Higher Emotion-Related Distress in Patients with Fibromyalgia versus Chronic Neuropathic Pain and Healthy Controls: Is It a Primary Affective Disorder?

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Abstract

Fibromyalgia is central sensitization pain disorder with various psychological symptoms. Our aim is to compare trait paranoia, self-esteem and impulsivity between fibromyalgia patients (FM), chronic neuropathic pain sufferers (CNP) and healthy control. We administrated the Mini International Neuropsychiatric Interview to 30 FM, 27 CNP and 22 HC. All participants completed the Paranoia, Rosenberg Self-Esteem and Short UPPS-P Impulsivity Behavior Scales, Beck Depression and State-Trait Anxiety inventories. Patients provided pain ratings and completed the French version of the McGill Pain Questionnaire and Pain Catastrophizing Scale. An analysis of variance compared the three groups, with adjustment for psychological distress, pain severity and education level. Anxiety-related psychiatric comorbidities were more prevalent in FM. Depression and state anxiety were higher in both CNP and FM, while trait anxiety was higher in FM compared to two other groups. Paranoia scores were significantly higher among FM than among HC, with intermediate scores in CNP. These group differences remained after adjustment for psychological distress, pain severity and education level. Lower self-esteem and higher negative urgency in patients with FM disappeared when results were adjusted for psychological distress. FM described sensory and affective aspects of pain as more severe and displayed higher pain catastrophizing than CNP group. These results suggest that emotion-related dis-
tress is higher in FM than in CNP.

**Keywords**

Paranoia, Chronic Pain, Self-Esteem, Impulsivity

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**1. Introduction**

Fibromyalgia (FM), described as a prototypical central chronic pain disorder, is characterized by widespread chronic pain as its core symptom, sleep disturbances, psychological distress, fatigue, cognitive dysfunction, and somatic symptoms (Häuser et al., 2015). It occurs in 2% - 4% of general population, mostly in women, and can induce severe functional disability (Häuser et al., 2015). The underlying pathophysiology is still poorly understood, even though an increasing number of researchers are interested in this challenging concept of complex imbrication between physical symptoms and psychological distress. The hypotheses of existence of FM-prone personality or fibromyalgia as a form of masked depression appear as still unresolved topic (Häuser & Fitzcharles, 2018). It has been suggested that an overall deficit in sustaining positive emotions in face of pain in FM is one of perpetuating factors of the illness (Rosselló et al., 2015), but other emotion-related processes have as yet been poorly explored in this population.

Emotion-related processes would refer to the psychological, psychopathological and neurological mechanisms by which distressed emotional reactions in individuals are converted to non-distressed reactions (Baker, 2007). Emotion-related processes strongly influence emotional stated such as anxiety and depression, but also mental, behavioral and physical health of the individual (Lumley et al., 2011). There are consistent literature data in cognitive sciences that highlighted the importance of affective state and emotions in learning (Baker et al., 2010; Prokofieva et al., 2019; Woolf et al., 2009). Yet, learning and memory are strongly involved in psychopathology of chronic pain and some authors suggest that “chronic pain is pain that does not extinguish its memory trace” (Mansour et al., 2014). Therefore, better understanding of emotion-related processes associated with chronic pain is fundamental for improving clinical interventions. Moreover, direct comparison of these processes in two distinct patients’ groups, chronic neuropathic pain sufferers (CNP) and FM, could give us insight into psychopathological mechanisms of vulnerability to central sensitization for pain.

Here we adopted clinical-based perspective to approach relevant emotion-related processes in chronic pain disorders. Our clinical experience guided our choice of clinical measures to be done, and rationale of our choice was inspired by DSM-5 pathological personality traits. We decided to measure paranoia as facet of antagonism, self-esteem of negative affectivity and impulsivity of disinhibition (Hopwood et al., 2013). Paranoia is defined as unjustified distrust and suspicion of others (Freeman et al., 2012). Trait paranoia has been associated with emotional deregulation, social isolation, fewer activities, and a feeling of powerlessness in
nonclinical individuals (Freeman et al., 2012). It is highly prevalent in patients with mood disorders, particularly depression accompanied by somatic complaints and sensory disturbances (Freeman et al., 2012), and as such appears as pertinent clinical dimension to be measured in chronic pain patients. In addition, patients with chronic pain have been found to have higher trait paranoia than healthy individuals (Conrad et al., 2007) but no direct distinction has so far been made between FM and other chronic pain conditions on this personality dimension.

