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REVIEW

Pain Comorbidities with Attention Deficit: A Narrative Review of Clinical and Preclinical Research

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Abstract: A negative correlation exists between attention and pain. The cognitive impairments linked to pain can significantly impede a patient's healing process and everyday tasks, particularly for individuals experiencing persistent pain. Furthermore, it has been demonstrated that diversion can effectively decrease pain levels in individuals. The focus of this review is to analyze clinical trials and fundamental investigations regarding alterations in focus and persistent discomfort. Moreover, we investigated the common neuroanatomy associated with attention and pain. Furthermore, we examined the impact of various neuromodulators on the transmission of pain and processes related to attention, while also considering the potential neural mechanisms that contribute to the co-occurrence of pain and attention deficits. Further investigation in this field will enhance our comprehension of patient symptoms and the underlying pathophysiology, ultimately resulting in more objective approaches to treatment.

Keywords: pain, attention deficit, brain, neuromodulator

Introduction

Pain is an individual and intricate feeling that hinders physical ability, emotional well-being, and social interaction, and its intensity can be influenced by different factors including biological, psychological, and social circumstances. The classic definition of pain is as follows: it represents an unpleasant sensory or emotional experience associated with actual or potential tissue damage.[1] From a "biopsychosocial" medical perspective, this new definition of pain adds cognitive and social dimensions to the old definition of pain used by the International Association for the Study of Pain (IASP) since 1979. The reason behind chronic pain (pain that persists for 3–6 months or more) is frequently a sudden noxious stimulus or injury. Chronic pain has neurological, inflammatory, or idiopathic origins. Studies have shown that chronic pain problems are already prevalent in the general population. The number of Americans suffering from chronic pain is estimated to be as high as 50 million.[2] The attentional aspects of cognitive functioning are also somewhat affected in patients with pain, in addition to sensory symptoms such as nociceptive hypersensitivity and pain hypersensitivity. It is hypothesized that attention and pain processing share neural systems and regulate each other.

Our environment generates a vast quantity of sensory data. By choosing the most relevant stimuli from the surrounding environment and filtering out less relevant information, we can promptly respond to important environmental changes and accomplish behavioral goals with greater efficiency. This cognitive process is generally known as attention.[3] Furthermore, attention has been identified as falling into two broad categories, top-down and bottom-up, with the difference primarily being whether or not one actively seeks target information in the environment based on voluntary selection factors.[4] Due to their biological salience, pain and attention are intrinsically linked; pain is essentially a sensory process that requires attention. The objective of this review is to review clinical studies on attention deficits in pain patients and determine whether pain negatively affects attention. Additionally, our research centers on the neurological foundations that potentially contribute to attentional

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deficits in individuals experiencing pain, encompassing neuroanatomical structures and neurotransmitter systems. We also focus on studies on the pain-relieving effects of attentional interventions, for example, whether shifting the focus of patients with pain results in a reduction or enhancement of pain levels. Furthermore, this review seeks to utilize clinical and preclinical research to help us comprehend the interactions between pain and attention.

Clinical Evidence of Pain Comorbidities in Attention Deficit

The growing number of patients with chronic pain who self-report difficulties with attentional focus, as well as the wide range of economic and psychological consequences of this comorbidity, have sparked an intense interest in the neurobiological mechanisms of attentional deficits in pain comorbidities and the impact of pain on a variety of attentional processes. Numerous studies have previously investigated disruptions in concentration processes in a variety of prevalent pain syndromes.[5–7] Pain questionnaires, numerical rating scales (NRS), and visual analog scales (VAS) were the frequently employed assessments in these studies to measure pain intensity. Additionally, attention tests were also utilized. Selective series reaction time tests (5-CSRTT) and continuous performance tests (CPTs) are the two main types of attention tests. The former is frequently employed in basic research, while the latter is utilized in clinical practice.

