Behavioral Characteristics and Neural Mechanisms of Pain Processing in Depression

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Abstract

Physiological pain and psychological pain represent two common pain types in depression, and their co-occurrence presents challenges for timely diagnosis, symptom relief, and quality of life improvement in depressive disorders. Literature reviews reveal that compared with healthy controls, depression demonstrates inconsistent pain sensitivity across different types of physiological pain in behavioral indicators, while exhibiting lower pain thresholds, longer duration, and greater distress in psychological pain; regarding neural mechanisms, the characteristic patterns of physiological and psychological pain in patients with depression are similar to those of healthy subjects. Future research should focus on investigating the features of comorbidity between these two pain types and depression, clarifying the factors influencing pain processing in depression, exploring the commonalities and differences between physiological and psychological pain processing in depression, and elucidating the functional neurological changes associated with pain in depression, thereby providing a foundation for more precise diagnosis and more effective treatment.

Full Text

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Abstract

Physical pain and psychological pain are two common types of pain associated with depression, and their coexistence poses challenges for timely diagnosis, symptom alleviation, and quality of life improvement in depressed patients. A review of the literature reveals that, compared to healthy controls, individuals

with depression exhibit inconsistent pain sensitivity across different types of physical pain at the behavioral level, while showing characteristics of lower pain thresholds, longer duration, and greater suffering in psychological pain. In terms of neural mechanisms, the characteristic patterns of both physical and psychological pain in depressed patients appear similar to those of healthy subjects. Future research should focus on investigating the features of these two types of pain-depression comorbidity, clarifying the influencing factors in pain processing in depression, exploring the commonalities and differences between physical and psychological pain processing in depression, and elucidating the functional neuroscientific changes associated with pain in depression, thereby providing a basis for more accurate diagnosis and more effective treatment.

Keywords: depression, physiological pain, psychological pain, behavioral characteristics, neural mechanisms

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric illnesses, characterized primarily by anhedonia and persistent low mood, accompanied by abnormal somatic symptoms and cognitive changes that significantly impair patients' normal functioning (Pizzagalli, 2014). A 2021 study published in *The Lancet Psychiatry* conducted the first nationwide epidemiological survey of mental disorders across 31 provinces in China, covering 157 nationally representative disease surveillance points and completing a cross-sectional survey of 28,140 Chinese adults ($ $18 years). The results indicated that the lifetime prevalence of depressive disorders among Chinese adults is 6.8%, with MDD at 3.4%, dysthymic disorder at 1.4%, and unspecified depressive disorder at 3.2% (Lu et al., 2021).

Existing research demonstrates that depression and pain are highly comorbid, with up to 55.2% of depressed patients experiencing unexplained physical pain (Liu et al., 2021). Current research on the mechanisms of depression-physical pain comorbidity has examined neurotransmitters, brain structure, and brain function, yielding certain insights. However, focusing solely on physical pain is insufficient for understanding the complex manifestations of pain in depression (林潇骁 et al., 2016).

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." Compared to the definition proposed in 1979 and used for 40 years, the revised definition emphasizes the importance of subjective pain experience under the biopsychosocial model (Raja et al., 2020). As a sensation, pain encompasses both physiological components (sensation and perception) and psychological components (mental experience). Psychological pain is a persistent, unbearable, and unpleasant feeling characterized by perceived inadequacy or deficiency of the self (Meerwijk & Weiss, 2013). Social pain, a subtype of psychological pain, refers to a negative emotional re-

sponse experienced when an individual feels socially rejected or devalued by significant others (MacDonald & Leary, 2005). Although both physiological and psychological pain originate from threat signals and serve to evaluate and process threat information while accompanied by negative emotions, they differ in etiology and duration: physiological pain is primarily triggered by organic damage and subsides as the damaged tissue heals, whereas psychological pain is mainly influenced by psychological and social damage or rejection, typically lasting longer and recurring.

In recent years, increasing attention has been directed toward psychological pain in depression, particularly social pain. Clinically, psychological pain overlaps with depression, such as exaggerated responses to negative stimuli, feelings of guilt, and painful rumination or self-deprecation. Some studies suggest that strong avoidance motivation toward psychological pain during depressive episodes may be an important predictor of suicidal behavior in depressed patients (Ji et al., 2022). Li et al. (2014) proposed a three-factor model of psychological pain comprising painful arousal, painful experience, and pain avoidance. Through interviews and questionnaires with depressed patients, they found that psychological pain predicts suicidal ideation and behavior risk in this population. These findings suggest that psychological pain may lead to adverse behavioral consequences in depressed patients. Therefore, this review adopts a biopsychosocial perspective, attempting to integrate behavioral and neuroscientific evidence by systematically examining relevant research on pain in depression. Our aim is to reveal the different clinical manifestations of physical and psychological pain in depression, elucidate their distinct neural mechanisms, and ultimately facilitate timely diagnosis, symptom improvement, and enhanced well-being for depressed patients.

