Potential mechanisms of non-suicidal self-injury (NSSI) in major depressive disorder: a systematic review

Baichuan Wu, Huifeng Zhang, Jinghong Chen, Jiaye Chen, Zhifen Liu, Yuqi Cheng, Tifei Yuan, Daihui Peng

ABSTRACT

Background Non-suicidal self-injury (NSSI) is a frequent and prominent phenomenon in major depressive disorder (MDD). Even though its prevalence and risk factors are relatively well understood, the potential mechanisms of NSSI in MDD remain elusive.

Aims To review present evidence related to the potential mechanisms of NSSI in MDD.

Methods According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines, articles for this systematic review were searched on Medline (through PubMed), Embase (through Elsevier), PsycINFO (through OVID) and Web of Science databases for English articles, as well as China National Knowledge Infrastructure (CNKI), Sinomed, Wanfang Data, and the Chongqing VIP Chinese Science and Technology Periodical (VIP) Databases for Chinese articles published from the date of inception to 2 August 2022. Two researchers (BW, HZ) independently screened studies based on inclusion and exclusion criteria and assessed their quality.

Results A total of 25,157 studies were searched. Only 25 of them were ultimately included, containing 3336 subjects (1535 patients with MDD and NSSI, 1403 patients with MDD without NSSI and 398 HCs). Included studies were divided into 6 categories: psychosocial factors (11 studies), neuroimaging (8 studies), stress and hypothalamic-pituitary-adrenal (HPA) axis (2 studies), pain perception (1 study), electroencephalogram (EEG) (2 studies) and epigenetics (1 study).

Conclusions This systematic review indicates that patients with MDD and NSSI might have specific psychosocial factors, aberrant brain functions and neurochemical metabolisms, HPA axis dysfunctions, abnormal pain perceptions and epigenetic alterations.

INTRODUCTION

Non-suicidal self-injury (NSSI) refers to the behaviour of deliberate self-injury to the surface of the body without any suicidal intention, including but not limited to cutting, burning, striking, needling, excessive friction, etc. It is a prominent phenomenon with a worldwide prevalence of around 17.2% in adolescents, 13.4% in young adults and 5.5% in adults. Moreover, the prevalence of NSSI in adolescents raised to 40.9% during the coronavirus disease 2019 (COVID-19) pandemic. Not surprisingly, NSSI is one of the strong predictors of future suicidal behaviours.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Relevant risk factors and prevalence of non-suicidal self-injury (NSSI) have been frequently investigated; however, the potential mechanisms of NSSI remain unclear, especially in major depressive disorder (MDD).

WHAT THIS STUDY ADDS

⇒ This systematic review summarised 25 case-controlled original studies, indicating the possible mechanisms of psychosocial factors, aberrant brain functions and neurochemical metabolisms, hypothalamic-pituitary-adrenal (HPA) axis dysfunctions, abnormal pain perceptions and epigenetic alterations in MDD with NSSI.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Because of the high heterogeneity of included studies, more original research concerning the mechanisms of NSSI in subjects with MDD should be conducted to tailor personalised treatments of NSSI.
and individuals with NSSI were more likely to be diagnosed as MDD.\textsuperscript{15–17} Supported by robust evidence, NSSI is related to emotional dysregulation\textsuperscript{18–21} and depressive symptoms,\textsuperscript{22 23} which are more strongly associated with MDD.\textsuperscript{24 25} It was demonstrated that MDD and NSSI share an interactive effect on the risk of suicide, which is higher than with either MDD or NSSI alone.\textsuperscript{26} Furthermore, NSSI may play a mediating role between emotional reactivity and suicide risk in patients with MDD.\textsuperscript{27} Given its high comorbidity and increased mortality risk, we focused on the subgroup of NSSI in MDD to tailor personalised treatment for patients with MDD and NSSI. However, because of the absence of obviously effective treatment for NSSI,\textsuperscript{28} further exploration of the mechanisms of NSSI behaviour is needed. In recent years, research on the mechanisms has progressed, including the development of a four-function model,\textsuperscript{29} a theory of endorphin and child trauma,\textsuperscript{30} a hypothesis of abnormal pain perception\textsuperscript{31} and a model of addiction.\textsuperscript{32} Nevertheless, the theories were all based on mixed samples; thus, for lack of scientific rigour, they could not be indiscriminately applied to MDD. To better clarify this pathological behaviour, this systematic review aimed to summarise the potential mechanisms of NSSI in patients with MDD.

