Do catastrophizing and autonomic reduced flexibility mediate pain outcomes in chronic headache?

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Abstract

Objectives

Maladaptive cognitive strategies and reduced autonomic flexibility have been reported in chronic pain conditions. No study to date addressed the effects of maladaptive coping and reduced autonomic flexibility, as indexed by heart rate variability (HRV), in chronic headaches. The present study aimed to assess the mediating role of pain catastrophizing and HRV on pain outcomes in patients with chronic headache.

Methods

32 Chronic headache patients and 28 healthy controls were recruited. Self-reported pain severity, pain interference on daily activity, and pain catastrophizing were assessed through the Multidimensional Pain Inventory and the Pain-Related Self Statements Scale. HRV was recorded at rest. Correlations and mediation analysis between self-report, HRV, and pain outcomes were run.

Results

Patients with chronic headache reported significantly higher pain severity ($p < .001$; $d = -1.98$), pain interference on daily activity ($p < .001$; $d = -1.81$), and pain catastrophizing ($p < .001$; $d = -0.96$) compared to controls. They also presented significantly lower HRV ($p < .05$; $d = 0.57$). Both Pain catastrophizing and HRV were associated with pain interference on daily activity. However, from mediation analysis, pain catastrophizing only emerged as the mediator for pain severity ($p < .001$; $\beta = 0.30$) and pain interference ($p < .001$; $\beta = 0.14$).

Conclusion

Present results showed that Chronic Headache patients are characterized by high catastrophizing and lower physiological adaptability. Pain catastrophizing emerged as the only mediator of pain outcomes, suggesting that cognitive factors might have a major influence on the severity of pain and its interference on daily activities. Further studies are needed to evaluate these autonomic-cognitive interactions in chronic pain.

Keywords: Chronic Migraine; Chronic Tension Type Headache; Coping Strategies; Heart Rate Variability; Pain.

Introduction

Chronic headache adversely affects patients' quality of life and is a risk factor for disability [1]. To deal with pain, chronic headache (CH) patients employ different coping strategies. Coping strategies, defined as psychological mechanisms applied to manage or tolerate stress, can be adaptive or maladaptive and include multidimensional affective, cognitive, behavioural, and physiological mechanisms of human functioning [2]. The utilization of maladaptive coping strategies has been reported to contribute to pain chronicity [3, 4], greater pain intensity and perceived disability [5, 6], and lower quality of life [7, 8] in chronic pain patients.

Among maladaptive coping strategies, catastrophizing is of particular relevance since it has been implied in the development and maintenance of pain [9]. Catastrophizing is the tendency to ruminate, exaggerate the threat value of painful stimuli, or the feeling of being helpless about pain [10]. Catastrophizing often leads to helplessness and depression [11]. and negatively influences the severity of pain, affective distress, pain-related disability, and the response to treatment [12, 13]. Additionally, higher catastrophizing has been linked to physiological modifications such as exaggerated muscle tension [14,15] and lower diurnal cortisol variability [16]. In patients with headaches, catastrophizing correlated with higher frequency and duration of the attacks [17,18], depression [19], impairments in daily activities and quality of life [20]. Interestingly, while catastrophizing has been consistently shown to increase pain intensity, the adoption of active coping strategies through promoting adaptive behavioural responses to pain does not systematically correlate with reduced pain intensity [21].

Whereas coping has been considered as a cognitive index of adaptation to stress, the activity of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) has been suggested as a psychophysiological indicator of adjustment to stress [22]. Heart rate variability (HRV), the continuous variation in heart periods reflects the activity of the ANS on the heart [23]. High HRV has been linked with flexible modulation to external stimuli and adaptive coping strategies utilization [24, 25]. On the contrary, reduced HRV, as a measure of poor autonomic flexibility, has been associated with psychopathological [26], medical [27], and chronic pain conditions [28]. Headache sufferers consistently showed reduced HRV compared to healthy controls [29].

To date, no study has examined the role of maladaptive coping strategies and physiological adaptability on pain outcomes in CH patients. The present study aimed at exploring the role of cognitive catastrophizing and reduced HRV on pain outcomes (i.e., pain severity and interferences of pain) in CH patients and healthy controls (HC). It was hypothesized that: i) CH patients would show higher catastrophizing and lower HRV than HC; ii) higher catastrophizing and lower HRV would correlate with worse pain outcomes in CH patients; iii) catastrophizing and HRV would mediate the relation between pain conditions and pain outcomes.

Materials and Methods

Participants

All consecutive patients attending either a diagnostic and therapy service for anxiety and psychosomatic disorders or a psychophysiology service of a clinical psychology university centre from January 2015 to July 2020 and suffering from chronic headache were recruited.

Fifty-five patients gave written informed consent and accepted to participate. Of the 55 patients, 35 patients received the diagnosis of Chronic Migraine (CM) (1.3) or a dual diagnosis of Episodic Migraine Without Aura (1.1) and Chronic Tension-Type Headache (CTTH) (2.3), according to ICHD-3 criteria (30). The diagnosis was formulated by a neurologist. Exclusion criteria were: inability to understand Italian, pregnancy, secondary headache, drugs other than those included in the preventive therapy (i.e., antiepileptics and antidepressants).

