PROTOCOLLO PSYCHOFIBRO

Title

Psychological layers of Nociplastic Pain: cluster analysis of the role of personality traits, defence mechanisms, central sensitization, and childhood traumatic experiences in patients with chronic migraine, fibromyalgia, and vulvodynia.

Abstract

Chronic pain (CP) is a substantial healthcare challenge with considerable economic costs. Recently, the term of Nociplastic Pain (NP) has been advanced as a third descriptor of mechanisms related to CP. NP describes conditions that arise from altered nociception despite no clear evidence of actual or threatened tissue damage. It is a new way of describing somatoform painful conditions, originating from altered central-nervous pathways (e.g., central sensitization) and with the important involvement of clinical psychological factors. Among nociplastic chronic syndromes have been included fibromyalgia (FM), chronic migraine (CM) and vulvodynia (VU). These chronic pain disorders have been usually studied separately, although the high comorbidity rates. Many studies evidenced the role of psychosocial variables in the onset and maintenance of the burden related to these conditions. Among them, personality traits, defense mechanisms, central sensitization, and childhood traumatic experiences may play a pivotal role in the onset of the NP. The first aim of this study is to highlight possible psychosocial clusters of variables that are specific for each condition (FM, CM, and VU). A second aim, to improve the tailored psychological treatment devoted to these conditions, is to explore the association between FM, CM, and VU with depression, anxiety, somatization, quality of life, alexithymia, social support, sexual satisfaction, and functioning. This will make it possible to identify specifically for each condition the areas of greatest interest that can be investigated and treated in clinical intervention. To identify specific descriptors, NP conditions will be compared with a control group of subjects reporting other types of CP (e.g., knee arthrosis, rheumatoid arthritis). The study involves the collection of data from a self-administered questionnaire in several Italian centers specializing in the above-mentioned clinical conditions under the guidance of the research team of the Department of Dynamic and Clinical Psychology and Health Studies, PI Professor Federica Galli.

Rational

Chronic pain (CP), defined as pain lasting more than 3 months, is a substantial healthcare challenge. Prevalence rates of CP are between 11% and 40% (Dahlhamer et al., 2018). A systematic review reported a pooled CP prevalence rate of 43.5%, with the rate of moderate-to-severe disabling pain ranging from 10% to 14% (Fayaz et al., 2016). CP prevalence increases with age, is greater among females, and among people with lower socioeconomic status (Tsang et al., 2008; Pergolizzi et al., 2013). CP affects relationships and self-esteem, and is associated with higher divorce and suicide rates, and an increased risk of substance abuse (Tang et al., 2016; Fitzcharles et al., 2021), psychopathology (Katz et al., 2015) and risk of medication overuse (Westergaard et al., 2015). The causes of CP are still poorly understood. Recently, the International Association for the Study of Pain (IASP, 2017) has proposed that three subtypes of CP may be differentiated based on unique causal mechanisms: nociceptive, neuropathic, and nociplastic.

Nociplastic Pain (NP) is a new descriptor of CP and includes conditions that arise from altered nociception despite no clear evidence of actual or threatened tissue damage. NP should be viewed as an overarching terminology that can be applied to a diverse range of clinical conditions that share common neurophysiological mechanisms, involving various organ systems (Galli, 2023). Among nociplastic chronic

syndromes have been included chronic migraine, fibromyalgia, and vulvodynia (Bergeron et al., 2020; Fitzcharles et al., 2021). NP is usually accompanied by other central nervous system-associated symptoms with a close link with clinical psychological factors: general symptoms (e.g., fatigue and cognitive problems), temperamental characteristics (e.g., hypersensitivity to environmental stimuli) and psychological symptoms (e.g., anxiety/depression) (Fitzcharles et al., 2021). Many emotional states, such as depression and anxiety, and emotional processes, such as emotional awareness and regulation, may influence the presence and severity of NP (Aaron et al., 2020; Lumley et al., 2021), opening to the importance of a psychological assessment for diagnosis and psychological interventions. The concept of NP opens a new framework for understanding the co-occurrence of different chronic disorders and the role of related psychological factors. Comorbid chronic disorders may be the expression of shared pathophysiological mechanisms, with etiological and psychological features differentiating them by "pure" forms of the same disease. The comorbid association of migraine, fibromyalgia, and vulvodynia, and the well-known link with clinical psychological factors (e.g., early traumatic events, anxiety and depression, alexithymia, dissociation, etc.) is quite established (Bergeron et al., 2020; Fitzcharles et al., 2021). However, these chronic pain disorders have been usually studied as separate diseases. On the one hand, this research project wants to observe the common basis of these chronic pain disorders, which can be traced back to central sensitization mechanisms, the influence of early adverse events, and other psychological factors, and on the other hand it wants to observe the psychosocial peculiarities of each assessed condition (fibromyalgia, migraine, and vulvodynia) for tailored treatment purposes.

