Understanding the Biology of Non-Suicidal Self-Injury: A Neurobiological Perspective on Emotion Regulation and Reward Processing

Ellen Drenth (S4765850)
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Research Group: Behavioural Neuroscience group GELIFES
Supervisor: Martien Kas

Abstract

Non-suicidal self-injury (NSSI) is a complex and heterogeneous behavior, often used as a maladaptive coping mechanism for emotion regulation. This essay integrates recent neurobiological research on NSSI, focusing on the roles of emotion regulation and reward processing. Neuroimaging studies highlight fronto-limbic dysfunction, where reduced prefrontal control and heightened limbic activity contribute to emotional reactivity and impulsivity, increasing vulnerability to self-harm. Additionally, alterations in reward-related neural circuits, including the dopaminergic and endogenous opioid systems, may reinforce NSSI as a habit-forming behavior. Further research is needed to clarify unresolved questions, such as the opioid homeostasis theory and the role of dopamine in self-injury. Understanding these mechanisms may improve treatment and prevention, potentially aiding in the development of pharmaceutical interventions. By studying NSSI independently of psychiatric diagnoses, an improved understanding of its neurobiological mechanisms can be unraveled, potentially improving therapeutic and pharmaceutical strategies.

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Introduction

Non-suicidal self-injury (NSSI), also known as self-harm or self-injury, is the behaviour of someone intentionally hurting themselves without suicidal intent. Most commonly, it involves cutting, burning and hitting oneself (Luo et al. 2024). NSSI is a problem especially among adolescents and college students, with a prevalence of 22% (Xiao et al. 2022; Esposito et al. 2023; Zheng et al. 2024). Since the COVID-19 pandemic, NSSI prevalence has increased even more (Deng et al. 2023; Zheng et al. 2022). Even though adolescents have matured physically, psychologically they are still developing. Consequently, adolescents have more difficulties with emotion regulation, are more impulsive and are therefore more prone to NSSI (Pfeifer and Allen 2021). This high prevalence of NSSI among young people poses a big burden on society (Lai et al. 2021). Even though NSSI is without suicidal intent, it significantly increases the risk of future suicide (Wang et al. 2022; Johnson et al. 2022).

Self-injury is associated with a wide range of psychiatric disorders, such as depression and borderline personality disorder (Westlund Schreiner et al. 2015). However, NSSI also occurs as a standalone symptom, without a psychiatric diagnosis (Case et al. 2021). Therefore, it is important to study NSSI independent of a diagnosis (Westlund Schreiner et al. 2015; Başgöze et al. 2021). Prior research has been predominantly focused on the social and psychological mechanisms underlying and influencing NSSI, which has contributed to the development of psychosocial treatments (Kothgassner et al. 2020). However, the underlying neurobiological mechanisms of this complex behaviour are essential for improving prevention, intervention and treatment (Yan and Yue 2023). Research on the neurobiology of NSSI is a relatively new field, in which a lot is still unknown (Kaess et al. 2021). Pharmaceutical and neuromodulatory interventions for treating NSSI specifically are therefore still very limited (Calvo et al. 2022; Plener et al. 2018). Unraveling the underlying mechanisms will greatly advance our understanding of NSSI both in research and clinical settings (Westlund Schreiner et al. 2015; Kaess et al. 2021; Yan and Yue 2023).

NSSI is a complex and highly heterogeneous behaviour influenced by biological, genetic, psychological, social and cultural factors (Wang et al. 2022; Lurigio et al. 2024). Because of its complexity and multi-modal influences, the neurobiological mechanisms of NSSI are not easily pinpointed or confined to a single brain area. Structural, functional and biochemical alterations across the entire brain are found in those engaging in NSSI, influencing multiple neuronal circuits. Prior studies have found neurobiological alterations in individuals with NSSI across several domains including brain structure, connectivity, activity, neurotransmitters, peripheral physiology and neurocognitive functioning (Kaess et al. 2021). Neuro-imaging studies found structural and activity alterations associated with NSSI in brain areas involved in emotional and reward processing (Lai et al. 2021). In individuals who engage in self-injurious behaviors, structural alterations have been identified particularly in components of the fronto-limbic system (Santamarina-Perez et al. 2019; Kaess et al. 2021). Additionally, the ongoing development of the fronto-limbic system during adolescence is linked to the high occurrence of NSSI in adolescents (Westlund Schreiner et al. 2017).