It has been postulated that trait paranoia is driven by low self-esteem and negative emotions (Thewissen et al., 2011). Self-esteem refers to thoughts, feelings, and evaluations about the self. Low self-esteem was previously reported in FM (Galvez-Sánchez et al., 2018). Low explicit self-esteem may be a vulnerability trait for a wide range of psychiatric conditions, from personality to affective disorders and psychosis (Bentall et al., 2009). It was suggested that positive self-esteem contributes to individual’s intrinsic motivation that further facilitates success in cognitive tasks (Galvez-Sánchez et al., 2018). Lack of self-esteem may thus constitute another possible affective feature involved in failure of FM patients to provide sustained effort in cognitive tasks (Bar-On Kalfon et al., 2016). Given this observation, it remains important to compare groups of chronic pain patients on this clinical dimension. The third dimension that we chose to measure is impulsivity. It is defined as deficient control over behavior, and manifests itself as a preference for immediate but smaller rewards over larger delayed ones. High impulsivity therefore reduces motivation to engage in tasks that require sustained effort (Zisner & Beauchaine, 2016) and further generates negative emotions. Higher impulsivity associated to higher prevalence of attention-deficit hyperactivity disorder was previously reported in FM (Yilmaz & Tamam, 2018). Importantly, Vest et al., 2016 suggested that chronic pain sufferers who react impulsively to negative mood states and cravings may be prone to opioid misuse in clinical practice.

Variability in nature of the symptoms reported by FM patients makes difficult our attempts to understand psychological mechanisms behind the illness. Dimensional approaches could therefore be useful to ascertain the precise psychopathological features of FM, particularly for emotion-related processes.

Our first aim was to assess trait paranoia, impulsivity and self-esteem in patients with FM, comparing them with CNP and healthy controls (HC) in order to elucidate if FM patients differed from others on these personality dimensions highly predictive of poor emotional coping. Further, we intended to analyze correlation between these dimensions, pain severity and psychological distress in patients’ groups in order to explore how personality dimensions of emotion-related processes associate with pain experience in patients.

Based on literature data and our clinical experience, we expected to observe higher paranoia and impulsivity and lower self-esteem in the FM group than in either the CNP or HC groups. In addition, we expected that higher scores of paranoia and impulsivity and lower self-esteem would correlate with higher pain intensity, in particular on the affective aspects of the pain evaluation.
2. Material and Method

2.1. Participants

We recruited 30 patients diagnosed with FM, according to American College of Rheumatology 2010 criteria, 27 patients with CNP eligible for invasive chronic motor cortex stimulation in a neurosurgical department and 22 HC. All patients reported experiencing pain for more than 6 months. Non-inclusion criteria for all groups were being under 18 years of age, any other chronic pain condition, current or past psychotic disorder, neurological disorder, and autoimmune disease or any other severe medical condition that might affect the clinical evaluation. We also excluded participants from the HC group if they took medication for pain or reported any chronic pain.

All participants were native French speakers. The research was conducted in accordance with the Declaration of Helsinki, and was approved by the local ethics committee. All participants gave their written informed consent before being included in the study.

2.2. Clinical Measures

We administered the Mini International Neuropsychiatric Interview (MINI) version 5.0 (Sheehan et al., 1998), a semi-structured clinical interview based on the DSM-IV Axis I diagnostic criteria, to assess mental disorder comorbidity.

All participants completed validated French versions of the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) to collect a subjective measure of depression, the State Trait Anxiety Inventory (STAI; Spielberger et al., 1984) to assess current anxiety and propensity to anxiety, the Paranoia Scale (PS; Fenigstein & Vanable, 1992) to obtain a dimensional measure of paranoia (Cronbach’s alphas: FM: 0.73; HC: 0.90; CNP: 0.81), the Rosenberg Self-Esteem Scale (RSES; Rosenberg, 1965) gauging overall explicit self-esteem (Cronbach’s alpha: FM: 0.82; HC: 0.85; CNP: 0.76), and the short version of the UPPS-P Impulsive Behavior Scale that evaluates negative urgency, positive urgency, lack of premeditation, lack of perseverance, and sensation seeking (Billieux et al., 2012; FM: α = 0.65; HC: α = 0.77; CNP: α = 0.78).

