Emotional memory and migraine: Effects of amitriptyline and sex related difference

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Abstract

Many studies suggest that emotional arousal improves memory storage. The aim of this study was to evaluate the effects of emotional content on explicit memory in untreated cephalalgic patients and in migraineurs treated with the antidepressant amitriptyline. 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.

Subjects of the present study were healthy subjects and cephalalgic patients, suffering from migraine headache, which included untreated migraineurs and migraineurs treated with the antidepressant amitriptyline. The findings of our experiments suggest that chronic migraine is related to 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, the untreated migraineurs, compared to treated, recalled the most emotional phase of the arousal story significantly better. Then, our data suggest that amitriptyline prevents the enhancing effects of emotional content on memory processes. Moreover, in agreement with our previous data, this study suggests the existence of gender differences in the processing of emotional stimuli and underscores the importance of sex on emotional memory mechanisms.

Keywords: Emotional stimuli; Antidepressant amitriptyline; Migraineurs

It is very well known that emotional events are better memorized than neutral events.

Migraine represents a common headache disorder with significant mental, physical and social health implications [16], and can be influenced by adrenergic, peptidergic and serotonergic systems [25,30]. Contradictory evidence exists about the effect of migraine on cognitive functions. Previous studies reported that the performance of migraineurs, compared to controls, was significantly lower on a variety of cognitive measures, including tests assessing attention, information processing, and memory [24,30]. Therefore, chronic migraine could cause a persistent, subtle central nervous system dysfunction. Conversely, other investigations failed to find impairing of cognitive functions of migraine headache patients, compared to controls, supporting the hypothesis that migraine is typically a neurologically benign syndrome [2,17].

The aim of this research was to evaluate the effects of emotional content on declarative memory on patients suffering of migraine, comparing differences in memory between subgroups of treated and untreated patients, and evaluating sex differences among the groups.

In this research, we utilized the adaptation to an Italian sample of two stories with different arousing properties (neutral and emotional), already employed in experiments with both brain injured and healthy subjects, involving the enhancing effects of emotions on memory retention [8,9,11,13,28].

We evaluated two kinds of migraineurs: one untreated and another treated with amitriptyline, a reference tricyclic antidepressant [1,29].
We also investigated the influence of gender on the evaluation of emotional content, taking into account that recent evidence from research on animals and humans revealed apparently large, but formerly unsuspected, sex-related effects on nervous mechanisms subserving the relation between emotion and memory [3,11,12,35,36]. Therefore, understanding brain responses to emotional material may require careful attention to the effects of sex.

Subjects were 151 volunteers divided into three groups, equivalent in terms of age (mean age 30 ± 3.7), gender, cultural level (college education with urban background), race, education: 48 (24 men and 24 women) healthy subjects (control group), 55 (24 men and 31 women) untreated migraineurs, 48 (24 men and 24 women) migraineurs treated with the antidepressant amitriptyline.

Healthy subjects were individuals with no physical or mental disorders. The migraine patients were recruited at the Neurological Clinic of the University of L’Aquila; migraine was diagnosed by clinic specialists based on the criteria of the Headache Classification Committee of the International Headache Society (2004). The two samples of patients were comparable and similar in the severity of illness, such as frequency and intensity of attacks, comorbidity with depressive illness, etc.

Self medicate migraineurs were excluded from the groups of migraineurs that were not on prescribed treatment.

The patients included in this study were not suffering from other conditions that may affect memory performance.

In this study, the patients participated at the experiments during headache-free intervals, as reversible cognitive decline was observed during migraine attacks [22,30]. In fact, it has been reported that subjects with headache pain during a memory task showed poorer performance because the pain interferes with their ability to pay attention during the memory task, rather than with retrieval [20].