METHOD

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. For studies from the date of inception to 2 August 2022, we searched Medline (through PubMed), Embase (through Elsevier), PsycINFO (through OVID), and Web of Science databases for published English articles and the China National Knowledge Infrastructure (CNKI), SinoMed, Wanfang Data, and the Chongqing VIP Chinese Science and Technology Periodical (VIP) Databases for articles published in Chinese. For English databases, keywords were the following: (“Self-Injurious Behavior”[Mesh] OR self injurious behavior*[tiab] OR intentional self injur*[tiab] OR intentional self harm*[tiab] OR nonsuicidal self injur*[tiab] OR deliberate self-harm*[tiab] OR deliberate self harm*[tiab] OR self-injur*[tiab] OR self injur*[tiab] OR self non suicidal self injur*[tiab] OR non suicidal self injur*[tiab] OR self harm*[tiab] OR self destructive behavior*[tiab] OR self destructive behavior*[tiab] OR NSSI*[tiab]) AND (“Depressive Disorder”[Mesh] OR Depressive Disorder*[tiab] OR Depressive Neuros*[tiab] OR Endogenous Depression*[tiab] OR Depressive Syndrome*[tiab] OR Neurotic Depression*[tiab] OR Melancholia*[tiab] OR Unipolar Depression*[tiab]). Similar search strategies were also performed in Chinese databases. More specifically, the main Chinese search terms were: (“Self-injurious behavior” OR “Self-injury” OR “Self-mutilation” OR “Self-destruction” OR “NSSI”) AND (“Depression” OR “Melancholia” OR “Depressive Disorder” OR “Depressive syndrome”). The retrieval strategy was modified accordingly for different databases. A more detailed research strategy can be seen in the online supplemental file. In addition, the reference lists of the included studies were manually searched to find further relevant research.

Eligibility criteria

We selected original articles on the mechanisms of NSSI in patients with MDD, including psychosocial and biological dimensions. Animal models can only imitate self-injurious behaviours, not replicate actual NSSI. So even using the popular primate model, the rhesus macaque, it is challenging to imitate NSSI when accompanied by an affective disorder.\textsuperscript{33} Therefore, we only selected the potential mechanisms research in humans.

The inclusion criteria were as follows: (1) original studies evaluating the mechanisms of NSSI in patients with MDD; (2) peer-reviewed journal articles written in English or Chinese (for Chinese articles, titles and abstracts in English were required); (3) case-control studies comparing patients with MDD and NSSI (MDD+NSSI) and patients with MDD without NSSI (MDD−NSSI) or healthy controls (HCs); (4) having a strict definition of NSSI, including a clear distinction from suicidal behaviour and suicide attempt; (5) the diagnosis of MDD was made by specialised psychiatrists or based on the International Statistical Classification of Diseases and Related Health Problems or DSM system. We excluded studies if they met the following criteria: (1) animal studies, reviews, case reports, meeting abstracts and editorials; (2) articles written in other languages or without peer review.

Study selection and data collection

Two researchers (BW, HZ) independently screened the titles and abstracts of the retrieved studies to assess their eligibility for recruitment into this systematic review. Full texts of eligible studies were further assessed to identify additional studies for inclusion. Any potential conflicts or disputes were resolved by discussion. Using standardised Excel sheets, the following data were extracted and recorded for all included studies: authors, year of publication, sample size, methods and main results (difference in descriptions between patients with MDD and NSSI and those without NSSI).

Quality evaluation of studies

According to the research type demanded by the eligibility criteria, the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control studies, commonly used in systematic reviews, was applied to evaluate the risk of bias of the selected studies.\textsuperscript{34} The scale is composed of three dimensions: selection, comparability and exposure. Judgement was based on...
the definition and representativeness of the subjects, the selection and definition of the controls, the main and additional factors controlled between groups, the ascertainment of exposure and the methods used for ascertaining the exposure between groups, and the non-response rate. A study could be awarded a maximum of nine stars to reflect the quality. Two researchers (BW, HZ) independently completed the quality assessment and the differences were resolved by discussion.

Statistical method
Because of the high heterogeneity of the included evidence that had completely different experimental designs and domains interested in (online supplemental table 1), we only performed qualitative research. Thus, effect measures, synthesis methods and certainty assessment which could be found in a meta-analysis were not used in this systematic review.

RESULTS
Study characteristics
The initial retrieval search yielded 25 157 records in English and Chinese, with a total of 21 177 studies remaining after removing duplicates. Then, an additional 21 100 were excluded from this systematic review by screening titles and abstracts. After assessing full texts, 17 English and 8 Chinese studies were included in this analysis. The included literature had no research that was repeated in the two languages. The research processes for the English and Chinese databases are shown in figures 1 and 2, separately. The 25 included studies containing 3336 subjects (1535 MDD+NSSI patients, 1403 MDD−NSSI patients and 398 HCs), are shown in the online supplemental table 1. They consisted of 13 MDD+NSSI versus MDD−NSSI studies, 2 MDD+NSSI versus HC studies and 10 MDD+NSSI versus MDD−NSSI versus HC studies. As reviewed below, the included studies were divided into 6 categories: psychosocial factors (11 studies), neuroimaging (8 studies), stress and hypothalamic-pituitary-adrenal axis (HPA axis) (2 studies), pain perception (1 study), electroencephalogram (EEG) (2 studies) and epigenetics (1 study). The details of the 25 studies included are shown in online supplemental table 1.