Historical Perspectives on Depression-Pain Comorbidity

In 1982, researchers first proposed that chronic pain might be a variant of depression (Blumer & Heilbronn, 1982). The precursor model suggests that depression may lead to physiological, cognitive, or behavioral changes that increase future pain risk, meaning chronic pain is a consequence of certain psychiatric disorders (Blackburn-Munro, 2001). Subsequent research supports this view, indicating that primary depression can cause chronic pain. For example, one study analyzing data from 5,001 patients in U.S. comorbidity surveys conducted between 1990-1992 and 2000-2001 found that patients with pre-existing depression showed a nearly 7% increase in cumulative incidence of chronic pain after 10 years. However, no association was found between prior chronic spinal pain and subsequent development of depression (Schmaling & Nounou, 2019). Nevertheless, some longitudinal studies have found that pregnancy pain can predict postpartum depression severity (Mathur et al., 2021). Later research suggests that depression with pain and pain with depression may represent two types of depression-pain comorbidity (Mo et al., 2022). For instance, Zheng et al. (2022) employed activation likelihood estimation (ALE) meta-analysis to systemati-

cally review quantitative studies on pain-depression comorbidity, revealing that the right amygdala may be associated with pain-accompanied depression, while the left dorsal prefrontal cortex and thalamus may be related to depression-accompanied pain. This indicates that although shared neural mechanisms underlie the high comorbidity between depression and pain, patients' brain activity patterns differ depending on which symptom is dominant.

As a crucial component of the affective network, the amygdala primarily participates in emotional processing, particularly emotions related to fear and disgust (Tassone et al., 2022). Abnormal amygdala activity in pain-accompanied depression may indicate that this type of pain triggers more negative emotional responses, thereby exacerbating depressive symptoms. The prefrontal cortex, as the brain' s executive control center, responds to extensive sensory and emotional inputs and generates central commands to guide behavior. It can flexibly and efficiently perform multiple tasks, including pain perception and modulation (Li et al., 2021). The thalamus also plays an important role in regulating and integrating painful stimuli (Habig et al., 2023). Patients with depression-accompanied pain may have deficits in perceiving, adjusting, and managing negative emotional responses to pain, which could contribute to abnormal pain experiences in depression. These perspectives remain speculative and require further neurophysiological research.

Behavioral and Neural Mechanisms of Physical Pain in Depression

3.1 Behavioral Characteristics

Previous survey results show that depressed patients are more likely than patients with other specific psychiatric disorders to experience somatic pain symptoms. For example, the prevalence of pain is 28.9% in bipolar disorder patients and 34.7% in schizophrenia patients, but reaches 55.2% in depressed patients (Stubbs et al., 2015; Liu et al., 2021). Clinically, depressed patients often seek care from primary care institutions with pain as their primary or sole complaint, yet this symptom is frequently overlooked (Michaelides & Zis, 2019). Physicians in primary care settings may view depression as a "normal" reaction in patients with serious medical conditions, leading to delays in psychiatric treatment (Endicott, 1984). Somatic symptoms in depression mainly include headaches, gastrointestinal discomfort, and other forms of chronic pain (Thom et al., 2019). Dipnall et al. (2016) used machine learning techniques to analyze large-scale community-based epidemiological data, finding that gastrointestinal symptoms predominated among key medical symptoms in depression. However, this conclusion should be treated cautiously as the sample did not include clinically depressed patients.

Despite growing recognition of the importance of somatic symptoms in depression, current clinical diagnosis tends to prioritize affective and cognitive symptoms over somatic symptoms (for example, DSM-V does not include pain as

a symptom of depression), resulting in some depressed patients being misdiagnosed. Koenig et al. (1997) recommended adopting an inclusive diagnostic approach that incorporates somatic symptoms into depression diagnosis, even if such symptoms may originate from other conditions. Currently, some depression rating scales (such as the Hamilton Depression Scale) already include items on back pain, headache, and muscle pain, and mood disorders have been incorporated into exclusion criteria for persistent somatoform pain or pain disorders. Given the high incidence of depression with pain, primary care physicians and psychiatrists should proactively inquire about pain symptoms and consider them important factors in clinical diagnostic decision-making.