In addition, pain is primarily a sensory process that requires focus. Patients with pain frequently report concentration difficulties;[8,9] at the same time, empirical studies have shown evidence of attention deficits among patients with chronic pain,[10–12] particularly with regard to attentional switching and attentional interference. Attention is a selection mechanism for prioritizing task-relevant information over irrelevant (distracting) information, ie, it is a filtering mechanism that involves some cognitive resources. Assuming that stimuli induced by pain must compete for limited cognitive resources with other stimuli requiring attention,[13] persistent stimulation may disrupt top-down attentional control mechanisms, impairing the ability to filter out irrelevant signals and resulting in poor task performance.[14] In addition, pain can lead to plastic changes in certain neural pathways, and this rewiring or reorganization of neural connections in particular areas of the brain can disrupt regular cognitive processes.[15,16] Furthermore, there is a suggestion that the neurochemical substances discharged throughout persistent pain could potentially impair cognitive functions.[17] Consequently, the abovementioned causes may contribute to cognitive dysfunction and even attention deficits due to pain. Multiple chronic pain disorders, such as fibromyalgia, migraine, chronic back pain, rheumatoid arthritis, diabetic neuropathy, osteoarthritis, CRPS, and multiple sclerosis, have been the subject of numerous studies that have shown their comorbidity with attention deficits.

Potential Neural Mechanisms of Comorbid Attention Deficits in Pain

Functional Areas of the Brain in Pain and Attention

Functional magnetic resonance imaging (fMRI) is a developing neuroimaging method that employs magnetic resonance imaging to identify hemodynamic alterations instigated by neural activity.[18] This allows researchers to pinpoint functional areas in the brain activated under specific experimental conditions. Recent studies utilizing this neuroimaging technique have contributed significantly to our comprehension of the neuroanatomical relationship between pain and cognitive processing. In a meta-analysis of 67 functional magnetic resonance imaging (fMRI) studies of vigilant attention, 14 functional areas of the brain that were consistently activated during various sustained attention tasks were identified.[19] These regions include (1) bilateral presupplementary motor area (pre-SMA) and midcingulate cortex, extending to more anterior medial prefrontal cortex (PFC); (2) bilateral inferior PFC extending to the ventral premotor cortex (vPMC); (3) bilateral anterior insula, including the right frontal cap; (4) bilateral thalamus; (5) right PFC; (6) right temporoparietal junction (TPJ); (7) right inferior parietal lobule and intraparietal sulcus (IPS); (8) left dorsal PMC (dPMC); and (9) cerebellar vermis.[19] In contrast, seven brain regions have been identified as the most frequently activated in the brain's processing of pain information in the body: somatosensory cortical areas 1 and 2 (SI and SII), insular cortex (IC), locus coeruleus (LC), thalamus, prefrontal cortex (PFC) and anterior cingulate cortex (ACC).[20]

ACC and Pain Comorbid with Attention Deficit

In the above studies, it was shown that functional brain regions involved in pain processing are also involved in the regulation of body attention. The ACC is a functional central region of the brain that influences the coordination between multiple neural networks in the brain. Klein et al identified synaptic connections between the ACC and limbic regions (eg, thalamus,

hippocampus, and amygdala) by fMRI and confirmed the ACC's function in the control of selective attention, working memory, and false consciousness.[21] This finding indicates that the ACC may serve as an essential component in maintaining the functional integrity of brain networks involved in attention. In a study by Buckingham et al comparing ACC activation in healthy subjects and patients with chronic pain, all subjects were required to simultaneously execute an executive, continuous task that demanded constant attention.[22] In the experiments, it was found that ACC activation is influenced by pain and sustained attention tasks, and an inverse relationship exists between these two different types of activation. Moreover, fMRI research has demonstrated that activation of attention-related ACC regions differs between patients and controls. In light of the above experimental results, it can be concluded that pain alters the normal processing of the ACC, which may be one of the causes of attention deficit disorder. Furthermore, according to the limited resources doctrine, the rivalry between pain and attention over limited cognitive resources in the anterior cingulate cortex (ACC) may impact the connectivity of attentional networks, resulting in attentional deficits in pain (Figure 1).