In this study, we used the same procedure as in previous researches [8,11,13,28,35]. Participants gave informed consent to participate in the study. The stimulus materials, already utilized in previous studies [8,11,13,35], consists in a set of slides, accompanied by the narrative of two versions of a simple story—one neutral and one arousal. The slides were the same, even though there was a difference in the arousing properties of the story content.

According to previous findings [8,11,13,35], the story can be divided into 3 phases: phases 1 and 3, consisting of relatively non emotional material, and phase 2 containing emotionally arousing elements; memory was tested by means of both free recall and recognition test.

A three-way ANOVA with repeated measures was utilized to analyze the data obtained. ANOVA included story (neutral, arousal), patients (healthy, untreated migraineurs, treated migraineurs), phase of story (1, 2, 3) as within-subjects factor and gender as between-subject factor. ANOVA was followed by the Tukey’s Honestly Significant Different (HSD) test. All results are presented as mean ± SEM. Statistical significance was set at p < 0.05.

The evaluation of the ratings of emotionality showed that in men, in the arousal group, the treated migraineurs rated the story as being more emotional compared to healthy subjects [F(1, 22) = 5.03; p < 0.035]. The healthy subjects and both the untreated and treated patients rated the emotionally arousing narrative as being more emotional than the neutral [F(1, 22) = 8.74; p < 0.007], [F(1, 22) = 6.64; p < 0.017] and [F(1, 22) = 25.09; p < 0.0001], respectively. The values of the mean emotional rating for the arousing versus the neutral story were the following: in the healthy subjects 6.00 (±0.36) versus 4.25 (±0.46), in the untreated migraineurs 6.25 (±0.59) versus 4.58 (±0.25), and in the treated migraineurs 7.16 (±0.36) versus 4.16 (±0.47).

In women, the healthy subjects and both the untreated and treated patients rated the arousing narrative as being more emotional than the neutral [F(1, 22) = 10.53; p < 0.003], [F(1, 29) = 23.01; p < 0.0001] and [F(1, 22) = 38.59; p < 0.0001], respectively. The values of the mean emotional rating for the arousing versus the neutral story were the following: in the healthy subjects 7.16 (±0.38) versus 4.66 (±0.66), in the untreated migraineurs 7.47 (±0.47) versus 4.33 (± 0.33), and in the treated migraineurs 7.83 (± 0.29) versus 4.25 (±0.49), respectively.

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

In men (Fig. 1A), the results of free recall showed that, in the arousal condition, the three groups showed a better memory in the healthy subjects, compared to both untreated [F(1, 22) = 8.96; p < 0.009] and treated [F(1, 22) = 10.28; p < 0.007] migraineurs; furthermore, the difference between the two groups of migraineurs was statistically different [F(1, 22) = 9.86; p < 0.004]. In the neutral group, significant differences between the total amount of information recalled was found between the treated migraineurs and healthy subjects [F(1, 22) = 7.97; p < 0.009]. The healthy subjects of the arousal group, compared to neutral, recalled a number of units of information significantly higher [F(1, 22) = 13.92; p < 0.001].

Mean recall of healthy subjects, in the arousal and neutral conditions, was 12.92 (±1.22) and 6.25 (±1.29) units of information for participants, respectively. In the untreated migraineurs, mean recall was 10.33 (±0.68) and 9.25 (±0.87) units of information for participants in the arousal and neutral conditions, respectively. In the treated migraineurs, mean recall was 10.83 (±0.50) and 10.17 (±0.48) units of information for participants in the arousal and neutral conditions, respectively.

In women (Fig. 1B), in the arousal group, significant differences were found between the total amount of information recalled by the healthy subjects and both the untreated [F(1, 29) = 11.31; p < 0.002] and treated migraineurs [F(1, 22) = 9.86; p < 0.004]; moreover, the difference between the two groups of migraineurs was statistically different [F(1, 29) = 10.98; p < 0.008]. In the neutral group, significant differences were found between the healthy subjects and both the untreated [F(1, 22) = 14.35; p < 0.001] and treated migraineurs [F(1, 22) = 15.31; p < 0.0007].