Patients with FM and CNP also provided ratings on a visual numerical scale (VNS) ranging from 0 (No pain) to 10 (Worst pain imaginable) for intensity of current pain and mean and maximum pain during the week before assessment. Pain was also measured with the French version of the McGill Pain Questionnaire (MPQ; Melzack, 1975), the Questionnaire de Saint Antoine composed of 58 pain descriptor items divided into 16 categories (9 for sensory dimension and 7 for affective dimension), where patients have to choose the best descriptor of their pain and rate its intensity, and the validated French version of Pain Catastrophizing Scale (PCS; Sullivan et al., 1995), where patients indicate the degree to which they endorse 13 items (thoughts or feelings when experiencing pain) assessing rumination, magnification, and helplessness.
2.3. Statistical Analysis

All the statistical analyses were conducted using SPSS Statistics Windows version 17.0. We ran an analysis of variance (ANOVA) to compare the three groups on clinical assessment scores and sociodemographic characteristics. Whenever a significant main effect of group was found, we conducted post hoc analyses with the Bonferroni test \((p < 0.05)\) to evaluate between-group differences. Pairwise comparisons were carried out with the t test or chi-square test. Pearson’s correlation coefficients were used to investigate the relations between PS, RSES and UPPS-P scores, pain parameters (pain duration, pain intensity, MPQ and PCS scores and sub scores), and psychological distress (BDI-II, STAI) in a whole participants sample. An analysis of covariance (ANCOVA) was used to evaluate the influence of psychological distress (BDI, STAI) and pain severity (duration, intensity) as covariates on each dependent variable (PS, RSES, UPPS-P scores) for any statistically significant Pearson’s correlations.

3. Results

3.1. Demographic and Clinical Data

Data and the results of statistical analyses of the sociodemographic variables and psychological distress, pain severity, trait dimensions and MINI assessment scores are detailed in Table 1.

| Table 1. Between-group comparisons on sociodemographic and clinical variables. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|------------------|
|                                 | HC \( (n = 22) \) | CNP \( (n = 27) \) | FM \( (n = 30) \) | Analyses | Post hoc |
| Age in years \( \text{Mean (SD)} \) | 50.73 (7.8) | 47.67 (9.9) | 49.83 (8.3) | 0.817 (ANOVA) | 0.445 — |
| Education in years \( \text{Mean (SD)} \) | 11.59 (1.7) | 10.30 (1.5) | 11.66 (1.4) | 6.695 | 0.002 CNP < FM, HC |
| BDI-II \( \text{Mean (SD)} \) | 5.45 (5.4) | 13.52 (10.1) | 30.3 (10.0) | 52.827 | <0.0001 HC < CNP < FM |
| STAI-State \( \text{Mean (SD)} \) | 28.14 (8.8) | 39.41 (14.1) | 41.80 (17.1) | 6.405 | 0.002 HC < CNP, FM |
| STAI-Trait \( \text{Mean (SD)} \) | 32.45 (8.5) | 36.78 (14.1) | 57.77 (10.9) | 51.476 | <0.0001 HC, CNP < FM |
| Paranoia Scale \( \text{Mean (SD)} \) | 29.55 (11.7) | 40.59 (13.7) | 59.60 (11.5) | 39.954 | <0.0001 HC < CNP < FM |
| RSES \( \text{Mean (SD)} \) | 36 (5.1) | 34.41 (5.2) | 24.13 (6.5) | 34.959 | <0.0001 FM < CNP, HC |
| UPPS-P negative urgency \( \text{Mean (SD)} \) | 8.09 (3.0) | 9.59 (4.1) | 10.60 (3.3) | 3.441 | 0.037 HC, CNP < FM |
| UPPS-P positive urgency \( \text{Mean (SD)} \) | 8.91 (2.6) | 9.89 (3.4) | 10.56 (2.6) | 2.059 | 0.135 — |
| UPPS-P lack of premeditation \( \text{Mean (SD)} \) | 6.73 (2.1) | 6.48 (2.4) | 7.76 (2.9) | 2.047 | 0.136 — |
| UPPS-P lack of perseverance \( \text{Mean (SD)} \) | 6.36 (2.2) | 5.93 (2.4) | 7.63 (3.4) | 2.677 | 0.075 — |
| UPPS-P sensation seeking \( \text{Mean (SD)} \) | 9.04 (3.7) | 7.89 (3.3) | 7.80 (2.6) | 1.131 | 0.328 — |

