresivo amitriptilina. No se efectúo análisis de los PRE en esta parte de la investigación. Los hallazgos del presente experimento sugieren que la migraña crónica es asociada con deterioros en la memoria. Considerando que la migraña se asocia con depresión mayor, la presente investigación evaluó también el efecto del antidepresivo amitriptilina. Nuestros resultados mostraron que la amitriptilina tiene un efecto dañino sobre la memoria. De hecho, en nuestro estudio los migrañosos sin tratamiento recordaron la parte más emotiva del relato, de manera significativamente mejor comparados con los migrañosos tratados con amitriptilina. Por lo tanto, nuestros datos sugieren que la amitriptilina bloquea los efectos de mejoría sobre el procesamiento de la memoria causados por el contenido emocional de la información.

Palabras clave: Memoria emocional, potenciales relacionados a eventos, componente P300, migraña, amitriptilina.

GENERAL INTRODUCTION

It has long been known that emotional events are more likely to be later recollected than non emotional events. In the last decade, the field of cognitive neuroscience of emotion has grown dramatically. Most studies have focused on emotional processing (perception and evaluation of emotional stimuli) and on emotional memory (the effects of emotion on memory formation). A critical distinction in this literature is the one between two affective dimensions: emotional *arousal* and emotional *valence.* Arousal refers to a continuum that varies from calm to excitement, whereas valence refers to a continuum that varies from pleasant to unpleasant, with neutral as an intermediate value.

An extreme example of this enhancement of memory by emotion is the so-called flashbulb memory: a highly vivid memory far an intensely emotionally engaging event, such as hearing the news of the death of a relative or cherished celebrity. From an evolutionary perspective, emotional arousal, whether of an appetitive or aversive nature, signals an event or stimulus that is likely to have both immediate and future relevance to survival and reproductive success. Accordingly, it is adaptive to enhance memory for stimuli that elicit emotional arousal, thus ensuring that important information is available on future occasions.

In recent years, brain mechanisms subserving emotion, and the influence of emotion on memory have received increasing attention. For example, strongly converging evidence from studies conducted on animals and human subjects implicates endogenous stress hormones and the amygdala as key, interacting components of a neural mechanism by which emotional arousal influences memory storage (1, 2, 3).

The aim of this research was to evaluate the effects of emotional content on declarative memory; in particular we evaluated whether retention is enhanced by an emotionally arousing story as compared to a neutral one. We utilized an adaptation to an Italian sample of two stories with different arousing properties (neutral and emotional), both presented with the same set of slides, explained through a narrative. These stories have been already employed in experiments with brain damaged and healthy adult subjects, involving the enhancing effects of emotions on memory retention (2, 4, 5, 6, 7). The use of the same set of slides for both versions represented a useful instrument in demonstrating the emotional effect on long-term declarative memory in studies with Urbach-Wiethe patients, suffering from a degenerative disease involving the amygdala (8), in research on amnesic patients (6, 7, 9, 10), and in studies on noradrenergic arousing effects on memory (11). The emotional and neutral versions of the story were as similar as possible in complexity and comprehensibility (2, 5, 6) in order to offer a better control for the evaluation of the principal effect (i.e. the emotional content). This also avoided that memory differences between the neutral and emotional groups could result from “story effects” (12), such as novelty or inherent memorability of the stimuli used, rather than “emotional effects”. The setting and “actors”

were taken from an Italian sample and the text was adapted to the local culture.

The study was divided in 2 parts. In the first part, conducted on healthy subjects (students), we used ERP to evaluate if there is a sex-related hemispheric lateralization of electrical potentials elicited by the emotional content of a story. In the second part of our research we evaluated the influence of emotional stimuli on declarative memory on cephalalgic patients, divided in 2 groups: migraineurs without any treatment and migraineurs treated with the antidepressant amitriptyline.

Event related potentials are ideally suited to study of cerebral processes requiring high temporal resolution as it is for investigation of emotional information processing (Lucchese and Mecacci, 1999).

STUDY 1

Sex-related lateralized effect of emotional content on declarative memory on healthy subjects: an event related potential study.Several studies show that emotions can be considered response dimensions defining affective states along two orthogonal axes of arousal and valence (Osgood et al., 1957; Russel, 1980; Watson & Tellegen, 1985). Arousal refers to the intensity of an emotion, related to the property of the stimuli (from neutral to exciting) whereas valence indicates the degree to which that emotion is pleasant or unpleasant (Lang et al, 1990; 1992; 1993).

INTRODUCTION

Recent evidence from research conducted on animals and humans began to reveal seemingly large, but previously unsuspected, sex-related influences on brain mechanisms subserving the relation between emotion and memory (2, 13). For example, the role of amygdala in memory for emotional material exhibits a different hemispheric lateralization depending on the sex of the subjects tested: activity of the right, but not left, hemisphere amygdala relates significantly to memory for emotional material in men; conversely, activity of the left, but not right, hemisphere amygdala relates significantly to memory for emotional material in women (14, 15, 16). Taking into account that each amygdala likely modulates information processing in other brain regions (17, 18), and amygdalo-cortical projections are almost exclusively ipsilateral, we hypothesized the possibility that a sex-related hemispheric lateralization of processing for emotional material may also exist to some degree in cortical regions.

Event related potentials (ERP) are ideally suited in many ways to study cortical processing, affording very high temporal resolution, including in the domain of emotional information processing.

In general, human response to emotional stimuli is stronger for emotionally arousing (pleasant and unpleasant) stimuli as compared to neutral. In skin conductance studies, changes were significantly larger for emotionally arousing pictures compared to neutral pictures (19). ERPs can be used to differentiate affective dimensions of emotional qualities of visual stimuli (20).

