Psychiatria Danubina, 2023; Vol. 35, No. 2, pp 174-179 https://doi.org/10.24869/psyd.2023.174 *Mini-Review Article*

PAIN THRESHOLD PARADOX IN SCHIZOPHRENIA: A NARRATIVE REVIEW BASED ON THE LASTEST NEUROSCIENCE

Takahiko Nagamine[1,2,*]

[1] Sunlight Brain Research Center, Hofu, Yamaguchi, Japan
[2] Department of Psychosomatic Dentistry, Tokyo Medical and Dental University, Tokyo, Japan
** Corresponding Author*

received: 19.07.2022; revised: 09.02.2023; accepted: 01.06.2023

Summary

Introduction: *Pain is one of the basic defense responses of living organisms. Although the threshold for pain perception varies from person to person, there is no doubt that pain reduces a person's quality of life. Assessing the subjective experience of pain is especially important in the treatment of patients with schizophrenia. In light of recent advances in neuroscience, we discuss pain thresholds in patients with schizophrenia.*

Methods: *A narrative review of pain thresholds in patients with schizophrenia was conducted. We electronically searched the PubMed and Google Scholar databases for articles in English with "pain," "schizophrenia," "neural circuits," and "neurotransmitters" in the title or abstract, for the period January 2000 through June 2022.*

Results: *A seemingly contradictory phenomenon has been noted with regard to pain thresholds in patients with schizophrenia. One phenomenon is a high pain threshold for nociceptive stimuli, and the other is a low pain threshold in chronic pain. As a result, a pain threshold paradox has been observed.*

Conclusions: *Many schizophrenia patients appear to have an excess of dopamine in the mesolimbic system, which stimulates both the descending pain inhibitory pathway and the salience network. As a result, a pain threshold paradox has been observed, in which the threshold for acute nociceptive pain is high and the threshold for chronic pain is low.*

Key words: *default mode network, descending pain inhibitory pathway, mesolimbic dopamine, pain threshold paradox, salience network, schizophrenia*

* * * * *

INTRODUCTION

The subjective sensation of pain is a complex phenomenon, and while its cause is usually an injury to the body, pain can also originate in the central nervous system itself. Although the threshold for pain perception varies from person to person, there is no doubt that pain reduces a person's quality of life. Assessing the subjective experience of pain is especially important in the treatment of patients with schizophrenia. However, it is not precisely known whether pain thresholds are altered in patients with schizophrenia. Recent advances in neuroscience have provided important insights into the neural circuitry of pain. This review of the recent literature addresses the following questions. Is the pain threshold in schizophrenia higher or lower, how is it explained by neuroscience, and what are the implications of these findings for the treatment of schizophrenia?

MATERIALS AND METHODS

We electronically searched the PubMed and Google Scholar databases for articles (types of studies: experimental studies, case reports, and reviews) in English with "pain," "schizophrenia," "neural circuits," and "neurotransmitters" in the title or abstract, for the period January 2000 through June 2022. The full text of retrieved articles was examined and included only if they covered pain thresholds in schizophrenia. The screening and selection process was performed by the author. Approximately 400 abstracts were initially scanned, but few studies fit the purpose of this study; ultimately, a total of 14 studies were included in the review, most of which were either basic research or descriptive in nature. Thus, this paper provides a narrative review focusing on recent clinical and experimental findings of pain sensitivity in patients with schizophrenia.

RESULTS

A seemingly contradictory phenomenon has been noted with regard to pain thresholds in patients with schizophrenia. One phenomenon is a high pain threshold for nociceptive stimuli, and the other is a low pain threshold in chronic pain. In other words, they rarely complain of numbness or pain in response to acute inflammation, but may suffer from chronic pain of unknown origin. A phenomenon of high pain thresholds is that patients with schizophrenia have relatively mild complaints of pain, even when they suffer from serious physical illnesses that induce severe pain (Potvin & Marchand 2008). On the other hand, however, a high percentage of patients with schizophrenia have chronic pain disorders and may suffer from intractable pain. The rate of chronic pain disorders in patients with schizophrenia is about twice that of controls (Birgenheir et al. 2013). The majority of the review articles noted that pain perception is impaired in various ways in patients with schizophrenia (Antioch et al. 2015), but the mechanisms are not yet fully understood, and the phenosmenon is seen in both high and low pain thresholds. Furthermore, at present, there is no single neuroscientific mechanism that can explain pain thresholds in schizophrenia, partly because there are several sites from peripheral to central that induce and recognize pain.

