Neurophysiological Mechanisms of Self-Injurious Behavior and Comparison of Comorbid Disorders

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Abstract

Self-injurious behavior represents a significant public mental health concern. Synthesizing recent research findings, abnormalities in emotional brain regions, control brain regions, pain brain regions, reward brain regions, the opioid and dopamine systems, and specific genes collectively contribute to self-injurious behavior. Comparative analyses with suicide, addiction, eating disorders, and depressive disorders reveal partially overlapping pathogenic mechanisms between self-injurious behavior and its comorbid conditions. Based on these findings, we propose a hypothetical model of the cognitive-neural mechanisms underlying self-injurious behavior and outline future research directions concerning gender differences, developmental characteristics, and interventions related to the neurophysiological mechanisms of self-injurious behavior.

Full Text

Preamble

Non-suicidal self-injury (NSSI) refers to the deliberate, repetitive alteration or infliction of damage to one' s own bodily tissue without explicit suicidal intent —a destructive behavior directed toward oneself that is non-lethal or has low lethality [**?**, **?**, **?**]. In the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5), NSSI is no longer classified as a symptom of borderline personality disorder (BPD) but as a distinct mental disorder [**?**, **?**, **?**]. Common forms of NSSI include cutting, biting, burning, and hitting oneself, with adolescence representing the peak period of onset [**?**, **?**, **?**]. Epidemiological surveys indicate that the detection rate of NSSI among Chinese adolescents reaches 36% [**?**, **?**]. NSSI poses a significant threat to public mental health, and the National Health Commission (2020) has called for improvements to the social psychological service system and the development of intervention protocols for at-risk

patients in the context of the COVID-19 pandemic. Elucidating the mechanisms underlying NSSI is a prerequisite for effective control and intervention.

Early explanations of NSSI mechanisms focused primarily on psychological and social dimensions, such as the emotion regulation model and the integrated model. Nixon et al. (2002) proposed that individuals who self-injure exhibit emotion management deficits, specifically alexithymia, emotion regulation difficulties, and high emotional intensity, which lead them to engage in self-injurious behavior to escape or control negative emotional experiences. This suggests that emotion-related brain regions (e.g., the amygdala) may be involved in the onset of NSSI. Subsequently, Nock (2009) integrated biological, psychological, and social factors into a comprehensive model, positing that NSSI serves both as a coping mechanism and a communication modality, with various risk factors (family environment, school environment, genetic factors, etc.) acting through specific vulnerability factors. Negative life experiences are regarded as the primary triggers for NSSI.

In recent years, with continuous advancements in neuroimaging technology, research on the neurophysiological mechanisms of NSSI has grown substantially in both quantity and scope. Moreover, due to high comorbidity rates and similar clinical presentations, many recent studies have compared NSSI with related disorders (such as suicide, addiction, eating disorders, and depressive disorders) in terms of neurophysiological characteristics to investigate shared and distinct mechanisms. Accordingly, this review synthesizes literature from the past decade, examining NSSI-related brain regions, neurotransmitters, and genes, as well as similarities and differences with comorbid disorders from a neurophysiological perspective, and proposes an integrative cognitive-neuroscience model of NSSI.

2.1 Brain Regions Related to NSSI

NSSI is generally believed to involve abnormalities in emotion, control, pain, and reward brain regions, with multiple neurophysiological explanatory models supported by extensive cognitive and behavioral research.

2.1.1 Emotion-Related Brain Regions

When confronted with stressful events and negative emotions, individuals with NSSI often exhibit varying degrees of emotion regulation deficits. Consequently, abnormalities in emotion-related brain regions within the limbic system (such as the amygdala) may constitute one mechanism underlying NSSI. The amygdala, located in the limbic area, is associated with emotion generation, recognition, and regulation [**?**, **?**]. Research has found that the amygdala in individuals with NSSI shows hyperactivation, yet the intensity of this activation is negatively correlated with self-reported emotional distress [**?**, **?**]. In other words, when individuals with NSSI experience more negative emotions, their amygdala activation actually decreases, indicating a deficit in emotion regulation function.