ERPs to emotional stimuli often generate the P300 component, which is robust around 300ms post-stimulus (21). The P300 event-related brain potential is thought to reflect neuroelectric activity related to cognitive processes, such as attention allocation and activation of immediate memory. Greater magnitude of the P300 as well as a strong positive waveform characterizes this waveform to emotionally salient stimuli (22). Indeed, pleasant and unpleasant pictures elicit larger P300 components than neutral stimuli (23). We focused on the P300 wave since it has been revealed sensitive to effects of emotional arousal (24). More specifically, on the basis of findings with the amygdala, and given evidence correlating P300 amplitude in response to visual stimuli with amygdala size (25), we hypothesized that emotionally arousing stimuli might elicit a stronger P300 response in the right hemisphere in men compared to women, but a stronger P300 wave in the left hemisphere in women than in men. We also anticipated that this effect may be most likely detected over parietal recording sites (Pz).

In theInvestigations of EEG to emotional visual stimuli showed showedhigher cortical positivity in response to emotional material compared to neutral than to neutral one, suggesting indicating a deeper processing of the emotional information (26). ERPs in response to emotional pictures showed that unpleasant visual stimuli, compared to neutral, produced more robust P300 components (27, 28, 29). Similarly, significantly larger evoked potentials to arousing versus neutral stimuli were reported (30, 31, 32).

Some studies involving EEG have focused more specifically on the role the two hemispheres play in emotional information processing; however the data from these studies appear somewhat conflicting. For example, a differential left hemisphere P300 response to line drawings of emotional compared with neutral faces was reported (33). In contrast, a differential P300 component from the right hemisphere centro-pariatel region in response to emotional versus neutral faces was later reported (34). One possible explanation for some of the inconsistencies in the literature is that, as far as we know, no study has controlled simultaneously for the influences

of *both* the sex of the subjects and the hemisphere over which recording electrodes were located when assessing evoked potentials to emotional stimuli. Regarding sex, studies frequently either pool men and women without reporting separate analyses of each (31), or restrict their population to only men (35) or women (32). Therefore, understanding brain responses to emotional material may require careful attention simultaneously to the effects of *both* sex and hemisphere.

MATERIALS AND METHODS

Subjects

Twenty four subjects (12 female and 12 male), mean age 26 (±4.7) years, all University of L'Aquila psychology students, participated as a course requirement. Their main age was 25 years. All the subjects were initially submitted to a screening interview for any health problems, drug use, or signs of mental retardation. All subjects were right-handed, had normal vision and were not suffering from any neurological disorder. Exclusionary criteria included any major medical or psychiatric illness, substance abuse, or history of head injury. After arrival at the laboratory, participants read and signed thean informed consent form before participating in the study, in accordance with the regulations of the University Institutional Review Board.

Material

The stimulus materials, utilized in this study, consist in an adaptation of instruments previously used (2, 5, 6, 36), which were kept as close to the original as possible. The materials consisted of a set of 11 slides, accompanied by the narrative of two versions of a simple story – one neutral and one arousal. Slides 1, 2, 3 4, 5, 6, 9, 10, 11 were new pictures taken locally. The general appearance of the "actors", in terms of age, physical characteristics, type of clothing, and the quality of the scenes were as similar as possible to the ones previously utilized (2, 4, 5, 6). The slides previously used and included in this paper were 7 and 8. The subjects viewed one of two versions of a simple story (either a neutral or an arousing one) each consisting of 11 slides presented for approximately 10 s each and accompanied by one sentence of narration. The slides were projected utilizing a multi-medial system consisting in a portable IBM PC Think Pad A31, with a color screen XGA TFT color 14, 1" (1024x768) and Pro-compatible Sound Blaster audio card and integrated loud speakers. The images were sequenced using Microsoft Power Point 2000 (Office 2000), integrating video signals with audio signals previously recorded in digital format. The synchronization of the image projections was obtained through a digital fototrigger, consisting in an amplified phototransistor and a Schmitt Trigger. Both stories depicted a mother taking her young son to visit his father's workplace. The slides were the same, even though there was a difference in the arousing properties of the story content (Tab I). The stories are about a mother and her young son going to visit the father boy's at the nearby hospital where he works. In the neutral version, on their way, they see a car accident that caught the attention of the child. In the arousal version, the boy is the victim of a serious car accident in which he is critically injured and thus operated on the emergency room of the hospital.

Table I - Narrative accompanying slide presentation

Slide	Neutral version	Arousal version
1)	A mother and her son are leaving home in the morning	A mother and her son are leaving home in the morning
2)	She is taking him to visit his father's workplace	She is taking him to visit his father's workplace
3)	The father is the chief laboratory technician at a nearby hospital	The father is the chief laboratory technician at a nearby hospital
4)	They check before crossing a busy road	They check before crossing a busy road
5)	While walking alone, they pass the scene of a minor accident, which the boy finds interesting	While crossing the road, the boy is struck by a runway car, which critically injures him
6)	At the hospital, the staff are preparing for a practice disaster drill, which the boy will watch	At the hospital, the staff prepare the emergency room, to which the boy is rushed
7)	All morning long, surgeons practiced the standard disaster still procedures	All morning long, surgeons struggled to save the boy's life
8)	Special make-up artist were able to create realistic injuries on actors for the drill	Specialized surgeons were able to successfully re-attach the boy's severed feet
9)	After the drill, while the father stayed with the boy, the mother left to phone her other child's preschool	After the surgery, while the father stayed with the boy, the mother left to phone her other child's preschool
10)	Running late, she phones the preschool to tell them she will soon pick up her child	Feeling distraught, she phones the preschool to tell them she will soon pick up her child
11)	Heading to pick up her child, she hails a taxi at the number nine bus stop	Heading to pick up her child, she hails a taxi at the number nine bus stop