DISCUSSION

The conflicting results on pain thresholds are discussed in the following two groups of pain. Pain has two aspects: sensory perception, in which a pain stimulus is present, and central perception, in which a pain stimulus is not necessarily present.

A. Schizophrenia and nociceptive pain

The phenomenon of high pain thresholds in schizophrenia is observed in response to acute pain stimuli (Girard et al. 2010). Pain is one of the basic defense responses of living organisms. An example of a pain defense response is the reflexive withdrawal of the hand when touching something hot. Pain produced by inflammation or injury helps to identify the site of inflammation or injury and to protect the site. Pain-inducing movements are also inhibited, aiding in the recovery of tissue damage. This is the sensory aspect of pain and is referred to as nociceptive pain. Typical nociceptive pain is tingling, sharp, or stabbing pain. When injury occurs, a pain-producing substance is produced that excites nociceptors. Patients with schizophrenia are thought to have no abnormalities in nociceptors. However, as has been said in clinical practice for some time, when patients with schizophrenia have a painful disease such as myocardial infarction or bowel perforation, the absence of pain complaints can delay the detection of the disease. Several studies examining pain thresholds in patients with schizophrenia have shown that they have elevated pain thresholds to nociceptive stimuli compared to controls, indicating that they are insensitive to pain (Singh et al. 2006). Pain thresholds to nociceptive stimuli may be higher in patients with schizophrenia. Nociceptive pain is controlled by both ascending pathways to the brain and descending pathways from the brain to the spinal cord. The periaqueductal gray matter is an important hub that relays the ascending and descending pathways of pain (**Figure 1**). The structure of periaqueductal gray matter is clearly different from that of the spinal cord and cerebral cortex, which are not clusters of neurons but a meshwork of bundles of nerve fibers interlaced with white matter, allowing for the coordination of various nervous systems via neurotransmitters (Samineni et al. 2019). In the ascending pathway of pain, when nociceptors are activated by a nociceptive stimulus, this information is transmitted to the spinal cord. This information passes through the periaqueductal gray matter and then through the spinal thalamic tract to the somatosensory cortex, where pain is perceived. At the same time, it is sent from the thalamus through the medial system to the anterior cingulate gyrus, insular cortex, limbic system, and prefrontal cortex, causing an emotional response due to pain. The periaqueductal gray matter not only receives ascending sensory input from the spinal cord, but also accepts information from the limbic system and transmits it descending to the dorsal horn of the spinal cord, where this pathway inhibits the transmission of pain. This descending pain inhibitory pathway is not a single neural pathway, but includes at least noradrenergic, serotonergic, GABAergic, and dopaminergic neurons (Lueptow et al. 2018). The possibility that dopamine levels in the periaqueductal gray matter could alter pain thresholds has been noted from studies of patients with fibromyalgia. A decrease in dopamine in the midbrain lowers the pain threshold and makes the patient more sensitive to pain, while an excess of dopamine raises the pain threshold for nociceptive stimuli (Wood 2004).

In schizophrenia, an excess of dopamine in the midbrain is hypothesized to be pathognomonic. Excess dopamine in the periaqueductal gray matter contributes to pain reduction via activation of the descending pain inhibitory pathway. Patients with schizophrenia in a state of psychomotor agitation have increased levels of dopamine and noradrenaline and are indeed sometimes insensitive

