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# Sensitivity to aversive stimulation, posttraumatic symptoms and migraines: What do they have in common?

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ABSTRACT

Studies have suggested that the high comorbidity observed between chronic migraine and anxiety disorders can be mediated through a third factor namely increased sensitivity to aversive stimulation. This trait may predispose for both chronic migraines, through medication overuse as an avoidance response, and anxiety disorders. Additional studies have shown that hyper sensitivity to aversive stimulation, migraine chronification and anxiety disorders share other characteristics such as serotonergic mediation and personality traits. Preliminary analysis of empirical data comparing the frequency the impact of traumatic events over chronic [CM] and episodic migraine [EM] patients gives further support to this hypothesis. In spite of CM and EM did not differ in terms of the occurrence of traumatic events, CM patients that had experienced at least one traumatic event during their lives had higher scores in re-experiencing and avoidance (but not in hyperarousal) symptoms than CM patients. These observations suggest that traumatic events have greater impact over CM than over EM patients.



## Background

One emergent theory proposes that avoidance of pain is an important factor for the migraine chronification [1]. It is known that physiological responses to stressors, such as the hormonal and catecholaminergic changes, perivascular inflammation, and pericranial muscle tenderness [2], participate in the pathogenesis of migraines. It seems obvious that, the more sensitive a subject to stressors, the higher these responses which, in turn, may exert influence over headaches severity and frequency. However, this theory highlights another effect of hypersensitivity to aversive stimulation. This factor may also be related to behavioral responses to stressors, changing how often and intensely a subject avoid a given aversive stimuli or condition. The higher the sensitivity, the stronger the avoidance. Pain, as an aversive condition, may be avoided by using analgesics in a much lower threshold than other people, leading to a much more frequent use of these medications, which, in turn, is a known cause of the chronification of migraines.

Hypersensitivity to aversive stimulation has shown to be related to anxiety disorders and depression as well, conditions frequently seen in comorbidity with chronic migraines. One anxiety disorder frequently seen in comorbidity with chronic migraines is Posttraumatic Stress Disorder (PTSD) [3,4], a psychiatric condition characterized by three clusters of symptoms: (1) re-experiencing the traumatic event (cluster B); (2) avoidance/numbing symptoms (cluster C); and (3) hyper arousal (cluster D) after the occurrence of a traumatic event.

## Hypothesis

We hypothesize that more sensitive subjects would be at higher risk to develop both stress-relates disorders, such as anxiety and depression, and CM. PTSD seems to be of particular interest to study the herein proposed hypothesis as: (1) the stressor leading to the disorder is known and easily established, namely the traumatic event; and (2) avoidance symptoms, as well as the hyperarousal symptoms, are specifically measured, independently from the other clusters of symptoms. In fact, PTSD was found to be more frequent in Chronic Migraine (CM) than in Episodic Migraine (EM) [3] and PTSD symptoms to be more frequent in chronic headache [migraine or tension-type] than in controls (chronic masticatory muscle pain) [5]. However, in this study, no differences in frequency of traumatic events between the groups were observed [5].

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## Evaluation of the hypothesis

According to this theory, avoidant subjects are more sensitive to signals of pain than other subjects. In other words, their threshold to escape from pain, by taking acute medication, would be lower. This means that acute medications may be used more frequently, which may lead to migraine chronification.

Even though avoidance responses of PTSD and the response of avoiding headaches by using analgesics may seem different, evidences suggests that sensitivity to aversive stimuli may be a generalized trait that differ between subjects [6]. We have been demonstrating that this must be the case of at least part of the patients that overuse acute analgesic medications for headaches [1]. Those who, for some reason, are more sensitive to a specific aversive stimulus, may be more sensitive to a broad range of other aversive stimuli as well, including, for instance, those involved in traumatic events. In line with this view, earlier studies show that harm-avoidance personality traits were higher in both migraneurs [7] and PTSD [8]. Moreover, the serotonergic system has been implicated in the underling mechanisms of PTSD [9], avoidance [10] and migraine [11].

It is proposed that an earlier common factor makes a subject more sensitive to aversive stimuli and, therefore, predisposed to both CM and PTSD. For instance, studies support that childhood abuse or neglect is a risk factor for both chronic pain [12] and PTSD [13] in adulthood, as well as causing alterations in the serotonergic system [14,15].

## Empirical data

To give further support to our hypothesis, we ran a reanalysis of 74 CM and 54 EM traumatized patients originally from other study [11].

The intensity of posttraumatic symptoms was accessed by the Clinician Administered PTSD scale (CAPS). Frequency of traumatized patients was compared between groups using the Pearson's chi-square test. Total and clustered mean CAPS scores were compared between the groups with the student's $t$ test [only include participants who reported traumatic events].

In spite of no significant differences between the groups in terms of the number of subjects that experienced at least one traumatic event throughout life (39 of 74 CM [52.7%]; and 20 of 54 EM patients [37%]; $\chi^2 = 3.083$; $p = 0.079$) nor in terms of the mean number of traumatic events (mean ± SD = 0.77 ± 1.22 versus 1.03 ± 1.32; $p = 0.12$ [Student's $t$ test. Only included participants who reported traumatic events]), the severity of posttraumatic symptoms, as measured by the Clinician Administered PTSD Scale (CAPS), were significantly higher in CM than EM for the re-experiencing cluster of symptoms [cluster B] and the avoidance/numbing cluster of symptoms [cluster C], but not for the Hyper arousal cluster of symptoms [cluster D]. Total CAPS showed a trend toward significance (Table 1).