Slide	Italian version	
1)	Una madre e suo figlio/ stanno uscendo di casa/ al mattino	Una madre e suo figlio/ stanno uscendo di casa/ al mattino
2)	La madre sta portando il figlio/ a visitare/ il posto dove lavora il padre	La madre sta portando il figlio/ a visitare/ il posto dove lavora il padre
3)	Il padre/ è tecnico di laboratorio/ all'ospedale	Il padre/ è tecnico di laboratorio/ all'ospedale
4)	Prestano attenzione prima di attraversare/ una strada abbastanza trafficata	Prestano attenzione prima di attraversare/ una strada abbastanza trafficata
5)	Lungo il cammino,/ si imbattono in un piccolo incidente,/ che il ragazzo/ si ferma a guardare incuriosito	Nell'attraversare la strada,/ il ragazzo/ viene investito da una macchina in corsa,/ che lo ferisce gravemente
6)	Nell'ospedale/ i medici/ si stanno preparando per un'esercitazione relativa alle procedure da adottare in un caso di urgenza,/ e il ragazzo viene invitato a guardare	All'ospedale,/ i medici/ stanno preparando la sala per le urgenze/ dove stanno portando velocemente il ragazzo
7)	Per tutta la mattinata,/ i medici/ si esercitano nelle procedure da usare in caso di urgenza	Per tutta la mattinata,/ i medici lottano per salvare la vita del ragazzo
8)	Truccatori specializzati/ realizzano finte ferite molto realistiche/ per l'esercitazione	Chirurghi specializzati/ ricostruiscono e riattaccano/ i piedi del ragazzo
9)	Dopo l'esercitazione,/ mentre il padre rimane con il ragazzo,/ la madre si allontana per andare a telefonare/ all'asilo dell'altro figlio	Dopo l'intervento,/ mentre il padre rimane con il ragazzo,/ la madre si allontana per andare a telefonare/ all'asilo dell'altro figlio
10)	Poiché era in ritardo,/ telefona all'asilo/ per avvisare che presto andrà a riprendere il figlio	Sconvolta dal dolore,/ telefona all'asilo/ per avvisare che presto andrà a riprendere il figlio
11)	Per andare a riprendere il figlio/ chiama un taxi/ alla fermata dell'autobus n. 9	Per andare a riprendere il figlio/ chiama un taxi/ alla fermata dell'autobus n. 9

According to previous findings (2, 4, 5, 6), the story can be divided into 3 phases: phase 1 (the first 4 slides), consisting of relatively non emotional material (the mother and her son are on their way to the hospital), phase 2 (the middle 4 slides) containing emotionally arousing elements (child's hospitalization, including a picture of the boy's badly hurt legs and the surgery ward), and phase 3 (the last 3 slides) consisting again of material that is normally judged as not being very emotional (the mother leaves the hospital to make a phone call and goes home).

A professional actor narrated both versions, in a flat and unemotional voice. The structure of the sentences was similar in both emotional and neutral versions of the story. The slides were adapted to the Italian environment.

A similar version of the questionnaire for the 11-slide sequence previously used (2, 5, 6) was translated into Italian. The questionnaire had 5-10 questions about each slide, with a total of 74 multiple-choice questions.

The scoring system for story recall was in agreement with the criteria used to score most memory test for stories (37). As shown in table I, each slide narration was divided into segments and the subjects received a point for the recall of each segment. The recall of each segment earned them 1 point; for example, for slide 1 the subject could earn up to 3 points, plus additional points for precise description of details, such as "the boy was carrying a ball" in slide 1. In the recall the subjects could use sentences that differed from the originals, but they had to express the same meaning and the same idea. The narration was segmented in agreement with criteria referring to its structure and content, such as main idea of the slide, action (what happened), complement to the main idea or to the action (what, how, to whom) and time complement (when, after, before). We scored also the recall of any additional details, not stated by the narrator of the stories (such as color of clothing, etc.), because they reflected increased visual memory of the slides.

Procedure

The subjects were randomly assigned to the arousing or neutral conditioning. The two groups were equivalent in terms of gender.

Participants were seated in a comfortable chair in a sound-attenuated, dimly lit room. After electrode attachment and laboratory adaptation, in both conditions they were told that the aim of our study was to evaluate how people pay attention to stories. They were told that they were going to watch a slide presentation accompanied by a short sentence narrating the story. They were instructed to concentrate on each slide for the duration of its presentation and to view the slide-show as if they were watching a movie, paying attention to everything seen and heard. Immediately after viewing the slide show, the participants were asked to rate the emotionality of the story using a scale from 0 to 10. A score of 0 indicated "not emotional", and a score of 10 indicated "highly emotional". At the end of the first session, the subjects were told that the second part of the study would be

carried out 10 days later and more details would be given after that session. They had no indication that their memory would be tested. The subjects were also asked not to discuss the experiment with other people, as this could jeopardize results. On their return, ten days later, the subjects were informed that their memory of the story viewed would be tested. Prior to starting memory testing, the subjects were asked whether they were expecting a memory test despite our efforts to avoid it. All reported that a memory test was unexpected to them. The memory was tested by means of free recall and recognition test. First, they were asked to perform a free recall of the story, which was recorded on a portable tape recorder. Then, they were asked to answer the multiple-choice questionnaire about it. The 74 questions were presented orally by the experimenter and, for each question, 1 correct and 3 incorrect but plausible choices were presented. Testing was individual in both sessions.

Psychophysiological recording procedures

Electroencephalogram (EEG) signals were recorded from 1 second before slide onset until 8 seconds after the end of the post-picture period, using Biopac Mod. MP150 system and 6 standard system amplifiers (Mod. EEG 100C, Biopac System, Inc, Santa Barbara, U.S).

The auditory stimulus (narration) is presented 1 s after the visual stimulus.

The EEG was measured through Ag/AgCl electrodes placed at P3, P4, according to the International 10/20 System (Jasper, 1958) and using A1 and A2 as reference. Electrode sites were cleaned with alcohol and abraded to reduce electrode impedance. Impedance of each electrode was checked to insure it was below 5KOhm. Vertical and horizontal electrooculogram (EOG) was recorded from electrodes placed above and below the left eye, in order to control for eye movement artifacts using miniature Ag/AgCl electrodes and the same frequency range as for the EEG.