The fronto-limbic system is a network of several interconnected brain areas that play a key role in generating emotional responses and regulating emotions. It consists of the amygdala, the anterior cingulate cortex (ACC), the insula, the hippocampus and the prefrontal cortex (see

Figure 1) (Li et al. 2022; Bi et al. 2022). Fronto-limbic alterations are associated with difficulties in processing emotional stimuli and are associated with multiple psychiatric disorders, such as ADHD, bipolar disorder and borderline personality disorder (Kaess et al. 2021; Kebets et al. 2021). Fronto-limbic connectivity is viewed as a predictor of success of psychotherapy in the treatment of NSSI (Santamarina-Perez et al. 2019). Especially the amygdala-prefrontal cortex connectivity has shown alterations. A decrease in amygdala-frontal connectivity is observed in those who engage in NSSI (Santamarina-Perez et al. 2019; Brañas et al. 2021).

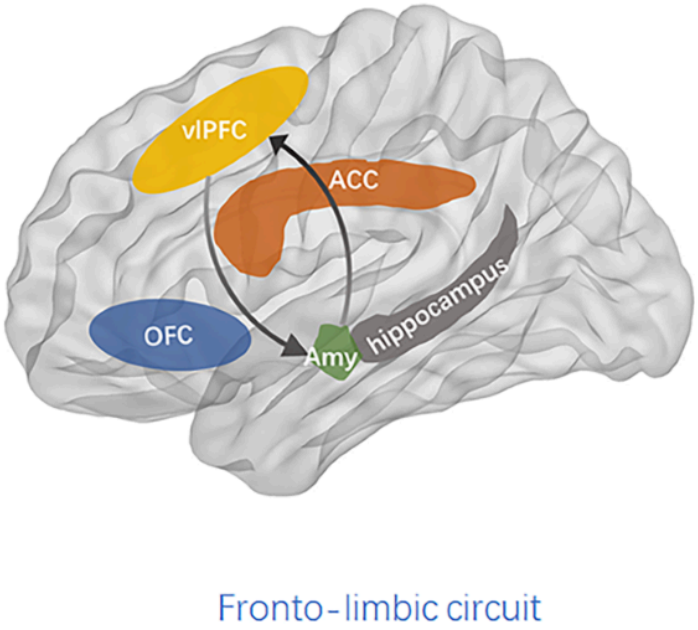

***Figure 1**: Schematic representation of the fronto-limbic system. Including the ventrolateral prefrontal cortex (vlPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala (Amy) and the hippocampus (Bi et al. 2022).*

Emotion regulation and reward processing are psychological and biological mechanisms that play a key role in NSSI behavior (Lang et al. 2024). Neuroimaging studies found that those with repetitive self-injurious behaviour showed alterations and deficits in brain circuits related to emotion regulation, cognitive control, reward and habit (Oudijn et al. 2022). Additionally, there are neurobiological chemical alterations found related to emotion and reward processes in individuals with NSSI (Lang et al. 2024).

This essay aims to provide a theoretical framework for NSSI, focusing on the neurobiological processes involved in emotion regulation and reward processing. By improving the understanding of self-injury, it can contribute to future therapeutic and pharmaceutical interventions based on the neurobiology of NSSI.

Emotion Regulation in NSSI

Regulating emotions is the main motive for people to engage in self-harm (Brown et al. 2022; Massoodi et al. 2025), particularly to alleviate intense negative emotions (Nagy et al. 2023; Bresin and Gordon 2013). Individuals with NSSI commonly have issues with emotion regulation and cognitive control (Lang et al. 2024). Emotion regulation is the ability to control an emotional reaction, which can be conscious or nonconscious, resulting in a physiological or behavioral response with the goal of returning to baseline (Koch et al. 2018). Difficulties in emotion regulation linked to NSSI include the tendency to suppress emotions (Petrovic et al. 2024), high amounts of self-blame and difficulties putting things into perspective (Zadehparizi and Kianimoghadam 2024). The greater the emotional regulatory issues, the greater the risk of engaging in NSSI (Petrovic et al. 2024). The neural mechanisms underlying emotion regulation are therefore essential for understanding the neurobiology of NSSI (Santamarina-Perez et al. 2019; Kebets et al. 2021).