Additionally, evidence shows that pain in depressed patients is associated with poor treatment outcomes (Wong et al., 2022). Liu et al. (2019, 2020) found that depressed patients with gastrointestinal symptoms had more severe conditions and poorer prognoses than those without such symptoms. Fava et al. (2004) discovered that depressed patients whose pain decreased by at least 50% had higher rates of depression remission than those without pain reduction (36% vs. 18%). Therefore, psychiatrists need to pay attention to patients' pain symptoms when treating depression.

Experimental pain paradigms objectively measure individual pain sensitivity through standardized stimuli and methods. Studies have found that depressed patients have significantly higher pain thresholds than healthy controls (Kizilkurt et al., 2019). However, other evidence shows that depressed patients have lower pain thresholds and tolerance, indicating increased pain sensitivity (Nitzan et al., 2019). One reason for these discrepant results may be the use of different stimulation modalities (such as thermal, cold, pressure, electrical stimulation) and intensities across studies. Some researchers have found that depressive mood reduces sensitivity to exogenous stimuli affecting the skin surface (such as thermal stimulation) but increases sensitivity to endogenous stimuli (such as ischemic pain), suggesting differential responses to different pain modalities (Bär et al., 2005). This view has received support from subsequent research. For example, Kim et al. (2022) reviewed studies on abnormal physical pain processing in different psychiatric conditions and found that among 31 studies on depression, patients showed reduced pain sensitivity to low-intensity stimuli but increased sensitivity to high-intensity stimuli (such as locally induced ischemic pain). Overall, although current results show some inconsistencies, they consistently indicate that depressed patients more frequently report endogenous pain (such as chronic pain and laboratory-induced ischemic pain) than healthy populations, while showing lower sensitivity to experimentally induced exogenous pain (王宁 et al., 2018). Kim et al. (2022) suggest this "pain paradox" may stem from differential effects on attentional processing of pain. Specifically, when depressed patients are chronically troubled by severe chronic pain, attentional resources may be more focused on endogenous physical pain, reducing attentional priority for minor pain stimuli. Current neuroimaging evidence provides some support for this view.

In summary, somatic pain in depression is a commonly reported yet frequently overlooked phenomenon in diagnosis and treatment. Somatic pain is not only a manifestation of depression but also closely related to prognosis and treatment efficacy. Therefore, incorporating somatic pain into clinical diagnostic and treatment strategies for depression is crucial. Additionally, the inconsistent pain sensitivity exhibited by depressed patients across different types of experimentally induced pain may reflect complex changes in attentional allocation and pain processing that require further investigation.

3.2 Neural Mechanisms

3.2.1 Brain Regions and Functional Connectivity in Depression-Related Physical Pain Research on the neural mechanisms of physical pain began relatively early, with researchers generally agreeing that pain processing involves extensive brain regions (程思 et al., 2022), including the lateral system of primary and secondary somatosensory cortices and thalamus, and the medial system of anterior cingulate cortex and insula (Schnitzler & Ploner, 2000). Jensen et al. (2016) found through ALE meta-analysis that the anterior cingulate cortex and insula play central roles in pain processing, regardless of pain paradigm or experimental subjects. Previous researchers believed that the anterior cingulate cortex primarily generates pain or emotional pain signals, while the insula transmits signals related to the sensory or affective properties of pain (Apkarian et al., 2005). Animal experiments and human brain imaging studies indicate that the anterior cingulate cortex may be involved in multiple pain-processing functions, such as processing emotions/motivation triggered by physical pain, predicting environmental cues for pain stimuli, and increasing/decreasing avoidance or escape behaviors related to physical pain (Gungor & Johansen, 2019). The insula participates in pain processing in extremely complex ways (Wang et al., 2021), not only processing autonomic responses to noxious stimuli (Schnitzler & Ploner, 2000) and involving affective-motivational components of pain (Holtmann et al., 2022), but also playing an important role in interoceptive awareness (Wang et al., 2019). Different subregions of the insula may have distinct functions; for example, the anterior insula may participate in processing the affective and cognitive dimensions of pain (Taniguchi et al., 2022), while the posterior insula may be involved in sensory pain processing (Centanni et al., 2021).