Data reduction and analysis

Data were collected for the entire time of the slides projection, including the intertrial interval with a sampling rate of 1000 Hz. Subjects presenting trials containing electrooculographic shifts exceeding 100 µV were automatically rejected from further analysis. Averaging was performed, and both amplitudes and latencies of P300 peak were considered. The amplitude of the P300 component to each slide and at each recording location was determined by subtracting the baseline (defined as the mean amplitude for the 100 msec period immediately before stimulus onset) from the peak value obtained 250-400 msec after stimulus onset. The latency was defined as the peak value observed in the 250 to 400 ms range after stimulus onset.

Statistical analysis

Data were analyzed using the analysis of variance, followed by the Tukey's Honestly Significant Different (HSD) test. Statistical significance was set at $p<0.05$.

In the figures the results are presented as mean ± S.E.M.

RESULTS

Ratings of emotionality

The ratings of emotionality of the arousal and neutral groups differed significantly in their main ratings of the emotionality of the stories [$F(1,22) = 37.91$; $p<0.0001$)] (Fig.1). The mean emotional rating for the arousal group was 6.62 (± 0.25) versus 4.12 (± 0.35) for the neutral group.

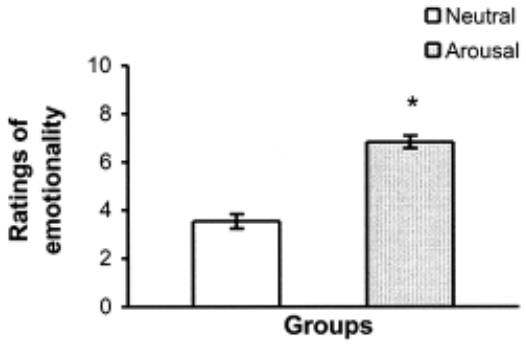

Figure 1. Mean (± SEM) ratings of emotional reaction to the neutral and emotionally arousing narratives. * $p< 0.0001$ compared to the neutral group.

Evoked Potentials

The P300 amplitude and latency were determined for P3 and P4 electrode sites in both men and women.

P300 Amplitude

At site P3, the arousal story produced a significantly larger P300 in women than neutral story did [$F(1,22)=75.84$; $p<0.0001$]. Also, the P300 amplitude in response to arousal story was significantly higher in women than in men [$F(1,22)=53.34$; $p<0.001$] (Fig. 2). At site P4, a significant difference between men and women in P300 amplitude was detected in response to the arousal version of the story [$F(1,22)=8.59$; $p<0.008$] (Fig. 2). A significant difference in amplitude between P3 and P4 was found both in men [$F(1,22)=12.28$; $p<0.002$] and women [$F(1,22)=30.78$; $p<0.0001$], in response to the arousal story (Fig. 3).

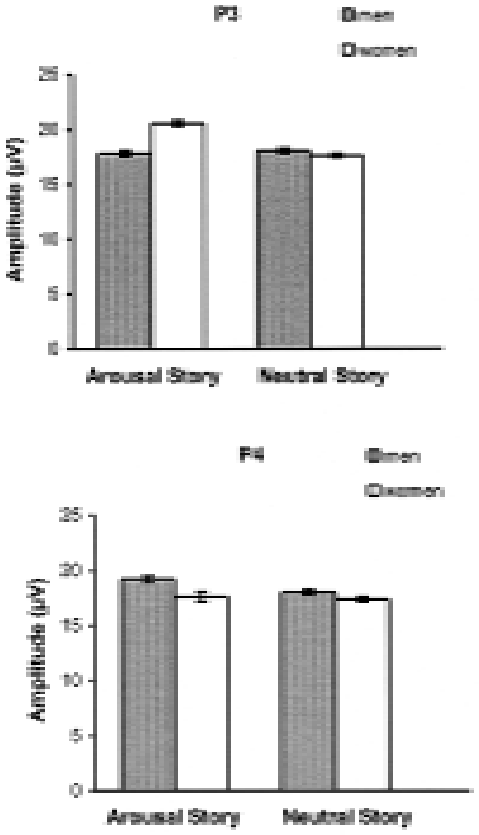

Figure 2. Mean amplitude (± SEM) of P300 wave in men and women at the P3 and P4 electrode sites. At site P3, the arousal story produced in women a significantly larger P300 than did the neutral story. Also, the P300 amplitude at site P3 in response to arousal story was significantly higher in women than in men. At site P4, the arousal story produced in men a significantly larger P300 amplitude than did the neutral story.

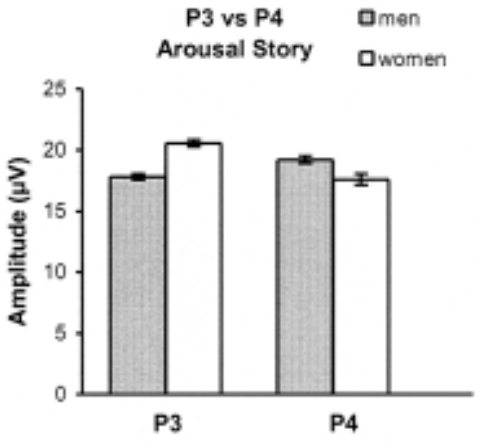

Figure 3. Mean amplitude (± SEM) of P300 wave in men and women at the P3 and P4 electrode sites in response to the arousal version of the story.

P300 Latency

The P300 latency was determined for P3 and P4 electrode sites in both men and women (Fig. 4). At site P3, the P300 latency in men after the presentation of arousal story was significantly longer than it was in response to neutral [F (1,22)=24,89; p<0.0001]. Furthermore, latency at site P3 was significantly longer in men than in women [F (1,22)=17,59; p<0.0005] in response to the arousal version of the story. At site P4, no significant difference between men and women was found in response to arousal version of the story, compared to neutral. Indeed, the latency in response to arousal story was significantly longer at P3 than at P4 electrode site in men [F (1,22)=90,91; p<0.0001], but not in women.

