PAIN AND DEPRESSION

EDITED BY: Qing Zhao, Yazhuo Kong and Li Wan
PUBLISHED IN: Frontiers in Psychology and Frontiers in Behavioral Neuroscience

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-969-0
DOI 10.3389/978-2-88974-969-0

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PAIN AND DEPRESSION

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Citation: Zhao, Q., Kong, Y., Wan, L., eds. (2022). Pain and Depression. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88974-969-0

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frontiers in Psychology

EDITORIAL
published: 30 March 2022
doi: 10.3389/fpsyg.2022.865071

Editorial: Pain and Depression

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Keywords: pain, depression, pain–depression comorbidity, neuroinflammation, non-opioid interventions

Editorial on the Research Topic

Pain and Depression

This special issue, *Pain and Depression*, aims to collect and present the current scholars' knowledge on pain–depression comorbidity. Pain and depression are intertwined and undermine the wellbeing of millions around the world. Nevertheless, the reasons for the association of pain and depression are still unclear. We consider that: (1) Pain–depression comorbid conditions might correspond to physiological–psychological spectral manifestations of underlying health problems (Von Korff and Simon, 1996); (2) Pain and depression could be in a bilateral causal loop (Nicolson et al., 2009). That is, pain might induce depression (Brown, 1990), and depression could increase people's sensitivity to pain as well as the risk of developing chronic pain (Hermesdorf et al., 2016); (3) The causal loop of pain and depression might evolve into a vicious circle without effective medical and mental intervention (Rosemann et al., 2007). A better summarization of the relationship between pain and depression could be the first step toward decoding the nature of the pain–depression loop.

Therefore, we presented the special issue of *Pain and Depression* to the Frontiers in Psychology (Health Psychology, Emotion Science, and Neuropsychology) and the Frontiers in Behavioral Neuroscience (Pathological Conditions). From the 8th July 2019 to the 20th September 2021, with dedications by 65 authors and 21 reviewers, 11 manuscripts have been published. These studies included three qualitative and quantitative reviews (Campos et al.; Davis et al.; Du et al.), three self-report studies (Boring et al.; Catalá et al.; Peng et al.), two behavioral examinations (Li et al.; Guo et al.), a brain imaging investigation (Jami et al.), a cross-species experiment (Zhang et al.), and a theoretical proposal (Cukić).

Du et al. reviewed the 100 top-cited studies of the pain-depression relationship. They found that 47% of the studies supported a causal effect from pain to depression (i.e., pain → depression), while 9% suggested the opposite relationship (i.e., depression → pain; see Table 1 of Du et al.). Meanwhile, 23% of the studies presented a positive correlation between pain and depression, but 3% reported an insignificant correlation (Du et al.).

From the physical viewpoint, Campos et al. proposed that neuroinflammation underpinned the pain–depression comorbidity. Through a cross-species investigation, Zhang et al. emphasized the role of inflammatory molecules in causing radicular pain. According to Campos et al., the key to alleviating the pain–depression symptoms could be the pharmacological modulation of inflammatory mediators (e.g., cytokines). Alternatively, Cukić sustained the efficiency of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) in treating depression featured by aberrant fronto-limbic functional connectivity. Essentially, abnormal neurotransmission in the mesolimbic dopamine system (i.e., a network connecting the prefrontal cortex and the limbic system) could underpin comorbidities among pain, depression, and addiction (Serafini et al., 2020). Therefore, identifying effective, specific,

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Specialty section:
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

Received: *29 January 2022*
Accepted: *23 February 2022*
Published: *30 March 2022*

Citation:
Zhao Q, Kong Y and Wan L (2022) Editorial: Pain and Depression. Front. Psychol. 13:865071. doi: 10.3389/fpsyg.2022.865071

and alternative non-opioid therapies for patients with pain and depression could be increasingly important (Serafini et al., 2020), specifically during the opioid epidemic (e.g., Rogers et al., 2021).

From the psychological viewpoint, Boring et al. indicated that the mediator between pain and depression could be the feeling of shame (e.g., self-doubt and self-criticism). With healthy volunteers, they found that previous experiences of "pain invalidation" from family, friends, and medical professionals might lead to the feeling of shame, which in turn could give rise to depression (Boring et al.). The above study highlighted the importance of empathy for pain in society (Jami et al.). Moreover, Li et al. observed that healthy volunteers with capsaicin-induced pain could show disturbed processing (e.g., a longer reaction time) of emotions, especially of sadness. It should be noted that the conscious and unconscious attentional biases for negative emotions are a risk marker of depression (Watters and Williams, 2011). These studies hinted at the necessity of psychological interventions for patients with pain and depression. For example, Davis et al. listed a spectrum of non-pharmacological interventions (e.g., mindfulness-based therapy and guided imagery with relaxation) for patients with inflammatory bowel disease, anxiety, and depression.

Intriguingly, Catalá et al. reported that although female patients living in rural areas suffered more pain symptoms, their psychological wellbeing (e.g., pain acceptance and mental fatigue) was better than their urban counterparts. More importantly, Guo et al. found that Chinese university students' depression was negatively correlated with their forced vital capacity. These studies suggested that depression symptoms might be related to insufficient oxygen intake (Miravitlles et al., 2014), and indicated the possibility of administering oxygen-enriched air while treating depressed patients (Bloch et al., 2021). Referencing Catalá et al., rural areas with advanced clinical facilities could be ideal for recovering from pain–depression comorbidity.

FOR THE FUTURE

Pain (Clauw et al., 2020) and depression (Peng et al.) are of growing concern in the current and post-COVID-19 eras. This special issue presented a glimpse of the pain–depression relationship. It is essential to keep on investigating the etiology of pain–depression comorbidity (e.g., neurological, neurohumoral, psychological, and physical mechanisms), identifying moderators of the comorbidity (e.g., living conditions, socioeconomic status, and view of life), and exploring the effective non-opioid pharmacological, physiological, and psychological treatments for the issue (e.g., acupuncture and biofeedback; Nicolson et al., 2009; Lee et al., 2019). Notably, males tend to conceal more physical and mental suffering than females to protect their masculinity (Shi et al., 2021). Therefore, the pain–depression causal relationship, its moderators, and its corresponding intervention could vary according to sex. Finally, the importance of empathy in helping patients suffering from pain, depression, and addiction deserves attention in the Age of Empathy (Jami et al.; De Waal, 2009).

AUTHOR CONTRIBUTIONS

QZ wrote the first draft of the editorial. YK and LW conducted the editorial revision. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank all authors and reviewers who worked on this project.

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frontiers in Psychology

OPINION
published: 13 January 2020
doi: 10.3389/fpsyg.2019.02923

The Reason Why rTMS and tDCS Are Efficient in Treatments of Depression

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Keywords: physiological complexity, rTMS, tDCS, depression, efficiency of treatment, neuromodulation

INTRODUCTION

The exact neurophysiological mechanisms of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) for treating patients diagnosed with depression are still not clear. Results of previous structural and functional MRI studies showed an aberated functional connectivity in major depressive disorder (MDD) (Vederine et al., 2011; de Kwaasteniet et al., 2013). Those, as well as several connectivity studies (Bluhm et al., 2009; Berman et al., 2011; Zhang et al., 2011; Kim et al., 2013; Chen et al., 2015) seem to support the hypothesis that aberrant functional connectivity within fronto-limbic system underlies the pathophysiology of depression. It should be noted that antidepressant application of both rTMS and tDCS is based on previous findings that these two methods help in the case of hypoactivity of the left dorsolateral prefrontal cortex (DLPFC) (Grimm et al., 2006). Those structural and functional differences probably introduce abnormal physiological complexity demonstrated in electroencephalographic (EEG) (Ahmadlou et al., 2012; Bachmann et al., 2013; Hosseinifard et al., 2014; De la Torre-Luque and Bornas, 2017; Jaworska et al., 2018; Lebiecka et al., 2018) as well as in electrocardiographic (ECG) signals in depression (Migliorinni et al., 2012; Rossi et al., 2016; Iseger et al., 2019).

TDCS is low-intensity modality of transcranial electrical stimulation (TES) which induces very mild sensations in the skin (Stagg and Nitsche, 2011). Much later developed TMS primarily uses a strong magnetic field to induce an electric field in the cortex painlessly, initiating optimally focused activation of neural structures (Barker et al., 1985). Some of its modalities used in psychiatry are repetitive TMS (rTMS) and intermittent theta burst TMS (iTBS). In the present abundant literature about both rTMS and tDCS, there is scarce evidence of *why* these two techniques are capable of ameliorating depressive symptoms. We still don't know what precise mechanisms behind them are. Only a fraction of published research (Amassian et al., 1989; Maccabee et al., 1990; Wassermann and Grafman, 2005; Miranda et al., 2009; Ilmoniemi and Kičić, 2010; Alam et al., 2016) describe the theoretical background of those mechanisms from electromagnetics/physics point of view. The majority of published studies are based on multi-centric comparisons of clinical efficiency (Brunoni et al., 2016; Antal et al., 2017; Mutz et al., 2018) and computational methods-or simulations (Miranda et al., 2001, 2006; Wagner et al., 2007; Huang et al., 2017). Recently, a team of leading researchers in low intensity electrical transcranial stimulation reviewed clinical outcomes for 8,000 people (Antal et al., 2017) confirming its safety and effectiveness, and defined the regulatory and application guidelines for future research.

A term "non-invasive" (attached to both rTMS and tDCS) stems from obsolete medical point of view that the stimulating electrodes do not enter the crania (and the stimulation is performed either via small electrical charges in case of tDCS or via Faraday's induction). The real effect of "non-invasive" electromagnetic stimulation (rTMS and tDCS) cannot be measured directly due to their non-invasive nature. Opitz stated in recent research, that the important point is in interpretability of stimulation effects (Opitz et al., 2015): "if electric fields are delivered inconsistently, but effects are observed nevertheless, the results are more difficult to interpret

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Specialty section:
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

Received: *03 October 2019*
Accepted: *10 December 2019*
Published: *13 January 2020*

Citation:
Čukić M (2020) The Reason Why rTMS and tDCS Are Efficient in Treatments of Depression. Front. Psychol. 10:2923. doi: 10.3389/fpsyg.2019.02923

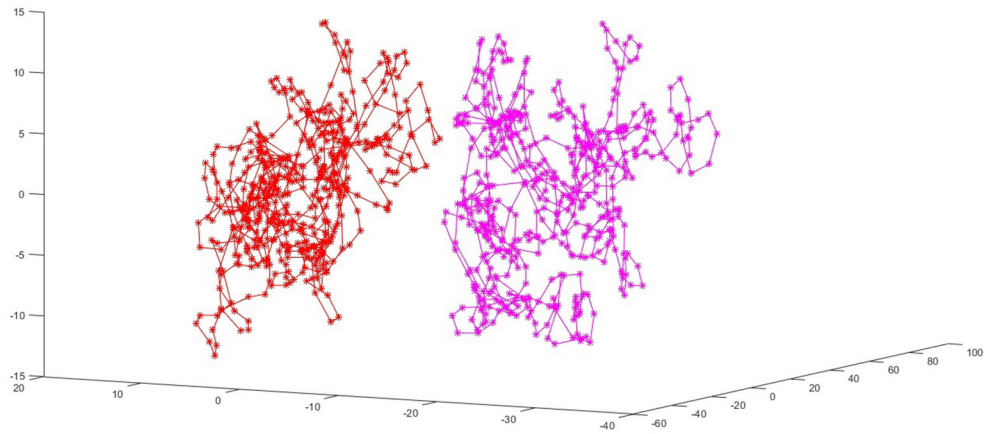

FIGURE 1 | The red voltage samples are taken from the EEG recording before the stimulation, and pink ones from 32 min after the tDCS stimulation. The first three principal components of raw EEG samples before and after tDCS stimulation are illustrating that they belong to separate parts of the phase space. Here is a PCA plot for person number 8, with cathodal (C) stimulation. This figure is part of results published in Chapter 3 in book (Čukić Radenković, 2019), but this particular PCA plot is not displayed before (due to limited space in previous publication).

because effect could be driven by other incidentally affected brain regions." Both tDCS and TMS are shown to initiate these "unintended" effects: Bestmann showed using MRI that TMS of motor cortex below the threshold power can activate some other deeper structures, contrary to previous belief and Li showed similar phenomena in the case of tDCS (Bestmann et al., 2003, 2004; Li et al., 2018).

The hypothesis here is that both non-invasive electromagnetic modalities of brain stimulation, rTMS and tDCS, are efficient in depression treatments because of *their proven ability to decrease the physiological complexity* (Čukić et al., 2013, 2019a; Lebiecka et al., 2018; Zuchowicz et al., 2019). The hallmark of MDD is elevated physiological complexity of EEG measured by various entropy measures, fractal dimension, symbolic dynamic approach measures, geometric techniques like recurrence plots and other measures stemming from complex systems dynamics theory (De la Torre-Luque and Bornas, 2017). There are also findings that link changes in heart rhythm complexity with depression (Migliorinni et al., 2012) and the outcomes of rTMS treatment (Royster et al., 2012; Lebiecka et al., 2018; Iseger et al., 2019).

The evidence supporting the close relationship between the electrophysiological complexity, depressive symptoms, and rTMS and tDCS treatment is sufficient but veiled. First, in our 2011 study we showed that even a single pulse transcranial magnetic stimulation (spTMS) can decrease the complexity of electrophysiological signal (Čukić et al., 2012, 2013). Second, Mutanen et al. (2013) used Global Recurrence analysis on concurrently recorded EEG to show that TMS is capable of inducing a "brain-shift" after the stimulation., that is moving the system of brain networks to higher-energy less-probable state in healthy controls. Based on this work we applied the same method but with tDCS (Čukić et al., 2018b, 2019a,b). Čukić et al. (2018b) showed for the first time the graphical representations of tDCS-induced "brain-shift" obtained by principal component analysis (PCA) applied on raw EEG signal samples. PCA was used in our data mining projects to check for separability of data for later classification. This study re-used EEG signals from 16 healthy controls recorded during cathodal and anodal tDCS stimulation protocols from Pelliciari et al. (2013) (which is also elaborating on the difference between cathodal and anodal stimulation). Obtained PCA plots are showing that more than a half an hour post stimulation the system is still in higher-energy lower-probable state "brain-shift" due to the tDCS stimulation. The first three principal components of raw EEG samples before and after tDCS stimulation are illustrating that they belong to separate parts of the phase space. One of participants PCA plot after cathodal stimulation is shown in **Figure 1**.

Several researchers who used various non-linear measures of complexity of EEG confirmed that physiological complexity is elevated in MDD (Ahmadlou et al., 2012; Bachmann et al., 2013; Bachmann et al., 2015, 2018; Faust et al., 2014; Hosseinifard et al., 2014; Akar et al., 2015; Čukić et al., 2018a, 2019a; Lebiecka et al., 2018). One of the most inclusive review studies on various spectral, fractal and other non-linear measures of relationship between physiological complexity and MDD, concluded that EEG signals in MDD are "probably more random than more complex" compared to those of healthy persons (De la Torre-Luque and Bornas, 2017). This might be due to impaired intrinsic feedback mechanisms important for many regulatory functions (Goldberger et al., 2002). This kind of abnormal functional connectivity is reported in several research papers from seemingly unrelated disciplines, like graph theory application in EEG connectomics (Lee et al., 2011; Van Essen et al., 2012; Castellanos et al., 2013; Kim et al., 2013), and Granger causality applied on fMRI signals (Hamilton et al., 2011). The fMRI and Fractional anisotropy (FA) research also found that within fronto-lymbic system there is abnormal functional connectivity in MDD (Vederine et al., 2011; de Kwaasteniet et al., 2013). De Kwaasteniet found that uncinate fasciculus,

important for connecting prefrontal with limbic system, is not fully functional in MDD patients (de Kwaasteniet et al., 2013). Moreover, several studies examining connectivity in MDD found a different dynamical features, and several different regions (anterior cingulate cortex, insula, cingulate and hippocampal network) were confirmed as candidates for these differences (Mayberg, 1997; Mayberg et al., 1997, 1999; Bluhm et al., 2009; Berman et al., 2011; Ge et al., 2019). It is challenging to compare these findings since their methodological approaches are different in so many aspects. Also, Mendez et al. (2012) detected a higher focus on local connections than on global ones in MDD. This can also be seen in persons with depression in remission: previously detected abnormal functional connectivity decreases (Mendez et al., 2012). Lebiecka et al. (2018) showed that elevated physiological complexities diminished after treatment in those MDD patients that reacted well on rTMS (as measured by the decrease in complexity corresponding to remission scores after the treatment was measured) (see also Jaworska et al., 2018). Iseger et al. (2019) also revealed the connection between successful iTBS applied to the DLPFC and modulation of autonomic nervous system (Iseger et al., 2019).

Bestmann et al. (2004) demonstrated that with TMS application below the motor threshold power, MRI can detect a response from areas that were not intended to be stimulated (Bestmann et al., 2004). Li et al. (2018) were the first research group to demonstrate that tDCS can activate some structures within DMN. Opitz et al. (2015) conclude in their work that even the conductivity constants (dielectric constants for tissue types) used for calculating the effect of stimulation, or simulation, are not adequate for describing the much more demanding reality. Opitz's team detected both higher and lower actual values measured directly (with the array of implanted electrodes in patients that were candidates for surgical intervention on epileptic foci) than those predicted with standard simulation procedures for TES (Opitz et al., 2015, 2018). The effect of a stimulation can depend on the geometrical shape of the surface of sulci, which cannot be monitored during the use of a non-invasive procedure, and that also can lead to major miss-predictions (Čukić, 2006; Čukić et al., 2009; Saturnino et al., 2015; Alekseichuk et al., 2018; Opitz et al., 2018).

Although it can seem impossible to compare the two non-invasive brain stimulation techniques that are so different in the sense of their electromagnetic properties and the level of power they can induce in the living tissue, we can still recognize the same functional pattern. In many review papers exploring the efficiency of both rTMS and tDCS in clinical applications (Brunoni et al., 2016; Antal et al., 2017; Mutz et al., 2018), the conclusions are in line: they are effective, and tDCS can be applied even in primary care, but also as a maintenance treatment for already successful rTMS (Mutz et al., 2018). In a study examining the effect of electroconvulsive therapy, it is demonstrated that multiscale entropy is changed after the treatment (Okazaki et al., 2013), pointing again at the link between complexity changes and the effective treatment for depression. Zuchowicz et al. (2019) reported on detected synchronization of EEG as a feature of successful rTMS which is pointing at reduction of complexity, too.

For all electromagnetic stimulation treatments, the effect is of temporary nature. The rationale is that they can at least ameliorate the symptoms for a limited time; after which they need to be repeated. The common advantage of non-invasive brain stimulation techniques over medications is that there are no foreseeable harmful side-effects (Antal et al., 2017).

Although study of physiological complexity changes is still in the realm of research and mainly not in use in clinical setting, it is expected that soon clinicians would start using varying electromagnetic modalities of stimulation with better understanding of how they work—as means to decrease complexity characteristic of depression. Further research based on empirical data is necessary before making the final conclusion that non-invasive brain stimulation treatments may work through changing physiological complexity.

CONCLUSION

To conclude, after all above mentioned results of various lines of research that tried to bring us closer to understanding various aberrations of depression, both rTMS and tDCS might be efficient because of their ability to decrease characteristically elevated levels of physiological complexity in depression.

AUTHOR CONTRIBUTIONS

MČ conceived the idea about the article, performed a literature research and wrote entire text.

ACKNOWLEDGMENTS

MČ thankful to colleagues Prof. Carlo Miniussi, Debora Brignani Ph.D., and Maria Concceta Pelliciari Ph.D. for sharing their data with me and for valuable discussions, and also to Prof. Danka Savić for valuable advice on imrpoving the text of this manuscript. Part of this work is supported by RISEWISE (H2020-MSCA-RISE-2015-690874).

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

MINI REVIEW
published: 11 February 2020
doi: 10.3389/fpsyg.2019.03072

The 100 Top-Cited Studies About Pain and Depression

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With the estimated high prevalence in the population, the two symptoms of pain and depression threaten the well-being of millions worldwide. Researches of the two symptoms increased year by year. Top-cited studies will help to understand the achievement and guide researchers toward the direction of the research field. However, it is unclear for researches in the field of pain and depression. In this paper, we reviewed the bibliometric characteristics of the top-cited papers about pain and depression. We will review the evidence of authorship, country of origin, institution, journal, study type, and publication year for the 100 top-cited studies on pain and depression based on the Web of Science Core collection. We also highlight studies with the highest cited times. Our study concluded that pain and depression were correlated, which may share common biological pathways.

Keywords: pain, depression, top-cited, bibliometric review, citation, citation analysis

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Emotion Science, a section of the journal Frontiers in Psychology

Received: *31 July 2019*
Accepted: *27 December 2019*
Published: *11 February 2020*

Citation:
Du L, Luo S, Liu G, Wang H, Zheng L and Zhang Y (2020) The 100 Top-Cited Studies About Pain and Depression. Front. Psychol. 10:3072. doi: 10.3389/fpsyg.2019.03072

INTRODUCTION

With the estimated prevalence in the adult population ranges from 5 to 60% (Gureje et al., 1998; Blyth et al., 2001; Smith et al., 2001), the pain has become the most common problem worldwide. Likewise, depression, the first cause of disability before 2030 forecasted by WHO (2017), prevalence of which in primary care is estimated at 5–10% (Katon and Schulberg, 1992). Current evidence suggests that pain and depression have reciprocal influence (Kroenke et al., 2011) and often co-occur (Kroenke et al., 2010). The prevalence of co-occurrence of pain and depression ranges from 30 to 65% (Arnow et al., 2006; Bair et al., 2008), even higher than the respective prevalence of pain and depression (Bair et al., 2003). Growing number of studies investigated the comorbidity of pain and depression (Campbell et al., 2003; Chopra and Arora, 2014; Li, 2015), yet there is no relevant evidence in the aspect of bibliometrics analysis.

Bibliometric method has been widely used to provide an analysis of books and articles and has been used to assess the impact of research outputs (Blakeman, 2018). Citation analysis is one of the key methods of bibliometric method, aiming at constructing indicators of research performance from a quantitative analysis of scholarly documents (Moed, 2009). The frequency of citation indicates the relative significance in the particular discipline (Iyengar et al., 2009; Kanter, 2009). Analysis of top-cited studies helps understand the current achievement and guide researchers toward the direction of development of the field (Zhang et al., 2019a,b).

Analysis of top-cited articles has been used in different fields, including cancer immunotherapy (Zhang et al., 2019a), cardiology (Shuaib et al., 2015), gastroenterology and hepatology (Azer and Azer, 2016), and urology (Ipekci et al., 2017). However, there is no top-cited analysis of the comorbidity of pain and depression. Intend to bridge this gap, in this study, we performed a bibliometirc review to assess 100 top-cited studies on pain and depressions based

on Web of Science Core Collection and discuss the relationship between pain and depression.

REVIEW METHODS

Studies of pain and depression published in journals were identified in the Web of Science Core Collection using the keywords "pain" and "depression" in July 2019. The Web of Science Core Collection database includes peer-reviewed publications indexed from more than 10,000 high impact journals in the world (Brown et al., 2019). All published papers since 1945 were searched in the database, and citation count ranked the results. Two researchers independently selected the 100 top-cited studies about pain and depression. Any article studied the comorbidity of pain and depression were included for further analysis. Articles mentioned pain and depression without investigating the relation between pain and depression were excluded. The disagreements were resolved by discussion. If necessary, the discrepancies were resolved by consulting the third researcher. A data extracted form was pre-defined, including the basic information, such as title, the first author and corresponding author's name, publication year, the number of citations, source of the journal, impact factor of the journal, article type, organization of corresponding author, country of origin based on the corresponding author. Each study was reviewed, and the information was collected. The relationships between the number of citations and journal, publication year, study type, country, institution, and authorship were analyzed. Descriptive statistics were used to present the results. The analyzed data and results could be assessed by contact with the corresponding author of this study. This is a bibliometric review, so ethics is not applicable.

THE CITATION CHARACTERISTICS OF THE 100 TOP-CITED STUDIES ON PAIN AND DEPRESSION

The 100 top-cited studies are listed in **Table 1** in descending order of the number of citations, which were published from 1979 to 2014. The number of citations ranged from 94 to 1,576, and the mean citation number was 191. The most frequently cited study was "Depression and pain comorbidity-a literature review" (Bair et al., 2003). It was published in Archives of Internal Medicine (now JAMA Internal Medicine), the author conducted a literature review to determine the prevalence of pain and depression, they also reviewed the effects of comorbidity on diagnosis, clinical outcomes, and treatment. The second most-cited paper was a review named "Chronic pain-associated depression: antecedent or consequence of chronic pain? a review" (Fishbain et al., 1997), which was published in Clinical Journal of Pain, it was cited by other studies about 618 times. The authors reviewed eighty-three studies and found that depression was more common in chronic pain patients (CPPs) than in healthy controls. The third most cited study was a review named "Chronic pain and depression-dose the evidence support a relationship" (Romano and Turner, 1985). It was published in Psychological Bulletin and been cited 523 times.

JOURNALS OF TOP-CITED STUDIES

Among the 100 top-cited studies, 20 were published in Pain, 6 from Clinical Journal of Pain, 5 from Psychosomatic Medicine, and 4 from Journal of Pain. 3 studies were published in each of the following journals: Jama-Journal of the American Medical Association, Journal of Abnormal Psychology, Journal of Pain and Symptom Management and Journal of Consulting and Clinical Psychology. The other journals had <3 studies. The total citation number of journals ranged from 94 to 3,508. The impact factors of all the journals in 2018 were between 1.438 and 51.273 (**Table 2**).

PUBLICATION YEARS OF 100 TOP-CITED STUDIES

The 100 top-cited studies were published between 1979 and 2014. The year 2003 and 2005 were the years with most citation number ($n = 8$), followed by 2008 ($n = 7$), and 2001 ($n = 6$), 2004 ($n = 6$), and 2009 ($n = 6$). Of all the years, the year 2003 contributed the most citation times ($n = 2{,}920$).

STUDY TYPES OF TOP-CITED STUDIES

Among the 100 top-cited studies, 21 studies were reviews, of which 2 were systematic reviews (SR)/meta-analyses; 79 were articles, of which 73 were observational studies, 5 were randomized controlled trials and 1 was basic research.

COUNTRIES OF THE TOP-CITED STUDIES

According to the country of origin of authors, the top-cited studies were mostly conducted in the USA ($n = 74$), followed by Canada ($n = 11$), and Germany ($n = 4$). China, England, Italy and Netherlands contributed two studies each, while Australia, Denmark and France only contributed 1 study each.

INSTITUTIONS PUBLISHED AT LEAST TWO OF THE TOP-CITED STUDIES

In our review, we listed the institutions contributed more than 1 study. Indiana University from the USA produced the most cited studies ($n = 8$), followed by University of Washington ($n = 7$). University of Pittsburgh and University of Michigan both contributed five studies. Johns Hopkins University produced four studies. The rest of the institutions contributed less than four studies. Of the top 16 institutions, 12 institutions were from the USA, and 14 were the university.

AUTHORS PUBLISHED AT LEAST TWO PAPERS AS FIRST AUTHOR OR CORRESPONDING AUTHOR OF THE TOP-CITED STUDIES

We also summarized the first authors or corresponding authors who published more than one studies of the 100 top-cited studies.

TABLE 1 | The 100 top-cited studies in pain and depression.

Ranking	Author, year	Journal	Article type	Total citation	Publication year	The relationship
1	Bair, 2003	*Arch. Intern. Med.*	Review	1576	2003	Positive correlated
2	Fishbain, 1997	*Clin. J. Pain.*	Review	618	1997	Pain caused depression
3	Romano, 1985	*Psychol. Bull.*	Review	523	1985	Pain caused depression
4	Banks, 1996	*Psychol. Bull.*	Review	455	1996	Pain caused depression
5	Tsang, 2008	*J. Pain.*	Trial	420	2008	Pain caused depression
6	Lin, 2003	*Jama-J. Am. Med. Assoc.*	Trial	380	2003	Positive correlated
7	Geisser, 1997	*Clin. J. Pain.*	Trial	335	1997	Pain caused depression
8	Currie, 2004	*Pain*	Trial	291	2004	Pain caused depression
9	McWilliams, 2004	*Pain*	Trial	289	2004	Pain caused depression
10	VonKorff, 1996	*Brit. J. Psychiatr.*	Trial	271	1996	Pain caused depression
11	Campo, 20040	*Pediatrics*	Trial	265	2004	Pain caused depression
12	Blackburn, 2001	*J. Neuroendocrinol.*	Review	258	2001	Both were related to Hypothalamo-pituitary-adrenal HPA axis
13	Rudy, 1988	*Psychosom. Med.*	Trial	256	2004	No correlation
14	Bair, 2004	*Pain*	Trial	252	1988	Pain caused depression
15	Arnstein, 1999	*Pain*	Trial	251	1999	Pain caused depression
16	Gore, 2005	*J. Pain. Symptom. Manag*	Trial	248	2005	Pain caused depression
17	Arnow, 2006	*Psychosom. Med.*	Trial	246	2006	Depression caused pain
18	Kroenke, 2009	*Jama-J. Am. Med. Assoc.*	Trial	241	2009	Positive correlated
19	Giesecke, 2005	*Arthritis Rheum.-Us*	Trial	238	2005	No correlation
20	Bair, 2008	*Psychosom. Med*	Trial	240	2008	Depression caused pain
21	Vonkorff, 1993	*Pain*	Trial	226	1993	No correlation
22	Edwards, 2011	*Nat. Rev. Rheumatol.*	Review	222	2011	Pain caused depression
23	Kroenke, 2011	*J. Pain.*	Trial	220	2011	Positive correlated
24	Campbell, 2003	*Biol. Psychiatr.*	Trial	219	2003	Pain caused depression
25	Sullivan, 1990	*J. Abnorm. Psychol.*	Trial	214	1990	Pain caused depression
26	Kashikar, 2001	*Clin. J. Pain.*	Trial	211	2001	Pain caused depression
27	Raskin, 2007	*Am. J. Psychiatr.*	Trial	208	2007	Positive correlated
28	Carroll, 2004	*Pain*	Trial	204	2004	Depression caused pain
29	Turk, 1994	*Behav. Res. Ther.*	Trial	203	1994	Pain caused depression
30	Brown, 1989	*J. Consult. Clin. Psych.*	Trial	199	1989	Pain caused depression
31	Brown, 1990	*J. Abnorm. Psychol.*	Review	197	1990	Pain caused depression
32	Chwastiak, 2003	*J. Clin. Epidemiol.*	Trial	196	2003	Pain caused depression
33	Brander, 2007	*Clin. Orthop. Relat. R*	Review	189	2007	Pain caused depression
34	Turk, 1995	*Pain*	Trial	186	1995	Pain caused depression
35	Wolfe, 1999	*Rheumatology*	Review	184	1999	Pain caused depression
36	Geisser, 1994	*Pain*	Trial	179	1994	Positive correlated
37	Turner, 1984	*J. Clin. Psychol.*	Trial	178	1984	Pain caused depression
38	Maletic, 2009	*Front. Biosci.*	Review	175	2009	Both were related to dysregulation of stress/inflammatory pathways
39	Eisenach, 2008	*Pain*	Trial	174	2008	Pain caused depression
40	Sullivan, 2001	*Pain*	Trial	171	2001	Pain caused depression
41	Ward, 1979	*Pain*	Trial	168	1979	Depression caused pain
42	Bigatti, 2008	*Arthritis Rheum. Arthr.*	Trial	168	2008	Pain caused depression
43	Lindsay, 1981	*Psychosomatics*	Trial	167	1981	Positive correlated
44	Kroenke, 2010	*Jama J. Am. Med. Assoc.*	Trial	166	2010	Positive correlated
45	SPIEGEL, 1994	*Cancer*	Trial	164	1994	Pain caused depression
46	Parmelee, 1991	*J. Gerontol.*	Trial	163	1991	Depression caused pain
47	Kim, 2012	*J. Clin. Invest.*	Basic research	158	2012	Both were related to brain indoleamine 2,3-dioxygenase 1

(Continued)

TABLE 1 | Continued

Ranking	Author, year	Journal	Article type	Total citation	Publication year	The relationship
48	Haythornthwaite, 1991	*Pain*	Trial	150	1991	Positive correlated
49	Sullivan, 1992	*Pain*	Review	147	1992	Pain caused depression
50	Wilson, 2002	*Clin. J. Pain*	Trial	145	2002	Depression caused pain
51	Diepenmaat, 2006	*Pediatrics*	Trial	145	2006	Pain caused depression
52	Dworkin, 1991	*Clin. J. Pain*	Review	145	1991	Pain caused depression
53	Walker, 2014	*Pharmacol. Rev.*	Review	143	2014	Both were related to several mechanisms
54	Ciechanowski, 2003	*Pain*	Trial	141	2003	Both were related to attachment theory
55	Mullen, 1987	*J. Rheumatol.*	Trial	141	1987	Both were related to psychoeducation
56	Suhr, 2003	*J. Psychosom. Res.*	Trial	141	2003	Both were related to fibromyalgia
57	Nicassio, 1992	*J. Abnorm. Psychol.*	Trial	140	1992	Pain caused depression
58	Karp, 2005	*J. Clin. Psychiatr.*	Trial	139	2005	Positive correlated
59	Dickens, 2003	*Psychosom. Med.*	Review	139	2003	Depression elevated pain perception threshold
60	Bar, 2005	*Pain*	Trial	139	2005	Depression caused lateralized perception of pain
61	Lepine, 2004	*Hum. Psychopharm. Clin.*	Trial	138	2004	Pain caused depression
62	Miller, 2009	*J. Pain*	Trial	134	2009	Pain caused depression
63	Kelsen, 1995	*J. Clin. Oncol.*	Trial	134	1995	Both were not related to recently diagnosed adenocarcinoma of the pancreas
64	Hassett, 2000	*Arthritis Rheum. Us*	Trial	132	2000	Both were related to fibromyalgia
65	Ciaramella, 2001	*Psycho-Oncology*	Trial	132	2001	Depression caused pain
66	Lautenbacher, 1999	*Psychosom. Med.*	Trial	129	1999	Depression elevated pain perception threshold
67	Elliott, 2003	*Pain Med.*	Trial	128	2003	Pain caused depression
68	So, 2009	*Oncol. Nurs. Forum.*	Trial	126	2009	Positive correlated
69	Cairns, 1996	*Arch. Phys. Med. Rehab.*	Trial	125	1996	Positive correlated
70	Williamson, 1992	*J. Gerontol.*	Trial	122	1992	Positive correlated
71	Hawker, 2011	*Arthritis Care Res.*	Trial	118	2011	Pain caused depression
72	Turk, 1993	*J. Prosthet. Dent.*	Trial	118	1993	Positive correlated
73	Keefe, 1986	*J. Consult Clin. Psych.*	Trial	116	1986	Depression caused pain
74	Braden, 2009	*Gen Hosp. Psychiatr.*	Trial	115	2009	Depression increased use of opioid therapy for non-cancer pain
75	Klauenberg, 2008	*Pain*	Trial	115	2008	Depression reduced pain perception threshold
76	Turner, 2005	*J. Pain*	Trial	114	2005	Self-efficacy for managing pain decreased depression
77	Sharpe, 2001	*J. Psychosom. Res.*	Trial	113	2001	Pain caused depression
78	Chiu, 2005	*Pain*	Trial	113	2005	Depression reduced pain perception threshold
79	Auerbach, 2001	*J. Oral Maxil Surg.*	Trial	112	2001	Pain caused depression
80	Davison, 2005	*J. Pain Symptom. Manage.*	Trial	111	2005	Pain caused depression
81	Gaston, 1999	*Cancer Pract.*	Trial	111	1999	Positive correlated
82	Brown, 2010	*Psycho-Oncology*	Trial	111	2010	Positive correlated
83	MAGNI, 1987	*Pain*	Review	110	1987	Positive correlated
84	Geerlings, 2002	*Soc. Psych. Psych. Epid.*	Trial	107	2002	Positive correlated
85	Coenen, 2011	*Neurosci. Biobehav. R*	Review	107	2011	Positive correlated
86	Jann, 2007	*Pharmacotherapy*	Review	107	2007	Both reduced by antidepressant
87	Munce, 2007	*Psychosomatics*	Trial	105	2007	Pain caused depression

(Continued)

TABLE 1 | Continued

Ranking	Author, year	Journal	Article type	Total citation	Publication year	The relationship
88	Blumer, 1982	*J. Nerv. Ment. Dis.*	Trial	104	1982	Depression caused pain
89	Illi, 2012	*Cytokine*	Trial	103	2012	Positive correlated
90	Haley, 1985	*Pain*	Trial	101	1985	Pain caused depression
91	Kroenke, 2008	*Pain*	Trial	101	2008	Positive correlated
92	Means, 2008	*Depress Anxiety*	Trial	100	2008	Positive correlated
93	Wolfe, 2009	*Arthritis Rheum-Arthr.*	Trial	100	2009	Pain caused depression
94	Kerns, 1988	*J. Consult. Clin. Psych.*	Trial	99	1988	Pain caused depression
95	O'Mahony, 2005	*J. Pain. Symptom. Manage.*	Trial	99	2005	Pain caused depression
96	Foley, 2007	*Am. J. Geriat. Psychiatr.*	Trial	96	2007	Positive correlated
97	Hendeler, 1984	*J. Clin. Psychiatr.*	Trial	96	1984	Pain caused depression
98	Geisser, 2000	*Clin. J. Pain*	Trial	95	2000	Pain caused depression
99	Schwartz, 2014	*Science*	Basic research	95	2014	Pain caused depression
100	Finan, 2013	*Sleep. Med. Rev.*	Review	94	2013	Both related to Dopamin

Reference details are provided in ***Supplementary Data Sheet 1***.

Among the nine first authors and ten corresponding authors, Kroenke, K published the highest number of papers as both the first author ($n = 4$) and corresponding author ($n = 4$).

DISCUSSION

With the growing awareness of the link between pain and depression, an increasing number of literatures have focused on the interaction between these two conditions. Although literature reviews of the comorbidity of pain and depression have been conducted (Fishbain et al., 1997; Bair et al., 2003; Gagliese et al., 2007), no bibliometrics study to describe the current situation and trend of this field yet, thus we performed the current review to assess it. This study aimed to review the development and progress of the relationship between pain and depression by identifying the top-cited studies in this field.

The 100 top-cited studies were cited from 94 to 1576 times, published in 52 different journals between 1976 and 2014. As it shown that the number of citations is rising as time goes by, of the 100 top-cited articles, 81 were published 10 years ago. Although, the oldest article may not be the most significant research in this field. Probably because the authors tend to cite the articles which were cited in the papers instead of reading and citing the original articles. *Pain,* with 20 of the 100 top-cited studies, received the highest number of citations of 3,508 times. Of the top 5 most cited journals, three journals featuring the spectrum of pain research, which indicated that studies published in professional journals might attract more attention and achieve higher academic value.

Although the studies of pain and depression have been done worldwide, 74% of the top-cited studies were originated from academic institutions in the USA. The most influential institution was the Indiana University, with eight top-cited articles published from 1984 to 2009. The significant influence of the USA may be attributed to its large number of scientific research institutions and the abundant research funds. Also, there may be some bias in this finding. On one hand, consideration of the subtle connection between pain and depression maybe more focused by developed countries than developing countries. On the other hand, researchers from unknown labs in developing countries are less influential in the field who may not have access or resources to publish articles in renowned journals.

Of all the first author and corresponding author, Kroenke, K contributed most of the top-cited articles, and 2 of the four papers were published in JAMA. In addition to the four studies, he also made contributions in other five papers of the top-cited articles. Dr. Kroenke is an internationally respected expert in physical and psychological symptoms, whose principal research interests include pain and depression, and has made a great contribution to this research field. A study concluded a phenomenon that once in control of the commanding heights of their fields, star scientists tend to hold on to their exalted position for a long time, and a burst of published research after the "star" in that field dies (Azoulay et al., 2019). This phenomenon may indicate that big names in science are in a way suppressing younger colleagues work.

The most highly cited articles in pain and depression were in the field of clinical trials, of which 94% were observational study. Pain and depression are the most common physical and psychological symptom-based conditions (Kroenke et al., 2011), respectively, which based on an individual's subjective feelings. Measurement of pain and depression according to the scores of scales. For these reasons, most of the studies were observational studies instead of basic study.

Studies showed that 65% of depressive patients complained about one or more pain, while 5–85% patients with pain reported depression (Bair et al., 2003; Lepine and Briley, 2004; Miller and Cano, 2009). As presented in **Table 1**, the relationship between pain and depression were investigated in the 100 papers. Forty seven of the 100 top-cited articles indicated that pain caused depression, 23 papers mentioned they were corelated, 9 papers revealed that depression caused pain, while 3 studies found no significant correlation between pain and depression. Five articles investigated the possible common mechanisms of these two

TABLE 2 | Journals of the 100 top-cited studies published.

Journal	Number of studies	Total citation	Average citation	Impact factor (2018)
Pain	20	3508	175	6.029
JAMA Intern. Med.	1	1576	1576	20.768
Clin. J. Pain	6	1549	258	2.893
Psychosom. Med.	5	1010	202	3.937
Psychol. Bull.	2	978	489	16.405
J. Pain	4	888	222	2.236
JAMA J. Am. Med. Assoc.	3	787	262	51.273
J. Abnorm. Psychol.	3	551	184	5.519
J. Pain. Symptom Manag.	3	458	153	3.378
J. Consult. Clin. Psych.	3	414	138	4.358
Pediatrics	2	410	205	5.401
Arthritis Rheum. Arthr.	2	370	185	9.002
J. Gerontol.	2	285	143	3.418
Psychosomatics	2	272	136	1.541
Brit. J. Psychiatr.	1	271	271	7.233
Arthritis Care. Res.	2	268	134	4.530
J. Neuroendocrinol.	1	258	258	3.040
J. Psychosom. Res.	2	254	127	2.722
Psycho-Oncology	2	243	122	3.430
J. Clin. Psychiatr.	2	235	118	4.023
Nat. Rev. Rheumatol.	1	222	222	18.545
Biol. Psychiatr.	1	219	219	11.501
Am. J. Psychiatr.	1	208	208	13.655
Behav. Res. Ther.	1	203	203	4.309
J. Clin. Epidemiol.	1	196	196	4.650
Clin. Orthop. Relat. R	1	189	189	4.154
Rheumatology	1	184	184	5.149
J. Clin. Psychol.	1	178	178	2.059
Front. Biosci.	1	175	175	2.214
Cancer	1	164	164	6.102
J. Clin. Invest.	1	158	158	12.282
Pharmacol. Rev.	1	143	143	18.886
J. Rheumatol.	1	141	141	3.634
Hum. Psychopharm. Clin.	1	138	138	2.265
J. Clin. Oncol.	1	134	134	28.245
Pain Med.	1	128	128	2.758
Oncol. Nurs. Forum.	1	126	126	1.438
Arch. Phys. Med. Rehab.	1	125	125	2.697
Arthritis Rheum-Us	1	118	118	4.530
J. Prosthet. Dent.	1	118	118	2.787
Gen. Hosp. Psychiatr.	1	115	115	3.220
J. Oral. Maxil. Surg.	1	112	112	1.781
Cancer. Pract.	1	111	111	1.553*
Neurosci. Biobehav. R	1	107	107	8.002
Pharmacotherapy	1	107	107	3.045
Soc. Psych. Psych. Epid.	1	107	107	3.152
J. Nerv. Ment. Dis.	1	104	104	1.859
Cytokine	1	103	103	3.078
Depress. Anxiety	1	100	100	4.935
Am. J. Geriat. Psychiatr.	1	96	96	3.488
Science	1	95	95	41.037
Sleep. Med. Rev.	1	94	94	10.517

*Impact factor of 2004.

symptoms. Three studies found the level of pain and depression were decreased after antidepressants therapy, which pointed out the direction of future research in mechanism and treatment of comorbidity of pain and depression.

In present study, most of the top-cited studies reported the comorbidity of pain and depression and indicated that pain and depression have strong and similar effects on one another (Kroenke et al., 2011). Based on the 100 top-cited articles, the presence of pain negatively affects the recognition and treatment of depression, and depression in patients with pain is similarly associated with more pain complaints and greater impairment (Bair et al., 2003, 2008). Higher prevalence of depression was found in patients with moderate or severe chronic pain compared to patients with mild or no pain (34.1 vs. 18.3%) (Davison and Jhangri, 2005). And a significantly lower Mental Composite Score t-score was found in chronic pain patients with major depressive disorder had than those with minor or no depression (Elliott et al., 2003). Pain and depression are interrelated and interacted. Lin et al. (2003) found benefits of improved depression care extended beyond reduced depressive symptoms and included decreased pain as well as improved functional status and quality of life. Optimized antidepressant therapy followed by a pain self-management program resulted in substantial improvement in depression as well as moderate reductions in pain severity (Kroenke et al., 2009). Cairns et al. (1996) pointed that changes in pain affected depression more than changes in depression affected pain. A 12-month longitudinal analysis in comorbidity of pain and depression also found that change in pain and depression severity was strong predictor of each other (Kroenke et al., 2011).

Pain and depression might share the same biological pathways and neurotransmitters, indicating the same treatment strategy of both concurrently. These mechanisms include direct effects of cytokines on the neuronal environment or indirect effects via downregulation of G protein–coupled receptor kinase 2, activation of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase that generates neurotropic kynurenine metabolites, increased brain extracellular gluta-mate, and the switch of GABAergic neurotransmission from inhibition to excitation (Romano and Turner, 1985; Bair et al., 2003; Kim et al., 2012). The mesolimbic dopaminergic system (DA) is also shown to associate with both symptoms of pain and depression. Endogenous opioids have been shown to functionally interact

with DA, and are directly implicated in pain processing and depression symptoms in regions with heavy DAergic innervation (Finan and Smith, 2013). Among these mechanisms, one possible way was the brain indoleamine 2,3-dioxygenase 1-mediated regulatory mechanism, which has been suggested as a new strategy for the treatment of both conditions (Kim et al., 2012). In addition, studies showed that pain and depression are parallel and independent. In patients with fibromyalgia, neither the extent of depression nor the presence of comorbid major depression modulates the sensory-discriminative aspects of pain processing, as measured by sensory testing or fMRI. The sensory and affective elements were independent of one another and respond differentially to both pharmacologic and non-pharmacologic interventions (Giesecke et al., 2005).

There are several limitations to our review work. Firstly, there may be the missing number of citations since the citation analysis only based on the Web of Science. Some databases, like Google and Scopus, are not included in the statistical collection of cited frequency in Web of Science. Secondly, we searched the database based on the contents of titles, and some studies which did not contain the keywords in their titles may be missed for inclusion. Thirdly, we used total citations as the measurement of impact, but as times goes by, the older the articles are the more citations they may receive. So, the list of top-cited articles may be dominated by some old articles. Fourthly, since the 100 top-cited articles were published before 2015, the results of relationship between pain and depression may not be the latest discovery.

To the best of our knowledge, this study is the first review of top-cited studies in pain and depression. Despite the limitations, we provided evidence of the status and progress in the research field of pain and depression based on the 100 top-cited articles by identifying the contributions made by authors, institutions, and journals. Given the high prevalence of pain and depression, the mechanisms and treatment of the comorbidity of both symptoms remains a key research field.

AUTHOR CONTRIBUTIONS

YZ and LD designed the study and analyzed the data. SL, GL, HW, YZ, and LZ drafted of the manuscript. All authors approved the final version of the manuscript.

FUNDING

This study was partly supported by National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z2018B16).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.03072/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

ORIGINAL RESEARCH
published: 15 April 2020
doi: 10.3389/fpsyg.2020.00652

Moderate-to-Severe Depression Adversely Affects Lung Function in Chinese College Students

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OPEN ACCESS

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Reviewed by:
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Specialty section:
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

Received: 28 January 2020
Accepted: 18 March 2020
Published: 15 April 2020

Citation:
Guo L, Cao J, Cheng P, Shi D, Cao B, Yang G, Liang S, Su N, Yu M, Zhang C, Liang R, Wang Y, Bai C, Chen C and Ren Z (2020) Moderate-to-Severe Depression Adversely Affects Lung Function in Chinese College Students. Front. Psychol. 11:652. doi: 10.3389/fpsyg.2020.00652

Depression is known to be correlated with increased risk for chronic obstructive pulmonary disease (COPD) in middle-aged and older adults, but there is scarce evidence regarding its association with lung function among healthy adults. Thus, we aimed to assess this association by measuring the lung function and depression severity in Chinese college students. This cross-sectional study was conducted among 3,891 college students aged 16–24 years. Lung function was assessed by measuring the forced vital capacity (FVC) using a spirometer, and depression severity was evaluated using the 20-item Zung self-rating depression scale (SDS), with SDS scores of ≥40 and ≥45 indicating mild and moderate-to-severe depression, respectively. After adjusting for potential confounders, the geometric means of the FVC levels for the normal, mild depression, and moderate-to-severe depression groups were 3,446.1 (95% confidence interval [CI]: 3,418.6–3,470.3), 3,415.2 (95% CI: 3,357.7–3,473.8), and 3,351.0 (95% CI: 3271.5–3432.3), respectively (*P* for trend: 0.031). These results indicated that depression severity was independently correlated with lung function decline in Chinese college students. Future prospective cohort or interventional studies are needed to confirm the negative association between depressive symptoms and lung function and investigate its causality.

Keywords: depression, depressive symptoms, lung function, forced vital capacity, chronic obstructive pulmonary disease

INTRODUCTION

Lung function has proved to be an effective and non-invasive measure of the respiratory health of individual patients and populations. Its assessment not only helps to identify people with a potential risk for COPD, but may also predict survival in asymptomatic adults who do not have chronic respiratory diseases or persistent respiratory symptoms (Burney and Hooper, 2011), as

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; IPAQ, international physical activity questionnaire; MET, metabolic equivalents; PA, physical activity; SDS, self-rating depression scale.

well as in people with numerous other adverse health conditions, including metabolic syndrome (Oda and Kawai, 2009), type 2 diabetes mellitus (Yeh et al., 2005), cardiovascular disease (Johnston et al., 2008), and lung cancer (Mannino et al., 2003). Thus, it is important to identify risk factors that negatively affect lung function in order to enable earlier detection of morbidity.

Although the exact mechanisms leading to lung function decline are not entirely clear, oxidative stress may play a crucial role. Oxidative stress occurs as a result of oxidant/antioxidant imbalance (Valko et al., 2007). It induces lipid peroxidation, protein oxidation, and DNA damage, which, in turn, results in the development of abnormalities in cell structures, eventually leading to cell death (Valko et al., 2007). Because the surface area for gas exchange is large, the respiratory system is particularly susceptible to oxidative stress-induced injury, which subsequently exacerbates pulmonary dysfunction (Santus et al., 2014).

Forced vital capacity, a simple and accurate measure of lung function, is one of the most important indexes for assessing vital capacity in adults (Chhabra, 1998) and determining the total lung capacity (Vandevoorde et al., 2008). In addition, evidence indicates that FVC predicts survival in asymptomatic adults without chronic respiratory diagnoses or persistent respiratory symptoms (Burney and Hooper, 2011). Therefore, FVC has been chosen as an indicator of lung function (Pellegrino et al., 2005). Furthermore, the results of a case-control study revealed that the level of malondialdehyde, which is a useful marker of exacerbation-associated oxidative stress in patients with COPD, was higher in patients with stable COPD than in healthy controls (Antus et al., 2014).

Similarly, a previous epidemiological study has shown that 36% of patients with COPD reported having depression (Rigual et al., 2017). This may be because oxidative stress is also a well-recognized factor in the pathophysiology of depression. A population-based meta-analysis showed that patients with depression have elevated oxidative stress levels (Black et al., 2015). This can be due to abnormal hypothalamic-pituitary-adrenal axis activity and immuno-inflammatory dysregulation (Penninx et al., 2013). These studies provided powerful evidence that depression is positively associated with lung function decline. However, thus far, it has only been observed that depression could increase the risk for COPD in middle-aged and older adults (Di Marco et al., 2006) and it remains unknown whether it has a negative effect on the lung function in healthy adults. The Global Initiative for Chronic Obstructive Lung Disease has also proposed that future studies should be conducted to evaluate the lung function in a variety of populations exposed to various risk factors, such as cigarette smoking, obesity, and depression (Pauwels et al., 2001).

Therefore, in this study, we aimed to investigate whether depression severity is associated with lung function decline in Chinese college students.

MATERIALS AND METHODS

Ethics Statement

Ethics approval was obtained from the Institutional Review Board of the College of Physical Education of Southwest University. All participants or the parents or legal guardians of those aged < 16 years provided written informed consent.

Study Design and Participants

This was a cross-sectional study that included college freshmen from 35 schools/colleges of Southwest University between October and December 2018. Participants were recruited by stratified cluster sampling. They were a part of the ongoing Southwest University Physical Fitness and Health cohort study (2018–2021) being conducted to assess the association between physical fitness and the health status of college students in Southwest University, a key national comprehensive university under the direct administration of the Ministry of Education. They were asked to participate in a structured and self-administered health status questionnaire survey. The detailed questionnaire content has been previously published (Ren et al., 2020). Only those who provided informed consent were included in this study.

All participants underwent annual physical fitness examinations, including assessment of lung function (FVC) and physical fitness status (50-m sprint, sit and reach, standing long jump, 800/1,000-m run, and sit-ups/pull-ups), at the physical fitness examination center of Southwest University. Participants with missing data were excluded.

Assessment of Lung Function

Lung function was assessed by measuring the FVC using a spirometer (CSTF-FH, Tsinghua Tongfang). All participants were requested to hold the spirometer and perform forced expiration in a standing and stationary position. Each participant was asked to make two attempts, and the higher value of the two measurements was recorded as the FVC.

Assessment of Depression Severity

A validated Chinese version of the Zung SDS was used to assess the severity of depression (Peng et al., 2013). The SDS has 20 items and the score of each item ranges from one to four, with a sum score ranging from 20 to 80. A higher SDS score indicates a greater depression severity. In the current study, SDS scores of $\geq$40 and $\geq$45 indicated mild and moderate-to-severe depression, respectively. Accordingly, participants were divided into three groups: normal, mild depression, and moderate-to-severe depression.

