

A simplistic perspective on the complex relationship between schizophrenia and pain from dopamine excess

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Summary

Schizophrenia is characterized by a paradoxical pain experience: the threshold for nociceptive pain is high, while the threshold for nociplastic pain is low. This phenomenon involves mesolimbic dopamine excess. Increased dopamine stimulates descending pain inhibitory pathways, alleviating nociceptive pain. However, dopamine excess induces changes in the large-scale brain network that generates nociplastic pain. This imbalance of monoamines, which is characteristic of schizophrenia, influences both psychotic symptoms and the unique pain paradox. Our results suggest that modulating dopamine levels appropriately may normalize pain thresholds and improve quality of life.

Keywords: default mode network, descending pain inhibitory pathway, mesolimbic dopamine, nociceptive pain, nociplastic pain, schizophrenia

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INTRODUCTION

Pain, a fundamental defensive mechanism for living organisms, presents a perplexing paradox in patients diagnosed with schizophrenia. Clinical observations suggest a phenomenon that appears to be contradictory: a high pain threshold for acute nociceptive stimuli, concomitant with a low pain threshold for chronic pain conditions (Carrasco-Picazo et al.,2023). Consequently, individuals diagnosed with schizophrenia may not exhibit acute discomfort in response to severe physical illnesses. However, they frequently experience intractable chronic pain of unknown origin. Indeed, the prevalence of chronic pain disorders in this population is approximately double that of the control group.

As previously mentioned in the existing literature, reviews have noted that individuals diagnosed with schizophrenia appear to experience impaired pain perception (Antioch et al.,2015). However, the underlying mechanisms that cause this phenomenon remain largely enigmatic. The objective of this paper is to furnish a lucid and accessible exposition of this intricate relationship, with a particular emphasis on the interplay between sensory and central pain processing. The exposition integrates recent insights into various classifications of pain, including nociceptive, neuropathic, and nociplastic pain (Nijs et al.,2023).

SCHIZOPHRENIA AND ACUTE PAIN: NOCICEPTIVE PAIN

Nociceptive pain functions as the body's immediate alarm system, arising from actual or potential tissue damage. The phenomenon under discussion is characterized by a sharp, localized pain that is experienced when an individual comes into contact with a heated object or sustains an injury. This acute pain is a vital protective response, prompting withdrawal and protecting the injured area to facilitate healing. While the function of nociceptors (the sensory receptors detecting noxious stimuli) in patients with schizophrenia is believed to be normal, a striking clinical observation is their often-blunted response to severe acute conditions, such as myocardial infarction or bowel perforation (Urban-Kowalczyk et al.,2015). This can result in a significant delay in diagnosis and treatment. Research consistently indicates that patients diagnosed with schizophrenia exhibit elevated pain thresholds to nociceptive stimuli, suggesting a significant insensitivity to this category of pain.

The modulation of nociceptive pain is a complex process involving a sophisticated interplay between ascending pathways to the brain and descending inhibitory pathways from the brain to the spinal cord. A critical hub in this system is periaqueductal gray (PAG) (Huang et al.,2019). The PAG is a critical node in the network of ascending sensory input, and it also receives information from the limbic system, transmitting inhibitory signals to the spinal cord. The descending pain inhibitory pathway

is intricate, involving various neurotransmitters, including dopamine. Research, particularly in conditions such as fibromyalgia, suggests a direct influence of dopamine levels in the midbrain on pain thresholds. A decrease in dopamine levels has been shown to result in a lowered pain threshold, while an excess has been demonstrated to raise the threshold (Wood,2008).

A hallmark feature of schizophrenia is an excess of dopamine in the midbrain, particularly within the mesolimbic system. This excess dopamine is hypothesized to robustly activate the descending pain inhibitory pathway, thereby increasing the pain threshold for nociceptive stimuli. This phenomenon elucidates the rationale behind patients in a state of psychomotor agitation, characterized by elevated dopamine and noradrenaline levels, manifesting a lack of responsiveness to acute pain, even in situations deemed life-threatening. Consequently, the heightened dopamine levels contribute to an elevated nociceptive pain threshold, thereby diminishing pain's critical role as an early warning sign of physical illness. Antipsychotic medications have been shown to help normalize this threshold by blocking excess dopamine, which may aid in the earlier detection of medical complications in these vulnerable patients.

SCHIZOPHRENIA AND CHRONIC PAIN: NOCIPLASTIC PAIN

In stark contrast to their insensitivity to acute nociceptive pain, individuals with schizophrenia frequently experience chronic pain. This chronic pain is not necessarily associated with ongoing tissue damage but is significantly influenced by emotional and cognitive factors, including anxiety, fear, and past memories (Fitzcharles et al.,2021). In contrast to nociceptive pain, chronic pain frequently involves central sensitization and alterations in the brain's processing of pain signals. These alterations encompass mechanisms consistent with neuropathic and, more notably, nociplastic pain.

While the paper does not explicitly address particular neuropathic conditions associated with schizophrenia, it is crucial to recognize that neuropathic pain, originating from damage or disease to the somatosensory nervous system, has the potential to contribute to chronic pain in any population, including those with schizophrenia. This type of pain is characterized by a burning, shooting, or

tingling sensation. However, the chronic pain experienced by many with schizophrenia aligns more closely with nociplastic pain, which arises from altered nociception without clear evidence of ongoing tissue damage or nerve lesion (Fitzcharles et al.,2021). This finding suggests a potential dysfunction in the brain's pain processing mechanisms, leading to an amplification of pain signals. Functional neuroimaging studies (fMRI) have elucidated the involvement of large-scale brain networks in chronic pain, revealing a pattern wherein the salience network strengthens and the default mode network weakens (Martucci et al.,2018). This altered functional connectivity is profoundly influenced by the excess mesolimbic dopamine observed in individuals diagnosed with schizophrenia.