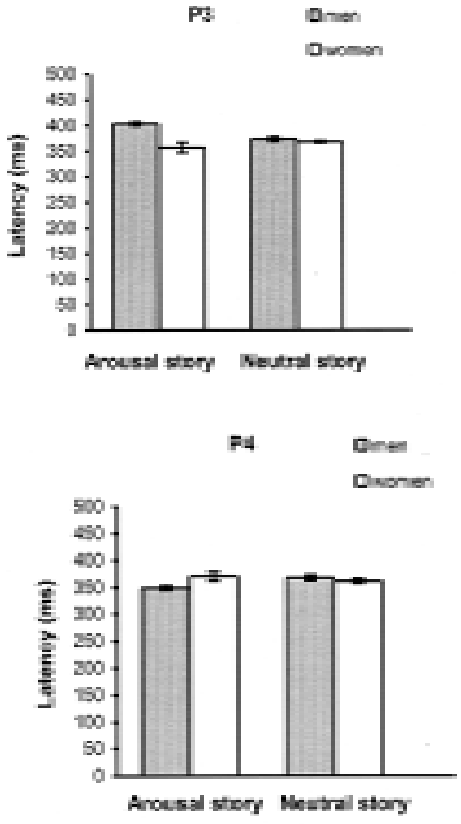

Figure 4. Mean latency (±SEM) of P300 wave at P3 and P4 electrode sites in men and women for each of the 2 versions of the stories. At *site P3*, the P300 latency in men, after the presentation of arousal story, was significantly longer than it was in response to neutral story. In men, the P300 latency in response to arousal story was also significantly longer than in women. *At site P4*, no significant difference between men and women was found in response to arousal version of the story, compared to neutral.

Indeed, the latency in response to arousal story was significantly longer at P3 than at P4 electrode site in men (p<0.0001), but not in women

Memory

The influence of the emotional content on memory was evaluated by means of free recall and recognition test.

Free recall.

The free recall test showed that men In men,memory forstimuliwas significantly higher toand women recalled the arousal version of the story more than the neutral version, even though the difference is statistically significant in men [F (1,10)=5.2 ; p<0.05], but not in women [F (1,10)=0.13; n.s.] (Fig. 5). The mean recall was 15.16 (±0.97) and 11.00 (±1.31) units of information for participants in the arousal and neutral conditions, respectively.

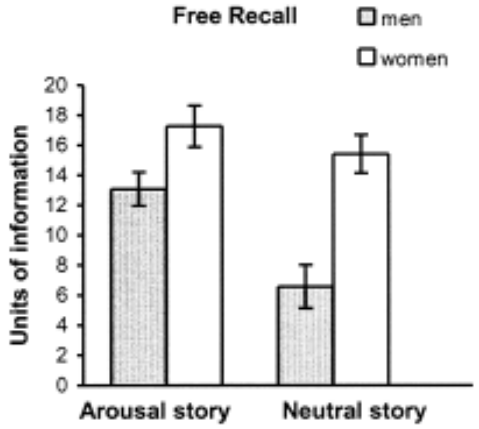

Figure 5. Recall scores (mean ± SEM) on arousal and neutral versions of the story. The free recall test showed that men In men,memory forstimuliwas significantly higher toand women recalled more the arousal than the neutral version of the story, even though the difference is statistically significant in men, but not in women.

Recognition test

The results of the recognition test indicated that there was no overall difference between the two groups. Subjects in the neutral condition answered an average of 61 % of the questions and subjects in the arousal condition were correct on 67 %. Nevertheless, a phase-by-phase comparison of the results revealed a difference between the two groups for phase 2 of the stories, which is the phase in which the emotionally arousing information was presented (Fig.6); in fact, the arousal group recalled more story elements than the neutral group [F (1,22)=7.18; p<0.01)]. The two groups did not differ for either phase 1 or phase 3. The mean recall score for the subjects in the arousal condition was 15.16 (± 0.97) versus 11.00 (± 1.31) for the subjects in the neutral condition (Fig.6).

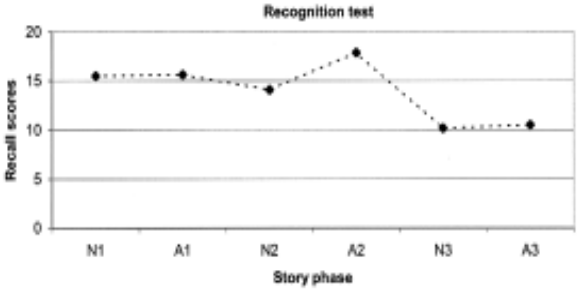

Figure 6. Recognition memory for the neutral and emotionally arousing versions of the stories. In phase 2, the arousal group recalled more story elements than did the neutral group.

DISCUSSION

Several key findings emerged from this investigation. First, the emotionally arousing version of the story evoked a differential EEG response depending both on the sex of the subjects and the hemisphere over which the potentials were recorded. Most interestingly, the arousal story evoked a significantly larger P300 component in location P3 (left hemisphere) in women than in men. The P300 amplitude significantly differ between men and women at site P4 (right hemisphere); in fact, the statistical analysis showed that it was larger in men than in women, and confirmed the existence of a significant interaction between sex and hemisphere in P300 amplitude, in response to the arousal version of the story, with this interaction being carried primarily by a significant difference between P3 and P4 both in men and women. Analysis of P300 latencies revealed a similar hemispheric lateralization: for the arousal version of the story, the latency at site P3 was significantly shorter in women compared to men. Sex and hemisphere also significantly interacted in influencing P300 latency. These results parallel those of recent brain imaging results indicating greater left hemisphere amygdala participation in processing into memory of emotionally arousing material in women, but greater right hemisphere amygdala processing into memory of the same material in men (14, 15, 16).