Additionally, the SDS also assesses anxiety symptoms via the following five questions: "Do you feel down-hearted and blue?" (Chan et al., 2010), "Do you have trouble sleeping at night?" (Zung, 1971), "Does your heart beat faster than usual?" (Zung, 1971), "Do you get tired for no reason?" (Zung, 1971), and "Do you still enjoy the things you used to?" (Chan et al., 2010). The scores of these five items are summed as a total score, which ranges from 5 to 20;

higher scores indicate greater anxiety severity. In this study, anxiety was defined as a score ≥6. In this study, Cronbach's α coefficient for the SDS was 0.738, indicating a good internal consistency.

Relevant Covariates

To control for covariates, we also measured potential relevant covariates, based on a previous study (Ren et al., 2020), including sex, age, BMI, only one child, parent's educational levels and marital status, smoking and drinking status, sleep duration and quality, breakfast frequency, and PA. The standing long jump was additionally used to assess muscular fitness. All participants stood behind the starting line and were told to push off vigorously and jump as far as possible. They had to land with their feet apart and remain upright. Each participant made two attempts and the greater of the measurements was recorded as the standing long jump.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 24.0 software (IBM SPSS Inc., Chicago, IL, United States). All continuous variables were expressed as geometric least square means (95% confidence intervals [CIs]), and categorical variables were expressed as percentages. Because the distributions of all continuous variables were skewed, all continuous variables were log-transformed prior to performing ANCOVA. Differences in the participants' characteristic among the groups were estimated using ANCOVA for continuous variables and multiple logistic regression analysis for categorical variables, after adjustment for sex (categorical variable) and age (continuous variable).

Forced vital capacity and depression severity were used as dependent and independent variables, respectively. ANCOVA was also conducted to examine the relationship between depression severity and FVC. In model 1, the analysis was conducted without any adjustments. Model 2 was adjusted for sex (categorical variable) and age (continuous variable). Model 3 was further adjusted for the following factors: BMI (continuous variable), one child (categorical variable), father's education (categorical variable), mother's education (categorical variable), parent's marital status (categorical variable), smoking status (categorical variable), drinking status (categorical variable), PA (categorical variable), sleep duration (categorical variable), sleep quality (categorical variable), breakfast frequency (categorical variable), standing long jump (continuous variable), and anxiety symptoms (categorical variable). P-values < 0.05 were considered statistically significant for all two-sided tests.

RESULTS

A total of 4,550 college freshmen were recruited. Among them, 4,258 provided written informed consent. We excluded 367 participants owing to missing data on sleep duration (n = 4) and FVC (n = 363). Finally, 3,891 participants (1,320 males and 2,571 females) with an age range of 16–24 years (mean 18.1 years, standard deviation 0.7) were included in the study.

Sex- and age-adjusted participants' characteristics according to the depression severity are shown in **Table 1**. The proportion of females was lower (P for trend: 0.002), whereas that of younger subjects was higher (P for trend: 0.004) in the moderate-to-severe depression group. Participants with moderate-to-severe depression reported a higher frequency of occasional drinking and skipping breakfast, had lower PA levels, and lower proportion of good sleep quality (all P for trends: ≤0.005). Depression severity was significantly negatively related to standing long jump (P for trend: 0.042). There were no significant differences between other participants' characteristics and depression severity. Distribution of FVC according to different depressive level are also shown in **Supplementary Table S1**.

Among the 3,891 participants, 299 (7.7%) had moderate-to-severe depression. ANCOVA revealed a significant negative relationship between depression severity and FVC after adjusting for potential confounders. The geometric means of the FVC levels for the normal, mild depression, and moderate-to-severe depression groups were 3,446.1 (95% CI: 3,418.6–3470.3), 3,415.2 (95% CI: 3,357.7–3,473.8), and 3,351.0 (95% CI: 3,271.5–3,432.3), respectively (P for trend: 0.031) (**Table 2**).

DISCUSSION

In this cross-sectional study, we examined the relationship between depression severity and FVC in Chinese college students. ANCOVA showed that moderate-to-severe depression was significantly and independently associated with a reduced FVC, after adjustment for potential confounders.

A meta-analysis, which included 16 prospective cohort studies and 28,759 individuals aged ≥ 42 years, demonstrated a positive association between depression and increased risk for COPD (Atlantis et al., 2013). However, it is noteworthy that the participants of those studies were limited to elderly patients with COPD. The present is the first study to examine the relationship between depression and lung function, assessed by FVC, among Chinese healthy adults.

Although the exact mechanism underlying the debilitating effect of depression on lung function remains unclear, it may be explained by the role played by the immune system. It is widely known that overproduction of pro-inflammatory cytokines in the body may cause deterioration of multiple subsequent immunological functions by elevating the levels of plasma adrenocorticotropic hormone, which is followed by an increase in cortisol levels, resulting in depression (Kiecolt-Glaser and Glaser, 2002). Additionally, it is known that depression could enhance the production of pro-inflammatory cytokines (Kiecolt-Glaser and Glaser, 2002). Interestingly, the overproduction of pro-inflammatory cytokines also induces abnormal endothelial function, leading to impaired lung alveolar function and consequent persistent lung function decline (Jiang et al., 2008).

Unhealthy dietary behaviors could also explain our findings. A previous study showed that the consumption of energy-dense foods was higher in individuals with depression than in healthy

TABLE 1 | Sex- and age-adjusted participants' characteristics according to depressed level.

***N* = 3891**	**Normal (*n* = 3018)**	**Mild depressed (*n* = 574)**	**Moderate and serious depressed (*n* = 299)**	***P* for trend[1]**
SDS range, score	23–39	40–44	45–60	–
Demographic characteristics				
Sex (female)	64.8	72.0	67.9	0.002
Age, year	18.1 (18.1, 18.1)	18.2 (18.1, 18.2)	18.2 (18.2, 18.3)	0.004
Only one child, %	50.9	50.7	49.8	0.859
Father education, %				
Senior high school or less	68.1	69.0	69.9	0.646
College	29.3	28.2	28.8	0.876
Mother education, %				
Senior high school or less	74.5	75.1	76.6	0.555
College	24.1	22.8	22.1	0.466
Parent's marital status, %				
Married	89.1	88.5	89.3	0.980
Widowed	8.5	9.6	8.0	0.871
Divorced	2.5	1.9	2.7	0.810
Lifestyle factors				
BMI, kg/m^2	20.4 (20.3, 20.5)	20.2 (20.0, 20.4)	20.3 (20.0, 20.6)	0.497
Smoking status, %				
Regularly	0.5	1.4	0.7	0.166
Occasionally	2.3	2.3	3.7	0.117
Drinking status, %				
Regularly	0.6	1.0	1.3	0.076
Occasionally	43.6	47.4	48.2	0.005
Breakfast frequency				
≤1 time/week	1.6	2.1	4.0	0.005
2–5 times/week	19.7	33.4	38.5	< 0.001
PA, MET·h·week^{-1} (≥23)	82.7	74.4	67.9	< 0.001
Sleep duration(6–8 h), %	90.7	90.2	91.0	0.773
Good sleep quality, %	92.1	73.3	62.9	< 0.001
Anxiety symptoms: "no," %	24.4	1.0	1.0	< 0.001
Standing long jump, cm	185.9 (185.3, 186.4)	185.7 (184.2, 187.2)	183.6 (181.6, 185.7)	0.042

[1]P for trends were assessed using multivariate logistic regression analyses. [2] Continuous variables were log-transformed and are expressed as the estimated geometric means (95% confidence intervals).

TABLE 2 | Adjusted relationships between depressed level and the FVC.

***N* = 3891**	**Model 1[a]**	**Model 2[b]**	**Model 3[c]**	**Model 4[d]**
FVC, ml				
Normal (*n* = 3018)	3,465.2 (3,431.5, 3,499.2)[e]	3,449.6 (3,422.4, 3,473.6)	3,446.1 (3,418.6, 3,470.3)	3,446.1 (3,418.6, 3,470.3)
Mild depressed (*n* = 574)	3,333.8 (3,260.0, 3,409.4)	3,408.4 (3,351.8, 3,467.8)	3,415.2 (3,357.7, 3473.8)	3,415.2 (3,357.7, 3,473.8)
Moderate and serious depressed (*n* = 299)	3,305.0 (3,204.0, 3,409.2)	3,330.9 (3,252.3, 3,409.2)	3,340.9 (3,261.7, 3,422.1)	3,351.0 (3,271.5, 3,432.3)
P for trend[f]	0.004	0.006	0.019	0.031

FVC = forced vital capacity; BMI = body mass index; PA = physical activity; MET = metabolic equivalents; ANCOVA = analysis of covariance. [a]Model 1: Crude. [b]Model 2: Adjusted for sex, age (continuous variable). [c]Model 3: Additionally adjusted for BMI (continuous variable), only on child (yes or no), father education (senior high school or less, college or undergraduate), mother education (senior high school or less, college, or undergraduate), parent's marital status (married, widowed, divorced), smoking status (regularly, occasionally, never), drinking status (regularly, occasionally, never), PA (≥23 MET·h·week-1 or not), sleep duration (6–8 h or not), good sleep quality (yes or no), anxious symptoms (yes or no), and breakfast frequency (≤1 time/week, 2–5 times/week, and ≥6 times/week). [d]Model 4: Additionally adjusted for standing long jump (continuous variable). [e]Adjusted data are expressed as estimated geometric means (95% confidence intervals). [f]P for trend were obtained using ANCOVA.

individuals (Payne et al., 2012). Consumption of such foods could result in systemic inflammation (Azadbakht et al., 2017), which directly induces the innate immune response via the activation of Toll-like receptor 4 by circulating free fatty acids. This may induce increased production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor alpha, and C-reactive protein. Of these, IL-6 is a powerful inducible factor of neutrophil responses, which could cause airflow obstruction (Shaw et al., 2007), subsequently contributing to lung function decline.

Finally, oxidative stress may also mediate this relationship. Depression is characterized by activated oxygen and nitrogen species pathways, which leads to lipid peroxidation, protein oxidation, and DNA damage (Maes et al., 2011; Moylan et al., 2014). Additionally, oxidative stress plays an important role in the development and progression of lung function decline due to lipid peroxidation, protein oxidation, and DNA damage, which, in turn, results in the development of abnormalities in cellular structures, eventually leading to cell death (Valko et al., 2007). The large surface area for gas exchange makes the respiratory system particularly susceptible to oxidative stress-mediated injury, which subsequently exacerbates pulmonary dysfunction (Santus et al., 2014). Unfortunately, we did not investigate pro-inflammatory cytokines, consumption of energy-dense foods, or biomarkers of oxidative stress. Thus, further studies are warranted to examine the relationship of these factors with depression and lung function. The inverse association observed between depression severity and lung function may also provide new insights into the role of depression in the lung function decline related to chronic pain, because severe depression was also present in individuals with COPD experiencing pain (Lee et al., 2017). Further studies should assess the possible association of depression severity with pain and lung function.

The limitations of this study are as follows. First, it was a cross-sectional study; therefore, the causal relationship between depression severity and lung function cannot be determined. Second, although two cut-off points (SDS scores 40 and 45) were used to define subjects having mild and moderate-to-severe depression, we were unable to accurately diagnose depression. Third, our participants were limited to regional Chinese adolescents aged 16–24 years. Hence, our regional results may not be representative of all Chinese college students. Therefore, further studies on other college students are essential to confirm our results. Fourth, pro-inflammatory cytokines and energy-dense foods were not assessed. Whether these factors play important roles as mediators between depression severity and lung function in our population is unknown. As breakfast skippers consume more energy-dense foods (Utter et al., 2007), although additional adjustment for breakfast frequency (Model 3) attenuated this relationship, the negative relationship was confirmed (P for trend: 0.031). Fifth, we only considered the influence of depression severity on lung function. The possible associations between other physical functions (50-m sprint, sit and reach, 800/1,000-m run, and sit-ups/pull-ups) and depression remain unknown. Because muscular fitness, but not other physical function components (50-m sprint, sit and reach, 800/1,000-m run, and sit-ups/pull-ups), is associated with both depression severity (Suija et al., 2013) and lung function (Smith et al., 2018), we further adjusted for standing long jump (index of muscular fitness), but the inverse association between depression severity and lung function remained. Therefore, in this study, muscular fitness did not confound the association between depression severity and lung function.

CONCLUSION

Our cross-sectional study demonstrated that moderate-to-severe depression was significantly and independently correlated with lung function decline in Chinese college students. Future prospective cohort or interventional studies are warranted to assess the causality of the effects of depression severity on lung function in healthy adults.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the College of Physical Education of Southwest University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CC and ZR conceived and designed the experiments. LG, JC, PC, DS, BC, NS, MY, YW, SL, CZ , RL and GY performed the experiments and conducted data collection. LG and JC analyzed the data and wrote the manuscript. CC and ZR contributed to the reagents, materials, and analysis tools. LG, JC, CC, ZR, BC, CB and PC revised the manuscript.

FUNDING

This study was supported by the Fundamental Research Funds for the Central Universities (Grant Nos. SWU1709116; SWU1909734; SWU1909105) and the Funds for Administration of Sport of Chongqing (Grant No. B2019027).

ACKNOWLEDGMENTS

We thank the freshmen of Southwest University who participated in this study. We would also like to thank our staff at Southwest University for their dedicated work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.00652/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

REVIEW
published: 31 July 2020
doi: 10.3389/fpsyg.2020.01825

Neuroinflammation, Pain and Depression: An Overview of the Main Findings

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Specialty section:
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

Received: *27 February 2020*
Accepted: *02 July 2020*
Published: *31 July 2020*

Citation:
Campos ACP, Antunes GF, Matsumoto M, Pagano RL and Martinez RCR (2020) Neuroinflammation, Pain and Depression: An Overview of the Main Findings. Front. Psychol. 11:1825. doi: 10.3389/fpsyg.2020.01825

Chronic pain is a serious public health problem with a strong affective-motivational component that makes it difficult to treat. Most patients with chronic pain suffer from severe depression; hence, both conditions coexist and exacerbate one another. Brain inflammatory mediators are critical for maintaining depression-pain syndrome and could be substrates for it. The goal of our paper was to review clinical and preclinical findings to identify the neuroinflammatory profile associated with the cooccurrence of pain and depression. In addition, we aimed to explore the regulatory effect of neuronal reorganization on the inflammatory response in pain and depression. We conducted a quantitative review supplemented by manual screening. Our results revealed inflammatory signatures in different preclinical models and clinical articles regarding depression-pain syndrome. We also identified that improvements in depressive symptoms and amelioration of pain can be modulated through direct targeting of inflammatory mediators, such as cytokines and molecular inhibitors of the inflammatory cascade. Additionally, therapeutic targets that improve and regulate the synaptic environment and its neurotransmitters may act as anti-inflammatory compounds, reducing local damage-associated molecular patterns and inhibiting the activation of immune and glial cells. Taken together, our data will help to better elucidate the neuroinflammatory profile in pain and depression and may help to identify pharmacological targets for effective management of depression-pain syndrome.

Keywords: neuroinflammation, pain, depression, depression-pain syndrome, glial cells

INTRODUCTION

Chronic pain is a complex disorder that significantly impacts society and is the leading cause of disability and financial burden worldwide (Global Burden of Disease Study 2016). It is considered a public health problem and affects approximately 20% of the general population (Breivik et al., 2006). This type of pain is defined as that is persistent or intermittent pain that lasts for more than 3 months despite a normal tissue healing time (Merskey and Bogduk, 1994). Nociceptive pain may occur as a consequence of non-neural damage (Cohen and Mao, 2014), while neuropathic

pain is induced by lesions or diseases involving the central nervous system (CNS) (Li et al., 2016). The prevalence of chronic pain ranges from 7 to 10% of the general population (van Hecke et al., 2014), and this disorder manifests as spontaneous pain, hyperalgesia and mechanical allodynia, which decrease quality of life (Baron, 2000). Because of its association with poor quality of life, chronic pain often induces depression (von Knorring et al., 1983; Lee et al., 2009; Agüera-Ortiz et al., 2011). Depression can be characterized by psychological and physical symptoms, including low mood or sadness, lack of energy, lack of motivation, insomnia, low sex drive and an inability to enjoy life (Cui, 2015). Depression is also considered a public health problem and is one the major contributors to global disease burden (Collins et al., 2011; Whiteford et al., 2013). Chronic pain may induce depression, and people suffering from depression may also present abnormal pain perception and modulation, which increases the risk of developing chronic pain (Currie and Wang, 2005). It has been estimated that 85% of people affected with chronic pain suffer from severe depression (Bair et al., 2003; Williams et al., 2003), supporting the concept that both conditions coexist and exacerbate one another (Gallagher and Verma, 1999; Blier and Abbott, 2001; Leo, 2005). This association has been labeled depression-pain syndrome or the depression-pain dyad (Lindsay and Wyckoff, 1981; Beckman, 2004; Cox et al., 2017).

A possible reason why these disorders are complex and difficult to treat is that they both involve neuroinflammation. Neuroinflammation is an innate immune response of the nervous system to injury, infection or neurodegenerative disease characterized by the activation of resident glial cells, including microglia and astrocytes; release of cytokines and chemokines; and activation and infiltration of leukocytes (Takeuchi and Akira, 2010; Domercq et al., 2013; Ji et al., 2014, 2016, 2018; Turner et al., 2014; Stephenson et al., 2018; Yang and Zhou, 2019). It has also been proposed that these conditions could be responsible for alterations in the permeability of the blood-brain barrier, immune cell infiltration, and activated microglia (Benatti et al., 2016). Persistent neuroinflammation plays an important role in the induction and maintenance of depression-pain syndrome (Ji et al., 2014; Burke et al., 2015). In this sense, classically activated resident glial cells lose the ability to control the synaptic environment (Liddelow et al., 2017). Specifically, improvements in the synaptic environment could promote symptomatic progress and modify disease progression (Pecina and Zubieta, 2018). However, the relationship between inflammation and the synaptic environment in depression-pain syndrome has been poorly investigated (Liddelow et al., 2017).

In the literature, much effort has been devoted to fully understanding the pathophysiology of chronic pain and depression as well as understanding why comorbidity of these two disorders is so common to guide the development of better treatments. It is not surprising that pain relief medications are still the second-most prescribed drugs (after cardiac-renal drugs) in the United States (Turk, 2002; Van Zee, 2009; Dowell et al., 2016; Volkow and McLellan, 2016). Pharmacological treatment options for chronic pain include opioids, non-steroidal anti-inflammatory drugs, gabapentinoids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, NMDA antagonists, and topical preparations (Turk, 2002; Cooper et al., 2017; Eccleston et al., 2017; Manchikanti et al., 2017; Riediger et al., 2017; Shanthanna et al., 2017; Szok et al., 2019). The use of opioids and non-steroidal anti-inflammatory drugs is limited by their adverse effects, tolerance, and potential for addiction (Barber and Gibson, 2009; Han et al., 2015; Vowles et al., 2015; Busse et al., 2018). Additionally, considering that chronic pain treatment frequently involves polypharmacy therapy, it is associated with an increased risk of drug interactions and additive adverse effects (Barber and Gibson, 2009; Taylor et al., 2013; Denk et al., 2014; Riediger et al., 2017; Busse et al., 2018). Furthermore, despite the range of drugs available, pharmacological therapies for chronic pain are often inefficient for the management of depression-pain syndrome, and as this condition can affect nearly every aspect of daily life; thus, the development of novel treatment strategies is critical (Bentley et al., 2014; Cohen and Mao, 2014; Crofford, 2015; Brant et al., 2017; Shamji et al., 2017). Treatment focusing on neuroinflammatory substances could help to inhibit glial cells in their activated state, improve the neuronal network in specific regions and induce alleviation of chronic pain and depression (Walker et al., 2013a; Ji et al., 2014, 2018). On the other hand, it has been hypothesized that treatments that modulate the neuronal network may decrease the formation of glial cell-recognized patterns and decrease inflammation, consequently modulating the symptoms of depression-pain syndrome. In this sense, the goal of our paper was to review clinical and preclinical findings to identify the inflammatory signature associated with depression-pain syndrome and the different types of treatments that modulate neuroinflammation. We hope to discuss the anti-inflammatory mechanisms observed in the studied articles and improvements in the neurocircuitry, which may be responsible for the optimal modulation of these symptoms.

METHODS

Search Strategy and Inclusion and Exclusion Criteria

A quantitative review search of PubMed, ScienceDirect and MEDLINE for original research articles supplemented by manual screening was conducted between November and December 2019. As this study aimed to review many published articles on the topics of neuroinflammation and pain-depression syndrome, there were no restrictions placed on the publication date for the search. Thus, we opted to not conduct a formal systematic review or meta-analysis. The studies were required to contain the relevant terms "neuroinflammation AND chronic pain AND depression OR glial cells AND chronic pain AND depression OR chronic pain AND depression OR negative effects AND patients AND animal model OR chronic pain AND depression AND animal models AND patients." The selection criteria included studies with (1) clinical and preclinical data; (2) human and rodent data; and (3) cooccurrence of pain, depression and neuroinflammation. Studies of all sample sizes were included

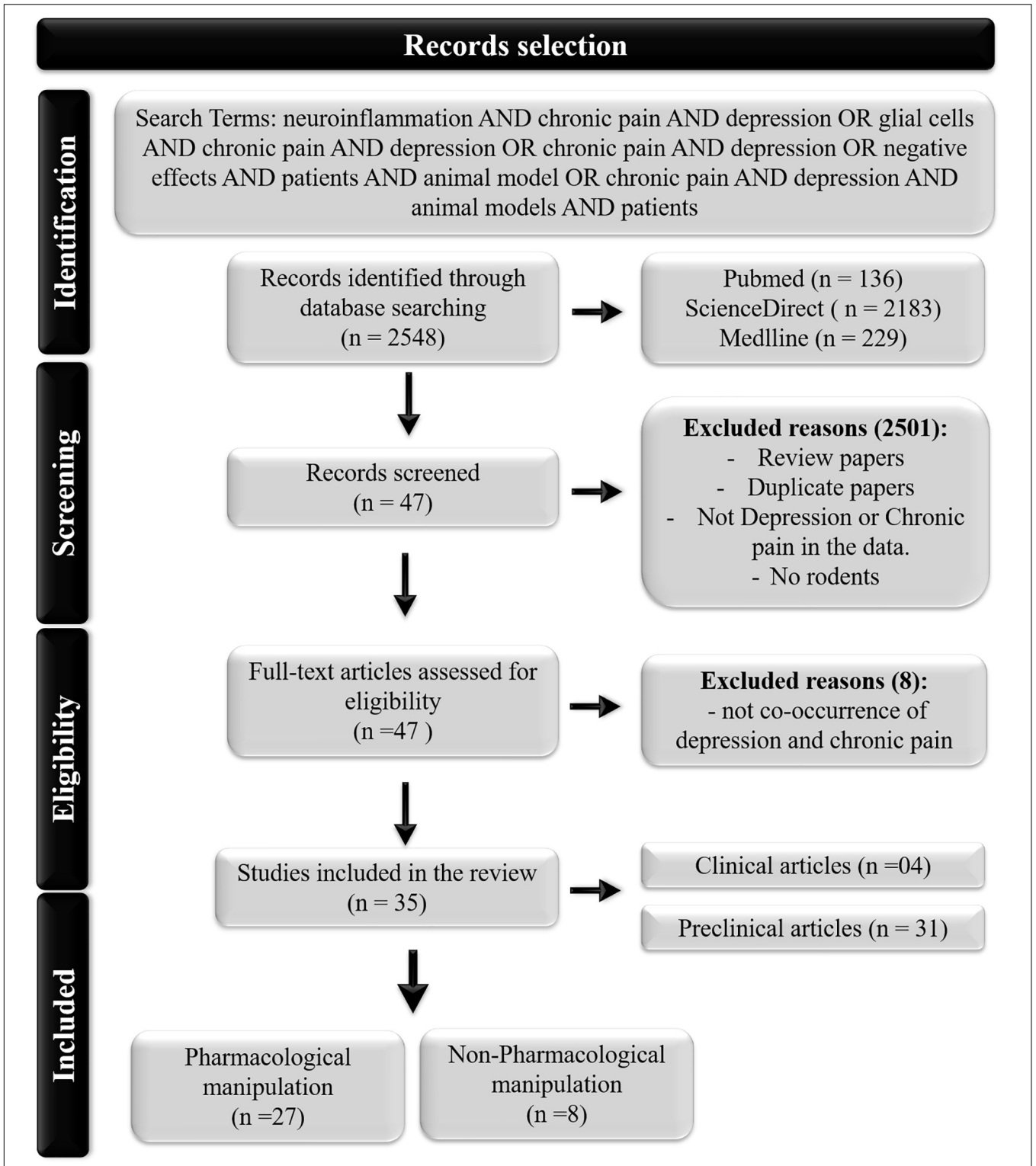

FIGURE 1 | Flowchart of the study.

in the analysis. Studies were excluded if they (1) were reviews or meta-analyses; (2) presented repeated data from previously included studies or (3) were not published in English.

As shown in **Figure 1**, the search yielded 2,548 records. We eliminated articles that did not investigate the cooccurrence of painful and depressive behaviors or did not investigate

any inflammatory biomarkers. Ultimately, 35 studies were included in this review.

RESULTS

Target Structures Involved in Pain and Depression

From the 35 selected papers, we found 31 and 4 reports of preclinical models and clinical investigations, respectively. Eight of the selected articles evaluated the inflammatory signature in the presence of painful and depressive behavior, while 27 articles evaluated the inflammatory response related to different types of treatments. The structures that play an important role in pain and depression states listed in the selected papers included the cerebral cortex and its subdivisions, the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the amygdala, the hippocampus, and the raphe nuclei, as alterations in plasma were observed in human subjects.

The main general markers of the cooccurrence of chronic pain and depression were related to central inflammation, particularly, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, as well as peripheral discrepancies in cortisol levels. Regarding treatment for depression-pain syndrome, we found that therapies with different mechanisms may attenuate central and peripheral inflammation, raising a discussion about the relationship between the neuronal network and inflammation modulation.

DISCUSSION

Target Structures Involved in Pain and Depression

During pain processing, structures such as the PFC, ACC, nucleus accumbens (NAc), thalamus, hippocampus and amygdala send projections to the periaqueductal gray (PAG) to activate the descending analgesic pathway, including the raphe nucleus and locus ceruleus (Fields and Basbaum, 1999; Apkarian et al., 2005; Seminowicz et al., 2019). These areas are connected and often modulate one another, as first described by Papez (1937). The original Papez circuit consists of the hippocampus, thalamus, cingulate gyrus and cerebral cortex; however, further structures have been added over the years, such as the insular cortex, amygdala, and other subcortical nuclei (Yakovlev, 1948; Nakano, 1998). In this sense, the limbic system, a network of brain structures involved in emotion, memory, learning and homeostatic processes that strongly affect behavior (Arora et al., 2011; Catani et al., 2013), suggesting a major correlation between pain and depression.

Therefore, many authors have searched for inflammatory signatures in limbic system structures, especially the PFC and hippocampus. It has been proposed that the expression of genes encoding proinflammatory cytokines are increased in these limbic structures responsible for pain processing and depression (Arora et al., 2011; Kim et al., 2012). A structure mentioned in 24% of the articles was the PFC. The medial PFC (mPFC), which is composed of the granular and agranular areas, including the ACC (Ong et al., 2019), was also investigated in the articles we found. Additionally, another 12% of the articles described the signature in the cerebral cortex without specifying which regions were involved. Some authors probably preferred to address the structures more generally due to the methodological difficulty of ensuring the extraction if the specific area of the brain from fresh tissue. The mPFC sends projections to the PAG (Bragin et al., 1984; An et al., 1998) that project to the nuclei raphe and are involved in the analgesic descending pathway (Fields and Basbaum, 1999; Apkarian et al., 2005; Seminowicz et al., 2019). The mPFC is important for pain processing and mediates antinociceptive effects due to its connections with other cortical areas and the PAG (Ong et al., 2019). However, increased and persistent activation of the thalamus, which projects to the somatosensory cortex and the PFC, mediates the chronification of pain, possibly via corticostriatal projections, dopaminergic system dysfunction and ventral tegmental area (VTA)-NAc reward pathways (Ong et al., 2019). Additionally, although the PFC is often thought of as the center of thinking and decision making, it is also associated with depression (Treadway et al., 2015). Lesions of the mPFC, which is responsible for affection and negative emotion (Miller and Cohen, 2001), may attenuate depression by decreasing the direct activation of the amygdala (Ellenbogen et al., 2005; Sachdev and Sachdev, 2005; Connolly et al., 2017).

It has been proposed that environmental stress can contribute to the development of depression through inflammatory and epigenetic mechanisms (Slavich and Irwin, 2014; Park et al., 2019). Specifically, the PFC and amygdala have opposite responses to stress since synaptic plasticity is enhanced in the amygdala after depression and is decreased in the PFC (Marsden, 2013). Inhibition of the amygdala by local GABAergic agonists changes pain sensitivity and depressive-like behavior (Seno et al., 2018). Additionally, the volume of the amygdala has been suggested to be correlated with the severity of depression (Li et al., 2014), demonstrating the importance of its activation in the pathophysiology of depression.

Persistent pain may cause dystrophy of hippocampal areas by reducing volume, increasing abnormal cytokine expression, and inducing deficits in long-term potentiation as well as impairing neurogenesis (Duric and McCarson, 2005; Kodama et al., 2007; Terada et al., 2008; Al-Amin et al., 2011; del Rey et al., 2011; Erickson et al., 2011; Mutso et al., 2012). These alterations can induce anxiety and stress since the hippocampus and PFC play critical roles in regulating the hypothalamus-pituitary-adrenal (HPA) axis (Jacobson and Sapolsky, 1991). After HPA activation, glucocorticoid hormones (corticosterone in rodents and cortisol in humans) are released from the adrenal gland in response to stress and easily penetrate into the human brain (Karssen et al., 2001). The hippocampus, PFC and brainstem monoaminergic nuclei strongly respond to the increased levels of these glucocorticoids (Reul and de Kloet, 1985). In this sense, dopamine release is increased in acute stress (Castro and Zigmond, 2001), while it is downregulated after chronic exposure, causing modulation of the VTA-NAc reward pathway (Thompson et al., 2004). Additionally, chronic exposure to

corticosterone/cortisol induces hippocampal dendritic atrophy (Landfield et al., 1981; Meaney et al., 1988), suggesting that depression and anxiety can induce changes in neural plasticity in areas also involved in controlling the nociceptive system and may "predispose" the brain to persistent pain sensitivity. The majority of the articles we found investigated the hippocampus, demonstrating the importance of this region in pain, depression, and depression-pain-syndrome. We also found that some authors investigated the dorsal root of the ganglia (DRG) and the spinal cord, structures strongly related to pain control (Todd, 2010; Krames, 2014), especially in models of pain induced by nerve damage.

Regarding the assessment of systemic samples, some articles evaluated corticosterone levels and some inflammatory biomarkers in the serum or plasma. Plasma and serum are more related to the neuroendocrine response and peripheral inflammation since the blood-brain barrier (BBB) can prevent the ability of substances in the blood circulation to access the CNS (Daneman and Prat, 2015); however, some studies have noted that neuroinflammatory settings may compromise the integrity of the blood-nerve barrier and alter the BBB (Skaper, 2016; Schaefer et al., 2017). A schematic review of target structures and inflammatory signatures is shown in **Figure 2**.

Neuroinflammatory Signature of Preclinical Models (Table 1)

In the peripheral nervous system, classic inflammatory modulators are secreted by neutrophils in a more acute stage of neuroinflammation and then by macrophages and T cells after the persistence of inflammation sensitizes either the nociceptor sensory receptors (Basbaum et al., 2009) or peripheral glial cells, such as Schwann cells and satellite glia cells (Ellis and Bennett, 2013), to potentially noxious stimuli in primary afferent neurons, modulating pain sensitivity (Ji R. R. et al., 2013). Infiltrating macrophages and Schwann cells can secrete proinflammatory cytokines, such as IL-1β and TNF-α (Nathan, 1987; Palmer and Weaver, 2010), which is consistent with the increase in plasma proinflammatory cytokines in people suffering from chronic pain (Vendrusculo-Fangel et al., 2019) and preclinical pain models (**Table 1**). Both peripheral and central inflammation are associated with symptoms of pain and depression (Walker et al., 2013b), as characterized by dysregulation of the immune system (Burke et al., 2014), neurotransmitters such as noradrenaline and serotonin (Stahl and Briley, 2004; Goldenberg et al., 2010), neuropeptides such as brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) (Kramer et al., 1998; Werner and Coveñas, 2010), oxidative stress (Arora et al., 2011) and cytokines (Wallace, 2006; Dowlati et al., 2010).

Where and how neuroinflammation starts in the absence of a pathogen or classic injury may be a complex question. In this sense, direct injury of peripheral nerves, as investigated in 57% of the articles regarding neuroinflammation in preclinical models without treatment (**Table 1**), begins with peripheral inflammation due to Wallerian degeneration that occurs in the distal axonal segment following nerve injury and is characterized by a process of demyelination and disintegration, release of proinflammatory cytokines and macrophage recruitment to the nerve (Toews et al., 1998; Shamash et al., 2002; Zuo et al., 2003; Perrin et al., 2005). In peripheral nerve injury, myelinating Schwann cells start proliferating and produce proinflammatory cytokines, such as TNF-α, IL-1β and monocyte chemoattractant protein 1 (MCP-1), which together with substance P (SP) and calcitonin gene-related peptide (CGRP) act as damage-associated molecular patterns (DAMPs) that activate innate immune resident cells (Zhang and An, 2007). These patterns activate different receptors present within the membrane of resident cells to induce the release of more proinflammatory cytokines and chemokines (Takeuchi and Akira, 2010).

Increased serum levels of TNF-α and IL-6 have been shown in two different BXD mouse lineages that are commonly used as genetic resources to study neuropharmacological phenomenon (Philip et al., 2010). In BXD21/TyJ RI mice, nuclear factor erythroid 2 (Nrf2) expression is upregulated, while BXD84/RwwJ RI mice exhibit low Nrf2 expression (López-Granero et al., 2017). Considering the role of Nrf2 in activating antioxidative mechanisms (Zhang et al., 2013), these mice show greater depressive-like behavior than wild-type mice (López-Granero et al., 2017). Interestingly, increases in TNF-α, IL-1β, IL-6 and caspase-1 are found in the serum of animals submitted to chronic stress paradigms that induce depressive behavior (Zhao et al., 2019). Stress models have been used to study the etiological and developmental components of depression and to screen antidepressant drugs (Nollet et al., 2013).

Increased systemic proinflammatory cytokines can also be found in people affected with major depression before any treatment (Zou et al., 2018), but the relevance of cytokine expression in the blood of people with depressive disorders is not clear (Himmerich et al., 2019). Additionally, even though the dorsal horn of the spinal cord (DHSC) is poorly related to depression, in a model of maternal separation, there is increased microglial activation in this structure. Interestingly, the same article also showed that animals submitted to maternal separation followed by spinal nerve ligation (SNL) exhibited more relevant activation of spinal microglia (Mizoguchi et al., 2019), corroborating the hypothesis that depression may "predispose" the CNS to the pathologic properties of persistent pain. Astrocytes and microglial cells are critical for the induction and maintenance of chronic pain in a preclinical pain model (Watkins et al., 2001). These cells express Toll-like receptors (TLRs), purinergic receptors (with ATP as ligands) and glutamatergic receptors (Domercq et al., 2013; Siracusa et al., 2019). For instance, a low ATP concentration increases the release of chemokines, including IL-2, MCP-1 and CX3CL1, which act by recruiting immune cells from other brain regions or from the bloodstream to the injured tissue (Domercq et al., 2013; Turner et al., 2014). When ATP or glutamate is increased in the synaptic environment, these cells secrete cytokines, such as TNF-α, IL-1β, IL-6, and interferon (IFN)-γ (Suzuki et al., 2004; Taylor et al., 2005; Di Virgilio et al., 2009), which are pivotal inflammatory mediators that further aggravate the inflammatory reaction and may also potentially serve as biomarkers of diseases and therapeutic efficacy (Goldstein et al., 2009; Miller et al., 2009; Chen et al., 2017).

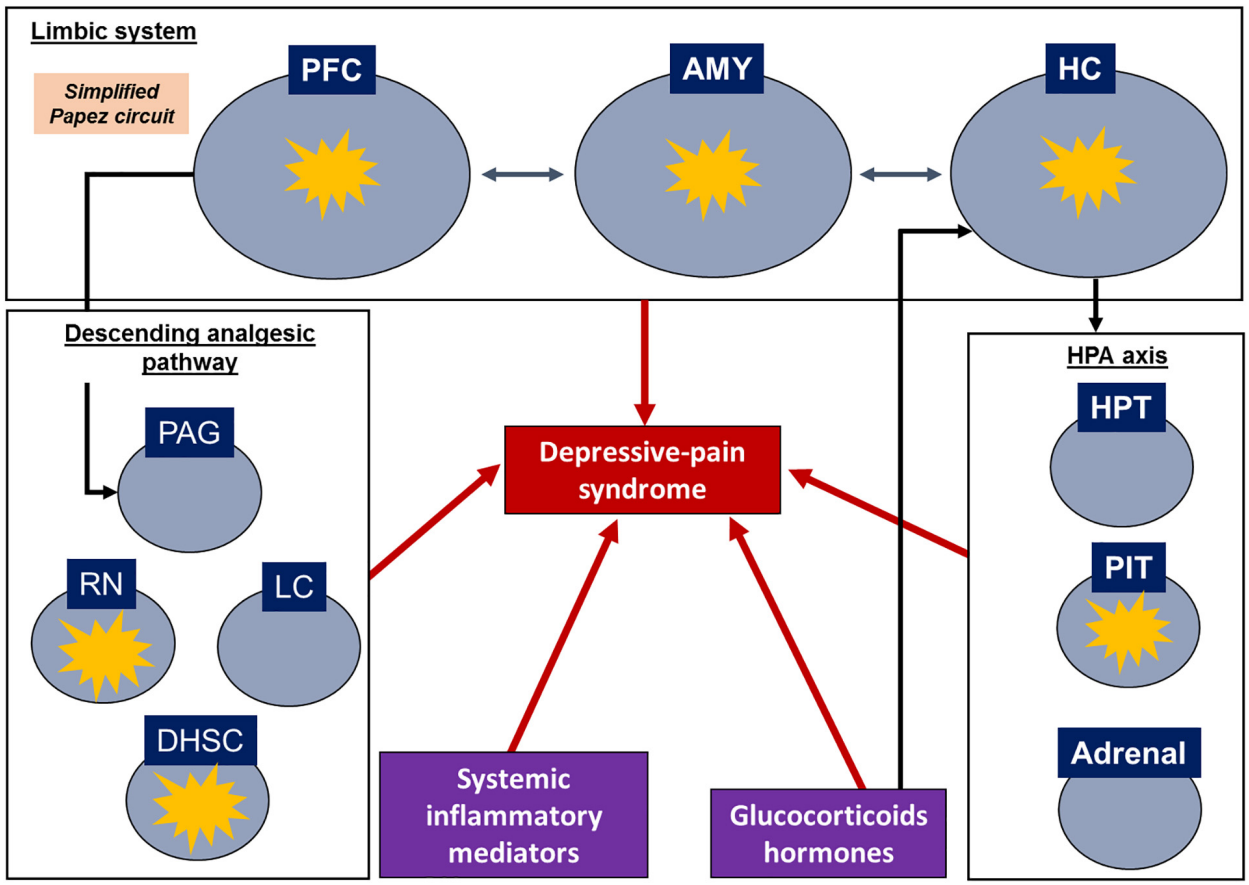

FIGURE 2 | Schematic representation of depressive-pain syndrome and the relationship between target structures and mediators. Target structures with inflammatory signatures in the identified articles. AMY, amygdala; DHSC, dorsal horn of the spinal cord; HC, hippocampus; HPT, hypothalamus; LC, locus coeruleus; PAG, periaqueductal gray matter; PFC, prefrontal cortex; PIT, pituitary; RN, raphe nuclei.

Peripheral nerve injury models present peripheral inflammation and increased proinflammatory cytokines in spinal and supraspinal structures, such as the PFC (González-Sepúlveda et al., 2016) and amygdala (Gonçalves et al., 2008) as well as with decreased thermal and mechanical nociceptive thresholds and depressive-like behavior. TNF receptor (TNFR) knockout mice are protected against CCI-induced pain; however, inflammation in the hippocampus and depressive-like behavior remain (Fischer et al., 2019). Inflammation of the limbic system also occurs in chronic stress models with increased proinflammatory cytokines in the PFC, hippocampus, raphe nuclei and pituitary (Zhao et al., 2019). Additionally, the olfactory bulbectomy-induced depression model exhibited increased CD11b (macrophage/microglia marker), GFAP (Glial fibrillary acidic protein, astrocyte marker) and IL-1β levels in the amygdala, but the spinal nerve ligation-induced neuropathic pain alone or combined with olfactory bulbectomy does not change the expression of these cytokines (Burke et al., 2013), demonstrating that although pain and depression have several similarities, they may also involve different pathways. Inflammation of the structures of the limbic system often correlates with increased serum ACTH and corticosterone levels (Zhao et al., 2019). Increased expression of these hormones is often used as a biomarker for the activation of the HPA axis, which is strongly related to stress (Abrahams et al., 2012; Stephens and Wand, 2012). Focusing on neuroinflammation, Arora and Chopra (2013) observed increases in TNF-α and IL-1β in the hippocampus and PFC after chronic administration of reserpine. In another study, chronic unpredictable mild stress and chronic corticosterone treatment induced an increase in TNF-α, IL-1β, and IL-6 in different brain structures, as well as in the hippocampus and PFC (Zhao et al., 2019). In combined models of pain and depression, increases in the cytokines IL-1β and IL-6 in the amygdala have also been noted (Burke et al., 2013). In this sense, the main general markers of the cooccurrence of chronic pain and depression are related to central inflammation, particularly TNF-α, IL-1β, and IL-6.

Understanding Treatments for Persistent Pain and Depression

Since chronic pain and depression-pain-syndrome are complex disorders, an extensive class of medications has been used to improve the quality of life of individuals suffering

TABLE 1 | Inflammatory signature upon presence of painful and depressive behavior in preclinical and clinical research.

Pain models investigating depression

References	Pain model	Painful behavior	Depressive-like behavior	Inflammatory effects
González-Sepúlveda et al., 2016	PSNL	↓ Thermal nociceptive threshold using the cold plate test	↓ Time spent in open arms in the EPM	↑ IL-1 β in the PFC
			↑ Murbles buried	
		↓ Mechanical nociceptive threshold using the von Frey test	↑ Immobility in the tail suspension	
			↑ Alcohol drinking in the dark	
Gonçalves et al., 2008	SNI	↓ Mechanical nociceptive threshold using the von Frey and pin-prick tests	↑ Immobility in the FST	↑ BrdU, BrdU + GFAP and BrdU + calbidin labeling in the amygdala
				No change in the BrdU + NeuN labeling in the amygdala

Depressive-live models investigating pain

References	Depressive-like model	Painful behavior	Depressive-like behavior	Inflammatory effects
Zhao et al., 2019	CUMS	↓ Thermal nociceptive threshold using the Hargreaves test	↓ Sucrose preference	↑ IL-1β and caspase-1 in the PFC and pituitary
				↑ IL-1β, IL-6 and caspase-1 in the hippocampus
		↓ Mechanical nociceptive threshold using the von Frey test	↑ Immobility in the FST	↑ TNF-α, IL-1β, IL-6 and caspase-1 in the raphe nuclei;
				↑ TNF-α, IL-1β, IL6 and CASP1 in serum
				↑ACTH and corticosterone in serum
	CORT	↓ Thermal nociceptive threshold using the Hargreaves test	↓ Sucrose preference	No change in the PFC
				↑ TNF-α, IL-1β, IL-6 and caspase-1 in HC
				↑ TNF-α in the raphe nuclei;
		↓ Mechanical nociceptive threshold using the von Frey test	↑ Immobility in the FST	↑ TNF-α, IL-1β, IL-6 and caspase-1 in the pituitary
				↑ TNF-α, IL-1β, IL6 and CASP1 in serum
				↑ACTH and corticosterone in serum
Mizoguchi et al., 2019	Maternal separation	↓ Thermal nociceptive threshold using the acetone test	↑ Immobility time in the FST	↑ Iba-1 (microglia activation) in the DHSC
			↓ Sucrose preference	
		↓ Mechanical nociceptive threshold using the von Frey test	↑ Performance in social interaction	
			↓ Time spent in open arms in the EPM	

(Continued)

TABLE 1 | Continued

Mouse lineage in basal measure

References	Lineage	Pain models	Painful behavior	Depressive-like behavior	Inflammatory effects
López-Granero et al., 2017	Two BXD RI mouse strains, BXD21/TyJ RI, BXD84/RwwJ RI and C57BL/6 wild-type mice	Not applicable	↓ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	↑TNF-α and IL-6 in serum
Dellarole et al., 2014	Wild-type	CCI	↓ Thermal nociceptive threshold using the Hargreaves test ↓ Mechanical nociceptive threshold using the von Frey test	↓ Sucrose preference ↓ Body weight ↓ Physical state	↑ TNF-α the hippocampus ↑ TNFR2 the hippocampus No change in TNFR1 the hippocampus
	TNFR1$^{-/-}$		No change in thermal nociceptive threshold using the Hargreaves test No change in mechanical nociceptive threshold using the von Frey test	↓ Sucrose preference ↓ Body weight ↓ Physical state	↑ TNF-α in the hippocampus No change in TNFR2 in the hippocampus

Pain and Depressive-live models

References	Depressive-like model	Pain Models	Depressive-like behavior	Painful behavior	Inflammatory effects
Burke et al., 2013	Sham	SNL	Not measure	↓ Thermal nociceptive threshold using the acetone test, but no change in Hargreaves test ↓ Mechanical nociceptive threshold using the von Frey test	No change in CD11b, GFAP, IL-1b and TNF-α in the amygdala
	OB	Sham	Not measure	↓ Thermal nociceptive threshold using the acetone test, but no change in Hargreaves test ↓ Mechanical nociceptive threshold using the von Frey test	↑ CD11b, GFAP and IL-1b in the amygdala
	OB	SNL	Not measure	↓ Thermal nociceptive threshold using the acetone test, but no change in Hargreaves test ↓ Mechanical nociceptive threshold using the von Frey test	No change CD11b, GFAP, IL-1β and TNF-α in the amygdala

Clinical data

References	Diagnosis	Painful behavior	Depressive-like behavior	Inflammatory effects
Euteneuer et al., 2011	Major depression	↑ Pain sensibility using the paw pressure test	↑ Scores in BDI-II and SCL-90T GSI	No change in TNF-α and IL-6 expression in serum

ACTH, adrenocorticotropic hormone; BDI-II, Beck Depression Inventory-II; BrdU, bromo-deoxyuridine; BXD RI, BXD recombinant inbred (RI) mice strains; BXD21/TyJ, BXD RI mouse strain; CCI, chronic constriction injury; CD11b, cluster of differentiation 11b; CORT, chronic corticosterone treatment; CUMS, chronic unpredictable mild stress; DHSC, dorsal horn of the spinal cord; EPM, elevated plus maze; FST, forced swimming test; GFAP, glial fibrillary acidic protein; HC, hippocampus; Iba-1, ionized calcium-binding adapter molecule 1; IL, interleukin; NeuN, neuronal nuclei; OB, olfactory bulbectomy; PFC, prefrontal cortex; PSNL, partial spinal nerve ligation; SCL-90T, Symptom Checklist 90 Revised; GSI, Global Severity Index; SNI, spared nerve injury; SNL, spinal nerve ligation; TNF-α, tumor necrosis factor alfa; TNFR1, tumor necrosis factor receptor 1; TNFR2, tumor necrosis factor receptor 2.

from depressive-pain syndrome. Classic non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are not efficient in attenuating persistent pain sensitivity (Johannes et al., 2010); hence, the use of benzodiazepines, tricyclic antidepressants, monoamine reuptake inhibitors, glutamatergic antidepressant drugs, and adjuvant psychotherapy has been investigated to attenuate pain sensitivity. In pharmacological treatment, there is also an overlap between pain and depression: much of the medication that can be used to treat persistent pain is also used to treat major depression (Bair et al., 2003). These treatments are often related to the control of monoamines (such as serotonin, noradrenaline and dopamine), as well as glutamate and GABA, which are pivotal in the modulation of pain and depression (Benson et al., 2015). However, as described above, inflammation plays an important role in both comorbidities and, in this sense, may be a successful target for treating individuals with these symptoms.

Different types of non-pharmacological treatments can be used considering the importance of social support and the environment demonstrated in depressed subjects with chronic pain (Trief et al., 1995). Additionally, there is a strong correlation between pain, depression, and poor quality of sleep (Wilson et al., 2002; Smith and Haythornthwaite, 2004; Ohayon, 2005; Staner, 2010; Koffel et al., 2016) that is directly correlated with the level of stress. It has been shown that a stressful environment can induce hyperalgesia in rats (Rivat et al., 2007), while an enriched environment can alleviate chronic pain symptoms (Vachon et al., 2013). In addition to environmental enrichment, another non-pharmacological treatment used to investigate the inflammatory signature is pulsed radiofrequency. Non-pharmacological treatments such as acupuncture, massage and transcutaneous electrical nerve stimulation (TENS) have been administered to people affected with spinal cord injury, and they were shown to improve pain sensitivity when combined with pharmacological treatments (Norrbrink and Lundeberg, 2004). Pulsed radiofrequency uses radiofrequency to generate electrical fields that can affect neuronal membranes, altering the transmission of pain pathways (Byrd and Mackey, 2008) and is a safe and effective treatment for radicular pain, trigeminal neuralgia, occipital neuralgia, shoulder and knee pain (Vanneste et al., 2017).

NSAIDs are the most consumed drugs worldwide (Bozimowski, 2015), and their efficacy, especially in acute and postsurgical pain has been established (KuKanich et al., 2012). NSAIDs inhibit cyclooxygenase enzyme isotypes (COX1-COX4) and prostaglandins, decreasing pain, fever and inflammation by disrupting the arachidonic acid pathway (Osafo et al., 2017). This inhibition may mediate peripheral nociceptor sensitization (Vane, 1971) and the central nociceptive pathway (Hunskaar, 1987; Björkman, 1995; Wang et al., 1995). Thus, in a model of acute pain (induced by formalin) and a stressful depressive (SD) model, the effect of aspirin was compared to that of benzodiazepines and a cholecystokinin (CCK) antagonist (Rivat et al., 2010). Cholecystokinin reduces the antinociceptive effects of opioids, and its antagonist may be an effective tool to prevent opioidergic tolerance (Wiesenfeld-Hallin et al., 2002). In this article, only benzodiazepine was unable to improve the mechanical and thermal nociceptive threshold; however, aspirin was not effective in improving anxious-depressive behavior (Rivat et al., 2010), demonstrating that NSAIDs may not be helpful in the comorbidity of pain and depression comorbidity. Another class of medications used for neuropathic pain is steroidal drugs, such as corticosteroids and dexamethasone (Watanabe and Bruera, 1994). Atkinson and coworkers showed that dexamethasone is not able to control cortisol levels in individuals with chronic pain and major depression (Atkinson et al., 1986), which is related to painful and depressive symptoms (France and Krishnan, 1985). In addition, different fatty acids have been studied in an attempt to attenuate pain and depression. Omega-3 improves anxiety and depression in people affected with chronic pain (Cortes et al., 2013), while omega-3, palmatine and β-caryophyllene attenuate pain and depression in a preclinical diabetic model (Redivo et al., 2016; Shen et al., 2018; Aguilar-Ávila et al., 2019). Berberine, a quaternary ammonium salt derived from a protoberberine group of alkaloids, is the principal bioactive compound found in *Coptis chinensis*, *Berberis vulgaris* and other medicinal plants that are effective in treating pain and depression (Tang et al., 2009; Ye et al., 2009). In addition to significantly reducing hypercholesterolemia in rats (Kim and Chung, 2008; Hu and Davies, 2010; Wang et al., 2014), berberine also exerts a depressant action in the central system and has beneficial antinociceptive effects on pain threshold (Shanbhag et al., 1970). Berberine reduces pain- and depressive-like behavior in a reserpine-induced persistent pain model, and this response is related to the inhibition of SP and reactive species in the cerebral cortex and hippocampus (Arora and Chopra, 2013). Another natural compound that has been studied is triptolide, which is extracted from the medicinal plant *Tripterygium wilfordii* and can be used to suppress different proinflammatory factors from macrophages and T cells (Qiu et al., 1999; Qiu and Kao, 2003). Triptolide shows the same effectiveness in providing pain relief and attenuating depression as fluoxetine, a classical antidepressant (Hu et al., 2017).

As previously described, one of the similarities between the pathophysiology of pain and depression is the importance of monoamines. Hence, treatment with monoamine reuptake inhibitors is very common and was found in 22% of the articles that investigated treatments for pain and depression involving inflammation. Since major depression is associated with decreased serotonin levels (Haase and Brown, 2015), as in the persistent pain state (Bardin, 2011), fluoxetine improves these symptoms by increasing the amount of serotonin in the synaptic environment by selectively inhibiting the reuptake of this monoamine (Fuller et al., 1991). Although fluoxetine is the most studied selective serotonin reuptake inhibitor (SSRI) used to treat chronic pain, its use in clinical trials has been contradictory (Walker et al., 1998); however, it is effective in a preclinical lumbar disk herniation model (Cai et al., 2019). Additionally, fluoxetine plus pioglitazone or metformin, both of which are antidiabetic drugs, attenuates pain and depression with better effects than each treatment individually (Murad and Ayuob, 2015). Pioglitazone is a peroxisome proliferator-activated receptor gamma (PPARy) agonist that inhibits hyperalgesia in a spared nerve injury model (Griggs et al., 2015), while

metformin inhibits mammalian target of rapamycin (mTOR) and decreases neuropathic pain and postsurgical pain (Kiałka et al., 2017). Rosiglitazone, another antidiabetic drug that also acts on PPARy, inhibits neuropathic pain induced by sciatic nerve transaction in rats by regulating macrophage polarization (Churi et al., 2008; Hasegawa-Moriyama et al., 2012). Like morphine, rosiglitazone improves mechanical allodynia, but unlike morphine, it improves depressive-like behavior by increasing BDNF and decreasing proinflammatory modulators in the hippocampus (Zong et al., 2018). Interestingly, an AMP-activated protein kinase (AMPK) inhibitor and an agonist of 3-MA (an autophagy inhibitor) block the antinociceptive, antidepressive and anti-inflammatory properties of rosiglitazone (Zong et al., 2018), suggesting that these compounds are involved in the control of pain and depression, probably due to their antidiabetic medication properties. Amitriptyline, similar to fluoxetine, is a monoamine regulator that is used regularly as an antidepressant, acts as a selective serotonin-noradrenalin reuptake inhibitor (SSNRI), and has antinociceptive effects dependent on α2-adrenergic receptors (Hiroki et al., 2017). However, in a spinal nerve ligation and olfactory bulbectomized model of pain and depression, amitriptyline treatment is not able to attenuate thermal hyperalgesia or allodynia but improves depressive-like behavior (Burke et al., 2015). According to the Cochrane Database Reviews (2014), there is not enough information to consider imipramine, which is in the same class of medicines as amitriptyline, a drug for neuropathic pain treatment. α-(Phenylselanyl)acetophenone (PSAP), a new selenium drug, has been tested for its ability to treat neuropathic pain because of its anti-inflammatory and antioxidant properties and its effect on serotonin receptors (Gerzson et al., 2012). According to Sousa et al. (2018), imipramine and PSAP improve pain sensitivity and depressive-like behavior after acute stress restriction (Sousa et al., 2018).