Adolescents engaging in self-harm lack healthy mechanisms to cope with intense emotions. NSSI provides a short-term relief of negative emotions and serves as a maladaptive emotion regulator (Bresin and Gordon 2013). Such negative emotions include frustration, (social) rejection, anger, anxiety and feeling overwhelmed. Negative emotions are reported to be more intense before the act of self-harm, or even thoughts of self-harm, compared to directly after it (Brown et al. 2022). Ultimately, this behavioural pattern leads to a vicious cycle, as dysfunctional emotion regulation is a risk for NSSI and engaging in NSSI leads to poorer emotion regulation (Kandsperger et al. 2022). NSSI then becomes the main method of regulating emotions. Self-harming individuals experience strong cravings of self-harm when experiencing negative emotions (Victor et al. 2012). These negative emotions are also more intense in people with NSSI due to heightened emotional reactivity. Emotional reactivity is an essential element of emotion regulation. It refers to how we experience emotions in terms of intensity, duration and the range of stimuli that can trigger them (Mayo et al. 2021; Kandsperger et al. 2022). Individuals engaging in NSSI more often experience higher levels of emotional reactivity, meaning they experience their emotions more intensely, for a longer period of time and they need less stimuli to feel such emotions compared to those without NSSI (Liu et al. 2020; Kim et al. 2020; Mayo et al. 2021). Adolescents are at higher risk of engaging in self-harming behaviours. They generally exhibit increased emotional reactivity and issues with controlling and inhibiting negative thoughts and emotions, because their brains are still developing. NSSI is used to escape such unwanted and intense emotions during highly emotional events (Kandsperger et al. 2022; Liu et al. 2022).

Neuroimaging studies found differences in activity of fronto-limbic areas in those engaging in self-harm. The study by Mayo et al. (2021) found an enhanced emotional reactivity to both positive and negative stimuli in subjects with NSSI. Additionally, they found a correlation between increased emotional reactivity and increased activation of the anterior insula in NSSI subjects. The anterior insula, part of the fronto-limbic system, is an essential node of the salience network, which is involved in attention and behaviour. The anterior insula is involved in the driving and regulation of other neural networks such as the default mode network and the lateral frontoparietal central executive network. Due to its high connectivity to other brain regions, the anterior insula node is able to integrate internal and external multisensory stimuli

and is therefore thought to be essential for cognitive control (Molnar-Szakacs and Uddin 2022). Additionally, the inferior frontal gyrus, involved in emotion regulation and processing, has been identified to show increased activation in NSSI. This was also the case for the medial frontal gyrus and the right ACC, both involved in reward mechanisms, which is associated with repetition of NSSI (Lai et al. 2021).

Self-harming adolescents have difficulties in processing the overload of emotions. Alterations in the fronto-limbic system are viewed as neurobiological characteristics of emotion dysregulation (Kebets et al. 2021). Limbic alterations are mostly seen in the amygdala and the striatum. The amygdala, the key emotion regulator of the brain, is known to be hyperactive in NSSI (Kandsperger et al. 2022; Westlund Schreiner et al. 2017). This has been observed upon positive, negative and neutral stimuli, suggesting a heightened emotional reactivity regardless of the type of emotion (Kandsperger et al. 2022). Additionally, a reduction in amygdala volume is linked with disordered emotional processing and regulation in NSSI (Won et al. 2023).

Amygdala circuitry anomalies are also mentioned as neurobiological alterations explaining emotion dysregulation in NSSI. A decreased amygdala-frontal connectivity is observed both in rest and during a task in those with NSSI, but can also be explained by depressive symptoms. An increased connectivity of the amygdala with the supplementary motor area connectivity, is only observed in those with NSSI. This functional alteration is therefore thought to contribute to the increased emotional distress and habitual behaviors of NSSI (Westlund Schreiner et al. 2017).