CHRONIC MIGRAINE (CM)

Migraine affects ~15% of the general population globally and is typically characterized by recurring, often highly disabling attacks of severe headache, nausea, vomiting, super- sensitivity to light and sound, and other variable physical, mental, and psychological signs and symptoms, lasting for 4–72 h (Ferrari et al., 2022). Migraine is listed by The Global Burden of Disease Study as the third most disabling disease worldwide (Vos et al., 2012). Most patients have episodic migraine, although some patients develop CM (the presence of ≥15 headache days per month). The 1- year prevalence of migraine is 8–15% worldwide, but is highly dependent on age, sex, and migraine subtype (Ferrari et al., 2015). Migraine is 40–60% determined by genetic factors and for the remainder by non- genetic risk- modulating and trigger factors. Although a progressive increase of the attack frequency can occur spontaneously, it is often aggravated and/or induced by overuse of acute headache medications and/or caffeine. Risk factors for migraine progression toward CM include high headache frequency, high headache-related disability, obesity, allodynia, anxiety, and depression (Ferrari et al., 2022). Comorbid migraine and anxiety/depression are common in the general population, but the mechanism(s) supporting the comorbidity are still unknown. Overall, there seems to be a bidirectional relationship between migraine and depression, and a shared pathophysiological mechanism has been recently outlined (Karsan & Goadsby, 2021). Indeed, in cohort studies, the risk of incident migraine in persons with existing major depression was threefold higher than in persons without depression, and incident major depression in persons with pre- existing migraine was more than fivefold higher than in persons without migraine history (Modgill et al., 2011). Comorbid anxiety/depression increases the risk of migraine chronification (Guidetti et al., 1998; Tietjen et al., 2007). However, there is no evidence that treating depression or anxiety mitigates migraine (Ferrari et al., 2022). Other psychological factors have been linked to migraine over time, as the case of alexithymia (Galli et al., 2017, Bottiroli et al., 2018), traumatic events (Bottiroli et al., 2019; Stensland et al., 2013), early episodes of maltreatment (Tietjen et al., 2016), personality characteristics (Bottiroli et al., 2016; 2021; Galli et al., 2019).

FIBROMYALGIA (FM)

FM is a chronic syndrome characterized by widespread musculoskeletal pain associated with fatigue, nonrestorative sleep, and cognitive deficits (Wolfe et al., 2016) with high incidence among women (Branco

et al., 2010). The prevalence of CP comorbidities among FM patients was also high ranging from 39% to 76% (with headache and irritable bowel syndrome that were the most prevalent). Although a central sensitization phenomenon seems to play a central role in FM (Arnold et al., 2016), the etiopathology of FM remains unknown (Thieme et al., 2017). For these reasons, researchers have proposed a biopsychosocial model of interacting variables that can activate and exacerbate FM symptoms (Sommer et al., 2012). FM patients experience excessive levels of psychological distress: 20–80% experience anxiety and 13–64% experience depression (Galvez-Sánchez et al., 2019). A recent systematic review on comorbidities in FM (Kleykamp et al., 2021) found that the most prevalent comorbidity across all studies reviewed was depression/major depressive disorder with over half of the patients included having this diagnosis in their lifetime. Another interesting personality construct involved in FM is 'distressed' personality (van Middendorp et al., 2016). Moreover, nearly one-third of FM patients had current or lifetime bipolar disorder, panic disorder, or post-traumatic stress disorder. Specifically, among environmental factors, stressful life events have been considered (Nakamura et al., 2014). Trauma and major life stress are unlikely to cause FM per se. In genetically susceptible persons, it is likely that early trauma and prolonged stress in adulthood will influence brain modulatory circuitry of both pain and emotions (Crofford, 2007; Schweinhardt et al., 2008) that could explain the increased pain responses and symptoms of patients with FM. Traumatic events have been shown to influence pain severity as well (Bote et al., 2013). Several theoretical models have suggested that some personality characteristics lead to a worse response to stressors and adjustment to diseases in people with CP, such as FM (Naylor et al., 2017; Galvez-Sánchez et al., 2019). A minority of studies have focused on the detection of personality disorders associated with FM (Attademo & Bernardini, 2018). In general, previous studies found a high prevalence of avoidance (41.4%), obsessive-compulsive (33.1%) and borderline personality disorder (5.2-27.4%) in FM (Thieme et al., 2004; Uguz et al., 2010; Gumà-Uriel et al., 2016). In recent years, many studies on FM have reported a high prevalence of alexithymia (15-20%) (Di Tella et al., 2017; Marchi et al., 2019; Atzeni et al., 2019).