Ketamine is an anesthetic drug with *N*-methyl-D-aspartate (NMDA) receptor antagonism properties. Since these receptors are related to the amplification of pain signals and opioid tolerance, ketamine acts by reducing these dysfunctions observed in chronic pain conditions (Trujillo and Akil, 1991; Laulin et al., 2002; Lilius et al., 2015). Additionally, ketamine may also regulate monoaminergic receptors (Peltoniemi et al., 2016) and increase the inhibitory serotonergic pathway (Mion and Villevieille, 2013). However, ketamine has been shown to improve depressive-like behavior without attenuating pain in a spared nerve injury model (Pan et al., 2018). Another possible antinociceptive mechanism of ketamine is the inhibition of astrocyte and microglia activation (Sleigh et al., 2014), as minocycline, an antibiotic with high lipid solubility, crosses the BBB and inhibits microglia activation (Yrjänheikki et al., 1998). Minocycline improves pain sensitivity and depressive-like behavior in a model of spinal nerve ligation combined with olfactory bulbectomy (Burke et al., 2014); however, it was shown to be ineffective in patients with lumbar radicular neuropathic pain in a double-blind clinical trial using amitriptyline as a comparator (Vanelderen et al., 2015). A summary of the pharmacological mechanisms of the treatments described in this review is shown in **Figure 3** and **Table 2**.

Because of the complexity and multifactorial aspects of persistent pain and depression, an extensive number of medications are already used by individuals suffering from depression-pain syndrome but are often not effective. Hence, it is important to investigate new mechanisms of classical drugs to improve their use and to find and develop new drugs and targets to treat these syndromes.

Understanding the Anti-inflammatory Signature of Depressive-Pain Treatments

Beyond understanding the neuroinflammatory signature of the pathophysiology of pain and depression, we found a total of 23 articles (39%) that investigated the role of different types of treatments in controlling pain, depressive-like behavior and neuroinflammation. We will address the treatments used in the articles found in our research, the identified neuroinflammatory signatures in response to treatment and the possible neuronal networks involved in the amelioration of depressive-pain symptoms.

In preclinical trials, it is common to investigate molecular inhibitors or antagonists in an attempt to understand the specific role of different neuromodulators. We found that in 39% of the preclinical models, treatments involving different inhibitors or antagonists were investigated. Acute or subchronic treatment with these inhibitors may shed light on the possible mechanisms of pain and depression or may indicate a new target for treating these syndromes.

Neuroimaging and postmortem studies have shown an increase in mitochondrial translocator protein (tryptophan-rich sensory proteins -TSPO) in subjects with major depressive disorder (Enache et al., 2019). It has been shown that during local or systemic inflammation, TSPO is overexpressed in inflammatory cells and can be considered a marker of proinflammatory microglia (Selvaraj and Tu, 2016; Owen et al., 2017; Beckers et al., 2018). Li et al. (2017) showed that *N*-benzyl-*N*-ethyl-2-(7,8-dihydro-7-benzyl-8-oxo-2-phenyl-9H-purin-9-yl) acetamide (ZBD-2), a TSPO ligand, decreases microglia and astrocyte activation and increases BDNF expression in the hippocampus and spinal cord in neuropathic rats subjected to spinal cord injury, improving pain sensitivity and depressive-like behavior by decreasing corticosterone levels in the plasma. This finding corroborates the idea that mitochondrial dysfunction plays a pivotal role in inflammation and DAMP formation (Shimada et al., 2012).

Different types of inhibitors of the inflammatory cascade have been used to attenuate painful and depressive-like behavior. The prokineticin family receptor (PKR) is present in the DRG and spinal cord and plays a role in sensitizing nociceptors via transient receptor potential vanilloid receptor 1 (TRPV1), inducing the release of proinflammatory cytokines (Negri et al., 2006; Li et al., 2016). PC-1, a PKR antagonist, was used in a model of chemotherapy-induced neuropathic pain with vincristine and was shown to decrease the levels of proinflammatory cytokines and infiltrating leucocytes without changing the expression of GFAP in the spinal cord (Moschetti et al., 2019), demonstrating that the antinociceptive properties of PKR inhibition may be

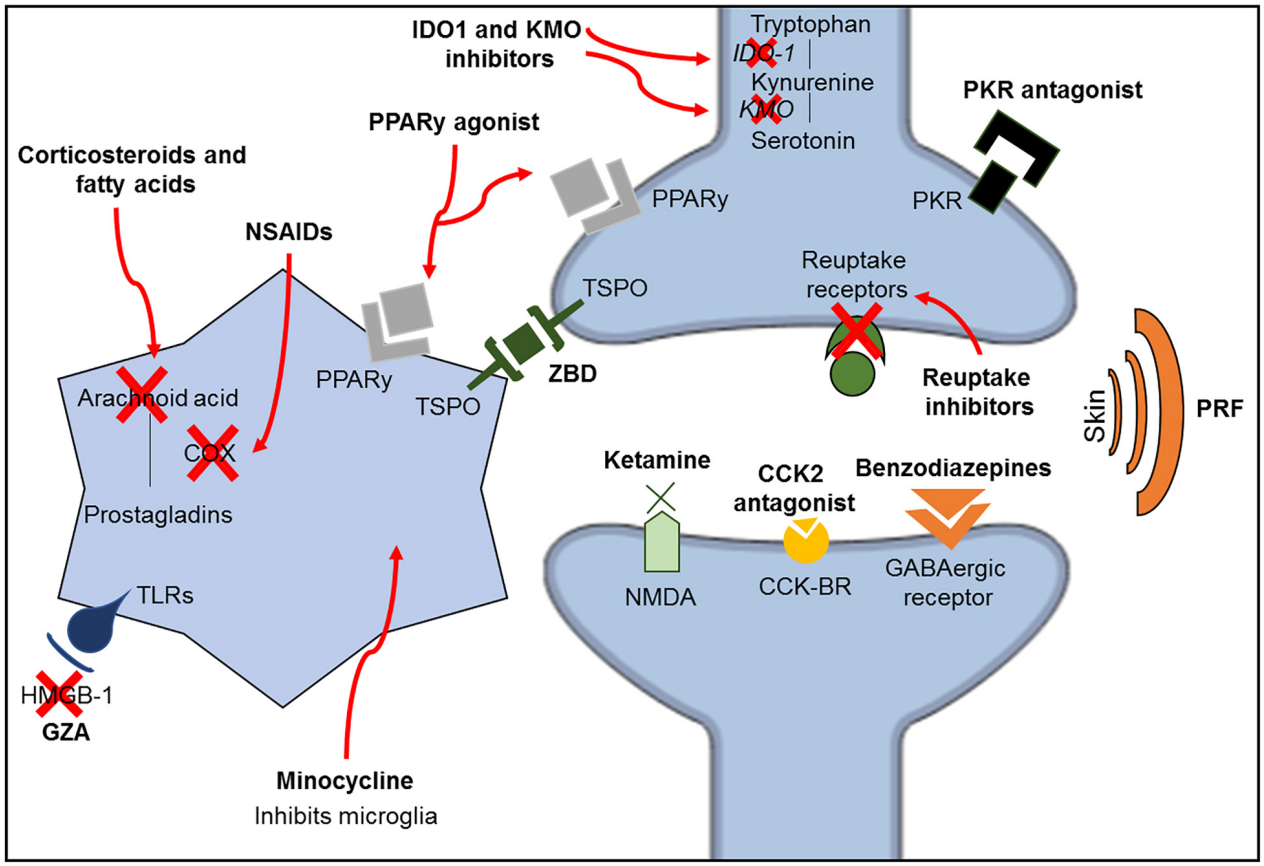

FIGURE 3 | Schematic representation of the classic mechanisms of the different classes of medications investigated in this review. CCK2, cholecystokinin 2; CCK-R, cholecystokinin receptors; GZA, glycyrrhizic acid; HMGB-1, high mobility group box-1; IDO1, indolamine 1,3 deoxygenase; KMO, kynurenine 3-monooxygenase; NMDA, *N*-methyl-D-aspartate; NSAIDs, non-steroidal anti-inflammatory drugs; PKR, prokineticin family; PPARy, peroxisome proliferator-activated receptor gamma; PRF, pulsed radiofrequency; TLRs, toll-like receptors; TSPO, translocator protein; ZBD, *N*-benzyl-Nethyl-2-(7,8-dihydro-7-benzyl-8-oxo-2-phenyl-9H-purin-9-yl) acetamide.

related to peripheral mechanisms. Reinforcing these results, 2-AP, another PKR inhibitor, was also shown to decrease inflammasome and caspase-1 expression in the hippocampus of rats subjected to chronic constriction injury (Li et al., 2019). The tryptophan-metabolizing enzyme indolamine 1,3 deoxygenase (IDO1) is a direct modulator of inflammatory cytokine release (O'Connor et al., 2009) and is pivotal for the metabolism of tryptophan into kynurenine (KIN), which is further converted to kynurenine 3-monooxygenase (KMO) (Schwarcz and Stone, 2017). In this sense, the effect of inhibition of IDO and KMO, which attenuates depressive-like behavior but weakly ameliorates painful behavior, was compared to that of an inhibitor of IL-1 receptor antagonist (IL-1RA) in two different articles (Zhou et al., 2015; Laumet et al., 2017).

As previously described, glial cells are very important for the maintenance of the inflammatory response within the nervous system. Interferon regulatory factor 8 (IRF8) deficiency prevents the activation of microglia (Liu et al., 2018), and the mechanisms by which IRF8 deficiency improves pain sensitivity and depressive-like behavior are very similar to those of pulsed radiofrequency, which decreases IRF8 in the spinal cord and BDNF in the NAc, demonstrating that non-pharmacological treatments also play an important role in microglial activation and the VTA-NAc reward pathway (Fang et al., 2019). High-mobility group box-1 (HMBG1) is secreted and activates immune cells via Toll-like receptor 4 (TLR4), inducing the production of cytokines and chemokines (Andersson and Tracey, 2011; Agalave and Svensson, 2015). Since HMBG1 is upregulated in the spinal cord and sciatic nerve in neuropathic pain models (Ren et al., 2012; Nakamura et al., 2013), the effect of glycyrrhizic acid (GZA), an inhibitor of HMGB-1, in a partial sciatic nerve ligation model was investigated. GZA attenuates depressive-like behaviors and decreases microglial activation in the PFC (Hisaoka-Nakashima et al., 2019). In relation to microglia and depressive-pain syndrome, minocycline, which also inhibits microglial activation, normalizes thermal and mechanical nociceptive thresholds and improves anxiety-depressive behavior (Burke et al., 2014; Xu et al., 2017; Dai et al., 2019). Additionally, similar to macrophages, microglia is also polarized toward the classical proinflammatory M1 phenotype or the alternative anti-inflammatory M2 phenotype (Jha et al., 2016). Although minocycline is able to increase the expression of IL-10 and

TABLE 2 | Inflammatory response regarding different types of treatments.

Pain models investigating depression					
References	**Pain model**	***Therapeutic intervention***	**After treatment**		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
Birmann et al., 2019	PSNL	*3-(4-Chlorophenylselany)-1-methyl-1H-indole*	↑ Thermal nociceptive threshold using the hot plate test ↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Grooming in the splash test	↓ ROS and lipid peroxidation in the cortex and hippocampus ↓ Costicosterone in plasma
Zhang et al., 2016	CFA	*Acute dose of ketamine*	↑ Thermal nociceptive threshold using the hot plate test ↑ Mechanical nociceptive threshold using the von Frey and paw pressure tests	↓ Immobility in the FST ↑ Sucrose preference	↓ IL-6 and IL-1β in the hippocampus ↓ Indoleamine 2,3-dioxygenase and kynurenine in the hippocampus
Vachon et al., 2013	SNI	*Environmental enrichment*	↑ Thermal nociceptive threshold using the hot plate and acetone tests ↑ Mechanical nociceptive threshold using the von Frey test	No change in time in close-arms in the EPM No change in time in the tail suspension	↓ SP and CGRP in the lumbar spinal cord
Murad and Ayuob, 2015	CCI	*Fluoxetine*	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	↓ TNF-α, IL-6, MCP-1 in plasma ↑ IL-10 in plasma ↓ GFAP expression in the spinal cord ↓ Myelin degeneration and leukocyte infiltration
		Pioglitazone	↑ Thermal nociceptive threshold using the Hargreaves test ↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	↓ TNF-a, IL-6, MCP-1 in plasma ↑ IL-10 in plasma ↓ GFAP expression in the spinal cord ↓ Myelin degeneration and leukocyte infiltration
		Metformin	↑ Thermal nociceptive threshold using the Hargreaves test	↓ Immobility in the FST	↓ TNF-α, IL-6, MCP-1 in plasma ↑ IL-10 in plasma

(Continued)

TABLE 2 | Continued

References	Pain model	*Therapeutic intervention*	After treatment		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
			↑ Mechanical nociceptive threshold using the von Frey test		↓↓ GFAP expression in the spinal cord ↓ Myelin degeneration and leukocyte infiltration
		Fluoxetine + pioglitazone	↑ Thermal nociceptive threshold using the Hargreaves test ↑ Mechanical nociceptive threshold using the von Frey test	↓↓ Immobility in the FST	↓ TNF-α, IL-6, MCP-1 in plasma ↑ IL-10 in plasma ↓↓ GFAP expression in the spinal cord ↓↑ Myelin degeneration and leukocyte infiltration
		Fluoxetine + metformin	↑ Thermal nociceptive threshold using the Hargreaves test ↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	↓ TNF-α, IL-6, MCP-1 in plasma ↑ IL-10 in plasma ↓↓ GFAP expression in the spinal cord ↓↓ Myelin degeneration and leukocyte infiltration
Cai et al., 2019	LDH	*Fluoxetine*	↑ Thermal nociceptive threshold using the Hargreaves test ↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Sucrose preference	↓ TNF-α in the hippocampus
Fang et al., 2019	SNI	*IRF8 siRNA*	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Sucrose preference	↓ IRF8 in the spinal cord ↓ BDNF in the NAc
		Pulsed frequency	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Sucrose preference	↓ IRF8 in the spinal cord ↓ BDNF in the NAc

(Continued)

TABLE 2 | Continued

References	Pain model	*Therapeutic intervention*	After treatment		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
Redivo et al., 2016	STZ	*Fish oil*	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST (modified)	↑ BDNF in the hippocampus and PFC
Li et al., 2017	SCI	*ZBD-2*	↑ Thermal nociceptive threshold using the Hargreaves test	↓ Immobility in the FST	↓ Iba-1 and GFAP expression in the hippocampus and spinal cord
			↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the tail suspension	↑ BDNF in the hippocampus and spinal cord
					↓ Costicosterone in plasma
Shen et al., 2018	STZ	*Palmatine*	↑ Thermal nociceptive threshold using the Hargreaves test	↓ Immobility in the FST	↓ GFAP and P2X7 expression in the hippocampus
			↑ Mechanical nociceptive threshold using the von Frey test	↑ Sucrose preference	↓ TNF-α and IL-1β in the hippocampus
Hisaoka-Nakashima et al., 2019	PSNL	*GZA (anti HMGB-1)*	Not measure	↓ Immobility in the FST ↑Social interaction ↓ Novelty suppressed feeding	↓ Iba-1 expression (activation) in the PFC
Li et al., 2019	CCI	*AcYVAD-CMK (caspase-1 inhibitor)*	No change in thermal nociceptive threshold using the Hargreaves test	↓ Immobility in the FST	Not measure
			No change in mechanical nociceptive threshold using the von Frey test	↑ Climbing in the FST No change in the EPM	
		2-AP (2-aminopurine - PKR inhibitor)	No change in thermal nociceptive threshold using the Hargreaves test	↓ Immobility in the FST	↓ Inflamassome (NLRP1) and caspase-1 expression in the hippocampus

(Continued)

TABLE 2 | Continued

References	Pain model	*Therapeutic intervention*	After treatment		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
			No change in mechanical nociceptive threshold using the von Frey test	↑ Climbing in the FST No change in the EPM	
Pan et al., 2018	SNI	*Ketamine*	No change in mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	↑ BDNF in the PFC ↑ NL1 and ↓ NL2 in the PFC ↑ BDNF in the ACC No change in NL1 and NL2 in the ACC ↑ BDNF in the hippocampus No change in NL1 and ↑ NL2 in the hippocampus
Brüning et al., 2015	PSNL	*acute (m-CF3-PhSe)2*	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	No change in pro-inflammatory cytokines in serum, cortex and hippocampus ↓ COX2 and NF-κB in the cortex ↑ BDNF in cortex ↓ COX2 and no change in NF-κB in the cortex ↑ BDNF in the hippocampus No change in ACTH and corticosterone
		subchronic (m-CF3-PhSe)2	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	↓ IL-1β, IL-6, TNF-α, IFN-γ and ↑ IL-10 in serum ↓ IL-1β, IL-6, TNF-α, IFN-γ in the cortex and hippocampus ↓ COX2 and NF-κB in the cortex ↑ BDNF in cortex

(Continued)

TABLE 2 | Continued

References	Pain model	*Therapeutic intervention*	After treatment		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
					↓ COX2 and no change in NF-κB in the hippocampus ↑ BDNF in the hippocampus ↓ ACTH and corticosterone in serum
Zhou et al., 2015	SNI	*IL-1RA*	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	↓ Ido-1 and IL-1β in liver
		Ido -/-	No change in mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Social interaction	Not measure
Laumet et al., 2018	SNI	*IL-1RA inhibitor*	No change in mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	Not measure
		Ro61-8048 (KMO inhibitor)	No change in mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST	Not measure
Hu et al., 2017	SNL	*Triptolide*	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Sucrose preference	↓ Iba-1 and p38 expression in the hippocampus ↓ IL-1β, TNF-α and ↑ IL-10 in the hippocampus
		Fluoxetine	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Sucrose preference	↓ Iba-1 and p38 expression in the hippocampus No change in IL-1β and TNF-α; ↑ IL-10 in the hippocampus

(Continued)

TABLE 2 | Continued

References	Pain model	*Therapeutic intervention*	After treatment		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
		Fluoxetine + triptolide	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Sucrose preference	↓ Iba-1 and p38 expression in the hippocampus ↓ IL-1β, TNF-α and ↑ IL-10 in the hippocampus
Moschetti et al., 2019	Vincristine	*PC1 (PK-Rs antagonist)*	↑ Thermal nociceptive threshold using the plantar and acetone tests ↑ Mechanical nociceptive threshold using the von Frey test	No difference in the FST and sucrose preference	↓ IL-1β, TNF-α, IL-6, TLR4, CD68 and CD11b and ↑ IL-10 in the DRG ↓ IL-1β, TNF-α, TLR4, CD68 and CD11b and ↑ GFAP in the spinal cord
Aguilar-Ávila et al., 2019	STZ	β-*Caryophyllene*	↑ Thermal nociceptive threshold using the hot-plate test ↑ Mechanical nociceptive threshold using the von Frey test and SMALGO®	↓ Immobility in the FST ↓ Immobility in the tail suspension ↓ Murbles touched	↓ SP, IL-1β, TNF-α and IL-6 in serum
Arora and Chopra, 2013	Reserpine	*Berberine*	↑ Thermal nociceptive threshold using the tail-immersion test ↑ Mechanical nociceptive threshold using the paw pressure and von Frey tests	↓ Immobility in the FST	↓ SP in the cortex and hippocampus ↓ Lipid peroxide, non-protein thiols, superoxide dismutase and nitrite levels in the cortex ↓ Lipid peroxide, non-protein thiols, superoxide dismutase and nitrite levels in the hippocampus

(Continued)

TABLE 2 | Continued

References	Pain model	*Therapeutic intervention*	After treatment		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
Zong et al., 2018	SNT	*Rosiglitazone*	↑ Mechanical nociceptive threshold using the von Frey test	↓ Immobility in the FST ↑ Sucrose preference ↓ Immobility in the tail suspension	↑ BDNF in HC ↓ TNF-α, IL-1β, SOD e MDA in the hippocampus
		Morphine	↑ Mechanical nociceptive threshold using the von Frey test	No change in immobility in the FST No change in the sucrose preference No change in immobility in the tail suspension	Not measure
		Rosiglitazone + Compound C (AMPK inhibitor)	No change in mechanical nociceptive threshold using the von Frey test	No change in immobility in the FST No change in the sucrose preference No change in immobility in the tail suspension	↓ TNF-α, IL-1β, SOD e MDA in the hippocampus
		Rosiglitazone + 3-methyladenine (3-MA - autophagic antagonist)	No change in mechanical nociceptive threshold using the von Frey test	No change in immobility in the FST No change in the sucrose preference No change in immobility in the tail suspension	No change in TNF-a, IL-1b, SOD e MDA in the hippocampus

(Continued)

TABLE 2 | Continued

Depressive-like models investigating pain					
References	**Depressive-like model**	***Therapeutic intervention***	**After treatment**		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
Sousa et al., 2018	Acute stress restriction	*α-(phenylselanyl) acetophenone (PSAP)*	↑ Thermal nociceptive threshold using the hot plate test	↓ Immobility in the FST	↓ Lipid peroxidation, reactive species, nitrite and nitrate in the cortex
				↑ Sucrose preference	↓ Lipid peroxidation, reactive species, nitrite and nitrate in the hippocampus
			↑ Mechanical nociceptive threshold using the von Frey	↑ Time spent in open arms in the EPM ↓ Murbles buried	↓ Costicosterone in plasma
		Imipramine	↑ Thermal nociceptive threshold using the hot plate test	↓ Immobility in the FST	↓ Lipid peroxidation, reactive species, nitrite and nitrate in the cortex
				↑ Sucrose preference	↓ Lipid peroxidation, reactive species, nitrite and nitrate in the hippocampus
			↑ Mechanical nociceptive threshold using the von Frey test	↑ Time spent in open arms in the EPM ↓ Murbles buried	↓ Costicosterone in plasma

(Continued)

TABLE 2 | Continued

Pain and depressive-like models						
References	**Pain model**	**Depressive-like model**	**Therapeutic intervention**	**After treatment**		
				Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
Burke et al., 2015	SNL	OB	Amitriptyline	No change in thermal nociceptive threshold using the Hargreaves and acetone tests ↑ Mechanical nociceptive threshold using the von Frey test	↓ Noxious avoidance behavior	↓ GFAP expression in the PFC ↓ IL-10 and CCL5 and ↑ TNF-α in the PFC
Rivat et al., 2010	Formaline	Social defeat	Chlordiazepoxide	No change in mechanical nociceptive threshold using the von Frey and paw pressure tests No change in nociceptive threshold by Dubusson and Dennis score	↑ Time spent in the open arms in the EPM	↓ iNOS and COX2 in the PFC
			Aspirine	↑ Mechanical nociceptive threshold using the von Frey and paw pressure tests ↑ Nociceptive threshold by Dubusson and Dennis score	No change in the EPM	↓ iNOS and COX2 in the PFC
			CCK2 antagonist (i.p)	↑ Mechanical nociceptive threshold using the von Frey and paw pressure tests ↑ Nociceptive threshold by Dubusson and Dennis score	↑ Time spent in the open arms in the EPM	↓ iNOS and COX2 in the PFC
			CCK2 antagonist (RVM injection)	↑ Mechanical nociceptive threshold using the von Frey and paw pressure tests ↑ Nociceptive threshold by Dubusson and Dennis score	Not measure	Not measure
Burke et al., 2014	SNL	OB	Mynocyclin	↑ Thermal nociceptive threshold using the acetone test ↑ Mechanical nociceptive threshold using the von Frey test	Locomotor hyperactivity in the OFT	↑ IL-1β, IL-6 and SOCS3 in the PFC ↑ IL-10 and MRC2 in the PFC

(Continued)

TABLE 2 | Continued

Clinical data					
References	**Diagnosis**	**Therapeutic intervention**	**After treatment**		
			Painful behavior	**Depressive-like behavior**	**Inflammatory effects**
Atkinson et al., 1986	Chronic pain with coexisting major depression	Dexamethasone	Not measure	Not measure	Non-suppressed cortisone levels
Wingenfeld et al., 2010	Fibromyalgia	DEX and DST	Pain Experience Scale Heat and pressure Pain	SCID-II BDI	MDD patients ↑ cortisol before or after DEX Patients with fibromyalgia + MDD ↑ cortisol ↑ depression x ↑ sensitivity to pressure pain
France and Krishnan, 1985	Chronic low back	DEX and DST	Not measure	DSM- III	↑ cortisol in chronic back patients with major depression (related with depressive symptoms)

BDI-II, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; CCI, chronic constriction injury; CD11b, cluster of differentiation 11b; CD68, cluster of differentiation 68; CFA, complete Freund's adjuvant; CGRP, calcitonin gene related peptide; COX2, cyclooxygenase 2; DEX, dexamethasone; DSM-III, Diagnostic and Statistical Manual of Mental Disorders III; DST, suppression test; EPM, elevated plus maze; FST, forced swimming test; GFAP, glial fibrillary acidic protein; HC, hippocampus; Iba-1, ionized calcium-binding adapter molecule 1; IL, interleukin; IL-1RA, interleukin 1 receptor antagonist; IRF8, interferon regulatory factor 8; Ido, indoleamine 2,3, dioxygenase inhibitor; iNOS, inducible nitric oxide synthase; LDH, lumbar disk herniation; MCP1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MDD, major depressive disorder; MRC2, mannose receptor C type 2; NF-κB, factor nuclear kappa B; NL1, neuroligins 1; NL2, neuroligins 2; NLRP-1 inflamassome, Nod-like receptor protein (NLRP)-1 inflammasome; OB, olfactory bulbectomy; P2X7, purinergic receptor P2X7; p38, p38 mitogen-activated protein kinases – MAPKs; PC1, triazine guanidine derivative selective; PFC, prefrontal cortex; PSNL, partial spinal nerve ligation; SCI, spinal cord injury; SCID-II, Structured Clinical Interview for DSM-IV Axis II Personality Disorders; siRNA, small interfering RNA; SNI, spared nerve injury; SNL, spinal nerve ligation; SNT, sciatic nerve transaction; SOCS3, suppressor of cytokine signaling 3; SOD, superoxide dismutase; SP, substance P; STZ, streptozotocin; TNF-α, tumor necrosis factor alfa.

mannose receptor (MRC2), both of which are markers of the M2 phenotype, it does not inhibit the increases in IL-1β, IL-6 or suppressor of cytokine signaling 3 (SOCS3) in the PFC in a spinal nerve ligation and olfactory bulbectomy model (Burke et al., 2014).

The compound *m*-trifluoromethyl-diphenyl diselenide (*m*-CF3-PhSe)2 permeates the BBB and modulates opioid receptors without inducing opioid tolerance (Brüning et al., 2015; Rosa et al., 2018). Acute and subchronic treatment with this compound improves mechanical nociceptive thresholds and depressive-like behavior, decreases COX-2 and increases BDNF in the cerebral cortex and hippocampus in a partial sciatic nerve ligation model; however, only subchronic administration decreases proinflammatory cytokines and increases IL-10 in the serum, cerebral cortex and hippocampus and decreases corticosterone in the serum (Brüning et al., 2015). Although aspirin, a classic NSAID, is not able to improve depressive-like behavior, like benzodiazepines and a cholecystokinin 2 (CCK2) antagonist, it decreases Inducible nitric oxide synthase (iNOS) and COX2 in the PFC in the formalin test and a social defeat model (Rivat et al., 2010). Fatty acids with anti-inflammatory properties, such as omega-3, which increases BDNF in the hippocampus and PFC (Redivo et al., 2016); palmatine, which decreases GFAP and purinergic receptor P2X7 expression in the hippocampus (Shen et al., 2018); and *b*-caryophyllene, which suppresses the levels of SP and proinflammatory cytokines in the serum of diabetic animals (Aguilar-Ávila et al., 2019), may be used to attenuate pain and depression. Additionally, like fluoxetine, triptolide decreases microglial activation in the hippocampus, but only triptolide or triptolide combined with fluoxetine decreases proinflammatory cytokines and increases IL-10 in the hippocampus after improving spinal nerve ligation-induced pain and depressive behavior (Hu et al., 2017).

Indeed, manipulation of monoamines may also involve anti-inflammatory mechanisms. In a lumbar disk herniation model, fluoxetine decreases TNF-α in the hippocampus (Cai et al., 2019), while in a chronic constriction injury model, it decreases proinflammatory cytokines in the plasma, increases IL-10, decreases myelin degeneration and leukocyte infiltration in peripheral nerves and decreases astrocyte activation in the spinal cord; additionally, it has better effects when combined with antidiabetic drugs (Murad and Ayuob, 2015). Despite having similar mechanisms, amitriptyline does not improve thermal nociceptive thresholds but decreases astrocyte activation (Burke et al., 2015). Interestingly, this decrease is accompanied by decreased IL-10 and C-C chemokine ligand 5 (CCL5/RANTES) but increased TNF-α in the PFC in a co-model of pain and depression induced by spinal nerve ligation and olfactory bulbectomy model (Burke et al., 2015). A possible explanation for this finding is that CCL5 is released upon TNF-α activation to regulate microglia-astrocyte crosstalk and glutamate reuptake in the PFC (Pittaluga, 2017). The antioxidant α-(phenylselanyl) acetophenone (PSAP) was compared to imipramine, another drug that modulates monoamines. PSAP also seems to interact with serotonin type 1A (5HT-1A) receptor but not with noradrenaline, dopamine or adenosine receptors (Gerzson et al., 2012). In addition to improving behavior, both drugs decrease lipid peroxidation, reactive oxygen species (ROS), nitrite and nitrate levels in the cerebral cortex and hippocampus and inhibit corticosterone levels in the plasma after acute stress restriction (Sousa et al., 2018). Another new compound with monoaminergic properties is 3-(4-chlorphenylselany)-1-methyl-1H-indole, which improves pain sensitivity and depressive-like behavior and, like PSAP and imipramine, also decreases ROS and lipid peroxidation in the cerebral cortex and hippocampus and corticosterone in the plasma (Birmann et al., 2019). In this sense, the regulation of monoamines is clearly pivotal to the control of neuroinflammation. Possibly, improvements in the synaptic environment by the normalization of neurotransmitter levels decreases DAMPs, such as ROS and reactive nitrogen species (NOS), and inhibits the activation of glial cells, decreasing the release of proinflammatory cytokines. Persistent activation of NMDA receptors by glutamate cytotoxicity also plays an important role in DAMP formation and, consequently, in the pathophysiology of pain and depression (Petrenko et al., 2003; Duman and Li, 2012). Acute ketamine decreases proinflammatory cytokines, IDO1 and kynurenine in the hippocampus after improving painful and depressive behavior in a model of complete Freund's adjuvant-induced acute pain (Zhang et al., 2016). However, in a persistent pain model, such as a sciatic nerve injury model, ketamine decreases depressive-like behavior and increases BDNF in the PFC and ACC but does not change the mechanical nociceptive threshold (Pan et al., 2018). These findings corroborate the strong evidence that ketamine decreases postoperative pain scores in acute nociceptive pain (Bell and Kalso, 2018) but that it seems to be less effective for chronic pain treatment. However, the central mechanism by which ketamine exerts neuroprotection in the PFC and ACC suggests that it is useful for treating major depression disorder (Daly et al., 2018).

Role of Inflammation in Neuronal Networks

Microglia is the most abundant resident immune cell in the CNS, able to recognize DAMPs and pathogen-associated molecular patterns (PAMPs) and respond by producing many inflammatory mediators (Dheen et al., 2007). In addition to being important for the immune response, microglia also play a pivotal role in the pruning of synaptic spines induced by sensory inputs or neuronal injury (Wake et al., 2009; Tremblay et al., 2010). In this sense, microglia-deficient brain slices show an increase in excitatory synapses, while the presence of microglia suppresses the AMPA receptor within the neuronal membrane and synaptic adhesion molecules (Ji K. et al., 2013). In addition, one astrocyte may interact with over 100,000 synapses to form a tripartite synapse (Halassa et al., 2007; Araque, 2008). Astrocytes can coordinate and control synaptic transmission through neurotransmitter receptors, transporters, and cell adhesion molecules (Halassa et al., 2007). The cytotoxicity induced by excessive glutamate in the synaptic environment is prevented by the astrocyte reuptake process (Hertz and Zielke, 2004), suggesting the pivotal role of these cells in the control of synapses.

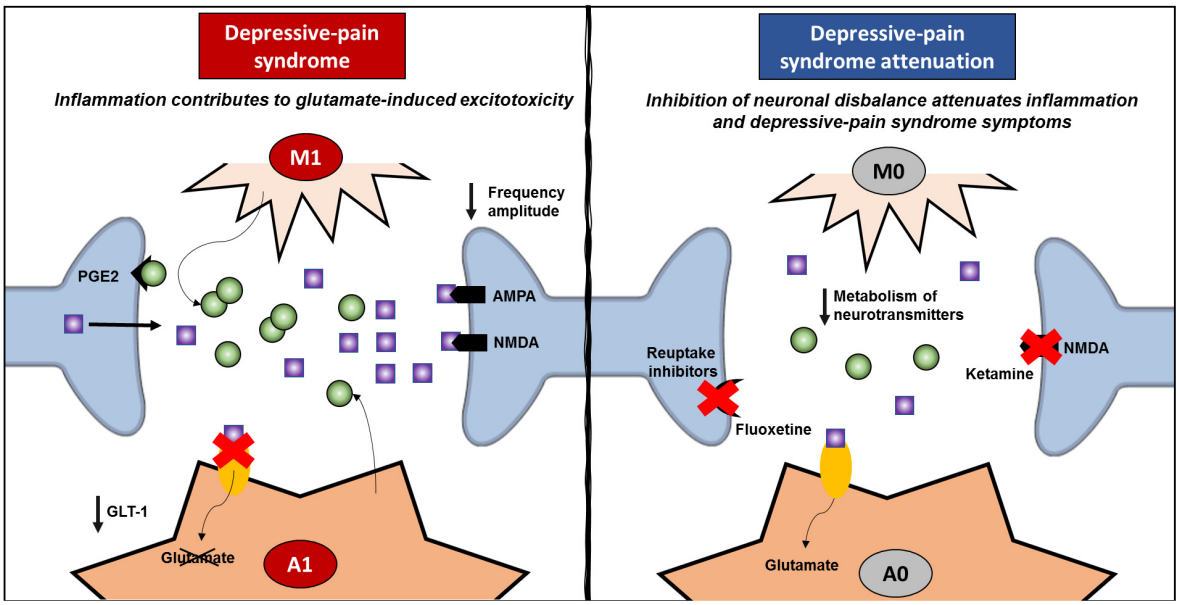

FIGURE 4 | Review of inflammatory signature and neural network modulation. Depressive pain syndrome is related to activation of glial cells, such as microglia and astrocytes. Once classically activated (M1/A1), these cells release proinflammatory cytokines, especially TNF-α and IL-1β, and upon specific receptor activation, increase glutamate release in the synaptic cleft. Classically activated astrocytes induce a decrease in GLT-1, which enables the reuptake of glutamate and decreases glutamate-induced cytotoxicity. Hence, both AMPA and NMDA postsynaptic receptors are strongly activated, decreasing the frequency amplitude and contributing to neural network imbalance. On the other hand, anti-inflammatory treatments inhibit the classic activation of glial cells and the exacerbated release of proinflammatory mediators, decreasing neural network imbalance. In addition, the success of pharmacological treatments that act through mechanisms related to neuronal dysfunction, such as ketamine and fluoxetine, which improve neuronal network dysfunction and attenuating depressive pain syndrome, also corroborate the negative feedback of inflammation. GLT, glutamate transporter; PGE, prostaglandin.

In pathological conditions after an injury or disease, microglial cells may show the classical activated pattern (M1) characterized by upregulation of nuclear factor-κB (NF-κB), signal transducer and activator of transcription (STAT), TNF-α, IL-1β and different proinflammatory mediators (Jha et al., 2016). M1 microglia have the capacity to induce changes in the phenotype of astrocytes to the classical activation phenotype (A1), which is consistent with the increase in inflammation and tissue damage (Liddelow et al., 2017) seen in depressive pain syndrome. A1 astrocytes decrease the formation of excitatory synapses in an *in vitro* coculture system and decrease the frequency and amplitude of excitatory postsynaptic currents in the remaining synapses (Liddelow et al., 2017). Indeed, pain and depression conditions induce the downregulation of glutamate type 1 transporter (GLT1) in response to inflammation (Medina et al., 2013; Guo et al., 2019), suggesting that the astrocyte-reuptake process involved in pruning synapses is impaired in depression-pain syndrome. As described above, the cooccurrence of chronic pain and depression is intimately related to increases in TNF-α, IL-1β, and IL-6 in target structures such as the PFC, ACC, amygdala and hippocampus, emphasizing the involvement of glial activation in limbic regions involved in pain and depression processing.

Even though IL-1β is related to resident glial cells, it has been shown that this cytokine plays a role in synaptic plasticity (Kelly et al., 2003; Mandolesi et al., 2013). Once recognized by neurons, IL-1 increases glutamate release through prostaglandin (PGE)-2 production (Sang et al., 2005; Mishra et al., 2012), activating NMDA receptors, increasing glutamatergic sensitivity and exacerbating excitotoxicity (Viviani et al., 2006; Fogal and Hewett, 2008). In the rat hippocampus, IL-1β decreases synaptic connections by increasing both pre- and postsynaptic glutamate release (Mishra et al., 2012). In this sense, inflammation inhibits the ability of astrocytes to reuptake glutamate, and IL1-β increases glutamate levels within the synaptic cleft. TNF-α also plays a role in increasing the exocytosis of AMPA receptors on hippocampal pyramidal cells (Ogoshi et al., 2005) while promoting the endocytosis of GABA A receptors (Stellwagen et al., 2005), triggering an imbalance between excitatory and inhibitory controls. The relationship between inflammation and the neuronal environment investigated by two articles is described in **Table 1**. González-Sepúlveda et al. (2016) showed that the increase in IL-1β in the PFC relates to an increase in the glutamate/glycine ratio, while Dellarole et al. (2014) demonstrated that TNFR-deficient mice are protected against increases in neurogenesis, neuroplasticity and myelin impairments induced by neuropathic pain. TNF-α also inhibits noradrenaline release in the hippocampus (Spengler et al., 2007), which is postulated as a common target in pain and depression (Fasick et al., 2015). Hence, inhibiting inflammation may be an important tool for restarting the optimal modulation and control of synapses within the CNS, improving depressive pain symptoms. However, ketamine, which acts on NMDA receptors, not only decreases inflammatory markers, as previously described but also inhibits the KYN/tryptophan ratio

while increasing the 5-HT/tryptophan ratio (Zhang et al., 2016). Accordingly, fluoxetine increases 5-HT in the hippocampus while decreasing inflammation (Cai et al., 2019), suggesting that improving the synaptic network also affects inflammation status (**Figure 4**). The same rationale may apply to other treatments, such as benzodiazepines, reuptake inhibitors, and CCK2 and PKR inhibitors, which classically involve pre- and postsynaptic neurons, as described above. In addition to acting through a neuronal mechanism, these drugs are able to inhibit inflammation in depressive-pain models.

Taken together, our findings suggest that neuronal deficits and the inflammatory response may trigger each other through a feedback mechanism, contributing to the complexity of the control of depression-pain syndrome. In this sense, it is important for treatments to address the role of neurotransmitters and receptors as well as to improve the entire synaptic cleft, including inhibiting classically activated resident cells and the inflammatory response. In other words, these data strongly support the idea that controlling neuroinflammation is closely connected with improving pain and depression states. Direct inhibition of the inflammatory cascade or indirect inhibition by decreasing cytotoxicity and DAMP formation in local synapses concomitant with controlling glial cell activation are important strategies for improving the quality of life of people suffering from depression-pain syndrome.

CONCLUSION AND FUTURE DIRECTIONS

Pain and depression are often comorbid and decrease the quality of life of many individuals worldwide. Indeed, much effort has been expended to investigate different classes of medications to ameliorate these symptoms. In this sense, preclinical models are a resource for the development of drugs or for better elucidating their peripheral and central mechanisms. It is important to take into consideration that preclinical models are tools to provide a better understanding of pathogenesis and for testing the potential of novel therapeutic approaches. However, there are limitations intrinsic from the experimental models referring to translate research into practice. The choice of the appropriate preclinical model to address pharmacological treatments should be consider as the most reliable and closer to reproduce a persistent pain as observed in clinical practice. Even though the models should be able to reproduce the nociceptive behavior, it is pivotal that they also reproduce depressive-anxiety behavior, mimicking what is observed in patients. Additionally, the experimental design should be carefully addressed taking into consideration the presence of peripheral and central sensibilization before the initiation of the pharmacological treatment as it happens with individuals suffering from persistent pain. In addition to directly targeting inflammation mediators such as cytokines and molecular inhibitors of the inflammatory cascade to improve pain sensitivity and depression, drugs that improve and regulate the synaptic environment and its neurotransmitters may act as anti-inflammatory compounds, reducing local DAMPs and inhibiting the activation of immune and glial cells. In this review, we highlight the inflammatory signature of different preclinical models and clinical articles related to depressive-pain syndrome. Additionally, we discuss the role of therapeutic interventions targeting depression, pain and neuroinflammation. We hope that shedding light on the inflammatory profile will aid in finding new targets and in improving classic treatments to bring benefits to individuals who suffer from these disorders.

AUTHOR CONTRIBUTIONS

AC and GA contributed to the conception of the study, acquisition of the data, and writing of the manuscript. MM and RP wrote and revised the manuscript. RM conceived the presented review, supervised the project, and wrote the manuscript. All the authors contributed to the article and approved the submitted version.

FUNDING

The authors are the recipients of grants from the Government of Brazil – São Paulo Research Foundation (FAPESP, ACPC 2018/18695-9) and Coordination for the Improvement of Higher Education Personnel (CAPES, GFA 88882.366209/2019-01).

ACKNOWLEDGMENTS

The authors wish to thank all the research assistants and staff of Hospital Sírio-Libanês.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

SYSTEMATIC REVIEW
published: 05 November 2020
doi: 10.3389/fpsyg.2020.538741

Non-pharmacological Interventions for Anxiety and Depression in Adults With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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Objectives: To assess the published randomized controlled trials (RCT) of non-pharmacological interventions systematically and to synthesize the evidence of these interventions for the management of anxiety and depression in adults with inflammatory bowel disease (IBD).

Background: Anxiety and depression are common symptoms in adults with IBD and can have many negative outcomes on their quality of life (QOL). Non-pharmacological interventions for anxiety and depression are important to improve the adaptive strategies of adults with IBD. Previously published reviews of non-pharmacological interventions to mitigate anxiety and depression in those with IBD have resulted in inconclusive evidence. This review is aimed to fill that gap.

Design: Systematic review and meta-analysis.

Method: Using a PRISMA diagram, English-language RCT published were searched using combined keywords of inflammatory bowel disease, Crohn's disease, ulcerative colitis, randomized controlled trial, anxiety, and depression. The Cochrane risk of bias tool is utilized to assess the methodological quality of each study. A meta-analysis of RCTs was conducted using Comprehensive Meta-Analysis (CMA) software.

Results: The final review included 10 studies. The overall risk of bias of the selected studies varied from low risk in three studies, some concerns in four of the studies, and high risk of bias in three of the studies. Interventions included cognitive-behavioral therapy, mindfulness-based therapy, breath–body- mind –workshop, guided imagery with relaxation, solution-focused therapy, yoga, and multicomponent interventions. The pooled evidence from all non-pharmacological interventions showed that these interventions significantly helped to reduce anxiety, depression, and disease specific quality of life (QOL) in adults with IBD compared to control groups. However, the effect sizes are small. The pooled standardized mean difference (SMD) was −0.28 (95% CI [−0.47, −0.09], $p = 0.004$) for anxiety, −0.22 (95% CI [−0.41, −0.03], $p = 0.025$) for depression and 0.20 (95% CI [0.004, 0.39], $p = 0.046$) for disease specific QOL.

OPEN ACCESS

Edited by:
Qing Zhao,
Second Affiliated Hospital of Guangzhou Medical University, China

Reviewed by:
Zhou Yang,
Southwest University, China
Fei Luo,
Chinese Academy of Sciences (CAS), China

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Specialty section:
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

Received: *28 February 2020*
Accepted: *23 September 2020*
Published: *05 November 2020*

Citation:
Davis SP, Bolin LP, Crane PB and Crandell J (2020) Non-pharmacological Interventions for Anxiety and Depression in Adults With Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Front. Psychol. 11:538741. doi: 10.3389/fpsyg.2020.538741

Conclusion: The addressed non-pharmacological interventions were multifaceted and demonstrated positive effects on anxiety and depression, and QOL in those with IBD. Healthcare providers can facilitate a discussion with adults with IBD about the availability of these interventions to mitigate their anxiety and depression and to improve their QOL.

Keywords: inflammatory bowel disease, non-pharmacological interventions, anxiety, depression, meta-analysis

INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated chronic gastrointestinal illness that encomapses Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by remission (disease-free interval) and relapse (active disease) (van de star and Banan, 2015). About 2.2 million Europeans, 1.5 million Americans, and more than 100,000 others worldwide are affected by IBD (Ananthakrishnan, 2015). IBD prevalence rate is rising in Asia, Africa, and South America, where formerly IBD was considered a rare disease (Ananthakrishnan, 2015). Clinical manifestations of IBD include diarrhea, fever, fatigue, pain in the abdomen, reduced appetite, loss of weight, and blood in stools. While most note the physical symptoms, psychological symptoms experienced by those with IBD and the associated treatments are prevalent with 35% reporting anxiety symptoms and 22% depressive symptoms (Nahon et al., 2012; Panara et al., 2014; Neuendorf et al., 2016).

Multiple factors can contribute to the development of anxiety and depression in adults with IBD. Active disease is the main factor, followed by female gender and socioeconomic deprivation or low socioeconomic status (Nahon et al., 2012; Clark et al., 2014; Panara et al., 2014). Other contributing factors depression and anxiety in patients with IBD are the adverse effects and associated mood disturbances of treatments such as corticosteroids, biologics and immunomodulators, and the fear of side effects (Nahon et al., 2012; Mikocka-Walus et al., 2016; Choi et al., 2019). Addressing these psychological symptoms is important because psychological stress is known to escalate disease activity in adults with IBD (Sajadinejad et al., 2012).

Psychological stress mediates IBD through the brain-gut axis. Stress leads to the secretion of peripheral corticotrophin-releasing factor, which contributes to the gut becoming more prone to inflammation by (a) altering intestinal motility and (b) increasing intestinal permeability, resulting in a reduction of the mucosal barrier action (Sajadinejad et al., 2012). Stress also leads to the dysfunction of the intestinal immune system in two ways: (1) the intestinal mucosa is attacked, and (2) the hypothalamic-pituitary-adrenal axis is activated. This results in the secretion of stress hormones (e.g., cortisol) and the release of inflammatory mediators (e.g., cytokines) (Sajadinejad et al., 2012). Caneo et al. (2016) reported an increased risk for depression in adults with physical ailments involving systemic inflammation compared to those without inflammation. Consequently, the risk for depression is high in adults with IBD due to systemic inflammation. Thus, the psychological symptoms of IBD, such as anxiety and depression, is likely related to a multitude of factors that include treatments, adverse effects of the pharmacological interventions, stress, and inflammation (Bannaga and Selinger, 2015; Keefer and Kane, 2017).

Anxiety and depression are inversely related to health behaviors, and quality of life (QOL) in adults with IBD (Faust et al., 2012). Several investigators have noted that anxiety and depression explain medication non-adherence among individuals with IBD (Nahon et al., 2012; Spekhorst et al., 2016). This is concerning, as medication non-adherence may lead to IBD exacerbations resulting in an increase of distressful symptoms. More importantly, results from a longitudinal study of more than 2,000 adults with IBD revealed a significant positive association between disease recurrence, and symptoms of depression or anxiety (Mikocka-Walus et al., 2016). Care for those with IBD should include not only treating physical symptoms but also the psychological manifestations of anxiety and depression.

Interventions to address depression and anxiety are important to improve the adaptive strategies of adults with IBD (McCombie et al., 2015) and should include both pharmacological and complementary interventions. A previous systematic review by Fiest et al. (2016) evaluated the outcomes of pharmacological and psychological interventions on depression and anxiety in adults with IBD, and their results revealed only one study which addressed pharmacological interventions to address anxiety. This systematic review did not support psychological interventions to manage anxiety and depression. However, the authors (Fiest et al., 2016) acknowledged the high risk of bias with this study. Previously published reviews of non-pharmacological interventions to mitigate anxiety and depression in adults with IBD resulted in inconclusive evidence. Most of these studies were more than 10 years old, and none focused on meta-analysis of non-pharmacological interventions to mitigate anxiety or depression among those with IBD. Hence, there is a need for synthesizing new evidence on the effectiveness of non-pharmacological interventions to mitigate anxiety and depression in those with IBD.

RESEARCH AIMS

This review aimed to focus on: (1) determine the types of non–pharmacological interventions published in literature to manage anxiety and depression among adults with IBD, (2) analyze the effectiveness of these non–pharmacological interventions to manage anxiety, depression and QOL in adults with IBD. We formulated the following research question: Are non-pharmacological interventions more effective compared to control groups in managing anxiety and depression, and improving QOL in adults with IBD?

METHODS

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009) was used as a framework to guide the search strategy. Using the databases of PubMed, CINAHL, EMBASE, PsychInfo, and Google Scholar, a search for English-language articles on randomized clinical trials (RCT) and IBD published with the primary or secondary outcome of depression and/or anxiety was conducted till December, 2019. A Boolean search strategy (Schuler et al., 2008) using combined keywords of *inflammatory bowel disease, Crohn's disease, ulcerative colitis, randomized controlled trial, anxiety,* and *depression* yielded 1,043 studies. Each database was searched to identify research articles by customizing the same medical subject heading (MeSH) terms and key words in consultation with a research librarian. The search strategy details for each of the database are included in **Supplementary Table 1**. An additional search was conducted manually by using the citation lists of the retrieved studies to identify other relevant articles related to the Research Topic. Studies that matched the criteria for inclusion were retained for this systematic review. The

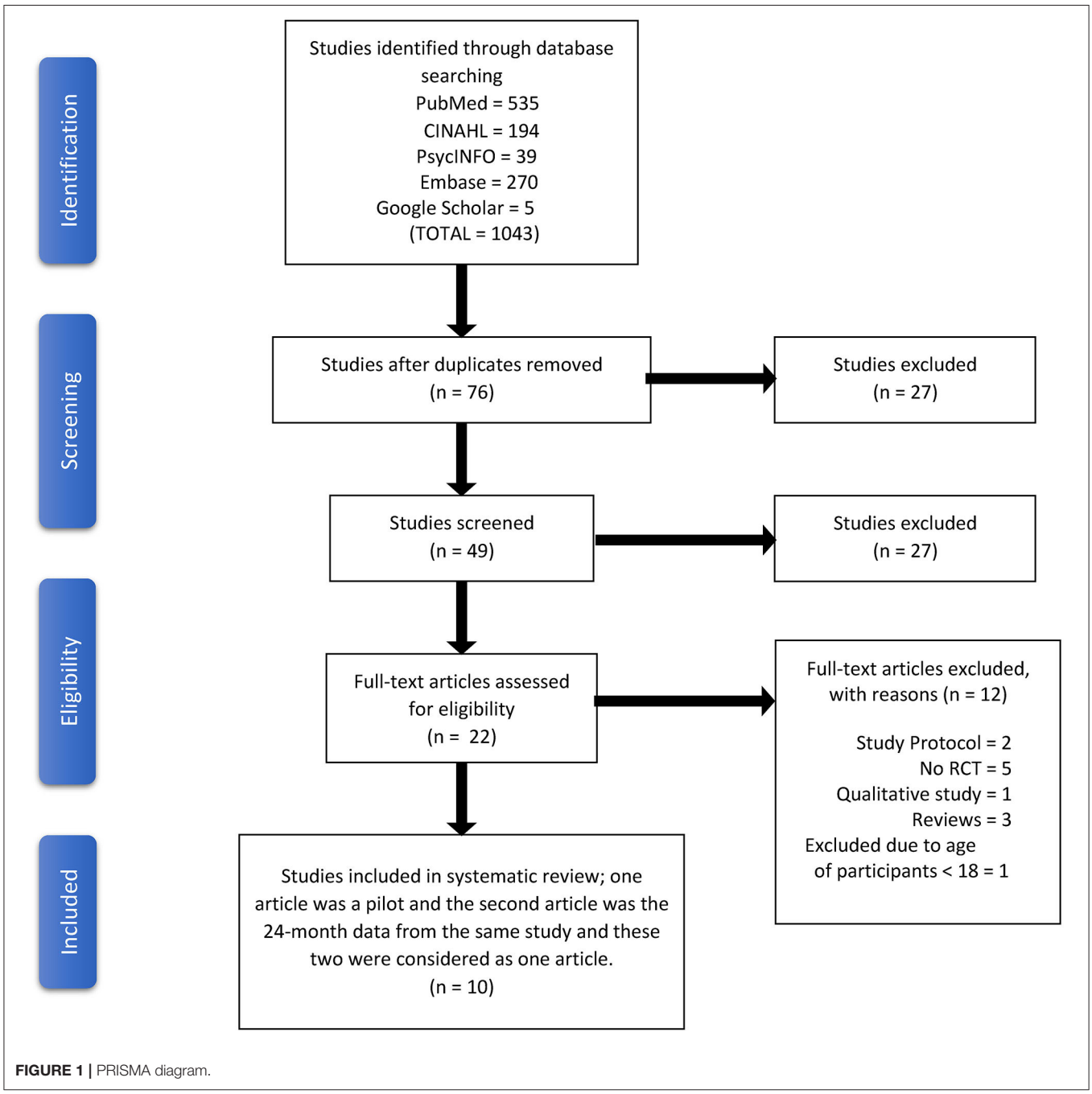

FIGURE 1 | PRISMA diagram.