The amygdala and the striatum are important emotion regulation networks and key regulators of reward processes in NSSI. An increased amygdala-ventral striatum connectivity has been observed in NSSI, which positively correlates with higher self-harm frequency. Both the amygdala and the ventral striatum circuits are involved in reward mechanisms. When regulating emotions while looking at self-harm images, an increased amygdala-precuneus and amygdala-inferior parietal lobe connectivity was observed in NSSI, both correlated with increased self-harm frequency. An increase in these circuitries implicates that individuals engaging in NSSI experience more emotions of self-identification and struggle more with regulating negative emotions evoked by images of self-injury, compared to healthy controls. A similar pattern was seen in the increased connectivity of the ventral striatum to the fusiform gyrus and the parahippocampus upon self-harm images and positive images. This circuit alteration implicates deficits in reward mechanisms and difficulties regulating positive emotions. Interestingly, alterations in ventral striatum circuits are associated with relief and NSSI frequency. These neural circuits are viewed as a neurobiological mechanism of how NSSI is reward-based and increases over time (Santana-Gonzalez et al. 2024). Besides connectivity, a reduction in volume of certain striatum areas is associated with emotional dysregulation in NSSI. Alterations of the striatum are pinpointed as key drivers of reward dysfunction and habitual behaviour in NSSI. An increase of external emotion regulation is linked to a reduction in putamen volume, a subarea of the striatum (Wang et al. 2022).

Frontal region alterations are mainly observed in the prefrontal cortex (PFC). People engaging in NSSI showed deactivation of the dorsolateral PFC during difficult cognitive tasks. An increase of oxygenation of the prefrontal cortex while doing a response inhibition task is also observed in NSSI. This indicates that people engaging in NSSI need more oxygen during inhibition, meaning their prefrontal cortex needs to work harder when regulating impulses, which explains difficulties

in suppressing emotional impulses such as NSSI (Zahid et al. 2022). A decrease in activity in the dorsolateral prefrontal cortex (dlPFC) has also been observed during inhibitory tasks. Decreased dlPFC activation leads to a decrease in inhibition of the ACC, which is correlated with higher NSSI severity. Severe NSSI is associated with decreased activation of the right dorsolateral PFC when inhibiting negative actions and increased activation when inhibiting positive actions. This means that negative emotions and actions are less likely to be inhibited compared to positive emotions and actions in people with NSSI. Additionally, increased activation of the right medial PFC and the right caudate, a nucleus involved in visual processing and movement control, is associated with more severe NSSI (Başgöze et al. 2023). These frontal region alterations lead to individuals with NSSI to act more impulsively upon negative emotions.

Now we have established that there are various fronto-limbic alterations associated with emotion dysregulation in NSSI, we want to know how these alterations contribute to difficulties in emotional regulation. The previously discussed neural alterations are linked to a reduction in top-down control. This means that the prefrontal regions have less control over limbic structures such as the insula and the amygdala. Less top-down control is associated with experiencing emotions more intensely and with having less control over emotions (Tschentscher et al. 2024). In order to successfully regulate emotions, you need the ability to evaluate multiple emotional regulatory approaches simultaneously and switch between them, which is where the prefrontal cortex comes into play (Koch et al. 2018). However, there is less dorsolateral PFC activation in individuals with NSSI during cognitive interference, which is the process of overruling and inhibiting negative thought patterns through attentional control. Additionally, ACC activation is increased in NSSI, which is associated with emotional reactivity (Dahlgren et al. 2018; Başgöze et al. 2023). More severe NSSI is linked to increased activity of the ACC and a reduction in structure thickness (Başgöze et al. 2023). The combination of these alterations in the PFC and the ACC is correlated to less emotional control and more impulsivity in people with NSSI (Dahlgren et al. 2018). This effect is most pronounced when processing negative emotions. Liu et al. (2022) found that adolescents with NSSI had less emotional sensitivity and less behavioral inhibitory control when processing negative content, compared to those without NSSI. This effect didn't occur when processing positive content, suggesting those with NSSI have inhibitory control deficits of negative emotions.

Overall, people with NSSI have deficits in the functional connectivity of their cognitive control network, resulting in less efficient communication between limbic and frontal regions when regulating behavior (Başgöze et al. 2023). This ultimately leads to difficulties in emotion regulation and the need for NSSI.