VULVODYNIA

Vulvodynia is a condition that occurs in 8-10% of women of all ages (Arnold et al., 2007; Harlow et al., 2014) and is characterized by localized pain in the vulva, either spontaneous or upon touch, and can occur during sexual and/or non-sexual situations (Bergeron et al., 2020). Vulvodynia has a negative effect on the quality of life of women and their partners and imposes a profound personal and social economic burden. The diagnosis is established through a careful history and pelvic examination, including the cotton swab test, based on persistent vulvar pain lasting more than 3 months without an identifiable cause and with several potential associated factors. These include musculoskeletal and neurological factors, comorbid pain syndromes (such as fibromyalgia, chronic migraine, and irritable bowel syndrome) and psychosocial factors (Reed et al., 2012; Wesselmann et al., 2014; Bergeron et al., 2020). Current literature suggests that the onset and maintenance of vulvodynia likely involves a complex interplay of peripheral and central pain mechanisms, pelvic floor muscle and autonomic dysfunction, anxiety, depression, and adverse childhood events, as well as cognitive-affective, behavioral, and interpersonal factors (Bergeron et al., 2020). Vulvodynia has traditionally been conceptualized in a dualistic manner, arising from either physical factors or psychological and sexual difficulties, although research contrary to this concept and other hypotheses suggest that these two perspectives should be combined. Therefore, future studies should move in this direction, seeking to identify specific pathophysiological mechanisms within the framework of a biopsychosocial model. Indeed, a more recent theorization has focused on an integrated model that considers the interdependence of biopsychosocial factors in vulvodynia and associated disorders, in which medical and psychosocial mechanisms are considered to contribute to the onset, chronicization and exacerbation of pain and associated difficulties (Bergeron et al., 2011). The neurophysiology of vulvodynia is multifaceted and is characterized by both peripheral and central sensory abnormalities (Wesselmann et al., 2014; Pukall et al., 2016). Furthermore, increased sensitivity to different sensory modalities at extragenital sites has been demonstrated in women with vulvodynia (Giesecke et al., 2004; Foster et al.,

2005; Sutton et al., 2015), suggesting central sensitization. This central sensitization could explain the observation of overlapping chronic pain conditions in women with vulvodynia, which need further investigation to be better understood.

PSYCHOLOGICAL FACTORS ASSOCIATED TO NP

As we have already pointed out separately for the three pathological conditions (chronic migraine, fibromyalgia, and vulvodynia), there is evidence that factors such as personality traits, defense mechanisms, central sensitization, and childhood traumatic experiences may contribute significantly to the genesis of these disorders through a process of central sensitization of pain pathways. Central sensitization (CS) is defined as increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input according to the IASP - International Association for the Study of Pain (Arendt-Nielsen et al., 2018). A sensitized nervous system has been considered one of the most important mechanisms involved in NP (Cohen, 2022). CS plays a role in fibromyalgia, in which alteration of central nociceptive processing occurs and pain can be worsened by psychological factors (Sluka & Clauw, 2016). In migraine, CS may contribute to acute allodynia and headache chronification (De Tommaso & Sciruicchio, 2016). Furthermore, in migraine CS may play a role in trigeminal nerve activation and cortical spreading depression (De Tommaso & Sciruicchio, 2016). It has been suggested that migraine may be considered as a brain state of altered excitability and a disorder of sensory processing (Goadsby et al., 2017), encompassing additional symptoms as fatigue and mood disorders (Karsan & Goadsby, 2021). Structural and functional MRI studies in women with provoked vulvar or distant/extra- genital pain have supported a role of central sensitization and dysregulation of endogenous pain modulatory systems in the central nervous system in the pathophysiology of vulvodynia (Bergeron et al., 2020).

In the process of central sensitization, psychological factors such as traumatic events in childhood, the development of specific personality expressions (traits), and the use of different forms of defense mechanisms also play a role. No study to our knowledge has yet tried to identify specific clusters of psychological factors (personality traits, defense mechanisms, central sensitization, and childhood traumatic experiences) capable of characterizing or differentiating between the different pathologies expressed by a NP.

In addition to this, the study of psychosocial factors associated with the experience of such pathologies or possible emerging clusters such as depression, anxiety, somatization, quality of life, alexithymia, social support, sexual satisfaction, and functioning. This will make it possible to identify specifically for each condition the areas of greatest interest that can be investigated and treated in clinical intervention tailored to the person.