**Table 1**
Mean [SD] CAPS scores in Chronic Migraine [CM] and Episodic Migraine [EM].

| Scale | Mean [SD] CAPS scores | | Student's $t$ test | Sig. |
|---|---|---|---|---|
| | EM | CM | | |
| Cluster B | 1.05 [2.50] | 4.44 [6.33] | −2.925 | 0.005 |
| Cluster C | 7.35 [7.31] | 12.64 [12.42] | −2.055 | 0.045 |
| Cluster D | 12.30 [10.64] | 16.90 [11.20] | −1.517 | 0.135 |
| Total | 20.70 [16.60] | 32.62 [24.38] | −1.961 | 0.055 |

## Consequences of the hypothesis and discussion

The present study shows no significant differences in the occurrence of traumas between CM and EM, which is in accordance with previous data [5]. In spite of that, traumatic events had higher impact in CM patients than in EM, especially in avoidance and re-experiencing clusters, as expected. These findings support the hypothesis that avoidant behavior is linked to migraine chronification.

However, in spite of our data allowing the associations between avoidance symptoms and CM, they do not allow attributing dependency relationship between them, i.e., it is not possible to say that one "caused" the other. It should be noticed that both groups had the same frequencies of traumatic events, so not migraines, PTSD or traumatic events seem to be the primary independent variables.

The reader should be aware that in our study, severity of traumas was not accessed and it is possible that comorbid depression can have biased our results and explain why they differ from Peterlin's [4]. Further prospective studies with greater sample-sizes may help to shed some light in this issue.

Psychological trauma and its avoidance and re-experience component are important to be identified in migraine patients.

## Conflict of interest statement

No conflicts of interests are declared by the authors. This article was not commissioned, funded or sponsored by any pharmaceutical company and has no conflict of interests of any other form.

## References

[1] Peres MF, Mercante JP, Guendler VZ, Corchs F, Bernik MA, Zukerman E, et al. Cephalalgiaphobia: a possible specific phobia of illness. J Headache Pain 2007;8:56–9.
[2] Nash JM, Thebarge RW. Understanding psychological stress, its biological processes, and impact on primary headache. Headache 2006;46:1377–86.
[3] Peterlin BL, Tietjen G, Meng S, Lidicker J, Bigal M. Post-traumatic stress disorder in episodic and chronic migraine. Headache 2008;48:517–22.
[4] Peterlin BL, Tietjen GE, Brandes JL, Rubin SM, Drexler E, Lidicker JR, et al. Posttraumatic stress disorder in migraine. Headache 2009;49:541–51.
[5] de Leeuw R, Schmidt JE, Carlson CR. Traumatic stressors and post-traumatic stress disorder symptoms in headache patients. Headache 2005;45:1365–74.
[6] Cloninger CR, Svrakic DM, Przybeck T. A psychobiological model of temperament, character. Arch Gen Psych 1993;50:975–90.
[7] Di Piero V, Bruti G, Venturi P, Talamonti F, Biondi M, Di Legge S, et al. Aminergic tone correlates of migraine and tension-type headache: a study using the tridimensional personality questionnaire. Headache 2001;41:63–71.
[8] Ruchkin VV, Eisemann M, Hagglof B. Juvenile male rape victims: is the level of post-traumatic stress related to personality and parenting? Child Abuse Negl 1998;22:889–99.
[9] Corchs F, Nutt DJ, Hood S, Bernik M. Serotonin and sensitivity to trauma-related exposure in selective serotonin reuptake inhibitors-recovered posttraumatic stress disorder. Biol Psych 2009.
[10] Graeff FG, Guimaraes FS, De Andrade TG, Deakin JF. Role of 5-HT in stress, anxiety, and depression. Pharmacol Biochem Behav 1996;54:129–41.
[11] Vieira DS, Naffah-Mazzacoratti Mda G, Zukerman E, Senne Soares CA, Cavalheiro EA, Peres MF. Glutamate levels in cerebrospinal fluid and triptans overuse in chronic migraine. Headache 2007;47:842–7.
[12] Davis DA, Luecken LJ, Zautra AJ. Are reports of childhood abuse related to the experience of chronic pain in adulthood? A meta-analytic review of the literature. Clin J Pain 2005;21:398–405.
[13] Davidson JR, Hughes D, Blazer DG, George LK. Post-traumatic stress disorder in the community: an epidemiological study. Psychol Med 1991;21:713–21.
[14] Manuck SB, Bleil ME, Petersen KL, Flory JD, Mann JJ, Ferrell RE, et al. The socio-economic status of communities predicts variation in brain serotonergic responsivity. Psychol Med 2005;35:519–28.
[15] Maestripieri D, Higley JD, Lindell SG, Newman TK, McCormack KM, Sanchez MM. Early maternal rejection affects the development of monoaminergic systems and adult abusive parenting in rhesus macaques [Macaca mulatta]. Behav Neurosci 2006;120:1017–24.