Of the 35 patients who received a diagnosis of chronic headache, two were excluded since they were on a pharmacological therapy with beta-blockers (i.e., atenolol) and one patient was excluded due to artifacts in the physiological recording. Therefore, 32 patients

were included in the final sample (see Figure 1). The sample included patients with CM (n = 17, 53%), Episodic Migraine and CTTH (n = 15, 47%). The frequency of headache episodes reported per month by the patients was 24.30 (5.95).

A total of 28 healthy controls (11 males, 39%) who had experienced at least one pain episode in the previous six months were enrolled. HC were asked to fill in a form with sociodemographic data, general health status and site, intensity, and frequency of the painful experience. Exclusion criteria were the same as the headache group. All participants in the control group did not satisfy diagnostic criteria for primary headache according to ICHD-3.

All participants gave written informed consent, the study was carried out in accordance with the Declaration of Helsinki; the protocol was approved by the Ethics Committee.

Questionnaires

To assess the headache episodes, CH patients were asked to complete a monthly diary, reporting the frequency of headache episodes.

To examine the impact of pain on the participants' lives the West Haven-Yale Multidimensional Pain Inventory (WHY- MPI), which is a 61-item self-report questionnaire, was administered [31, 32]. According to the literature, pain severity (i.e., the level of pain severity) and interference of pain subscales (e.g., interference with family functioning, work or work-related and social activities) are the most representative and used subscales of the WHY-MPI [12, 33, 34]. Therefore, the present study focused specifically on these two subscales. All participants recorded their responses on a Likert scale from 1 to 6, higher scores correspond to worse severity and/or interference.

To assess coping strategies, and specifically catastrophizing, two questionnaires were administered to all participants: the Pain-Related Self Statements Scale (PRSS) and the Pain-Related Control Scale (PRCS) [35, 36]. The PRSS is an 18-item questionnaire assessing the frequency of cognitive coping strategies application in painful situations. PRSS is divided into two subscales: "Catastrophizing" and "Active Coping". Participants respond on a Likert scale from 0 (almost never) to 5 (almost always).

The PRCS is a 15-item questionnaire evaluating participants' general attitudes towards pain. Participants respond on a Likert scale from 0 (it does not match at all) to 5 (it matches perfectly) and it is divided into two subscales: "Helplessness" and "Resourcefulness". Both questionnaires have been reported to be reliable and sensitive to change [37, 38].

To assess anxiety and depressive symptoms two subscales of the Cognitive Behavioural Assessment (CBA) were administered [39]: State-Trait Anxiety Inventory X2 (STAI X2) and Dysphoria Questionnaire (DQ). STAI X2 assesses trait anxiety through 20 items rated on a Likert scale (from 1 to 4). Higher scores reflect a higher level of trait anxiety. DQ, composed of 24 dichotomous items, evaluates the presence of dysphoric and depressive symptoms.. Higher scores signal more severe depressive symptoms. Percentiles were calculated from raw scores for both the STAI X2 and DQ.

HRV Assessment

Cardiac activity was recorded employing electrocardiography (ECG) in 31 participants or photoplethysmography in 33 participants. Photoplethysmography and ECG were collected in a standardized fashion using the Bio-Graph Infinity 6.0 software on computerized recording hardware (ProComp Infiniti, Thought Technology; Canada). Given that electrical and mechanical activity of the heart are coupled, there is consistent evidence that photoplethysmographic variability highly correlates with HRV extracted from ECG recordings [40, 41] therefore they can be used interchangeably to assess cardiac activity [42]. ECG signal was obtained from three disposable Ag⁄AgCl electrodes that were positioned on the participant's chest in a modified lead II configuration. ECG signal was amplified, band-pass filtered (1–100 Hz), and sampled at 256 Hz. All ECG data were visually inspected for artifacts and a digital trigger detecting R-waves was applied to the ECG signal to obtain inter-beat intervals (IBIs). Blood volume pulse (BVP) was recorded through a photoplethysmographic detection sensor attached to the non-dominant middle finger. BVP signal was visually

inspected to identify movement or electrical artifacts, then the IBIs derived from the analog output of the BVP amplifier were processed via a 12-bit analog-to-digital converter. After obtaining inter-beat intervals series from all participants, data were exported in the Kubios-HRV 2.2 software (University of Kuopio, Finland) to further correct for possible artifacts with a piecewise cubic spline interpolation method that generates missing or corrupted values into the IBIs series. Then the heart rate (HR) and the standard deviation of normal to normal intervals (SDNN) were calculated. SDNN reflects the cyclic components responsible for HRV and is an index of the total HRV [43]. Finally, the natural logarithm of SDNN was calculated to normalize the data distribution.

Procedure

Participants in both groups were requested to complete all the questionnaires, then they were asked to seat on a comfortable armchair in a quiet room. A sensor to record cardiac activity was attached. After ten minutes of habituation, HR recording was carried out for 4 minutes under resting condition. A 4-min period of cardiac recording has been previously shown to be an adequate procedure to measure short-term time (i.e., HR and SDNN) domain HRV indexes examined in the present study [43]. During recordings, all participants were instructed to avoid movements to reduce artifacts.

Statistical Analyses

As our first step, t-test or chi-square analyses were conducted to compare the two groups (CH patients and HC) in terms of age, gender, questionnaires' scores (WHY-MPI, PRSS, PCRS, STAI X2, and DQ), and cardiac indexes (HR and lnSDNN; see Table 1).

To ensure that sociodemographic variables, questionnaires, and cardiac activity were not affected by headache diagnoses, the two subgroups of patients (CM and CTTH with episodic migraine) were compared.