Impulsivity is a behavioural result of emotional dysregulation and is together with emotion regulation a key psychological risk factor for NSSI (Lang et al. 2024; Liu et al. 2022; Oudijn et al. 2022). People with NSSI are generally more prone to make risky decisions (Bao et al. 2024). The combination of increased emotional reactivity, due to amygdala dominance, and decreased cognitive control, due to prefrontal dysfunction, leads to difficulties in controlling impulses in NSSI (Liu et al. 2022). Difficulties with response inhibition and impulsivity make people more vulnerable to self-harm (Malejko et al. 2022). People with NSSI often have low serotonin levels which is also associated with emotion dysregulation and impulsivity (Oudijn et al. 2022; Fikke et al. 2013). Low serotonin levels are especially a risk factor for female adolescents to tend to

NSSI as an emotion regulatory approach (Fikke et al. 2013). People with NSSI show alterations in the cognitive control network, which consists of the brain circuitries responsible for impulsivity (Başgöze et al. 2023; Oudijn et al. 2022). When comparing brain activity during inhibition tasks, people with only major depression showed increased activity, whereas people with both major depression and NSSI showed relative decreased activity in these regions, implying impaired inhibitory control in those with NSSI (Malejko et al. 2022). In combination with this increased impulsivity, people with NSSI often have a preference for actively trying to escape unpleasant emotions (Blacutt et al. 2024).

Besides changes in neural activity, there are also changes in white and grey matter volumes detected in NSSI associated with increased impulsivity. In these individuals, it was found that several white matter tracts within the fronto-limbic system had decreased integrity. An increase in white matter disruptions is associated with decreased impulse control and increase of NSSI duration. It is even suggested that these white matter disruptions increase overtime during ongoing NSSI (Westlund Schreiner et al. 2019). There are also decreases found in grey matter volume of fronto-limbic areas in NSSI. Especially in the frontal gyri , the insula and the ACC (Ando et al. 2018; Pang et al. 2024). On top of the decrease in volume, a reduced cortical complexity is observed in the left insula and the right frontal gyrus in those with NSSI (Pang et al. 2024).

The combination of increased emotion dysregulation and increased impulsivity make a person more vulnerable to engage in NSSI. Furthermore, these neurobiological mechanisms also contribute to the addictive nature of NSSI (Liu et al. 2022). The role of reward in NSSI behaviour will be discussed later in this essay. All in all, people who engage in NSSI have increased emotional reactivity, difficulties with emotion regulation and are more impulsive. This explains why they are more likely to engage in NSSI and maintain this behaviour, due to its emotion regulatory function.

Reward Processing in NSSI

Reward is another major factor influencing the onset and progression of NSSI (Lang et al. 2024; Liu et al. 2024). Neuroimaging studies found differences in brain circuits involved in reward and habits in people engaging in NSSI (Oudijn et al. 2022). One of the characteristics of individuals engaging in self-harm is an altered neural response to reward and punishment (Bao et al. 2024). Especially adolescents experience different levels of reward sensitivity. Some studies observed an increase in neural reactions to reward in self-harming adolescents (Cummings et al. 2021; Bettis et al. 2022; Poon et al. 2019). Especially negative emotions to losses are reported to be stronger compared to positive responses to reward. This increased intensity of negative outcome processing is associated with enhanced impulsivity seen in self-harming adolescents (Bao et al. 2024). However, other studies found a decrease in neural responses to reward (Case et al. 2021; Kautz et al. 2020), such as a decreased activity of the striatum, amygdala and the OFC (Sauder et al. 2016).

Alterations of the reward system are often seen as a characteristic of people engaging in self-injury (Blacutt et al. 2024). This includes both structural and biochemical alterations of neural circuits involved in reward. Biological processes involved in altered reward processing are similar to the processes underlying emotion dysregulation and impulsivity (Lai et al. 2021).

Deficits in emotional regulation and reward processing are both associated with altered activation patterns of the fronto-limbic areas. People with NSSI can experience heightened reward activation, especially adolescents, due to the combination of increased activity of emotion-and reward-related brain areas and decreased activity of prefrontal regions (Poon et al. 2019). However, a decrease in reward sensitivity has also been associated with alterations and disruptions in connectivity of fronto-limbic regions. This was found in the insula, dorsal striatum and the ventromedial PFC (Case et al. 2021). Deficits in reward processing in NSSI are linked to altered activation patterns in fronto-limbic circuits, primarily from the right medial frontal gyrus to the rostral ACC and from the left inferior frontal gyrus to the insula. Increased activity in the inferior frontal gyrus-insula circuit is associated with difficulties in emotional processing and regulation in NSSI, while heightened medial frontal gyrus-rostral ACC circuit activity is linked to impaired reward regulation. The rostral ACC is considered a key regulator of the reward system (Lai et al. 2021). Similar patterns of altered activation are observed in those with substance or non substance addictions, such as alcohol (Maurage et al. 2012) and gaming addictions (Meng et al. 2015). This increase in activity is hypothesized to be underlying the repetitive and addictive nature of NSSI (Lai et al. 2021).