Some researchers have alternatively interpreted this phenomenon, suggesting that individuals with NSSI exhibit relatively weak amygdala activation only when processing NSSI-related stimuli, thereby reducing aversion to self-injury cues and facilitating the act of self-injury, whereas amygdala activation increases when processing stimuli unrelated to NSSI [**?**, **?**].

Beyond activation abnormalities, the connectivity between the amygdala and other brain structures also differs in individuals with NSSI. Schreiner et al. (2017) employed a negative emotional face-matching paradigm and multimodal neuroimaging to examine amygdala networks in adolescents with NSSI, revealing deficits in functional connectivity between the amygdala and frontal lobe, as well as excessive resting-state functional connectivity between the amygdala and supplementary motor area (SMA) and dorsal anterior cingulate cortex (dACC). While the amygdala is involved in emotion processing, the SMA is associated with habitual behaviors. This excessive connectivity may establish habitual associations between negative emotions and self-injury, representing a mechanism for the repetitive nature of NSSI [**?**, **?**].

Overall, the negative correlation between amygdala activation and emotional response, combined with heightened connectivity between the amygdala and prefrontal cortex, suggests that individuals with NSSI may become desensitized to negative emotions and self-injurious behavior. These abnormalities can lead to emotion regulation deficits that trigger NSSI.

2.1.2 Control-Related Brain Regions

Generally, dysregulation of the emotion system does not directly lead to NSSI; rather, abnormalities in control-related brain regions may mediate the pathway from negative emotions to self-injury. Previous neuroimaging studies have noted that differences in brain electrical topography between individuals with NSSI and healthy controls primarily manifest in the prefrontal lobe [**?**, **?**]. The prefrontal cortex (PFC) is the most complex neocortical region in humans, playing a crucial role in top-down processing and controlling thoughts and actions [**?**, **?**]. Dahlgren et al. (2018) investigated PFC activation in individuals with NSSI during a cognitive interference task (selecting a specified number when the button sequence was incongruent with the displayed number sequence) and found altered neural activation patterns, specifically reduced dorsolateral prefrontal cortex (DLPFC) activation that was negatively correlated with emotional response intensity and impulsivity levels—a relationship not observed in healthy controls. These results indicate that individuals with NSSI utilize different neural circuits when processing cognitive interference.

These abnormalities in control brain regions are often behaviorally manifested as uncontrollable impulsivity. Multiple surveys have demonstrated that individuals with NSSI exhibit deficient inhibitory control and significantly higher levels of behavioral impulsivity than the general population [**?**, **?**, **?**, **?**, **?**]. Yu et al. (2013) used a Go/Nogo paradigm to study impulsivity in adolescents with

NSSI, finding that self-reported impulsivity was positively correlated with NSSI severity, and that during inhibitory tasks, these individuals showed higher N2 amplitudes and longer latencies, indicating deficits in inhibitory control. Regarding the mechanism underlying these deficits, Kim et al. (2015) provided an explanation by discovering elevated plasma levels of the pro-inflammatory cytokine TNF-α in individuals with NSSI, which were positively correlated with frontal theta amplitude. These findings suggest that NSSI is associated with increased behavioral impulsivity and inflammation, which may alter major neurotransmitter metabolism, ultimately affecting frontal lobe function and reducing inhibitory capacity.

In summary, abnormalities in control-related brain regions lead to impaired inhibitory control in individuals with NSSI, making it difficult for them to suppress negative emotions and self-injurious impulses, resulting in uncontrolled self-injurious behavior. This may represent one neurophysiological mechanism underlying NSSI.

2.1.3 Pain Perception Brain Regions

Previous research indicates that abnormalities in pain perception also play a role in the pathway from emotion regulation deficits to NSSI. Pain is a complex subjective experience that, as a biological instinct, serves an evolutionary function by alerting us to external stimuli [**?**, **?**]. NSSI represents an active pursuit of wounds and pain, revealing a craving for pain among individuals who self-injure and suggesting that their pain perception abilities may be abnormal.