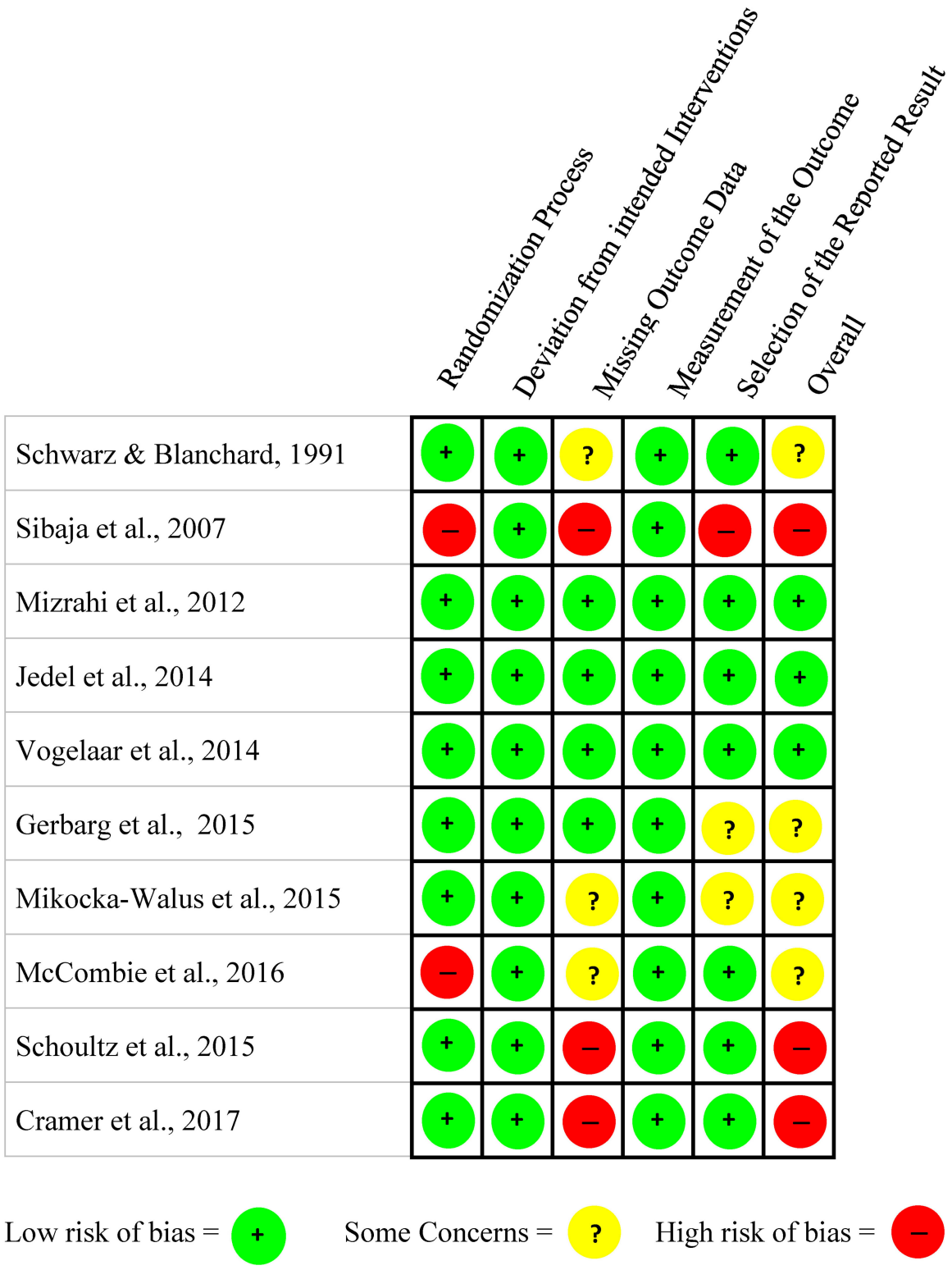

FIGURE 2 | Methodological quality evaluation of RCTs using Cochrane risk assessment tool.

PRISMA flow diagram (**Figure 1**) summarizes the processes of the systematic review.

Inclusion and Exclusion Criteria

This review had the following inclusion criteria: (1) RCTs in English-language in published journals that focused non-pharmacological components of interventions to mitigate anxiety, depression and QOL among adults with IBD, (2) measured anxiety, depression and QOL as an outcome at both before and after intervention, (3) studies that include adults who are 18 years or above with a diagnosis of ulcerative colitis or Crohn's disease, and (4) participants with IBD in remission or relapse were included for the study. This review excluded the studies of : (1) pediatric and adolescent population (2) expert opinion and general reviews, and (3) RCTs in other languages.

Quality Appraisal

Independent assessment of the methodological quality of each RCT was conducted by the first and second authors using the Cochrane risk of bias tool, version 2 (RoB 2; Sterne et al., 2019). The RoB 2 is designed for quality appraisal of RCTs based on five domains with pre-determined questions to generate an algorithm for each of the domains to indicate the bias for each study (Sterne et al., 2019). For each study, the results of the risk of bias were categorized as low risk (color coded as green), some concerns (color coded as yellow) and high risk (color coded as red) for each domain as well as for the overall risk. If the risk assessment of all the domains resulted in low, then the study's overall risk is considered to be low (Sterne et al., 2019). The selected studies' overall risk of bias varied from a low risk in three studies (Mizrahi et al., 2012; Jedel et al., 2014; Vogelaar et al., 2014), some concerns in four of the studies (Schwarz and Blanchard, 1991; Gerbarg et al., 2015; Mikocka-Walus et al., 2015; McCombie et al., 2016), and three studies showed a high risk of bias (Sibaja et al., 2007; Schoultz et al., 2015; Cramer et al., 2017). A consensus was noted among the authors while evaluating the quality appraisal of the nine selected studies. The quality appraisal results of the studies are reported in **Figure 2**.

Data Extraction

The first and the second author independently extracted the data, which was verified by the third author after reading all the articles that matched the criteria for inclusion. The first and second authors examined the extracted data and came to an agreement after discussion. The authors organized the extracted data in the following: (1) author name, study design; (2) details of sample (sample size in intervention and control groups, type of IBD); (3) details of interventions; (4) duration of intervention and follow up (5) instruments used; and (6) major results of outcomes.

Analyses

The search yielded 1,043 studies; 76 articles were retained after the duplicates were removed. We excluded 27 studies after screening their abstracts. From the remaining 49 articles, we removed an additional 27 studies following the exclusion and inclusion criteria. The remaining 22 were assessed for eligibility. Eleven articles were eligible for the final synthesis. Out of these 11, one article was a pilot (Mikocka-Walus et al., 2015) and the second article was a 24-months data set analysis from this same pilot study (Mikocka-Walus et al., 2017). The end resulted in 10 unique studies. Because the intervention was the same, these two articles were considered one study and the parent study article authored by Mikocka-Walus et al. (2015) was selected for the final review. These steps are summarized in a PRISMA diagram (**Figure 1**).

Each article was analyzed by the sample characteristics, study interventions, length of time for interventions, along with primary and secondary outcome measures related to anxiety and depression (see **Table 1**). Quantitative data were sufficient enough to conduct meta-analysis for seven (Mizrahi et al., 2012; Jedel et al., 2014; Gerbarg et al., 2015; Mikocka-Walus et al., 2015; Schoultz et al., 2015; McCombie et al., 2016; Cramer et al., 2017) of the 10 studies to evaluate the efficacy of non-pharmacological interventions to mitigate anxiety and depression in adults with IBD. Three studies had (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Vogelaar et al., 2014) limited data on anxiety and depression to include in our meta-analysis. The primary author attempted to contact the corresponding authors of two studies (Sibaja et al., 2007; Vogelaar et al., 2014) without any success. The contact information for the corresponding author was not included in this third study (Schwarz and Blanchard, 1991). Therefore, all three studies were synthesized narratively.

Meta-Analysis

The meta-analyses were computed using Comprehensive Meta-Analysis (CMA) software version 3 (Comprehensive Meta-Analysis, 2019) with the help of a University statistician. The authors used the CMA software to compute the efficacy of non-pharmacological interventions, to mitigate anxiety and depression in those with IBD, as well as to examine the influence of the interventions on QOL. The effect of non-pharmacological interventions on disease specific QOL (assessed using inflammatory bowel disease questionnaire [IBDQ]), and both mental and physical health QOL (evaluated by the short form health questionnaire [SF-12 or SF-36]) were assessed. Meta-analysis conclusions were drawn from pooled standardized mean differences (SMD) and 95% confidence intervals (CI), which were estimated using random-effects models. The standardized mean difference in anxiety and depression between the treatment and control groups was computed for each study. The extent of heterogeneity between the selected studies was evaluated based on the I^2 value. The I^2 is a value that can range from 0 to 100%, where 0 indicates no heterogeneity and larger values denote marked heterogeneity (Higgins et al., 2003). The authors did not evaluate publication bias through examining the funnel plot nor by conducting the Egger test due to the limited number of studies ($N < 10$) available for meta-analysis.

RESULTS

Characteristics of Included Studies

All of the selected studies reported a control group. The design of these control groups varied among the studies. Four of the

TABLE 1 | Summary of study findings.

References	Study method/Country	Type of sample	Study sample (1) Total sample (total enrolled/completed) (2) Intervention/ Control	Intervention component and type	Duration of intervention period and *Follow up	Instruments	Outcome results
Schwarz and Blanchard (1991)	RCT USA	All IBD patients (UC and Crohns)	(1) 21/21 (2) 11/10	**Multicomponent Intervention Procedure** ***Muscle relaxation** *Biofeedback *Training on cognitive coping skills *IBD education	One hour face to face sessions twice a week for 4 weeks, followed by weekly sessions for 4 weeks	**The State Trait Anxiety Inventory (STAI)-**measured anxiety **Beck depression inventory**—measured depression	Although anxiety and depression scores lowered after the intervention, the change was not statistically significant.
Sibaja et al. (2007)	RCT Spain	All IBD patients (UC and Crohns)	**Initial** (1) 57/57 (2) 33/24 **At 3 months** (2) 33/0 **At 6 months** (2) 22/0 **At 12 months** (2) 18/0	**CBT (face to face group therapy)** *Information about IBD *Training on coping skills *Training on problem solving *Relaxation techniques Social skill improvement *Methods of distraction * Strategies to address cognitive restructuring techniques	2 h face to face group session for 10 weeks *A document with important content and tasks were given after each session * A relaxation tape or CD was provided	**Beck depression inventory**—measured depression **Hospital anxiety and depression scale (HADS)**—measured anxiety and depression	(+) outcomes with anxiety ($p < 0.001$) and depression ($p < 0.001$) till 12 months among CBT group
Mikocka-Walus et al. (2015)	RCT Australia	IBD patients in remission	**Initial** 176/174 (2) 90/84 **At 6 months** (2) 51/65	**CBT (both face to face and computerized)** The CBT program included *Education about IBD and CBT *Relaxation and stress reduction *Interpretation of unpleasant events *Restructuring the events that led to negative thoughts Techniques to overcome avoidance *Strategies to improve coping skills *Empowering themselves *strategies to improve relationships *Techniques to improve distraction	The CBT was offered 2 h each week for 10 weeks. Both face to face group therapy and computer based CBT were available. *No follow up noted	**HADS**—measured anxiety and depression **The State Trait Anxiety Inventory (STAI)-** measured anxiety **The short form 36 health status questionnaire (SF-36)—**measured QOL **Disease activity**—CDAI measured Crohn's disease and SCCAI measured disease activity of ulcerative colitis. **Diseases activity** is also measured by CRP, hemoglobin, platelet and white cell count.	*(+) outcomes with trait anxiety ($p = 0.042$) and depression ($p = 0.018$) till 12 months among CBT group.

(Continued)

TABLE 1 | Continued

References	Study method/Country	Type of sample	Study sample (1) Total sample (total enrolled/completed) (2)Intervention/ Control	Intervention component and type	Duration of intervention period and *Follow up	Instruments	Outcome results
Mikocka-Walus et al. (2017)	RCT Australia	IBD patients in remission	(1) 176/174 (2) 30/45	**CBT (both face to face and computerized)** CBT techniques were same as that of the previous study (Mikocka-Walus et al., 2015)	Same as that of the previous study (Mikocka-Walus et al., 2015) *No follow up noted	**HADS**—measured anxiety and depression **STAI-** measured anxiety **SF-36—**measured QOL **Disease activity**—CDAI measured Crohn's disease and SCCAI measured disease activity of ulcerative colitis. **Diseases activity** is also measured by CRP, hemoglobin, platelet and white cell count.	*Both state and trait anxiety trended down among CBT group at 24 months, but not statistically significant. Depression scores did not change at 24 months. * No change in anxiety and depression among 'in need" patients at 24 months.
McCombie et al. (2016)	RCT Newzealand	All IBD patients	**Initial** (1) 131/100 (2) 113/86 **At 3 months** (2) 65/78 **At 6 months** (2) 53/66	**Computerized CBT** The CCBT sessions included *Relaxation techniques Influence of the thoughts on behavior, *Coping skills *Communication skills *Distraction techniques	A total of 8 sessions with 62 resources in the CCBT *Email reminder once per week for 8 weeks and text messaged at 6 weeks	**HADS**—measured anxiety and depression **IBDQ—**measured IBD specific HRQOL **SF-12** - measured general HRQOL	Anxiety and depression were not associated with CCBT.
Schoultz et al. (2015)	Pilot RCT UK	IBD patients	**Initial** 21/22 **Post intervention** 12/12 **At 6 months** (2) 12/12	**Mindfulness based cognitive therapy (MBCT)** The MBCT program a mixture of exercises/meditations such as Scanning of the entire body Meditation by sitting and walking *Mindful stretching *Exercises with a focus on cognitive behavioral techniques *Personal reflections of every day	8 weeks of face to face MBCT each lasting 2 h * Guided home practice with follow up sessions.	**Beck Depression Inventory**—measured depression **STAI—**measured anxiety **Disease activity**—CDAI measured Crohn's disease and SCCAI measured disease activity of ulcerative colitis. **IBDQ—**measured IBD specific HRQOL	*(+) outcomes with trait anxiety ($p = 0.048$) and depression ($p = 0.027$) in the MBCT intervention group after the intervention and at 6 months follow up.
Jedel et al. (2014)	RCT USA	Ulcerative colitis patients who were in remission.	**Initial** (1) 27/26 (2) 27/26 **2 months** (2) 27/26 **6 months** (2) 27/26 **12 months** (2) 27/26	**Mindful based stress reduction (MBSR)** The MBSR included *Meditation, *Scanning of the body *Yoga techniques *Personal reflections	8 weeks of MBSR intervention that spanned 2.5 h. * Homework assignment included 45 min/day of MBSR, for 6 days in a week with the help of a CD disc.	**Beck Depression Inventory**—measured depression **STAI -** measured anxiety **IBDQ—**measured IBD specific HRQOL **Inflammatory Biomarkers**–fecal calprotectin, cytokines, CRP	*Anxiety and depression were not associated with MBSR. **Post-hoc* analysis revealed positive effect of MBSR in the subset of UC adults with increased stress ($p < 0.001$).

(Continued)

TABLE 1 | Continued

References	Study method/Country	Type of sample	Study sample (1) Total sample (total enrolled/completed) (2) Intervention/ Control	Intervention component and type	Duration of intervention period and *Follow up	Instruments	Outcome results
Gerbarg et al. (2015)	RCT USA	IBD patients	**Initial** (1) 29/27 (2) 15/12 **6 weeks** (2) 15/12 **26 weeks** (2) 14/11	**BBMW** The participants were taught *4 breathing techniques (core breath technique, resistance breathing, breath moving and 'Ha' breath) *Breathing synchronized with Qigong movements *Open focus meditation.	The BBMW was offered for 1.5 h for 6 weeks, then very month until week 26. *20-min breathing practice at home followed by a 3-min supine rest and were informed to keep a daily practice log. A CD provided.	**Beck Anxiety Inventory—**measured anxiety **Beck Depression Inventory**—measured depression **IBDQ—**measured IBD specific HRQOL **Inflammatory Biomarkers**–fecal calprotectin, and CRP	*(+) outcomes with anxiety at 6 weeks ($p = 0.02$) and at 26 weeks ($p = 0.03$). *(+) outcomes with depression at 26 weeks ($p = 0.01$).
Mizrahi et al. (2012)	RCT Israel	IBD patients	(1) 56/39 (2) 18/21	**Guided imagery with relaxation** The intervention consisted of *Different relaxation Guided imagery *Discussion of forms to monitor relaxation Brief review of struggles faced by patients to reach relaxation	Three individual relaxation training for 50 min × 5 weeks. *Home practice at least once a day for 5 weeks. A relaxation and guided imagery audio disc was provided.	**STAI—** measured anxiety **VAS**—measured depression **IBDQ—**measured IBD specific HRQOL	*(+) outcomes with anxiety ($p < 0.01$). *No significant improvement noted with depression.
Vogelaar et al. (2014)	RCT Netherlands	IBD patients in remission	I**nitial** (1) 49/49 (2) 48/49 **At 3 months** (2) 48/49 **At 6 months** (2) 48/49	**SFT** SFT is a short version of psychotherapy focused on the present coping skills, instead of addressing the problems. The SFT was modified to addresses fatigue for this study.	Six group sessions (each lasted for 1.5 h) for 3 months' followed by a booster session at 6 months. A family member, partner or a close relative participated in the 5th session. *None	**HADS**—measured anxiety and depression **SF-36—**measured HRQOL **IBDQ—**measured IBD specific HRQOL **Inflammatory Biomarkers**–fecal calprotectin, and CRP	*(+) outcomes with depression ($p = 0.03$) in the SFT group at 3 months. The change in depression scores did not sustain after 3 months. * No difference in anxiety noted between the SFT and control group.
Cramer et al. (2017)	RCT Germany	Ulcerative colitis patients who were in remission	I**nitial** (1) 39/38 (2) 39/38 **At 12 weeks** (2) 27/34 **At 24 weeks** (2) 27/30	**Yoga** *Three trained yoga instructors taught Hatha yoga techniques. Each session has Exercises to loosen the body *Pre-defined yoga posture *Yogic breathing techniques (alternate nostril breathing) *Voiced breathing technique with a medication focus *Positive inhalation followed by forceful exhalation *Yogic meditation techniques (mantra meditation and Yoga nidra)	Yoga was administered 90 min per week /12 weeks *A manual was provided to each patient and they were instructed to practice at home on a daily basis. A daily log was provided to enter home practice at home.	**HADS**—measured anxiety and depression **SF-36—**measured HRQOL **Inflammatory Biomarkers**–fecal calprotectin, and CRP	*(+) outcomes for anxiety ($p = 0.001$) and for depression ($p = 0.03$) at 12 weeks for yoga group. *(+) outcomes for anxiety ($p = 0.003$) and depression ($p = 0.007$) at 24 months in yoga group.

selected studies (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Mizrahi et al., 2012; Schoultz et al., 2015) had waitlist control groups; and two of them (Jedel et al., 2014; Gerbarg et al., 2015) had attention control groups. Control group participants were taught about IBD and its management (Gerbarg et al., 2015) and the influence of stress on sleep, psychological and physical health was the subject for teaching by Jedel et al. (2014). Three of the studies (Vogelaar et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016) used standard care as the control group. Lastly, one study (Cramer et al., 2017) used a combination of attention control (self-care advice with a focus on disease process, lifestyle changes and alternative treatments) and waitlist control groups.

Twelve articles were excluded. Five were not RCTs (Bregenzer et al., 2005; Evertsz et al., 2012; Jedel et al., 2013; Neilson et al., 2016; Jordan et al., 2019). Two were study protocols (Schoultz et al., 2013; van den Brink et al., 2016). Three were reviews (McCombie et al., 2013; Fiest et al., 2016; Taft et al., 2017), along with one qualitative study (Schoultz et al., 2016) and one study which included participants <18 years of age (Jantschek et al., 1998).

All of the selected studies reported exclusion or inclusion criteria and included both men and women; only one study was double-blinded (Jedel et al., 2014). Three of the articles (Jedel et al., 2014; Vogelaar et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016) demonstrated adequate sample size by reporting the power analyses. Only one study (Jedel et al., 2014) informed the details of blinding procedures. Objectives, outcomes, details of the intervention, and statistical outcomes were clearly addressed in all studies. Sample sizes ranged from 11 to 51 in experimental groups and 12–66 in control groups. The selected studies were from Spain, Australia, Netherlands, United Kingdom (UK), New Zealand, Israel, United States (US), and Germany.

Hospital Anxiety and Depression scale (HADS) was employed to measure anxiety and/or depression in five of the studies (Vogelaar et al., 2014; Mikocka-Walus et al., 2015 Sibaja et al., 2007; McCombie et al., 2016; Cramer et al., 2017). Other studies (Schwarz and Blanchard, 1991; Mizrahi et al., 2012; Schoultz et al., 2015) utilized the State Trait Anxiety Inventory (STAI) to evaluate anxiety, and some studies (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Jedel et al., 2014; Gerbarg et al., 2015; Schoultz et al., 2015) used the Beck depression inventory to measure depression.

The majority of the RCTs examined the influence of non-pharmacological interventions on other health related outcomes. Seven studies (Mizrahi et al., 2012; Jedel et al., 2014; Vogelaar et al., 2014; Gerbarg et al., 2015; Schoultz et al., 2015; McCombie et al., 2016; Cramer et al., 2017) examined QOL using the inflammatory bowel disease questionnaire (IBDQ). QOL was also measured utilizing the short form 36 health status questionnaire (SF-36) (Vogelaar et al., 2014; Mikocka-Walus et al., 2015; Cramer et al., 2017) and the short form 12 (SF−12) health status questionnaire (McCombie et al., 2016). Biomarkers of inflammation, such as C-reactive protein (CRP), cytokines, and fecal calprotectin were also assessed in three of the selected studies (Vogelaar et al., 2014; Gerbarg et al., 2015; Cramer et al., 2017).

Categories of Non-pharmacological Interventions Addressed in Studies

The selected ten articles addressed various non-pharmacological interventions to mitigate anxiety and depression among those with IBD (**Table 2**). The interventions included components of mindfulness-based therapy; cognitive behavioral therapy (CBT); breathing, movement, and meditation; guided imagery with relaxation; solution-focused therapy; education; a multicomponent regimen with muscle relaxation, biofeedback, coping skills, and education; and yoga.

Intervention length and dose differed significantly between studies, ranging from 2 days to 12 weeks. Six of the studies had a home component to the intervention. Three included a computer disc (Mizrahi et al., 2012; Jedel et al., 2014; Gerbarg et al., 2015), one had a manual (Cramer et al., 2017), and two had both disc and manual (Sibaja et al., 2007; Schoultz et al., 2015). Additionally, researchers of one study sent emails or text messages to participants in between sessions as a reminder to engage in the suggested interventions (McCombie et al., 2016).

Each study intervention was examined for components. All of the reviewed studies had multiple components to each intervention. The most common component of the interventions found in five of the studies was relaxation, including muscle relaxation and guided imagery (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Mizrahi et al., 2012; Jedel et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016). Different relaxation techniques were noted across the studies. Meditation was incorporated as part of the interventions in four studies (Jedel et al., 2014; Gerbarg et al., 2015; Schoultz et al., 2015; Cramer et al., 2017), followed by three studies employing breathing techniques (Mizrahi et al., 2012; Gerbarg et al., 2015; Cramer et al., 2017), as well as the use of mental body scanning in three (Jedel et al., 2014; Schoultz et al., 2015; Cramer et al., 2017) studies. Meditation was recorded as part of yoga (Cramer et al., 2017), mindful movements including Qigong movement (Gerbarg et al., 2015), sitting meditation (Jedel et al., 2014), and mindful stretching (Schoultz et al., 2015). Cramer et al. (2017) concentrated on yoga nidra as a technique to center their attention on various body parts. Different yoga postures were incorporated into the interventions by both Cramer et al. (2017) and Jedel et al. (2014).

Cognitive behavior interventions were noted in four studies (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Mikocka-Walus et al., 2015; Schoultz et al., 2015; McCombie et al., 2016). The techniques included awareness and mindfulness training, problem-solving, attention distraction (Sibaja et al., 2007; Mikocka-Walus et al., 2015; McCombie et al., 2016), and cognitive restructuring (Sibaja et al., 2007; Mikocka-Walus et al., 2015). Education was a component of four studies (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Vogelaar et al., 2014; Mikocka-Walus et al., 2015). Education included information on coping with IBD, communication and assertiveness, relaxation, and relapse prevention. All of these studies addressed communication, while three addressed coping (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Vogelaar et al., 2014; McCombie et al., 2016). Vogelaar et al. (2014) implemented solution-focused therapy (SFT) as an intervention to mitigate

TABLE 2 | Analyses of interventions.

Study name	TIME	Breathing	Qigong movement	Meditation	Home	Experiment/ control group	Yoga	Relaxation	Guided imagery	Mindful stretching	Cognitive Behavior	Discussion reflection	Body scan	Education	SFT
Gerbarg et al. (2015)	9 h × 2 Days (6 h day 1 and 3 days 2)	X	X	X	X (CD)	1.4-Exp / 11-Control									
Cramer et al. (2017)	90 min over 12 weeks	X (10 minu)		X (15)	X (Manual)	39-Exp / 38-Control	X						X (Yoga Nidra)		
Mizrahi et al. (2012)	3–50 min Sessions every 2 weeks (total 6 weeks)	X			X (CD)	18-Exp / 21-Control		X (Muscle)	X						
Schoultz et al. (2015)	8 Weekly F2F-2 h each			X	X (CD/Manual)	12- / 12-				X	X	X	X		x
Jedel et al. (2014)	FLAIR 8 Weeks 1X/week for 2–2.5 h			X	X (CD)	No flare 12/ 10 control and flare 4/ 3 control		X (Posture)			X (Awareness mindfulness)		X		
Sibaja et al. (2007)	10 Weeks 2 hours/ weeks	X				33-Exp / 14-Control		X (Muscle)			X (Problem Solving Att./Distraction)			X (On Relaxation IBD Coping Communication. Assertiveness.)	
McCombie et al. (2016)	8 Sessions-−62 resources self-paced over 8 weeks (computer access)					Completed 50% 29-Exp / 66-Control		X			X (Distraction Thoughts /Behavior)			X (Communication Coping)	
Mikocka-Walus et al. (2015) Pilot	10 weeks F2F and Online					6 Months 55-Exp / 65-Control (42-Exp / 64-Control)		X			X (Att. Distraction)			X (IBD / CPT Assertive Coping Strategies, Comm/Relationships, relapse prevention)	
Mikocka-Walus et al. (2017) 24 Months	10 week Group 2 hours/Week					24 Months 30-Exp / 45-Control									
Vogelaar et al. (2014)	6 group sessions- 1.5 hrs X 3 months; a booster session at 6 months					6 months- 48 exp/49 control									Focused on the present coping abilities
Schwarz and Blanchard (1991)	F 2 F two session × 4 weeks and one session × 4 weeks							X (Muscle)			X			X (IBD)	

depression and anxiety in adults with IBD which focused on the present coping abilities of the patient.

Effectiveness of Non-pharmacological Interventions

Meta-Analysis Results

Meta-analysis was conducted to generate pooled SMD and confidence intervals (CI) for intervention effects on anxiety, depression, disease specific QOL which was measured by IBDQ, mental, and physical QOL which were measured by SF-12/SF-36. In fixed effects models, the I^2 values ranged from 0.0 to 0.74 indicating low to moderate heterogeneity. Despite the fact that some values were low, we report random effects models, as between-study heterogeneity is to be expected given the diverse populations and interventions.

Seven of the 10 studies presented enough quantitative data to compute a meta-analysis to evaluate the influence of non-pharmacological interventions on anxiety and depression (Mizrahi et al., 2012; Jedel et al., 2014; Gerbarg et al., 2015; Mikocka-Walus et al., 2015; Schoultz et al., 2015; McCombie et al., 2016; Cramer et al., 2017). We estimated the pooled standardized mean differences (SMD) between the non-pharmacological intervention and control groups for both anxiety and depression.

The forest plot (**Figure 3**) shows the individual study estimated effects on each outcome, along with the pooled SMD from the random effects models. The SMDs represent the standardized mean difference in the change over time (pre to post-intervention) for the intervention vs. control group. When multiple time points were available, we used the one most immediately following the end of the intervention, which ranged from 5 weeks to 12 months from baseline.

For the effect of non-pharmacological interventions on anxiety, the pooled standardized mean differences (SMD) was −0.28 (95% CI [−0.47, −0.09], $p = 0.004$). This suggests that, on average, non-pharmacological interventions from seven RCTs significantly reduced anxiety among adults with IBD by about ¼ of a standard deviation. The pooled SMD was −0.22 (95% CI [−0.41, −0.03], $p = 0.025$) for the effect of non-pharmacological interventions on depression, indicating that non-pharmacological interventions significantly helped to reduce the depression among adults with IBD. Refer to **Figure 2** for forest plot.

We fit random effects models to examine the efficacy of non-pharmacological interventions on QOL. Seven studies (Mizrahi et al., 2012; Jedel et al., 2014; Vogelaar et al., 2014; Gerbarg et al., 2015; Schoultz et al., 2015; McCombie et al., 2016; Cramer et al., 2017) measured disease specific QOL using IBDQ. Pooled SMD revealed a significantly higher IBDQ in the intervention group, suggestive of improved disease specific QOL in the intervention groups, with a standardized mean differences value of 0.20 (95% CI [0.004, 0.39], $p = 0.046$). Three of the selected studies (Mikocka-Walus et al., 2015; McCombie et al., 2016; Cramer et al., 2017) examined the impact of non-pharmacological intervention on the mental health component of QOL. The pooled effect on mental health QOL (using SF-12 or SF-36) was 0.13 (95% CI [−0.10, 0.36], $p = 0.27$). Four studies measured non-pharmacological intervention's effect on the physical health component of QOL (Vogelaar et al., 2014; Mikocka-Walus et al., 2015; McCombie et al., 2016; Cramer et al., 2017). For physical health QOL (assessed by the SF-12 or SF-36), the pooled SMD was 0.06 (95% CI [−0.14, 0.26], $p = 0.54$). Although the results of pooled SMD estimates for mental and physical QOL are positive (favoring the treatment group), neither is statistically significant.

Synthesis of Two Studies

Findings of three of the selected studies (Schwarz and Blanchard, 1991; Sibaja et al., 2007; Vogelaar et al., 2014) were synthesized narratively due to insufficient quantitative data for meta-analysis for the outcomes of anxiety and depression. The interventions implemented were multicomponent regimens (Schwarz and Blanchard, 1991), CBT (Sibaja et al., 2007) and solution-focused therapy (Vogelaar et al., 2014). Both CBT and solution-focused therapy significantly reduced depression (Sibaja et al., 2007, $p < 0.001$; Vogelaar et al., 2014, $p = 0.03$). However, only CBT was effective in reducing anxiety which was persistent at 12 months after the intervention (Sibaja et al., 2007, $p < 0.001$). No statistically significant change in anxiety or depression scores was noted among the participants of the multicomponent regimen (Schwarz and Blanchard, 1991).

DISCUSSION

The goal of this systematic review and these meta-analyses were to examine RCTs of non-pharmacological interventions and their effectiveness for managing anxiety and depression in adults with IBD. This systematic review analyzed the evidence from a variety of interventions (CBT, yoga, guided imagery with relaxation, SFT, mindful-based stress reduction, and breath–body- mind – workshop [BBMW]) to mitigate anxiety and depression among adults with IBD. Unlike the findings of a prior systematic review (Fiest et al., 2016), the evidence synthesized from this systematic review and meta-analysis supports different non-pharmacological interventions, as the pooled effect of these interventions were found to be beneficial in reducing depression and anxiety among adults with IBD.

Another important result was that the pooled effect from IBDQ data supported the finding that non-pharmacological interventions improved disease specific QOL of adults with IBD. Previous findings confirmed the close association between depression, anxiety, and QOL of those with IBD. Depression and anxiety scores significantly lowered the QOL scores of adults with IBD (Evertsz et al., 2012). In light of this findings, non-pharmacological interventions to manage depression and anxiety in those with IBD ultimately help to improve their QOL and should be promoted.

Because a subgroup analysis was not possible due to the limited number of studies, we conducted a qualitative synthesis of individual interventions to understand how interventions influenced depression and fatigue. Among the different interventions, CBT was the most commonly used intervention (Sibaja et al., 2007; Mikocka-Walus et al., 2015; McCombie et al., 2016) followed by mindful based interventions (Jedel et al., 2014; Schoultz et al., 2015). The remaining interventions varied among the studies. However, examining

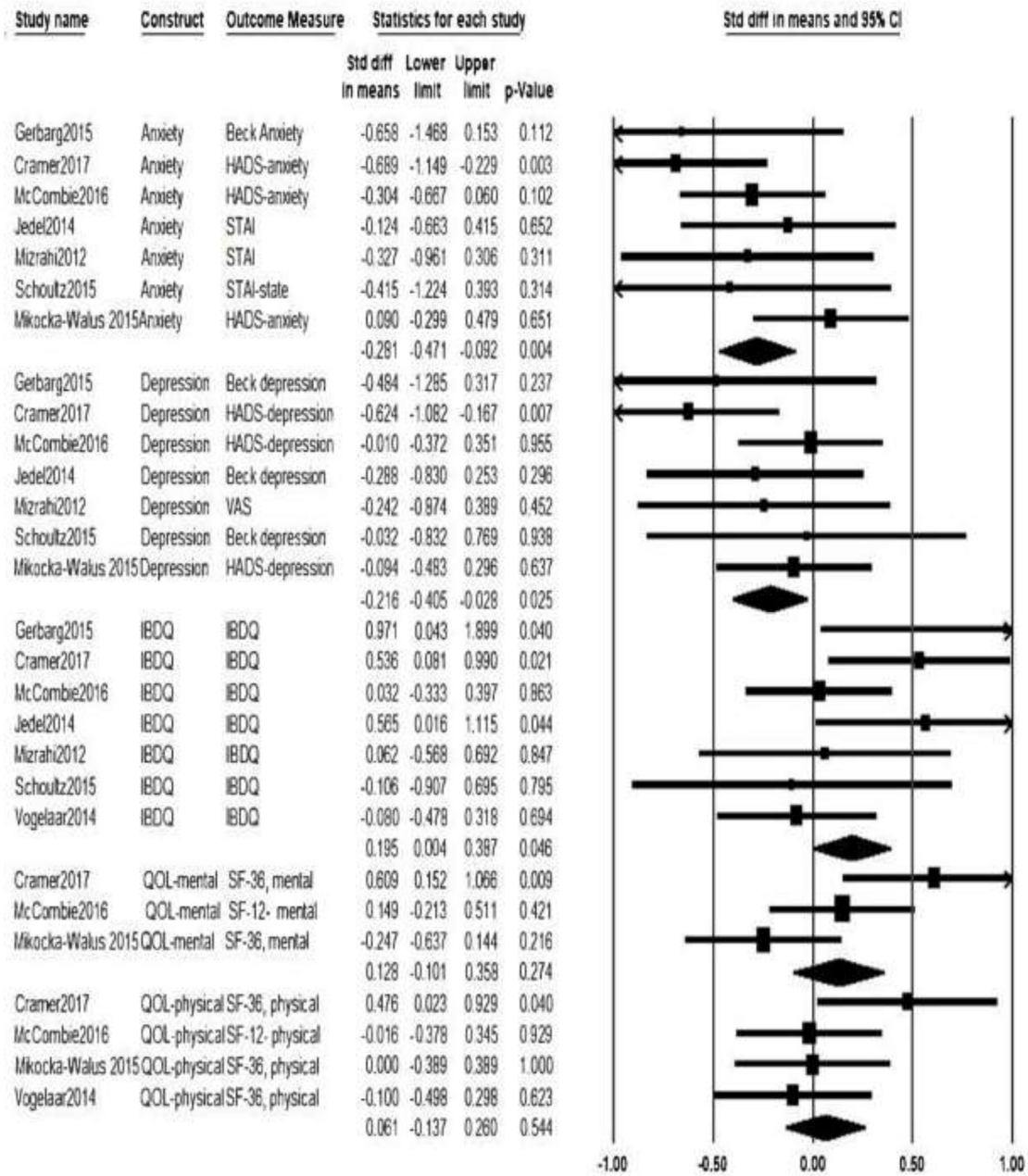

FIGURE 3 | Forest plot with meta–analysis results. HADS, Hospital Anxiety and Depression Scale; STAI, State Trait Anxiety Inventory; VAS- Visual Analog Scale; IBDQ, Inflammatory Bowel Disease Questionnaire; QOL, Quality of Life; SF-36, The Short Form 36 health status questionnaire; SF-12, The Short Form 12 health status questionnaire.

the components of interventions revealed the use of several common therapeutic modalities (**Table 2**) in each of the reviewed RCTs. For example, as displayed in **Table 2**, cognitive behavioral interventions, relaxation, meditation, breathing, body scan and education were common therapeutic modalities as part of different interventions in many studies. This finding supports incorporating various therapeutic components to manage depression and anxiety among adults with IBD, as suggested by Knowles et al. (2013). Of the seven studies that evaluated QOL, three of them (Jedel et al., 2014; Gerbarg et al., 2015; Cramer et al., 2017) demonstrated statistically significant differences after the intervention. The interventions included in these studies were yoga (Cramer et al., 2017), breath–body-mind–workshop (BBMW; Gerbarg et al., 2015) and mindful based interventions (Jedel et al., 2014).

Out of 10, six of the reviewed studies included all adults with IBD and did not differentiate if the IBD was in remission or active state. Significant improvement was noted on both

anxiety and depression in three of the studies (Sibaja et al., 2007; Gerbarg et al., 2015; Schoultz et al., 2015) and improvement was noted on anxiety in only one study (Mizrahi et al., 2012). Two studies did not report changes in depression and/or anxiety. Two studies were conducted among adults with IBD in remission and significant improvement was noted on both anxiety and depression in one study (Mikocka-Walus et al., 2015), and only on depression in the second study (Vogelaar et al., 2014). Two studies included participants with ulcerative colitis (a subtype of IBD) in remission, and the findings of only one study (Cramer et al., 2017) noted an improvement in anxiety and depression.

Not only did the interventions differ, but the dose and strength of the interventions differed. Although the evidence is supportive of non-pharmacological interventions to manage anxiety and depression in adults with different types of IBD, further research is recommended with more studies to identify the distinct evidence on adults with different types of IBD.

All the studies included in this synthesis had longitudinal assessments of outcomes to determine if effects were sustained. Sustained improvement on anxiety and depression outcomes was present only in the results of the study by Sibaja et al. (2007); however, the control group of this study was included only for initial assessment, with no comparison between treatment and control groups at three, six, and 12 months. Further research is warranted with the inclusion of treatment and control groups in follow-ups to determine the persistent effects of non-pharmacological interventions.

All the studies except one (Gerbarg et al., 2015) included some form of initial psychological screening as inclusion criteria before initiating the non-pharmacological interventions in their RCTs, forming a homogeneous group of study participants among the eight studies regarding their mental health. However, Jedel et al. (2014) acknowledged that participants' self-reporting of sound baseline mental health status might have caused a ceiling effect on the results of the study and recommended the consideration of baseline mental status as a sampling criterion.

The setting varied across the studies from Spain, Australia, New Zealand, UK, US, Israel, Netherlands, and Germany. Therefore, it is important to consider the acceptability and feasibility of various non-pharmacological interventions across diverse healthcare settings and cultures. Overall, the review presented a variety of non-pharmacological modalities to mitigate anxiety and depression and noted the positive effects of most of these therapeutic modalities on the anxiety and depression outcomes of those with IBD.

Few studies documented the type of reinforcement or reminder about the interventions to enhance compliance or to improve the effects of interventions. This synthesis found multiple studies using a home component as part of the intervention. However, neither the dosage, adherence, nor timing of intervention were clearly detailed. The majority of the researchers used the same methodology as Vogelaar et al. (2014) and included an extended treatment period with a follow- up to maintain a persistent effect of non-pharmacological interventions in those with IBD.

Some limitations were observed among the studies selected for review. We noticed a heterogeneous control groups among the studies that included in meta-analysis which varied from waitlist control groups, attention control groups, and standard control groups. Therefore, the results of the meta-analysis need to be interpreted with caution due to the different control groups of the reviewed studies. Many studies did not evaluate anxiety or depression as a primary outcome. Most of them assessed anxiety or depression along with other variables such as quality of life, physical symptoms, inflammatory biomarkers, and stress. Due to this weakness, further research is recommended to evaluate the distinct contribution of non-pharmacological interventions on anxiety and depression in adults with IBD.

Additionally, the disease activity of samples varied across the studies. They included IBD in general, IBD in remission, ulcerative colitis with remission, and those with active IBD. Moreover, no consistency was observed among the delivered non-pharmacological interventions in these different samples with IBD disease activity. Consequently, it was difficult to conclude the suitability of a particular intervention for certain disease activity of IBD. More research targeting various disease activities is required to understand the effectiveness of these interventions on the various disease activities of IBD.

Failure to retain participants after six and 12 months were an observed problem among many studies (Mikocka-Walus et al., 2015; Schoultz et al., 2015; McCombie et al., 2016; Cramer et al., 2017). This might have affected the results with long-term effects of non-pharmacological interventions in these studies; future research should be designed to improve participant retention with longitudinal assessment of anxiety and depression.

CONCLUSION AND IMPLICATIONS FOR PRACTICE

Analysis of the reviewed RCTs indicates that non-pharmacological interventions can be an option for the management of anxiety and depression among adults with IBD. Non-pharmacological interventions can be considered as concurrent therapy with pharmacological treatment to manage depression and anxiety in adults with IBD. Thus, all healthcare providers in the acute or outpatient care settings should facilitate a discussion with adults with IBD about the availability of these interventions to manage their anxiety and depression. In conclusion, providers should screen adults with IBD based on the disease activity of IBD and refer them to the appropriate non-pharmacological intervention of their choice, as anxiety and depression have been related to the disease recurrence in the IBD population (Mikocka-Walus et al., 2016).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

SD contributed to the conception, design, systematic search, data extraction, quality appraisal, and analysis. LB and PC contributed

to the design, data extraction, quality appraisal, analysis, and critical revision of the draft. JC contributed to meta-analysis, interpretation of meta-analysis results, and critical revision of the draft. Finally, all authors have reviewed and approved the final paper.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.538741/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

ORIGINAL RESEARCH
published: 09 November 2020
doi: 10.3389/fpsyg.2020.595987

Pain Modulates Responses to Emotional Stimuli

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Pain and emotion are common subjective experiences that play vital roles in daily life. Pain has been clinically confirmed to increase depressive mood. However, little is known about how pain modulates cognitive emotional judgment processing. A better understanding of this may help explain the effect of pain on the development of depressive moods. We recruited 30 adult participants to test their responses to pictures of scenes (Experiment 1) and faces (Experiment 2) that represented happy, neutral, and sad emotions, while experiencing painful (induced via topical capsaicin cream) and control (hand cream) treatments. Results showed that participants in the painful condition showed lower accuracy to emotional scene stimuli and longer reaction times to both emotional scene and face stimuli, relative to the control condition. In addition, the difference values of the reaction times between the painful and control conditions were larger for sad scenes than for happy or neutral scenes. These results suggest that pain alters attentional processing of emotional stimuli, especially with regards to sad scene stimuli, which may explain how painful stimuli affect the development of depressive moods.

Keywords: pain, emotional stimuli, sad scenes, negative emotional stimuli processing, attentional processing

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Emotion Science, a section of the journal Frontiers in Psychology

Received: *18 August 2020*
Accepted: *09 October 2020*
Published: *09 November 2020*

Citation:
Li W, Liu P, Hu Y and Meng J (2020) Pain Modulates Responses to Emotional Stimuli. Front. Psychol. 11:595987. doi: 10.3389/fpsyg.2020.595987

INTRODUCTION

Pain has evolutionary significance to humans, whereby the behaviors evoked by pain are critical for human survival (Wang et al., 2019). Recently, the International Association for the Study of Pain (IASP) revised pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020).

Pain and emotion are closely related. From a theoretical perspective, pain can be defined as a type of unpleasant emotional experience and includes the feelings of depression and sadness (Mokhtari et al., 2019). Particularly, the motivational-affective dimension of pain is closely linked with emotion (Melzack and Casey, 1968). From a neuropsychological perspective, similar brain regions represent both pain and emotion. For example, the medial frontal cortex (including the anterior midcingulate cortex; Kragel et al., 2018), the midbrain periaqueductal gray (Buhle et al., 2013), and the hippocampus (Mokhtari et al., 2019) are involved in both pain and negative emotions, suggesting that the experience of pain influences the processing of negative emotions.

There are bidirectional influences of pain and emotion processing (Reicherts et al., 2013). There has been substantial behavioral and neurobiological research on the effects of emotional stimuli on pain processing. For instance, Lu et al. (2019) identified that positive emotional stimuli from music could reduce the unpleasantness of pain. Further, Willoughby et al. (2002)

used a laboratory-induced depressive mood to examine its effects on responses to pain, which revealed that a depressive mood lowered pain tolerance and increased pain catastrophizing. In contrast, the way that pain might modulate emotion processing has been rarely investigated. Clinical evidence has indicated that patients with pain often experience emotional disturbances, especially depressive moods (Hawker et al., 2011; Craig et al., 2013), and experience dysfunctional processing of emotional stimuli (Bartley et al., 2008; Rosselló et al., 2015; Giel et al., 2018), which hints at a potential effect of pain on emotion processing. One study that required participants to assess emotional scenes under painful or innocuous electrical shocks showed that painful stimuli significantly reduced the emotional ratings of pleasant pictures and decreased visually evoked brain responses to pleasant emotional stimuli (Godinho et al., 2008). Similarly, in a study by Gerdes et al. (2012), where pressure pain was experimentally induced during the viewing of emotional faces, researchers observed that painful stimuli slowed individuals' facial muscle responses to happy emotional faces, while emotional ratings of the pictures remained the same. However, Wieser et al. (2012) reported that emotional ratings and early emotion discrimination in response to happy emotional faces did not change with tonic pressure pain. With regard to the processing of negative emotional stimuli, the aforementioned studies reported no significant influences of pain on the processing of negative emotional stimuli, regardless of the type of pain stimuli used (Godinho et al., 2008; Gerdes et al., 2012; Wieser et al., 2012). However, another study found that thermal pain enhanced the processing of negative emotional faces (Reicherts et al., 2013). This inconsistency may be the result of differences in the modalities used to induce pain or the duration of pain. For example, Godinho et al. (2008) used a brief electrical shock, which only appeared at the beginning and end of each block. Similarly, the pressure stimuli used in the studies by Gerdes et al. (2012) and Wieser et al. (2012) also only lasted for several seconds. In contrast, the thermal pain stimuli used in the study by Reicherts et al. (2013) had a considerably longer duration that lasted throughout the experiment.

Laboratory-induced pain allows experimental control and enables causal inferences to be drawn (Bresin et al., 2017). Cold pressor pain (e.g., Hollin and Derbyshire, 2009), pressure pain (e.g., Wieser et al., 2012), electrical shock pain (e.g., Godinho et al., 2008), and thermal pain (e.g., Reicherts et al., 2013) are commonly used approaches to experimentally induce pain. However, the limitation of these modalities is that they are often short in duration. Recently, according to the heat/capsaicin sensitization model (Modir and Wallace, 2010), capsaicin has been used to induce a moderate level of sustained painful sensations (Wang et al., 2018, 2019). Furthermore, capsaicin can reproduce the common symptoms of neuropathic pain (Shenoy et al., 2011). In healthy participants, pain induced by capsaicin is reproducible in repeated experiments (Harding et al., 2001). Therefore, we selected capsaicin to induce pain in the current study.

Top-down attention could affect the processing of negative emotional stimuli (Meng et al., 2019), and the attentional effect of pain has now been well documented. According to the cognitive-affective model of pain (Eccleston and Crombez, 1999), intense pain has an interruptive function that draws the attention of the person experiencing the pain. Several findings have supported this notion (Ochsner and Gross, 2005; Wieser et al., 2012; Reicherts et al., 2013). Research has demonstrated that this attentional effect of pain can weaken the processing of emotional stimuli (Wieser et al., 2012). In particular, altered attention toward negative emotional stimuli has been observed in patients experiencing pain frequently. In the study of Duschek et al. (2014), patients experiencing pain had longer reaction times in response to negative emotional words in the Stroop task, which suggests an attention bias for negative emotional stimuli. In a study that used eye tracking technology to assess attentional processing of emotional stimuli in patients with back pain, they showed an attentional bias for negative stimuli, which was expressed as more fixation, larger pupil diameter, longer average fixation duration, and faster first fixation to negative stimuli (Franklin et al., 2018). Fashler and Katz (2016) found that attentional biases toward negative stimuli in individuals experiencing pain appeared primarily in the late phase of attention. Based on these findings, it appears that pain can induce dysfunctional processing of emotional stimuli. The current study aims to examine whether this effect on emotional stimuli processing also occurs in healthy people who do not experience pain frequently.

Images of faces include more emotional information, while pictures of scenes include more perceptual information (Li et al., 2019). Although emotional scene and face stimuli are commonly utilized to experimentally induce emotional states (Godinho et al., 2008; Gerdes et al., 2012; Wieser et al., 2012; Reicherts et al., 2013), there are strikingly distinct patterns of physiological and neurobiological responses between the two types of stimuli. Startle amplitudes and orbicularis oculi responses to positive scene stimuli have shown to be larger than those of positive face stimuli, while heart rate deceleration and skin conductance responses to negative emotional scenes have shown to be greater than those of negative emotional faces (Alpers et al., 2011). Larger right amygdala responses have been observed for emotional faces, while larger left amygdala responses were seen for emotional scenes (Hariri et al., 2002). The processing of emotional faces has also been associated with activations in the anterior fusiform gyrus and middle temporal gyrus, while emotional scenes have shown to activate the lateral occipital cortex, pulvinar, medial dorsal nucleus of the thalamus, extrastriate cortex, and inferior frontal gyrus (Keightley et al., 2010; Sabatinelli et al., 2011). Additionally, both the valence and arousal of emotional scenes and faces can differ (Alpers et al., 2011). Individuals also show different behavioral and neural responses to faces and scenes (Li et al., 2019). In view of these differences, the different modulatory effects of pain on emotional scene stimuli and emotional face stimuli need to be examined in one study. To explore the effects of pain on different emotional stimuli, we decided to use emotional scenes as experimental stimuli in Experiment 1 and emotional faces in Experiment 2.

In an effort to gain a better understanding of the modulatory effect of pain on emotion, we conducted two experiments using emotional scenes (Experiment 1) and faces (Experiment 2) to

examine the changes in response to emotional stimuli following laboratory-induced pain. The motivational priming hypothesis (Lang, 1995) assumes that pain may augment the processing of unpleasant stimuli and lessen the processing of pleasant stimuli. Based on this supposition, we hypothesize that (1) pain will prolong attention toward negative (sad) emotional stimuli, and (2) pain will dampen responses to positive (happy) emotional stimuli.

MATERIALS AND METHODS

Participants

Thirty adults (15 females) participated in this study as paid volunteers. All participants were right-handed, aged 21–27 years [mean (M) = 23.47, standard deviation (SD) = 1.74], had normal or corrected-to-normal vision, and had no neurological or psychiatric conditions or chronic pain. Written informed consent was obtained prior to participation. The current study conforms to all provisions of the Declaration of Helsinki and was approved by the local research Ethics Committee of Chongqing Normal University. All procedures were performed in accordance with ethical guidelines and regulations.

Pain Induction and Assessment

In accordance with previous studies (Wang et al., 2018, 2019), two treatments were applied to the participants. In the painful treatment, 0.1 mL of Capzasin-HP cream (capsaicin 0.1%; CHATTEM, United States) was applied to a 2 cm× 2 cm area on the inside of the left forearm. Then, this area was covered with plastic film to ensure skin contact and heat generation that resulted in a steady and persistent pain sensation. Participants had no prior experience of capsaicin. After the experiment, Capzasin-HP cream was wiped away with tissue paper and soapy water. In the control treatment, an equivalent amount of hand cream was applied to the same area. Pain intensity was assessed using a subjective numerical pain visual analog scale (VAS, 0 = no sensation, 10 = utmost pain imaginable; Carlsson, 1983; Bijur et al., 2001) before treatment (baseline), at 15 min after treatment (pretest), and after the whole study (posttest) for both the painful and control treatments.

Pain intensity ratings for this study were assessed with two-way repeated-measure analysis of variance (ANOVA) of "treatment" (painful, control) and "time" (baseline, pretest, posttest) (see **Table 1** and **Figure 1**). The interaction of "treatment" × "time" [$F(1,29) = 255.64$, $p < 0.001$, $\eta_p^2 = 0.90$] indicated that throughout this study, pain intensity ratings of the baseline did not differ significantly in the painful and control treatments ($p = 0.763$). Pain intensity ratings of the pretest and the posttest were both significantly higher in the painful treatment than in the control treatment (both $p < 0.001$). In addition, pain intensity ratings of the posttest (6.73 ± 0.24) were significantly higher than that of the pretest (5.47 ± 0.22, $p < 0.001$) in the painful treatment, demonstrating successful sustained, moderate pain induction from Capzasin-HP cream application.

TABLE 1 | Summary of the statistical analysis of pain intensity ratings of the two treatments.

	F	*p*	η^2
Treatment	299.86	<0.001	0.91
Time	213.35	<0.001	0.88
Treatment × Time	255.64	<0.001	0.90

In this study, statistics were obtained using two-way repeated-measure ANOVA with treatment and time. df: (1,29).

Stimuli

Experiment 1

Thirty pictures representing various emotional scenes (10 happy, 10 neutral, and 10 sad) were selected from the Chinese Affective Picture System (CAPS; Bai et al., 2005) that have been previously validated and used in published studies (Zhao et al., 2016; Wang et al., 2017). All scene pictures were in color, as illustrated in the top panel of **Figure 2**. We recruited 30 undergraduate students (who did not participate in the actual experiment) to assess the valence (1 = very sad, 5 = neutral, 9 = very happy) and arousal (1 = very calm, 5 = neutral, 9 = very exciting) values of the scenes. A one-way repeated ANOVA reported a significant difference among the three categories in "valence" [$F(2,27) = 61.33$, $p < 0.001$, $\eta_p^2 = 0.87$] and "arousal" [$F(2,27) = 23.27$, $p < 0.001$, $\eta_p^2 = 0.72$] values (**Table 2**). The *post hoc* test on the valence showed that it was higher for happy (6.76 ± 0.73) than for neutral (5.11 ± 0.59, $p = 0.001$) and sad (2.71 ± 0.99, $p < 0.001$) scenes, and higher for neutral than for sad scenes ($p < 0.001$). A *post hoc* test showed that the arousal values of the pictures were lower for neutral (3.60 ± 0.41) than for happy (5.26 ± 0.65, $p < 0.001$) and sad (5.85 ± 1.25, $p < 0.001$) scenes, while the latter two categories did not differ significantly ($p = 0.189$).