| t-test \( \text{Mean (SD)} \) | VNS current pain | 6.37 (2.1) | 5.60 (2.0) | 1.403 | 0.166 — |
|                             | VNS mean pain | 7.56 (1.6) | 7.46 (1.4) | 0.221 | 0.826 — |
|                             | VNS maximum pain | 8.56 (1.3) | 8.60 (1.2) | −0.131 | 0.896 — |
|                             | MPQ sensory pain | 24.33 (5.9) | 28.16 (5.6) | −2.511 | 0.015 — |
|                             | MPQ affective pain | 17.41 (5.9) | 22.40 (4.8) | −3.505 | 0.001 — |
|                             | PCS rumination | 10.74 (4.8) | 12.10 (3.1) | −1.271 | 0.209 — |
Continued

| PCS magnification | 4.44 (3.5) | 6.76 (2.8) | −2.773 | 0.007 |
| PCS helplessness  | 13.33 (7.1) | 17.73 (4.8) | −2.773 | 0.007 |
| Pain duration (years) | 7.26 (11.5) | 14.00 (11.5) | 2.704 | 0.009 |
| MQS III          | 11.21 (11.3) | 18.52 (12.8) | 1.284 | 0.027 |

| MINI | % (n) | % (n) | % (n) | F (ANOVA) | p | Post hoc |
|---|---|---|---|---|---|---|
| Current depressive disorder | 4.55 (1) | 7.41 (2) | 36.67 (11) | 46.531 | <0.0001 | HC < CNP < FM |
| Past depressive disorder | 18.18 (4) | 44.44 (12) | 33.33 (10) | 12.419 | 0.002 | HC < CNP, FM |
| Bipolar disorder | — | 0 (0) | 3.33 (1) | 3.387 | 0.066 | — |
| Current panic disorder | — | 0 (0) | 10 (3) | 10.526 | 0.001 | — |
| Agoraphobia | — | 3.70 (1) | 16.67 (5) | 9.195 | 0.002 | — |
| Current social phobia | — | 11.11 (3) | 10 (3) | 0.236 | 0.627 | — |
| Current OCD | — | 0 (0) | 3.33 (1) | 3.387 | 0.066 | — |
| Current PTSD | — | 0 (0) | 0 (0) | — | — | — |
| Current GAD | — | 11.11 (3) | 56.67 (17) | 46.323 | <0.0001 | — |
| Anorexia nervosa | — | 0 (0) | 3.33 (1) | 3.387 | 0.066 | — |
| Bulimia nervosa | — | 0 (0) | 0.10 (3) | 0.526 | 0.001 | — |

HC = Healthy Controls; CNP = Patients with Chronic Neuropathic Pain; FM = Patients with Fibromyalgia; BDI-II = Beck Depression Inventory-II; STAI = Spielberger State Trait Anxiety Inventory; RSES = Rosenberg Self-Esteem Scale; UPPS-P = Impulsive Behavior Scale; VNS = Visual Numerical Scale; MPQ = McGill Pain Questionnaire; PCS = Pain Catastrophizing Scale; MINI = Mini International Neuropsychiatric Interview; OCD = Obsessive Compulsive Disorder; PTSD = Posttraumatic Stress Disorder; GAD: Generalized Anxiety Disorder.