Some scholars have proposed that individuals with NSSI have lower pain sensitivity and higher pain thresholds, which may explain why most NSSI is repetitive and potentially escalates in severity over time [**?**, **?**]. After painful stimulation, individuals with NSSI show enhanced emotional and bodily awareness with prolonged physiological arousal, changes that may be associated with emotion dysregulation, self-criticism, neuroticism, and negative experiences [**?**, **?**, **?**]. In a study examining the relationship between early experiences and pain in adolescents with NSSI, researchers found that childhood adversity was associated with altered cortisol secretion during adolescence, which weakened the hypothalamic-pituitary-adrenal (HPA) axis—the endogenous stress response system. However, this stress response system simultaneously exhibited hyperreactivity to pain, thereby compensating for inadequate stress responses [**?**, **?**]. Consequently, individuals with NSSI seek the pain associated with self-injury to maintain HPA axis reactivity.

Beyond abnormalities in pain intensity perception, individuals with NSSI may also perceive pain types differently than typical individuals. In an experiment investigating acute pain perception in individuals with NSSI, researchers compared pain from actual arm incisions (4mm wide, 5-7mm deep) with non-invasive mechanical pain (needles, lasers, etc.). They found that the NSSI group showed reduced pain sensitivity, perceiving both stimuli equally during the first 7 sec-

onds, but experiencing more persistent pain from actual incisions later on. Additionally, self-reports from the NSSI group revealed an absence of sharpness perception. Potential pathological mechanisms may include persistent pain induced by incision-related neuroinflammation, abnormalities in the opioid system, and parasympathetic nervous system dysfunction [**?**, **?**]. A similar study using resting-state magnetic resonance imaging found that the incision group showed significantly reduced aversive tension and diminished amygdala activity compared to controls, suggesting that individuals with NSSI may create pain to alleviate tension induced by negative experiences [**?**, **?**]. Another explanation posits that NSSI is often accompanied by the elimination of negative emotions, and individuals who self-injure may have established associations between self-injury tools and this emotion regulation function. Through classical conditioning, self-injury tools and the pain they cause become increasingly associated with positive emotions, reducing aversion to self-injurious behavior and pain, thereby facilitating NSSI [**?**, **?**].

In summary, negative experiences and emotion dysregulation result in lower pain sensitivity among individuals with NSSI, while abnormalities in their HPA axis and amygdala drive them to actively seek pain to counteract various negative emotions.

2.1.4 Reward Brain Regions

After engaging in NSSI, individuals experience temporary emotional release, yet often repeat the behavior after some time. This may be related to abnormalities in reward brain regions, specifically the orbitofrontal cortex (OFC) located in the prefrontal lobe. The OFC is associated with subjective evaluation of rewards and is considered a key region for integrating sensory, hedonic, and emotional information [**?**, **?**]. Research has found that individuals with NSSI show stronger OFC activation than controls when receiving unexpected rewards, with weakened functional connectivity between the left OFC and right parahippocampal gyrus, indicating abnormal functioning in processing associations between choices and their outcomes [**?**, **?**]. In other words, due to reward system abnormalities, individuals with NSSI may have difficulty correctly associating the long-term behavior of self-injury with its negative consequences (such as pain and more severe emotion dysregulation), making it difficult for them to stop the behavior.

Reward system abnormalities may also manifest in the reinforcing functions of NSSI, including positive reinforcement (seeking positive outcomes such as attention or help from others) and negative reinforcement (avoiding negative consequences such as regulating negative emotions or escaping tasks). The abnormal reward circuitry in these patients continuously reinforces and perpetuates NSSI. Therefore, in terms of intervention, it is important to distinguish patients' reinforcement goals, such as reducing dependence on others' attention or altering cognitions about negative events and tasks [**?**, **?**, **?**].

In summary, individuals with NSSI exhibit stronger OFC activation and weaker hippocampal connectivity. These reward system abnormalities may continuously reinforce NSSI and lead to misevaluation of its harmful consequences, contributing to the repetitive nature of the behavior.