Mean recall of healthy subjects was 17.58 (±1.70) and 16.50 (±1.46) units of information for participants in the arousal and neutral conditions, respectively. In the untreated migraineurs, mean recall was 12.00 (±0.79) and 10.58 (±0.52) units of information for participants in the arousal and neutral conditions,
respectively. In the treated migraineurs, mean recall was 11.75 (±0.73) and 10.33 (±0.56) units of information for participants in the arousal and neutral conditions, respectively.

In the free recall of the arousal story (Fig. 1C), the comparison between male and female healthy subjects showed in women a better memory compared to men \([F(1, 22) = 4.94; p < 0.036]\).

In the free recall of the neutral story (Fig. 1D), the comparison between male and female healthy subjects showed a better memory in women, compared to men \([F(1, 22) = 27.34; p < 0.0001]\).

The recognition test (Fig. 2) evidenced no overall difference between all the groups, but a phase-by-phase comparison revealed a difference between the groups for phase 2 of the stories, which contains the emotional informations. The numbers after the letters indicate the story phase of the arousal (A) and neutral (N) conditions.

As shown in Fig. 2A, in men, in the healthy subjects, the total recognition in phase 2 of the arousal group statistically differed from those of the neutral group \([F(1, 22) = 14.56; p < 0.0009]\);
moreover, both in the untreated and treated migraineurs, in phase 2, the recognition for participants who heard the emotionally arousing narrative statistically differed from the subjects of the neutral group \( F(1, 22) = 14.59; p < 0.0008 \) and \( F(1, 22) = 6.29; p < 0.019 \), respectively. The comparison of the three male groups for the phase 2 of the arousal version highlighted a statistically better recognition memory in the healthy subjects compared to both untreated \( F(1, 22) = 12.37; p < 0.001 \) and treated migraineurs \( F(1, 22) = 36.33; p < 0.0001 \). Furthermore, the two groups of migraineurs were statistically different \( F(1, 22) = 15.82; p < 0.0006 \). No statistically significant difference between the participants in the neutral and arousal condition was evidenced for both phase 1 and phase 3.

In addition, the healthy subjects in the neutral conditions answered an average of 54% and 60% of the questions, respectively. The untreated and treated migraineurs in the neutral condition answered an average of 51% and 42% of the questions, respectively, and participants in the arousal condition correctly answered 52% and 48%, respectively.

In the healthy women, the total recognition for participants of the arousal group statistically differed from the subjects of the neutral group \( F(1, 22) = 13.50; p < 0.001 \). Moreover, both in the untreated and treated migraineurs, the total recognition for subjects of the emotional group statistically differed from those of the neutral group \( F(1, 29) = 6.68; p < 0.015 \) and \( F(1, 22) = 14.34; p < 0.001 \), respectively (Fig. 2B).

The comparison of the three female groups for the phase 2 of the arousal version of the story highlighted a statistically better recognition memory in healthy subjects compared to both untreated \( F(1, 29) = 7.87; p < 0.008 \) and treated migraineurs \( F(1, 29) = 79.66; p < 0.0001 \). Furthermore, the two groups of migraineurs were statistically different \( F(1, 29) = 13.25; p < 0.001 \).

The healthy subjects of the neutral and arousal conditions answered an average of 65% and 71%, respectively. Both the untreated and treated migraineurs in the neutral condition answered an average of 56% and 48% of the questions, respectively, while participants in the arousal condition were correct on 57% and 50%, respectively.

No statistically significant difference between the participants in the neutral and arousal condition was evidenced in the recognition memory for both phase 1 and phase 3.

The comparison between men and women of the three groups did not show any statistical difference both in arousal and neutral versions of the story.