The Salience Network: Amplifying Pain Signals

The salience network, which includes key regions such as the anterior cingulate gyrus and the insular cortex, plays a critical role in detecting and filtering relevant stimuli, both internal and external. In cases of chronic pain, this network frequently demonstrates enhanced functional connectivity. As demonstrated by experimental models, such as the Cyberball social exclusion task, psychological pain has been shown to activate components of the salience network. The degree of activation of these components has been found to correlate with the intensity of felt distress. The medial cortical midline structures, which receive projections from the midbrain dopaminergic system, also become activated during intense psychological pain (Jefferson et al.,2021).

The prevailing hypothesis suggests that in cases of schizophrenia, the enhanced functional connectivity within the salience network, influenced by elevated dopamine levels, plays a substantial role in the development of chronic pain vulnerability. This phenomenon renders individuals more vulnerable to perceiving and being consumed by pain. Intriguingly, the insular cortex, a component of the salience network, has the capacity to store "molecular memories" or "pain engrams" of past inflammation and pain (Labrakakis,2023). The activation of this region, in the absence of nociceptive input, has the capacity to induce a pathological state of pain, thereby effectively triggering chronic pain through the re-experiencing of past painful encounters. This mechanism provides a compelling explanation for "unexplained" chronic pain in schizophrenia.

The Default Mode Network: Diminished Pain Regulation

The default mode network (DMN) is a network of brain regions, including the posterior cingulate gyrus and medial frontal lobes, that are active when the brain is at rest and not engaged in specific tasks. Conversely, during periods of active task performance, the executive control network exhibits increased activation, while the DMN activity undergoes a decline (Johansson et al., 2024). In individuals experiencing chronic pain, a consistent finding is a weakened functional connectivity within the DMN and reduced coordination with other brain regions. This phenomenon is accompanied by a reduction in the degree of coupling between the posterior cingulate and right insular cortex. In addition, studies have indicated a decrease in functional coordination between the default mode network (DMN) and descending pain inhibitory pathways. This diminished activity and connectivity in the DMN may result in impaired regulatory and disengagement abilities from pain signals within the brain.

The equilibrium of monoamines, especially dopamine and serotonin, exerts a substantial influence on the activity of large-scale brain networks. While the DMN is often functionally activated in serotonergic systems, dopamine and serotonin imbalances can profoundly affect emotional processing, including anxiety, through structures like the bed nucleus of the stria terminalis. In the context of chronic neuropathic pain, for instance, alterations in inhibitory inputs to this nucleus have been shown to exacerbate anxiety. A weakened functional connectivity between the DMN and the bed nucleus of the stria terminalis (BNST) in states of chronic pain could further contribute to increased anxiety (Van de Poll et al., 2023). Consequently, the monoamine imbalance characterized by elevated dopamine and diminished serotonin in individuals diagnosed with schizophrenia may further disrupt the function of the DMN, thereby exacerbating chronic pain and the associated anxiety that frequently accompanies it.

LIMITATIONS

While this paper presents a compelling explanation for the pain paradox in schizophrenia, emphasizing dopamine excess as a central mechanism, a dopamine-centric perspective has potential limitations. To illustrate this point, let us consider the following scenario: A patient diagnosed with schizophrenia is undergoing treatment with an antipsychotic medication that has been developed to selectively target dopamine receptors. The paper's

hypothesis states that the drug should help normalize the patient's acute pain threshold by reducing the excessive activation of descending pain inhibitory pathways. Nevertheless, despite the efficacy of symptom management and dopamine receptor blockade, the patient exhibits a markedly diminished response to acute painful stimuli, such as severe burns or internal injuries. This observation suggests the presence of limitations, as it indicates that the mechanism underlying the elevation of acute pain thresholds may not be solely attributable to dopamine excess. The potential contributions of other neurobiological pathways and factors, which have not been fully addressed in this dopamine-focused model, to altered pain perception warrant further investigation. The intricacies of pain modulation in schizophrenia might not be fully captured by a singular neurotransmitter explanation. Such discrepancies may indicate that, while dopamine plays a significant role, the comprehensive understanding of pain perception in schizophrenia may encompass hitherto unexplored mechanisms.

CONCLUSION

The "pain paradox" observed in patients with schizophrenia—a high threshold for acute nociceptive pain and a low threshold for chronic pain (often involving nociplastic mechanisms and potentially neuropathic components)—can be largely attributed to an excess of dopamine in the mesolimbic system. This dopamine excess has been shown to simultaneously stimulate the descending pain inhibitory pathway, leading to a state of insensitivity to acute noxious stimuli. Concurrently, this excess has also been demonstrated to alter the functional connectivity of large-scale brain networks. Specifically, it has been demonstrated to enhance the salience network, thereby rendering individuals more vulnerable to the experience and recollection of chronic pain. Concurrently, it has been observed to diminish the function of the default mode network, which is associated with the regulation of pain and the exacerbation of anxiety.

The psychotic symptoms of schizophrenia and this paradoxical pain experience appear to stem from a common underlying monoamine imbalance, characterized by increased dopamine and decreased serotonin. Consequently, the strategic modulation of dopamine levels through the administration of antipsychotic medications offers a promising avenue for addressing both psychotic symptoms and pain thresholds. This could facilitate the appropriate perception of nociceptive pain (which is crucial for detecting physical illness) and, concurrently, reduce the

burden of chronic pain and anxiety. To optimize patient care, further research is necessary to elucidate the intricate relationship between monoamine modulation, brain network dynamics, and pain perception in schizophrenia.

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