Paulus and Stein (2010) hypothesized that the insula plays an important role in integrating emotional and interoceptive stimuli, a process in which depressed patients show deficits. Although few studies have examined the insula in depressed patients during interoception (Wiebking et al., 2010; Wiebking et al., 2015), these studies support the hypothesis of abnormal neural activity in the insula during interoceptive processing (Wiebking et al., 2015). For example, Wiebking et al. (2010) found that compared to healthy controls, depressed patients scored higher on body perception questionnaires and showed reduced bilateral anterior insula activation during rest. Abnormal body perception scores

were positively correlated with depression severity, while reduced bilateral anterior insula activation during rest was negatively correlated with depression severity. The researchers suggested that abnormal body perception and altered insula activity in depression may be related to patients' inability to shift their perceptual/attentional focus from their own bodies to the environment, resulting in increased interoceptive awareness. Subsequently, Wiebking et al. (2015) used task-based fMRI to examine insula activity during interoceptive attention tasks in currently depressed, remitted depressed, and healthy subjects, finding that currently depressed patients showed reduced anterior insula activation compared to both healthy controls and remitted patients. Additionally, Mutschler et al. (2012) conducted a meta-analysis of 11 emotion studies in depression, 44 emotion studies in healthy subjects, and 57 physical pain studies in healthy subjects, finding that depression-related brain activation was located in the dorsal anterior insula, a region associated with physical pain in healthy subjects. This region may play a role in "emotional allodynia," which may explain why depressed patients respond to normally non-painful stimuli with pain reactions. These studies may partially explain the common unexplained somatic pain symptoms in depression.

Increasing evidence suggests that "emotional allodynia" in depression occurs not only during pain experience but also abnormally early, during the anticipation phase before pain stimuli appear. For example, researchers using task-based fMRI with experimental pain paradigms found that compared to healthy controls, depressed patients showed enhanced activation in the right anterior insula, dorsal anterior cingulate cortex, and right amygdala during pain anticipation. Moreover, amygdala activation during pain anticipation was positively correlated with perceived helplessness (Strigo et al., 2008). Tesic et al. (2023) reviewed studies on pain processing in depressed patients and found enhanced activation in brain regions such as the anterior cingulate cortex during pain anticipation. This suggests that depression may involve greater emotional reactivity and fear than healthy controls even before stimulus presentation.

Physical pain in depression is associated not only with abnormal emotional experience of pain but also with abnormal cognitive regulation of pain emotion. Cognitive control plays an important role in emotion regulation (Ochsner & Gross, 2005) and is closely related to affective disorders (Vanderhasselt & De Raedt, 2009). Miller and Cohen (2001) proposed that cognitive control or goal-directed behavior is a primary function of the prefrontal cortex. When emotional arousal is inconsistent with other expressed goals, the prefrontal cortex must signal other brain regions to generate appropriate responses (Salehinejad et al., 2017). The lateral prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC), plays a key role in cognitive control (Friedman & Robbins, 2022). The DLPFC has long been considered a critical brain region in depression pathology (Lai et al., 2019; Brosch et al., 2022). As mentioned earlier, Zheng et al. (2022) suggested that reduced DLPFC activation is associated with depression-accompanied pain. Strigo et al. (2008) found that compared to healthy controls, depressed patients showed reduced DLPFC activation, and

that DLPFC activation levels were negatively correlated with perceived pain intensity during painful stimulation. These studies suggest that reduced DLPFC activation may be related to impaired pain emotion regulation control, which may be one cause of abnormal pain processing in depression.

In addition to regional brain activity, functional connectivity between brain regions plays an important role in pain experience. To test whether impaired pain information processing in depression is related to dysfunction in both bottom-up perceptual networks and top-down regulatory networks, Strigo et al. (2013) collected task-based fMRI data from unmedicated depressed patients and healthy controls during a pain anticipation paradigm. Functional connectivity analysis revealed that compared to healthy controls, depressed patients showed enhanced functional connectivity between the dorsal insula and posterior thalamus, but reduced connectivity between the dorsal insula and right inferior frontal gyrus. Another study comparing resting-state functional connectivity between depressed patients and healthy controls found reduced functional connectivity between the insula and centromedial amygdala in depression, and that this connectivity was negatively correlated with somatic symptom severity scores (Zu et al., 2019). These results support the hypothesis that depression involves abnormally enhanced bottom-up processing (e.g., increased connectivity between posterior thalamus and dorsal insula) and abnormally weakened top-down processing (e.g., reduced connectivity between insula and centromedial amygdala), highlighting the important role of insula functional connectivity in depression-related physical pain processing.