Aims

The first aim of this study is to highlight possible psychosocial clusters of variables that are specific to the onset and maintenance for each condition (FM, CM, and VU). Specifically, the observation of possible clusters will be made based on variables such as personality traits, defense mechanisms, central sensitization, and childhood traumatic experiences. The hypothesis is that specific psychological factors (clusters of high number of early traumatic events, high levels of central sensitization, and specific traits and defense mechanisms) characterize FM, CM, and VU groups compared to controls reporting other types of CP (e.g., knee arthrosis, rheumatoid arthritis).

A second aim, to give directions for tailored psychological treatments devoted to these conditions, is to explore the association between FM, CM, and VU with depression, anxiety, somatization, quality of life, alexithymia, social support, sexual satisfaction, and functioning. In line with our hypothesis that each of

these conditions has specific areas of psychological sensitivity, this will make it possible to identify specifically for each condition the areas of greatest interest that can be investigated and treated in clinical intervention.

Methods

Participants

The study involves the collection of data from a self-administered questionnaire in several Italian centers specializing in the above-mentioned clinical conditions under the guidance of the research team of the Department of Dynamic and Clinical Psychology and Health Studies, PI Professor Federica Galli.

The four centers involved in the recruitment of the participants will be the Università di Milano IRCCS Sant'Ambrogio Galeazzi under the haed of Prof. Sarzi-Puttini and Dott. Valeria Giorgi, the IRCCS Mondino di Pavia under the head of Prof. Cristina Tassorelli and Prof. Sara Bottiroli, The Policlino San Matteo of Paviaunder the head of Prof. Rossella Nappi and Dott. Lara Tiranini, and the Policlinico Umberto I of Sapienza University of Rome under the head of Dott. Cristina Iannuccelli.

Questionaires will be accessible online through a web survey available on the Google.forms platform. Participants will provide an informed consent before accessing the survey, and the questionnaire will be anonymous with no remuneration provided. The institutional ethics committee of the Dept. of Dynamic, Clinical and Health Psychology, Sapienza University of Rome, Italy (protocol code 0001979) approved the study on 25th November 2022 [UOR: SI000092 - Classif. VII/15].

Inclusion criteria:

- age range 18-65 years

- education > 5 years

- diagnosis of FM according to Wolfe, 2016

- diagnosis of CM according to Olesen, 2017

- diagnosis of VU according to Bornstein et al., 2016

Exclusion criteria

- severe psychiatric disorders and/or cognitive impairment

- difficulties in comprehension/expression in Italian

- history of other chronic pain disorder(s)

- history of other neurological disorders besides migraine

MEASURES

The study involves the administration of a protocol of self-report questionnaires consisting of two parts: the main (about 25 minutes for the administration) and the optional one (additional 20 minutes). This decision stems from the realization of the length of the protocol, to increase the collection of data in pursuit of the main objective of the study (cluster analysis).

Self-report questionnaires

Main questionnares (all the participants are requested to complete them)

- Highly Sensitive Person Scale (HSP-12) (Aron & Aron, 1997; Lionetti et al., 2018): this questionnaire investigates the theoretical framework of Sensory Processing Sensitivity, referring to a temperamental trait that predisposes to a broader sensory processing of information captured by a variety of indicators, rather than simple sensitivity to sensory stimuli. The questionnaire reports a total sensitivity score and 3 sub-factors (Easy of Excitation (EOE), Aesthetic Sensitivity (AES) and Low Sensory Threshold (LST)).

- Central Sensitivity Inventory (CSI) (Chiarotto et al., 2018): The Central Sensitisation Inventory was developed to assess the overlapping symptomatic dimensions of the central sensitivity syndrome. This measure is intended as a screening tool to help identify the presence of the syndrome and to alert clinicians that presenting symptoms may be related to it. It consists of two parts: part A provides a 0-100 total score for 25 items on current health symptoms with five response options ranging from 'never' (0) to 'always' (4); part B investigates if patients were previously diagnosed by a physician with one or more of seven different conditions.

- Traumatic Experiences Checklist (TEC) (Nijenhuis et al., 2002): the instrument investigates 29 types of potential trauma, including the events listed in criterion A of PTSD, as well as other potentially overwhelming events: loss of significant others, life-threatening illness or aggression, experience of warehousing, emotional neglect, emotional abuse, physical abuse, sexual harassment and sexual trauma. The questionnaire includes a total complex trauma score and 5 subscales investigating emotional neglect, emotional abuse, physical threat, sexual harassment, and sexual abuse.