PFC and Pain Comorbid with Attention Deficit

The prefrontal cortex (PFC) is involved in executive function, attention, nonverbal memory, and visuospatial ability. It has been found that the PFC is responsible for both emotion processing and the downregulation of emotional states such as pain, as well as for several cognitive functions such as cognitive flexibility, working memory, and planning.[23] Silva[10] et al used transcranial direct current stimulation (tDCS) on the dorsolateral prefrontal cortex (DLPFC) of patients with fibromyalgia to assess attentional indices with the attentional network test (ANT). According to the results, the experimental group showed improved performance on the attentional networks of orientation and execution compared to the control group but did not affect performance on the attentional networks of alertness. However, it has also been discovered that the input of harmful information may have a dual impact on the activity of the prefrontal cortex. For example, the medial prefrontal cortex responds directly to injurious input with an intensity-dependent increase in activity.[24] Nonetheless, nociception activation inhibits the activity of the medial prefrontal cortex, which may be regulated by dopamine in the amygdala.[25,26] Although externally

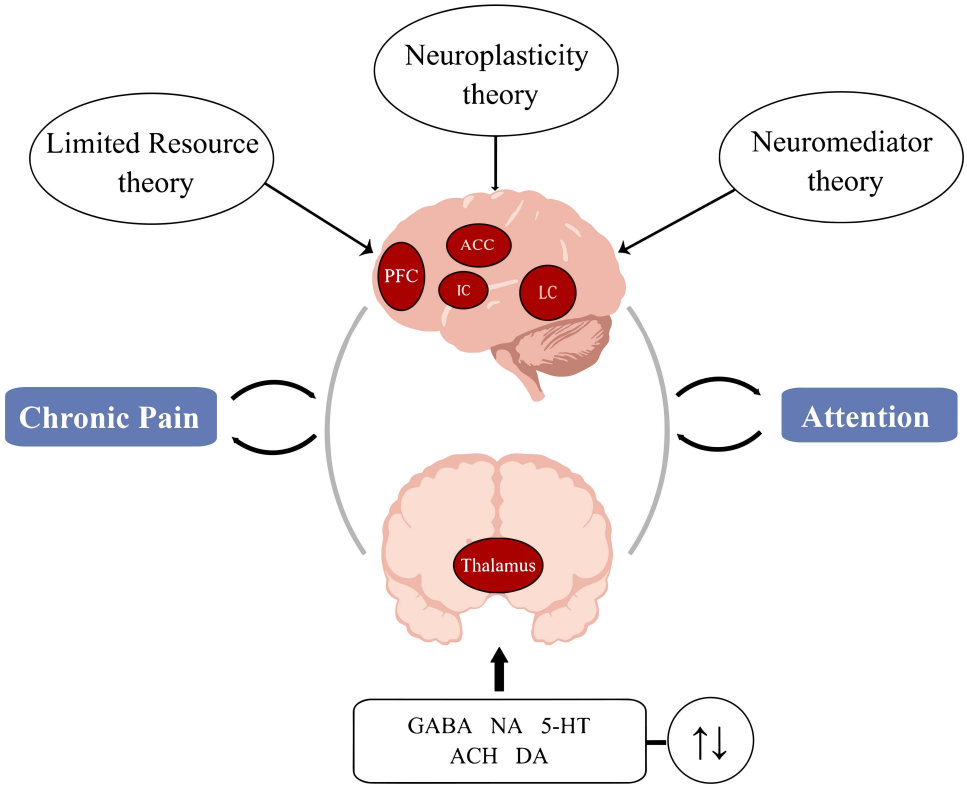

Figure 1 Potential Neural Mechanisms of Comorbid Attention Deficits in Pain. Changes in cognitive resource redistribution, neurotransmitters, and neuroplasticity may underlie the comorbid neural basis of the interaction between pain and attention deficit. Created by figdraw.