Figure 1 Flowchart of the search for relevant English references. MDD, major depressive disorder; NSSI, non-suicidal self-injury.
Research quality
The results of the quality evaluation are displayed in online supplemental table 2. The total quality-rating scores of most of the included literature varied from 4 to 7, except for the study by Taş Torun et al which did not adjust for age or other demographic factors. The overall quality of the 25 studies was low because more than half of the included studies did not establish an HC group, and nearly all the studies identified the exposures without blinding. Only Xu et al grouped the depressive participants after completing the experiment. Nevertheless, all the studies applied the same method for ascertaining cases and controls and clarified the definition of controls.

Psychosocial factors
As of the retrieval date, 11 studies had investigated psychosocial profiles of NSSI in patients with MDD, including goal-directed control, emotional regulation, personality traits, childhood maltreatment, impulsivity, alexithymia and interpersonal relationships. Chen et al used the Pavlovian-to- Instrumental Transfer (PIT) paradigm to investigate the dysfunction of goal-directed control in patients with MDD and NSSI. The results showed that compared with HCs, the MDD+NSSI group had significantly poorer performance on PIT, which was negatively associated with NSSI frequency. This study figured out goal-directed control deficits and a correlation with compulsivity in patients with MDD and NSSI.

The remaining studies only adopted clinical interviews and questionnaires to identify psychosocial risks and protective factors for the occurrence of NSSI in patients with MDD, and they omitted HCs. Specifically, nearly half of the literature mentioned that child abuse, especially emotional abuse and emotional neglect, might contribute to the generation of NSSI in patients with MDD and NSSI. Additionally, compared to patients with MDD–NSSI, significant differences showed that patients with MDD+NSSI usually suffered from worse interpersonal and family relationships and more negative and stressful life events. Qian et al revealed that childhood maltreatment and stressful life events had an indirect effect on NSSI via adaptive cognitive emotional regulation instead of maladaptive strategies. Furthermore, Zuo et al enrolled a relatively large sample of 573 patients with MDD and figured out a diagnostic model in which childhood trauma and peer rejection might

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**Figure 2** Flowchart of the search for relevant Chinese references. MDD, major depressive disorder; NSSI, non-suicidal self-injury.
predict the development of NSSI in adolescents with MDD.39

Apart from child abuse and interpersonal relationships, Kang et al also found that compared to patients with MDD−NSSI, those with MDD+NSSI showed significant differences in personality traits (ie, psychoticism and neuroticism).14 By comparison, a higher level of impulsivity and a lower level of self-consciousness were found in adolescents with MDD+NSSI.42 Moreover, Shen et al discovered different parenting styles and alexithymia in patients with MDD+NSSI when opposed to depressed patients without NSSI.43 These results may provide potential evidence that these psychosocial factors may affect the occurrence of NSSI through chain mediation.

Considering that NSSI has motivational factors and multiple functions, Taş Torun et al focused on two types of its functions: interpersonal functions (eg, to influence others’ behaviour, to hurt/punish others) and intrapersonal functions (eg, emotional regulation, anti-dissociation, anti-suicide, and self-punishment).44 The results showed that the most common intrapersonal functions associated with NSSI were emotional regulation and marking distress, and the most frequent interpersonal functions were interpersonal boundaries and toughness. Interestingly, childhood trauma, alexithymia and emotional regulation abilities were also associated with the interpersonal or intrapersonal functions of NSSI.

**Neuroimaging**

Many of the included studies focused on neuroimaging, advancing our understanding of the neural substrates underlying NSSI. According to neuroimaging approaches, we divided the eight neuroimaging studies into task-state functional magnetic resonance imaging (task-fMRI) studies, resting-state fMRI (rs-fMRI) studies and magnetic resonance spectroscopy (MRS) studies.

Two studies used the task-fMRI technique to reveal brain activation patterns in patients with MDD+NSSI. Using the ‘Cyberball’ paradigm, a well-established experimental tool to arouse feelings of social exclusion, Groschwitz et al aimed to identify distinct neural processing of social rejection in MDD+NSSI versus MDD−NSSI versus HC.45 This study reported that compared to patients with MDD−NSSI and HCs, patients with MDD+NSSI had enhanced brain activation in the ventrolateral prefrontal cortex, and the medial prefrontal cortex, indicating specific neurophysiological responses of social exclusion in patients with MDD and NSSI. The others used an interpersonal self-processing task, including direct (self) and indirect (best friends’, mothers’ or classmates’) perspectives to reflect self-characteristics.46 Across all perspectives of self-processing, patients with MDD+NSSI showed higher brain activation in the superior frontal gyrus and less deactivation in the limbic structures, superior parietal lobule and middle temporal gyrus compared to patients with MMD−NSSI and HCs. Engaging in self-reflection, the NSSI group, from their mother’s perspective, showed more enhanced activation in the left and right amygdala, parahippocampus, hippocampus and fusiform than the other two groups.