P300 latency is generally considered a metric of stimulus classification speed, with shorter latencies thought to reflect superior cognitive perform (24). In addition, P300

latency and amplitude are negatively correlated (24). Thus our finding of shorter P300 latencies in the left hemisphere in women, in response to the arousal version of the story fits well with our findings concerning P300 amplitude in suggesting a greater left hemisphere parietal response to arousing stimuli in women, and a greater right hemisphere parietal response to the same pictures in men. Of course, EEG recorded at left and right parietal scalp locations may have generators other than parietal ones. However, converging neuropsychological, intracranial recording, and imaging evidence points towards a major P300 source in temporal-parietal cortex (38). Furthermore, there exists a significant correlation between amygdala volume and visual P300 responses (25), suggestive of an amygdala-parietal cortex functional linkage which may underlie the present sex-related differences in P300 response.

We obtained greater left hemisphere P300 responses in women, and right hemisphere responses in men, to arousing stimuli, which were also better remembered in a long-term (10 days) incidental free recall test, raising the hypothesis that the enhancement of P300 response could be related to the enhancement of memory.

Sex-related influences on the EEG have been reported sporadically for many years, but mostly without being the subject of sustained, systematic investigation. Sutton and Davidson (39) found that, only in women and not in men, frontal EEG asymmetry is significantly related to an index of "positivity". Consistently with earlier studies examining only women (40) greater left and right frontal activation related to enhanced defensiveness was found in women and men, respectively (41, 42). Similarly, opposite relationships between frontal asymmetry and mood in men and women was reported (43). Finally, in female a sex-specific effect on N400 response using emotional stimuli was recently observed (44).

Studies focused on amygdala reported a differential effect of left versus right temporal lobectomies on memory for an emotional story depending on the sex of the subjects was reported (2, 3, 10).

These findings clearly indicate that subject sex is a crucial variable in understanding cerebral hemisphere function, in particular in relation to emotional conditions. Indeed, future studies should control for menstrual cycle activity as well in female subjects, at least in studies such as the present concerning arousing stimuli, as an influence of the menstrual cycle on P300 responses to relatively arousing stimuli has been reported (30).

A rapidly increasing number of studies involving human subjects document neurobiological differences between men and women. Functional sex-related differences have been reported in brain correlates of emotional (45) and facial processing (46, 47), auditory (48, 49, 50) and language processing (51, 52), working memory (53), and even in visual cortex responsiveness to specific light wavelengths (54). The present findings underscore the view that the influences of both subject sex and cerebral hemisphere must be considered in future studies of neural correlates of emotion, and of emotion's relation to memory.

STUDY 2

Effect of emotional content on declarative memory on migraine headache patients.

In the second part of our research we evaluated the influence of emotional stimuli on declarative memory on cephalalgic patients. The cephalgic subjects partecipating in this study were all migraine headache patients.

Migraine headaches have been attributed to a genetically determined defect of cranial neurovascular function (55, 56), occurring in approximately 18% of females and 6% of males over 11 years old (57), with the onset appearing before age 40 in about 90% of cases (58). Migraine is typically characterized by recurrent and extended episodes of unilateral, pulsating, and moderate to severe pain. For migraines with aura, visual disturbances are the most commonly reported aura symptom, but other sensory, motor, affective, and cognitive symptoms may occur in the prodrome, aura, and/or headache phase of an attack (58, 59, 60, 61). Conflicting evidence exists regarding the effect of chronic migraine headache on neuropsychological test performance. The performance of migraine headache patients has been reported to be significantly below the level of normal controls on a variety of cognitive measures, including tests assessing sensorimotor functioning, attention and information processing, language, and memory (62, 63, 64, 65, 66). These results lead to the hypothesis that chronic migraine may result in persistent, subtle central nervous system dysfunction. This hypothesis is consistent with the association of migraine attacks with vascular and neuronal disturbances (67, 68), and with findings that migraineurs may show difference from healthy controls on neurophysiologic and neuroradiological measures including cerebral blood flow, auditory and visual evoked potentials, and MRI (69, 70, 71, 72, 73, 74, 75, 76). However, other neuropsychological studies, with similar sample sizes, have found no differences between migraine

headache patients and controls (77, 78, 79). These data are in agreement with the hypothesis that migraine is typically a neurologically benign syndrome (58, 80, 81).

The present study was designed to examine the effect of emotional content on declarative memory in migraineurs. We evaluated 2 groups of migraineurs, one without treatment and the other one treated with the antidepressant amitriptyline, one of the first "reference" tricyclic antidepressants (82).

MATERIALS AND METHODS

Subjects

The participants were volunteers divided in 3 groups: healthy subjects, patients with migraine headache without any prescription, migraineurs treated with the antidepressant amitriptyline. There were 48 individuals in the healthy group (24 men and 24 women), 29 in the migraineurs group without prescription (8 men and 21 women), and 19 subjects (5 men and 14 women) in migraineurs treated with the antidepressant amitriptyline. The groups did not differ in race, education, or intelligence, as measured by the National Adult Reading Test (83). ~~Their main age was 25 years.~~ All the subjects were initially submitted to a screening interview for any health problems, drug use, or signs of mental retardation. All subjects had normal vision. Exclusion criteria included recent substance abuse, systemic disease, a history of a learning disability or special education, and central nervous system disease. A history of head trauma with persistent cognitive sequel was an exclusionary criterion for the migrainers group. The medical history was acquired from medical records and/or patient interviews. The migraine patients were recruited in part (60%) at the Neurological Clinic of the University of L'Aquila, and in part (40%) at the Neurological Clinic of the Hospital of Penne (PE). Migraine was diagnosed by clinic specialists based on the criteria of the Headache Classification Committee of the International Headache Society (84).

After arrival at the laboratory, participants read and signed thean informed consent form before participating in the study, in accordance with the regulations of the University Institutional Review Board. to the participation in this research

Material

The stimulus material utilized in the second part of this study is the same we utilized in the first part, consisting in 2 versions (emotional and neutral) of the same story (2, 5, 6, 36).

Procedure

The procedure followed in the second part of our study was analogous to the one followed in the first part of the research, except that no ERP analysis was performed.

Statistical analysis

Data were analyzed using ANOVA, followed by the Tukey's Honestly Significant Different (HSD) test. Statistical significance was set at $p<0.05$.