### 3.2. Correlation Analysis

Paranoia scale score positively correlated with BDI-II (r = 0.738, p < 0.001), STAI-state (r = 0.411, p < 0.001), STAI-trait (r = 0.691, p < 0.001), current, average and maximal VNS pain evaluation (r = 0.409, 0.566, 0.549 respectively; p < 0.001), sensory and affective MPQ (r = 0.600, 0.658 respectively; p < 0.001), PCS ruminations, magnification and helplessness (r = 0.554, 0.628, 0.636 respectively; p < 0.001), pain duration (r = 0.391, p < 0.001). Rosenberg self-esteem scale scores negatively correlated with BDI-II (r = −0.797, p < 0.001), STAI-state (r = −0.691, p < 0.001), current, average and maximal VNS pain evaluation (r = −0.236, −0.381, −0.389 respectively; p < 0.001), sensory and affective MPQ (r = −0.434, −0.563 respectively; p < 0.001), PCS ruminations, magnification and helplessness (r = −0.472, −0.487, −0.557 respectively; p < 0.001), pain duration (r = −0.319, p < 0.01). UPPS-P Negative urgency scale score positively correlated with BDI-II (r = 0.456, p < 0.001), STAI-state (r = 0.453, p < 0.001), STAI-trait (r = 0.439, p < 0.001), average and maximal VNS pain evaluation (r = 0.289, p = 0.01, 0.302, p < 0.01 respectively) but not with current VNS (r = 0.150, p = 0.10), sensory and affective MPQ (r = 0.297, 0.289 respectively; p < 0.01), PCS ruminations, magnification and helplessness (r = 0.328, p < 0.01; r = 0.420, 0.366 respectively; p < 0.001), pain duration (r = 0.391,
p < 0.001). UPPS-P Positive urgency scale score positively correlated with BDI-II (r = 0.249, p = 0.025), STAI-trait (r = 0.295, p < 0.01), sensory and affective MPQ (r = 0.251, p = 0.022, r = 0.293, p < 0.01 respectively), PCS ruminations, magnification and helplessness (r = 0.242, p = 0.028, r = 0.413, p < 0.001; r = 0.351, p < 0.01, respectively), pain duration (r = 0.264, p = 0.017). UPPS-P Lack of premeditation scale score positively correlated with STAI-trait (r = 0.266, p = 0.016) and education level (r = 0.246, p = 0.027). UPPS-P Lack of perseverance positively correlated with BDI-II (r = 0.338, p < 0.01), STAI-state (r = 0.411, p < 0.001), STAI-trait (r = 0.476, p < 0.001). Finally, UPPS-P Sensation seeking scale score negatively correlated with STAI-state (r = −0.290, p < 0.01).

The ANCOVA revealed group differences on paranoia as a dependent variable and the following covariates: 1) psychological distress (depression, trait anxiety, state anxiety), F = 3.654, p = 0.031; 2) pain severity (intensity of current, mean and maximum pain, pain duration), F = 13.769, p < 0.001; and 3) education level, F = 38.890, p < 0.001. An ANCOVA with self-esteem (RSES score) as the dependent variable and psychological distress as a covariate yielded a nonsignificant effect, F = 1.240, p = 0.295, as did analyses with UPPS-P negative urgency as the dependent variable and psychological distress as the covariate, F = 0.452, p = 0.638.

4. Discussion

Our findings were consistent with the literature data that affective disorders are more prevalent in FM than in other chronic pain conditions (Häuser et al., 2015), as current and past mood and anxiety disorders were more prevalent in the FM group than in the CNP or HC. We found higher depression and state anxiety scores in patients with CNP than in HC, but trait anxiety was only higher in patients with FM. Paranoia scores were significantly higher for FM than for HC, with intermediate scores in CNP, and group differences remained after adjustment for psychological distress (depression and anxiety), pain severity, and education level. Compared with CNP and HC, the FM group had a lower self-esteem score and a higher UPPS-P negative urgency sub score, but this difference could be explained by psychological distress. Moreover, patients with FM described the sensory and affective aspects of perceived pain as being more severe, and expressed higher pain catastrophizing than patients with CNP, suggesting that these aspects should be addressed in nonpharmacological therapies of the illness.

4.1. Affective Disorder and FM

Our results suggest that patients with FM are characterized by higher emotion-related distress and more prevalent affective disorders than patients with CNP or HC. We suggest two explanations for this association. First, FM and affective disorders may share the same intermediate phenotype of vulnerability, meaning that FM may be a variant of affective disorder with a predominance of somatic symptoms. Second, affective dysregulation with high depression and
anxiety may be the consequence of disturbed coping with chronic painful disease.