2.2 Neurotransmitters and Genes Related to NSSI

In addition to brain regions, researchers have examined the role of specific neurotransmitters and genes in NSSI. Serotonin (5-HT) is a widely distributed neurotransmitter involved in neurotransmission in the central nervous system, regulating behavioral activity, emotion, appetite, and body temperature. Lower 5-HT levels may trigger NSSI [**?**, **?**, **?**]. The serotonin transporter (5-HTT) acts as a regulator of this system, controlling 5-HT concentration in the synaptic cleft, and its gene-linked polymorphic region (5-HTTLPR) short allele (S) reduces 5-HTT regulatory function [**?**, **?**], altering the structure and functional connectivity of emotion-related brain regions such as the hippocampus and amygdala, leading to emotion regulation deficits and increasing NSSI risk [**?**, **?**].

Abnormalities in the opioid system may also be involved in NSSI. Endogenous opioid peptides (EOP) are roughly divided into three types: enkephalins, endorphins, and dynorphins, which are associated with the endocrine system, pain perception, and schizophrenia [**?**, **?**]. Stanley et al. (2010) proposed a homeostatic model suggesting that early adversity and genetic factors lead to low endogenous opioid peptide levels, while NSSI can promote EOP release to achieve internal balance. In other words, EOP participates in pain and emotion regulation processes, serving as a mediator between pain and emotional release and establishing a connection between them [**?**, **?**]. Another study found that NSSI severity was positively correlated with salivary beta-endorphin levels, supporting this conclusion [**?**, **?**].

Following opioid receptor stimulation, dopamine levels increase in individuals who self-injure [**?**, **?**]. Dopamine is the most abundant catecholamine neurotransmitter in the brain, regulating action, motivation, and pleasure [**?**, **?**, **?**]. Elevated dopamine produces feelings of pleasure, which over time leads to desensitization, causing patients to repeat and intensify NSSI to maintain normal dopamine levels [**?**, **?**]. Additionally, the A1 allele of the dopamine D2 receptor encoding gene (DRD2) can help maintain emotional balance and reduce dopamine' s rewarding effects; its abnormalities may increase NSSI likelihood [**?**, **?**, **?**].

In summary, abnormalities in serotonin, opioid, and dopamine systems may constitute the neurophysiological basis for repetitive NSSI. Specifically, the S allele of 5-HTTLPR and the A1 allele of DRD2 can affect neurotransmitter function, causing emotion regulation difficulties and increasing NSSI risk, representing potential genetic factors that may trigger the behavior.

3 Comparative Studies of NSSI

Comparative research between NSSI and certain psychological disorders represents a hot topic in the field, with most studies selecting disorders with high comorbidity rates, focusing on suicide, addiction, eating disorders, and depressive disorders, while other disorders have received less attention. Among these, NSSI and suicide have not been well-distinguished in some studies, potentially reducing the credibility of findings, making it necessary to discuss their relationship. Additionally, since both NSSI and addiction are repetitive, can NSSI be considered a behavioral addiction? The underlying mechanisms warrant comparison. Whether eating disorders constitute indirect self-injury through bodily harm and why they show high comorbidity with NSSI have also become research hotspots. Finally, why do patients with depressive disorders engage in NSSI, and which aspect should interventions target? These questions deserve attention. Therefore, this article adopts a behavioral comparison perspective, selecting these four psychological disorders to elucidate their relationships with NSSI.

Studying this issue can provide a more comprehensive understanding of NSSI and enable cross-domain integration in intervention based on commonalities across different disorders. Currently, most research in this area conceptually explains cognitive mechanisms, but is increasingly moving toward neurophysiological mechanisms. This article therefore integrates both types of research to more fully understand the distinctions and connections between NSSI and related disorders.

3.1 NSSI and Suicide

Some researchers consider NSSI and suicide to be fundamentally different psychological disorders, with the former motivated by escaping negative emotions and oriented toward survival (with low fatality rates), while the latter aims for death [**?**, **?**]. Maciejewski et al. (2017) investigated the intergenerational transmission of NSSI and suicidal behavior, finding that individuals with genetic predisposition to depression were more likely to develop suicidal ideation, but this predisposition could not predict NSSI. Iznak et al. (2021) examined EEG frequency and spatial differences between adolescents who engaged in NSSI only and those with both NSSI and suicide attempts, finding that NSSI-only participants showed more right hemisphere activity with low consistency, while those with both behaviors showed more left hemisphere activity, suggesting these features might be used to estimate suicide risk in NSSI patients.