Experiment 2

Thirty emotional face pictures (10 happy, 10 neutral, and 10 sad) were chosen from the Chinese Facial Affective Picture System (CFAPS; Gong et al., 2011) that have been previously validated and used in published studies (Ma and Zhu, 2014; Tan et al., 2018). Half of the pictures were of male faces and half were of female faces. Luminance, contrast, and color were matched among the happy, neutral, and sad pictures, and all face pictures were in gray scale, as illustrated in the bottom panel of **Figure 2**. As with Experiment 1, we recruited 30 undergraduate students (who did not participate in the actual experiment) to assess the valence (1 = very sad, 5 = neutral, 9 = very happy) and arousal (1 = very calm, 5 = neutral, 9 = very exciting) values of the faces. A one-way repeated ANOVA reported a significant difference among the three categories in "valence" [$F(2,27) = 347.56$, $p < 0.001$, $\eta_p^2 = 0.98$] and "arousal" [$F(2,27) = 118.20$, $p < 0.001$, $\eta_p^2 = 0.93$] values (**Table 2**). The *post hoc* test on the valence showed that it was higher for happy (6.39 ± 0.40) than for neutral (4.82 ± 0.24, $p < 0.001$) and sad (3.14 ± 0.43, $p < 0.001$) faces, and higher for neutral than for sad faces ($p < 0.001$). A *post hoc* test showed that the arousal response of the faces was lower for neutral (3.46 ± 0.26) than for happy (5.42 ± 0.34, $p < 0.001$) and

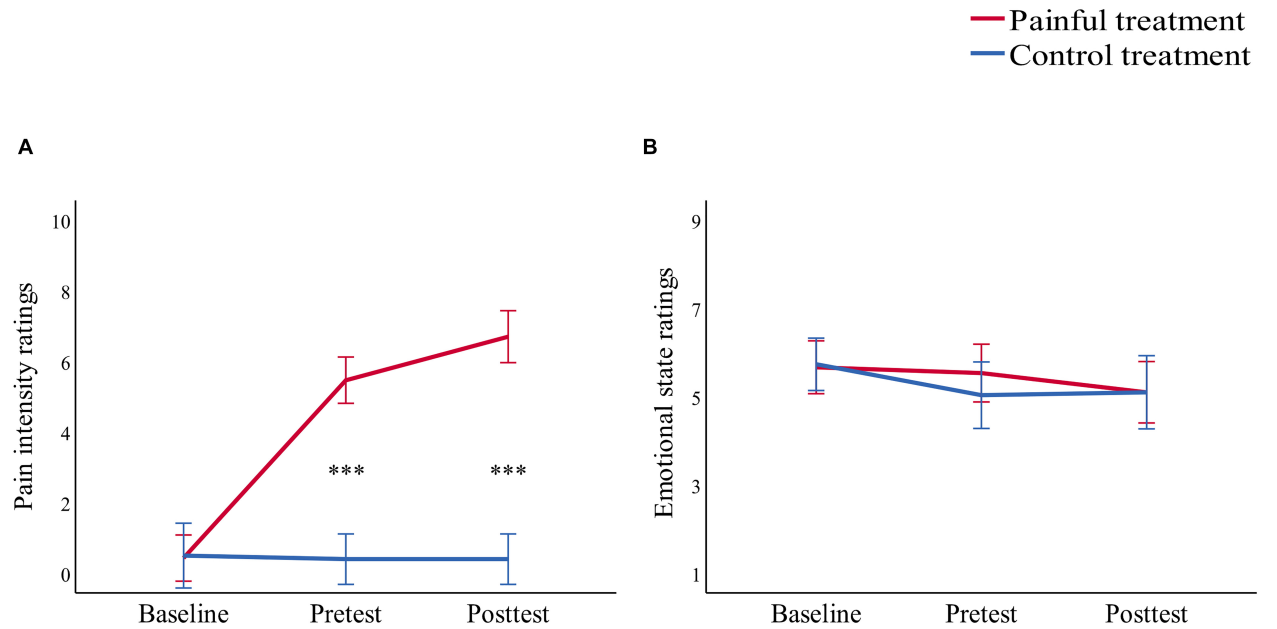

FIGURE 1 | Line charts describing **(A)** pain intensity ratings and **(B)** emotional state ratings before treatment (baseline), 15 min after treatment (pretest), and after the study (posttest) in the painful (red line) and control (blue line) treatments. Data are expressed as mean ± standard error of the mean, ***$p < 0.001$.

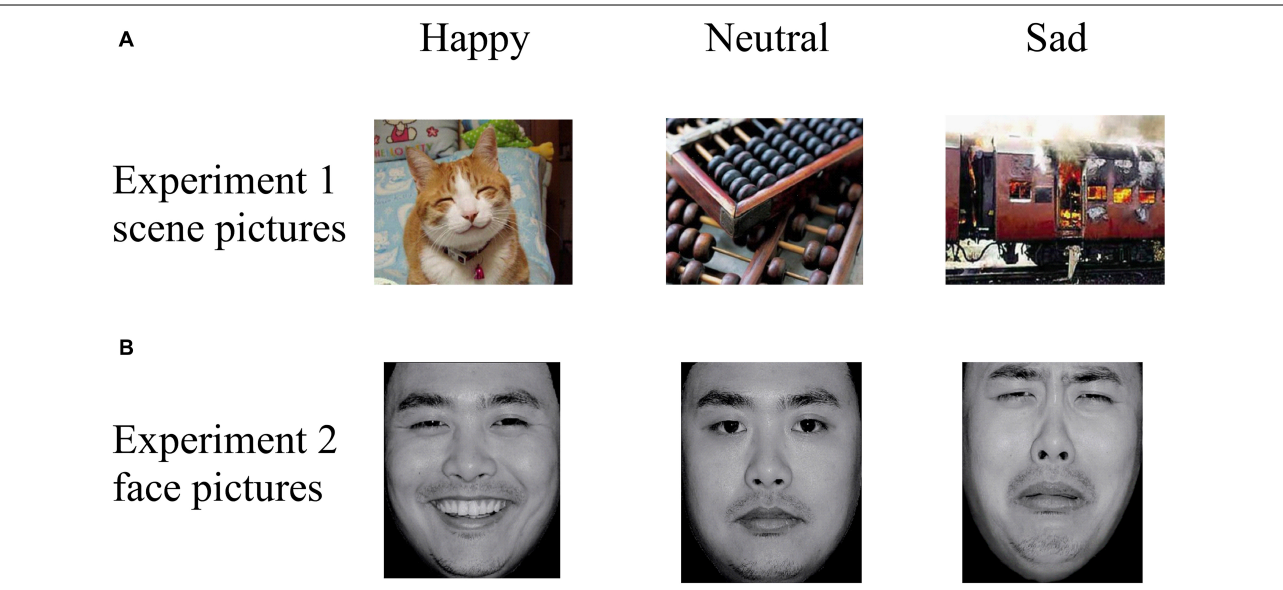

FIGURE 2 | Examples of stimuli in **(A)** Experiment 1 and **(B)** Experiment 2, with examples of happy (left column), neutral (middle column), and sad (right column) pictures. Pictures were selected from the CAPS and the CFAPS that have been previously validated and used in published studies (Bai et al., 2005; Gong et al., 2011; Ma and Zhu, 2014; Wang et al., 2017).

TABLE 2 | Summary of one-way repeated ANOVA for valence and arousal values of the emotional stimuli.

		Happy	Neutral	Sad	*F*	*p*	η^2
Face pictures	Valence	6.76 ± 0.73	5.11 ± 0.59	2.71 ± 0.99	61.33	<0.001	0.87
	Arousal	5.26 ± 0.65	3.60 ± 0.41	5.85 ± 1.25	23.27	<0.001	0.72
Scene pictures	Valence	6.39 ± 0.40	4.82 ± 0.24	3.14 ± 0.43	347.56	<0.001	0.98
	Arousal	5.42 ± 0.34	3.46 ± 0.26	5.18 ± 0.38	118.20	<0.001	0.93

sad (5.18 ± 0.38, $p < 0.001$) faces, while the latter two categories did not differ significantly ($p = 0.158$).

Procedure

The experiment was carried out in a comfortable and quiet room. Participants partook in both experiments. Pictures were presented in a pseudo-random order using the E-Prime (3.0) program. The order of the two experiments was counterbalanced to control for order effects. The procedures of the two experiments are illustrated in **Figure 3**.

Experiment 1

Each participant carried out the task twice. Participants were randomly given a treatment (painful or control) for the first session and were given the other treatment after a 1-week interval. The order of the two treatments was counterbalanced across participants. All participants were asked to assess their current emotional state based on a 9-point (1 = very unhappy, 5 = neutral, 9 = very happy) Likert scale before the treatment (baseline), 15 min after treatment (pretest), and after the study (posttest) for both the painful and control treatments (**Figure 1**). Results showed that there were no significant differences (all $p > 0.05$) in emotional states in either the painful or control treatments. These results suggest that the emotional states of the participants were similar for both treatments.

Prior to the experiment, participants were instructed to do a training session in order to get acquainted with the procedure. Two happy pictures, two neutral pictures, and two sad pictures were selected from the CAPS for the training session and were not used in the main experiment. The training session started 15 min after the treatment, and the duration of the training session was about 5 min. Thus, the first formal experiment started at 20 min after the treatment was administered. The duration of the entire experiment was about 15 min.

Each trial involved the following steps:

A fixation cross was presented on a gray screen for a duration of 500 ms. After a 200-ms interval, a picture was presented, during which participants were instructed to respond as accurately and quickly as possible with a key-press ("1," "2," or "3") to judge the emotion type (happy, neutral, or sad) of the picture. The order of key-presses was counterbalanced among participants. The picture remained on the screen until a response was made. After 100 ms, a 9-point emotional assessment scale appeared (1 = very unhappy, 5 = neutral, 9 = very happy), where participants were required to assess their subjective emotional reaction to the picture. The scale disappeared when a response was made. There was an intertrial interval of 500 ms.

Experiment 2

Procedures were identical except that the stimuli of the training session and the main experiment were emotional face pictures selected from the CFAPS (Ma and Zhu, 2014; Tan et al., 2018).

Both experiments included two blocks each with a 5-min break between blocks. Each block consisted of 45 trials. The stimuli for each block were pseudo-randomly delivered so that the same emotion type never occurred for three consecutive trials. Each picture was presented three times in each experiment. The order of Experiment 1 and Experiment 2 was counterbalanced among participants, and participants could take a 10-min break between the two experiments.

Data Analysis

Accuracies (ACCs) and reaction times (RTs) for emotion type judgment, and emotional reactions to pictures were calculated for each participant for each condition. RTs out of the Mean ± 3SD

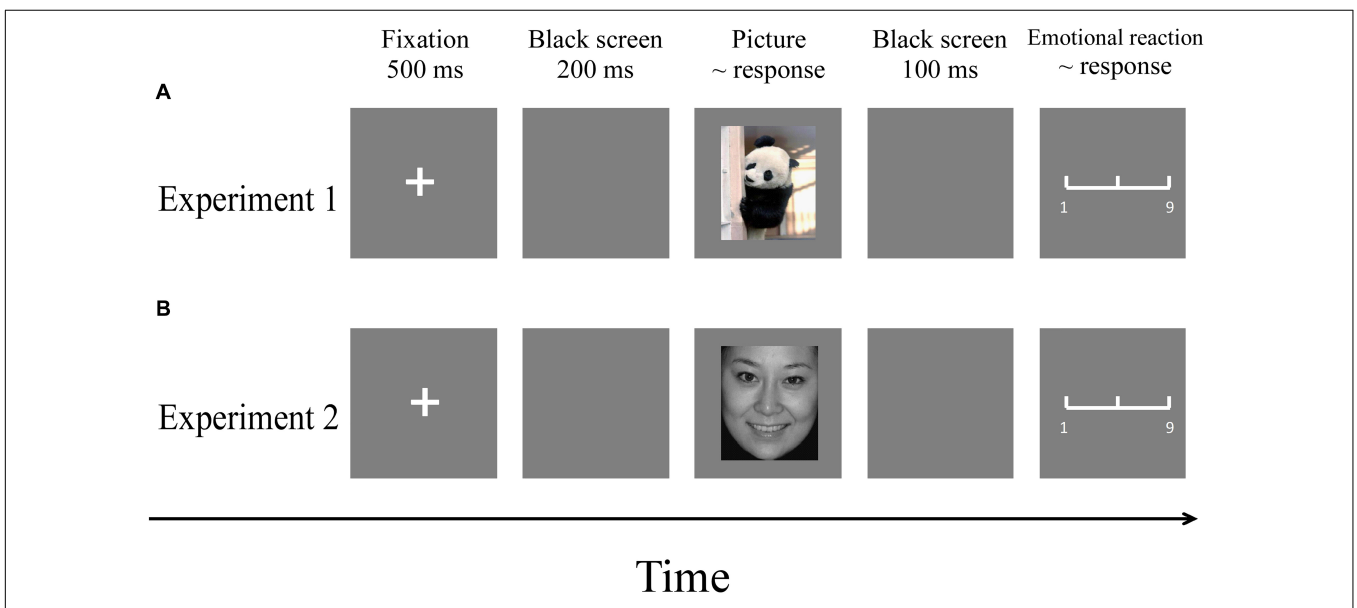

FIGURE 3 | Flowchart describing the experimental designs. **(A)** Procedure of Experiment 1. **(B)** Procedure of Experiment 2. Note: Pictures were selected from the CAPS and the CFAPS that have been previously validated and used in published studies (Bai et al., 2005; Gong et al., 2011; Ma and Zhu, 2014; Wang et al., 2017).

(Experiment 1: 8.78%, Experiment 2: 8.31%) were deleted from the original data. Statistical analyses of the two experiments were performed using SPSS 15.0, using a two-way repeated-measure ANOVA, with two within-participant factors of "treatment" (painful, control) and "emotion" (happy, neutral, sad). The difference values of ACCs, RTs, and emotional reactions between the two treatments (painful–control) were analyzed for three categories of emotional pictures (happy, neutral, sad) using a separate one-way ANOVA for each experiment. The *p*-values of the main effects and interactions were corrected using the Greenhouse–Geisser method. Statistical differences were considered significant at $p < 0.05$.

RESULTS

Accuracies, RTs, and emotional reactions for each condition in the two experiments are summarized in **Table 3** and **Figures 4**, **5**.

Experiment 1

ACC

There was a significant main effect of "treatment" [$F(1,29) = 7.91$, $p = 0.009$, $\eta_p^2 = 0.21$], which indicated that participants were significantly more accurate in the control treatment (90.0 ± 1.3%) than in the painful treatment (86.8 ± 1.7%, $p = 0.009$). There was a significant main effect of "emotion" [$F(2,28) = 19.42$, $p < 0.001$, $\eta_p^2 = 0.58$], which indicated that participants were significantly more accurate in recognizing neutral emotional scenes (96.3 ± 0.8%) than happy (80.6 ± 3.9%, $p = 0.001$) and sad (88.2 ± 1.5%, $p < 0.001$) scenes; there was no significant difference in ACCs between happy and sad emotional scenes ($p = 0.074$). There was no significant interaction.

RT

There was a significant main effect of "treatment" [$F(1,29) = 31.21$, $p < 0.001$, $\eta_p^2 = 0.52$], which indicated that RTs were significantly shorter in the control treatment (1260.41 ± 67.00) than in the painful treatment (1660.57 ± 95.20, $p < 0.001$). The main effect of "emotion" was significant [$F(2,28) = 25.52$, $p < 0.001$, $\eta_p^2 = 0.65$]. This result indicated that RTs were significantly shorter for neutral emotional scenes (1093.39 ± 51.44) than for happy (1596.34 ± 101.36, $p < 0.001$) and sad (1691.73 ± 96.02, $p < 0.001$) scenes, while there was no significant difference between happy and sad emotional scenes ($p = 0.100$). There was a significant "treatment" × "emotion" interaction [$F(2,28) = 12.57$, $p < 0.001$, $\eta_p^2 = 0.30$], which indicated that RTs for recognizing happy, neutral, and sad emotional pictures were significantly shorter in the control (happy: 1445.66 ± 97.58; neutral: 962.20 ± 56.35; sad: 1373.35 ± 79.41) than in the painful treatment (happy: 1747.01 ± 125.36, $p = 0.004$; neutral: 1224.58 ± 63.97, $p < 0.001$; sad: 2010.11 ± 128.61, $p < 0.001$). Furthermore, the one-way ANOVA revealed a significant difference between the three categories of emotional pictures [$F(2,87) = 5.74$, $p = 0.005$, $\eta_p^2 = 0.12$]. The *post hoc* tests showed that the difference values of RTs for sad emotional scenes (636.76 ± 514.14) were significantly larger than for happy (301.35 ± 530.27, $p = 0.007$) and neutral (262.37 ± 344.34, $p = 0.003$) scenes, while the difference values of RTs for happy and neutral emotional scenes did not differ significantly ($p = 0.749$).

Emotional Reaction

There was a significant main effect of "emotion" [$F(2,28) = 123.39$, $p < 0.001$, $\eta_p^2 = 0.90$], which indicated that emotional reactions to happy scenes (6.28 ± 0.11) were more positive than neutral (4.96 ± 0.01, $p < 0.001$) and sad (3.23 ± 0.14, $p < 0.001$) scenes. Further, emotional reactions to neutral scenes were more positive than sad scenes ($p < 0.001$). No other main effect or interaction was significant.

Experiment 2

ACC

There were no significant main effects or interactions.

RT

There was a significant main effect of "treatment" [$F(1,29) = 12.71$, $p = 0.001$, $\eta_p^2 = 0.31$], which indicated that RTs were significantly shorter in the control (1404.00 ± 72.51) than in the painful treatment (1654.59 ± 87.70, $p = 0.001$). The significant main effect of "emotion" [$F(2,28) = 16.92$, $p < 0.001$, $\eta_p^2 = 0.37$] indicated that RTs were significantly shorter for neutral emotional faces (1343.08 ± 57.44) than for happy (1593.43 ± 96.60, $p = 0.001$) and sad (1651.37 ± 79.13, $p < 0.001$) faces, while there was no significant difference

TABLE 3 | Summary of two-way repeated-measure ANOVA for Experiment 1 and Experiment 2.

		ACC			RT			Emotional reactions		
		F	***p***	**η^2**	***F***	***p***	**η^2**	***F***	***p***	**η^2**
Experiment 1	Treatment	**7.91**	**0.009**	**0.21**	31.21	**<0.001**	0.52	0.02	0.879	<0.01
	Emotion	**19.42**	**<0.001**	**0.58**	25.52	**<0.001**	0.65	**123.39**	**<0.001**	**0.90**
	Treatment × Emotion	0.98	0.371	0.03	12.57	**<0.001**	0.30	2.71	0.085	0.09
Experiment 2	Treatment	3.75	0.063	0.12	12.71	0.001	0.31	0.38	0.543	0.01
	Emotion	1.24	0.295	0.04	16.92	**<0.001**	0.37	**57.70**	**<0.001**	**0.81**
	Treatment × Emotion	1.16	0.322	0.04	0.44	0.636	0.02	0.45	0.628	0.02

Statistics were obtained using two-way repeated-measure ANOVAs with within-participant factors of treatment and emotion in both Experiment 1 and Experiment 2. df: (2,28). Significant comparisons ($p < 0.05$) are shown in boldface.

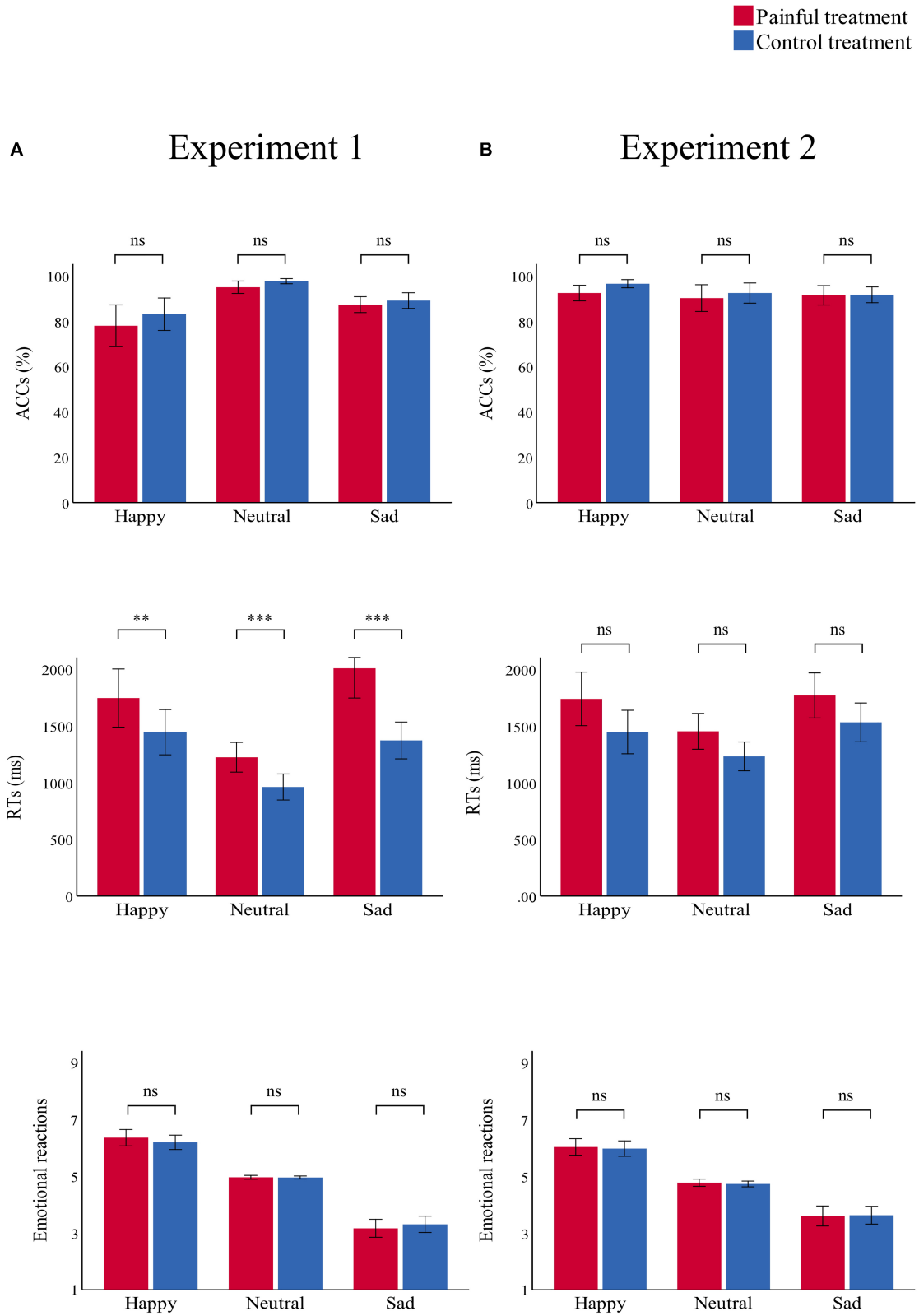

FIGURE 4 | Bar charts representing the results of "treatment" × "emotion" interactions. RTs (top panel), ACCs (middle panel), and emotional reactions (bottom panel) in the painful (red) and control treatment (blue) in **(A)** Experiment 1 and **(B)** Experiment 2. Data are expressed as mean ± SEM. ns: $p > 0.05$; $^{**}p < 0.01$, $^{***}p < 0.001$.

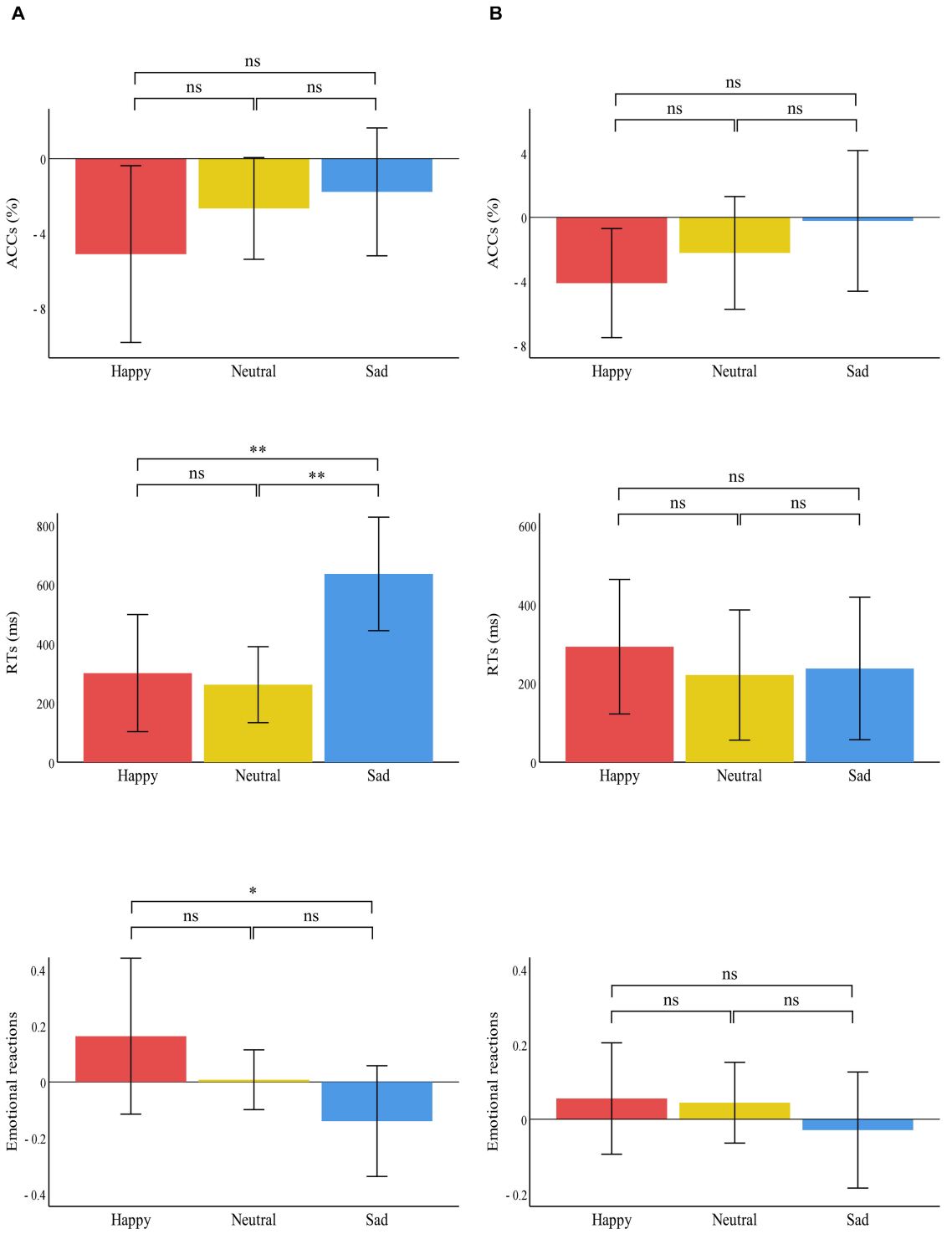

FIGURE 5 | Bar charts representing the results of the one-way ANOVAs of the difference values between the two treatments (painful–control). RTs (top panel), ACCs (middle panel), and emotional reactions (bottom panel) for happy (red), neutral (yellow), and sad (blue) pictures in **(A)** Experiment 1 and **(B)** Experiment 2. Data are expressed as mean ± SEM. ns: $p > 0.05$; $^{*}p < 0.05$, $^{**}p < 0.01$.

between happy and sad emotional faces ($p = 0.263$). There was no significant interaction.

Emotional Reaction

There was a significant main effect of "emotion" [$F(2,28) = 57.70$, $p < 0.001$, $\eta_p^2 = 0.81$], which indicated that emotional reactions to happy emotional faces (6.00 ± 0.13) were more positive than neutral (4.75 ± 0.05, $p < 0.001$) and sad (3.61 ± 0.16, $p < 0.001$) faces, and emotional reactions to neutral faces were more positive than sad faces ($p < 0.001$). No other main effect or interaction was significant.

DISCUSSION

The main goal of this study was to investigate how pain modulates emotional stimuli processing to provide insight into how painful stimuli affect the development of depressive moods. Therefore, we designed two within-subjects experiments using the affective picture paradigm: Experiment 1 tested the effect of pain on responses to emotional scene stimuli, and Experiment 2 tested the same effect using emotional face stimuli. Results of Experiment 1 showed that participants had lower ACCs and longer RTs (especially for sad scenes) for recognizing emotional stimuli in the painful condition, compared to the control condition. In addition, the difference values of RTs between the painful and control conditions for sad scenes were significantly larger than for happy and neutral scenes. In Experiment 2, participants had significantly longer RTs for recognizing emotional face stimuli in the painful condition compared to the control condition.

Pain Modulates Emotional Stimuli Processing

For both ACCs and RTs, we found that in the painful condition relative to the control condition, participants were less accurate at recognizing emotional scene stimuli and had longer reaction times for recognizing both emotional scenes and faces. These results align with previous research that showed a significant main effect of pain on explicit emotional processing (emotional ratings of emotional stimuli; Godinho et al., 2008). Rosselló et al. (2015) found that compared with healthy participants, patients experiencing pain showed lower startle eyeblink reflex and heart rate variability in all emotional environments, whereby painful stimuli significantly inhibited the processing of emotional stimuli. According to the cognitive-affective model of pain (Eccleston and Crombez, 1999) and previous research (Wieser et al., 2012), the interruptive function of intense pain can distract and divert attention from emotional contents (Ochsner and Gross, 2005). During painful conditions, more attentional resources are allocated to the painful stimuli rather than the emotional stimuli (Reicherts et al., 2013), and thus, the attentional effect of pain weakens the processing of emotional stimuli (Wieser et al., 2012). Accordingly, physical pain shifted individuals' attention away from the emotional stimuli and thereby reduced the attentional and cognitive resources to process the emotional stimuli. Individuals took significantly longer to attend to and recognize emotional stimuli when experiencing pain than when they had no pain. These results suggest an altered attentional processing of emotional stimuli due to pain, especially regarding sad scene stimuli.

Pain Modulates Negative Emotional Stimuli Processing

A notable finding was the interaction effect of treatment and emotion observed in Experiment 1, which reflected the larger difference values of RTs for sad scenes between painful and control conditions. These results may suggest attention distraction toward emotional stimuli, especially for sad emotional scenes stimuli when individuals were in pain. The findings support the motivational priming hypothesis (Lang, 1995), as well as partly supporting our own hypothesis. That is, pain can distract people's attention (Eccleston and Crombez, 1999; Wieser et al., 2012), which was shown in our findings as pain having a strong distracting effect on sad scene stimuli in particular. This result was consistent with previous research that indicated that patients experiencing pain had longer RTs (Duschek et al., 2014) and average fixation durations (Franklin et al., 2018) toward negative emotional stimuli compared with pain-free people. This altered attention processing of negative emotional stimuli may be closely related to the development of depression and may be useful in predicting depression (Armstrong and Olatunji, 2012; Ajilchi and Nejati, 2013). Altered attention processing of negative emotional stimuli may play a vital role in the vicious circle between pain and negative emotions (Duschek et al., 2014). Therefore, pain-induced altered attention processing of sad emotional stimuli might contribute to explaining the effect of painful stimuli on the development of depressive moods.

However, pain did not modulate happy emotional stimuli processing in our study. This result corresponds to an earlier finding of Wieser et al. (2012), which indicated no impact of pain on explicit and implicit emotion processing of happy emotional face stimuli. When emotional stimuli were irrelevant to the present painful stimuli, the processing of emotional stimuli may not be disturbed by pain (Wieser et al., 2012). The contents of the happy face and scene pictures we selected were not directly associated with the current pain experience. As a result, individuals did not pay much attention to happy emotional stimuli. Thus, painful stimuli could not significantly modulate individuals' responses to happy emotional stimuli.

The Link Between Pain and Emotional State

Although we observed increased subjective pain intensity in the painful condition, we found that emotional states did not significantly alter with pain. This result suggested that our pain stimuli were not able to induce any negative subjective emotional states during the short duration of the tasks. This outcome is at odds with the pain-depressive mood link, where pain has been shown to significantly augment depressive moods of patients (Hawker et al., 2011; Craig et al., 2013). However, it is possible

that the duration and recurrence of pain may play important roles in this link. Moreover, according to the four stages of the pain processing model (Wade et al., 1996; Price, 1999), pain intensity causes pain unpleasantness, which then evokes pain-related emotions, including negative emotions. The pain intensity reported by our participants was moderate, which may not have been sufficiently intense to alter their emotional states negatively.

Difference Between Responses to Emotional Scenes and Faces

Our results demonstrated different responses to emotional scenes and faces. We found a significant main effect of "treatment" for ACCs for emotional scenes but not for emotional faces. One possible explanation is that emotional stimuli processing was disturbed by pain because of a close association between emotional stimuli and pain experience at the time (Wieser et al., 2012). For example, emotional scenes may have been more relevant than emotional faces to their present pain perception in our study. Moreover, there was a main effect of "emotion" for ACCs for scenes but not for faces. Faces transmit not only emotional information but also social information (Li et al., 2019). From an evolutionary perspective, emotional faces have a survival value in terms of identifying potentially negative information (Straube et al., 2011). In addition, focusing on face stimuli could increase the processing of others' faces (Li et al., 2020), and people tend to rapidly process emotional faces even in the absence of awareness (Kiss and Eimer, 2010). Therefore, relative to emotional scene stimuli, the processing of emotional face stimuli was not susceptible to pain.

Several limitations of this study should be noted. First, participants may have felt nervous due to their unfamiliarity with the experimental procedure, which may have lowered the accuracy for identifying positive emotional stimuli. Second, all the face stimuli were in gray scale, which may have influenced participants' responses to emotional face stimuli. Third, we did not examine gender differences. Given that there are differences between men and women in the accuracy of pain detection (Ruben and Hall, 2013) and physiological reaction to emotional stimuli (Šolcová and Lačev, 2017), it is possible that the effects of pain on emotion processing are different in men and women. Future research should include gender as a between-subject factor in the experimental design. Finally, pain and emotion were induced experimentally, so the degree to which the results can be generalized for real-world situations requires further investigation.

CONCLUSION

In this study, we employed emotional scene and face pictures to examine how pain modulates responses to emotional stimuli. Results illustrated that recognizing emotional scene stimuli took longer in the painful than control condition, especially for negative emotional scenes. This result supported the notion that pain distracts attentional processing of negative emotional stimuli. Our observation of altered attentional processing of negative emotional stimuli during pain provides insight into understanding how painful stimuli affect the development of depressive moods.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://pan.baidu.com/s/1YeVRSS4gFwWrf0LHdLbCGg (code: 2020).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Research Ethics Committee of Chongqing Normal University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WL and JM: concept and design of study. WL and PL: data acquisition, analysis, and interpretation. YH: stimulus materials selection and manuscript revision. WL, PL, and JM: drafting the work or revising it critically for important intellectual content and agreement to be accountable for all aspects of the work in ensuring that questions to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the final the version to be published.

FUNDING

This work was supported by the Youth Foundation of Social Science and Humanity, China Ministry of Education (19YJC190016).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

ORIGINAL RESEARCH
published: 23 December 2020
doi: 10.3389/fpsyg.2020.616723

Prevalence and Associated Factors for Depressive Symptomatology in Chinese Adults During COVID-19 Epidemic

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

Received: 13 October 2020
Accepted: 17 November 2020
Published: 23 December 2020

Citation:
Peng S, Lai X, Du Y, Li Y, Tian K and Gan Y (2020) Prevalence and Associated Factors for Depressive Symptomatology in Chinese Adults During COVID-19 Epidemic. Front. Psychol. 11:616723. doi: 10.3389/fpsyg.2020.616723

Background: The coronavirus disease 2019 (COVID-19) has been rapidly transmitted worldwide, which contributed to various psychological problems (such as fear, depression, and anxiety) among the general population in China. The purpose of this study is to investigate the prevalence and associated factors of depressive symptoms among Chinese adults.

Methods: A cross-sectional study of Chinese adults was conducted during 17–29 February 2020. Symptoms of depression were assessed using the Center for Epidemiologic Studies Depression scale (CES-D).

Results: A total of 3,399 respondents were included in the analysis. It was observed that 14.2% (481/3,399) of the participants were screened positive for depressive symptoms. In a multivariate logistic regression analysis, older age (OR = 0.98; 95% CI, 0.97–0.99), smoking (OR = 1.57; 95% CI, 1.10–2.26), self-rated health (good: OR = 0.49; 95% CI, 0.37–0.66; fairly: OR = 0.60; 95% CI, 0.45–0.80), having greater support scores (OR = 0.95; 95% CI, 0.94–0.96), knowledge about the main symptom of COVID-19 (very clearly: OR = 0.58; 95% CI, 0.42–0.79; relatively clearly: OR = 0.59; 95% CI, 0.44–0.79), and staying in Wuhan within 3 months before the outbreak of epidemic (OR = 1.78; 95% CI, 1.34–2.38) were associated with depressive symptoms.

Conclusion: A considerable proportion of the general population in China had depressive symptoms during the COVID-19 epidemic. Routine screening and targeted interventions for depression are needed among high-risk depressed individuals during the COVID-19 epidemic.

Keywords: epidemic, COVID-19, risk factors, prevalence, depression symptoms

BACKGROUND

The coronavirus disease 2019 (COVID-19) spread rapidly worldwide, causing high morbidity and heavy economic burden (Docherty et al., 2020; Karagiannidis et al., 2020; Onder et al., 2020; Tadesse et al., 2020; Tang et al., 2020; Wu and McGoogan, 2020; Loomba et al., 2021). In December 2019, a pneumonia of unknown cause was detected and became an epidemic in Wuhan, China. On 7 January 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the etiological agent of the epidemic by genome sequencing (Zhu et al., 2020). Because of the quick spreading of the virus in multiple countries, at the meeting of the emergency committee of the World Health Organization (WHO) on 30 January 2020, COVID-19 was declared a Public Health Emergency of International Concern (PHEIC) (World Health Organization, 2020a). Subsequently, WHO formally named COVID-19 on 11 February 2020 (World Health Organization, 2020b). According to the official website of the National Health Commission, on 17 February 2020, a total of 72,436 confirmed cases and 1,868 death cases were identified in China, with a fatality rate of 2.6% (The National Health Commission of China, 2020). The COVID-19 outbreak posed great threat to human life (Wang et al., 2020a). Additionally, findings from previous studies suggested that outbreaks of major communicable diseases, including severe acute respiratory syndrome and Middle East respiratory syndrome, increased the risk of depression in the populations affected (Mak et al., 2009; Keita et al., 2017). Compared with previous epidemics and pandemics, COVID-19 is more contagious and spreads faster (Meo et al., 2020), which may further aggravate the public's depression. Therefore, timely psychological assessment and appropriate intervention to prevent depressive symptom is necessary.

Depression is a common mood disorder characterized by persistently low mood state, affecting 1.4–37.5% of the population (Maske et al., 2016; Rotenstein et al., 2016; Arias-de la Torre et al., 2018). Several studies had shown that depression not only reduces the quality of life of patients but also increases the risk of chronic physical diseases and suicide (Whooley and Wong, 2013; Kozela et al., 2016; Lopez et al., 2018). Recent studies have shown that the prevalence of depressive symptoms in the general population is high during the COVID-19 epidemic, ranging from 3.7 to 68% (Ettman et al., 2020; Goularte et al., 2020; Rodríguez-Rey et al., 2020; Tan et al., 2020; van der Velden et al., 2020). A published meta-analysis study included 14 studies and suggested that 33.7% of the general population had depressive symptoms during the COVID-19 pandemic (Salari et al., 2020). Additionally, several Chinese studies reported the prevalence of depressive symptoms in the general population during the COVID-19 outbreak. For example, a survey study conducted by Shi et al. (2020) with 56,679 Chinese participants reported 27.9% of the general population had depressive symptoms. A previous study from Shenzhen suggested that the prevalence of depressive symptom was 6.2% in the general population quarantined (Peng et al., 2020), performing in subjects with quarantine experience. Another study by Lei et al. (2020) found the prevalence of depression was approximately 14.6%, with mixed samples including people affected and people unaffected. Therefore, the prevalence of depressive symptoms among the general population is still inconsistent, probably due to the different population and sampling issues in these studies, which deserves further study.

In the past decades, risk factors for depressive symptoms have frequently been examined (Hammen, 2018). However, few studies have explored epidemic-related factors causing depressive symptoms. As a newly emerging disease, the public has limited knowledge about main symptoms, latent period, and route of transmission of COVID-19, and the number of confirmed cases varies from region to region, which may influence the degree of depressive symptoms in the general population. Additionally, Wuhan, as the center of the epidemic in China, whether people with a history of exposure to Wuhan before the COVID-19 epidemic outbreak have a higher risk of depression, it is unclear. To better allocate limited medical resources and formulate effective interventions, the prevalence of depressive symptoms and epidemic-related factors that are associated with them during the COVID-19 outbreak need to be determined urgently.

Therefore, we enrolled a large number of participants and investigated sociodemographic information and epidemic-related factors, which would provide a more complete overview of the risk factors of depressive symptoms. This study aimed to investigate the prevalence and identify the associated factors of depressive symptoms among the general public during COVID-19 epidemic.

MATERIALS AND METHODS

Study Design and Participants

We conducted a cross-sectional online survey to assess the prevalence and risk factors of depressive symptoms among the general population in China during the COVID-19 epidemic. An online survey was used because of the self-isolation of the general population in China. We adopted snowball sampling strategy to recruit participators; potential participators were electronically invited via WeChat. The recruitment information of the study was posted on the university website. Data collection was completed during 17–29 February 2020 period. This survey period corresponded to the reduction stage after the peak point of the COVID-19 epidemic outbreak in the country.

The present study was approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology. Informed consent was obtained from the participants before their participation in the study.

Data Collection

A self-administered questionnaire was used to collect data on sociodemographic characteristics, knowledge about COVID-19, information regarding depressive symptoms and social support, and additional information related to COVID-19. Sociodemographic data included age (continuous variable, ranged from 18 to 99), gender (dummy coded, 0 = female,

1 = male), nationality (dummy coded, 0 = Han, 1 = Other), marital status (dummy coded, 0 = unmarried, 1 = married), employment status (dummy coded, 0 = unemployed, 1 = employed), education (dummy coded, 0 = high school and below, 1 = college, 2 = bachelor or above), type of residence (dummy coded, 0 = urban, 1 = rural, 2 = urban-rural district), smoking (dummy coded, 0 = non-smoker, 1 = smoker) and drinking status (dummy coded, 0 = non-drinking, 1 = drinking), and history of chronic diseases (dummy coded, 0 = no, 1 = yes). Respondents were asked to rate their physical health status (dummy coded, 0 = average/poor, 1 = fairly good, 2 = very good). Knowledge about COVID-19 included the main symptom, latent period, and routes of transmission of COVID-19 (dummy coded, 0 = general, 1 = relatively clear, 2 = very clear). Additionally, respondents were asked to answer if they stayed in Wuhan within 3 months before the epidemic outbreak or had any relatives or friends who were infected with COVID-19 (dummy coded, 0 = no, 1 = yes). Depressive symptoms and social support were assessed by the Center for Epidemiologic Studies Depression scale (CES-D) and Perceived Social Support Scale (PSSS), respectively.

Social Support

The PSSS was designed by Zimet et al. (1990). The scale has 12 items including three dimensions, namely, family support, friend support, and other support. It is scored on a 7-point Likert-type scale, with higher scores indicating higher perception of social support. The Chinese version of PSSS has been proven to be highly reliable and valid among the Chinese population (Ye et al., 2017). Here, the Cronbach's alpha value was 0.96.

Depression Symptoms

The CES-D was used to assess depressive symptoms. It comprises 20 items; each item is rated on a 4-point scale ranging from 0 ("rarely or none of the time") to 3 ("most or almost all of the time"). The total score ranges from 0 to 60, with a higher score indicating more severe depressive symptoms. For the original CES-D scale, a total score of 16 is used to detect the presence of depressive symptoms (Radloff, 1977). However, a large number of studies have assessed the diagnostic accuracy of the CES-D to detect depression in the general population and proposed a variety of cut-off scores, such as a cut-off score of 18 among elders living in residential homes (Dozeman et al., 2011) and a cut-off score of 22 in older Chinese (Cheng and Chan, 2005). A meta-analytic study systematically reviewed 28 CES-D studies including several Chinese studies and proposed an optimal cut-off score of 20 (Vilagut et al., 2016). Hence, a cut-off value of 20 or a greater total score was considered indicative of depressive symptoms, consistent with the previous research (Jiang et al., 2019). This Chinese version of the CES-D has good reliability and validity and has been widely adopted in the Chinese population. In the present study, the Cronbach's alpha coefficient for this scale was 0.96.

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation (SD) and compared using Student's *t*-tests. Categorical data were presented as percentages and compared using Chi-square tests. A multivariable logistical regression model was used to identify the risk factors for depression. Statistical significance was assessed at 5% level (two-tailed test). All analyses were performed using SPSS software version 18.0 (SPSS, Chicago, IL, United States).

RESULTS

Characteristics of Study Population

A total of 3,405 completed questionnaires were received, and six respondents who lived abroad were excluded from this study. Finally, 3,399 respondents were included in the analysis. The 3,399 respondents from 280 cities in China had an average age of 27.5 years (range, 18–80) with standard deviation of 11.4 years; 95.5% of them were of Han nationality, and 66.5% were female.

Based on the presence of depressive symptoms, all participants were categorized into two groups: the depression and non-depression groups; 14.2% (481/3,399) of the participants were screened positive for depressive symptoms in the present study and included in the depression group. **Table 1** compares the sociodemographic and behavior characteristics of participants with and without depressive symptoms. Participants in the depression group were more likely to have a younger age, lower medical insurance coverage, worse self-rated health,

TABLE 1 | Demographic and behavior characteristics of participants with or without depressive symptoms.

Characteristics	Depression (*n* = 481)	Non-depression (*n* = 2,918)	t/x^2	*P*-value
Age (years, mean ± *SD*)	26.3 ± 12.5	27.8 ± 11.2	2.42	0.016
Female (%)	299 (62.1)	1, 962 (67.2)	4.78	0.029
Han nationality	455 (94.6)	2, 794 (95.8)	1.31	0.253
Married	121 (25.2)	985 (33.8)	13.91	0.000
Educational level (years)			0.47	0.790
High school and below	55 (11.4)	331 (11.3)		
College	65 (13.5)	429 (14.7)		
Bachelor or above	361 (75.1)	2, 158 (74.0)		
Type of residence			0.05	0.975
Urban	282 (58.6)	1, 695 (58.1)		
Rural	154 (32.0)	946 (32.4)		
Urban–rural district	45 (9.4)	277 (9.5)		
Employed	163 (33.9)	1, 167 (40.0)	6.46	0.011
Smoker (%)	51 (10.6)	226 (7.7)	4.51	0.034
Alcohol (%)	72 (15.0)	398 (13.6)	0.61	0.434
Chronic disease	49 (10.2)	240 (8.2)	2.04	0.153
Medical insurance coverage	398 (82.7)	2, 544 (87.2)	6.99	0.008
Self-rated health			57.09	0.000
Very good	194 (40.3)	1, 527 (52.3)		
Quite good	170 (35.3)	1, 040 (35.6)		
Average	117 (24.3)	351 (12.0)		
Support scores	57.8 ± 13.8	67.4 ± 11.6	14.34	0.000

SD, standard deviation.

and lower support scores compared with those in the non-depression group. In contrast, participants in the non-depression group were likely to be married and employed, female, and non-smoker. However, there was no significant difference in nationality, education, types of residence, alcohol use, and history of chronic disease between the depression and non-depression groups.

Comparison of Concerns and Knowledge About COVID-19 Among Depression and Non-depression Groups

Regarding concerns and knowledge about COVID-19, **Table 2** shows that participants in the depression group reported a higher exposure of staying in Wuhan within 3 months before the epidemic outbreak compared with those in the non-depression group. Additionally, participants in the depression group were less knowledgeable about the main symptoms, latent period, and routes of transmission of COVID-19 than those in the non-depression group.

Multivariate Regression Analysis in Identifying Risk Factors of Depression

This study used multivariate logistical regression analysis to identify risk factors of depressive symptoms. Variables with statistical significance in univariate analysis, including age, gender, marital status, employment status, smoking status, medical insurance coverage, self-rated health, support scores, staying in Wuhan within 3 months before the epidemic outbreak, and knowledge about the main symptoms, latent period, and routes of transmission of COVID-19, were included in the logistical regression model. Results showed that older age (OR = 0.98; 95% CI, 0.97–0.99; $P = 0.000$), very good self-rated health (OR = 0.49; 95% CI, 0.37–0.66; $P = 0.000$), fairly good self-rated health (OR = 0.60; 95% CI, 0.45–0.80; $P = 0.001$), greater support scores (OR = 0.95; 95% CI, 0.94–0.96; $P = 0.000$), very clear knowledge about the main symptoms of COVID-19 (OR = 0.58; 95% CI, 0.42–0.79; $P = 0.001$), and relatively clear knowledge about the main symptoms of COVID-19 (OR = 0.59; 95% CI, 0.44–0.79; $P = 0.000$) were associated with a decreased risk of depressive symptoms. However, smoking (OR = 1.57; 95% CI, 1.10–2.26; $P = 0.014$) and staying in Wuhan within 3 months before the epidemic outbreak (OR = 1.78; 95% CI, 1.34–2.38; $P = 0.000$) were associated with an increased risk of depressive symptoms (**Table 3**).

TABLE 2 | Comparison of concerns and knowledge's of COVID-19 between people with or without depressive symptoms.

Characteristics	Depression (n = 481)	Non-depression (n = 2,918)	x^2	P-value
Local cases			2.14	0.544
< 500	100 (20.8)	542 (18.6)		
500–1,000	271 (56.3)	1,743 (59.7)		
1,000–10,000	53 (11.0)	304 (10.4)		
> 10,000	57 (11.9)	329 (11.3)		
Staying in Wuhan during 3 months before the outbreak of epidemic?			6.74	0.009
Yes	76 (15.8)	339 (11.6)		
No	405 (84.2)	2,579 (88.4)		
Whether you or your relatives are confirmed by COVID-19?			2.13	0.144
Yes	5 (1.0)	12 (0.4)		
No	476 (99.0)	2,906 (99.6)		
Do you know the main symptom of COVID-19?			57.72	0.000
Very clear	134 (27.9)	1,098 (37.6)		
Relatively clear	245 (50.9)	1,533 (52.5)		
General	102 (21.2)	287 (9.8)		
Do you know the latent period of COVID-19?			37.77	0.000
Very clear	185 (38.5)	1,446 (49.6)		
Relatively clear	229 (47.6)	1,270 (43.5)		
General	367 (13.9)	202 (6.9)		
Do you know the routes of transmission of COVID-19?			44.58	0.000
Very clear	181 (37.6)	1,396 (47.8)		
Relatively clear	234 (48.6)	1,347 (46.2)		
General	66 (13.7)	175 (6.0)		

COVID-19, 2019 coronavirus disease.

DISCUSSION

This cross-sectional study, based on 3,399 participants assessed the prevalence and risk factors of depressive symptoms among the Chinese general population during the COVID-19 epidemic. We found that 14.2% of the general population suffered from depressive symptoms during the COVID-19 epidemic. Furthermore, some demographic and concerns as well as knowledge about COVID-19 variables were found to be the influencing factors for depressive symptoms, including age, smoking status, self-rated health, social support, knowledge about the main symptoms of COVID-19, and staying in Wuhan within 3 months before the outbreak.

The prevalence of depressive symptoms among the general population in China during the COVID-19 epidemic in the present study is similar to that in recent published studies. The study by Wang et al. (2020b) with 1,210 respondents from 194 cities in China reported that 16.5% of the general population had moderate to severe depressive symptoms. Lei et al. (2020) reported that the prevalence of depressive symptoms in the public affected and those unaffected was 14.6% during the COVID-19 epidemic. However, a high prevalence of depressive symptoms among general population was observed in other countries, such as 16.9% in Netherlands (van der Velden et al., 2020), 27.8% in America (Ettman et al., 2020), 68% in Brazil (Goularte et al., 2020), and 41% in Spain (Rodríguez-Rey et al., 2020). This discrepancy in terms of prevalence of depression may be explained, to some extent, by differences in diagnostic criteria, severity of the epidemic, and intervention measures taken. The Chinese government had taken several measures to control and reduce COVID-19 transmission, such as city closure, traffic control, isolation at home, and wearing of masks. Majority of the Chinese general population considered that these measures were effective and believed that they would win the battle against COVID-19.

TABLE 3 | Multivariable logistic analyses for factors related to depressive symptoms.

	Coefficients B	SE	Wald	*P*-value	OR	95% confidence interval for OR	
						Lower	Upper
Age	−0.019	0.005	14.702	0.000	0.981	0.972	0.991
Smoking	0.454	0.184	6.078	0.014	1.574	1.097	2.258
Self-rated health			23.296	0.000			
Very good	−0.7	0.145	23.171	0.000	0.497	0.373	0.660
Fairly good	−0.511	0.147	12.039	0.001	0.600	0.450	0.801
Average/poor					Reference		
Support scores	−0.055	0.004	169.889	0.000	0.947	0.939	0.955
Do you know the main symptom of COVID-19?			14.583	0.001			
Very clear	−0.551	0.162	11.528	0.001	0.577	0.42	0.792
Relatively clear	−0.525	0.146	12.96	0.000	0.591	0.444	0.787
General					Reference		
Staying in Wuhan	0.578	0.147	15.382	0.000	1.783	1.335	2.38
(Constant)	2.98	0.309	93.239	0	19.698		

COVID-19, 2019 coronavirus disease; OR, odds ratio; CI, confidence interval.
Included variables: age, gender, married status, employment status, smoking status, medical insurance coverage, self-rated health, social support, staying in Wuhan within 3 months before the outbreak of epidemic, knowledge's about the main symptoms, latent period, routes of transmission of COVID-19.