In the figures the results are presented as mean ± S.E.M.

RESULTS

Ratings of emotionality

The healthy subjects rated the emotionally arousing narrative as being more emotional than the neutral [$F(1,46)=66.98$; $p<0.0001$)] (Fig.7). The mean emotional rating was 6.62 (±0.25) for the emotionally arousing narrative versus 4.12 (±0.35) for the neutral narrative.

In the patients with migraine headache without any prescription and the migraineurs treated with amitriptyline the mean emotional rating for the emotionally arousing narrative did not significantly differ from the neutral narrative [$F(1,29)=0.47$; n.s.)] and [$F(1,15)=0.004$; n.s.)], respectively (Fig.7). In the untreated migraineurs group, the mean emotional rating for the arousal group was 7.38 (±0.42) versus 6.50 ± 0.68 for neutral group. In the group of migraineurs treated with amitriptyline, the mean emotional rating for the arousal

group was 6.7 ± 0.93 versus 6.55 ± 0.60 for neutral group.

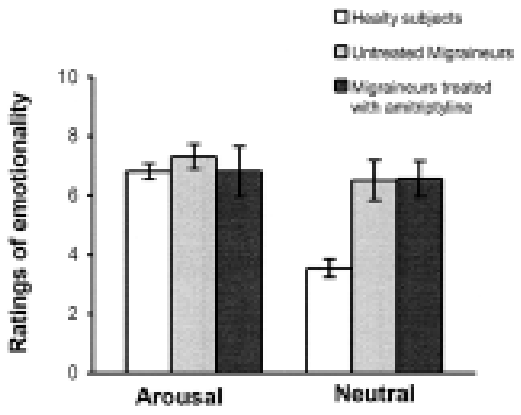

Figure 7. Mean (± SEM) ratings of emotional reaction to the neutral and emotionally arousing narratives in healthy subjects, untreated migraineurs and migraineurs treated with amitriptyline.

Memory

The influence on memory of the emotional content was evaluated by means of free recall and recognition test.

Free recall

In all the 3 groups, there were no statically significant differences between the total amount of information recalled by participants who heard the neutral narrative and participants who heard the emotionally arousing narrative (Fig. 8). In the healthy subjects group, mean recall was 15.16 (±0.97) and 11.00 (±1.31) units of information for participants in the arousal and neutral conditions, respectively. In the untreated migraineurs group, mean recall was 16.33 (±0.79) and 12.87 (±0 0.83) units of information for participants in the arousal and neutral conditions, respectively. In the group of migraineurs treated with amitriptyline, mean recall was 11.50 (± 1.13) and 9.44 (±0. 55) units of information for participants in the arousal and neutral conditions, respectively.

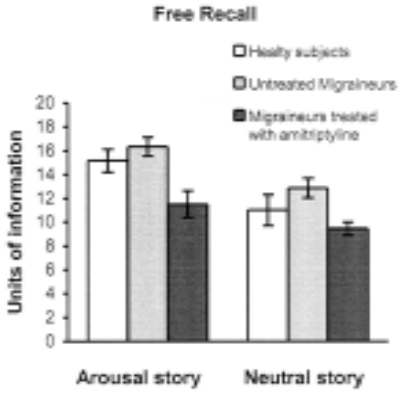

Figure 8. Recall scores (mean ± SEM) on arousal and neutral stories in healthy subjects, untreated migraineurs and migraineurs treated with amytriptyline. The free recall test showed that in all the 3 groups, there were no statically significant differences between the total amount of information recalled by participants who heard the neutral narrative and participants who heard the emotionally arousing narrative.

Recognition memory.

The results of the multiple choice test were analyzed for percent correct of total information recognition, as well as for percent correct as a function of narrative phase. In all the 3 groups the total recognition for participants who heard the emotionally arousing narrative did not statically differ from the subjects who heard the neutral story. Nevertheless, as is shown in

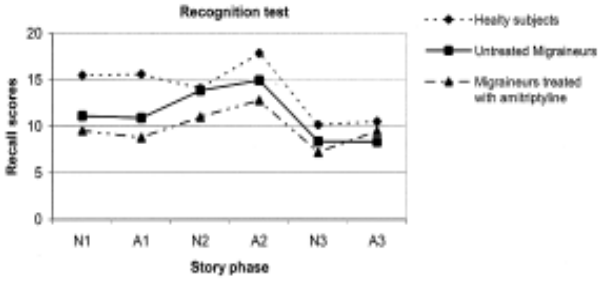

Figure 9. Recognition test. In the 3 groups, the total recognition for participants who heard the emotionally arousing narrative did not statically differ from the subjects who heard the neutral story. Nevertheless, an enhanced recognition for the emotionally arousing of the narrative, compared to the neutral narrative was evidenced in the phase 2 of the story, which is the phase where the emotionally arousing information was presented. A significantly enhanced recognition was evidenced in the phase 2 of the arousal narrative in the group of untreated migraineurs compared to the group of migraineurs treated with amitriptyline. The comparison of the 3 groups for the phase 2 of the arousal version of the story evidenced in the healthy subjects a statistically better recognition memory compared to both untreated migraineurs and migraineurs treated with amitriptyline. In all the groups, no statistically significant difference between the participants in the neutral and arousal condition was evidenced in the recognition memory for either phase 1 or phase 3.

Figure 9, an enhanced recognition for the emotionally arousing of the narrative, compared to the neutral narrative was evidenced in the phase 2 of the story, which is the phase containing emotionally arousing information. In particular, in the healthy subjects group, participants in the neutral condition answered an average of 61% of the questions and participants in the arousal condition were correct on 67%. An enhanced recognition for the emotionally arousing of the narrative was evidenced in phase 2 of the narrative. Participants in the arousal condition recalled more story elements than did the subjects in the neutral condition [$F(1,94)= 15.87$; $p<0.0002$)].