Furthermore, reward-related alterations in NSSI are found in large-scale brain networks such as the salience network. This is a network of several regions that evaluate the importance of internal and external stimuli and orchestrate a proper behavioural response. These include the amygdala, the striatum, the anterior insula and the dorsal anterior cingulate cortex (dACC) (Ho et al. 2021). Several studies found that adolescents with NSSI show a reduced neuronal connectivity at rest within the salience and the default mode networks, compared to those without NSSI (Ho et al. 2021; Başgöze et al. 2023). Overall, people with NSSI exhibit a decreased fronto-amygdala resting state functional connectivity and decreased network connectivity within the default mode network and the salience network (Başgöze et al. 2023; Auerbach et al. 2021). The striatum, a sub-area of the salience network, is connected with the limbic system and consists of multiple areas such as the nucleus accumbens (NAcc), the caudate and the putamen. In response to financial reward, people with thoughts of NSSI have shown increased activation of the putamen (Poon et al. 2019). Additionally, altered functional connectivity of the striatum and motor circuits have been associated with past experiences of self-harm (Marchand et al. 2013).

The dysfunction of the reward system can be further explained by disrupted neural connectivity. Case et al. (2021) found alterations in connectivity in those with NSSI in the dorsal striatum (DS), insula, parietal operculum cortex and the ventromedial PFC. They proposed that deficits in these circuits explain the alterations in inhibitory emotion regulation, pain processing and dysfunctional reward processes. Additionally, an increase in functional connectivity of the right putamen accumbens and the right angular gyrus has been observed in individuals with NSSI. A decreased connectivity was found between the right NAcc and the left inferior cerebellum, left cingulate gyrus (CG) and left middle temporal gyrus, right CG and bilateral middle temporal gyrus (MTG) and between the left CG and the left MTG. Interestingly, this decreased connectivity between the right NAcc and the left inferior cerebellum is associated with addictive characteristics of NSSI (Chen et al. 2023). Besides a decrease in NAcc connectivity, there has also been a decrease in NAcc activation found in NSSI. The NAcc is a brain area involved in reward processing and avoiding punishment. A decrease in activity was found in NSSI subjects

during a punishment avoidance test, in which self-harming individuals had more difficulties with avoiding punishment options than at choosing reward options. Deficits in activity of punishment related brain areas, such as the NAcc, are coherent with the fact that people engaging in NSSI have difficulties with learning from punishment. Even though they do experience punishment stimuli from harming themselves, this effect is decreased and has less effect on their behaviour compared to adolescents without NSSI. Ultimately resulting in repetition of NSSI despite the negative consequences in the long-term (Nicolaou et al. 2025). This finding is in line with the theory that not only reward sensitivity contributes to self-harming behaviour, also punishment sensitivity (Liu et al. 2024). A decreased punishment sensitivity means that one's behaviour is less effectively inhibited by punishment stimuli (Kim et al. 2015). When NSSI is used to regulate emotions, it results in the vicious cycle of repetitive NSSI (Liu et al. 2024). The study by Pollak et al. (2023) found that people with increased activity of the amygdala after social punishment, were more likely to engage in NSSI in the future.