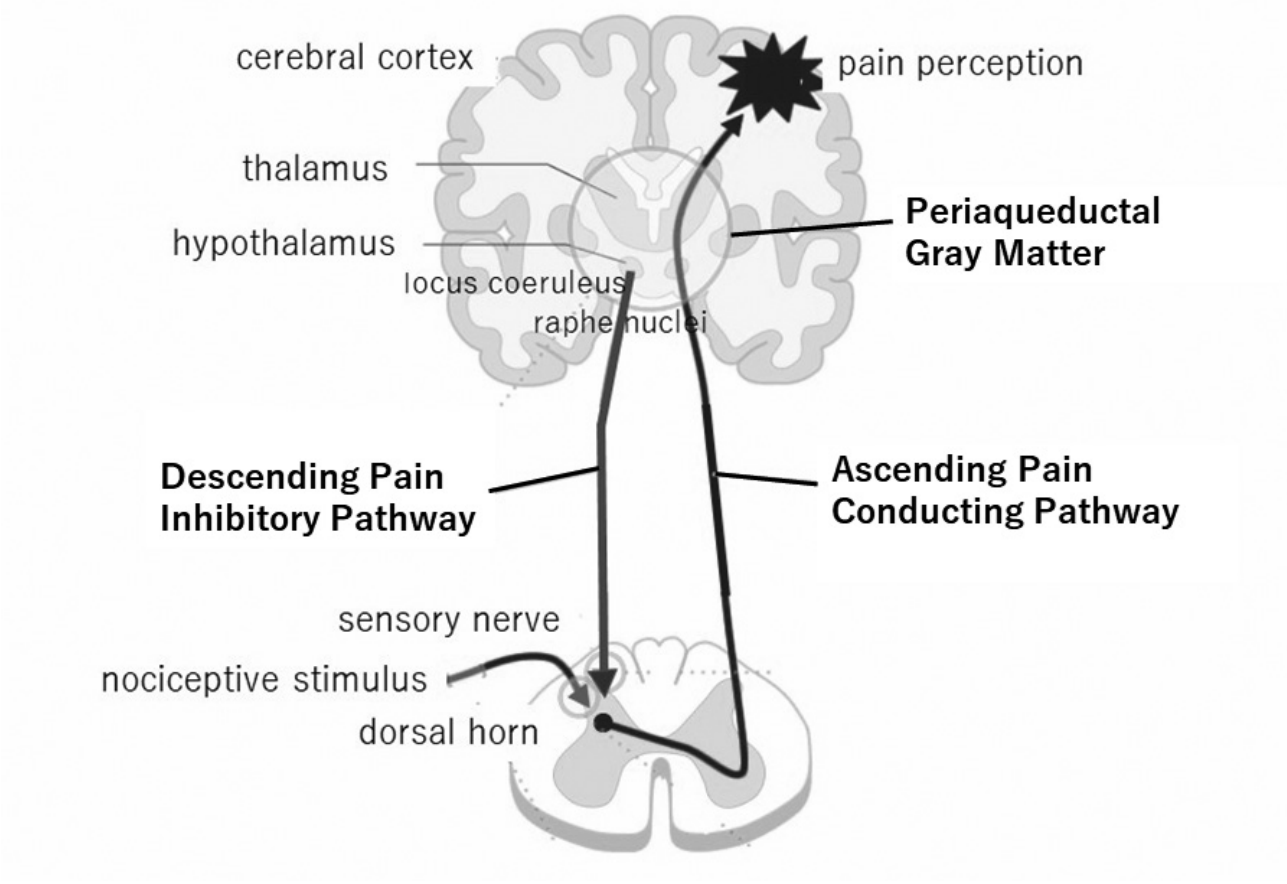

Figure 1. The Role of Periaqueductal Gray Matter in Nociceptive Pain Pathways
The periaqueductal gray matter of the midbrain is an important hub that relays the ascending and descending pathways of nociceptive pain. It receives sensory input from the spinal cord, but also receives information from the limbic system, which descends to the dorsal horn of the spinal cord to inhibit pain transmission.

to nociceptive pain, and may not report pain even if they have a significant physical illness including myocardial infarction, which may delay its detection. Therefore, an excess of dopamine contributes to an elevated pain threshold and decreases the role of pain as an early sign of physical disease. Antipsychotic drugs block excess dopamine, which may normalize nociceptive pain threshold and could contribute to early detection of physical complications in patients with schizophrenia.

B. Schizophrenia and chronic pain

The phenomenon of low pain thresholds in schizophrenia has been reported in prolonged pain or chronic pain (Lévesque et al. 2012). Chronic pain is common in patients with schizophrenia and is caused by emotional cognitions influenced by anxiety, fear, or past memories. In contrast to nociceptive pain, chronic pain including psychological pain does not involve sensory receptors but stimulates the same cortical pain areas. Multiple brain regions are active when the brain perceives pain in the absence of nociceptive stimuli. Functional connectivity of brain regions has been elucidated by functional magnetic resonance imaging (fMRI) and are called large-scale brain networks. Chronic pain is associated with changes in the functional connectivity of large-scale brain networks, with the salience network becoming stronger and the default mode network becoming weaker (van Ettinger-Veenstra et al. 2019).