In order to evaluate any influence of pharmacological therapy and overuse on cardiac indexes (i.e., HR and lnSDNN) in CH patients, cardiac indexes were compared between patients with and without a preventive pharmacological therapy (i.e., antiepileptics and antidepressants) and between patients with and without overuse.

Partial correlations (Pearson r) between scores on the questionnaires and cardiac indexes (HR and lnSDNN) were computed separately in the two groups (CH patients and HC) controlling for age. Correlations were controlled for age since cardiac activity including HRV indexes is well known to be influenced by age [44, 45]. Moreover, in the CH patients, the possible confounding effect of the duration of chronic pain condition (in years) was controlled by computing the partial correlation with all the questionnaires scores and cardiac indexes controlling for age, but they proved unrelated (all *p*'s > .11).

Two GLM mediation model analyses were run to examine whether cognitive coping strategy (i.e., PRSS subscale catastrophizing) and/or physiological measure of adaptation (i.e., lnSDNN) mediated the relationship between the pain condition (i.e., chronic headache or no pain, HC) and pain-related outcomes (i.e., pain severity and the interference of pain in daily activities).

All analyses were performed using Jamovi (46). The significance level was set at two-tailed $p < 0.05$.

Results

Sociodemographic variables, questionnaires, and cardiac activity.

Compared to HC, CH patients reported greater pain severity (t = -7.63, $p < .001$, Cohen's d = -1.98), higher interferences of pain in daily activity (t = -7.00, $p < .001$, Cohen's d = -1.81), higher catastrophizing (t = 3.69, $p < .001$, Cohen's d = -0.96), lower active coping (t = 3.51, $p < .001$, Cohen's d = 0.91) on the PRSS, higher helplessness (t = -3.53, $p < .001$, Cohen's d = -0.91) on the PRCS, higher anxiety (t = -2.09, $p = .04$, Cohen's d = -0.56) and depressive symptoms (t = -3.57, $p < .001$, Cohen's d = -0.95), and lower total heart rate variability (as measured by lnSDNN; t = 2.19, $p = .03$, Cohen's d = 0.57). Also, HR was marginally higher in chronic pain (t = -1.93; $p = .058$, Cohen's d = -0.50) than in controls (see Table 1).

No other differences emerged (all *p's* > .19).

No differences emerged between the two subgroups of patients (CM and CTTH with episodic migraine) in terms of sociodemographic variables, questionnaires, and cardiac activity (all p's>0.16).

Effects of pharmacological therapy on cardiac indexes in patients with chronic headache.

Among CH patients, 17 (55%) were following a preventive pharmacological therapy while 14 (45%) were not and no effect of pharmacological therapy on HR (t = 0.63, p = .54) or lnSDNN (t = -1.11, p = .27) emerged. Twenty (69%) patients showed overuse and 11 (33%) had no overuse and no effect of overuse on HR (t = 0.46, p = .65, Cohen's d = 0.19) or lnSDNN (t = -1.35, p = .19, Cohen's d = -0.64) emerged.

Associations between questionnaire scores and cardiac activity.

In CH patients, greater catastrophizing (PRSS) emerged to be significantly related to higher helplessness (r = 0.40, p = .02), higher pain severity (r = 0.46, p = .01) and pain interferences (r = 0.54, p < .001) measured with the WHY-MPI (see Table 2). Higher positive coping strategies (PRSS) significantly correlated with lower helplessness (r = -0.48, p = .01) and higher resourcefulness (r = 0.40, p = .03). Higher helplessness was positively associated with anxiety symptoms (r = 0.44, p = .02). Higher reported pain severity (WHY-MPI) was associated with greater pain interferences (r = 0.68, p < .001) and higher depressive symptoms (r = 0.42, p = .03). Greater pain interferences (WHY-MPI) correlated with higher anxiety (r = 0.63, p < .001) and depressive symptoms (r = 0.65, p < .001). Higher reported pain interferences also correlated with higher HR (r = 0.40, p = .03) and lower total HRV (lnSDNN; r = -0.38, p = .04). Higher anxiety symptoms (STAI X2) emerged to be associated with greater depressive symptoms (DQ; r = 0.61, p < .001). Higher depressive symptoms (DQ) significantly correlated with lower total HRV (lnSDNN; r = -0.51, p = .005). Finally, higher HR correlated with lower lnSDNN (r = -0.71, p < .001). No other correlation emerged (all p's > .05).

In healthy controls, greater catastrophizing (PRSS) emerged to be significantly related to greater helplessness (r = 0.58, p < .01; see Table 3). Higher positive coping strategies (PRSS) significantly correlated with higher resourcefulness (r = 0.71, p < .001). Also, higher reported pain severity (WHY-MPI) was associated with greater pain interferences (r = 0.71, p < .001). Higher anxiety symptoms emerged to be associated with greater depressive symptoms (r = 0.72, p < .001). Finally, higher HR correlated with lower lnSDNN (r = -0.57, p < .001). No other significant correlation emerged in the control group (all p's > .05).

Catastrophizing and heart rate variability as mediators of pain outcomes.