In addition, 5 of the included studies also identified alterations of neural activity using resting state approaches, including amplitude of low-frequency fluctuation (ALFF) analysis, fractional amplitude of low-frequency fluctuation, regional homogeneity, functional connectivity (FC) and the brain network. In the research of Xin et al, only ALFF was applied; higher ALFF values were discovered in the left thalamus and right caudate nucleus and lower ALFF values were found in the right precuneus of patients with MDD+NSSI when contrasted with subjects with MMD−NSSI and HCs.47 Nevertheless, consistent results did not reappear in the other research. Specifically, Yan et al adopted FC and ALFF measures to explore the NSSI-related neural circuits and suggested that aberrant ALFFs were observed in the right middle occipital gyrus, right lingual gyrus and right superior frontal gyrus as well as altered FCs in these brain circuits in subjects with MDD+NSSI compared to subjects with MDD−NSSI.48 Additional inconsistent findings were reported in another study using FC and ALFF measures: significant neural activity alterations were observed in the right fusiform gyrus, the right median cingulate and the paracingulate gyri.49 Critically, Zhou et al also confirmed the above-mentioned neural activity alterations, especially those located in the default mode network (DMN).50 To address the question of how intrinsic brain networks communicate with each other in patients with MDD and NSSI, Ho et al compared groups in network coherence (ie, within-network connectivity) of the DMN, the salience network (SN) and the central executive network (CEN).51 This study demonstrated that patients with MDD+NSSI showed lower coherence in the insula-SN and anterior DMN and higher DMN-CEN connectivity compared to patients with MDD−NSSI and HCs. Interestingly, NSSI was specifically related to lower network coherence in insula-SN and all DMN subnetworks which were implicated with disruptions in interoceptive awareness.

Additionally, Zhang et al adopted an MRS technique to detect the neurobiochemical metabolic changes and executive dysfunction of NSSI in adolescents with MDD.52 This study suggested that patients with MDD+NSSI may suffer executive dysfunction and choline-containing compound metabolic alterations in the thalamus. Furthermore, the executive dysfunction may be implicated with the abnormal N-acetyl aspartate metabolism in the left thalamus and anterior cingulate cortex.

**Stress and HPA axis**

Only two studies concerning psychosocial stress were included; they were focused on the association between stress and HPA axis dysregulation. Klimes-Dougan et al used the Trier Social Stress Test and collected salivary cortisol during laboratory testing.53 The results showed that compared to subjects with MDD−NSSI and HCs, subjects with MDD+NSSI had the lowest level of salivary cortisol and the highest ratings of observed stress.
suggestions for patients with MDD+NSSI. The other study explored the association between childhood trauma and cortisol levels instead of measuring cortisol response during stress tests.\textsuperscript{54} Peng \textit{et al} reported that in comparison to subjects with MDD−NSSI, the resting level of serum cortisol was lower in those with MDD+NSSI after controlling for interference factors. Moreover, a significantly negative correlation between serum cortisol levels and emotional neglect was only found in the subjects with MDD+NSSI.

**Pain perception**

Only one study focused on the pain perception of patients with NSSI. Manipulating an electronic pain measuring instrument, Xu \textit{et al} measured the pressure pain threshold in the forearm to explore the potential pain mechanism.\textsuperscript{55} A higher pressure pain threshold with significant differences was found in adolescents with MDD+NSSI when compared with the MDD−NSSI group. The researchers also considered skin pressure pain threshold as an independent risk factor for NSSI behaviour in MDD.

**Electroencephalogram**

Only two EEG studies were included in the systematic review, both of which identified group effects among the subjects with MDD+NSSI versus those with MDD−NSSI versus HCs. Event-related potentials (ERPs) were used to assess the cognitive function of adolescents with NSSI in the study by Wen \textit{et al}, where P50, P300, N400 and N170 were applied to evaluate the ability to selectively process stimuli, executive function and memory, language function as well as facial recognition ability, respectively.\textsuperscript{56} However, no statistically significant difference was found between the MDD+NSSI versus the MDD−NSSI subjects. Notable prolongation of the latency of the P3a, P3b, P50 and N1, N2 components, as well as a decrease of the amplitude of P50 and increasing inhibition of P50 (S1/S2), were observed in MDD+NSSI subjects compared with HCs. Moreover, the other EEG study concerned addictive perspectives of NSSI.\textsuperscript{57} Providing neutral pictures and self-injury-related pictures, researchers used a two-choice Oddball paradigm to examine the neural reactivity of NSSI. The amplitude of P3d, reflecting the process of response inhibition, showed a significant main effect of cue as well as a significant group×cue interaction. When exposed to the self-injury-related cues, the MDD+NSSI subjects showed a larger amplitude of P3d than the HCs. Only in the MDD+NSSI group were significant differences observed between the P3d amplitude with self-injury cues and with neutral cues.