Our study found that younger individuals are more likely to have depressive symptoms compared with older individuals; similar results can be seen in the study of Huang and Zhao (2020), which concluded that younger people had a significantly higher prevalence of depressive symptoms than older people. However, most cross-sectional studies showed that higher age was associated with a higher risk of depressive symptoms in a non-disaster situation (Liu et al., 2015; Zhang et al., 2019). This discrepancy could be due to adaptive mechanisms, older people developed this ability to dealing with crises, which can be used to manage the stress associated with the current pandemic (Goularte et al., 2020). Additionally, young people tend to quickly obtain COVID-19 information from social media, which can easily trigger stress (Qiu et al., 2020).

The present study also showed that a higher prevalence of depressive symptoms was observed among individuals with a smoking habit, poor self-rated health, and low social support, which is consistent with most published studies (Pasco et al., 2008; Hu et al., 2018). Interestingly, depressive symptoms and the risk factors mentioned above had a bidirectional correlation. A 10 years study by Naicker et al. (2013) reported that depressed adolescents had higher proportion of smoking habit, poorer self-rated health, and lower social support compared with non-depressed adolescents 10 years later. Similarly, smoking habit, poor self-rated health, and low social support could increase the risk of depressive symptoms (Rousou et al., 2016; Holden et al., 2019).

Our study showed that individuals with an unclear understanding of the main symptoms of COVID-19 were more likely to report depressive symptoms, which is similar to the study of Wang et al. (2020b). The possible explanation for this phenomenon is that a more comprehensive understanding of the related knowledge about COVID-19 will help individuals face the epidemic rationally and judge effectively whether one is infected or not. Additionally, with a higher cognitive level regarding COVID-19, individuals would have more confidence and motivation to adopt effective measures to protect themselves. Therefore, improving public awareness of COVID-19 is necessary to improve mental health.

Our study suggested that staying in Wuhan within 3 months before the COVID-19 outbreak was associated with a higher risk of depressive symptoms. Lai et al. (2020) investigated 1,257 medical staff from fever clinics or wards of hospitals for patients with COVID-19 in China and reported that health-care workers in Wuhan had severe symptoms of depression, anxiety, insomnia, and distress. Wuhan is the origin and epicenter of the COVID-19 epidemic in China. Nearly 60% of the cases occurred in China, and a fatality rate of 5% was reported in Wuhan (Wu et al., 2020). Therefore, individuals with exposure in Wuhan before the COVID-19 outbreak were at an especially high risk for infection, which further increased the level of negative emotion, such as depression, anxiety, stress, and fear.

In this study, no significant correlation was observed between the number of local confirmed cases, COVID-19 infection status, COVID-19 latent period, route of transmission, and depressive symptoms. However, related studies have found that these factors may also affect the occurrence of depressive symptoms (Nelson et al., 2020; Zhang et al., 2020). This difference may be related to the study population and sampling methods. With the wide dissemination of information in China, the difference in the prevalence of depressive symptoms between severe and mild areas of the epidemic may have been weakened. Additionally, only 17 people reported that they or their relatives had COVID-19 infection in this study, which may affect the reliability of the results. Therefore, it is necessary to explore this correlation in a large sample population.

This study had multiple strengths. Firstly, the study included a large number of subjects, which made it possible to obtain more convincing results. Secondly, this study explored the

association between factors connecting COVID-19 epidemic to depressive symptoms.

However, there were limitations too. First, we adopted a snowball sampling strategy. The snowball sampling selects potential respondents based on existing respondents, which is not a random sampling method. The recruitment information of study was posted on the university website, resulting in most of the respondents coming from young students. Therefore, there was bias in the selection of participants in our study and the study's sample population may not be a good representation of the actual pattern of the general population. Second, our study was cross-sectional; we could not infer causal relationship of risk factors and symptoms of depression. Therefore, a cohort study is needed to certify this temporal relationship. Third, the CES-D is just a screening tool and not a diagnostic one, although it has been widely used and validated in China. Fourth, this study adopted a self-administered online questionnaire, thus participants need to be able to use network tools, which might have affected how they responded to the questionnaire. However, given the COVID-19 epidemic, an online survey was considered more appropriate.

CONCLUSION

This study indicates that during the COVID-19 epidemic in China, a considerable proportion of the general population suffered from depressive symptoms. Those with younger age, a smoking habit, poorer self-rated health, and lower social support had a higher risk of depressive symptoms. Moreover, depressive symptoms were found to be significantly associated with knowledge about the main symptoms of COVID-19 and staying in Wuhan within 3 months before the COVID-19 outbreak. Given our findings, we recommend the establishment of targeted psychological interventions for the public to improve their mental health during the COVID-19 epidemic.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Tongji Medical College, Huazhong University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SP participated all preparation of this manuscript. XL contributed to statistical analysis. YD and YL took part in the sample collection. KT and YG contributed to study design and the critical revision of the article. All authors reviewed the manuscript, approved the final draft, and contributed significantly to this work.

FUNDING

This study was approved by the Guizhou Province Science and Technology Support Project [(2020)4Y165].

ACKNOWLEDGMENTS

We are particularly grateful to the participators who agreed to participate in our study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychology

ORIGINAL RESEARCH
published: 29 April 2021
doi: 10.3389/fpsyg.2021.658974

Does the Rural Environment Influence Symptomatology and Optimize the Effectiveness of Disease Acceptance? A Study Among Women With Fibromyalgia

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OPEN ACCESS

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Specialty section:
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

Received: *26 January 2021*
Accepted: *07 April 2021*
Published: *29 April 2021*

Citation:
Catalá P, Blanco S, Perez-Calvo S, Luque-Reca O, Bedmar D and Peñacoba C (2021) Does the Rural Environment Influence Symptomatology and Optimize the Effectiveness of Disease Acceptance? A Study Among Women With Fibromyalgia. Front. Psychol. 12:658974. doi: 10.3389/fpsyg.2021.658974

The present study aims to explore whether the symptoms associated with fibromyalgia are contextually influenced by the area of residence (rural/urban). Furthermore, it is analyzed whether the effect of the acceptance of the disease on the emotional, cognitive and physical symptoms is moderated by the patients' place of residence. Using a cross-sectional design, a total of 234 women with fibromyalgia (mean age = 56.91 years; SD = 8.94) were surveyed, of which 55.13% resided in rural areas and 44.87% in urban areas. Self-reported questionnaires were used to assess pain severity, anxiety and depression, functional limitation, physical and mental fatigue and acceptance of the disease. The results show significant differences in acceptance ($p = 0.040$), pain ($p < 0.001$), and physical and mental fatigue ($p = 0.003$ and $p = 0.004$, respectively) between patients from rural and urban areas. The rural area patients presented higher levels of acceptance and pain and lesser levels of physical and mental fatigue compared to the urban area. The moderation analysis add that, only in patients from the rural area, the variables of physical symptoms (pain, functional limitation, and physical fatigue) were significantly and negatively associated with acceptance. This study addresses for the first time the role of the place of residence in suffering from fibromyalgia, suggesting that the rural or urban environment plays a relevant role in the severity and/or management of symptoms in fibromyalgia women. Limitations and practical implications are also discussed.

Keywords: rural/urban health, fibromyalgia symptoms, women, pain, disease acceptance

INTRODUCTION

Fibromyalgia (FM) is considered a chronic disease characterized not only by chronic widespread pain but also by other symptoms such as fatigue, sleep problems, anxiety, or depression. Fibromyalgia causes a negative impact on the quality of life of patients (Campos and Vázquez, 2012; Arnold et al., 2016) and has been linked to substantial impairments in both physical and mental health and functionality (Wolfe et al., 2014; Walitt et al., 2015).

From the recognition of FM as a disease to the present, the scientific community has tried to identify which biopsychosocial factors are involved in its appearance, maintenance and severity (Fitzcharles et al., 2014; Häuser et al., 2015). It is known that, in FM patients, well-being and adaptation to the disease are related to affective, cognitive and behavioral variables (Thompson and McCracken, 2011). For example, fear related to pain, impotence, or passive coping strategies such as avoidance, increase pain levels and decreases functionality (Mayangsari et al., 2019; Higuchi, 2020). Instead, active coping strategies (e.g., mindfulness), self-efficacy, willingness to change or acceptance of illness have been shown to reduce psychological distress, pain, or functional limitation (Dorado et al., 2018; Van Liew et al., 2019). Specifically, acceptance, understood from the model of psychological flexibility integrated into acceptance and commitment therapy (ACT) (Hayes et al., 2016), refers to the ability to learn to live with discomfort without the need to reduce, avoid or try to change it (McCracken and Velleman, 2010). Studies with mixed samples of patients with chronic pain show that higher levels of acceptance are associated with better daily functioning and less disability and symptoms (Kratz et al., 2007). In patients with fibromyalgia specifically, the previous literature is consistent with the positive role of acceptance in the suffering (Tangen et al., 2020). In this vein, it seems that accepting the disease reduces the levels of anxiety, depression and pain and improves the functioning of these women (Rodero et al., 2011; Yu et al., 2017; Lami et al., 2018; Trainor et al., 2019).

The literature also suggests that the relationship established between psychological factors and health outcomes is not always linear, but depends, to a large extent, on the context (Suso-Ribera et al., 2017). As suggested by the environmental competence model (Lawton, 1986; Moore et al., 2003), the environment-person relationship is determined by the relationship between the level of personal competence and environmental demand. While the level of personal competence depends on health, sensory capacity, motor performance, and cognitive abilities, environmental demand is determined by actual and perceived physical characteristics (Lawton, 1977; Rousseau et al., 2002). From this model, it is hypothesized that the lower the level of competence, the greater the influence of contextual factors on well-being. Therefore, the physical environment (i.e., residence area) would have a special influence on people with a worse state of physical or mental health. Specifically, Lawton's Competence and Environmental model (Lawton, 1986) has been used as a conceptual framework especially in relocation and gerontology (Perry et al., 2014). As an example, this model has proven useful to explain the relationship between person-environment fit and apathy (Jao et al., 2020) and well-being (Calkins, 2018) in long-term care residents with dementia, and for the ability to comply with a medication regimen in elderly persons (LeRoux and Fisher, 2006). Recent literature confirms the differential role of the environment in patients with multiple chronic conditions. In general terms, it seems that rural patients have a worse physical and mental health status compared to urban participants (Wang et al., 2015; Cheng et al., 2020). To our knowledge, the Lawton's Competence and Environmental model (Lawton, 1986) has not been used in patients with fibromyalgia.

Given the increasing prevalence of FM, both in rural (between 0.1 and 5.2%) and urban (between 0.7 and 11.4%) populations (Marques et al., 2017), the first aim of the present study has been to explore whether the symptoms associated with this syndrome (i.e., pain, anxiety, depression, functional limitations, and physical and mental fatigue) are contextually influenced by the area of residence (rural/urban). Furthermore, as a secondary objective, it is analyzed whether the effect of the acceptance of the disease on emotional, cognitive, and physical symptoms is moderated by the residence area of these patients.

MATERIALS AND METHODS

Study Design

The study design was a cross-sectional cohort. The Ethics Committee of the Rey Juan Carlos University approved the study protocol and evaluation procedures (Reference PI17/00858; number 160520165916). In this study, the Strengthening of the Notification of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies was followed and applied (Von Elm et al., 2008).

Participants

Two hundred thirty-four women with FM were recruited with a mean age of 56.91 years (SD = 8.94). Of these, 129 participants (55.13%) reside in rural areas and 105 (44.87%) reside in urban areas. Six percent of the women had completed higher education studies, 29% completed secondary studies and 65% primary studies. Fifty-three percent of the women were married or in a stable relationship, 11% were single, and 36% of them were divorced or widowed. The vast majority of the participants were housewives (78%). Participants had a diagnosis of FM for an average of 12.14 years (SD = 8.45; range 1 to 46 years). The mean intensity of perceived pain was 7.28 (SD = 1.74, range 0–10).

Eligibility Criteria

Only female adults were included in this study (for homogeneity purposes because almost all FM patients are females). The eligibility criteria to participate in the present study included having a diagnosis of FM according to the American College of Rheumatology (ACR) criteria (Wolfe et al., 1990, 2010), being over 18 years of age, and providing a written consent to participate in the investigation. In addition, as exclusion criteria, not having the physical and mental ability to provide informed consent and to complete the surveys was included.

Procedure

A convenience sample was selected by contacting several patient associations from different Spanish regions during the years 2018 and 2019. In total, 268 participants agreed to participate in the study and met our initial inclusion criteria. Finally, effective responses were obtained from 234 patients (25 patients did not attend the scheduled evaluation appointment, 6 questionnaires were left blank, and 3 questionnaires contained a large amount of missing data that could not be retrieved because the data could no longer be reached participants). The initial sample size

was calculated based on recommendations for similar studies (Westland, 2010). The 234 participants were classified according to the place of residence (rural area/urban area), based on the Publication of Urban Areas in Spain 2019, published by the Ministry of Transport, Mobility and Urban Agenda, DG of Housing and Floor (Ministerio de Transportes, Movilidad y Agenda Urbana and Direccion General de Vivienda y Suelo, 2020). Once the participants gave their informed consent to participate in the study, they were given a questionnaire booklet that took approximately 30 min to complete. The questionnaires were completed in the associations of the different regions evaluated, they were carried out individually and with the supervision of a professional psychologist (in groups of between eight and ten patients).

Measures

Pain

To assess pain intensity, the mean score of the four pain intensity items from the Brief Pain Inventory (BPI) was used (Cleeland and Ryan, 1994): maximum, minimum, and overall pain intensity during the last 7 days and pain intensity at the current time. Each rating is evaluated using an 11-point numerical scale (0 = "no pain" and 10 = "the worst pain you can imagine"). This procedure to measure pain severity has been widely used in the pain literature (Jensen et al., 1996). In this study, the internal consistency of this scale was high (0.86).

Anxious and Depressive Symptoms

The Spanish version of the Hospital Anxiety and Depression Scale (HADS) was used to measure the presence and severity of symptoms of anxiety and depression (Herrero et al., 2003). The HADS is a 14-item questionnaire that comprises two subscales: the HADS-A (7 items) that measures anxiety and the HADS-D (7 items) that measures depression. Participants were asked to rate the degree to which they experienced various emotions in the past week. The scale is composed of items such as "I feel tense or nervous" for anxiety or "I have lost interest in my appearance" for depression. All items were scored on a 4-point Likert scale (0–3). Scale scores were calculated by summing the scores on the individual items of a subscale. Scale score range from 0 to 21 with higher scores indicating more symptoms. This questionnaire has shown good psychometry properties (Herrero et al., 2003). Cronbach's α coefficients for HADS-A and HADS-D in this study were 0.87 and 0.85, respectively.

Functional Limitation

The dimension of "physical function or functional limitation" of the Spanish adaptation of the Revised Fibromyalgia Impact Questionnaire (FIQ-R) was used for this study (Salgueiro et al., 2013). The FIQ-R questionnaire consists of 21 items with a Likert response format of 11 points (from 0 to 10) that assesses three associated domains: physical function, general impact and symptoms. The physical function (used in this study) is the sum of the first 9 items divided by 3, and can take a value between 0 and 30. It evaluates the degree to which they were experienced difficulties when carrying out a series of basic physical activities of daily life (for example, "shopping" or "climbing stairs"). Higher scores indicate less functionality. Cronbach's alpha in the present study was 0.88. The sub-scale has obtained good reliability and validity indices in the past (Ciapetti et al., 2013).

Physical and Mental Fatigue

For this study, the dimensions of physical and mental fatigue were selected from the Spanish version of the Multidimensional Fatigue Inventory (MFI) (Munguía-Izquierdo et al., 2012). This questionnaire is a 20-item assessment tool with a 5-point Likert (1–5) response scale. It evaluates five domains of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. Each dimension consists of four elements and the score for each one of them ranges from 4 to 20 points. Higher scores indicate a high degree of fatigue symptoms. The physical fatigue subscale contains items such as "Physically, I feel like I can only do a little bit" and the mental fatigue subscale contains items such as "I can concentrate well". The selection of these two dimensions was motivated by their conceptualization of fatigue as a physical and mental symptom, according to the previous literature on the relationship between both physical and mental fatigue and acceptance (Brooks et al., 2011). In the present study, the internal consistency of physical fatigue was 0.68 and of mental fatigue was 0.73.

Acceptance

For this study, the subscale of "commitment to activity" of the Spanish version of the Chronic Pain Acceptance Questionnaire (CPAQ) was selected (McCracken et al., 2004). The CPAQ is a 20-item self-report questionnaire that assesses the acceptance of chronic pain. The questionnaire is made up of two subscales, the pain disposition subscale (11 items) and the activity commitment subscale (9 items). The last, used for this study, contains items such as "Although things have changed, I am living a normal life despite my chronic pain." All items are rated on a scale from 0 (never true) to 6 (always true). This measure provides total scores ranging from 0 to 54; higher results mean high pain acceptance. Cronbach's alpha for this study of the commitment to activity subscale was 0.76. The validity and reliability of this instrument has been demonstrated in the past (Rodero et al., 2010).

Sociodemographic and Clinical Data

An *ad hoc* questionnaire was used to evaluate age, place of residence, educational level, employment status, and marital status. Regarding clinical variables, duration of FM was recorded.

Statistical Analysis

For data analysis, SPSS version 22.0 statistical program was used (IBM Corp, 2013). The comparisons between the rural area and urban area groups in the sociodemographic variables were made using the *t*-test and the Chi-square test for continuous and categorical variables, respectively. For the analysis of differences between the rural and urban groups in the symptoms of the disease controlling for age, a one-way multivariate analysis of covariance (MANCOVA) was conducted. Effect size differences were assessed using η_p^2 (η_p^2 = 0.01 small effect, η_p^2 = 0.06 medium effect, and $\eta_p^2 > 0.13$ large effect) (Cohen, 1988).

Next, a series of multivariate regressions were computed with model 1 of the PROCESS macro (Hayes, 2017). Bootstrap-based bias-corrected confidence intervals (95%) were generated for indirect effects using 5000 iterations of bootstrap. In each regression, a combination of the independent variable (i.e., acceptance), the moderator (i.e., rural and urban area), and their interaction, controlling for the sociodemographic variables, were entered to predict the study outcome (i.e., pain, anxiety, depression, physical and mental fatigue, and functional limitation). *Post hoc* analyses were then computed when a significant moderation was found. This was done to obtain the conditional effects of the independent variables on outcomes at different levels of the moderator and to graphically represent the moderation findings.

RESULTS

Differences in Sociodemographic Variables Between the Rural Area and the Urban Area Group

Table 1 shows the significant differences in the sociodemographic variables between the patients from rural and urban areas. Specifically, the findings show significant differences in age (t = 4.20, p < 0.001), educational level (Chi-square p-value < 0.001), employment status (Chi-square p-value < 0.001) and marital status (Chi-square p-value = 0.014). Specifically, patients from rural areas are older and have a lower educational level; furthermore, they are mostly housewives and are married.

TABLE 1 | Differences in sociodemographic variables between the rural area and the urban area group.

	Rural areas (n = 129)	Urban areas (n = 105)	p^a
Age, mean (SD)	59.04 (SD = 9.32)	54.19 (SD = 7.65)	<0.001
Educational level, n (%)			<0.001
Primary education	101 (78.29)	51 (48.57)	
Secondary education	25 (19.38)	42 (40)	
University education	3 (2.33)	12 (11.43)	
Employment status, n (%)			<0.001
Working	7 (5.42)	21 (20)	
Sick leave	6 (4.65)	17 (16.19)	
Domestic work	116 (89.93)	67 (63.81)	
Takes care of work at home, n (%)			
Yes	115 (89.14)	98 (93.33)	0.146
No	14 (10.86)	7 (6.67)	
Marital status, n (%)			
Married or in a stable relationship	108 (83.72)	74 (70.48)	0.014
Single	5 (3.88)	9 (8.57)	
Divorced or widowed	16 (12.40)	22 (20.95)	

[a]p-values of the t-test or the Chi-square test for quantitative and categorical variables, respectively.

Differences in Acceptance Between the Rural Area and the Urban Area Group

The results show significant differences in acceptance regarding the area of residence (F = 5.13, p = 0.007, η_p^2 = 0.05), obtaining the rural area (mean = 32.66, SD = 11.23) higher levels of acceptance with respect to the urban area (mean = 29.40, SD = 12.31).

Differences in Disease Symptoms Variables Between the Rural Area and the Urban Area Group

As shown in **Table 2**, rural patients obtained significantly higher scores in pain (p < 0.001) and lower in physical fatigue (p = 0.008) and mental fatigue (p = 0.008). Pain has the highest effect size (medium effect). No statistically significant differences were observed in the rest of the symptoms considered.

Multivariate Linear Regression and Moderation Analysis

Table 3 shows the results of the regression analysis, including moderations, controlling for the sociodemographic variables (i.e., age, educational level, employment status, and marital status). Analysis revealed a direct (negative) effect of acceptance on anxiety (p = 0.008), depression (p = 0.018) and mental fatigue (p < 0.001). No direct effects of acceptance were observed on pain, functional limitation and physical fatigue (all p's > 0.05). That is, once the sociodemographic variables have been controlled, acceptance is negatively related to anxiety, depression, and mental fatigue, regardless of the place of residence (rural/urban).

Regarding the moderation analyzes, the results revealed that the residence area moderated the relationship between acceptance and pain (p = 0.016), acceptance and functional limitation (p = 0.029), as well as between acceptance and physical fatigue (p = 0.042). The relationship between acceptance and anxiety, depression and mental fatigue was not moderated by area of residence (all p's > 0.05). That is, once the sociodemographic variables have been controlled, the relationship between acceptance and pain, functional limitation, and physical fatigue depends on the area of residence.

The evaluated models predicted a significant variance of 9% for pain, 5% for functional limitation and 14% for physical fatigue (all p's < 0.01).

TABLE 2 | Differences in symptoms between patients from rural and urban areas.

	Rural areas (n = 129) Mean (SD)	Urban areas (n = 105) Mean (SD)	F	p	η_p^2
Pain	7.48 (1.52)	6.75 (1.42)	13.76	<0.001	0.06
Anxiety	12.38 (3.95)	12.00 (3.76)	0.56	0.455	0.01
Depression	9.07 (4.23)	9.49 (4.35)	0.53	0.467	0.01
Functional limitation	21.31 (5.79)	21.64 (5.79)	0.47	0.486	0.01
Physical fatigue	14.59 (3.46)	15.93 (3.16)	8.99	0.003	0.04
Mental fatigue	14.69 (3.08)	15.89 (3.13)	8.39	0.004	0.04

Post hoc analysis were planned to analyze significant moderations in greater depth and are presented in **Table 4** and **Figure 1** for acceptance on pain, in **Table 4** and **Figure 2** for acceptance on functional limitation and in **Table 4** and **Figure 3** for the acceptance of physical fatigue. Specifically, as indicated in these tables and figures, in rural patients a significant negative relationship is observed between acceptance and pain, functional limitation, and physical fatigue. That is to say, in rural patients, the greater the acceptance, the less the pain, the functional limitation and the physical fatigue. However, in urban patients there is no association between these variables.

DISCUSSION

The present study provides the first exploration of contextual influences (rural/urban environment) on health symptoms and disease acceptance in FM patients. Specifically, it was found that patients residing in rural settings reported significantly higher levels of pain and lower levels of physical and mental fatigue than those residing in urban areas. To our knowledge, similar studies have not been carried out in FM patients, which makes it difficult to compare results. Despite this, previous literature in the general population also indicates that women in rural areas have higher pain scores than those in urban areas (Tripp et al., 2006; Wang et al., 2015). It could be hypothesized that these differences may be due to the different treatments for chronic pain, and for fibromyalgia in particular, that patients in rural and urban areas receive. Regarding drug treatment, there seem to be no differences, neither in primary nor specialized care, between rural and urban areas. Elective drugs for fibromyalgia are psychiatric drugs that act on central pain circuits (Calandre et al., 2014). These drugs are used for the treatment of pain and for the associated emotional symptoms (anxiety and depression) that in turn contribute to the chronification of pain (Pidolle and El Hage, 2020). However, there is a growing recognition that chronic pain (Kress et al., 2015), and fibromyalgia in particular (Arnold and Clauw, 2017), must be approached from a multidisciplinary perspective that includes professionals from medicine, rehabilitation, physiotherapy, nursing, and psychology, among others (Arnold and Clauw, 2017). The therapeutic approaches that should be given priority in fibromyalgia are exercise and cognitive-behavioral therapy (treatments with the most evidence and net benefit), always respecting a multimodal approach and reserving the use of drugs for episodes of intense pain or uncontrolled symptoms (García et al., 2016). An explicit way to operationalize this multimodal approach is Pain Units or Fibromyalgia Units, which, although still scarce, are frequently located in urban settings. This less access to multidisciplinary resources of fibromyalgia patients in the rural context is in line with the current imbalance between urban and rural areas in specialized health resources (Murawski and Church, 2009; Song et al., 2018). The location of specialized units for the care of pain in urban areas probably favors that patients resident there present less pain than patients in rural areas (Hogg et al., 2012). Specifically, feeling more cared for, having better treatments or follow-ups, feeling more supported or assisted could be the main reasons why these patients present less pain. Furthermore, despite the existence of evidence in FM patients that pain severity increases with age (Jiao et al., 2014), the analysis performed precludes that these differences in pain could be due to differences in age. Fatigue, on the other hand, being a symptom that patients can control to a certain extent, is possible that it is favored by the

TABLE 3 | Prospective prediction of fibromyalgia symptoms from acceptance, rural areas, and their interaction.

	R^2	*F*	*p*	Beta	*t*	*p*	95% CI
DV = Pain	0.09	7.80	< 0.001				
Acceptance				0.01	0.553	0.580	–0.03, 0.05
Residence area				0.72	3.67	< 0.001	0.33, 1.10
Interaction				–0.06	–2.41	0.016	–0.11, –0.01
DV = Anxiety	0.06	5.103	0.002				
Acceptance				–0.13	–2.66	0.008	–0.22, –0.03
Residence area				0.22	0.44	0.656	–0.76, 1.21
Interaction				< 0.01	0.11	0.913	–0.12, 0.13
DV = Depression	0.05	4.335	0.005				
Acceptance				–0.12	–2.37	0.018	–0.23, –0.02
Residence area				–0.59	–1.07	0.285	–1.69, 0.50
Interaction				< 0.01	0.03	0.972	–0.14, 0.14
DV = functional limitation	0.05	4.212	0.006				
Acceptance				–0.02	–0.26	0.795	–0.16, 0.12
Residence area				–0.08	–0.11	0.915	–1.54, 1.38
Interaction				–0.21	–2.18	0.029	–0.39, –0.02
DV = Physical fatigue	0.14	11.980	<0.001				
Acceptance				–0.07	–1.66	0.096	–0.14, 0.01
Residence area				–1.39	–3.31	0.001	–2.22, –0.56
Interaction				–0.11	–2.04	0.042	–0.21, –0.01
DV = Mental fatigue	0.09	7.363	<0.001				
Acceptance				–0.08	–2.231	0.027	–0.16, –0.01
Residence area				–1.23	–3.042	0.002	–2.02, –0.43
Interaction				–0.02	–0.395	0.692	–0.12, 0.08

Residence area: 0 (urban area), 1 (rural area).

TABLE 4 | Conditional effects of acceptance on pain, functional limitation and physical fatigue at residence area (urban/rural).

DV	Residence area	Beta (acceptance)	*t*	*p*	95% CI
Pain					
	Urban area	0.010	0.553	0.580	–0.03, 0.05
	Rural area	-0.049	–2.985	0.003	–0.08, –0.02
Functional limitation					
	Urban area	-0.02	–0.259	0.795	–0.18, 0.18
	Rural area	-0.22	–3.545	< 0.001	–0.35, –0.10
Physical fatigue					
	Urban area	-0.06	–1.668	0.096	–0.15, 0.01
	Rural area	-0.18	–4.880	< 0.001	–0.25, –0.11

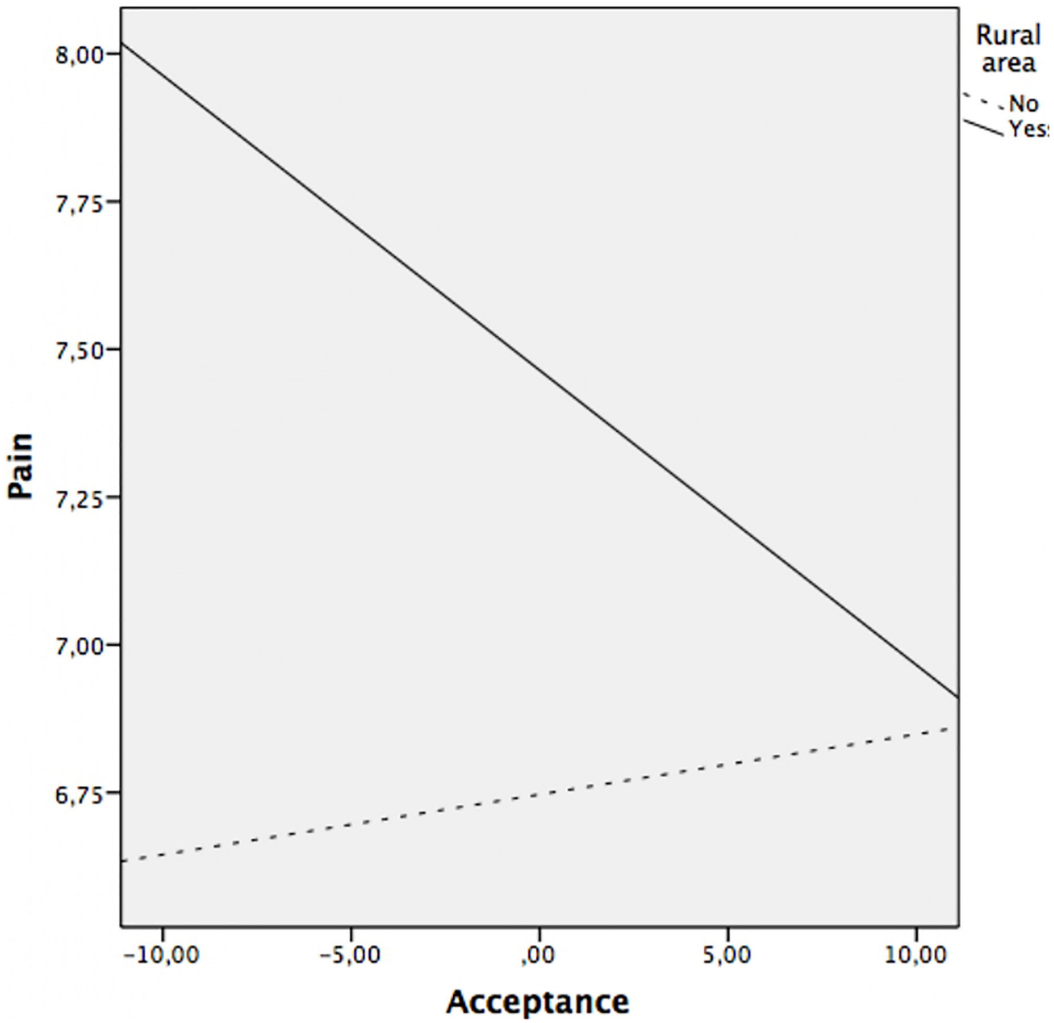

FIGURE 1 | Relationship between acceptance and pain at rural area (yes/no).

characteristics of the rural environment. Moreover, significant differences in employability may be affecting these results. The patients in rural areas are, for the most part, housewives, so they have more time to self-manage the activities of daily living based on their state of health. Likewise, it has been verified that rural patients report greater social support (i.e., family and friends) on a day-to-day basis (Goh et al., 2016), which could make them feel less fatigued.

Interestingly, our findings did not reveal significant differences in anxiety, depression, and functional limitation between the rural/urban groups. Previous literature in clinical and non-clinical populations is not consistent with the results obtained in this regard. Specifically, studies in patients with multiple chronic conditions report that rural subjects have more symptoms of anxiety and depression (Cheng et al., 2020). In the general population, it seems that higher levels of these symptoms occur in the urban population (Blazer, 1985; Wang, 2004). However, studies in the elderly population find contradictory results. Some find higher levels of anxiety and depression in rural populations (Li et al., 2016; Cheng et al., 2020), others in urban population and others find no relationship (Chiu et al., 2005; St John et al., 2006; Salinas et al., 2010). In addition, another study in the elderly population finds that functional limitation is less likely in urban areas (Zimmer et al., 2010). These contradictions may be due to differences in the samples. However, it is important to note that the aforementioned research is based on the responses given preferably by non-clinical population in randomized surveys. The sample in this study is inherently different as it focuses exclusively on clinical subjects diagnosed with FM. This disease is characterized by its high comorbidity with other types of emotional disorders (i.e., anxiety and depression) and physical (i.e., functional limitation) (Arnold et al., 2016), which could explain the absence of differences, in the present study, in the mentioned variables. Another explanation could be related to the treatments prescribed to mitigate the effect of this symptomatology, since being very generic treatments they are prescribed by primary care or psychiatry services and these services do not differ in rural areas from urban

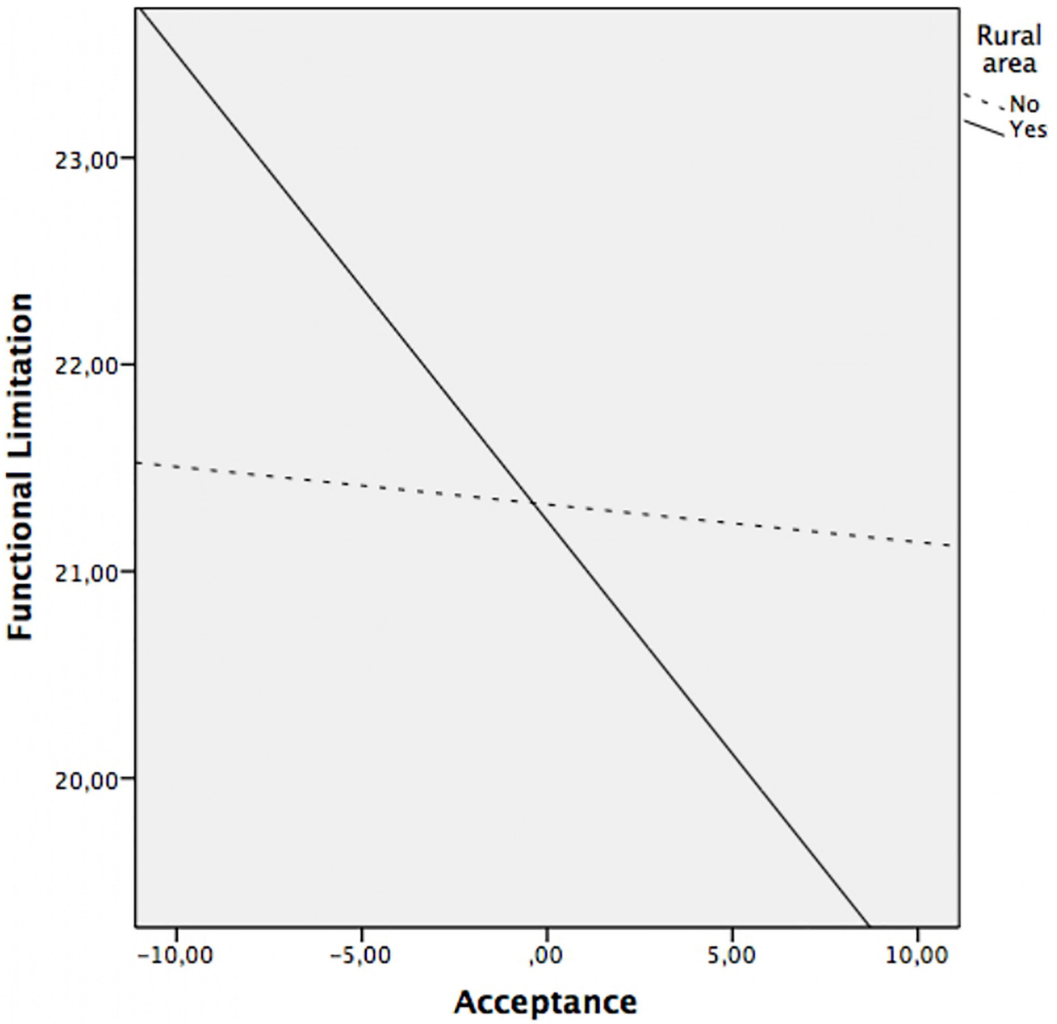

FIGURE 2 | Relationship between acceptance and functional limitation at rural area (yes/no).

areas (Lawson, 2017). Based on the model of environmental competencies (Lawton, 1977), which takes into account the environment-person interaction and the interpretation that the subject makes of the availability of resources, this fact could be explained. As there is no gap in the perception of resources available to treat symptoms between the health services in both areas, patients could interpret that treatment is being equal regardless of the place of residence.

Regarding acceptance, the results show significant differences with respect to the area of residence. Specifically, patients from rural areas obtain higher scores in this variable compared to those from urban areas. Previous literature on the matter in patients with FM is non-existent. Studies carried out on samples with other diseases (e.g., cancer or mental disorders) did not find significant differences on acceptance according to the place of residence (Bogusz and Humeniuk, 2017; Cipora et al., 2018). It is important to note that, in this study, the acceptance component is analyzed as a facilitator of commitment to daily activity despite pain. In this sense, it has been pointed out that finding fewer barriers to continue with the lifestyle prior to diagnosis, favors self-management of the disease (Huygens et al., 2016). It could be hypothesized that the ability to control, organize, set times, ultimately autonomy, is more favored in the rural environment than in the urban environment. In urban settings, women with fibromyalgia have to combine their work as a housewife with their work outside the home in a greater proportion than women in rural areas. This fact could have consequences on their management capacity and on the distribution of their time, affecting the performance of tasks depending on other contextual variables, such as pain, fatigue or "having a bad day" (Sanz-Baños et al., 2016). Some items of the acceptance dimension used in our study (McCracken et al., 2004) such as "I continue to do the things of daily life regardless of my level of pain" or "I do not need to control the pain to be able to lead my life well" point in this direction. In urban women with fibromyalgia, to a greater extent, work outside the home could constitute a "demanding" context with little capacity for self-management based on their symptoms.

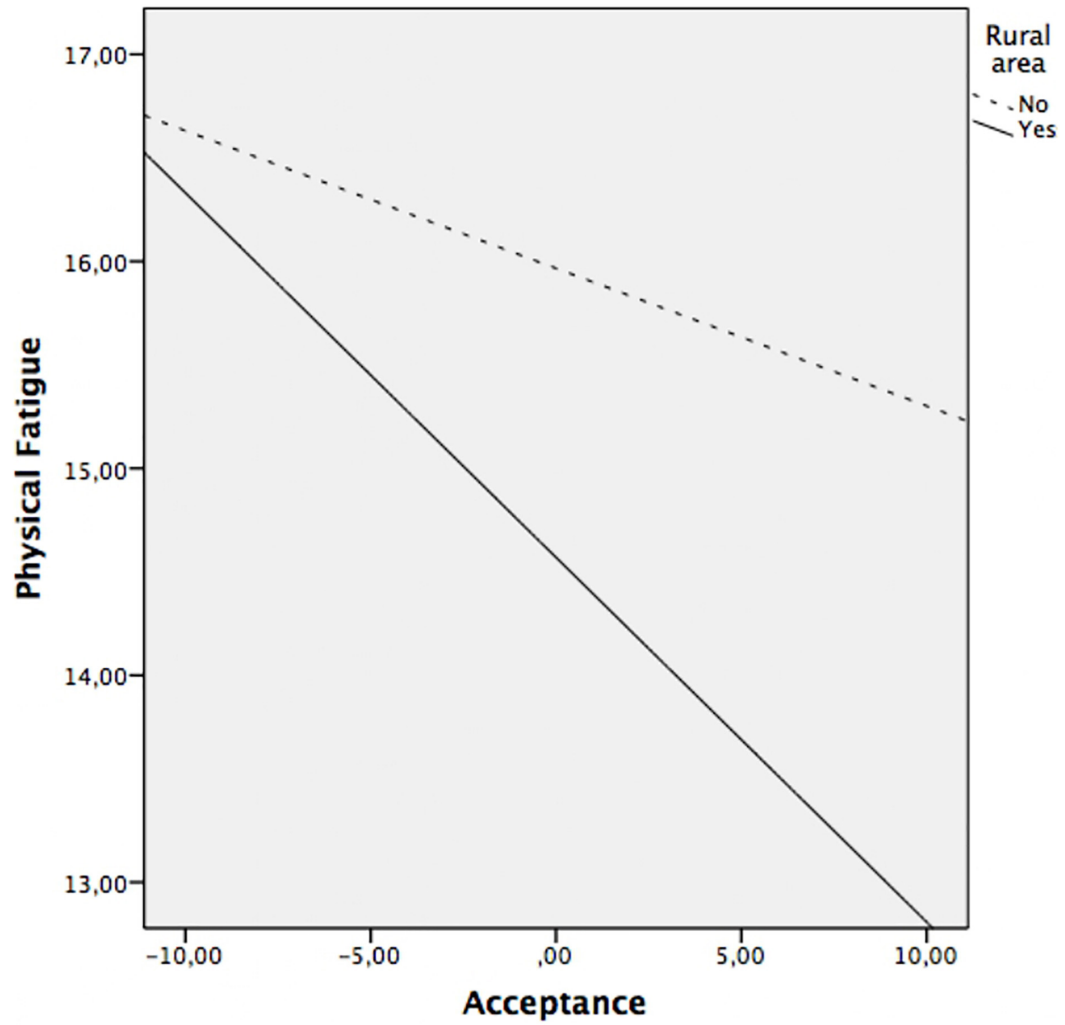

FIGURE 3 | Relationship between acceptance and physical fatigue at rural area (yes/no).

Regression analyzes revealed that the role of place of residence (rural/urban) in the effect of acceptance on emotional, cognitive, and physical symptoms differed by symptom. It is described that regardless of the context, acceptance has a direct negative effect on variables of emotional and cognitive symptoms (anxiety, depression, and mental fatigue) but not on physical symptoms. This is possible since the concept of acceptance (derived from ACT) is aimed at improving emotional states (Hayes et al., 2016). The previous literature is consistent with the role of acceptance in the suffering of FM patients (McCracken and Velleman, 2010). It has been proven that chronic pain patients with high levels of acceptance have a better state of mental health (Kanzler et al., 2019). The results found here may be due to the field of application of the technique. In recent years, the use of ACT in patients with FM has spread (Simister et al., 2018), but this therapy has been applied fundamentally to reduce the psychological symptoms associated with pain (i.e., anxiety or depression) but not in the reduction of pain itself (Graham et al., 2016).

The moderation analysis add that the variables of physical symptoms (pain, functional limitation, and physical fatigue) were significantly and negatively associated with acceptance, only in patients from the rural area. That is, in rural patients, the greater the acceptance, the less pain, functional limitation, and physical fatigue. However, in urban patients there is no association between these variables. As mentioned above, the sociodemographic characteristics of patients from rural areas compared to those from urban areas differ significantly. The rural environment favors continuing a similar lifestyle despite the disease. By not feeling substantial changes in their daily lives, it is possible that patients perceive less severity in physical symptoms. The characteristics of the environment and the lifestyle of rural women favor acceptance of the disease and the impact of it does not significantly affect their daily lives (Rahim-Williams et al., 2012). In this sense, our results indicate that the rural environment not only favors the acceptance of FM but also the positive effects of the latter on the symptoms associated with the disease.

Together, the results presented suggest that the area of residence plays a role in the severity and management of symptoms in patients with FM. This has important practical implications to consider. The findings make it clear that the characteristics of FM patients in rural and urban settings differ so much that studies should not generalize the results in this population. It is considered necessary to develop specific treatment programs taking into account the characteristics of the patients depending on the demographic area. Specifically, it is recommended that interventions in patients in urban areas, due to the impact that the disease can have on their lifestyle, are focused on its acceptance. Instead, in rural areas, efforts should focus on increasing resources for specialized care for chronic pain.

While acknowledging the relevant practical implications of the present research, this study certainly has some limitations. First, the associations must be interpreted according to the observational nature of the design, as this is not an experimental study. Furthermore, since the present study focuses exclusively on women with FM, the generalizability of the findings to other populations of musculoskeletal and non-musculoskeletal pain cannot be guaranteed. As the literature indicates, important differences have been revealed between this population and other populations with chronic pain (Arnold et al., 2016). Therefore, researchers are encouraged to replicate these findings in different pain populations. Finally, it is important to mention the absence of studies conducted in FM that explore the differences between rural and urban patients makes it difficult to compare results. Given the important clinical repercussions that these studies can have on the health system, it would be advisable to carry out more research in this line.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The study was approved by the Bioethics Committee of Rey Juan Carlos University (Reference PI17/00858; number 160520165916). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PC and CP contributed equally to this article in terms of study conceptualization, design, and procurement of funding. SB and SP-C organized data collection. OL-R analyzed the data. DB contributed to the development of the assessment materials. All authors contributed to the writing of the manuscript.

FUNDING

This work was funded by the Health Research Fund (Fondo de Investigación en Salud), grant number PI17/00858 from the Instituto de Salud Carlos III (Spain), co-financed by the European Union through the Fondo Europeo de Desarrollo Regional (FEDER).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 16 July 2021
doi: 10.3389/fpsyg.2021.689304

Do Histories of Painful Life Experiences Affect the Expression of Empathy Among Young Adults? An Electroencephalography Study

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Specialty section:
This article was submitted to Emotion Science, a section of the journal Frontiers in Psychology

Received: *31 March 2021*
Accepted: *29 June 2021*
Published: *16 July 2021*

Citation:
Yaghoubi Jami P, Han H, Thoma SJ, Mansouri B and Houser R (2021) Do Histories of Painful Life Experiences Affect the Expression of Empathy Among Young Adults? An Electroencephalography Study. Front. Psychol. 12:689304. doi: 10.3389/fpsyg.2021.689304

Previous research suggests that prior experience of pain affects the expression of empathy. However, most of these studies attended to physical pain despite evidence indicating that other forms of pain may also affect brain activity and emotional states in similar ways. To address this limitation, we compared empathic responses of 33 participants, some of whom had experienced a personal loss, across three conditions: observing strangers in physical pain, psychological pain, and a non-painful condition. We also examined the effect of presence of prior painful experience on empathic reactions. In addition, we examined the stimulation type, prior experience, and ERPs in the early Late Positive Potential (300–550 ms), late Late Positive Potential (550–800 ms), and very late Late Positive Potential (VLLPP; 800–1,050 ms) time windows. Behavioral data indicated that participants who had personally experienced a loss scored significantly higher on perspective taking in the psychological-pain condition. ERP results also indicated significantly lower intensity in Fp2, an electrode in the prefrontal region, within VLLPP time window for participants experiencing a loss in the psychological-pain condition. The results of both behavioral and ERP analysis indicated that prior experience of psychological pain is related to cognitive empathy, but not affective empathy. The implication of these findings for research on empathy, for the study of psychological pain, and the moderating influence of prior painful experiences are discussed.

Keywords: empathy, ERP, physical pain, psychological pain, similarity

INTRODUCTION

Historically, empathy is considered an automatic emotional response that leads to either "self-oriented"—known as personal distress—or "other-oriented"—known as empathic concern—feelings (Cuff et al., 2016). These two expressions of empathy are also differentially related to altruistic behavior (Endresen and Olweus, 2001). Nevertheless, such one-dimensional ideology has changed toward a more complex, multidimensional perspective (Decety and Hodges, 2004; Fan and Han, 2008) supporting the integration of affective and cognitive processes in empathic behavior. For

example, Fan and Han (2008) observed an activity over the frontal-central lobe around 140 ms stimulus onset followed by a later activity (at 380 ms after stimulus presentation) over the central-parietal region, while participants were witnessing others' pain. Similarly, fMRI studies identified the activation of distinct brain areas in limbic system [anterior insula (AI) and dorsal anterior cingulate cortex (dACC)] and the medial prefrontal cortex in empathic-inducing situations. According to these results, the aforementioned regions showed stronger activity in empathic-inducing conditions compared with control conditions (Rameson et al., 2012; Morelli et al., 2014) suggesting that empathy is an integration of bottom-up automatic and top-down cognitive responses. Following the results of these studies (see Cuff et al., 2016, for review), the current paper defines empathy as a multidimensional concept consisting of three distinct, but interrelated, components, namely, empathic concern, personal distress, and perspective taking (Davis, 1983).

The empirical literature informing our understanding of empathic behavior is derived from studies that compare people's reaction after receiving pain versus observing others' pain. More specifically, these studies assess observers' feelings while receiving pain or witnessing others in pain using different methodologies, especially neuroimaging methods, to better understand the mechanism of empathy (Eisenberger et al., 2003; Singer et al., 2004; Lamm et al., 2010). Although, in most of these studies, physical pain was used to trigger empathic responses, a more comprehensive review of the pain literature indicates that there are three types of pain: physical pain resulting from tissue damage, such as acute injury, social pain associated with losing social bonds as the result of social isolation/rejection, and psychological pain associated with the loss of a loved one through death, divorce, or a relationship break up (Mee et al., 2006; Eisenberger, 2012). Depending on the type of pain assessed, results suggest that the suffering person will sense either the pain and the associated emotions or a lesser experience of an unpleasant feeling without actually sensing the pain (MacDonald and Leary, 2005; Jaremka et al., 2011). Because of the growing interest in the distinctiveness of psychological pain, the focus of this study is on empathic responses toward observing others' psychological pain.

Empathy and Physical Pain

Neuroscientific discoveries have broadened the understanding of functional neuroanatomy of physical pain, particularly through the development of a pain matrix consisting of two distinct, but interrelated, components. The affective component of the matrix mostly relates to activity in the dACC, cerebellum, and the anterior insula, while the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), and posterior insula (PI) are associated with the sensory component (Peyron et al., 2000; Wager et al., 2013). In this view, a person senses pain through activation of the sensory component of the pain matrix. Similarly, through activation of affective component, the person feels unpleasant emotions associated with the pain (see Eisenberger, 2012, for discussion).

Numerous studies have shown that observing others' physical pain activates the affective facet of the pain matrix. That is, the empathizer cannot sense the pain of the suffering person; however, they can feel the negative emotional reactions of the pain (Wicker et al., 2003; Lloyd et al., 2004; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005; Bufalari et al., 2007; Decety et al., 2008).

Empathy and Social Pain

Unlike physical pain, experiencing social pain activates the affective facets of the pain matrix. In other words, being socially rejected/excluded is associated with the unpleasant emotions of pain rather than sensing the pain (Eisenberger et al., 2003; Eisenberger and Lieberman, 2004; O'Connor et al., 2008; Bolling et al., 2011). On the other hand, observing others' social pain activates brain areas involved in mentalizing (i.e., dorsal medial prefrontal cortex, precuneus, and temporal pole; Meyer et al., 2012).

Empathy and Psychological Pain

Current evidence suggests that psychological and physical pains are experienced similarly (Woo et al., 2014). Thus, suffering from psychological pain would activate the whole pain matrix (Kross et al., 2011). Previous studies also explored empathic response toward others' psychological pain (i.e., grief) and reported activation in middle and posterior cingulate gyrus, the inferior frontal gyrus, the middle temporal gyrus, the thalamus, and the brainstem (Gündel et al., 2003; O'Connor et al., 2008; Kersting et al., 2009).

Summary

To summarize, people experiencing physical or psychological pain not only *sense* the pain, but also *feel* the unpleasant emotions associated with it, whereas being in social pain is associated with only having negative feelings of the pain (Eisenberger et al., 2003; Singer et al., 2004; O'Connor et al., 2008; Kross et al., 2011). Similarly, observing others suffering from physical or psychological pain also differs from observing others in social pain. In the case of the first two types of pain and depending on the context, either the whole pain matrix (psychological pain) or only affective facet of pain matrix (physical pain) would be activated for an empathic reaction (Damasio et al., 2000; Meerwijk et al., 2013). On the other hand, responding empathically after observing another individual being rejected/excluded from their social group requires cognitive processes (mentalize the suffering person's situation) rather than the activation of the pain matrix (see Yaghoubi Jami et al., 2021, for review). It should be emphasized that these three types of pain are inter-connected in everyday life, given that psychological pain is likely interwoven with social relations of various kinds.

In addition, it should be noted that regardless of the type of pain people are witnessing, empathic behavior is moderated by the relationship between the empathizer and the target of empathy (Twenge et al., 2007; Xu et al., 2009; Mathur et al., 2010; Beeney et al., 2011), or having a shared painful experience with the target of empathy (Eklund et al., 2009). The following section is a review of studies exploring the links between empathic behavior and empathizer's personal experience of the observed pain.

Prior Painful Experience and Empathic Response

Most of us have heard the phrase, "*I've been there too*" referring to undesirable experiences, such as grief. The literature suggests that sharing similar painful experiences is a predictor of empathic responsiveness (Batson et al., 1996; Eklund et al., 2009; Preis and Kroener-Herwig, 2012). For example, Barnett et al. (1987) investigated the association between empathy and similarity by asking participants to listen to a conversation between a rape victim and her therapist. According to the result, those participants with an experience of abusive behavior showed higher empathy toward the victim. The reported results were confirmed by other studies (Barnett, 1984; Barnett et al., 1986).

Hoffman (2001) clarified the rationale of the relevance of similarity for empathy by highlighting the important role of memory. Accordingly, encountering another individual in a situation similar to the one experienced by the empathizer evokes the memory of the prior experience and elicits emotions similar to the observed individual. For example, if an individual has experienced the loss of a loved one and later observes another individual in mourning, the past experience of grief facilitates the affective and cognitive interpretation of the grieving person's situation.

According to this brief review, similarity of painful experience – whether it be physical or psychological – is important for empathic responses. The effect is observed primarily when the observed pain refers to *similar painful experiences* rather than drawing attention to similarities between the observer and observee. For this reason, similarity is treated as a similar prior *painful experience* in the present study.