Mediation is established when four criteria are satisfied: 1) the independent variable must affect the dependent variable. A direct effect emerged, computed keeping the mediators constant, showing that CH patients had higher pain severity compared to HC (effect estimate = 0.27, β = 0.59; p < .001; see Table 4, effect 1). 2) The independent variable must affect the mediator. Significant effect of group emerged both for catastrophizing (effect estimate = 0.49, β = 0.44; p < .001; see Table 4, effect 2a) yielding that CH patients had higher scores on the catastrophizing subscale, as well as for lnSDNN (effect estimate = -0.14, β = -0.28; p = .03; see Table 4, effect 2b) yielding that CH patients had significantly lower total HRV than HC. 3) The mediators must affect the dependent variable. A significant effect of catastrophizing on pain severity emerged (effect estimate = 0.12, β = 0.30; p = .001; see Table 4, effect 3a) showing that higher catastrophizing scores were associated with greater pain severity. The effect of lnSDNN on pain severity did not emerge (p > .05; see Table 4, effect 3b). Finally, 4) the effect of the independent variable on the dependent variable must be reduced in the presence of the mediator. An indirect effect emerged for catastrophizing scores (effect estimate = 0.06, β = 0.13; p = .01; see Table 4, effect 4a) showing a mediation effect of catastrophizing over pain severity (see Figure 2a). No significant mediation of lnSDNN on pain severity emerged (p > .05, see Table 4, effect 4b).

Regarding the mediation model on the interference of pain, the first criterion was satisfied, hence a direct effect emerged showing that CH patients had higher interference of pain compared to HC (effect estimate = 0.06, β = 0.49; p < .001; see Table 5, effect 1). The second criterion was satisfied for both mediators, in fact CH patients had higher scores on the catastrophizing subscale

compared to HC (effect estimate = 0.49, β = 0.44; $p < .001$; see Table 5, effect 2a) as well as lower heart rate variability (i.e., lnSDNN) (effect estimate = -0.14, β = -0.28; $p = .03$; see Table 5, effect 2b). The third criterion was satisfied by both catastrophizing scores (effect estimate = 0.03, β = 0.33; $p < .001$; see Table 5, effect 3a) and lnSDNN (effect estimate = -0.04, β = -0.18; $p = .03$; see Table 5, effect 3b). Finally, the fourth criterion was satisfied for the catastrophizing subscale yielding a mediation of catastrophizing over interference of pain (effect estimate = 0.02, β = 0.14; $p = .01$; see Table 5, effect 4a and Figure 2b). As shown in Figure 3a and in Figure 3b in CH patients catastrophizing scores seem to explain the higher pain severity and the higher interference of pain reported by these patients. No significant mediation of lnSDNN on interference of pain emerged ($p > .05$, see Table 5, effect 4b).

Discussion

The aims of the present study were threefold: first, to compare pain outcomes, coping strategies, and autonomic flexibility between CH patients and healthy controls; second, to evaluate the association between pain outcomes, coping strategies, and autonomic flexibility separately in CH patients and controls; third, to assess the mediation role of coping and autonomic flexibility on the relationship between groups (CH patients and HC) and pain outcomes.

Results revealed that CH patients reported higher pain severity and greater interference of pain, as well as higher catastrophizing and lower HRV (as measured by lnSDNN) compared to HC. These results are in line with previous literature supporting the presence of maladaptive cognitive coping and reduced autonomic flexibility in chronic pain [47, 48] and in CH patients [29, 49, 50].

In patients with chronic headache, but not in healthy controls, catastrophizing was associated with worse pain outcomes, such as pain severity and pain interference. To note, this association was not present in controls. It is important to note that, among cognitive coping, catastrophizing was the only component significantly associated with pain outcomes, while other strategies that are considered maladaptive (e.g., helplessness), as well as adaptive strategies (e.g., active coping and resourcefulness), were unrelated to both pain severity and pain interferences. This result is in line with the literature on coping in pain conditions that indicate how maladaptive coping, and specifically catastrophizing, is predictive of poor outcomes [47, 51–54], while adaptive coping strategies (also called active or positive) did not show significant effects on improved outcomes [21, 55].

Moreover, in CH patients, HRV was inversely associated with pain interference but not with pain severity. It could be speculated that lower autonomic flexibility could be mostly linked to the pain-related psychosocial effects, as indexed by perceived interference with family functioning, work-related activities, and social aspects. Supporting this hypothesis, Allen and colleagues [31] found that lower HRV was related to inflexibility and greater pain interference, but unrelated to pain intensity, in a group of neurofibromatosis patients. These data add to the literature showing that low HRV, as an index of poor autonomic flexibility, is detrimental to the adaptive modulation of behaviour [22, 23] rather than to pain itself. Intriguingly, the association between maladaptive psychological responses (e.g., cognitive coping) and physiological flexibility was reported in a recent study showing that catastrophizing negatively correlated with HRV in chronic whiplash-associated pain [56].

In the present study, catastrophizing and HRV were unrelated in both groups. Up to date there are no experimental data on catastrophizing and HRV in CH patients. Differences in results could be determined by differences in patients' characteristics (e.g., diagnosis, age) and both catastrophizing and HRV index measurements. Importantly, from the present results, in CH patients catastrophizing and HRV were both associated with at least one pain outcome. It could be hypothesized that high pain catastrophizing and low HRV independently reflect inflexibility that sustains pain chronicity in chronic headaches. Further studies are warranted to explore this aspect.