induced pain may activate the medial prefrontal cortex, chronic deleterious input may increase activity elsewhere, thereby decreasing output from the medial prefrontal cortex. For instance, the activation of the medial prefrontal cortex by initial pain will lead to increased attention, awareness, and concentration. However, sustained noxious input may activate the amygdala, resulting in a preponderance of inhibitory input from the medial prefrontal cortex, which reduces activity and impairs attentional operations.[27] Additionally, fMRI studies have shown that patients with autism spectrum disorders have insufficient activation of the medial prefrontal cortex during reward inversion,[28] as well as insufficient activation of the DLPFC during sustained attention and working memory.[29]

IC and Pain Comorbid with Attention Deficit

The insular cortex (IC) is a functionally heterogeneous region of the brain associated with somatic and visceral sensory processes, autonomic regulation, and motor processing.[30] In the early stages, the insula was primarily considered a low-level "marginal" structure. In recent years, an increasing number of studies have demonstrated that the functions of the insula are varied and intricate. In addition to detecting salience[31] and predicting risks,[32] the right anterior insula also contributes to the regulation of attention.[33] Given that this part of the brain is important for many cognitive tasks, it recently came to light that the right anterior insula (AI) is an essential component in a large-scale brain network that also includes the anterior cingulate cortex (ACC).[34] It has also been found that IC activation induced by experimental heat pain decreases when subjects are distracted by visual stimuli.[35] The pain-induced changes in neuronal activity in the insular cortex of healthy subjects were also reduced when other distracting tasks were performed.[36]

Thalamus and Pain Comorbid with Attention Deficit

In primates, the thalamus receives sensory input from all parts of the body, including pain (except smell), and transmits it to the cerebral cortex. In addition to acting as a switching station for sensory information, parts of the thalamic nucleus also receive input from cortical or subcortical structures. Among the main sources of thalamic inhibition is the thalamic reticular nucleus (TRN), which is thought to govern thalamic cortical interactions and is crucial for sensory processing, attention, and cognition.[37–39] Previous studies have also confirmed that TRN dysfunction is associated with sensory abnormalities, attention deficits, and sleep disorders in various neurodevelopmental disorders.[40–42]

LC and Pain Comorbid with Attention Deficit

The locus coeruleus (LC) contains a significant number of norepinephrine (NE) synthetic neurons, which form synaptic connections with numerous functional nuclei of the central nervous system; therefore, the LC-NE system may be associated with the regulation of arousal, attention, and stress response. Previous studies have shown that pain can lead to neuroplasticity and neurochemical changes in the LC-NE system; for example, peripheral nerve injury can increase excitatory synaptic transmission of LC neurons in the experimental mouse brain after 7 days of chronic contractile injury.[43] Additionally, alterations in LC activity have been linked to attention deficits. Since LC-NE activity is the primary source of prefrontal norepinephrine, it influences all cognitive processes that support attentional executive function.[44] When a person engages in cognitive processes, cortical norepinephrine activity may regulate cognitive function, particularly attention, by modulating overall arousal levels and setting basal levels of cortical activity.[45] Therefore, the above studies suggest that pain alters the activity of the LC-NE system, and that the LC plays a crucial role in the regulation of attentiveness, both of which suggest that the LC-NE system serves as an important mediator system in the occurrence and development of pain comorbid with attention deficit.

Neurotransmitters and Receptors in Pain and Attention Processes

Numerous prior studies have argued, either directly or indirectly, that several neurotransmitter systems involved in pain processing may also be implicated in attentional activity regulation.[27,46–48] This paper's objective is to review the evidence that indicates that different neuromodulators (GABA, ACH, DA, NA, and 5HT) play a direct or indirect role in pain and attention. However, there is currently no direct evidence linking the two.