1. Salience Network

Alterations in large-scale brain networks are beginning to be investigated in a variety of painful diseases, but accurate measurements in clinical patients are limited because the presence of pain itself prevents some time-consuming testing. Therefore, measurements of active regions of large-scale brain networks have been made by inducing psychological pain in healthy subjects in experiments. Brain regions associated with psychological pain have been studied in detail in the cyberball

social exclusion task, an online game of catch. In the cyberball task, experimental participants are asked to play catch with two other players. In reality, however, the other players are computer programs. The number of passes given to the experimental participant is pre-set by the experimenter, and if the number of passes received during the game is extremely small, the experimental participant feels psychological distress. Participants who receive fewer passes during the game feel psychological pain, have lower self-esteem, and value their existence less than participants who receive the same number of passes as other players (Xu et al. 2022). A fMRI study of brain function during psychological exclusion in the Cyberball task reveals activation of the anterior cingulate gyrus and insular cortex, components of the salience network (**Figure 2**), and activation of the anterior cingulate gyrus was positively correlated with the degree of pain (Kim 2019). When psychological pain is intense, medial cortical midline structures, consisting of the medial orbitofrontal cortex, dorsomedial prefrontal cortex, anterior cingulate gyrus, precuneus, and posterior cingulate gyrus, to which the midbrain dopamine nervous system projects, are activated. Although still in the validation phase, it has been suggested that the salience network may have stronger functional connectivity in patients with schizophrenia, and it has been speculated that it may be related to not only to psychotic symptoms but also to chronic pain. Excess dopamine may alter functional connections in the brain, making it more susceptible to chronic pain.

2. Default mode network

Another large-scale brain network associated with chronic pain is default mode network. When the brain performs certain tasks while conscious, the dorsolateral prefrontal cortex becomes more active, while the posterior cingulate gyrus and medial frontal lobe, two regions located farther apart, become less active. This is referred to as the executive control network. Conversely, the regions of reduced activity in the executive control network are activated when the brain does not perform any task, referred to as the default mode network. The default mode network, so named because it does not involve thought, interest, or attention, and thus is the resting basal state, is interestingly much higher than the executive function network in terms of brain energy consumption, with the posterior cingulate gyrus and medial frontal lobes consuming more energy (Raichle 2015). A triple network model has recently been proposed for chronic pain. The salience network and the executive control network are correlated, and both are anti-correlated to the default mode network (De Ridder et al. 2022). In chronic pain, functional connectivity in the posterior cingulate and right insular is decreased with functional coupling within the default mode network weakened **(Figure 2)**. Recent studies have also suggested reduced functional coordination between default mode network and descending pain inhibitory pathways (Cottam et al. 2018). In chronic pain, the default mode network itself is less active and its functional connectivity with other brain regions is reduced.