Finally, the mediation models showed that pain catastrophizing was the only significant mediator for both pain outcomes (pain severity and interference of pain) in the relationship between chronic headache and pain outcomes. These results are in line with the literature showing that maladaptive cognitive coping, and specifically catastrophizing, seems to hold a major role in determining

clinical pain-related symptoms, such as greater pain severity and disability. Besides, it is well known how cognitive factors such as catastrophizing and helplessness can greatly influence pain perception and chronicity [19, 36, 57, 58]. Higher catastrophizing has been shown to contribute to pain aggravation, perseverance, interference in daily activity, and analgesic overuse risk [59]. More to the point, catastrophizing is representative of the failure to inhibit pain anticipations and thoughts, and of patients' incapability to deal with environmental demands [60].

From the present results, no significant mediation of HRV on pain outcomes emerged, indicating that when controlling for the influence of pain catastrophizing, reduced HRV does not explain differences in pain outcomes. In line with the present results, Allen et al. (2018) showed that psychological inflexibility fully mediated the relation between HRV and pain interference in neurofibromatosis patients. Taken together, these data support the hypothesis that cognitive coping has a paramount role in determining pain outcomes suggesting that cognitive coping interventions should be encouraged as a relevant treatment in CH patients. It could also be argued that a broader complex top-down psychological self-regulatory strategy, including cognitive appraisal of pain, could influence autonomic functioning, including HRV in relation with pain [24, 25]. Further studies are needed to evaluate this hypothesis.

Supporting the literature on the association between pain outcomes, mood, and anxiety symptoms [61, 62], the present results confirmed that pain interference was associated with more severe depressive and anxiety symptoms in CH patients. Moreover, higher depressive symptoms were negatively linked to HRV, in line with a previous study [63].

This study has limitations that need to be addressed. First, preventive and acute medications, such as antihypertensives, antidepressants, and antiepileptics can have a significant impact on HRV. Since CH patients were on preventive pharmacological therapy, it was not possible to record HRV in a complete washout condition. However, the effects of preventive drugs and acute medications on HRV were examined and no differences emerged between patients on and off a pharmacological therapy.

Second, given that our main interest was in chronic headache independently of its pathophysiology, no distinction has been made between chronic tension-type headache and chronic migraine. A growing number of studies have highlighted similarities between migraine and Tension Type Headache in symptomatology, response to treatment, and pathophysiology, supporting a continuum perspective, especially in chronic forms [64]. Moreover, the two subgroups of patients (CM and CTTH with episodic migraine) were compared for sociodemographic variables, questionnaires, and cardiac activity and no differences emerged. Supplementary studies are needed to investigate HRV changes associated with specific headache diagnoses in relation to catastrophizing. Third, autonomic flexibility was evaluated only through resting HRV, while it has been proposed that HRV changes related to a challenging and/or stressful task could be a better index of autonomic flexibility [65]. Future studies should investigate whether HRV in response to challenging and/or stressful tasks could be more tightly related to catastrophizing and pain outcomes in CH patients.

In conclusion, the present study showed that CH patients are characterized by high catastrophizing as a maladaptive cognitive coping mechanism and lower physiological adaptability. Moreover, maladaptive cognitive coping mediated the relationship between chronic headache and pain outcomes, such as pain intensity and interference of pain in daily functioning. Chronic pain conditions, including chronic headache, should be approached with a multidimensional evaluation including cognitive, emotional, evaluative, and physiological aspects [66] in order to identify those patients who could better benefit from a cognitive or psychophysiological intervention to be included in the treatment plan. According to this viewpoint, non-pharmacological treatments of chronic headache should be focused on adaptability improvement, which should be achieved through interventions targeted on cognitive, affective, and physiological flexibility.

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Table 1 Socio-demographic characteristics, questionnaires scores of patients with Chronic Primary Headache and controls.

Participant's characteristics	Chronic headache (N = 32)	Controls (N = 28)	*t/ χ2*	*p*	*Cohen's d/φ*
Age (year)	28.13 (12.97)	30.68 (11.46)	0.80	*.42*	*0.21*
Sex (Male)	8 (25)	11 (39)	1.41	*.23*	*0.15*
WHY- MPI					
Pain Severity	1.21 (0.37)	0.58 (0.56)	-7.63	< *.001*	*-1.96*
Interferences of Pain	0.30 (0.11)	0.14 (0.06)	-7.00	< *.001*	*-1.81*
PRSS					
Catastrophizing	2.54 (1.05)	1.57 (0.98)	-3.69	< *.001*	*-0.96*
Active Coping	2.83 (0.75)	3.50 (0.72)	3.51	< *.001*	*0.91*
PRCS					
Helplessness	2.06 (1.01)	1.27 (0.68)	-3.53	< *.001*	*-0.91*
Resourcefulness	2.53 (0.71)	2.42 (0.73)	-0.58	*.56*	*-0.15*
STAI X2	57.17 (24.98)	42.71 (27.15)	-2.09	*.04*	*-0.56*
DQ	61.57 (25.37)	35.50 (29.60)	-3.57	< *.001*	*-0.98*
Cardiac indexes					
HR (bpm)	75.42 (15.24)	69.10 (8.75)	-1.93	*.058*	*-0.50*
lnSDNN (ms)	3.72 (0.57)	3.99 (0.34)	2.19	*.03*	*0.57*

Note: Data are *M (SD)* of continuous and *N* of categorical variables. PRSS = Pain Related Self Statements Scale; PRCS = Pain Related Control Scale; WHY-MPI = West Haven-Yale Multidimensional Pain Inventory; STAI X2 = State Trait Anxiety Inventory X2; DQ = Dysphoria' Questionnaire; HR = heart rate; lnRMSSD = natural logarithm of the square root of the mean squared differences in successive heart periods; lnSDNN = natural logarithm of the standard deviation of normal to normal intervals.