GABA and Pain Comorbid with Attention Deficit

Gamma-aminobutyric acid (GABA) was discovered to be extensively dispersed throughout the neuraxis. As an inhibitory neurotransmitter, GABA inhibits neuronal activity by inhibiting the release of other neurotransmitters.[49] Consequently, it is

hypothesized that GABA reduces the perception of pain by delaying sensory transmission. GABA receptors come in three subtypes: GABAA receptors, GABAB receptors, and GABAC receptors. GABAB receptors are metabotropic receptors, while GABAA receptors and GABAC receptors are ionotropic receptors. Various studies have shown that GABAB agonists can effectively relieve thermal nociceptive sensitization associated with acute or inflammatory pain when administered systemically or intrathecally.[50,51] The relatively high concentrations of GABA in the brain and spinal cord, as well as its widespread distribution, indicate that it plays a substantial role in modulating the majority of functions of the central nervous system, including slowing cognitive processes and inducing sedation. Thus, it may be possible to link pain transmission and cognitive systems (including the attentional system) through GABA. In an inflammatory pain model, overactivation of the basolateral amygdala led to increased levels of GABA in the PFC and impaired performance on pain-induced emotional decision-making tests in rats.[27] Nagai et al found that spiny neurons (MSNs) in the striatum trigger astrocyte signaling via y-aminobutyrate B (GABAB) receptors and then selectively activate this pathway by chemogenetic means, thereby causing acute hyperactivity and disruption of attention.[52] GABAB receptors also play a regulatory role in pain pathways. Clinically, the GABAB receptor agonist baclofen is the drug of choice for multiple sclerosis and spinal cord injury spasticity. Additionally, it can be used to relieve pain from spinal cord injury and trigeminal neuralgia. In normal rats, administration of GABAA receptor antagonists or GABAB receptor antagonists produces hypersensitivity to heat and touch. In contrast, the GABAB receptor agonist baclofen, when administered trans-spinally, produced antinociceptive effects in the tail-flick assay.[53] The co-expression of GABA receptors subtypes may be linked to the neural mechanisms of chronic pain alongside attention deficits. However, additional research is required to elucidate the underlying mechanisms.

NA and Pain Comorbid with Attention Deficit

The noradrenergic system is closely associated with the transmission of nociception in the spinal cord, with downstream noradrenergic neurons playing a key role in endogenous analgesia. In rats subjected to injurious stimuli, excitatory activity in the bilateral LCs and release of norepinephrine through projections to the bilateral spinal dorsal horns can be observed.[54–56] This is because the LC, located in the brainstem, is the largest noradrenergic nucleus in the brain.[57] LC neurons are capable of projecting through the noradrenergic system to almost the entire central nervous system to modulate sensory gating and responses, including cognitive function (attention and memory), sleep and arousal, anxiety, and pain.[58] It has been demonstrated that the noradrenergic downstream inhibitory system from the LC to the dorsal nucleus of the spinal cord plays an essential function in the analgesic mechanism of gabapentin and antidepressants (tricyclic antidepressants and 5-hydroxytryptamine noradrenaline reuptake inhibitors). Previous research has demonstrated that drugs that inhibit the reuptake of norepinephrine, like atomoxetine (ATO) or nortriptyline, have the ability to markedly decrease impulsive conduct in rodents. The evidence for this can be seen in fewer premature responses when performing the 5-Choice Serial Reaction Time Task (5-CSRTT) or enhanced performances in the Stop Signal Reaction Time Task.[59–61] Similarly, the administration of NE receptor agonists enhanced rodent attentiveness and decreased impulsivity.[44,62] For instance, guanfacine, a drug that stimulates the alpha-2 adrenergic receptor, has proven to be effective in treating attention deficit hyperactivity disorder.[63,64] Correspondingly, studies have shown that certain NE receptor blockers (mainly α-1 receptors) do not have any notable or negative impact on impulsivity and sustained attention in rodents when administered in isolation.[60,65] In conclusion, the aforementioned clinical and basic studies have demonstrated that the noradrenergic system is involved in the regulation of attention and plays a key part in the transmission of nociception within the body and that additional research is required to determine how pain influences attention via the NE system.