Based on the biopsychosocial model of FM, it is strongly suggested that psychosocial factors like child abuse or neglect contribute to predisposing, triggering and perpetuating FM symptoms (Häuser et al., 2015). Even though, there is growing number of studies suggesting that FM and depression or somatoform pain disorder are not interchangeable clinical concepts (Häuser & Fitzcharles, 2018), it is acknowledged that psychosocial stress and emotional conflicts could trigger or aggravate the illness (Häuser & Henningsen, 2014). The best-established psychopathological features on FM suggest that it is a brain disease with central pain sensitization (Häuser & Fitzcharles, 2018). We suggest that higher paranoia and lower self-esteem could contribute to poor stress coping and further central pain sensitization in FM, while the mechanisms of pain maintenance in CNP could be different.

4.2. Paranoia in Affective Disorders and Chronic Pain

The main result of our study was a higher level of paranoia in FM compared with the other two groups. Whereas the lower self-esteem in the FM population could be explained by higher levels of anxiety and depression, the higher PS score appeared to be independent of psychological distress, pain severity, and education level as confounding factors.

The literature suggests that in a nonclinical sample, higher trait paranoia and lower self-esteem are significantly correlated with experiential avoidance (Udachina et al., 2009), defined as intolerance toward negatively evaluated bodily sensations, thoughts or emotions, such that individuals make more effort to avoid, suppress or control these mental experiences. Authors further suggest that engaging in these mental control strategies is predictive of paranoid thought occurrence. Experiential avoidance is a theoretical concept that has contributed to the fear-avoidance model of chronic pain, extensively studied in the literature (Kroska, 2016). Moreover, an avoidant behavioral style in the chronic pain population is predictive of higher disability, physical disuse, and depression (Kroska, 2016). Our results suggest that the higher level of paranoia found in FM compared with CNP correlates with the sensory and affective severity of pain, as well as with pain catastrophizing, which could be predictive of functional disability.

High paranoia scores are found in a range of affective disorders, including social phobia (Schutters et al., 2012), posttraumatic stress disorder (Freeman et al., 2012), depression (Wigman et al., 2012), and bipolar disorder (Goodwin & Jamison, 1990). Moreover, some authors have suggested that specific personality traits such as high harm avoidance and low self-directedness correlate with both the propensity to develop chronic pain (Naylor et al., 2017) and major depressive and bipolar II disorder (Zaninotto et al., 2015).

The high trait paranoia in FM may therefore reflect activated schemas of a negative self and hostile others, combined with difficulty reappraising situations...
in order to effectively downregulate trait anxiety and other negative emotions in the face of pain. Coping with disease appeared less maladaptive in patients with CNP, in terms of emotion-related processes. We suggest that in FM, chronic pain perception is related to central sensitization induced by a preexisting affective disorder, whereas in CNP, emotion-related distress is the consequence of the cognitive integration of chronic pain. Moreover, a high prevalence of FM-like symptoms (musculoskeletal pain, disturbed sleep and fatigue) is associated with paranoid ideation in veterans with posttraumatic stress syndrome (Moldofsky et al., 2016), suggesting that an affective disorder can be the cause of somatic complaints. Therefore, the hypothesis that FM is a primary affective disorder should be addressed in future studies, in order to identify endophenotype markers and explore the time course of emotion-related distress.

4.3. Limitations and Conclusion

Our study had several limitations. First, this is a cross-sectional comparison of the relatively small samples that limits further generalization of our results. Second, responses to self-report questionnaires can be biased by participants’ personal feelings and their motivation for taking part in the study. Third, our sample was consecutively recruited in naturalistic conditions, in hospital units of pain management, and not perfectly matched. These aspects could limit further generalization and reliability of our findings. In addition, our findings could have other interpretations, like differential social acceptance and FM-associated stigma that could contribute to higher paranoia. Nevertheless, this is the first study that reports higher paranoia scores in FM patients. While prospective studies have demonstrated different trajectories of the relationship chronic pain-depression (Zhu et al., 2014), it would be interesting to explore if higher paranoia trait is consistent in otherwise heterogeneous profile of FM patients.

In conclusion, this preliminary study revealed significantly higher emotion-related distress in FM compared with CNP and HC. We suggest that FM and CNP do not share the same intermediate phenotype. Future studies should undertake comparisons between patients with mood disorders, particularly major depression and bipolar II disorder, and patients with FM on the paranoia, self-esteem and impulsivity trait dimensions. Findings from this pilot study may help improve the psychological evaluation associated to diagnostic and therapeutic challenges of chronic pain management in general and in FM management that requires multidisciplinary approaches in particular.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.
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