Table 2 Partial correlation (Pearson R) in the Chronic headache group (controlling for age).

		1. PRSS Cat.	2. PRSS Act.	3. PRCS Help.	4. PRCS Res.	5. WHY-MPI Pain	6. WHY-MPI Int.	7. STAI X2	8. QD	9. HR
2. PRSS Active Coping	R	-0.12								
	p	.52								
3. PRCS Helplessness	R	0.40	-0.48							
	p	.02	.01							
4. PRCS Resourcefulness	R	-0.06	0.40	-0.30						
	p	.74	.03	.10						
5. WHY-MPI Pain Severity	R	0.46	-0.16	0.14	-0.09					
	p	.01	.38	.46	.62					
6. WHY-MPI Interferences	R	0.54	-0.23	0.17	0.09	0.68				
	p	< .001	.21	.35	.65	< .001				
7. STAI X2	R	0.32	-0.33	0.44	0.08	0.23	0.63			
	p	.09	.09	.02	.69	.24	< .001			
8. DQ	R	0.17	-0.17	0.09	-0.01	0.42	0.65	0.61		
	p	.37	.39	.63	.94	.03	< .001	< .001		
9. HR	R	0.22	-0.02	0.22	-0.005	0.15	0.40	0.20	0.25	
	p	.23	.92	.23	.98	.43	.03	.31	0.20	
10. lnSDNN	R	-0.17	0.19	-0.22	-0.02	-0.01	-0.38	-0.31	-0.51	-0.71
	p	.36	.31	.24	.90	.96	.04	.10	.005	< .001

Note: PRSS = Pain Related Self Statements Scale; PRCS = Pain Related Control Scale; WHY-MPI = West Haven-Yale Multidimensional Pain Inventory; STAI X2 = State Trait Anxiety Inventory X2; DQ = Dysphoria' Questionnaire; HR = heart rate; lnRMSSD = natural logarithm of the square root of the mean squared differences in successive heart periods; lnSDNN = natural logarithm of the standard deviation of normal to normal intervals.

Table 3 Partial correlation (Pearson R) in the Control group (controlling for age).

		1. PRSS Cat.	2. PRSS Act.	3. PRCS Help.	4. PRCS Res.	5. WHY-MPI Pain	6. WHY-MPI Int.	7. STAI X2	8. QD	9. HR
2. PRSS Active Coping	R	0.13								
	p	.54								
3. PRCS Helplessness	R	0.58	0.06							
	p	< .01	.76							
4. PRCS Resourcefulness	R	0.03	0.71	0.12						
	p	.90	< .001	.56						
5. WHY-MPI Pain Severity	R	0.22	0.18	0.21	0.14					
	p	.26	.36	.30	.50					
6. WHY-MPI Interferences	R	0.31	0.16	0.24	-0.12	0.71				
	p	.12	.41	.23	.55	< .001				
7. STAI X2	R	0.29	-0.13	0.12	-0.12	0.22	0.34			
	p	.15	.53	.56	.55	.26	.08			
8. DQ	R	0.05	0.11	0.25	0.08	0.24	0.36	0.72		
	p	.81	.59	.22	.71	.22	.06	< .001		
9. HR	R	0.04	0.07	0.20	-0.08	0.18	0.20	0.38	0.38	
	p	.85	.72	.33	.71	.37	.32	.05	.06	
10. lnSDNN	R	-0.31	0.002	-0.30	0.13	-0.24	-0.15	-0.21	-0.07	-0.57
	p	.13	.99	.13	.54	.22	.47	.30	.72	< .01

Note: PRSS = Pain Related Self Statements Scale; PRCS = Pain Related Control Scale; WHY-MPI = West Haven-Yale Multidimensional Pain Inventory; STAI X2 = State Trait Anxiety Inventory X2; DQ = Dysphoria' Questionnaire; HR = heart rate; lnRMSSD = natural logarithm of the square root of the mean squared differences in successive heart periods; lnSDNN = natural logarithm of the standard deviation of normal to normal intervals.

Table 4 General linear model simple mediation model on Pain Severity.

	Effect description	Effect estimate	SE	95% C.I. Lower	95% C.I. Upper	β	z	*p*
1	**Direct effect:**							
	Group ⇒ Pain Severity	1.59	0.26	1.08	2.10	0.59	6.11	< .001
	Component effects:							
2a	Group ⇒ Catastrophizing	0.97	0.26	0.46	1.48	0.44	3.75	< .001
2b	Group ⇒ lnSDNN	-0.27	0.12	-0.51	-0.03	-0.28	-2.23	.03
3a	Catastrophizing ⇒ Pain Severity	0.37	0.11	0.15	0.59	0.30	3.25	.001
3b	lnSDNN ⇒ Pain Severity	0.20	0.24	-0.27	0.67	0.07	0.82	.41
	Indirect effects:							
4a	Group ⇒ Catastrophizing ⇒ Pain Severity	0.36	0.15	0.07	0.64	0.13	2.46	.01
4b	Group ⇒ lnSDNN ⇒ Pain Severity	-0.05	0.07	-0.19	0.08	-0.02	-0.77	.44
	Total model:							
	Group ⇒ Pain Severity	1.89	0.25	1.41	2.38	0.71	7.70	< .001