5-HT and Pain Comorbid with Attention Deficit

Serotonin, also known as 5-HT, is a monoamine neurotransmitter found widely in both the peripheral and central nervous systems (CNS). It plays a role in various physiological and behavioral conditions, including but not limited to major depression, anxiety disorders, schizophrenia, bipolar disorder, autism spectrum disorder, obesity, and pain perception. A well-established fact is that downstream 5-HT pathways influence nociceptive information processing in the spinal cord either in an inhibitory (downstream inhibitory) or facilitative (downstream facilitative) manner, according to the type of receptor and the underlying pain state.[66,67] Based on pharmacological, structural, and transduction properties, the 5-hydroxytryptamine receptor family is divided into seven subfamilies (5-HT1-5-HT7), comprising 15 receptor subtypes. However, the role of the different receptor subtypes in nociceptive

neurotransmission is still unclear. 5-Hydroxytryptamine receptors play various roles in regulating pain, but the 5-HT1a receptor appears to play a more critical role.[68] Research conducted on individuals has indicated that numerous areas implicated in pain regulation or modification, including the central suture nucleus, amygdala, cingulate cortex, insula, and prefrontal cortex, exhibit significant concentrations of 5-HT1a receptors.[68–70] A significant quantity of 5-HT2a receptors were discovered in various regions of the rat brain involved in pain modulation pathways downstream from the brainstem, such as the nucleus raphe magnus, ventrolateral periaqueductal gray, spinal dorsal horn, reticular formation, central gray, thalamus, cerebral cortex, and limbic structures.[71] Compared to ACh, DA, and NA, 5-hydroxytryptamine acts less directly on top-down attention, but it does affect top-down attention and spatial working memory. As an example, systemic administration of 5-HT2A agonists in rats resulted in decreased accuracy (attention) and increased impulsivity (response disinhibition) in the 5-CSRTT.[72] Nevertheless, direct injections of a 5-HT2A/C antagonist into the rodent mPFC decreased impulsivity but not attention.[73] This difference may suggest that the effect of 5-HT on attention/accuracy is elicited in a different region than the mPFC. Additionally, blocking 5-HT1A and 5-HT2A receptors may counteract the deficit in 5-CSRTT performance that occurs when NMDA receptors are blocked.[74] In spite of this shared impact on precision, the two receptor subtypes operate distinctively when it comes to focus (accuracy). For example, 5-HT1A blockers improve accuracy by reducing the effect of NMDA receptor blockers, whereas 5-HT2A blockers affect accuracy by reducing impulsivity. Due to this dissociation, it has been suggested that 5-HT2A receptors are crucial in the attentional regulation of regulatory response inhibition.[75] In conclusion, the serotonergic system is implicated in both pain and attention, but distinct 5-HT receptors may regulate each differently.

ACH and Pain Comorbid with Attention Deficit

According to recent studies, the cholinergic system of cortical projection starts in the basal forebrain (BF) and is involved in cognitive processes like wakefulness, focus, acquisition of knowledge, retention, and even awareness.[76,77] Several prior investigations have demonstrated that the cholinergic system plays a vital function in the control of attention from higher cognitive processes. Selective attention deficits occur in primates and rodents when the cholinergic system is damaged, while other cognitive functions like learning and memory remain unaffected.[78] The increase in cholinergic drive facilitates attentional performance, especially when the task demands are high and distracting stimuli are present.[79] There is less proof to support the role of the cholinergic system in pain regulation. Nevertheless, this transmitter plays a direct and indirect role in the downstream inhibition of pain,[80] and the involvement of nicotinic and muscarinic receptors on neurons in pain transmission has been suggested. Studies have shown that centrally administered nicotine and nicotinic receptor agonists, like epibatidine, have analgesic properties.[81] Muscarinic receptor agonists, such as CMI-936 and CMI-1145, have also been found to have potent analgesic effects.[82,83] Furthermore, neostigmine, which inhibits acetylcholine degradation, reverses abnormal pain and hyperalgesia in a rat model of neuropathic pain.[81] Radzicki et al observed that SNI rats had a loss of excitatory cholinergic regulation in the mPFC, which may help to explain mPFC inactivation associated with neuropathic pain and contribute to specific cognitive deficits associated with neuropathic pain (attention and working memory).[47] Thus, the cholinergic system may facilitate the interaction between pain and attention.