**Epigenetics**

Only one included study addressed epigenetics in MDD+NSSI patients.\textsuperscript{58} Epigenetic alterations, especially those in the expression of the pro-opiomelanocortin (\textit{POMC}) gene, which encodes the precursor of the adrenocorticotropic hormone, have been implicated with the occurrence and progression of MDD.\textsuperscript{59} Zheng \textit{et al} aimed to assess the relationship between the DNA methylation of the \textit{POMC} gene and NSSI in MDD. Compared with HCs, a higher methylation level of the \textit{POMC} gene promoter region was displayed at the cytosine-guanine dinucleotide 1 site in subjects with NSSI.

**DISCUSSION**

**Main findings**

This systematic review identified the psychosocial and biological mechanisms underlying NSSI in patients with MDD, providing a preliminary step for understanding this clinical issue. Unfortunately, limited to the heterogeneity of the methodology and research design of the included studies, this review is unable to specify a rigorous model of NSSI in MDD. Thus, we have only discussed the potential mechanisms of NSSI in MDD in this section and briefly expanded upon NSSI in other disorders. Herein, we display a joint hypothesis theoretically incorporating childhood trauma, epigenetics and other biological factors which may, to a degree, underlie the behaviours of NSSI (figure 3).

Some of the included studies in our review,\textsuperscript{14 20 36–44 55} demonstrated that psychosocial factors may play an important role in the occurrence of NSSI in MDD, especially childhood trauma, which was comparably crucial in patients with other disorders.\textsuperscript{66–65} The relationship between NSSI and childhood trauma has also been pointed out in a high-level meta-analysis.\textsuperscript{66} Moreover, the relationship between NSSI and impulsivity,\textsuperscript{65} rumination,\textsuperscript{66} and alexithymia\textsuperscript{67–69} has also been explored in mixed samples that had not been limited to patients with MDD.

Exposure to childhood trauma may trigger psychiatric disorders by altering the function of the HPA axis.\textsuperscript{70 71} As the correlation between the hyperactivation of the HPA axis and chronic stress has been indicated,\textsuperscript{72} childhood maltreatment could lead to higher cortisol levels.\textsuperscript{73} Our included studies demonstrated the dysfunction of the HPA axis and relevant epigenetic alteration in patients with MDD+NSSI.\textsuperscript{53 54 58} Moreover, an elevated cortisol awakening response was discovered in patients with NSSI and MDD\textsuperscript{54} or with non-specific disorders.\textsuperscript{75} In addition, a sibling study of adolescents reported more severe childhood adversity and showed higher hair cortisol levels in those with NSSI than their healthy siblings.\textsuperscript{76} Interestingly, as for resting-state cortisol, there was little difference between our study\textsuperscript{54} and self-injurious behaviour animal models, which had lower plasma cortisol levels than HCs.\textsuperscript{77} There may be an essential mechanism excluded because ofnism between NSSI and the HPA axis, but it is too early to draw a conclusion regarding the complex relationship among MDD, childhood trauma, NSSI and the HPA axis.

Notably, there was only one study focusing on the pain perception of NSSI in MDD. However, in mixed samples, relevant research has been repeated constantly. Higher
hot pain and cold pain thresholds have been discovered in adolescents with NSSI when compared with HCs.\textsuperscript{78,79} A higher pain tolerance of patients with NSSI was also revealed in a systematic review.\textsuperscript{80} Interestingly, in the theory of childhood trauma, pain and endorphins, early psychological trauma may influence the system of the HPA axis and endogenous opioids, which ultimately alter the pain perception and trigger NSSI.\textsuperscript{81} Combining the above evidence, there might be a potential association between childhood trauma, pain perception and NSSI, but more research is needed, especially regarding MDD.

Over the past decade, an exciting discovery has been that the psychosocial environment can affect gene expression and even trigger epigenetic modifications of DNA.\textsuperscript{82,83} As discussed in the reviewed studies, childhood trauma may play a pivotal role in NSSI involved in hereditary mechanisms. An Australian study conducted multivariate biometric modelling and showed the correlation between high-risk trauma exposure and NSSI, regulated to some degree by the heritable factors in a mixed sample.\textsuperscript{84} Dopaminergic genes also have been investigated adequately. Additionally, a remarkable three-way interaction between the monoamine oxidase A gene, the catechol-O-methyltransferase gene, and childhood maltreatment was found in a sample of Chinese male teenagers with NSSI who had no major diseases.\textsuperscript{85} Furthermore, the brain-derived neurotrophic factor Val66Met polymorphism was found to regulate the relationship between NSSI and childhood emotional environments.\textsuperscript{86} Also, by detecting DNA methylation and mRNA expression, Wang et al found a higher methylation level of silent information regulator 2 related enzyme 1 (SIRT1) gene promoter region and a lower expression of Sirt1 protein, related to MDD in some manner, in subjects with MDD+NSSI compared with HCs. However, this study was excluded because of the possibility that the samples were shared with the research of Zheng et al.\textsuperscript{58}