However, more research findings emphasize the connection between NSSI and suicide. For example, some researchers propose that early NSSI can predict subsequent suicidal ideation and behavior [**?**, **?**, **?**]. Multiple epidemiological surveys support this view [**?**, **?**, **?**, **?**]. On one hand, as NSSI is repeated, individuals' pain tolerance increases while its function in countering negative emotions weakens, causing it to become a new stressor, and suicidal thoughts may replace NSSI

as a more effective means of regulating negative emotions [?, ?]. On the other hand, NSSI can reduce suicide rates by regulating negative aversive emotions, thereby serving an anti-suicide function [?, ?]. Brain functional imaging also shows some overlap, with both individuals who self-injure and suicide attempters showing reduced gray matter volume in the ventral prefrontal cortex (vPFC), OFC, and anterior cingulate cortex, as well as diminished striatal activation and reduced prefrontal connectivity [?, ?]. Additionally, suicide attempters show stronger connectivity between the amygdala and anterior cingulate during self-recognition tasks (identifying emotions in one' s own face), similar abnormal connectivity has been observed in individuals with NSSI [?, ?, ?].

In summary, NSSI and suicidal behavior differ in motivation, genetics, and cerebral hemisphere activation, but more research supports their connection and similarities in brain mechanisms. Given these mechanistic similarities, future research should pay greater attention to patients' personality traits and developmental environments to comprehensively prevent suicide attempts in individuals with NSSI.

3.2 NSSI and Addiction

Previous research has found a comorbid relationship between substance addiction and NSSI, with drug use potentially triggering or exacerbating self-injurious behavior. For example, Escelsior (2021) examined the relationship between cannabis use and NSSI, finding a significant correlation, with long-term use, psychiatric disorders, emotion dysregulation, and high impulsivity further increasing the likelihood of NSSI among cannabis users. Other research found that the timing of cannabis initiation differentially affected NSSI risk, with those who began using before age 17 being more susceptible to NSSI risk factors than those who started later [?, ?].

Some researchers consider NSSI itself a "process addiction," exhibiting addictive characteristics including compulsivity, loss of control, difficulty terminating the behavior, and increased tolerance [?, ?, ?], with similarities to substance addiction in etiology, emotional experience, family environment, and the nature of stress release responses [?, ?]. For instance, both NSSI and addiction patients show inhibitory control deficits due to prefrontal cortex damage [?, ?, ?], share a desire to eliminate negative emotions [?, ?], and have similar reinforcement sensitivity foundations [?, ?, ?]. The addiction model of NSSI more comprehensively explains its neural basis, positing that abnormalities in the dopamine system, opioid system, and stress system jointly contribute to NSSI. Under normal conditions, stress system activation increases adrenocorticotropic hormone levels, promoting cortisol, endogenous opioid peptide, and dopamine secretion to alleviate stress. However, when the stress system is overactivated, individuals may introduce NSSI, which directly affects the opioid and dopamine systems through the central nervous system, establishing a direct link between NSSI behavior and opioid release, ultimately leading to pain tolerance and addiction [?, ?]. Based on this, some researchers have proposed applying addiction treat-

ment approaches to individuals with NSSI [?, ?].

Overall, NSSI and addiction share certain neurophysiological mechanisms, such as impaired inhibitory control, craving induced by opioid and dopamine system abnormalities, and behavioral repetition due to reward system dysfunction. Investigating these similarities helps us understand NSSI from different perspectives and develop diversified intervention measures to reduce NSSI behavior.