DA and Pain Comorbid with Attention Deficit

The limbic dopamine system in the midbrain includes neurons in the ventral tegmental area (VTA) and substantia nigra (SN), which project to the ventral striatum. It has been well documented that pain can cause dopaminergic deficiency, which impairs motivated behavior. According to human imaging studies, the limbic dopamine system in the midbrain of patients with chronic pain responds in a less sensitive way to significant stimuli.[48] For instance, patients with chronic pain have lower D2 receptor binding[48,84] and presynaptic dopamine activity[85] in the striatum at rest and following acute painful stimuli. According to studies conducted on animals, chronic pain resulted in reduced c-Fos activation in the VTA and reduced overall dopamine levels and striatal D2 receptors.[86] In addition, the DA system is a major pharmacological target for the treatment of attention deficit hyperactivity disorder (ADHD), schizophrenia, and Parkinson's disease, among other disorders associated with attention deficit.[87] Within the limbic dopamine system of the midbrain, the signaling of SN-DA might have a stronger correlation with task execution and focus, while the signaling of VTA-DA might have a stronger correlation with the experience of gratification. Indeed, these disparities have been noted in tasks involving working memory.[88] The question remains as to whether these discoveries will be valid in a task that demands

focused attention from the beginning. Nonetheless, in mice participating in a 5-choice series reaction time task (5-CSRTT), enhancing the function of midbrain dopaminergic neurons using chemical genetics hinders attentional performance while not suppressing the act of responding.[89] As a result, it is theorized that persistent pain might impact the functioning of VTA or SN-DA neurons, leading to a decrease in different facets of focus.

Analgesic Effects of Distraction

Distraction through the management of cognitive behaviors has become a prevalent approach in pain management. Nevertheless, various studies have yielded differing results in terms of its analgesic effectiveness. Some studies have reported moderate pain relief,[7] while others have indicated weak[90] or no discernible effect.[91] These variations in outcomes may partly stem from differences in research methodologies and study populations. However, recent research indicates that individual differences in cognitive inhibition may also influence pain perception.[92,93] In a recent study, participants completed a series of cognitive inhibition tasks before undertaking a working memory task. The findings of this study suggest that selective attention plays a crucial role in the effectiveness of pain relief associated with task engagement. This is possibly because selective attention enables individuals to sustain their focus on a distracting task while suppressing the inclination to concentrate on their pain.[5] Additionally, emerging research underscores the potential benefits of cognitive behavioral management in pain relief. For example, recent studies have shown that through cognitive-behavioral interventions, patients can effectively learn to regulate their pain perception, leading to reduced pain intensity and duration.[94] This discovery implies that cognitive behavioral management can serve not only as a distraction technique but also as a tool to help patients modify their psychological responses to pain, potentially resulting in more extensive pain relief.

In conclusion, despite variations in the analgesic effects of cognitive behavioral management, recent research emphasizes the significance of individual differences and cognitive inhibition in this process. Moreover, cognitive behavioral management offers patients an opportunity to acquire effective pain coping strategies, expanding its applicability. This dynamically evolving field presents novel prospects for pain management and merits further comprehensive research and exploration.

Conclusions and Future Directions

In conclusion, past basic research and clinical research have provided sufficient evidence to support the theory that pain is related to attention deficits. The results of attention tests with high behavioral validity suggest that pain patients often experience poor sustained attention performance, which dramatically impacts the patient's quality of life. This review also outlines some of the neuropathological mechanisms underlying pain-related attentional deficits and provides evidence for considerable overlap between brain nuclei and neurotransmitter systems involved in pain and attentional processes (Figure 1). However, this review also has limitations in that, due to the complexity of pain transmission and attention processes, individual nuclei or individual neurotransmitter systems may not be able to explain their comorbidity, and there are still no clear findings to confirm what the key brain nuclei and neurotransmitters involved in pain-comorbid attention deficits are and whether there is a dominant neural circuit for the occurrence and development of attention deficit in pain complications needs to be further studied from the perspective of neural network coordination.

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Disclosure

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