Apart from structural alterations, studies have shown biochemical alterations related to reward in NSSI, mainly in the dopaminergic and endogenous opioid system. The opioid and the dopaminergic system interact with each other in the forebrain and are both key regulators of reward (Blasco-Fontecilla et al. 2016). Dopamine is viewed as the main neurotransmitter that regulates reward and habitual behaviours (Dresp-Langley 2023). Together with the HPA axis, these systems can be activated by drugs, but also by behaviours and are believed to be contributing to the addictive nature of NSSI (Blasco-Fontecilla et al. 2016). Deficits in the dopaminergic system have been found in self-harming rhesus monkeys (Novak and Meyer 2021). A reduction in dopaminergic neurons is associated with self-injurious behavior in animal models (Oudijn et al. 2022). In human studies, the dopaminergic system is believed to play a role in the active-escape response among self-harming individuals. Besides reward system dysfunction, those engaging in NSSI tend to actively try to escape unpleasant emotions. This escape response is thought to be regulated through nigrostriatal and mesolimbic dopamine systems. Individuals with a history of NSSI often perceive negative emotions as escapable, which results in an active escape response, involving motion activation pathways and suppression of motor inhibition pathways. Ultimately leading to NSSI being used as an escape and coping mechanism. These dopaminergic systems reinforce the urge of NSSI as an escape mechanism during the experience of negative emotions, contributing to the repetition and addiction of NSSI (Blacutt et al. 2024).

The opioid system also regulates reward, motivation, pain perception, pain relief and lowering the experience of negative emotions (Oudijn et al. 2022). Endogenous opioids are considered addictive and are believed to contribute to both the onset of self-injurious behavior (Lai et al. 2021) and the maintenance. Opioids mediate the short-term relief from emotional distress that individuals experience through the physical pain of NSSI (Johnson et al. 2022). Individuals engaging in NSSI generally have lower basal levels of endogenous opioids (Johnson et al. 2022; Bresin and Gordon 2013). One opioid associated with NSSI pathology is beta-endorphin. Lowered levels of beta-endorphins have been found in the plasma and cerebrospinal fluid of those with NSSI. Lower levels of beta-endorphins are associated with an increase in depressive symptoms (Kao et al. 2024), an increased pain threshold and a decreased experience of pain intensity (van der Venne et al. 2021). Beta-endorphins levels appear to be lower directly before the act of NSSI compared to directly after. This finding suggests that the increase in

endogenous opioids after self-injury stimulate NSSI behaviour (Störkel et al. 2021). Similar patterns of reduced opioid levels have been found in self-harming rhesus macaque monkeys. The mRNA expression of a μ-opioid receptor was decreased in the amygdala of monkeys with NSSI. These monkeys also showed a reduced expression of prodynorphin, an opioid precursor, in the hypothalamus (Jackson et al. 2023).
According to the opioid-homeostasis theory, NSSI serves to increase lower baseline levels of endogenous opioids. The theory hypothesizes that NSSI results in a short-term increase of opioids, therefore acting as a way to restore the opioid balance, especially during stress (Bresin and Gordon 2013; Sher and Stanley 2008; Bandelow et al. 2010). However, this theory has been disputed by multiple researchers over the past years. Stating that it is unlikely that the body has a certain opioid setpoint and therefore NSSI cannot be a mechanism to maintain it. Additionally, NSSI often occurs during periods of stress in which opioid levels are elevated, contradicting the homeostasis theory which states that opioid levels preceding NSSI are lower (Hooley and Franklin 2018). This is further supported by Kao et al. (2024), who found that changes in beta-endorphin levels were not associated with a change in NSSI behaviour.
More recent theories propose that the alterations of the opioid system found in self-harming individuals are more likely to be associated with depressive symptoms (Kao et al. 2024) and with pain sensitivity (Oudijn et al. 2022; van der Venne et al. 2021). Dysregulation of the opioid system is believed to contribute to pain insensitivity in self-harming adolescents together with borderline symptomatology and high amounts of self-criticism (Lalouni et al. 2022). A higher pain threshold is associated with an increased risk of NSSI, especially among those with emotion dysregulation (Boyne and Hamza 2025).
Another biological marker underlying reduced pain sensitivity in NSSI is decreased gray matter volumes in pain processing regions. A decrease in gray matter volume has been observed in the inferior frontal gyrus, the ACC, the insula and the bilateral secondary somatosensory cortex in those with NSSI. A reduced insula volume is associated with the emotion regulatory function of NSSI. The reduction in SII is associated with the need for the sensation and pain of NSSI (Lee et al. 2023).
There is no consensus whether self-harming individuals have an increased or decreased response to reward, but it is clear that there are alterations compared to those without NSSI and that there are multiple neurobiological processes and mechanisms involved in this altered reward and punishment response. Therefore more research on the role of the reward system in NSSI is needed.