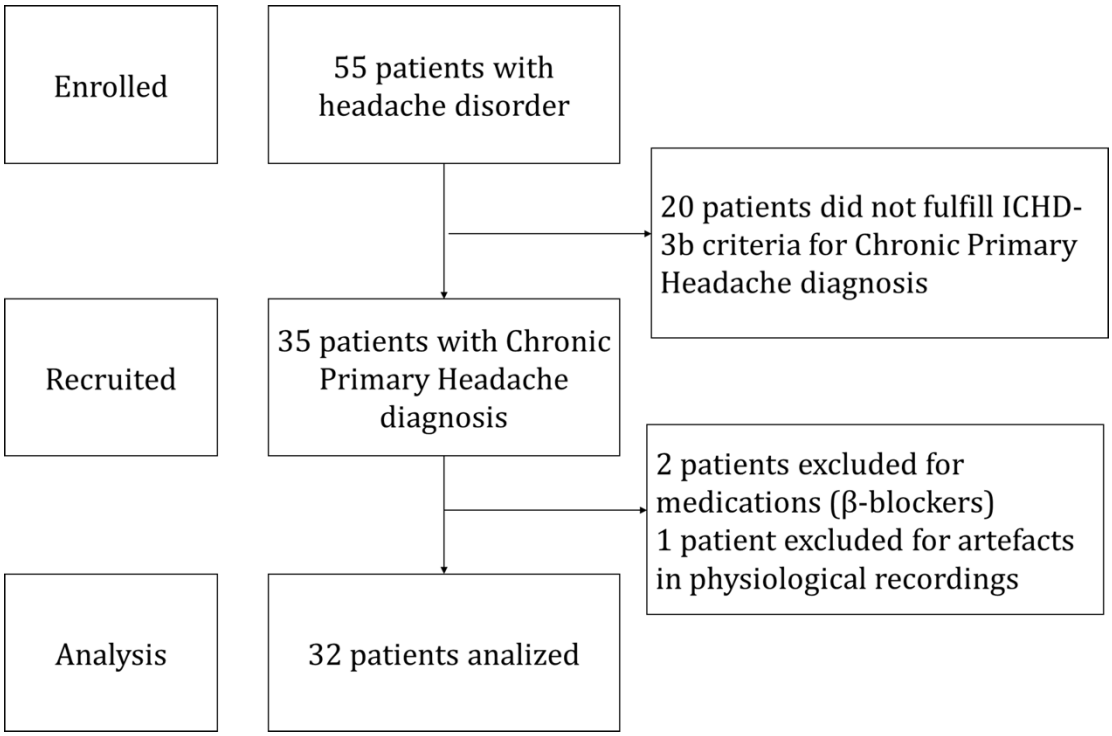
Note: for variable Group the contrast is: Chronic headache – Controls

Table 5 Mediation model on Interferences of Pain.

	Effect description	Effect estimate	SE	95% C.I. Lower	95% C.I. Upper	β	z	*p*
1	**Direct effect:**							
	Group ⇒ Interferences of Pain	1.27	0.24	0.79	1.74	0.49	5.23	< .001
	Component effects:							
2a	Group ⇒ Catastrophizing	0.97	0.26	0.46	1.48	0.44	3.75	< .001
2b	Group ⇒ lnSDNN	-0.27	0.12	-0.51	-0.03	-0.28	-2.23	.03
3a	Catastrophizing ⇒ Interferences of Pain	0.38	0.11	0.17	0.59	0.33	3.62	< .001
3b	lnSDNN ⇒ Interferences of Pain	-0.48	0.22	-0.92	-0.04	-0.18	-2.14	.03
	Indirect effects:							
4a	Group ⇒ Catastrophizing ⇒ Interferences of Pain	0.37	0.14	0.09	0.65	0.14	2.60	.01
4b	Group ⇒ lnSDNN ⇒ Interferences of Pain	0.13	0.08	-0.04	0.30	0.05	1.54	.12
	Total model:							
	Group ⇒ Interferences of Pain	1.77	0.25	1.28	2.26	0.68	7.06	< .001

Note: for variable Group the contrast is: Chronic headache - Controls

468 Figure 1.



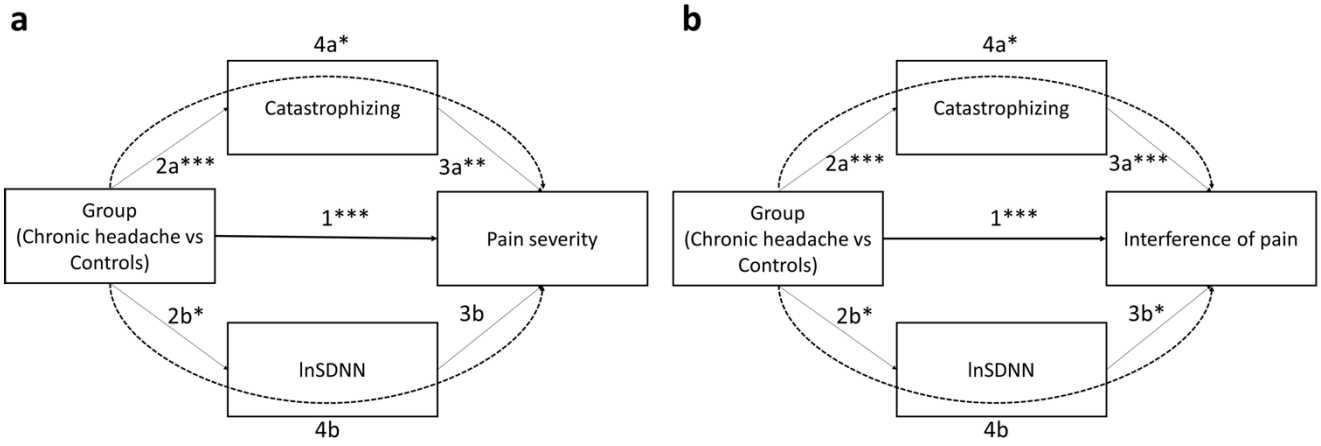
469

470 **Figure 1.** STROBE diagram of patient enrolment.