PURPOSE OF THE STUDY

Although many research traditions assess empathic reactions toward others' physical and social pain, there is a dearth of research on the mechanisms and perceptions of psychological pain (see Meerwijk et al., 2013, for review). Moreover, most of the studies in the realm of empathy and pain are either behavioral or fMRI studies. What remains unaddressed in the literature is exploring the temporal aspects of empathic responsiveness in psychologically painful situations. The literature suggests that an accurate understanding of psychological pain could lead to preventing its dire consequences, such as mental health breakdown or even suicide (Bosticco and Thompson, 2005; Mee et al., 2006). This knowledge could not be gained without studying how this type of pain is perceived and processed in the brain. Additionally, there is a lack of conclusive evidence on the individual characteristics contributing to empathic behavior.

To circumvent the issues that have challenged previous researchers, this study focused on the association between prior experience of psychological pain in form of grief and associated empathic responses. To achieve these goals, the current paper employed EEG to investigate neural correlates of people's reaction to observing others' pain with and without apparent signs of pain (physical and psychological). In addition, the study assesses the feelings and reactions that might be aroused by attending to observed person. Moreover, to clarify the relationship between similarity and empathic reactions, the authors assessed the impact of being familiar with a possible psychological pain-inducing situation on empathic behavior.

Prior studies assessing neural correlates of empathy have reported significant differences in prefrontal regions across painful and non-painful conditions across subject groups (Decety and Jackson, 2004; Light et al., 2009; Leigh et al., 2013; Reniers et al., 2014). Thus, although our study is primarily exploratory, we hypothesized that significant effects of the condition and prior experience of psychological pain would be found in frontal regions electrodes. Whole-brain analysis was also performed for further exploration. In terms of time windows of interest, we focused on relatively late components of ERPs (e.g., 500 ms and even 1,000 ms) given previous EEG/ERP studies suggesting such late components were useful indicators to examine between-person and between-condition differences (e.g., Hajcak et al., 2010; Blanchette and El-Deredy, 2014). In addition, for exploratory purposes, we examined correlations between participants' ERPs, behavioral responses, and dispositional empathy.

MATERIALS AND METHODS

Participants

A total of 41 undergraduate college students (six males; M = 19.50, SD = 1.39, all right-handed) participated in this study. Although we could not estimate the required sample size based on power analysis due to the lack of relevant previous studies and because of exploratory nature of our study, we referred to similar social neuroscientific ERP studies (Fan and Han, 2008; Blanchette and El-Deredy, 2014). These previous studies were conducted with 16 to 31 participants; therefore, we recruited 41 participants after considering potential exclusions.

Participants consented to be part of the study and were compensated by receiving a course credit. The study was approved by the Institutional Review Board of a southern university in the United States and was performed in accordance with the Declaration of Helsinki (1964) and its later amendments. The primary inclusion criteria were age (18 to 22 years) due to developmental path of empathy (Yaghoubi Jami et al., 2018), having no self-reported history of any psychiatric diagnoses and no uncorrected vision deficits.

To ensure eligibility, interested participants provided information about their medical conditions and any history of neurological disorders using a short medical history form. The medical form was used to identify participants for whom the procedures may be of risk (e.g., prone to seizure and taking particular medicine). Participants who failed the screening test (N = 1) were compensated and dismissed.

After removing incomplete responses or responses in which participants had excessive motion causing artifacts on neural recording, the analyses were performed on 33 participants.

Stimuli and Apparatus

The experiment had two parts: an online self-reported questionnaire, Interpersonal Reactivity Index (IRI; Davis, 1983), measuring dispositional empathy as a multidimensional concept (affective and cognitive facets), and a computer-based task. Affective empathy and cognitive empathy were measured through *empathic concern* (EC), and *perspective taking* (PT), items, respectively. *Personal distress* (PD) items were used as a separate measurement of personal distress. Because of debates over the validity of the *fantasy scale* (FS) items in measuring empathy (Yaghoubi Jami et al., 2018), this subscale was not included in the analysis. Following Davis' (1983) guidelines, items were scored on a 5-point Likert scale (0 = *does not describe me well* to 4 = *describe me well*—some items were reverse-coded) with a final score range of 0 to 28 on each scale. Higher score on each scale indicates higher tendency on that subscale (e.g., score of 28 on *empathic concern* scale suggests participants reported themselves as having high affective empathy). The IRI showed acceptable internal consistency reliability: $\alpha_{\text{empathic concern}} = 0.79$, $\alpha_{\text{personal distress}} = 0.69$, and $\alpha_{\text{perspective taking}} = 0.75$.

Additionally, to assess the degree of prior psychological painful experience, five questions were presented to participants asking about their personal experience of loss. Following the self-disclosed loss experience, participants were asked: How close was the person to you? (1: "*Very close*" to 5: "*Not at all*"), How severe was the loss for you? (1: "*Extremely painful*" to 5: "*Not painful at all*"), How did you feel immediately after the loss? (1: "*Desperate/Depressed*" to 5: "*No feeling*"), Do you still think about that person? (1: "*Always*" to 5: "*Never*"), and How do you feel now? (1: "*Desperate/Depressed*" to 5: "*No feeling*"). This researcher-constructed questionnaire showed acceptable reliability ($\alpha = 0.80$). Based on these responses, any participant who did not have a first-hand experience of grief, or who reported that they did not have a relationship with the person, barely thought about them, and did not have any feelings after losing them, were identified as the *No-Loss* group ($N = 15$). By contrast, participants in the *Loss* group ($N = 18$) reported to have lost a (very) close relative, felt (very) much pain after their loss, thought about the deceased person frequently, and were still feeling (very) sad because of their loss. Demographic backgrounds did not differ significantly between the two groups ($p > 0.05$).

Visual Stimuli

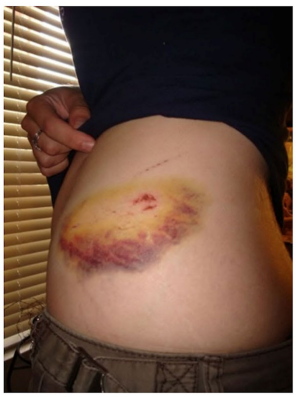
In a previous study, a picture database was created and validated in order to record participants' empathic reaction to various situations (Yaghoubi Jami et al., 2021). Specifically, the picture database was created using a series of steps. First, a pilot study was conducted using 90 pictures which depicted painful physical (e.g., needle injection) and psychological (e.g., grieving mother) situations as well as non-painful incidents (e.g., happy babies). These pictures were selected using an online search engine (Google image search) and were grouped into three categories (i.e., physical pain, psychological pain, and non-painful) based on the keyword used for the initial search. As part of this measure development stage, volunteers (both male and female; $N = 90$) varying in age, educational level, and nationality rated the pain intensity of the pictures on a 5-point scale ranging from *very painful* (1) to *not at all* (5). Based on participants' rating, pictures that received an average ranking between *very painful* to *moderately painful* were placed into one of two painful conditions: physical-pain ($N = 7$): $M = 1.89$, $SD = 0.41$, and psychological-pain ($N = 7$): $M = 1.54$, $SD = 0.46$. The selected pictures in each category showed an acceptable internal consistency reliability: $\alpha_{\text{physical-pain}} = 0.68$, $\alpha_{\text{psychological-pain}} = 0.79$. For the non-painful condition, seven pictures ranked by the same participants as *not at all painful* were selected. The pictures were matched based on gender (three males, three females, and one child), number of people in the frame, face or faceless, and picture size (800 × 600 pixels) between conditions. The final database consisted of 21 color pictures representing strangers in physical pain, psychological pain, and non-painful conditions (**Figure 1**). To ensure that participants interpreted the pictures in the intended way, all pictures were labeled by the associated category so that each participant always viewed a picture *plus* a category label; for example, a picture of a man standing in a graveyard was labeled as "psychological pain." The categorization of pictures used in this study was supported by a previous study in which 91% of participants used similar labels for the pictures. The manipulation used in the current study was further supported in two additional studies (Yaghoubi Jami et al., 2021).

The stimuli were presented using Presentation Software.[1] All pictures were presented in the center of a gray background on a 15-inch CRT monitor. Participants viewed the display from a distance of 60 cm and used an external numeric keypad (that was placed next to them) to press the appropriate button (ranging from 1 to 5) for responding to questions following each picture (see Section "Procedure").

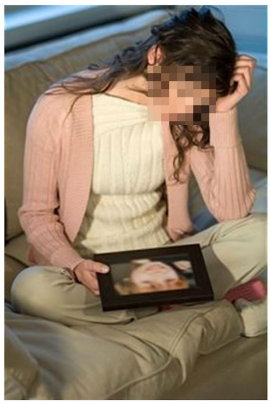
EEG Recording

Continuous EEG was recorded from 21 active electrodes using MITSAR EEG system with an amplifier model 201 (Mitsar Co., Ltd., St. Petersburg, Russia; distributed by Nova Tech, Inc., Mesa, AZ, United States). For recording EEG signals, a 19-channel ElectroCap electrode cap (Electro-Cap International Inc., Eaton, OH, United States) was placed on participant's scalp based on the international 10–20 system (American Electroencephalographic Society, 1994). The other two electrodes (A1 and A2) were placed in left and right ears. The ground electrode was placed on the forehead. Following the system manual and previous studies using the same device (Kropotov et al., 2005), impedance was kept below 10 kΩ. EEG signals were collected at a sampling rate of 512 Hz and processed online with the Mitsar EEG Acquisition software using a Dell XPS 15 laptop. EEG data were referenced online at vertex electrode (Cz) and re-referenced again using mastoids. To remove any possible contamination of muscle artifacts, appropriate filters were applied (100 Hz low-pass, 0.5 Hz high-pass, and 60 Hz notch filters) and every trial was inspected visually.

[1]https://www.neurobs.com



Physical-pain



Psychological-pain

Non-painful

FIGURE 1 | Stimulus examples.

Procedure

Three days after completing the IRI, participants were scheduled for the recording session. Upon participants' arrival to the laboratory, they were informed about the procedure and signed the written consent. To avoid social desirability bias (Eklund et al., 2009), participants were debriefed about the real aim of experiment at the end of the study.

The study started with participants filling out the medical history form. Eligible participants (i.e., those who passed the screening) received demographic and researcher-made questionnaires. While participants were completing the two mentioned questionnaires, experimenters prepared participant for the study (putting the EEG cap, connecting the electrodes, connecting the amplifier to the electrodes and stationary computer, checking the signals, and so on). The experiment was held in a quiet room with a sufficient and quiet air conditioner. Before data recording, one of the researchers explained the procedure and underwent a training session with the participant to become familiar with the study. Specifically, participants observed a picture from one of the conditions (selected randomly) and answered subsequent questions, while the experimenter explained instructions and questions. The practice trial was not recorded. When the participant was comfortable with the procedure and instruction, the experimenter left the room, and the recording session began.

Participants were presented with pictures showing a person in one of three conditions: non-painful, physical-pain, and psychological-pain. In total, the experiment consists of three blocks of seven pictures with 60-s inter-block intervals. To reduce exhaustion and allow participants to move freely without disturbing the data, a fixation mark was displayed on the screen for 10 s between the trials. Participants observed each picture for 5 s and used an external keypad to answer questions regarding their **pain intensity** (1: *very pain* to 5: *no pain*), **feeling** (1: *sad*, 2: *distress*, 3: *no feeling,* and 4: *happy*), **empathic concern** (1: *extreme empathic concern* to 5: *no empathic concern*), **perspective taking** (1: *can imagine* to 5: *no understanding of the situation*), and **intention to help** (1: *definitely help* to 5: *will not help*) on a 5-point Likert scale. To avoid ordering effect, the questions were counterbalanced across the trials. See **Figure 2** for the visualized description of the procedure.

The pictures were shown randomly to balance participants' negative emotions that could have been elicited by pictures. In case of any emotional breakdown or feeling uncomfortable resulted from observing pictures, participants could have a session with a counselor who was sitting in the other room. To ensure task compliance, participants were told that each session was being recorded and they might be selected for follow-up questions about the pictures. The videotapes were

FIGURE 2 | Experimental procedure.

deleted after each session. The whole data recording lasted on average 21.55 (SD = 3.69) minutes.

Data Analyses

Behavioral Data Analysis

To compare dispositional empathy between the two groups, an independent t-test was used. Next, to assess the effect of condition and participants' group affiliation and any interaction between the two on participants' reactions, we conducted a doubly multivariate analysis of variance (MANOVA) with condition as the within- and group as the between-subject factors. Doubly MANOVA was chosen because one of the dependent variables (i.e., participants' feelings) had a different scaling than the other four dependent variables (Ho, 2006). In case of any significant multivariate effect, the result of univariate ANOVA with Bonferroni correction (α = 0.025) and Greenhouse-Geisser correction (whenever applicable) is reported. No univariate or multivariate outliers ($p < 0.001$) were found, and all assumptions (i.e., sampling distributions normality, homogeneity of variance-covariance matrices, and linearity) of doubly MANOVA were met. All analyses were conducted using IBM SPSS, version 24.

ERP Analysis

EEGlab software[2] (Delorme and Makeig, 2004) was used for preprocessing the collected data and analyzing the EEG signal. The analyses were based on computer off-line on stimulus-locked ERPs meaning only trials in which participants observing a picture from one of the conditions were included in ERP analysis. All trials in which participants were required to provide a response (e.g., rating pain intensity) were excluded from ERP analysis and included in behavioral analysis.

The collected data were first filtered with a high-pass filter (lower edge frequency) at 1 Hz. The filtered dataset was re-referenced by using Cz as the reference channel following the EEGLAB tutorial manual (Delorme et al., 2007). The EEG data were then epoched from 100 ms before the stimulus (for the baseline correction) and 1,500 ms after the stimulus. The epoched dataset was further processed with the independent component analysis (ICA) for artifact removals. For the ICA, the *runica* algorithm implemented in EEGLAB was used. In short, EEG recording data are a mixture of the source signal. By applying ICA filters, we can produce the maximally temporally independent signals available in the channel data. ICA components are temporally distinct even when their scalp maps are overlapping. With the help of ICA, we can determine whether a signal is an artifact (e.g., muscle or eye movement) or it is cognitively related. After applying ICA, components are ordered based on their contribution to the original signal. Therefore, movement artifacts can be detected as they have the strongest contribution (Delorme and Makeig, 2004; Delorme et al., 2007).

[2]http://sccn.ucsd.edu/eeglab

Following the relevant literature (Kropotov et al., 2005; Cheng et al., 2014), using WinEEG Advanced Software,[3] any trial having electrooculogram artifacts exceeding ±100 μV threshold were excluded from analysis. Additionally, trials containing eye or muscle movements were excluded from the analysis.

Once all artifacts were removed from the dataset, ERP were compared across groups and conditions within three time-windows: the early Late Positive Potential (ELPP), late Late Positive Potential (LLPP), and very late Late Positive Potential (VLLPP) time windows. The ELPP was defined 300–550 ms after each response. The LLPP was defined 550–800 ms after each response. The VLLPP was defined 800–1,050 ms after each response. We focused on these three time-windows as they are reported to be significantly involved with development of emotional regulation and reappraisal (Hajcak et al., 2010; Blanchette and El-Deredy, 2014; Cheng et al., 2014).

We calculated the mean ERP within the aforementioned time windows with a customized MATLAB script. It should be noted that several previous studies have utilized other EEG/ERP indicators, such as the peak latency and the amplitude of each individual ERP, in their analyses. However, we decided to use the time window-specific mean because it has found to produce less biased analysis outcomes; in fact, the supporters of use of the mean ERP have argued that the use of peak components should be avoided due to its relatively greater bias and worse efficiency (Luck, 2005; Clayson et al., 2013).

For statistical analysis, we first performed a mixed-effects analysis for each time window. This statistical analysis was conducted using a customized R script. Because responses were nested within each participant, we set the mean ERP as the dependent variable, the electrode location, condition, and group as the fixed effects, and participants' ID and trial numbers as the random effects. We also entered the two- and three-way interaction effects among the electrode location, group, and condition, into the model as fixed effects. The mixed-effects analysis was performed with an R package, *lme4*. The aforementioned analyses, including both the mixed-effect analyses and electrode-wide comparisons, were performed within the hypothesized regions, frontal regions, and the whole brain. For the region-specific analyses, Fp1, Fp2, Fz, F7, F3, F4, and F4 were included. We intended to focus on the frontal regions since previous studies have shown that activity in the regions was significantly associated with empathic responses and pain perception (Rameson et al., 2012; Morelli et al., 2014). These seven electrodes are associated with the frontal regions (Minnerly et al., 2019) and were used as the foci of statistical analyses.

Moreover, we compared ERP for each electrode to examine the effects of group affiliation and condition as well. We performed additional mixed-effects analysis while setting ERP in each electrode as the dependent variable. Similar to the whole-brain analysis, in this analysis, participants' ID and trial numbers were used as the random effects, and the group and condition were used as the fixed effects. We also examined the group and condition interaction effect. In this process, in order to deal with the issue associated with false discovery rate during multiple tests, we adjusted the false discovery rate to $q = 0.05$ by using an R package, *fdrtool*. Once we found significant effect(s) within a specific electrode, we plotted ERP per group and condition for visual demonstration. In addition, we performed additional *t*-tests to examine differences between groups across conditions as well.

[3]https://bio-medical.com/wineeg-advanced-software-for-mitsar

Exploratory Correlational Analysis

To explore the relationships between participants' behavioral responses, dispositional empathy, and ERPs, we conducted correlational analyses. Prior to this analysis, we first calculated the mean of each of the behavioral responses recorded as continuous variables, the pain perception, empathic concern, perspective taking, and intention to help, per condition per participation. Second, we calculated the mean of the ERP in each electrode per condition per participant. Third, dispositional empathy scores in terms of IRI-EC, IRI-PT, and IRI-PD per participant were used.

The large number of variables associated with the correlational analysis raised the possibility of false positives. To address this concern, we performed a Bayesian correlational analysis. According to Bayesian methodologists, the focus of a statistical analysis does not depend on values of p and the rejection of null hypotheses. By contrast, Bayesian analyses attend to the extent to which the obtained evidence supports the presence of a significant effect (Han et al., 2018; Wagenmakers et al., 2018). This shift in focus buffers Bayesian analysis from the possibility of false positives due to multiple test (Gelman et al., 2012).

Bayesian correlational analysis was performed with *BayesFactor* package in R (Morey et al., 2018). The analysis was performed for the *physical-pain* and *psychological-pain* conditions. In the case of the correlational analysis with ERPs, we focused on the time window(s) that showed significant ANOVA and electrode-wise analysis results. While interpreting results, we used the resultant Bayes factor (BF) that indicates to which extent an alternative hypothesis was supported by evidence. We used $2\log BF \geq 2$ as the threshold indicating the presence of positive evidence (Han et al., 2018; Wagenmakers et al., 2018).

RESULTS

Behavioral Analysis

The results of behavioral data analysis are reported based on the order of analytical approach explained in Section "Data Analyses."

Prior Psychological Painful Experience and Dispositional Empathy

There were no significant group differences in the self-reported questionnaire subscales: IRI-EC, $t(31) = -0.02$, $p = 0.98$, $d = 0.01$; IRI-PD, $t(31) = -1.57$, $p = 0.13$, $d = 0.54$; and IRI-PT, $t(26.57) = -0.09$, $p = 0.93$, $d = 0.03$. Regardless of group affiliation, participants' affective empathy was significantly

higher than cognitive empathy, $t(32) = 4.42$, $p < 0.001$, $d = 0.77$. Regarding personal distress, the *Loss* group reported to have less distress compared to their peers in *No-Loss* group; however, the difference was not statistically significant (**Table 1**).

TABLE 1 | Group comparison of dispositional empathy.

	Loss		No-Loss		Value of *p*
	Mean	***SD***	**Mean**	***SD***	
IRI-EC	20.50	3.59	20.53	4.42	0.98
IRI-PT	17.28	4.87	17.40	2.56	0.93
IRI-PD	10.44	3.01	12.40	4.15	0.13

Means and standard deviations are reported. IRI-EC, empathic concern; IRI-PT, perspective taking; and IRI-PD, personal distress. There is no difference between the two groups (i.e., Loss and No-Loss) with respect to dispositional empathy.

Prior Psychological Painful Experience and Situational Empathy

Condition Comparison

Results indicated a significant multivariate effect of condition on participants' responses, Wilks' $\lambda = 0.008$, $F(10, 22) = 268.03$, $p < 0.001$, $\eta^2 = 0.99$. The detailed results for each item are explained below.

Pain Intensity

A significant effect of conditions on participants' pain intensity was found, $F(2, 62) = 1599.44$, $p < 0.001$, $\eta^2 = 0.98$. Psychological-pain and non-painful conditions were rated as the most and least painful conditions. Pairwise comparisons indicated significant difference between all conditions (ps < 0.025).

Intensity of Feelings

Condition had a significant effect on participants' feelings, $F(1.654, 51.263) = 24.34$, $p < 0.001$, $\eta^2 = 0.44$. The distribution of emotion that was aroused by each condition is as follows: physical-pain, distressed ($N = 17$), sadness ($N = 13$), and no feeling ($N = 3$); psychological-pain, sadness ($N = 31$), distressed ($N = 1$), and no feeling ($N = 1$); and non-painful, happiness ($N = 28$), and no feeling ($N = 5$).

Empathic Concern

There was a statistically significant difference between conditions with respect to participants' empathic concern, $F(1.107, 34.312) = 103.517$, $p < 0.001$, $\eta^2 = 0.77$. Observing another individual's psychological pain evoked higher empathic concern than physical pain and non-painful. Expectedly, all conditions differed significantly in the level of empathic concern they aroused (ps < 0.001).

Perspective Taking

Follow-up analysis results indicated a significant effect of condition on participants' perspective taking, $F(2, 62) = 22.67$, $p < 0.001$, $\eta^2 = 0.42$. As the pairwise comparison indicated, participants reported to be able to imagine or put themselves in the protagonists' position while observing a stranger in non-painful or psychological-pain situation, which was significantly different from physical-pain condition (ps < 0.001). No significant difference was observed between non-painful and psychological-pain conditions ($p = 0.256$).

Intention to Help

There was a significant effect of condition on participants' responses, $F(1.292, 40.041) = 44.85$, $p < 0.001$, $\eta^2 = 0.673$. Pairwise comparisons showed statistically significant differences between non-painful and the other two conditions (ps < 0.001). Participants reported to have almost similar empathic behavior toward a stranger suffering from either physical or psychological painful incidents. On the other hand, on the non-painful condition, they indicated they will "*probably help*" or "*don't know*" if they will help.

Interaction Between Loss Experience and Conditions

The final analysis focused on the interaction between participants' past experience of psychological pain and conditions. Accordingly, there was a significant multivariate interaction effect, Wilks' $\lambda = 0.291$, $F(10, 22) = 5.35$, $p = 0.001$, $\eta^2 = 0.71$, as the follow-up univariate analysis indicated the only significant difference was observed in the reported perspective taking ability, $F(2, 62) = 6.290$, $p = 0.003$, $\eta^2 = 0.169$. Participants in the *Loss* group reported to have higher perspective taking for the individuals in the psychological-pain condition following by the non-painful condition. On the contrary, the *No-Loss* group showed a reverse pattern meaning they could take the perspective of protagonists in the non-painful condition more than psychological-pain condition. Both groups reported to have almost similar perspective taking for the individuals suffering from one sort of physical pain. On average, participants in the *Loss* group reported to have higher perspective taking in all conditions especially in the psychological-pain condition.

For the other dependent variables, the interaction between group affiliation and condition did not reach statistical significance: pain perception, $F(2, 62) = 1.025$, $p = 0.365$, $\eta^2 = 0.032$; feeling, $F(1.654, 51.263) = 0.465$, $p = 0.594$, $\eta^2 = 0.015$; empathic concern, $F(1.107, 34.312) = 0.228$, $p = 0.661$, $\eta^2 = 0.007$, and intention to help, $F(1.292, 40.041) = 2.953$, $p = 0.084$, $\eta^2 = 0.087$. See **Figure 3** for details.

ERP Analysis

Frontal Region ERP Analysis

We performed the mixed-effects analysis and electrode-wise comparison within seven electrodes in frontal regions. First, when we analyzed the ELPP, all main effects of condition, $F(2, 2421.91) = 0.07$, $p = 0.93$, group, $F(1, 38.07) = 0.45$, $p = 0.51$, electrode location, $F(4, 2382.66) = 0.97$, $p = 0.42$, and all interaction effects of condition × group, $F(2, 2422.50) = 0.40$, $p = 0.67$, electrode location × condition, $F(8, 2382.66) = 0.16$, $p = 1.00$, electrode location × group, $F(4, 2382.66) = 1.72$, $p = 0.14$, and electrode location × group × condition, $F(8, 2382.66) = 0.34$, $p = 0.95$, were non-significant.

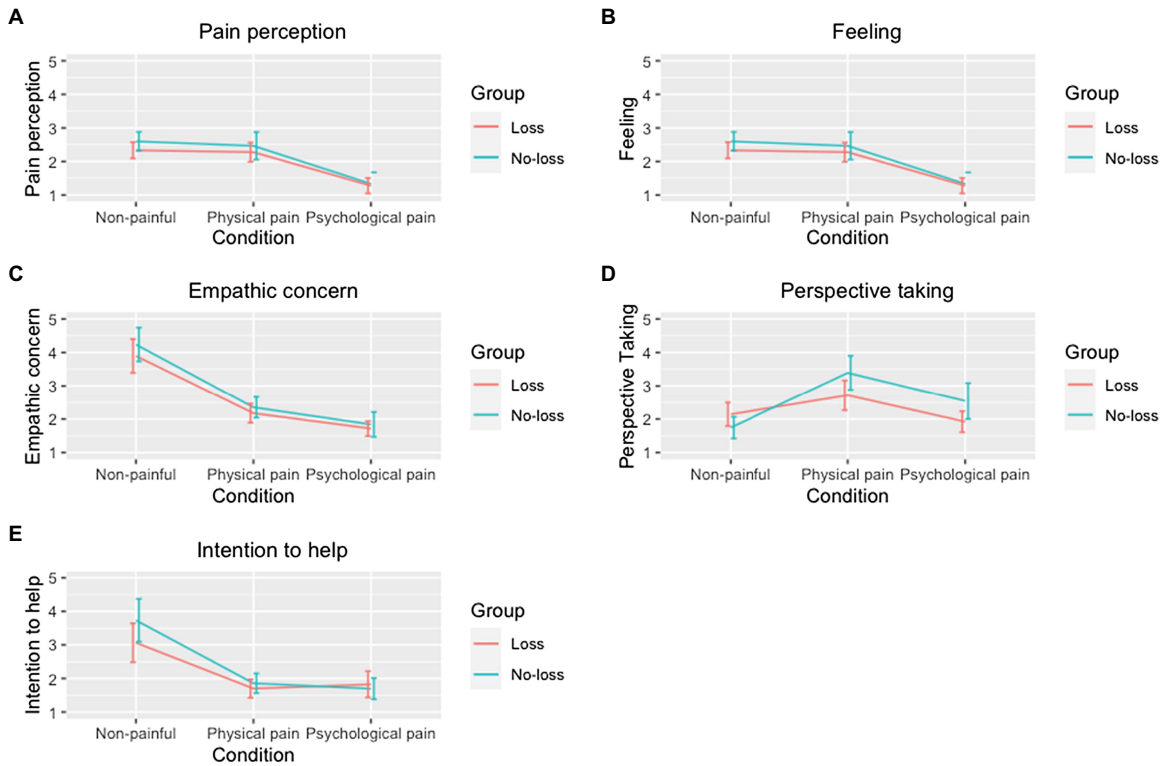


FIGURE 3 | Group comparison based on conditions. **(A)** Pain perception. **(B)** Intensity of feeling. **(C)** Empathic concern. **(D)** Perspective taking. **(E)** Intention to help. Each line plot compares the responses per condition and group within each variable. In the Y-axis, 1 means the strongest response (e.g., the greatest pain judgment), while 5 means the weakest response (e.g., the weakest pain judgment).

Second, in the analysis of the LLPP, we found only the significant main effect of electrode location, F (4, 2356.17) = 6.36, p < 0.001. All other main effects of condition, F (2, 2372.43) = 1.31, p = 0.27, and group, F (1, 26.57) = 0.04, p = 0.84, and interaction effects of condition × group, F (2, 2378.82) = 1.91, p = 0.15, electrode location × condition, F (8, 2356.17) = 0.28, p = 0.97, electrode location × group, F (18, 2356.17) = 0.48, p = 0.75, and electrode location × group × condition, F (8, 2356.17) = 0.45, p = 0.89, were non-significant.

Third, for the analysis of the VLLPP, the main effect of electrode location, F (4, 2352.95) = 4.04, p < 0.01, and the interaction effect of group × condition, F (2, 2388.43) = 4.04, p < 0.05, were significant. However, the main effects of condition, F (2, 2380.99) = 1.62, p = 0.20, group, F (1, 14.78) = 0.29, p = 0.60, and the interaction effects of electrode location × condition, F (8, 2352.95) = 0.86, p = 0.55, electrode location × group, F (4, 2352.05) = 0.35, p = 0.85, and electrode location × group × condition, F (8, 2352.95) = 0.64, p = 0.74, were non-significant.

Whole-Brain ERP Analysis

In addition, we explored whole-brain ERP analysis for each time window. First, we conducted the whole-brain ERP analysis within the ELPP. In this analysis, the main effects of condition, F (2, 9314.30) = 8.23, p < 0.001, and electrode location, F (18, 9591.00) = 133.99, p < 0.001, were significant. The main effect of group, F (1, 44.90) = 3.56, p = 0.07, and all interaction effects, including condition × group, F (2, 9331.80) = 0.62, p = 0.96, electrode location × condition, F (36, 9591.00) = 0.62, p = 0.96, electrode location × group, F (18, 9591.00) = 1.52, p = 0.07, and electrode location × group × condition, F (36, 9591.00) = 0.34, p = 1.00, were non-significant.

Second, from the analysis of the LLPP, we found the significant main effects of condition, F (2, 9394.60) = 12.10, p < 0.001, and electrode location, F (18, 9593.30) = 33.44, p < 0.001, and interaction effect of condition × group, F (2, 9416.0) = 3.34, p < 0.05. All other main effects of group, F (1, 31.00) = 2.47, p = 0.20, and interaction effects of electrode location × condition, F (36, 9593.30) = 0.962, p = 0.96, electrode location × group, F (18, 9593.30) = 0.97, p = 0.49, and electrode location × group × condition, F (36, 9593.30) = 0.37, p = 1.00, were non-significant.

Third, when we examine the VLLPP, the main effects of condition, F (2, 9638.00) = 4.69, p < 0.01, electrode location, F (18, 9582.00) = 9.42, p < 0.001, and the interaction effect of group × condition, F (2, 9642.50) = 9.20, p < 0.001, were significant. However, the main effects of group, F (1, 18.50) = 1.38, p = 0.26, and the interaction effects of electrode location × condition, F (36, 9582.00) = 0.68, p = 0.93, electrode location × group, F (18, 9582.00) = 0.50, p = 0.96, and electrode

location × group × condition, F (36, 9582.00) = 0.83, p = 0.75, were non-significant.

ERP Analysis Within Each Electrode

We analyzed ERP within each electrode with mixed-effects analysis. The analysis was performed within (1) seven hypothesize frontal electrodes and (2) the whole brain. In the cases of the ELPP and LLPP, we could not find any electrode location that showed at least one significant main or interaction effect from both the analysis within seven frontal electrodes and the whole-brain analysis when the false discovery rate correction was applied.

In the case of the VLLPP, we found the significant interaction effect of group × condition only in Fp2 from both the analysis of frontal electrodes, F (2, 425.09) = 5.01, $p < 0.01$, q = 0.02, and the whole-brain analysis, $p < 0.01$, q = 0.05 (see **Figure 4**). When we performed the additional t-tests, we found that participants in the *Loss* group showed significantly lower ERP in Fp2 compared with those in the *No-Loss* group in the psychological-pain condition, t(137.45) = −2.40, $p < 0.05$, D = 0.38. However, such ERP difference was non-significant in the physical-pain condition, t(151.43) = 1.64, p = 0.10, D = 0.25, and non-painful condition, t(153.94) = 0.34, p = 0.73, D = 0.05 (see **Figure 4**). The scalp topography of the VLLPP in the *Loss* condition in both groups is presented in **Figure 5** for readers' information. For additional information, the mean ERPs within the defined time windows across groups are summarized in **Supplementary Tables S1** (for the physical-pain condition), **S2** (for the psychological-pain condition), and **S3** (for the non-painful condition).

Exploratory Correlational Analysis

Given that we found significant ANOVA and electrode-wide analysis results only from the analysis of VLLPP, we focused on this time window in exploratory correlational analysis. The result showed a significant association ($2\log BF \geq 2$) between ERPs, behavioral responses, and IRI subscale scores in the physical-pain condition. Significant correlations were found in these pairs: F4 and pain perception, r = 0.40, $2\log BF$ = 2.64; T3 and intention to help, r = 0.39, $2\log BF$ = 2.29; C4 and IRI-PT, r = −0.39, $2\log BF$ = 2.31; and Cz and IRI-PD, r = 0.40, $2\log BF$ = 2.60.

DISCUSSION

This study compared the empathic behavior (in forms of dispositional and situational empathy) and neural correlation of participants toward observing strangers in painful (physical and psychological) and non-painful conditions. In addition, the effect of having prior experience of psychological pain on empathic reactions was assessed. For this study, participants were grouped into *Loss* and *No-Loss* based on prior experience of grief. As the result of behavioral analysis indicated, prior experience of psychological pain did not affect participants' dispositional empathy as observed in self-reported questionnaire. Both groups reported to have higher affective empathy than cognitive empathy. This result was in line with previous study in which American college students answered the IRI self-reported questionnaire and had a higher score on affective empathy (Yaghoubi Jami et al., 2019). On the other hand, having first-hand experience of psychological pain did affect situational cognitive empathy; those with an experience of psychological pain reported to have higher ability in understanding another individual in psychologically painful condition. Moreover, ERP analysis suggested that participants with prior loss experience demonstrated significantly lower activity in right frontal region, Fp2, within VLLPP time window in the psychological-pain condition compared with those without prior loss experience.

Participants' empathic responses when observing different types of pictures support the validity of this study. As expected, non-painful pictures received the lowest ratings in all aspects of empathic reaction. The pictures in this category were intended to trigger no pain, no negative emotion, and no empathic concern, and there was no need for participants to help the pictures' protagonists, as there was no suffering involved in the pictures of this category. Given the nature of pictures and participants' reactions in this category, it could be concluded that this study was successful in capturing people's reaction to different types of pain.

Discussion on Behavioral Analysis Results

Conditions and Aspects of Situational Empathy

As expected, the *loss/no-loss* condition affected participants' empathic responsiveness across assessments. Regardless of prior experience of psychological pain, all participants reported feeling higher levels of pain after observing another grieving individual than witnessing others' physical pain. The findings that feeling more pain from others' psychological pain along with feeling almost no pain after observing a non-painful picture suggest that participants could accurately judge the situation and had a precise understanding of the other person's physical and emotional states. Similar results were found in previous studies in which participants with and without prior experience of pain reported similar amount of pain resulted from observing others' pain (e.g., Batson et al., 1981; Yaghoubi Jami et al., 2021). Unlike the position advanced by Nordgren et al. (2011), our findings suggest that having a first-hand painful experience is not necessarily linked to an accurate estimation of others' emotional pain. However, it is possible that having a similar pain perception may not lead to empathic responsiveness; therefore, other aspects of empathy (e.g., feeling, empathic concern, and perspective taking) need to be considered.

The reported feelings after observing different types of pictures were interesting; sadness, distressed, and happy were the most frequent feelings reported after observing psychological, physical, and non-painful pictures, respectively. This result is consistent with previous studies in which similar emotions were evoked by different painful stimuli (Yaghoubi Jami et al., 2021). Feeling sadness for others' grief is not a surprising emotion as psychological pain is recalled as the "most negative experience in life" (Jaremka et al., 2011, p. 46). Similarly, psychological-pain condition triggered the highest levels of empathic concern as well as intention to help compared to

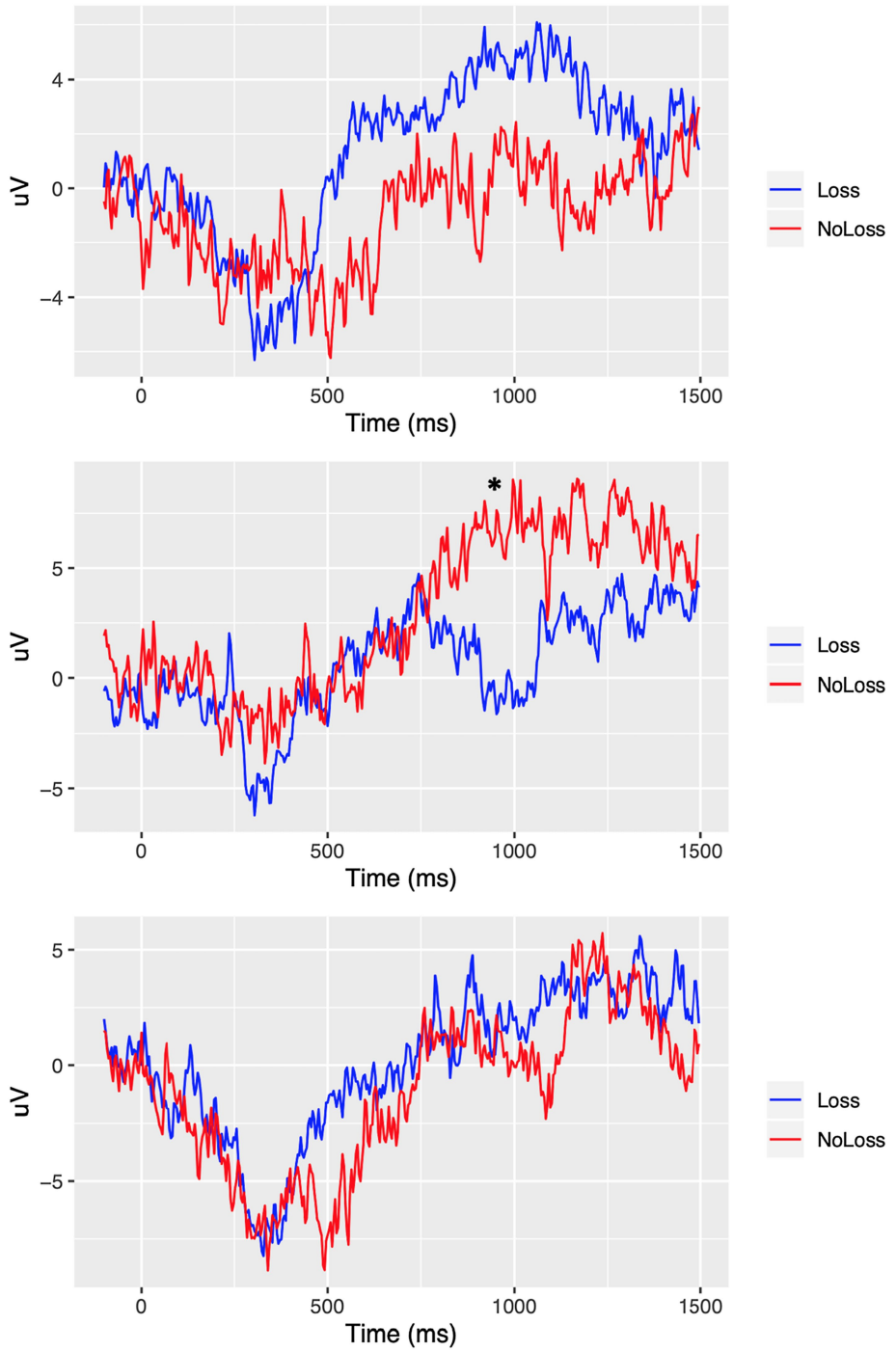


FIGURE 4 | ERP comparison in Fp2 between *Loss* versus *No-Loss* groups. Top: physical-pain condition. Middle: psychological-pain condition. Bottom: non-painful condition. * represents a significant different at $p < 0.05$ (FDR adjusted).

the other two conditions. Considering the non-significant effect of prior experience of psychological pain on participants' dispositional empathy (i.e., self-reported questionnaire), it is not surprising to observe both groups rated the same amount of empathic concern and were willing to alleviate the suffering of strangers in psychological pain.

Prior Psychological Pain Experience and Situational Empathy

The only aspect of empathy affected by prior experience of psychological pain was participants' ability in taking others' perspective. That is, those who had lost a loved one were more able to understand the pain caused by similar incidents.

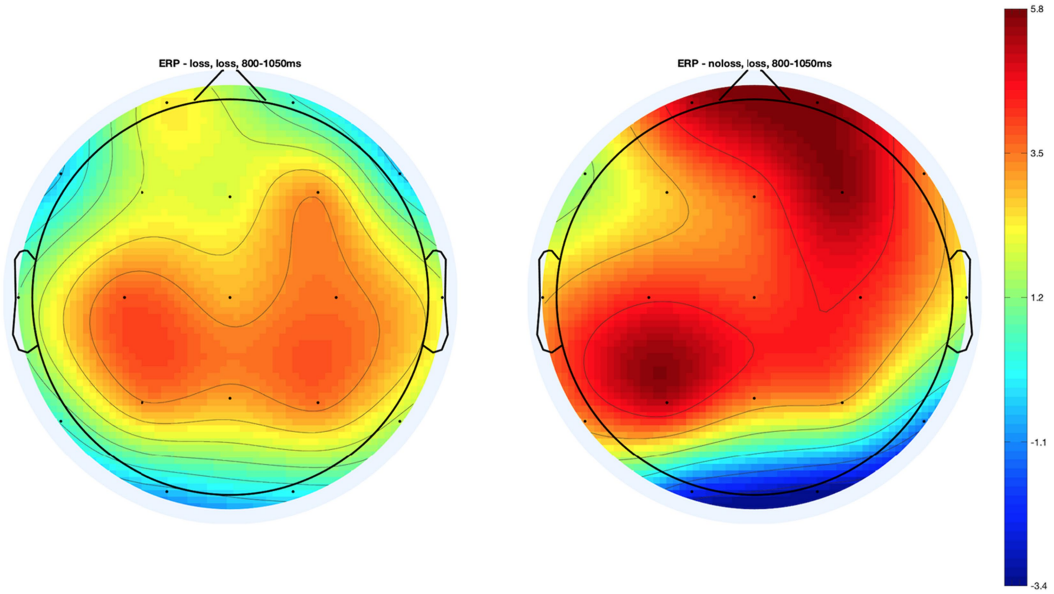


FIGURE 5 | Topography maps of the very late Late Positive Potential (VLLPP) in the *Psychological-pain* condition in two groups.

Recently, Yaghoubi Jami et al. (2021) argued that a comprehensive understanding of psychological pain is attributed to the observer's personal experiences regarding similar sources of pain. Accordingly, an observer's empathic response to someone else's pain is tied to their personal experience of the same type of pain. This finding suggests that although pain can come in a variety of forms – pain as a result of a physical injury, social isolation, or losing a loved one (Eisenberger, 2012) – it may be that experience of pain in one context enhances the individual's ability to experience empathy, but not in another painful context. For example, an individual with experience of social exclusion could feel the pain of another individual in a similar situation (i.e., social isolation) but might have limited understanding of grieving person's pain and suffering. Given the rationale proposed by Hoffman (2001) for how having shared experience could facilitate empathy by bringing back memories and feeling associated with such experiences, it seems that such experiences helped participants to develop a more accurate understanding of similar traumas and be more aware of emotional states caused by this type of pain.

Discussion on ERP Analysis Results

Whole-Brain ERP Analysis

In our ERP analysis, as expected we found significant difference in the VLLPP in Fp2 between the *Loss* versus *No-Loss* groups in the psychological-pain condition. This result suggests that the prior experience of grief may be associated with the brain activity in the frontal region near Fp2. According to Hajcak et al. (2010), the increased VLLPP is associated with the increased intensity of emotional arousal after watching pleasant or unpleasant visual stimuli. In addition, prior research has shown that right frontal region, which is connected with Fp2, is related to emotional aspects of empathic responses to painful situations (Decety and Jackson, 2004; Leigh et al., 2013; Reniers et al., 2014). Furthermore, more directly, Maratos et al. (2000) reported that the LPPs in an electrode attached on the right prefrontal region, which corresponds to Fp2 in the present study, were significantly associated with perception of novel negative emotional stimuli; the LPPs in the same electrode were significantly smaller while perceiving old stimuli. The findings from Maratos et al. (2000) might suggest that the right prefrontal region corresponding to Fp2, which was analyzed in the present study, shall be focused while analyzing the LPPs associated with emotional perception. Given these, the relatively decreased Fp2 VLLPP among participants who experienced prior psychological pain perhaps suggests that such participants might be less strongly aroused by visual stimuli presenting others' loss compared with participants who did not experience any prior loss.

One explanation for less emotional arousal for people with an experience of psychological pain could be linked to emotional numbness. Experiencing a negative emotional state, such as grief, could affect people capacity in being sensitive toward others' pain as well as their pain tolerance (Twenge et al., 2007). This alteration may serve as a survival mechanism for the grieving individual; individuals protect themselves from further harm by becoming emotionally numb or detached. Therefore, these individuals might not be as aroused as those without such painful experience when they see another individual in the same situation. Nevertheless, less emotional arousal does not mean they cannot be empathic, or their empathic behavior is decreased as a result of their experience. This argument can be supported by the result of our behavioral analysis and a previous study in which participants stated that their painful experience actually helped them acquire a deeper understanding toward the person in the same situation (Yaghoubi Jami et al., 2021).

Interestingly, the observed decrease in the VLLPP in Fp2, which is associated with emotional empathic responses to pain (Decety and Jackson, 2004; Leigh et al., 2013; Reniers et al., 2014), among participants in the *Loss* group is consistent with the findings from behavioral analysis and prior research on loss. At the behavioral level, the *Loss* group showed significantly higher perspective taking in the psychological-pain condition as compared to the *No-Loss* group. However, there was no difference in affective empathy or emotional arousal in the psychological-pain condition between the two groups.

Previous behavioral studies have indicated that although people are often significantly depressed after bereavement, a negative emotional state is likely to be negated in 1–2 months (for review, see Dutton and Zisook, 2005). Moreover, Preis and Kroener-Herwig (2012) reported that having previous painful experience was significantly positively associated with perspective taking; however, the same experience was not significantly associated with emotional reaction. Given this previous research, it may be that people experience emotional and cognitive adaptation after loss. Therefore, in the current study, participants who experienced loss did not necessarily show increased affective arousal, but showed more cognitively sophisticated reaction, such as perspective taking, in the psychological-pain condition. It is interesting to note that our findings at the neural level are consistent with this view since the eventual adaptation to loss would be associated with decreased VLLPP activity in Fp2.

Correlation Between ERP and Behavioral Responses

Interestingly, the VLLPP analyses did not indicate any significant correlations in the psychological-pain condition. Given that the ERP in Fp2 in this condition was significantly different between *Loss* and *No-Loss* groups, it may be that the ERP in processing this type of stimuli, the psychological pain, might be more closely associated with prior experience rather than behavioral responses or dispositional empathy. This relationship was reversed in the physical-pain condition, which was supposed to present physical-pain stimuli that might be perceived to be vivid to all participants regardless of their prior experience of pain.

As argued by Nordgren et al. (2011), people may have a better understanding of others' psychological pain only if they experienced the same pain. This effect is likely the result of remembering one's own experiences accompanied by associated emotions (Hoffman, 2001). However, when encountering a person experiencing the agony of grief, most people would be motivated to help in preventing the life-threating consequences of complicated grief (Bosticco and Thompson, 2005; Mee et al., 2006; Goodrum, 2008). As de Waal (2010, p. 124) stated, "advanced empathy requires both mental mirroring and mental separation"; therefore, to efficiently help someone who needs us, one needs to be aware of self-other boundaries and mentally separate their emotional state from the other individual to behave empathically.

Limitations and Suggestions for Future Research

Each study has some limitations that could threaten the generalizability of its results and interpretations. The current study is no exception, and our results should be interpreted with caution especially before making any generalizations to the larger population. Perhaps, the most important limitation of the present study is related to sample size in each group. As stated previously and given the exploratory nature of the study, we determined the sample size based on similar published studies. However, we noted that the number of relevant studies was not large, which limited the guidance they provided. Our results may help highlighting the needs for conducting more studies on empathic behavior and psychological pain to better estimate the required sample size.

In addition to sample size concerns, we would note that there were unequal numbers of participants in each group. Although the sample size inequality was very small and any characteristic differences between each group were controlled for in the analysis, still it may be that the unbalanced groups affected the observed results. Therefore, replicating this study with the goal of increasing the power of analysis could be a promising area for future studies.

Another limitation was related to unbalanced number of female and male participants in each group. As noted previously, there were more female participants in each group. Although the present study applied Type III Sum Squares, the suggested analytical approach for unbalanced sample sizes (Pituch and Stevens, 2015), the present study failed to explore gender differences in participants' responses. There is numerous theoretical and empirical evidence showing gender effect on empathic responses (Yaghoubi Jami et al., 2019); thus, future studies may benefit from having balanced number of male and female participants in exploring the relationship between prior psychological pain and empathy.

Stimulus selection could also pose a limitation to this study. Specifically, the number of trials in each condition was limited, which could affect the result and interpretation. Considering the existing database for psychological pain has been used in only one previous study (Yaghoubi Jami et al., 2021), it was not possible to include more validated pictures in each condition. Future studies can follow the same procedure of validation with a different picture pool and create a larger standardized picture database.

Finally, the EEG recording system has some limitations. This study used a 21-channel EEG; therefore, the recorded data are limited. Although there is no clear guideline regarding the minimum required number of channels for ERP analysis, some have suggested that robust ERP sources are efficiently captured with an EEG system using 35 channels (Lau et al., 2012). Thus, further investigations employing an EEG system with more electrodes might be beneficial to address any signal quality-related issue that might exist in the current study.

CONCLUSION

In the present study, we examined participants' behavioral responses to different types of painful (in the form of physical and psychological pain), and non-painful contexts and the neural correlates associated with these contexts. Our statistical analyses focused on the associations between the stimulation type, prior painful experience, behavioral responses, and ERPs. The findings from both the behavioral and neural components of the study demonstrated that empathic reactions—in form of pain intensity, subjective feeling, empathic concern, perspective taking, and intention to help—were dependent on the type of conditions. In addition, the presence of prior psychological painful experience was also significantly associated with the differences in behavioral and neural responses particularly in cognitive empathy. These findings provide useful insights about directions for future research examining factors associated with empathic responses in painful situations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the University of Alabama. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PJ, ST, BM, and RH contributed to conception and design of the study. PJ conducted the experiments and collected the data. PJ and HH performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.689304/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 23 November 2021
doi: 10.3389/fnbeh.2021.760547

TNF-α Induces Methylglyoxal Accumulation in Lumbar Herniated Disc of Patients With Radicular Pain

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Lumbar disc herniation (LDH) with radicular pain is a common and complicated musculoskeletal disorder. Our previous study showed that LDH-induced methylglyoxal (MG) accumulation contributed to radicular pain. The underlying mechanisms through which MG accumulates are poorly understood. In the present study, we found that both MG and tumor necrosis factor-alpha (TNF-α) levels in the herniated disc of patients with radicular pain were significantly increased, and the activity of Glyoxalase 1 (GLO1), the rate-limiting enzyme that metabolizes MG, was decreased. In rats, the LDH model was mimicked by implantation of autologous nucleus pulposus (NP) to the left lumbar five spinal nerve root. The mechanical allodynia was observed in LDH rats. Besides, MG and TNF-α levels were increased, and GLO1 activity was significantly decreased in the implanted NP. In cultured rat NP cells, stimulation with the inflammatory mediator TNF-α reduced GLO1 activity and expression. These results suggested that TNF-α-induced GLO1 activity decrease contributed to MG accumulation in the herniated disc of patients with radicular pain.

Keywords: lumbar disc herniation, methylglyoxal, TNF-α, pain, GLO1

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Pathological Conditions, a section of the journal Frontiers in Behavioral Neuroscience

Received: *18 August 2021*
Accepted: *20 October 2021*
Published: *23 November 2021*

Citation:
Zhang X, Wang X, Gao L, Yang B, Wang Y, Niu K, Lai J, Wan S and Luo J (2021) TNF-α Induces Methylglyoxal Accumulation in Lumbar Herniated Disc of Patients With Radicular Pain. Front. Behav. Neurosci. 15:760547. doi: 10.3389/fnbeh.2021.760547

INTRODUCTION

Lumbar radicular pain after intervertebral disc herniation is one of the most prevalent causes of physical disability. It is caused not solely by mechanical compression of the nerve root but also by the release of many inflammatory molecules (Takahashi et al., 1996; Ahn et al., 2002; Scuderi et al., 2006; Pedersen et al., 2015). Clinical data indicate that 20–76% of nerve root compression due to a disc herniation is painless, and some cases with slight disc herniation suffer severe pain (Takada et al., 2001; Djuric et al., 2020). Therefore, a chemical factor may play an important role in radicular leg pain, following lumbar disc herniation (Andrade et al., 2013; Hasvik et al., 2019; Wang et al., 2020). Experimental studies indicate that inflammatory molecules are released from leaked nucleus pulposus (NP) and attracted immune cells, which include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), metalloproteinases, cyclooxygenase-2, nitric oxide, and so on (Andrade et al., 2011; Pedersen et al., 2015; Djuric et al., 2020).

The intervertebral disc is the largest avascular and immune-privileged tissue in our body. Oxygen and glucose diffused into the disc can be exhausted when nucleus pulposus material

degenerates or herniates into the epidural space (Guehring et al., 2009). Therefore, glycolysis has been enhanced as the main source of energy for disc cells. Methylglyoxal (MG), as the reactive glycolytic by-product, has serious toxicological effects when it is excessively accumulated. Increased MG was found in cerebrospinal fluid of patients with Alzheimer's disease, and this was associated with poorer cognitive function and lower brain volume (Angeloni et al., 2014). The levels of plasma MG in patients who experienced diabetic pain were significantly higher than those in patients with diabetes without pain (Bierhaus et al., 2012). Previous data from our group suggest patients who suffered from a lumbar disc herniation (LDH)-induced pain had elevated plasma methylglyoxal (MG) levels and increased MG in dorsal root ganglions (DRG)-induced radicular pain in a rat model of lumbar disc herniation (Liu et al., 2017). It is well-known that the glyoxalase system is the main enzyme that metabolizes MG, especially GLO1, as the rate-limiting step of this series of reactions uses L-glutathione (GSH) as a cofactor (Gaffney et al., 2020). Previous studies have shown that GLO1 levels and activity can be altered in disease states, including diabetes, cardiomyopathy, and endothelial dysfunction (Jack et al., 2012; Skapare et al., 2013; Hanssen et al., 2014; Yumnam et al., 2020). Therefore, both GLO1 and GSH are key factors in maintaining MG at low tolerable levels, preventing protein and cell dysfunction. However, we still do not know where MG is released from and how it increases in patients with LDH with radicular pain. Herein, we hypothesize that, when NP material herniates into the epidural space, inflammation factors including TNF-α are released, which decreases GLO1 activity and increases the MG level in a herniated disc.