Discussion

This essay has integrated recent research on the neurobiological mechanisms underlying NSSI into a theoretical framework, with the focus on the biological processes of emotion regulation and reward processing. These factors were selected due to their key role in driving self-injurious behaviour. Adolescence was chosen as the main age group, given their high vulnerability to NSSI and the high prevalence in this age group. The findings discussed in this essay enhance the understanding of the complex neural circuitries involved and their role in this complex behaviour.

Emotion regulation is the primary driving force behind self-harm, making it essential in improving understanding of the neurobiological underpinnings of NSSI. Major alterations in individuals with NSSI are observed in the fronto-limbic system, where reduced frontal activity, combined with heightened limbic activity, results in a decreased top-down control. This imbalance results in increased emotional reactivity, greater emotion dysregulation, and heightened impulsivity. The combination increases an individual's vulnerability to NSSI, as self-injury serves as a maladaptive emotion regulation strategy.
In addition to emotion regulation deficits, reward processing plays a significant role in the onset and progression of NSSI. Multiple neurobiological mechanisms contribute to these alterations, including structural alterations and biochemical alterations in the dopaminergic system and the endogenous opioid system. While there is no clear consensus on whether individuals who self-harm exhibit an increased or decreased reward response, it is clear that their reward processing differs from those without NSSI. These conflicting findings can be potentially explained by the high heterogeneity of NSSI behaviour (Liu et al. 2024). Results can also be conflicting due to studies not studying NSSI as a stand-alone symptom. Comorbidities such as borderline personality disorder and major depressive disorder can have influenced the results. Emotion regulation and reward processes are not the only neurobiological mechanisms involved in NSSI. This essay has not covered the influence of genetics (Guo et al. 2023), stress (Höper et al. 2024; Klimes-Dougan et al. 2019; Carosella et al. 2023), social pressure and social skill difficulties (Lai et al. 2021; Nelson et al. 2023; Auerbach et al. 2021) or default mode network alterations in NSSI (Ho et al. 2021; Başgöze et al. 2023; Chin Fatt et al. 2021). However, emotion regulation and reward are widely viewed as core factors underlying self-injurious behaviour (Lang et al. 2024), which is why this essay has chosen them as focuspoints. Additionally, neural regions apart from the fronto-limbic areas that have been found to show structural and functional alterations in NSSI have not been discussed, such as the cerebellum (Kang et al. 2022) and the thalamus (Won et al. 2023).

A lot of progress and advancements have been made in research on the neurobiological mechanisms of NSSI. This had led to the identification of several mechanisms involved in the pathogenesis and repetition of self-injury. Further research is needed on this complex and heterogeneous behaviour, as still a lot remains unclear and unknown (Kaess et al. 2021). For example, there is no clear consensus on the opioid homeostasis theory, there are mixed results regarding the correlation between NSSI and serotonin levels (Oudijn et al. 2022) and there is still a lot unknown about the role of dopamine in NSSI in humans (Blacutt et al. 2024). Future research could contribute to dopaminergic based pharmaceutical interventions. The finding of lowered endogenous opioid levels in NSSI has already led to the development and use of the drug naltrexone (LDN), which has shown promising results (Karakuła-Juchnowicz et al. 2024). More research is needed on the neurobiological process underlying NSSI to improve our knowledge and understanding. This is important for prevention and treatment strategies. The neurobiological systems discussed are still undergoing development during adolescence (Marchand et al. 2013), future research is needed to understand how abnormalities in these systems change over time during development. Knowing which neurobiological traits make someone more vulnerable to engaging in NSSI, such as difficulties in emotion regulation, emotional reactivity and punishment sensitivity, can help in prevention (Wang et al. 2022).

This essay has provided a theoretical framework for understanding the neurobiological mechanisms underlying NSSI, with a focus on emotion regulation and reward processing. In short, NSSI is used for self-regulation of both biochemical (e.g., lowered endogenous opioid levels) and psychological (e.g., emotion dysregulation and heightened emotional intensity) alterations, offering short-term relief. This reinforces self-harming behavior, making it repetitive and habit-forming.
Studying NSSI independently of psychiatric diagnoses and in a neurobiological framework has the potential to significantly advance the field. Integrating biological insights may improve prevention strategies, therapeutic interventions, and pharmaceutical treatments.

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