3.3 NSSI and Eating Disorders

Eating disorders can be broadly categorized into anorexia nervosa, bulimia nervosa, restrictive eating disorder, and binge eating disorder [?, ?]. Research has found high comorbidity between eating disorders and NSSI. For example, Warne et al. (2021) found that one-third of individuals with eating disorders had engaged in NSSI, and the frequency of NSSI could positively predict eating disorder severity three months later [?, ?]. One perspective views eating disorder behaviors as a form of indirect self-injury [?, ?]. For instance, individuals with eating disorders who also engage in NSSI show greater rigidity [?, ?] and more severe obsessive-compulsive symptoms [?, ?] than those without NSSI, suggesting that high impulsivity may be a shared risk factor [?, ?], while alcohol use, purging, and depression can also predict NSSI in eating disorder patients [?, ?]. On the other hand, both NSSI and eating disorder patients exhibit emotion management deficits, and needs for emotion regulation, countering dissociation, and managing peer relationships may trigger both conditions [?, ?, ?].

The brain mechanisms of the two conditions also show both connections and distinctions. For example, both individuals with NSSI and those with restrictive eating show stronger neural activation in reward-related brain regions such as the OFC compared to healthy controls [?, ?, ?], but the former shows reduced OFC gray matter volume [?, ?] while the latter shows increased volume [?, ?]. Additionally, abnormal food craving in binge eating disorder may be associated with hyperactivation of the anterior cingulate cortex (ACC) and hippocampus [?, ?], similar to findings in individuals with NSSI [?, ?]. Furthermore, both conditions involve inhibitory control deficits, but with some differences in electrophysiological indicators. The N2 amplitude, a common index of inhibitory control reflecting automatic attentional bias to cues, is larger in individuals with NSSI when inhibiting responses to neutral cues (e.g., upright/inverted triangles), whereas it is smaller in individuals with restrictive eating when inhibiting responses to relevant cues (e.g., food) [?, ?, ?]. A possible explanation is that, under conditions of impaired inhibitory control, inhibiting neutral cues requires more neural energy (larger N2 amplitude), whereas attentional bias to relevant cues is unconscious and automatic, resulting in smaller N2 amplitude [?, ?].

The similarities between NSSI and eating disorders suggest the feasibility of cross-domain interventions. Future empirical research should more directly compare their neurophysiological mechanisms to identify overlapping pathogenic factors for more efficient prevention and control of both conditions.

3.4 NSSI and Depressive Disorders

Depressive disorders fall under the category of mood disorders, characterized by significant and persistent changes in emotion or mood. As an affective mental disorder, depression shows high comorbidity with NSSI, with most patients engaging in repetitive self-injury [**?**, **?**]. The reason may be that individuals with depression need to seek means to regulate emotions, and the function of NSSI in alleviating negative emotions meets this need, leading to repeated self-injury to achieve emotional equilibrium [**?**, **?**]. Additionally, depressive disorders and NSSI share common risk factors such as childhood abuse [**?**, **?**] and genetic factors [**?**, **?**], which may cause some individuals with depression to choose NSSI over other behaviors for emotion regulation.

Moreover, NSSI and depressive disorders share certain neurophysiological mechanisms. For example, both show abnormalities in cortisol secretion levels and HPA axis reactivity, causing changes in activation and structure of related brain regions [**?**, **?**, **?**]. Subsequently, emotion and stress response systems including the amygdala and hippocampus show abnormal activation, resulting in similar emotion regulation difficulties [**?**, **?**, **?**]. It is these similar neural mechanisms that contribute to the high comorbidity between NSSI and depression. However, NSSI has unique mechanisms; for instance, high impulsivity resulting from control brain region abnormalities is not a primary feature of depressive disorders [**?**, **?**].

In summary, NSSI and depressive disorders show high comorbidity with shared risk factors and partially overlapping neural mechanisms, which explains why some individuals with depression engage in NSSI. Furthermore, in treating NSSI patients, interventions should address not only the behavior itself but also potential root causes such as depressive disorders, adopting an integrated approach. Finally, to facilitate readers' understanding, we have compiled some brain imaging studies on NSSI and the four disorders discussed above, as shown in Table 1 .

[Table content would appear here with all the study details preserved exactly as in the original]

Finally, while comorbidity research enables a broader understanding of NSSI, it is also susceptible to confounding factors. Although DSM-5 (2013) has classified non-suicidal self-injury as a distinct diagnostic category with independent criteria, many studies, as shown in Table 1, have not selected independent NSSI patients as participants, with patients often having multiple comorbid disorders. Therefore, future research should pay greater attention to the purity of NSSI samples, exercising caution in participant selection to ensure reliable findings.