3.2.2 Altered Brain Function in Depression with Physical Pain Not all depressed patients experience obvious pain, and individual differences may vary. Does depression with physical pain alter brain regional function and interregional connectivity? Currently, relevant research is relatively limited. Liu et al. (2020) conducted a resting-state fMRI study comparing depressed patients with physical pain, depressed patients without physical pain, and healthy controls. They found that compared to depressed patients without pain, those with pain showed significantly reduced regional homogeneity (ReHo) and amplitude of low-frequency fluctuation (ALFF) in bilateral precentral and postcentral gyri. The precentral and postcentral gyri belong to the brain' s somatomotor and somatosensory regions, and functional abnormalities in these areas may affect the integration and processing of afferent and efferent signals, thereby manifesting as physical discomfort. These abnormal ReHo and ALFF values were negatively correlated with the severity of physical pain and depressive symptoms, suggesting that functional changes in the precentral and postcentral gyri may be an important neural mechanism underlying depression with physical pain. Geng et al. (2019) compared resting-state fMRI data among depressed patients with physical pain, depressed patients without pain, and healthy controls, finding that compared to depressed patients without pain, those with pain showed lower ReHo in the right middle frontal gyrus and left precentral gyrus. The right middle frontal gyrus connects the ventral attention network (responsible

for stimulus-driven exogenous attention) and dorsal attention network (responsible for goal-directed endogenous attention) (Corbetta et al., 2008). Numerous studies have found that abnormal middle frontal gyrus function is associated with negative attentional bias in depression (Beevers et al., 2015). These findings suggest that middle frontal gyrus abnormalities may cause inappropriate allocation of attentional resources to somatic cues, which may be a key mechanism in depressed patients with physical pain.

Behavioral and Neural Mechanisms of Psychological Pain in Depression

4.1 Behavioral Characteristics

Psychological pain is a prominent symptom of depression (Fujimoto et al., 2022) that can be triggered by social rejection, loss of loved ones, and grief (Frumkin et al., 2021). The intensity of psychological pain may vary across different stages of depression: it intensifies during active episodes and diminishes or disappears during recovery (Baryshnikov et al., 2018). Previous studies indicate that compared to healthy controls, depressed patients show distinct characteristics on psychological pain measures, such as lower pain thresholds (Gillard et al., 2021), longer duration (Klawohn et al., 2020), and greater suffering (Pompili et al., 2022). Some research suggests that heightened sensitivity to negative social information may contribute to abnormal psychological pain experiences in depression (Jankowski et al., 2018). Rejection sensitivity (RS) refers to a cognitive-affective processing tendency where individuals readily perceive and strongly react to rejection cues in others' behavior (Downey et al., 1997). Numerous studies have found that increased rejection sensitivity is associated with depression onset, course, and symptom severity (Pegg et al., 2021; Hill et al., 2022; Stroud et al., 2023). For example, De Rubeis et al. (2017) surveyed 72 males during treatment, at treatment completion, and 6 months post-treatment, finding that after controlling for Beck Depression Inventory scores at treatment end, rejection sensitivity during treatment predicted Beck Depression Inventory scores 6 months later.

Although psychological pain is associated with depression, not all depressed patients experience it (Michaelides & Zis, 2019). In China, the lifetime prevalence of suicidal ideation and suicide attempts among patients with major depression is 53.1% and 23.7%, respectively (Dong et al., 2019). Some studies indicate that psychological pain plays a key role between depression and suicidal ideation/behavior, meaning that during major depressive episodes, individuals experiencing greater psychological pain develop more suicidal ideation, thereby increasing suicide risk (Pompili et al., 2022; 甄子昂 et al., 2021). Therefore, depressed patients show distinct characteristics on psychological pain-related behavioral measures, which may be associated with more severe consequences such as suicide.

4.2 Neural Mechanisms

4.2.1 Brain Regions and Functional Connectivity in Depression-Related Psychological Pain Despite being a prominent symptom in depressed patients, few studies have examined the relationship between psychological pain and biological indicators (Jollant et al., 2020). The orbitofrontal cortex, anterior cingulate cortex, limbic system, and their extensive connections may constitute the important neural basis of psychological pain (Rolls et al., 2020; Xiao & Zhang, 2018) and are the focus of research on psychological pain in depression (Gong et al., 2020; Jankowski et al., 2018). Although findings in this area are mixed, the general consensus is that depression may involve abnormal activation in these relevant brain regions, specifically enhanced activity in the orbitofrontal cortex and amygdala (related to negative emotional experience) and reduced activity in the prefrontal cortex (related to negative emotion regulation) compared to healthy controls.