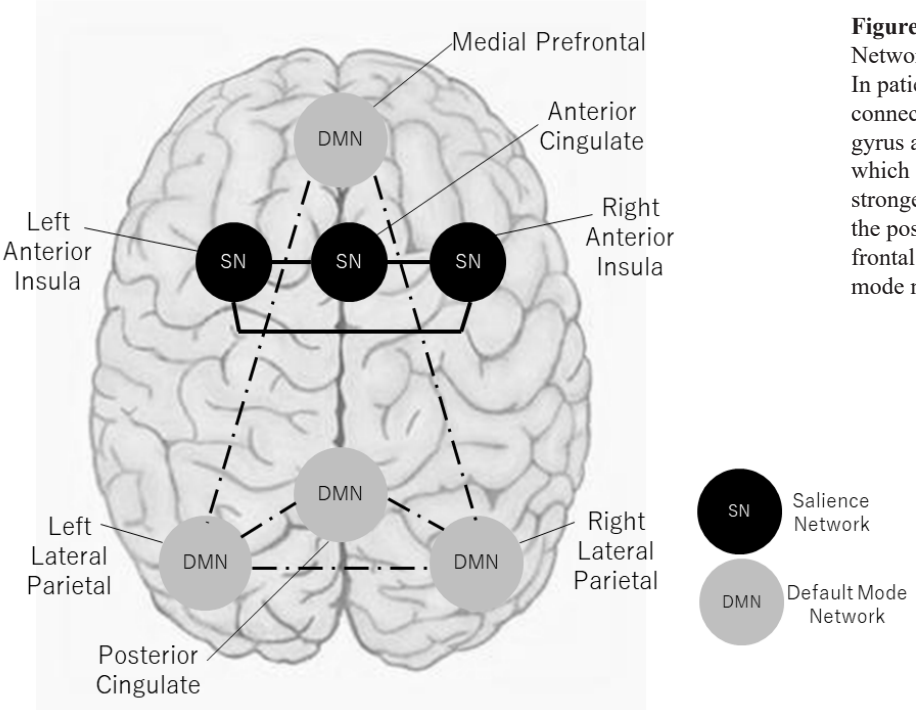

Figure 2. Alterations in Large-Scale Brain Networks in Chronic Pain
In patients with chronic pain, the functional connectivity between the anterior cingulate gyrus and the left and right insular cortices, which forms the salience network, are stronger. In contrast, connectivity between the posterior cingulate gyrus and medial frontal cortex, which forms the default mode network, are weaker.

Dopamine and serotonin have opposing effects on the activity of large-scale brain networks, and the default mode network often functionally activated in serotonergic systems (Conio et al. 2020). Moreover, dopamine and serotonin imbalances have been shown to affect the emotional system via the bed nucleus of the stria terminalis. Inhibitory inputs to the bed nucleus of the stria terminalis, which projects to the lateral hypothalamus, are increased in chronic neuropathic pain. Release of persistent inhibition of the bed nucleus of the stria terminalis by chemogenetic manipulation reduces pain-induced anxiety (Yamauchi et al. 2022). Chronic pain weakens the functional connectivity between the default mode network and the bed nucleus of the stria terminalis, making it more likely to induce anxiety. Thus, changes in monoamines, e.g., increased dopamine and decreased serotonin, alter the functional connectivity of large-scale brain networks (Bannister & Dickenson 2016).

3. The insular cortex and molecular memories of pain

The patients with schizophrenia may experience chronic pain syndromes even in the absence of nociceptive stimuli. However, pain is usually not elicited without triggers. If past pain information is encoded within the salience network, it theoretically reinforces that the salience network is closely related to development of chronic pain. In a recent elaborate experiment, when intestinal inflammation was artificially induced in mice, this inflammation and pain memory was stored in the insular cortex, and after recovery from inflammation, activation of the insular cortex by chemogenetics reproduced intestinal inflammation and pain (Koren et al. 2021). The insular cortex stores information about past inflammation and pain, and surprisingly, this immunological "memory engram" may be pathologically replayed after the activation of the insula cortex, a part of salience network. When the salience network is activated, past pain memories are reproduced, triggering chronic pain even in the absence of nociceptive stimuli.

Patients with schizophrenia show a duality with respect to pain thresholds: an elevated pain threshold in acute pain and a lowered pain threshold in chronic pain. The altered function of the nervous system, which is regulated by dopamine and other monoamines in the pain circuit from the periphery to the cortex, may explain this phenomenon.

LIMITATIONS

This is the first narrative review, based on the latest neuroscience data, to consider two aspects of pain thresholds in schizophrenia. A major limitation of this review, however, is that most reported study participants are investigated when on antipsychotic medications, dopamine blockers which undoubtedly affect their pain thresholds. Nevertheless, there are studies of drug-naïve schizophrenia patients who have shown increased pain thresholds for nociceptive pain (Potvin & Marchand 2008). Thus, an elevated threshold for acute pain may be present even if drug effects are excluded. Ideally, what is needed are pain studies in drug naïve schizophrenia patients and in pain patients after administration of antipsychotic medication. Another overarching limitation, present in all schizophrenia studies, is that schizophrenia is a heterogeneous disorder. Patients given this diagnosis do not all respond in the same way. The pain paradox reviewed here may, thus, be true for some schizophrenia patients and not for others.

CONCLUSION

Many schizophrenia patients appear to have an excess of dopamine in the mesolimbic system, which stimulates both the descending pain inhibitory pathway and the salience network. As a result, a pain threshold paradox has been observed, in which the threshold for acute nociceptive pain is high and the threshold for chronic pain is low. However, most studies of pain thresholds in schizophrenia patients are on antipsychotic medications, and their influence cannot be ruled out. Nevertheless, it is possible to conclude that appropriate regulation of dopamine transmission via dose modulation of antipsychotic medications could normalize pain thresholds. Monoamine modulation in schizophrenia patients may, thus, be effective not only in improving psychotic symptoms but also in removing the pain threshold paradox. Further research is needed on pain thresholds in drug-naïve schizophrenia patients and the effects of antipsychotic medications on pain.