To this point, we have discussed the potential correlation between psychosocial traits, hereditary factors, HPA axis dysfunction, pain perception alteration and NSSI, where childhood trauma might play a role, according to the studies focused on MDD and other disorders. Aside from these domains, researchers have been exploring the brain function alteration of NSSI by neuroimaging and EEG, providing new angles to understand this behaviour. Addictive models, proposed to better tailor treatment approaches and strategies for NSSI,\textsuperscript{88,89} have elucidated the development of this behaviour. Although only one included study focused on it,\textsuperscript{57} cue reactivity, a crucial characteristic of addiction, has been examined repeatedly in the field of NSSI without the restriction of disease. Using a dot probe task (ie, NSSI-related cues, neutral cues and negatively valenced cues), Riquino et al measured the mechanism of attentional bias in young adults with NSSI who had no specific disorders.\textsuperscript{90} They showed significant attentional bias and experienced the torture of NSSI urges when exposed to NSSI-related cues rather than the other two cues. Moreover, Hooley et al used the task-fMRI technique and anNSSI-related experimental paradigm (namely, consisting of NSSI-related images, positive images, neutral images and negative images); they showed that when exposed to NSSI-related images and negative images, the NSSI group, who had no specific diagnosis, had significantly decreased amygdala activation and increased cingulate cortex and orbitofrontal cortex (OFC) activation compared with HCs.\textsuperscript{91} Although no similar study in our retrieval was conducted in patients with MDD and NSSI, aberrant limbic regions and frontal cortexes may be involved in the development of NSSI in MDD. Coincidentally, despite the difference in study design, aberrant limbic regions and frontal cortexes were also observed in our included studies,\textsuperscript{45,46,50} suggesting potential neural alteration in NSSI patients.
Close to the model of addiction, reward circuits have received widespread attention. Using monetary and social reward tasks, researchers also found reward process dysfunction in youth with MDD and NSSI. Disrupted connectivity between the bilateral caudate and putamen, insula, ventromedial prefrontal cortex and parietal operculum cortex was associated with NSSI when depressive symptoms were controlled. This study was excluded because it lacked diagnostic criteria for MDD. To our knowledge, by the final retrieval date, no additional related studies of MDD and NSSI have been reported. Thus, the following describes the results in NSSI patients without a specific diagnosis. Sauder et al conducted task-state fMRI with a monetary incentive delay task and found that NSSI participants showed less activation in the striatum, OFC and bilateral amygdala during reward anticipation compared with those without NSSI. Similarly, an ERP study, which revealed a heightened neural initial reward responsiveness to loss versus reward task in children with NSSI, provided further evidence for reward response alterations.

**Limitations**

Although our review may shed insights into a deeper understanding of potential mechanisms of NSSI in MDD, there are still several limitations when interpreting our findings. First, to reduce the impact of disease heterogeneity, we only reviewed those studies that focused on the mechanisms of NSSI in MDD and included control groups. Hence, only a limited number of studies were included in this systematic review, and these have yielded inconsistent findings. Moreover, domain heterogeneity (ie, neuroimaging, HPA axis, pain perception, EEG, epigenetics and psychosocial factors) among the reviewed studies hinders drawing overall conclusions and applying quantitative methods. Also, all the studies included and discussed were observational studies from which we could not draw causal relationships. And there also existed limitations on methodology. We did not register on PROSPERO and did not publish a protocol in advance. Finally, limited by language, we could not search and include all published original articles on the mechanisms of NSSI.

**Implications**

Even though NSSI has become an increasingly serious clinical problem, effective interventions remain in the development phase. Thus, there is an urgency for more exploration of the mechanisms of NSSI. As this review pointed out, the mechanisms in psychosocial factors, aberrant brain functions, HPA axis dysfunctions, abnormal pain perceptions and epigenetic alterations may, to some extent, play an important role in the behaviours of NSSI. However, limited by the available evidence, we could not draw a scientific and linked hypothesis. To date, research on the mechanisms of NSSI in MDD has been insufficient (eg, in this systematic review we could not find even one article focusing on the theory of the endogenous opioid system in MDD and NSSI, which is so popular in the domain of NSSI). Researchers have preferred to investigate the mechanisms in mixed samples of NSSI, so further work is required that specifically addresses NSSI and MDD or other specific disorders. Furthermore, research covering multiple dimensions is needed to delve deeper into the integrated mechanisms of NSSI.