4.1 Construction and Testing of a Cognitive-Neural Mechanism Model of NSSI

Overall, abnormalities in emotion-related brain regions, control regions, reward regions, the opioid system, and specific genes collectively contribute to NSSI. Existing research has proposed various perspectives on NSSI mechanisms, such as Nixon et al.' s (2002) emotion regulation model and Stanley et al.' s (2010) homeostatic model. Integrating these perspectives, we propose that NSSI may be caused by a combination of emotion regulation deficits, high impulsivity, and abnormal pain perception. However, a comprehensive model integrating cognitive processes and neurophysiological mechanisms of NSSI is still lacking. Therefore, this article attempts to synthesize existing neuroscientific findings with cognitive processes to construct a cognitive-neural mechanism model of NSSI, as illustrated in Figure 1 [Figure 1: see original paper].

[Figure content would appear here]

As shown in Figure 1, we link the cognitive processes of NSSI with the primary neurophysiological mechanisms at each stage. First, abnormalities in emotion-related brain regions (amygdala, etc.) and specific genes (e.g., S allele of 5-HTTLPR) lead to emotion regulation difficulties [**?**, **?**, **?**]. Second, dysfunction in control-related brain regions (prefrontal cortex, cingulate cortex, etc.) results in impaired inhibitory control and high impulsivity [**?**, **?**, **?**]. Third, under the influence of the opioid system, HPA axis, and amygdala, individuals develop high pain tolerance and seek pain to restore homeostatic balance [**?**, **?**, **?**]. Finally, abnormalities in reward brain regions (OFC, etc.) and opioid and dopamine systems lead to desensitization [**?**, **?**, **?**], causing NSSI to occur repeatedly.

The dashed lines in Figure 1 represent possible shared neurophysiological mechanisms across different cognitive processes. We hypothesize that abnormalities in emotion brain regions may affect not only emotion management but also impulsivity levels. Similarly, control brain region abnormalities may cause not only inhibitory control deficits and high impulsivity but also emotional dyscontrol leading to emotion regulation deficits. Reward system abnormalities may cause individuals to perceive pain as a negative reinforcer, triggering pain craving. These hypotheses require empirical support.

The third row in Figure 1 marks shared mechanisms between NSSI and its comorbid disorders. First, depending on individual traits and environments, abnormalities in emotion and control brain regions can lead to depressive disorders, NSSI, or suicidal behavior [**?**, **?**, **?**, **?**]. Second, the uncontrollable impulses to eat or restrict food in eating disorders may, like the high impulsivity in NSSI, originate from control brain region abnormalities [**?**, **?**]. Finally, addiction and NSSI share high mechanistic consistency, with both showing high impulsivity from control region abnormalities, craving from opioid system abnormalities, and repetitive behavior from reward region abnormalities [**?**, **?**, **?**, **?**].

This preliminary cognitive-neural mechanism model of NSSI integrates cogni-

tive, neurophysiological, and comorbidity comparison perspectives to explain the development of NSSI, facilitating more comprehensive understanding, precise risk factor identification, and targeted intervention. However, the model is currently built upon numerous independent empirical studies; future research should adopt an integrated approach to validate the overall cognitive process and neurophysiological mechanisms of NSSI.

4.2 NSSI and Attention Brain Regions

Recent research has identified attentional bias as a factor in the development and recurrence of certain psychological disorders [**?**, **?**]. For individuals with NSSI, alternative emotion regulation strategies (such as talking to others) should be available, yet their unique preference for NSSI suggests abnormalities in attention brain regions. Lu et al. (2015) supported this view, finding that when presented with different emotion regulation strategies, adolescents with NSSI paid more attention to NSSI-related materials than to other regulation strategies, showing an attentional bias toward their commonly used self-injury methods. In other words, the attentional orienting network may be abnormal in individuals with NSSI, causing them to choose NSSI more frequently when emotion regulation is needed. Moreover, increased attention to NSSI-related stimuli may deplete attentional resources, impairing effective self-regulation.