471

472 Figure 2a & Figure 2b

473 * $p < .05$, ** $p < .01$, *** $p < .001$



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476 **Figure 2a** Diagram representing the mediation model on Pain severity. Arrow 1 represents the

477 significant direct effect of group on pain severity ($p < .001$, $\beta = 0.59$), arrow 2a represents the

significant effect of group on catastrophizing ($p < .001$, β = 0.44), arrow 2b represents the significant effect of group on total HRV (lnSDNN, $p = .03$, β = -0.28), arrow 3a represents the significant effect of catastrophizing on pain severity ($p = .001$, β = 0.30), arrow 3b represents the effect of lnSDNN on pain severity ($p > .05$), arrow 4a represents the significant mediation of catastrophizing on pain severity ($p = .01$, β = 0.13), arrow 4b represents the mediation effect of lnSDNN on pain severity ($p > .05$). **Figure 2b** Diagram representing the mediation model on Interference of pain. Arrow 1 represents the significant direct effect of group on the interference of pain ($p < .001$, β = 0.49), arrow 2a represents the significant effect of group on catastrophizing ($p < .001$, β = 0.44), arrow 2b represents the significant effect of group on total HRV (lnSDNN, $p = .03$, β = -0.28), arrow 3a represents the significant effect of catastrophizing on the interference of pain ($p < .001$, β = 0.33), arrow 3b represents the significant effect of lnSDNN on the interference of pain ($p = .03$, β = -0.18), arrow 4a represents the significant mediation of catastrophizing on the interference of pain ($p = .01$, β = 0.14), arrow 4b represents the mediation effect of lnSDNN on the interference of pain ($p > .05$). Bold arrows represent direct effects, black arrows represent component effects, dotted arrows represent mediation effects.

Figure 3a & Figure 3b

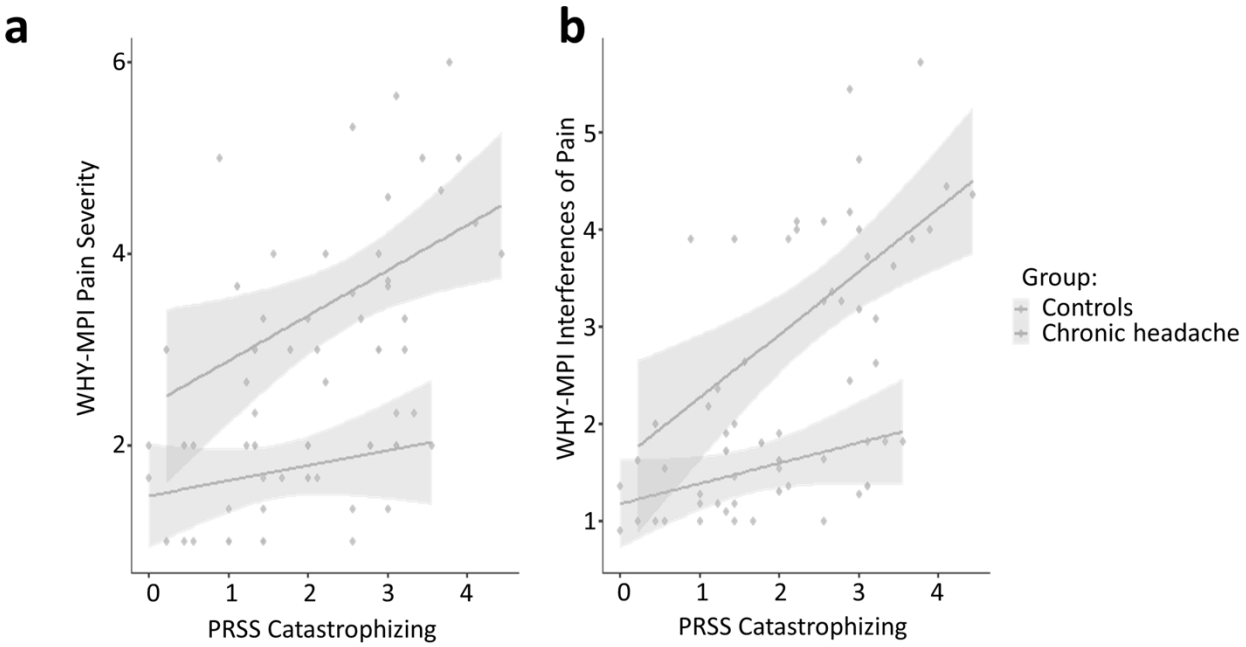

Figure 3a Scatterplot of Pain severity as a function of catastrophizing scores in the two groups.

Figure 3b Scatterplot of Interferences of pain as a function of catastrophizing scores in the two groups.