**CONCLUSIONS**

Focusing on patients with MDD and NSSI, our systematic review included 25 original studies that involved various domains of mechanisms underlying NSSI. In summary, the above-mentioned findings indicated that patients with MDD and NSSI might have specific psychosocial factors, aberrant brain functions and neurochemical metabolisms, HPA axis dysfunctions, abnormal pain perception and epigenetic alterations. Although a large number of studies have focused on the mechanisms of NSSI regardless of disease diagnosis, limited research on combined MDD and NSSI impede our ability to draw overall conclusions. To address this gap, future research should incorporate relevant methodological and clinical covariates and pay more attention to the clinical implications of the mechanisms of NSSI in MDD.


Baichuan Wu graduated from Shanghai Jiao Tong University School of Medicine, China in 2021. He is currently studying on a Doctorate’s program at Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, China. Since 2021, he has been engaged in research activities in the Division of Mood Disorders of Shanghai Mental Health Center as a student. His main research interests include the neurobiological mechanisms of non-suicidal self-injury, and he is participating in several cohort studies on depression.
## Supplementary Table 1 Characteristics of studies included in the systematic review

<table>
<thead>
<tr>
<th>Author</th>
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<th>Methods</th>
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<td></td>
<td>(N=MDD+NSSI/MDD-NSSI/HC)</td>
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<tr>
<td>L. Kang [1]</td>
<td>2021</td>
<td>152/292/00</td>
<td>Clinical interview and questionnaire</td>
<td>MDD+NSSI/MDD-NSSI: child abuse↑; psychoticism↑; interpersonal and family relationship ↓.</td>
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<td>H. Qian [2]</td>
<td>2022</td>
<td>56/58/00</td>
<td>Clinical interview and questionnaire</td>
<td>MDD+NSSI/MDD-NSSI: childhood maltreatment↑; SLE↑; depression↑; adaptive CERS using ↓.</td>
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<tr>
<td>Q. Chen [3]</td>
<td>2022</td>
<td>35/00/34</td>
<td>Pavlovian-to-Instrumental Transfer paradigm</td>
<td>MDD+NSSI/HC: goal-directed control ↓; compulsivity↑.</td>
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<tr>
<td>C. Shao [4]</td>
<td>2021</td>
<td>65/88/00</td>
<td>Clinical interview and questionnaire</td>
<td>MDD+NSSI/MDD-NSSI: interpersonal and family relationship ↓; emotional abuse and neglect ↑; suicidal ideation and attempt ↑.</td>
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<td>Author</td>
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<tr>
<td>J. Xiang [7]</td>
<td>2022</td>
<td>42/38/00</td>
<td>Clinical interview and questionnaire</td>
<td>MDD+NSSI/MDD-NSSI: anxiety↑; depression↑; interpersonal relationship↓.</td>
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<td>M. Xu [8]</td>
<td>2020</td>
<td>93/19/00</td>
<td>Clinical interview and questionnaire</td>
<td>MDD+NSSI/MDD-NSSI: anxiety↑; depression↑; interpersonal relationship↓; negative life events↑.</td>
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<tr>
<td>X. Shen [10]</td>
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<td>Clinical interview and questionnaire</td>
<td>MDD+NSSI/MDD-NSSI: alexithymia↑; depression↑; punishment↑, over intervention and protection↑, rejection/denying↑ in parenting style.</td>
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<tr>
<td>Y. Taş Torun [11]</td>
<td>2022</td>
<td>43/24/00</td>
<td>Clinical interview and questionnaire</td>
<td>MDD+NSSI: the most used intrapersonal functions: affect regulation and marking distress; the most frequent interpersonal functions: toughness and interpersonal boundaries.</td>
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**Neuroimaging**