Notably, no neuroimaging studies have specifically examined attention brain regions in individuals with NSSI. However, attentional bias abnormalities are generally believed to be associated with amygdala hyperactivation and reduced prefrontal cortex activity. Future research should focus more on this area.

4.3 Gender Effects in Neural Mechanisms of NSSI

The aforementioned model may also be moderated by gender. In recent years, to deepen understanding of NSSI and enable timely prevention and control, numerous epidemiological surveys have been conducted across different populations. Regarding gender differences in NSSI, the literature has not reached a consensus. Some studies suggest that females have higher NSSI rates than males [**?**, **?**, **?**, **?**], while others find no significant gender differences [**?**, **?**, **?**]. These discrepancies may be related to sampling regions, participant age, and other factors. The neural mechanisms underlying gender differences in NSSI warrant greater attention. For example, research has found that males regulate positive emotions more efficiently, possibly because their cognitive systems are less involved in regulating the amygdala and nucleus accumbens [**?**, **?**]. Do these gender differences in emotion-related brain regions contribute to differential NSSI rates? Additionally, females show higher pain perception intensity and duration than males [**?**, **?**]. Do these gender differences in pain perception lead to variations in NSSI methods and severity? Current intervention protocols for NSSI do not differentiate by gender, and investigating gender differences in neural mechanisms could facilitate more targeted interventions.

4.4 Patterns of Neural System Changes in NSSI

Due to the uncertain timing of NSSI and the large sample sizes required, few longitudinal studies have been conducted in this field. For example, Liu et al. (2019) conducted a one-year longitudinal study of over 5,000 middle school students without NSSI history, finding that exposure to suicide-related information increased NSSI likelihood. Another similar study examined the relationship between impulsivity and NSSI over one year, finding a significant positive correlation [**?**, **?**]. To date, no longitudinal studies have examined the neural mechanisms of NSSI, and existing findings cannot answer whether neural system changes trigger NSSI, whether NSSI causes neural changes, or whether both occur alternately.

To more accurately understand the causal relationship between NSSI and related neural abnormalities, future research should employ longer-term, methodologically diverse longitudinal designs. For example, researchers could track individuals without NSSI history but in high-risk environments (e.g., those who have experienced childhood abuse), record early neuroimaging data, and conduct follow-up scans after NSSI onset (while ensuring timely intervention and ethical compliance) to investigate longitudinal patterns of neural system changes in individuals with NSSI.

4.5 Intervention Research on NSSI

Common interventions for NSSI include interviews and support groups, specifically dialectical behavior therapy (DBT), cognitive behavioral therapy (CBT), and emotion regulation group therapy (ERGT), all showing significant effectiveness [**?**, **?**, **?**, **?**, **?**]. Some researchers have examined the effects of these treatments on relevant brain regions. For example, Santamarina et al. (2019) studied frontolimbic connectivity in adolescents with NSSI and found that after psychotherapy, 50% of patients reported fewer NSSI episodes than at baseline, with stronger negative connectivity between the amygdala and medial prefrontal cortex (mPFC) predicting better treatment outcomes, suggesting the amygdala could serve as an indicator of psychotherapy efficacy. However, current psychotherapies primarily target emotion problems, while high impulsivity—another major feature of NSSI—has not received adequate attention. Future efforts could develop training programs to help patients reduce impulsivity levels.

In addition to psychotherapy, certain medications can improve NSSI, such as N-acetylcysteine (NAC), used to treat repetitive maladaptive behaviors. One clinical trial found that reduced NSSI frequency after treatment was associated with decreased connectivity between the amygdala and SMA and increased connectivity between the amygdala and inferior frontal artery, suggesting the amygdala may be a therapeutic target for this medication [**?**, **?**]. Additionally, neurotensin is an important modulator of dopamine and glutamate function in the nigrostriatal and limbic systems, and research indicates that pharmacologically altering neurotensin levels may be another important target for medication-based NSSI

intervention [**?**, **?**]. Currently, research on pharmacological interventions for NSSI remains scarce, necessitating greater exploration in this area.

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