MATERIALS AND METHODS

Patients and Volunteers

This study was approved by the Ethics Committee at Henan Provincial People's Hospital, Zhengzhou University. Thirty patients were prospectively enrolled at the Spinal Surgery Department and included 20 patients with LDH, suffering from radicular leg pain for less than 3 months and 10 patients with scoliosis or lumbar burst fracture as the control without leg painful symptomatology or degenerative disc disease. The LDH patient group had a mean age of 43 years and consisted of 11 men and 9 women. The control patient group had a mean age of 36 years and consisted of seven men and three women. Patients with LDH had assessed the intensity of leg pain on a 0–10 (0, no pain; 10, worst pain) visual analog scale (VAS) 1 day before discectomy. Patients with LDH were divided into two groups according to their preoperative pain scores (VAS $\leq$ 3 as mild pain group; VAS $\geq$ 4 as severe pain group). Intraoperative-collected herniated disc (HD) tissues, obtained during discectomy in patients with LDH and during orthopedic surgery in control patients, were collected. Immediately upon collection, tissues were divided into two parts. One part was flash frozen in liquid nitrogen and stored at −80°C for further use, and the other part was fixed in 4% formaldehyde solution for histopathological assessment.

Animals and Surgery

Male Sprague Dawley rats (200–220 g) were obtained from the Institute of Experimental Animals of Zhengzhou University. All rats were housed in a temperature- and humidity-controlled environment on a 12/12-h light/dark cycle and provided with food and water *ad libitum*. All experimental procedures were approved by the Institutional Animal Care Committee of Zhengzhou University and were carried out in accordance with the guidelines of the National Institutes of Health Guide for the care and use of laboratory animals. Efforts were made to minimize animal suffering and to reduce the number of animals used.

Surgery for the lumbar disc herniation model was performed as previously described by Anzai et al. (2002) and Liu et al. (2017). In brief, rats were anesthetized intraperitoneally with sodium pentobarbital (50 mg/kg), and laminectomies were performed in which the left L5 nerve roots and corresponding dorsal root ganglion (DRG) were exposed. Autologous NP harvested from the coccygeal intervertebral disc was applied to the left L5 nerve roots just proximal to the corresponding DRG. The surgical procedure in the sham group was identical to the LDH group except for the application of NP to the left L5 nerve roots. TNF-α inhibitor (500 μg Etanercept) was injected into the implanted NP after the application of NP to the left L5 nerve roots. The dose of Etanercept was determined based on the results from previous experiments (Horii et al., 2011; Inage et al., 2016). Special care was taken to prevent infection and minimize the influence of inflammation.

Behavioral Test

The 50% withdrawal threshold was assessed using von Frey hairs as described previously (Chaplan et al., 1994). Briefly, each rat was loosely restrained beneath a plastic box on a metal mesh for at least 15 min one time daily for 3 separate days, and mechanical allodynia in the LDH and sham groups were examined 1 day before surgery. Following 7 days of recovery, the test was performed weekly until 4 weeks postoperatively. Mechanical allodynia was assessed by the hind paw withdrawal threshold in response to probing with a series of von Frey filaments (bending force from 0.55 to 20.30 g) for 6 s or until the rat withdrew. A nociceptive response was defined as a brisk paw withdrawal or flinching of the paw, following von Frey filament application. Each test was repeated two to three times at approximately 2 min intervals, and the average value of von Frey filament force was determined as the force to evoke a withdrawal response. The experimenter who conducted the behavioral test was blinded to all treatments.

Western Blot

The herniated disc tissue was collected and immediately stored at −80°C until use. The tissue was homogenized on ice. Protein samples were separated by gel electrophoresis (SDS-PAGE) and transferred onto a PVDF membrane. The blots were incubated with a primary antibody against GLO1 (1:200, ABCAM, United States) and β-actin (1:2,000, Cell Signaling Technology, United States) overnight at 4°C according to the instructions

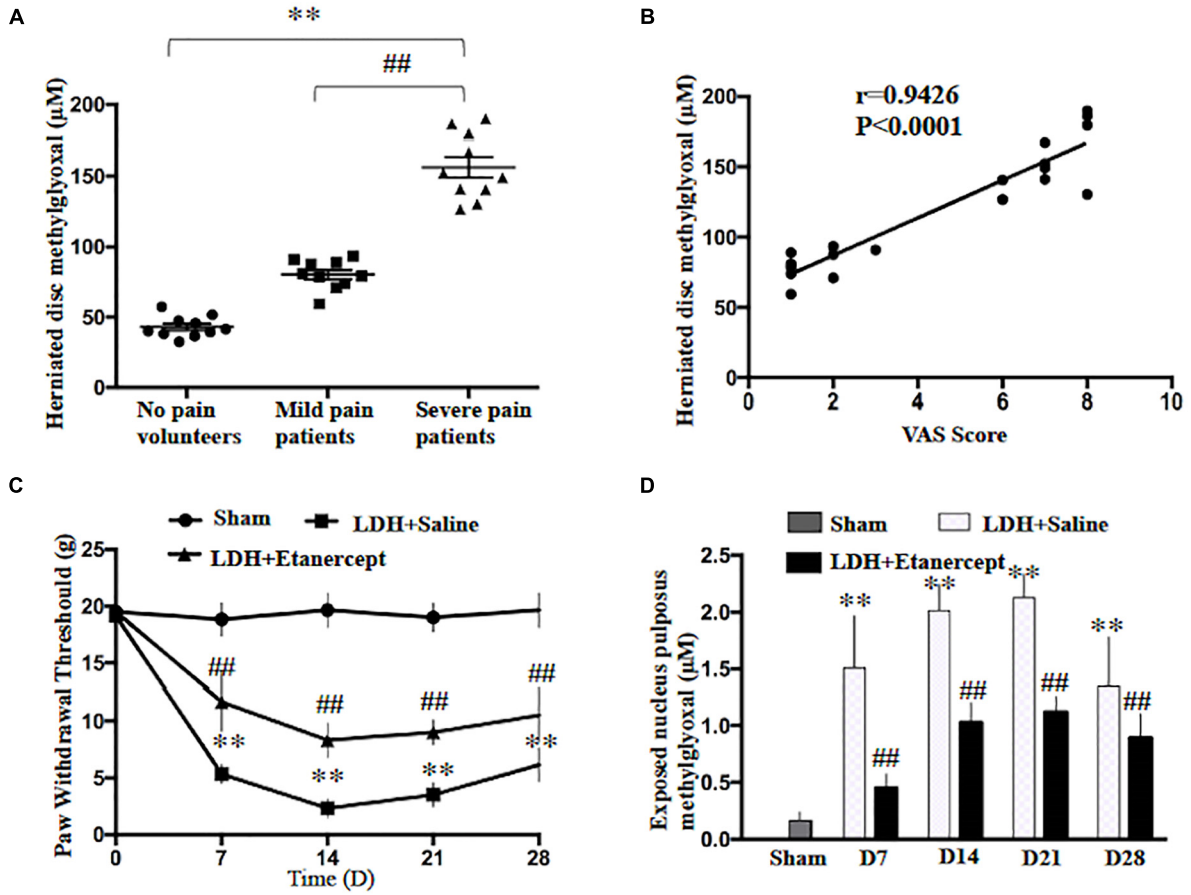

FIGURE 1 | Lumbar-herniated disc (LDH)–induced radicular pain and methylglyoxal (MG) accumulation in herniated disc. **(A)** MG levels were evaluated in herniated disc of the patients or volunteers (One-way ANOVA: $F = 143.679$, $p < 0.001$; *post hoc* Dunnett: $^{**}p < 0.001$, volunteers with no pain vs. patients with severe pain. $^{\#\#}p < 0.001$ patients with mild pain vs. patients with severe pain, $n = 10$). **(B)** The analysis of linear correlation between visual analog scale (VAS) and the herniated disc MG level in patients. **(C)** The paw withdrawal threshold of rats was significantly decreased following NP implantation (Two-way ANOVA: $F = 3.893$, $p = 0.004$. *Post hoc* Tukey; sham vs. LDH + Saline at 7, 14, 21, 28 days: $^{**}p < 0.001$. Lumbar-herniated disc (LDH) + Etanercept vs. LDH + Saline at 7, 14, and 21 days: $^{\#\#}p < 0.001$, at 28 days: $^{\#\#}p = 0.002$. $n = 6$). **(D)** The MG level of exposed NP was examined at different time points following NP implantation (One-way ANOVA: $F = 37.061$, $p < 0.001$. *Post hoc* Dunnett: sham vs. LDH + Saline at 14 and 21 days: $^{**}p < 0.001$, at 7 days: $^{**}p = 0.005$, at 28 days: $^{**}p = 0.007$. One-way ANOVA, LDH + Etanercept vs. LDH + Saline: $F = 29.944$, $^{\#\#}p < 0.001$ at 7 days; $F = 71.625$, $^{\#\#}p < 0.001$ at 14 days; $F = 54.421$, $^{\#\#}p < 0.001$ at 21 days; $F = 5.464$, $^{\#\#}p = 0.042$ at 28 days. $n = 6$).

of the manufacturer. The blots were then incubated with a secondary antibody. ECL (Pierce, United States) was used to detect the immune complex. After exposure for 2 min, the bands were achieved under Chemiluminescence and Fluorescence Imaging System (G:BOX XT4, Syngene, United Kingdom). The bands were quantified with a computer-assisted imaging analysis system (NIH Image J).

Culture of Nucleus Pulposus Cells

Nucleus pulposus cells were collected from the lumbar disc of 10 male Sprague-Dawley rats (3 months old). All experimental procedures described below were reviewed and approved by the Ethics Committee at Henan Provincial Peoples' Hospital, Zhengzhou University, China. In brief, the rats were killed by an intraperitoneal overdose injection of 10% chloral hydrate, and the NP tissue was collected from the coccygeal intervertebral disc under aseptic conditions. After cutting the tissues into 1×1 mm^3 sections, 0.2% type 2 collagenase (Sigma-Aldrich, St. Louis, MO, United States) was added and digested for 4 h. After washing with phosphate-buffered saline (PBS) and centrifuging for 5 min at 1,500 *g*, the isolated cells were cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS) and antibiotics (100 U/ml penicillin and 100 U/ml streptomycins) at 37°C in a 5% CO_2 incubator. The total number of cells was less than 1,000. NP cells from the second passage were treated with different doses of TNF-α.

Glyoxalase 1 (GLO1) Activity Assays

Nucleus pulposus material was dissected on dry ice and stored at −80°C until use. The samples were homogenized, and the supernatant was collected for further assays. The total protein concentration was determined using the BCA Protein Assay Kit

(Pierce, United States). GLO1 activity was measured as described by Hovatta et al. (2005) and the Glyoxalase 1 Assay Kit (Sigma-Aldrich, United States) according to the instructions of the manufacturer. The GLO1 activity rate was calculated by the absorbance at 240 nm.

Reduced/Oxidized Glutathione (GSH/GSSG) Ratio Detection Assays

The GSH/GSSG ratio was measured by using the described method with a minor modification (Baig et al., 2020). Briefly, NP material was dissected on dry ice and stored at −80°C until use. The samples were homogenized in 1.5 ml of a cold homogenization buffer for 1 min, and the supernatant was collected for further assays. GSH and GSSG were quantified on a fluorescent microplate reader at an excitation/emission wavelength set to 490/520 nm. Absolute amounts of GSH and GSSG were determined using GSH and GSSG standard curves.

Methylglyoxal (MG) Determination by HPLC

The concentration of methylglyoxal was determined by HPLC using a simple derivatization procedure (Liu et al., 2017). Briefly, NP material was homogenized on dry ice, and the supernatant sample was supplemented with internal standard 5-methylquinoxaline (5-MQ) and the o-phenylenediamine (o-PD) at room temperature for 4 h. Perchlorate (PCA) was added to the derived sample and incubated on ice for 10 min. Methylglyoxal (2-MQ) and the quinoxaline internal standard (5-MQ) were measured using the conditions below. The analysis conditions were applied as follows: detector wavelength, 315 nm; mobile phase flow rate, 1. ml/min; typical sample size, 15 μl; and column temperature, 20°C. Duplicate injections of each sample were made. Samples were calibrated by comparison with a 2-MQ standard. The average retention times of 2-MQ and 5-MQ were 3.76 and 7.55 min, respectively.

Statistical Analysis

All results are statistically confirmed SPSS 13.0 (SPSS, United States) and expressed as mean ± SEM. Statistical differences between the two groups were analyzed by one-way ANOVA. One-way or two-way ANOVA with repeated measures followed by Tukey, Dunnett, or Bonferroni *post hoc* test was carried out to compare differences between more than two groups. The criterion for statistical significance was $p < 0.05$. Complete statistical analysis is detailed in figure legends.

RESULTS

Increased Methylglyoxal Levels in Herniated Disc Contribute to Radicular Pain Induced by Lumbar Disc Herniation

In the present study, we first found that the methylglyoxal levels of the herniated disc were significantly increased in the patients who suffered from the radicular leg pain accompanied by LDH compared with the patients with no-leg pain (**Figure 1A**). The analysis of Pearson correlation showed a strong positive linear correlation between VAS scores and a herniated disc MG level in patients with LDH (**Figure 1B**). To further investigate the causal relationship between MG- and LDH-induced radicular pain, the mechanical withdrawal threshold and the MG level in exposed NP tissues were examined in a rat NP implantation-induced LDH model. These animals exhibited significant mechanical allodynia on Days 7, 14, 21, and 28 after NP implantation (**Figure 1C**). Meanwhile, the MG level in exposed NP tissues was also significantly increased compared with that in the native NP tissue (**Figure 1D**). Note that the time course of increased MG was consistent with that of mechanical allodynia.

GLO1 Activity Decrease Contributes to Excessive Accumulation of Methylglyoxal in the Herniated Disc

It is well known that the glyoxalase system in the cytoplasm is the main enzyme that metabolizes methylglyoxal and Glo1 as the rate-limiting enzyme and uses L-glutathione (GSH) as a cofactor (Gaffney et al., 2020). In the present study, we found that GLO1 activity of HD decreased in the patients who suffered from the LDH-induced radicular pain compared to the patients with no-leg pain (**Figure 2A**). The analysis of Pearson correlation showed a strong negative linear correlation between VAS scores and herniated disc GLO1 activity in patients with LDH (**Figure 2B**). In comparison with the patients with no-leg pain, immunoblotting and immunohistochemistry showed GLO1 expression decreased significantly in patients with radicular pain (**Figures 2C,D**). However, for GSH, there was no significant difference between patients with LDH-induced radicular pain and patients with no-leg pain (**Figure 2E**). Moreover, both GLO1 activity and expression decreased in the rats with NP implantation compared with that in the native NP tissue (**Figures 2F,G**).

TNF-α Induced Methylglyoxal Accumulation Through Reducing GLO1 Activity in the Herniated Disc and Cultured Nucleus Pulposus Cell

Research showed that stimulation with the inflammatory mediator TNF-α reduced GLO1 activity in human U937 monocytes (Hanssen et al., 2014). In the present study, we found that TNF-α level increased in the patients who suffered from the radicular leg pain, accompanied by LDH compared to the patients with no-leg pain (**Figure 3A**). Meanwhile, the analysis of Pearson correlation showed a strong negative linear correlation between TNF-α and GLO1 activity in HD (**Figure 3B**). To further investigate the relation between TNF-α and GLO1 activity, the primary NP cells were cultured. The GLO1 activity and expression of NP cells exposed to TNF-α were decreased significantly compared with that in the control group (**Figures 3C,D**). Furthermore, etanercept treatment (500 μg), a known TNF-α inhibitor, significantly inhibited the mechanical allodynia induced by NP implantation in the LDH rat model (**Figure 1C**). Meanwhile, etanercept treatment (500 μg) also significantly attenuated the decrease of GLO1 activity and

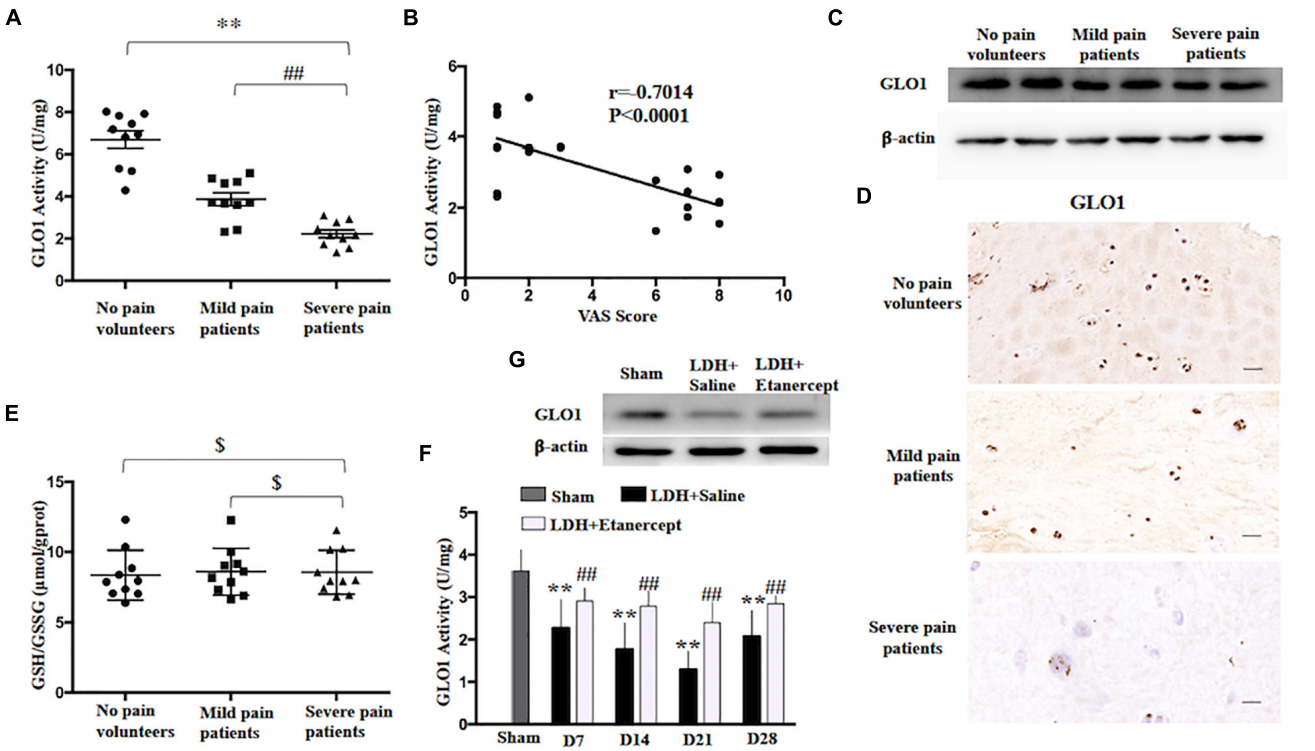

FIGURE 2 | Glyoxalase 1 (GLO1) activity decrease contributes to excessively accumulation of MG in herniated disc. **(A)** GLO1 activity was evaluated in herniated disc of the patients or volunteers (one-way ANOVA: $F = 51.276$, $p < 0.001$; *post hoc* Bonferroni: $^{**}p < 0.001$, volunteers with no pain vs. patients with severe pain. $^{\#\#}p = 0.003$ patients with mild pain vs. patients with severe pain, $n = 10$). **(B)** The analysis of linear correlation between VAS and herniated disc GLO1 activity in patients. **(C,D)** Representative immunoblotting and immunohistochemistry showed the downregulation of GLO1 in herniated disc of patients. **(E)** GSH/GSSG was evaluated in herniated disc of the patients or volunteers (One-way ANOVA: $F = 0.062$, \$ $p = 0.94 > 0.05$. $n = 10$). **(F)** The GLO1 activity of exposed NP was evaluated at different time points, following NP implantation (one-way ANOVA: $F = 13.986$, $p < 0.001$. *Post hoc* Bonferroni: sham vs. LDH + Saline at 14 days and 21 days: $^{**}p < 0.001$, at 7 days: $^{**}p = 0.003$, at 28 days: $^{**}p = 0.001$. One-way ANOVA, LDH + Etanercept vs. LDH + Saline: $F = 8.116$, $^{\#\#}p = 0.017$ at 7 days; $F = 12.039$, $^{\#\#}p = 0.006$ at 14 days; $F = 17.944$, $^{\#\#}p = 0.002$ at 21 days; $F = 8.866$, $^{\#\#}p = 0.014$ at 28 days. $n = 6$). **(G)** Representative immunoblotting showed the downregulation of GLO1 in exposed NP of rats on Day 14 after NP implantation.

expression and the increase of MG in the implanted NP of LDH rat (**Figures 1D**, **2F,G**).

DISCUSSION

Previous studies have shown that MG, as a reactive byproduct of several metabolic pathways in cells, has been linked to painful neuropathies (Bierhaus et al., 2012; Ciobanu et al., 2016; Barragan-Iglesias et al., 2019). Our previous study also showed that MG accumulation contributed to radicular leg pain in patients with LDH and the NP implantation-induced LDH rat model (Liu et al., 2017). But, it is still unknown that where MG is released from and how it increases. In the present study, we found that the MG level in HD of patients who suffered radicular leg pain was significantly higher than that in the patients with no-leg pain. In addition, the MG level in herniated disc positively correlated with a leg VAS score in patients with LDH. Moreover, this phenomenon was verified in the NP implantation-induced LDH rat model. Hence, it is reasoned that MG may be released from the HD.

It is well-known that the glyoxalase system is the main enzyme that metabolizes MG to D-lactate, which is composed of two enzymes, glyoxalase 1 (GLO1) and GLO2. GLO1 is the rate-limiting step of this series of reactions, which uses L-glutathione (GSH) as a cofactor (Gaffney et al., 2020). GLO1 levels and activity can be altered in disease states, including diabetes, cardiomyopathy, and endothelial dysfunction (Jack et al., 2012; Skapare et al., 2013; Hanssen et al., 2014; Yumnam et al., 2020). Therefore, both GLO1 and GSH are key factors in maintaining MG at low tolerable levels, preventing protein and cell dysfunction. A recent study comparing the expression of GLO1 in various inbred mouse strains showed a negative correlation between GLO1 expression and mechanical hyperalgesia, implying that GLO1 might be linked to painful neuropathies (Jack et al., 2012). In the present study, we found that GLO1 activity and expression decreased significantly in the herniated disc of patients with radicular leg pain compared to that in patients with no-leg pain, and there was no difference between groups for GSH. We further found that the increased MG level in HD of patients and exposed NP of the rat model was concurrent with the decreases of GLO1 activity and expression. Therefore,

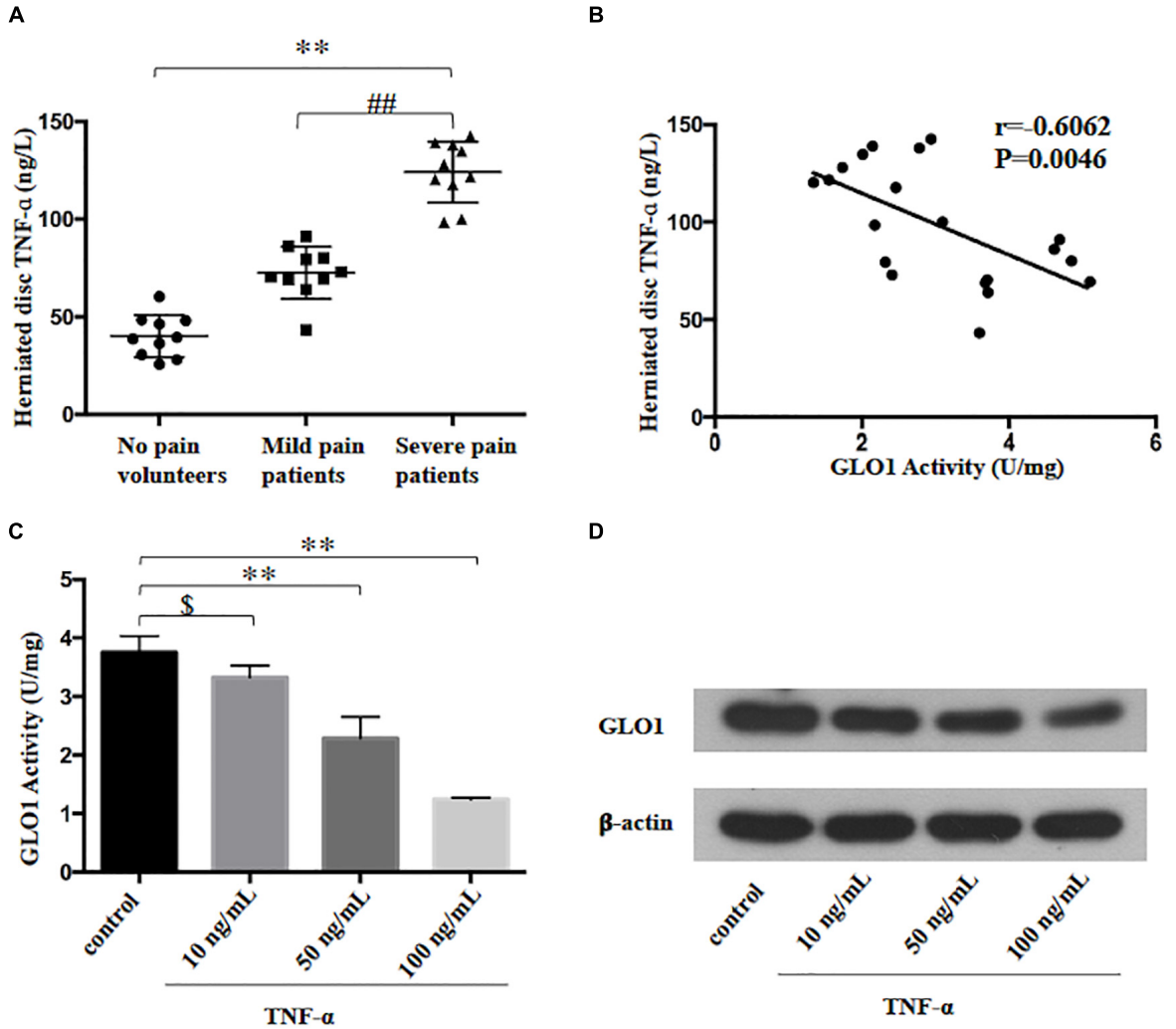

FIGURE 3 | Tumor necrosis factor-alpha (TNF-α)-reduced GLO1 activity and expression in herniated disc and cultured nucleus pulposus cell. **(A)** TNF-α levels were evaluated in herniated disc of the patients or volunteers (One-way ANOVA: $F = 100.443$, $p < 0.001$; *post hoc* Bonferroni: $^{**}p < 0.001$, volunteer with no pain vs. patients with severe pain. $^{\#\#}p < 0.001$, patients with mild pain vs. patients with severe pain, $n = 10$). **(B)** The analysis of linear correlation between TNF-α levels and GLO1 activity in herniated disc of patients. **(C,D)** Both GLO1 activity and expression of NP cells were decreased by different doses of TNF-α (One-way ANOVA: $F = 58.312$, $p < 0.001$; *post hoc* Bonferroni: control vs. 10 ng/ml TNF-α: \$ $p = 0.446$; control vs. 50 ng/ml TNF-α: $^{**}p = 0.001$; control vs. 100 ng/ml TNF-α: $^{**}p < 0.001$).

GLO1 activity decrease may contribute to MG accumulation in a herniated disc.

When the immune-privileged nucleus pulposus migrates out of the normal intervertebral space, an inflammation reaction occurs (Shamji et al., 2010; Takada et al., 2012; Djuric et al., 2020). Various cytokines have been reported in disc biopsy samples from patients with LDH and experimental models (Takahashi et al., 1996; Shamji et al., 2010; Hiyama et al., 2021); among these, TNF-α levels in herniated nucleus pulposus correlate with preoperative pain in patients with LDH (Genevay et al., 2008; Andrade et al., 2016). Rat models showed that the application of a TNF-α inhibitor (etanercept) after disc puncture could decrease mechanical allodynia and downregulate the neuroinflammation factors (Horii et al., 2011). Therefore, we could speculate that an early vicious cycle created by TNF-α-producing pain is perpetuated by different players. Recently, studies have shown that treatment with inflammatory cytokines, such as TNF decreased GLO1 activity in U937 monocytes, which suggested that inflammatory response may be involved in the onset and maintenance of MG excessive accumulation (Hanssen et al., 2014). So, it is possible to reason that TNF-α secreted from herniated nucleus pulposus cells or immune cells reduced the GLO1 activity, which leads to the MG excessive accumulation. In our data, TNF-α expression negatively correlated with GLO1 activity in herniated nucleus pulposus from patients with LDH and exposed NP of the rat model. In cultured nucleus pulposus cells, TNF-α treatment decreased GLO1 activity and increased the accumulation of MG.

Taken together, our study supplies unique data, showing an association between TNF-α and GLO1/MG in a herniated disc. When nucleus pulposus herniates, TNF-α produced from herniated tissue or inflammatory cells may reduce GLO1 expression and activity in herniated nucleus pulposus, which increases the accumulation of MG, eventually inducing radicular pain. However, the TNF-α/GLO1/MG pathway-involved mechanisms underlying radicular pain in the LDH need further investigation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee at Henan Provincial People's Hospital, Zhengzhou University. The patients/participants provided their written informed consent to participate in this study. The animal study was reviewed and approved by the Institutional Animal Care Committee of Zhengzhou University.

AUTHOR CONTRIBUTIONS

XZ conceived the study, participated in its design, carried out the experiment of HPLC, western blot, nucleus pulposus cell culture, and drafted the manuscript. JLu conceived the study, participated in the design, and revised the manuscript. XW, BY, and YW carried out the collection of biopsies. LG and KN performed the statistical analysis and helped to revise the manuscript. JLa and SW carried out the behavioral tests, GLO1 activity assays, and GSH/GSSG assays. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation of China (81801108) and the Programs for Medical Science and Technology Development of Henan (2018010024).

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frontiers in Psychology

ORIGINAL RESEARCH
published: 03 December 2021
doi: 10.3389/fpsyg.2021.743584

Shame Mediates the Relationship Between Pain Invalidation and Depression

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The experience of pain is subjective, yet many people have their pain invalidated or not believed. Pain invalidation is associated with poor mental health, including depression and lower well-being. Qualitative investigations of invalidating experiences identify themes of depression, but also social withdrawal, self-criticism, and lower self-worth, all of which are core components of shame. Despite this, no studies have quantitatively assessed the interrelationship between pain invalidation, shame, and depression. To explore this relationship, participants recounted the frequency of experienced pain invalidation from family, friends, and medical professionals, as well as their feelings of internalized shame and depressive symptoms. As shame has been shown to be a precursor for depression, we further explored the role of shame as a mediator between pain invalidation and depressive symptoms. All sources of pain invalidation were positively associated with shame and depressive symptoms, and shame fully mediated the relationship between each source of pain invalidation and depression. Relative to other sources, pain invalidation from family was most closely tied to shame and depression. Overall, findings indicate that one mechanism by which pain invalidation may facilitate depression is *via* the experience of shame. Future research may explore shame as a potential upstream precursor to depression in the context of pain. Findings provide more insight into the harmful influence of pain invalidation on mental health and highlight the impact of interpersonal treatment on the experiences of people in pain.

Keywords: mental health, self-worth, social support, pain, discounting, pain invalidation

OPEN ACCESS

Edited by:
Qing Zhao,
Chinese Academy of Sciences (CAS), China

Reviewed by:
Fushun Wang,
Nanjing University of Chinese Medicine, China
Sean T. H. Lee,
James Cook University, Singapore

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Specialty section:
This article was submitted to Health Psychology, a section of the journal Frontiers in Psychology

Received: *18 July 2021*
Accepted: *11 November 2021*
Published: *03 December 2021*

Citation:
Boring BL, Walsh KT, Nanavaty N and Mathur VA (2021) Shame Mediates the Relationship Between Pain Invalidation and Depression. Front. Psychol. 12:743584. doi: 10.3389/fpsyg.2021.743584

INTRODUCTION

Pain is an often invisible affliction with neither an obvious outward expression nor a unifying underlying pathology that together with its subjective nature makes it difficult to be supported and/or understood by social circles and healthcare providers alike (Kool et al., 2009, 2010). Lay people, nurses, and doctors frequently think that others are experiencing less severe pain than they report (Guru and Dubinsky, 2000; Marquié et al., 2003; Panda et al., 2006; Mathur et al., 2014; Ng et al., 2019), or sometimes do not believe they are in pain at all (Kool et al., 2009), thus discounting their pain and invalidating their experience. Pain invalidation can involve discounting and/or lack of understanding: Discounting specifically involves disbelieving, dismissing, or punishing a person in pain because of their expression of pain, whereas lack

of understanding may come from people who acknowledge an individual's pain but do not consider it serious, consequential, or requiring support (Kool et al., 2010; Nicola et al., 2019). Importantly, pain invalidation is associated with detrimental effects on mental health and subjective well-being, including greater negative affect, pain disability, pain severity, and most notably, depression (Vangronsveld and Linton, 2012; Kool et al., 2013; Crow et al., 2014; Edlund et al., 2017; Wernicke et al., 2017; Molzof et al., 2020). In addition, qualitative research indicates that experiences of pain invalidation evoke experiences of stigmatization – a societal judgment that enforces shame – and other constructs that are closely tied to shame, such as lower self-worth and social withdrawal (Asbring and Närvänen, 2002; Jones et al., 2004; Drossman et al., 2009; Oehmke et al., 2009; Nicola et al., 2019, 2021). Further support for the relationship between pain invalidation, shame, and depression comes from qualitative research indicating people often feel shame and shame-related constructs, such as self-consciousness, due to the experience of pain itself (regardless of exposure to invalidation) and that illness invalidation broadly is associated with depression (Osborn and Smith, 1998; Smith and Osborn, 2007; Sehlo et al., 2016; Boring et al., 2021). However, no studies have examined shame and depression together directly in relation to pain invalidation.

Shame is a self-conscious emotion characterized by global feelings of inadequacy and low self-worth (Tangney and Dearing, 2003). Shame has been linked to myriad negative psychological constructs, such as depression, anxiety, stress, PTSD, paranoia, and non-suicidal self-injury (Andrews et al., 2000; Robinaugh and McNally, 2010; Pinto-Gouveia and Matos, 2011; Johnson et al., 2014; Schoenleber et al., 2014; Bannister et al., 2018). Shame is also related to pain experiences in general; shame proneness has been found to be higher in those with chronic pain relative to those without (Turner-Cobb et al., 2015), and shame is a common theme described in qualitative reports examining pain experiences (Asbring and Närvänen, 2002; Turner-Cobb et al., 2015; Nicola et al., 2019). Those suffering from chronic pain have reported that the shame they feel is more unbearable than the pain itself (Smith and Osborn, 2007). Scholars have described pain as "an assault on the self" because it leads people to question themselves and their experiences, similar to the ruminative and critical self-views held by shame-prone individuals (Smith and Osborn, 2007; Tangney et al., 2007; Milia et al., 2021). Additionally, people living with chronic lower back pain have described "comparing the self with others" and "withdrawing from others," both of which are behaviors exhibited by those feeling shame (Osborn and Smith, 1998; Tangney et al., 2007). As such, the shame that often is described in relation to the experience of pain itself may be further compounded by pain invalidation.

Ultimately, the power of invalidation lies in its attack on subjective experiences that cannot be objectively observed by others. Experiencing invalidation of any kind is an interpersonal harm that negatively impacts health (Tanaka et al., 2011; Westphal et al., 2016). Invalidation in other domains (e.g., emotional invalidation) is associated with poorer mental health, including shame proneness, depression, anxiety, bipolar disorder, and suicidal behaviors (Johnson et al., 2002; Krause et al., 2003; Fruzzetti et al., 2005; Yap et al., 2008; Crow et al., 2014; Mahtani et al., 2018, 2019; Naismith et al., 2019). Furthermore, the relationship between shame and other interpersonal harms, such as abuse and neglect, has consistently been documented (Feiring and Taska, 2005; Robinaugh and McNally, 2010; Pinto-Gouveia and Matos, 2011; La Bash and Papa, 2014). Frequent exposure to emotional invalidation, abuse, and neglect can lead to the internalization of these events as representative of self, harmfully mirroring the unfounded thoughts of others that one is "globally defective" (Pinto-Gouveia and Matos, 2011; Matos and Pinto-Gouveia, 2014). It is thus similarly possible that consistent exposure to pain invalidation may begin to cause the individual to question or discount not just their pain, but their core feelings and experiences as well, and to hide their pain to meet the expectations of others, gradually developing into internalized shame (Asbring and Närvänen, 2002; Nicola et al., 2019). When these invalidating and shame provoking events become central to one's sense of self, people are then increasingly likely to experience more intense symptoms of depression (Robinaugh and McNally, 2010). Indeed, shame has been recognized as a precursor for the development of depression and may be a primary driver of the established link between pain invalidation and depression (Birk, 2013; Mills et al., 2015).

One limitation of previous studies on pain invalidation and depression is that they have focused on patients with chronic pain, where confounding and mutually reinforcing relationships between these experiences may limit interpretation. Examination of acute pain invalidation might allow for exploration of potential preclinical predictors of depressive symptoms. Further, as acute pain is a primary reason for seeking medical attention (i.e., nearly 50% of all emergency healthcare visits (Chang et al., 2014)), opportunity for invalidation of acute pain in clinical contexts is high. Considering that depression increases the risk of transition from acute pain to chronic pain (Magni et al., 1994; Currie and Wang, 2005; Apkarian et al., 2013), identifying pathways that contribute to depression in acute pain contexts is clinically relevant for both the physical and mental health of the person in pain. However, invalidation of acute pain has received limited attention. Extant studies have observed invalidation in relation to controlled pain applied in the laboratory rather than to naturally occurring pain (e.g., muscle soreness and headache) and have assessed aspects of the pain experience, such as tolerance and intensity or broad psychological constructs (e.g., positive/negative affect) with mixed results (Linton et al., 2012; Moore et al., 2013; Birnie et al., 2017; D'Agostini et al., 2020; Pester et al., 2020). Furthermore, pain invalidation within these studies was often manipulated or influenced by the experimenters, which may not convey the same connotations and magnitude of invalidation that could organically arise during typical social interaction. Importantly, no previous studies have examined the interrelationship between invalidation of naturally occurring acute pain, shame, and depression.

In the current study, we bridge the gaps above and examine the interrelationship between pain invalidation, shame, and

depression. Using self-report surveys, we examined bivariate correlations between frequency of experiences with pain invalidation from three separate domains (family, friends, and medical professionals) and shame and depressive symptoms. To control for potential confounding and mutually reinforcing relationships in the context of chronic pain and to explore potential preclinical predictors, we explored these relationships among young adults without chronic pain. We hypothesized that people who have had their pain invalidated from any source more frequently would report greater shame and depression. Furthermore, as shame is often a precursor for the development of depression, we hypothesized that shame would mediate the relationship between frequency of invalidation experiences and depression (Birk, 2013; Mills et al., 2015).

MATERIALS AND METHODS

Participants

Participants ($n = 478$; $M_{age} = 18.48$, ± 0.82 years old; 328 women, 139 men, 1 identified as "other" (unspecified gender identity), and 10 chose not to disclose gender; and 270 White, 111 Hispanic/Latinx, 53 Asian, 21 multiracial, 9 Black, 2 American Indian/Alaskan Natives, 1 identified as "other" and specified "Hispanic/White," and 11 chose not to disclose racialized group identity) were recruited from a student research pool from September to November, 2020. Inclusion criteria were being at least 18 years of age and free from current chronic pain. Thirty-five participants reported current naturally occurring acute pain (e.g., non-chronic muscle soreness and headache), and 21 were currently taking pain medication. This study was approved by the Texas A&M Institutional Review Board; all participants provided electronic informed consent to agree to participate.

Procedure

This study was part of a larger project assessing the role of shame in pain experiences. The measures described here were presented first. Other measures (e.g., assessment of social and environmental factors) were included to support exploratory secondary analyses. Interested participants completed the study online and were compensated with course credit. The survey was created and accessed within Qualtrics (Provo, UT).[1] The survey took approximately 30 min to complete.

Materials

Pain Invalidation

Pain invalidation was assessed using the Illness Invalidation Inventory (3*I; Kool et al., 2010). Similar to previous studies, the survey was modified slightly to specifically assess invalidation of pain (Molzof et al., 2020). Furthermore, due to the undergraduate population, the sources of Work Environment and Social Services were not included from the original survey, and the domain of Friends was added to tap into more likely and relevant domains encountered by this group. Participants recounted the frequency with which they experienced invalidation about their pain over the previous year from three separate sources – Family ($\alpha = 0.728$), Friends ($\alpha = 0.691$), and Medical Professionals ($\alpha = 0.658$) – in the way described by each item (Kool et al., 2010). Specifically, participants were prompted with "We are interested in how others react to people experiencing pain. Each of the sections below refers to different people in your life. We would like you to rate how often during the past year each person or category of people reacted toward you in the way described. After each statement, select a number between 1 (never) and 5 (very often) to indicate how often they reacted toward you that way. The questionnaire has 3 sections, and you will rate the same reactions a number of times, but referring to different people. If a particular section does not apply to you, you may skip that part of the questionnaire and go on to the next section. Remember, rate the items with respect to how others reacted toward you as a person when experiencing pain." Eight items were asked for each source (e.g., *My family makes me feel like an exaggerator*) using a scale of 1 (never) to 5 (very often). The eight items were averaged within each domain, such that higher total scores represent more frequent experiences of pain invalidation.

Shame

Shame was assessed using the 24 shame items (e.g., *I feel insecure about others' opinions of me*) of the internalized shame scale ($\alpha = 0.929$) using a response scale from 0 (never) to 4 (almost always; Cook, 1988). Total scores were summed such that higher scores indicate greater internalized shame.

Depression

Depression was assessed using the 20-item (e.g., *I was bothered by things that do not usually bother me*) Centers for Epidemiological Studies – Depression scale (CES-D; $\alpha = 0.926$; (Radloff, 1977). Participants responded using a 0 (rarely or none of the time) to 3 (most or all of the time) scale, and total scores were summed such that higher scores indicate greater depression.

Analysis Plan

Analyses were conducted using SPSS (version 25; IBM Corp, Armonk, NY). First, we conducted bivariate correlations to examine the relationship between pain invalidation from each domain with shame and depression. We then probed shame as a mediator between pain invalidation from each separate source and depression using Hayes' PROCESS macro. Confidence intervals were evaluated based on bias-corrected bootstrapping with 5,000 permutations. To control for Type I error increased by conducting three-related mediation models, we used a Bonferroni adjusted α of 0.017 to determine statistical significance. Although not the focus of the current research, we also examined these relationships within-group (i.e., gender and racialized group identity) as an initial test of generalizability.

[1]Qualtrics.com

RESULTS

Descriptive statistics for the predictor and outcome variables are reported in **Table 1**. Prevalence of pain invalidation from all sources was very high in this sample: 99.4% of participants reported some (3*I score > 1) experience of invalidation from family members, 98.9% from friends, and 95.5% from their doctors. Within this sample, the full range of possible responses across invalidation experiences and shame scores was observed. Nearly, a full range of scores for symptoms of depression was seen (max CES-D score = 57), with 59.3% of participants meeting or exceeding the recently suggested cutoff score of 20 indicating a risk for clinical depression (Vilagut et al., 2016).

Greater frequency of pain invalidation from any source was associated with greater shame and depressive symptoms ($0.250 \leq r \leq 0.443$; **Table 1**). Mediation analyses revealed that pain invalidation from family ($B = 6.45$, 95% CI [4.85, 8.04], $p < 0.001$), friends ($B = 5.27$, 95% CI [3.41, 7.12], $p < 0.001$), and medical professionals ($B = 5.59$, 95% CI [3.50, 7.68], $p < 0.001$) had a significant positive total effect on depressive symptoms. The confidence intervals of the indirect effects of pain invalidation from family ($B = 6.42$, 95% CI [5.11, 7.79]), friends ($B = 4.20$, 95% CI [2.73, 5.66]), and medical professionals ($B = 4.53$, 95% CI [2.73, 6.36], $p < 0.001$) on depression through shame also did not include zero. However, this relationship was driven by shame which fully mediated the relationship between invalidation and depression, such that the direct effect of invalidation on depressive symptoms was substantially reduced and was no longer significant for family ($B = 0.03$, 95% CI [−1.15, 1.21], $p = 0.96$), friends ($B = 1.06$, 95% CI [−0.17, 2.29], $p = 0.09$), or medical professionals ($B = 1.05$, 95% CI [−0.33, 2.44], $p = 0.13$). Pain invalidation from each domain strongly predicted increased feelings of shame, which in turn predicted greater symptoms of depression (**Figure 1**). Although not the focus of the current research, we assessed if these results held within certain groups. Results were consistent for men and women separately, except for men/doctor invalidation, with the overall model not significant but trending in the same direction. The results were also consistent for White and Latinx (the most represented minoritized population) participants across all invalidation domains.

DISCUSSION

Pain invalidation is the undermining of the subjective experience of pain by people external to the experience and has previously been linked to depression. Here, we provide evidence that one mechanism by which this interpersonal experience influences depression is through shame. Shame fully mediated the relationship between frequency of pain invalidation – whether from one's family, friends, or medical professionals – and depression symptoms. Shame is ultimately an interpersonal emotion that involves gauging one's self in relation to others' expectations, whether that be behavioral or emotional in nature. When other people invalidate a person's pain, they may communicate that the person in pain is not worthy of empathy or support. This in turn may cause the person suffering from pain to question their own subjective state and their value as a human, creating feelings of shame, and inadequacy. Doubting one's self-worth while still experiencing pain that others do not believe may culminate in depressive states (Mirels et al., 2002; McGregor et al., 2008). This is particularly concerning considering the facilitating role of depression in the transition of acute pain to chronic pain (Magni et al., 1994; Currie and Wang, 2005; Apkarian et al., 2013). To the extent that invalidating acute pain experiences contribute to depression through shame, it may also compound the mutually reinforced depression-pain relationship and increase the risk prolonged trajectories of pain. Although frequency of invalidation experiences was intercorrelated across domains, and all were associated with shame and depression, experiences were distinct and invalidation from family was most strongly correlated with shame. While future studies are needed to support interpretation of this finding, it is possible that those who experience pain invalidation in their home environments may also be subjugated to other forms of invalidation (e.g., emotional) and neglect that also evoke feelings of shame, compounding experiences that could contribute to depression (Mahtani et al., 2018, 2019; Naismith et al., 2019). This may clarify prior research that has demonstrated emotional invalidation from family is associated with depression as well as negative affect, physiological stress reactions (e.g., increased heart rate and skin conductance), reduced social engagement, and maladaptive behavioral responses to distress (Krause et al., 2003; Mountford et al., 2007; Yap et al., 2008; Shenk and Fruzzetti, 2011; Crow et al., 2014; Greville-Harris et al., 2016).

TABLE 1 | Descriptive statistics and bivariate correlations for primary variables of interest.

	Descriptive Statistics				Bivariate Correlations (*r*)			
Variable	**Min**	**Max**	**Mean**	**SD**	**Invalidation: Friends**	**Invalidation: Medical**	**Shame**	**Depression**
Invalidation: Family	1.00	4.63	2.37	0.66	0.349*	0.411*	0.443*	0.347*
Invalidation: Friends	1.00	4.50	2.25	0.59	–	0.406*	0.264*	0.250*
Invalidation: Medical	1.00	4.13	1.85	0.53		–	0.254*	0.239*
Shame	24.00	120.00	61.45	24.23			–	0.781*
Depression	4.00	57.00	24.75	12.33				–

*$p < 0.001$.

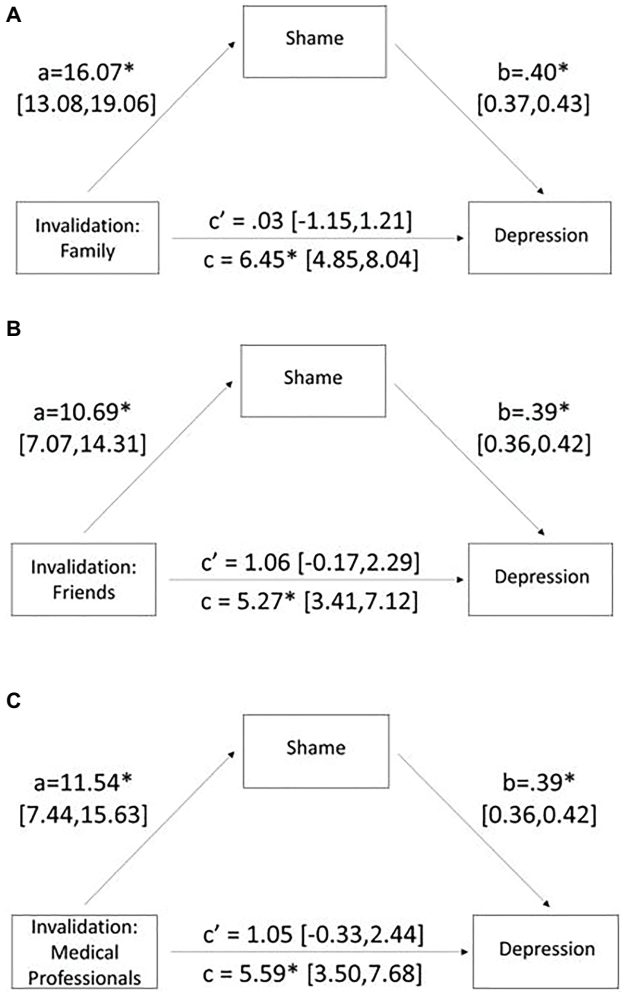

FIGURE 1 | Mediation analysis with pain invalidation as the predictor, shame as the mediator, and depression as the outcome variable for **(A)** pain invalidation from family, **(B)** pain invalidation from friends, and **(C)** pain invalidation from medical professionals. Numbers represent unstandardized betas, and brackets indicate 95% confidence intervals. *$p < 0.001$.

The current study also provides further insight into the social nature of pain. While pain is subjective and felt only by the person experiencing it, the expression and communication of pain exist to enable the person suffering from pain to receive aid (Craig, 2015). Social support (or lack thereof as observed in pain invalidation) is known to contribute to the overall experience of pain, but the specific psychosocial mechanisms through which this occurs are still being uncovered (López-Martínez et al., 2008; Woods et al., 2019). Here, we show that the self-conscious emotion of shame is a potential link between social interactions – specifically pain invalidation – and personal health outcomes in the pain experience. This is partially supported by prior research showing that shame mediates the association between abuse and somatization, as well as between neglect and somatization, suggesting that shame is a key mechanism in facilitating painful health outcomes following forms of interpersonal/social harms (Kealy et al., 2018). As such, the relationship between experiences of pain invalidation, another interpersonal harm, and increased pain severity and disability may also be driven by shame (Molzof et al., 2020).

This is also the first study to our knowledge to examine invalidation of naturally occurring (i.e., not induced in a laboratory) acute pain. The present result that acute pain invalidation is commonly experienced even by healthy young adults points to the prevalence of pain invalidation as a sociocultural norm affecting clinical and non-clinical samples of all ages. Furthermore, we show that experiencing invalidation of acute pain may be harmful to mental health, similar to effects previously demonstrated in chronic pain. As acute pain is highly prevalent in clinical settings, invalidation of acute pain and its correlates of mental health warrant further clinical and empirical attention. Future research may also examine the potential role of invalidation-related increases in depression through shame and the development of chronic pain.

There were limitations to this study that should constrain interpretation. First, the sample was composed of young adults and may therefore not be representative of all those who have experienced pain invalidation. However, the frequency with which the participants indicated they had experienced invalidation suggests that pain invalidation is pervasive and relevant – even among young people without chronic pain. With that said, the relationship between invalidation, shame, and depression should be explored among those suffering from chronic pain to further understand the clinical implications of the current findings. In the current study, we also did not collect information about the type or source of pain that was invalidated by others. Although participants were not suffering from chronic pain at the time of their participation, we are not able to rule out the possibility that some may have experienced chronic pain within the last year nor are we able to distinguish between the range of acute pains that could have received varying levels of invalidation. Such investigations may be the focus of future research. Additionally, we assessed general internalized shame and not shame specifically in response to the invalidating experiences. However, the experiences may be intertwined regardless of assessment of the direct source of feelings of shame, as other findings have linked invalidating experiences with general shame (Mahtani et al., 2018, 2019; Naismith et al., 2019). Future studies may examine pain invalidation-specific shame to determine if this enhances prediction of depression or more fully mediates the relationship between invalidation and depression. Finally, while the percentage of participants at risk for clinical depression may seemingly be higher than what has typically been found in college students (~46%), it must be noted that these data were collected during the COVID-19 pandemic which had been shown to increase symptoms of depression among this group (Vilagut et al., 2016; Acharya et al., 2018; Wang et al., 2020); future studies should attempt to replicate this outside of the presence of a global stressor.

Pain is frequently underestimated or dismissed by others, and the experience of having one's subjective pain experience invalidated confers additional harm and suffering (Guru and Dubinsky, 2000; Marquié et al., 2003; Panda et al., 2006). Validation of pain from providers, family members, and social circles alike (and promotion of such validation through clinical and community intervention)

has the capacity to impact psychological repercussions associated with the experience of pain. Listening to the pain reported by patients and validating their subjective pain experience may foster interpersonal trust between patients and providers and improve pain outcomes. Furthermore, broader cultural understanding about the subjective nature of pain and the importance of social support for those experiencing pain may protect against the mutually reinforcing depression-pain cycle. Ultimately, invalidation of one's internal pain experience may foment shame through self-doubt, self-criticism, and social withdrawal that drives the established link between invalidation and depression. Addressing feelings of shame and validating subjective pain experiences may decrease the burden of depression in the context of pain.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Texas A&M University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BB, KW, and VM contributed to study conception and design. BB and KW collected data. BB conducted data analysis and wrote the first draft of the manuscript. All authors (BB, KW, NN, VM) edited the manuscript, have read the final draft, and have approved submission.

FUNDING

NN was supported by a NSF Graduate Research Fellowship.

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