Acknowledgements: None.
Conflict of interest: None to declare.
Sources of funding: None.

References

1. Antioch I, Ciobica A, Paulet M, Bild V, Lefter R, Timofte D: Pain manifestations in schizophrenia – clinical and experimental aspects in human patients and animal models. Psychiatr Danub 2015;27:142-52.
2. Bannister K & Dickenson AH: What do monoamines do in pain modulation? Curr Opin Support Palliat Care 2016;10:143-8.
3. Birgenheir DG, Ilgen MA, Bohnert AS, Abraham KM, Bowersox NW, Austin K et al.: Pain conditions among veterans with schizophrenia or bipolar disorder. Gen Hosp Psychiatry 2013;35:480-4.
4. Conio B, Martino M, Magioncalda P, Escelsior A, Inglese M, Amore M et al.: Opposite effects of dopamine and serotonin on resting-state networks: review and implications for psychiatric disorders. Mol Psychiatry 2020;25:82-93.
5. Cottam WJ, Iwabuchi SJ, Drabek MM, Reckziegel D, Auer DP: Altered connectivity of the right anterior insula drives the pain connectome changes in chronic knee osteoarthritis. Pain 2018;159:929-38.
6. De Ridder D, Vanneste S, Smith M, Adhia D: Pain and the Triple Network Model. Front Neurol 2022;13:757241. doi: 10.3389/fneur.2022.757241.
7. Girard M, Plansont B, Bonnabau H, Malauzat D: Experimental pain hypersensitivity in schizophrenic patients. Clin J Pain 2011;27(9):790-5.
8. Kim J: Somatotopically specific primary somatosensory connectivity to salience and default mode networks encodes clinical pain. Pain 2019;160:1594-605.
9. Koren T, Yifa R, Amer M, Krot M, Boshnak N, Ben-Shaanan TL et al.: Insular cortex neurons encode and retrieve specific immune responses. Cell 2021;184:5902-15.
10. Lévesque M, Potvin S, Marchand S, Stip E, Grignon S, Pierre L et al.: Pain perception in schizophrenia: evidence of a specific pain response profile. Pain Med 2012;13(12):1571-9.
11. Lueptow LM, Fakira AK, Bobeck EN: The Contribution of the Descending Pain Modulatory Pathway in Opioid Tolerance. Front Neurosci 2018;12:886. doi: 10.3389/fnins.2018.00886.
12. Potvin S & Marchand S: Hypoalgesia in schizophrenia is independent of antipsychotic drugs: a systematic quantitative review of experimental studies. Pain 2008;138:70-8.
13. Raichle ME: The brain's default mode network. Annu Rev Neurosci 2015;38:433-47.
14. Samineni VK, Grajales-Reyes JG, Sundaram SS, Yoo JJ, Gereau RW 4th: Cell type-specific modulation of sensory and affective components of itch in the periaqueductal gray. Nat Commun 2019;10:4356. doi: 10.1038/s41467-019-12316-0.
15. Singh MK, Giles LL, Nasrallah HA: Pain insensitivity in schizophrenia: trait or state marker? J Psychiatr Pract 2006;12:90-102.
16. van Ettinger-Veenstra H, Lundberg P, Alföldi P, Södermark M, Graven-Nielsen T, Sjörs A et al.: Chronic widespread pain patients show disrupted cortical connectivity in default mode and salience networks, modulated by pain sensitivity. J Pain Res 2019;12:1743-55.
17. Wood PB: Stress and dopamine: implications for the pathophysiology of chronic widespread pain. Med Hypotheses 2004;62:420-4.
18. Xu M, Zhang J, Li Z: Social exclusion modulates neural dynamics of monetary and social reward processing in young adult females. Biol Psychol 2022;171:108344. doi: 10.1016/j.biopsycho.
19. Yamauchi N, Sato K, Sato K, Murakawa S, Hamasaki Y, Nomura H et al.: Chronic pain-induced neuronal plasticity in the bed nucleus of the stria terminalis causes maladaptive anxiety. Sci Adv 2022;8:eabj5586. doi: 10.1126/sciadv.abj5586.

Correspondence:
Takahiko Nagamine, MD, PhD
Sunlight Brain Research Center
4-13-18 Jiyugaoka, Hofu, Yamaguchi, 747-0066, Japan
tnagamine@outlook.com, +81-835-25-6610