Zhang et al. (2023) combined cross-sectional and longitudinal data, finding that during active episodes, depressed patients showed higher activation in the amygdala and ventral anterior cingulate cortex when experiencing negative loss outcomes, while amygdala activation decreased during recovery. This provides some neural basis for differences in psychological pain across depression stages. Silk et al. (2014) manipulated acceptance and rejection in online peer interactions to examine brain activation in depressed and healthy subjects under peer acceptance and rejection conditions. They found that under peer rejection, depressed patients showed higher activation than healthy controls in bilateral amygdala, subgenual anterior cingulate cortex, left anterior insula, and left nucleus accumbens, with no significant differences under acceptance conditions. Using the classic social exclusion task (Cyberball), researchers found that depressed patients showed stronger amygdala, anterior insula, and anterior cingulate activation but weaker prefrontal activation after social exclusion compared to healthy controls (Jankowski et al., 2018). However, in Kumar et al.' s (2017) study, depressed patients showed higher amygdala, insula, and ventrolateral prefrontal activation than healthy controls under social exclusion conditions. The researchers suggested that since there were no significant differences in subjective psychological pain reports between groups, the higher ventrolateral prefrontal activation might represent a compensatory phenomenon. 莫李澄 et al. (2021) used transcranial magnetic stimulation to activate the ventrolateral prefrontal cortex in depressed patients and had them employ cognitive reappraisal strategies, finding that activating the right ventrolateral prefrontal cortex could improve patients' emotional regulation of psychological pain and reduce negative emotional experiences, partially supporting the hypothesis that insufficient ventrolateral prefrontal activation may contribute to psychological pain in depression.

Previous research has found that depression may involve increased limbic system activity (anterior cingulate cortex, insula, and amygdala) and decreased prefrontal activity during negative emotion processing, possibly reflecting height-

ened processing of negative information and weakened reappraisal (Hamilton et al., 2013). Some researchers propose that inefficient or maladaptive emotion regulation in depression may be related to prefrontal-limbic dysfunction (Perlman et al., 2012). The findings of Zhang et al. (2023) and Kumar et al. (2017) on psychological pain in depression are similar to previous negative emotion studies, suggesting that psychological pain in depression may be related to impaired emotion regulation capacity or excessive processing of negative social cues.

Additionally, neuroimaging evidence from healthy subjects indicates that psychological pain may involve social cognitive processing (Morese et al., 2019). The social brain is a complex network that enables us to recognize others and evaluate their mental states, feelings, personalities, and behaviors, including the medial prefrontal cortex, anterior cingulate cortex, inferior frontal gyrus, superior temporal sulcus, amygdala, and anterior insula (Blackmore, 2008). The inferior occipital gyrus, fusiform gyrus, and superior temporal sulcus process basic, invariant, and variable aspects of faces; the amygdala and ventromedial prefrontal cortex process the emotional significance of social stimuli; and the inferior frontal gyrus is involved in understanding others' behaviors and forms a functional network with the superior temporal sulcus and inferior parietal lobule (Sato & Uono, 2019). van Heeringen et al. (2010) found that compared to depressed patients with low psychological pain, those with high psychological pain showed increased cerebral blood flow perfusion in the right inferior frontal gyrus, dorsolateral prefrontal cortex, occipital lobe, and left temporal lobe at rest. This suggests that psychological pain in depression may be related to abnormalities in the social brain network.

4.2.2 Brain Connectivity in Depression with Psychological Pain As mentioned in the behavioral characteristics section, psychological pain plays an important role in depression and suicide. What are the neural mechanisms underlying this relationship? 甄子昂 et al. (2021) collected clinical scale scores for psychological pain and resting-state fMRI data from suicide-attempt depressed patients, non-suicidal depressed patients, and healthy controls to examine depression suicide-related functional connectivity and its relationship with psychological pain. They found that compared to healthy controls and non-suicidal depressed patients, suicide-attempt patients showed enhanced functional connectivity between the left medial orbitofrontal cortex (a key region in pain processing circuits) and left insula (a key region in cognitive regulation), and this connectivity coefficient was positively correlated with psychological pain scores. This suggests that this brain region' s functional connectivity may be one of the neural bases of suicide in depression. The enhancement may result from orbitofrontal cortex damage in suicide-attempt patients (Sudol & Mann, 2017), with the left insula increasing connectivity to the damaged region to achieve functional compensation. The orbitofrontal cortex plays an important role in emotion regulation and decision-making and is related to rumination in depression (Rolls et al., 2020). Orbitofrontal cortex dysfunction may cause depressed patients to repeatedly dwell on their suffering and be unable to effectively con-

trol inappropriate behaviors such as suicide.