In the groups of the untreated migraineurs and the migraineurs treated with amitriptyline, participants in the neutral condition answered an average of 51% and 42 % of the questions, respectively, and participants in the arousal condition were correct on 52 % and 48 %, respectively. A significantly enhanced recognition was evidenced in the phase 2 of the arousal narrative in the group of untreated migraineurs compared to the group of migraineurs treated with amitriptyline [$F(1,29)=4.32$; $p<0.05$)]. The comparison of the 3 groups for the phase 2 of the arousal version of the story evidenced in the healthy subjects a statistically better recognition memory

compared to both untreated migraineurs [F (1,43)= 13.92 ; p<0.0006)] and the migraineurs treated with amitriptyline [F (1,32)= 25.72; p<0.001)].

In all the groups, no statistically significant difference between the participants in the neutral and arousal condition was evidenced in the recognition memory for either phase 1 or phase 3.

DISCUSSION

The findings of the present experiments suggest that chronic migraine is associated with memory impairment. As mentioned in the introduction, memory dysfunctions in migraineurs have already been reported (59, 63, 66, 85, 78, 85, 86). Among studies who found deficiencies in the cognitive processing of migraineurs, it was reported that migraineurs show significantly poorer performances in memory and information processing tests (66). Also, neuropsychological impairment and cognitive defects were also reported in migraine patients (59, 63). Impairment of short and long term memory was also showed in children suffering common migraine, compared to controls (62). Verbal and visual memory was also lower in patients with common migraine, compared to controls (87). Defects both in verbal and visual memory were detected either in patients suffering migraine with aura and patients suffering migraine without aura (88). These cognitive defects, however, were not confirmed by other authors who did not find significant differences between migraineurs and controls in any of the neuropsychological tasks administered (85). Also, other studies did not report cognitive impairment in samples of female migraine patients (77, 78). Likewise, a study evaluating the cognitive and psychomotor capacity in migraineurs with aura, migraineurs without aura, and healthy controls showed similar results in every group (89). Previous neuropsychological studies suggesting that frequent migraine headache may lead to a subtle decline in cognitive functioning as a result of the repeated paroxysms in hemodynamic associated with migraine. For example, it was suggested that chronic migraine is not typically associated with meaningful cognitive impairment (90). This conclusion is reinforced by the fact that there was no significant correlation between duration of migraine and cognititive performance.

Taking into account that personality traits and /or psychological factors may influence the neuropsychological performance, some of the above mentioned authors studied also some of these aspects. In this respect, many authors have found that neuroticism personality profile is higher among migraineurs than in healthy subjects (91, 92), and that migraine patients have also been found to be at increased risk for affective and anxiety disorders (92, 93). It was also found that, even though migraine patients scored higher in free-floating anxiety, obsessionality and somatic complaints, there was no correlation between these data and cognitive results (66). Besides, even though scores obtained in the Hamilton Depression Scale from both migraineurs with aura and without aura were higher than those of the control group, the difference was not statically different (88). In disagreement with the results of Burker et al. (77), Leijdekkers et al. reported that migraine patients, compared to controls, had higher traits and state anxiety levels, as well as more depressed mood and lower vigour scores; no correlation between any of these parameters and the results of cognitive tests was found. Other studies reported that patients with migraine with aura and without aura showed impaired neuropsychological performances only on some cognitive tests. Both groups were similarly affected on visuo-spatial memory tasks, whereas only the migraineurs without aura showed significantly impaired verbal performances and attention defects compared to controls (88). Disturbances in visuomotor speed processing, attention, and memory were observed among migraineurs with a long history of migraine and in those experiencing higher frequency of attacks (94).

The discordances in results between the studies which found cognitive affectation in migraine, and those who did not, might be explained by differences in the selection of subjects: the patients of previous studies (62, 63, 66, 87, 94) and also the subjects we examined in the present research came from headache clinics, whereas others (77, 78, 88, 89) were recruited among the general population or students.

Moreover, results from headache pain and memory studies suggest that pain, as it adversely affects memory, may operate at a threshold level rather than on a dose-response continuum (95, 96, 97, 98)

It is interesting to note that migraine has also been reported in association with two important syndromes: the transient global amnesia (TGA) and the antiphospholipid syndrome (APS, Hughes' syndrome). The TGA is a benign clinical neurological syndrome consisting of an acute onset and short-lasting episode of global memory loss, repetitive queries, and disorientation in time. The attack resolves within 24 h, with no sequel except amnesia for the attack itself. Many attacks are triggered by special circumstances as sexual intercourses, highly emotional experiences, pain (99, 100).

APS is a prothrombotic disease in which neurological events feature prominently. Strokes, transient ischemic attacks, headaches (including migraine) and memory loss are important complications (101).

Taking into account that migraine with and without aura is associated with major depression, in the present research we also evaluated the effect of the antidepressant amitriptyline, which represented the treatment of the subjects of one of the 2 groups of migraineurs we examined. The tertiary tricyclic antidepressants (TCAs), such as amitriptyline, are highly effective in the treatment of panic disorder, migraine and major depression, which is also associated with migraine (102). Antidepressants may ameliorate the social and occupational life of depressed patients, but also impair these domains due to the negative impact on psychomotor and cognitive functions (103). The risk of impairment varies widely among antidepressant drugs, depending also on their pharmacological properties. TCAs block histaminergic, adrenergic and cholinergic receptors which may induce sedation and performance impairment in a wide range of tasks (103, 104). Moreover, drugs with anticholinergic properties may interfere particularly with attention and memory processes, although studies reporting conclusions on the specificity of the cognitive effects of TCAs are rare (105). The results of our research showed that expectations concerning the effects on memory of the amitriptyline were confirmed. In fact, in our study the healthy subjects and the untreated migraineurs recalled the most emotional phase of the arousal story significantly better compared to migraineurs treated with the TCA amitriptyline. Then, our data suggest that amitriptyline prevents the enhancing effects of emotional content on memory processes.

Acknowledgements

We thank Dr. Liliana Ercole for language assistance and Dr. Alessandro Sevi for the excellent narration of the stories he provided.

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