Our results support the view that processes promoting recollection are facilitated for negative events [18,33] and that chronic migraine is associated with memory impairment. Pain negatively impacts cognitive functioning, such as learning and memory, and memory dysfunctions in migraineurs have already been reported [7,23,30]. These cognitive defects, however, were not confirmed by other authors who did not find significant differences between migraineurs and controls [26]. These discordances might be explained by differences in the choice of subjects: the patients of previous studies [4], together with the subjects we examined in the present research, came from headache clinics, whereas others [21,24] were recruited among the general population or students.

In addition, 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 [20].

Our data suggest that chronic migraine is related to memory impairment. In fact, the performance of both the memory tests of men and women in the arousal group evidenced significant differences between the healthy subjects and the two groups of migraineurs (Fig. 2). In the female neutral group (Fig. 2A), significant differences were found between the healthy subjects and both the treated and untreated migraineurs; in the male neutral group (Fig. 2B), differences were found between the treated migraineurs and healthy subjects: this apparent discrepancy could be explained in terms of higher level of attention showed by treated migraineurs, who expressed to the experimenters their great motivation for any scientific study focused on migraine.

Taking into account that migraine can be associated with major depression, we also evaluated the effect of the antidepressant amitriptyline, which represented the treatment of the subjects of one of the two groups of migraineurs we examined. Tertiary tricyclic antidepressants (TCAs), such as amitriptyline, are very effective in the treatment of panic disorder, migraine and major depression, which is also associated with migraine [14,29]. Even though, antidepressants may ameliorate the social and occupational life of depressed patients, they can also have a negative effect due to the negative impact on psychomotor and cognitive functions [37]. The risk of impairment varies widely among antidepressants, depending also on their pharmacological properties. TCAs block histaminergic, adrenergic and cholinergic receptors, which may induce sedation and performance impairment in a variety of tasks [37]. Moreover, drugs with anticholinergic properties may interfere particularly with attention and memory processes, although very few studies report conclusions on the specificity of the cognitive effects of TCAs [6]. Our findings show that expectations concerning the effects on memory of the amitriptyline were confirmed. In fact, the performance of both the memory tests of men and women in the arousal group evidenced significant differences between the healthy subjects and the two groups of migraineurs; in the neutral group, statistically significant differences were found between the healthy subjects and both the treated and untreated migraineurs. Moreover, statistical differences in the recognition test were found between treated and untreated migraineurs, both in male and female, suggesting that amitriptyline prevents the enhancing effects of emotional content on memory processes.

In our experiments, we considered separately men and women, taking into account that a rapidly increasing number of studies involving human subjects document neurobiological differences between the sexes. Functional sex-related differences have been reported in brain correlates of emotional [10,12] and facial processing [19,38], auditory [27,31] and language processing [5,32], working memory [15,34]. In agreement with our previous data [11,12], the findings from free recall suggest the existence of gender differences in the processing of emotional
studies and, therefore, the importance of taking these differences into account during investigation of emotional processing. They are also consistent with the interpretation that women are more susceptible than men towards negative experiences and lowered mood, and this may have implications on the pathophysiology of mood disorders, such as depression [18].

Although, memory disturbances in migraineurs have already been reported, the mechanisms relating emotional memory and migraine, and the brain regions involved are still unknown. In migraine patients, brain perfusions abnormalities, mostly hypoperfusion areas, were found. It has been postulated that persistent abnormalities in regional cerebral blood flow of migraineurs could reflect vascular factors involved in the pathogenesis of the headache [4]. However, as decreased brain perfusion could result also from impaired neuronal activity, an alternative explanation is that these changes could be the consequence of frequently repeated migraine attacks. This last possibility would be coherent if a link between neuropsychological disturbances and hypoperfusion of specific areas, such as medial temporal lobe (MTL) structures, involved in emotional memory, can eventually be established. Then, a connection between MTL structures and migraine could be hypothesized. Future research will need to examine the possibility that migraine could impair memory consolidation through a mechanism involving MTL.

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References