Neural Mechanisms of Physical and Psychological Pain in Depression

[Figure 1: see original paper] Main abnormal brain regions that may be involved in physical and psychological pain in depressed patients

Although social pain and physical pain may be biologically coupled, both involving brain regions such as the anterior insula, anterior cingulate cortex, and prefrontal cortex (Eisenberger, 2012), some studies using task-based fMRI to scan brain activity while subjects experienced high versus warm temperatures and viewed photos of former partners versus friends found that physical pain and social rejection do not share neural representations within core pain-processing brain regions. Social rejection may involve human affective representations rather than shared pain circuits (Woo et al., 2014). 程思 et al. (2022) reviewed literature on the neural mechanisms of physical and psychological pain and found differences mainly in two aspects: first, unlike physical pain, numerous studies found that psychological pain processing does not activate somatosensory brain networks; second, compared to physical pain, psychological pain activates brain regions involved in theory of mind and social cognitive processing. Combined with the above studies, we find that patterns of physical and psychological pain in depressed patients are similar to those in healthy subjects. Specifically, physical pain in depression may involve somatosensory brain regions such as the precentral and postcentral gyri, while psychological pain in depression may involve the social brain network (see Figure 1). Notably, research on physical pain in depression suggests it may involve abnormalities in brain regions and connectivity related to emotion and pain regulation, meaning non-noxious stimuli may also elicit physical pain in depression (Agüera-Ortiz et al., 2011), which may differ from brain regions involved in physical pain in healthy subjects.

Summary and Future Directions

Both pain and depression involve many of the same neurotransmitters (Goldenberg, 2010), immune systems (Kim et al., 2007), and neural pathways (Michaelides & Zis, 2019). Therefore, reviewing relevant research reveals that many brain regions abnormal in depression itself also appear in abnormal pain processing in depressed patients. However, only some brain regions show repeatedly emerging patterns that deserve attention (Tesic et al., 2023). Although research on pain in depression started relatively late, investigators have used multiple techniques to explore physical and psychological pain in depression from multiple angles and levels, achieving certain progress. This provides scientific evidence for revealing the neural mechanisms of abnormal pain processing in depression and assisting clinical diagnosis and treatment. However, numerous issues in this field urgently require further exploration.

5.1 Characteristics of Two Types of Pain-Depression Comorbidity

Depression and pain are mutual risk factors that frequently co-occur and exacerbate each other (IsHak et al., 2018). Currently, compared to qualitative comparisons of brain regions related to pain or depression to reveal potential "shared" neural mechanisms, quantitative research on pain-depression comorbidity is relatively lacking, and studies on pain-accompanied depression versus depression-accompanied pain are even rarer (Zheng et al., 2022). Depression may cause abnormalities in emotional perception and regulation of pain processing, leading to abnormal pain processing, while pain may affect emotions and cause depression. Some researchers proposed a neural circuit hypothesis mediating chronic pain-accompanied depressive symptoms: persistent pain causes disinhibition of the 5-HTDRN→SOMCeA circuit through 5-HT1ARs in SOMCeA neurons, leading to activation of LHb neurons that induce depressive symptoms. Activating the 5-HTDRN→SOMCeA circuit was found to alleviate depressive-like behavior in chronic pain mice (Zhou et al., 2019). Recently, Zhu et al. (2021) found that tissue injury and depression-induced pain hypersensitivity involve different circuits, with the prefrontal Glu→anterior cingulate GABA→Glu circuit related to allodynia associated with depressive-like symptoms. This suggests that pain-accompanied depression and depression-accompanied pain may involve different neural circuits requiring different therapeutic drugs and protocols. More research is needed to reveal this.

5.2 Influencing Factors in Pain Processing in Depression

Depression is highly heterogeneous, with factors such as age of onset, episode duration, number of episodes, symptoms, and severity potentially affecting brain function (Tassone et al., 2022). Currently, research on pain processing in depression mostly uses a dichotomous classification of depression versus non-depression, with less subdivision of factors affecting brain function in depression. He et al. (2020) used transcranial direct current stimulation (tDCS) to stimulate the right ventrolateral prefrontal cortex to regulate negative emotions induced by social pain in depression-prone individuals. They found that tDCS activation of the right ventrolateral prefrontal cortex modulated negative emotions from social pain, but this modulation was affected by individual depression severity. Specifically, tDCS effects were more pronounced in individuals with low depression than those with high depression, indicating that single-session tDCS has smaller effects on negative emotion regulation in individuals with high depression induced by psychological pain. Therefore, factors such as depression severity should be considered when exploring abnormal pain processing in depression. Additionally, screening criteria for depressed patients vary across current studies, with some samples from clinical diagnoses and others from community questionnaire screening, which may affect result consistency. Future research needs more homogeneous populations and stricter methods to expand our understanding of pain processing in depression.