- PID-5 Short form (Thimm et al., 2016): This instrument represents the short version of the PID-5 self-report inventory designed to assess the 25 facets of pathological personality traits and the five higher-order domains of DSM-5 Criterion B. It assesses 5 personality trait domains including negative affect, detachment, antagonism, disinhibition, and psychoticism, with each trait domain consisting of 5 items.

- Defense Mechanism Rating Scales - DMRS-SR-30 (Di Giuseppe et al., 2020); is an instrument based on the identification of 30 individual defenses arranged hierarchically in 7 levels according to similarity of function and level of adaptability. The DMRS provides a definition of each defense mechanism, a description of its intrapsychic function and criteria for discriminating one defense from its neighboring defenses. Defense levels can be categorized as mature and immature neurotic, and the latter is further subdivided into depressive and non-depressive.

- Mental Pain Questionnaire (Svicher et al., 2019): is a 10-item true-false style self-report questionnaire developed to assess mental pain.

Optional questionnaires (the participant decides whether to complete them)

- Brief Symptom Inventory (BSI-18) (Franke et al., 2017): an abbreviated version of Derogatis' Brief Symptom Inventory, contains the three six-item scales of Somatization, Depression, Anxiety and the Global Symptom Score (GSI).

- SF-12 - Quality of Life Assessment (Apolone et al., 2001): The SF-12 is a generic short-form health survey developed in the United States from the original SF-36. It produces two summary measures for the assessment of self-perceived physical and mental health that are interchangeable with those of the SF-36.

- Toronto Alexithymia Scale (TAS-20) (Bagby et al., 1994): The Toronto Alexithymia Scale is a 20-item self-administered questionnaire that measures difficulty in identifying and describing emotions, which is an important part of alexithymia.

- Chronic Pain acceptance Questionnaire (CPAQ-8) (Fish et al., 2010): is an 8-item inventory measuring the acceptance of chronic pain.

- SPQ - Social Support Questionnaire (SPQ) (van der Lugt et al., 2012): is a short measure of perceived social support in relation to pain.

- Sexual Satisfaction Scale (SSS) - Short form) (Meston & Trapnell, 2005): represents a short 6-item measure of sexual satisfaction and discomfort.

- Short Form McGill Questionnaire (SF-MGQ) - Adapted for genito-pelvic pain (Melzack & Raja, 2005). Represents a qualitative and quantitative measure of pain, adapted to the genito-pelvic area.

- Female Sexual Function Index (FSFI) (optional) and International Index of Erectile Function (IIEF) (optional) (Rosen et al., 1997; 2000): represents a differentiated questionnaire for females and males on sexual function (desire, arousal and orgasm and satisfaction).

STATYSTICAL PLANNED ANALYSES

The required sample size was estimated a priori for the ANOVA procedure that tested the cluster model sensitivity having 4 groups (migraine, fibromyalgia, vulvodynia, and controls). Using the G*power program, p= 0.05, statistical power of 85%, and effect size of 0.35, the calculation yielded a total sample size of n = 108 participants per group (432 as total) The four centers involved in the recruitment of the participants will be the Università di Milano IRCCS Sant'Ambrogio Galeazzi under the haed of Prof. Sarzi-Puttini and Dott. Valeria Giorgi, the IRCCS Mondino di Pavia under the head of Prof. Cristina Tassorelli and Prof. Sara Bottiroli, The Policlino San Matteo of Paviaunder the head of Prof. Rossella Nappi and Dott. Lara Tiranini, and the Policlinico Umberto I of Sapienza University of Rome under the head of Dott. Cristina Iannuccelli.

ANOVAs and chi^2 analyses will be carried out to compare groups on sociodemographic characteristics for descriptive reasons and to select possible covariates based on selection bias.

A group of cluster analyses will be performed to classify the samples based on personality traits, defense mechanisms, central sensitization, and childhood traumatic experiences (twenty-two variables corresponding to total scores and thematic subscales of the related measures), aiming to identify different clinical phenotypes within the study samples. A statistical procedure of Two-Step Cluster Analysis will be preferred due to its ability to ensure that one variable does not dominate the cluster solution. Furthermore, it enables the user to identify the importance of each item in the cluster solution. The model fit will be assessed by Schwarz's Bayesian Information Criterion and evaluated by the average silhouette coefficient, an internal validity index representing cluster cohesion and separation quality, ranging between 0 and 1; the closer to 1, the better the model.

Crosstab analyses will be performed to test the association and their strength, and MANOVAs to detect differences in the classification variables based on cluster groups, and Pearson's correlation to explore associations among clusters and other psychological domains. The statistical analyses will be performed using IBM SPSS v. 27.0 and AMOS v.22 (SPSS Inc., Chicago, IL, USA).

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