5.3 Commonalities and Differences in Physical and Psychological Pain Processing

Currently, most pain studies examine physical and psychological pain separately, but investigating both simultaneously facilitates understanding of their commonalities and differences in depression. Direct experimental evidence examining the similarities and differences in neural mechanisms between physical and psychological pain in depressed patients is still lacking. Although overlapping brain activation in relevant physical and psychological pain studies suggests possible shared neural bases in emotion-processing brain regions, overlapping activation does not necessarily mean shared representations at all analytical levels. For example, the dorsal anterior cingulate cortex contains multiple functionally specific neuronal subpopulations, such as those specific to nociception and those encoding various motivation-related events (Woo et al., 2014). Therefore, even if physical and psychological pain in depression elicit overlapping brain activation, it does not necessarily mean their underlying neural representations overlap. More research is needed from multiple dimensions to reveal the commonalities and differences between these two types of pain.

Additionally, traditional analgesics show limited efficacy for most depressed patients (Calvo et al., 2019). One study using positron emission tomography examined changes in the -opioid receptor system (which can alleviate physical pain) in healthy subjects and depressed patients under social rejection and acceptance conditions. They found that under social rejection, depressed patients showed reduced endogenous opioid release in brain regions regulating stress, emotion, and motivation compared to healthy controls, along with slower emotional recovery. This suggests that altered endogenous opioid activity in depression may hinder emotional recovery from negative social interactions, leading to repeated episodes and poor treatment efficacy (Hsu et al., 2015). Task-based fMRI studies in healthy subjects suggest that physical pain relief may be associated with enhanced activity in sensory pain systems (primary and secondary somatosensory cortices and posterior insula), while psychological pain relief may depend on the dorsomedial prefrontal cortex involved in affective state processing (Meyer et al., 2015). Therefore, future research should distinguish between pain types (physical vs. psychological) when exploring neural mechanisms of pain relief in depression, which is important for revealing pathological mechanisms and improving intervention and treatment efficacy.

Furthermore, Eisenberger (2012) raised two questions about the relationship between physical and psychological pain: First, regarding pain experience, might there be an association between individual sensitivity to physical pain and sensitivity to psychological pain? Second, regarding pain relief, might increases or decreases in one type of pain affect perception of the other? Regarding the first question, Eisenberger et al. (2006) assessed baseline physical pain sensitivity and then used a social exclusion task to examine how physical pain sensitivity affected social pain, finding that individuals sensitive to physical pain reported greater feelings of exclusion after social rejection. Regarding the second ques-

tion, some behavioral and neuroimaging studies found that relief or exacerbation of social pain affects physical pain. For example, Canaipa et al. (2016) randomly assigned healthy subjects to social acceptance or rejection tasks and examined their pain experience to electrical stimulation before and after the tasks, finding that subjects reported lower physical pain intensity ratings after social acceptance. In a task-based fMRI study, researchers used a gender discrimination paradigm to induce social pain and examined its effect on physical pain (thermal stimulation) evaluation, finding that viewing discrimination images increased subjects' physical pain ratings and significantly increased dorsal anterior cingulate activation during subsequent thermal stimulation, suggesting that experiencing discrimination enhanced activation in pain-processing brain regions (Zhang et al., 2021). However, these studies focused on healthy subjects. What is the relationship between physical and psychological pain sensitivity in depressed patients? Investigating this question could provide comprehensive evidence for clinical diagnosis and reveal whether commonalities exist between physical and psychological pain in depression. Additionally, can relieving one type of pain alleviate the other in depression? Research on this question could not only reveal potential shared mechanisms between the two pain types but also provide new ideas for pain intervention and treatment in depression. Although significant progress has been made in recent years, research on the commonalities, differences, and complex dynamic interactions between physical and psychological pain in depression remains relatively scarce and urgently needs future investigation.

5.4 Functional Neurological Changes in Depression with Pain

Depressed patients with pain often have severe problems, showing more severe depressive symptoms and poorer treatment outcomes compared to those without pain (Bair et al., 2004). Therefore, depression with physical/psychological pain should be a focus of research and practice (Liu et al., 2021). Taking research on depressed patients with physical pain as an example, Geng et al. (2019) were the first to use ReHo based on resting-state fMRI data to study regional activity synchronization in depressed patients with pain. Liu et al. (2021) also used resting-state fMRI data. Neither study found abnormalities in brain regions related to somatic symptoms (such as the anterior cingulate cortex and insula). This may be because results from structural or task-based fMRI studies involve measurement methods very different from ReHo in resting-state fMRI data. Therefore, future research should employ multiple neuroimaging methods to further reveal characteristics of brain regions and connectivity in depressed patients with pain, providing potential targets for depression pain treatment.

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Note: Figure translations are in progress. See original paper for figures.