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>ID</th>
<th>Method</th>
<th>Findings</th>
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<tbody>
<tr>
<td>R. C. Groschwitz [12]</td>
<td>2016</td>
<td>14/14/15</td>
<td>Cyberball paradigm; task-state fMRI</td>
<td>MDD+NSSI/MDD-NSSI/HC: brain activation↑ in the parahippocampus, vIPFC, mPFC during social exclusion and inclusion.</td>
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<tr>
<td>Author</td>
<td>Year</td>
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<td>Method(s)</td>
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<tr>
<td>K. Quevedo</td>
<td>2016</td>
<td>50/36</td>
<td>rsfMRI</td>
<td>MDD+NSSI/MDD-NSSI/HC</td>
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<tr>
<td>B. Xin</td>
<td>2022</td>
<td>27/23</td>
<td>rsfMRI, ALFF</td>
<td>MDD+NSSI/MDD-NSSI/HC</td>
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<tr>
<td>R. Yan</td>
<td>2022</td>
<td>54/68</td>
<td>rsfMRI, ALFF, FC</td>
<td>MDD+NSSI/MDD-NSSI</td>
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<tr>
<td>Q. Huang</td>
<td>2021</td>
<td>31/36</td>
<td>rsfMRI, ALFF, FC</td>
<td>MDD+NSSI/MDD-NSSI</td>
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<tr>
<td>Y. Zhou</td>
<td>2022</td>
<td>25/25</td>
<td>rsfMRI, ALFF, fALFF, ReHo</td>
<td>MDD+NSSI/MDD-NSSI</td>
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<tr>
<td>Stress and HPA axis</td>
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**Pain perception**
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<tr>
<td>L. Xu [22]</td>
<td>2022</td>
<td>Clinical interview and questionnaire; pressure pain threshold measurement</td>
<td>MDD+NSSI/MDD-NSSI: pressure pain threshold↑; psychological resilience↓.</td>
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<td>EEG</td>
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<td>Y. Wen [23]</td>
<td>2021</td>
<td>ERP (P50, P300, N400 and N170); Oddball Paradigm</td>
<td>MDD+NSSI/MDD-NSSI: no statistically significant differences of ERP components.</td>
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<tr>
<td>Epigenetics</td>
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Abbreviations:
↓: inhibited, decreased, reduced; ↑: elevated, increased, heightened; ALFF: amplitude of low-frequency fluctuation; BOLD: blood oxygen level dependent; CEN: central executive network; CERS: cognitive emotion regulation strategies; Cho: choline-containing compounds; Cr: creatine; DCG: median cingulate and paracingulate gyri; DMN: default mode network; dPFC: dorsal prefrontal cortex; DST: Digital symbol test; ERP: Event-related potential; fALFF: fractional amplitude of low-frequency fluctuation; FC: functional connectivity; FFG: fusiform gyrus; fMRI: functional magnetic resonance imaging; HC: healthy control; IPL: inferior parietal lobule; MCG: median cingulate gyrus; MDD: major depressive disorder; MDD+NSSI/MDD-NSSI: MDD patients with NSSI compared to those without NSSI; MDD+NSSI/HC: MDD patients with NSSI compared to HC; MOG: middle occipital gyrus; mPFC:
medial prefrontal cortex; MTG: middle temporal gyrus; NAA: N-acetyl aspartate; NSSI: nonsuicidal self-injury; ORBsupmed: medial orbital of the superior frontal gyrus; PCC: posterior cingulate cortex; PCG: posterior cingulate gyrus; PoCG: postcentral gyrus; POMC: Proopiomelanocortin; ReHo: regional homogeneity; rsfMRI: resting-state functional magnetic resonance imaging; SFG: superior frontal gyrus; SFGmed: medial superior frontal gyrus; SLE: stress life events; SN: salience network; SPL: superior parietal lobule; STG: superior temporal gyrus; TMT-B: Trail Making Test, part B; TSST: Trier Social Stress Test; VF: Verbal fluency; vlPFC: ventrolateral prefrontal cortex; WCST: Wisconsin Card Sorting Test.

References


## Supplementary Table 2 Quality evaluation of studies included in the systematic review

**Newcastle-Ottawa Quality Assessment Scale for Case Control Studies**

<table>
<thead>
<tr>
<th>Author</th>
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<th>Comparability</th>
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<th>Score</th>
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<td>L. Kang</td>
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<td>★</td>
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<td>★</td>
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<td>C. Shao</td>
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<td>★</td>
<td>★</td>
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<td>Y. Zhong</td>
<td>2020</td>
<td>★</td>
<td>★</td>
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<td>T. Zuo</td>
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<td>★</td>
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<td>2022</td>
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<td>★</td>
<td>★</td>
<td>★</td>
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<td>M. Xu</td>
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<td>★</td>
<td>★</td>
<td>✔</td>
<td>★</td>
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<td>X. Lu</td>
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<td>★</td>
<td>★</td>
<td>✔</td>
<td>★</td>
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<td>★</td>
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<td>★</td>
<td>★</td>
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<td>★</td>
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<td>K. Quevedo</td>
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<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
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<td>T. Ho, J. Walker [18]</td>
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<td>★ ★ ★ ★</td>
<td>★ ★ ★ ★ 6</td>
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</table>

**Selection:**
(1) Is the case definition adequate? (2) Representativeness of the cases; (3) Selection of Controls; (4) Definition of Controls

**Comparability:**
(1) Comparability of cases and controls based on the design or analysis: a) the most important factor; b) a second important factor

**Exposure:**
(1) Ascertainment of exposure; (2) Same method of ascertainment for cases and controls; (3) Non-Response rate
References


16. Huang Q, Xiao M, Ai M, *et al.* Disruption of Neural Activity and Functional Connectivity in Adolescents With Major Depressive Disorder


Related Cues: Electrophysiological Evidence From a Two-Choice Oddball Paradigm. *Front Psychiatry* 2022;13.

Supplementary Search Strategy

Medline (through PubMed):


Embase (through Elsevier):

('automutilation'/exp OR 'artificial skin lesion':ab,ti OR 'deliberate self harm':ab,ti OR 'mutilation, auto':ab,ti OR 'non suicidal self harm':ab,ti OR 'non suicidal self injury':ab,ti OR 'self cutting':ab,ti OR 'self directed violence':ab,ti OR 'self harm':ab,ti OR 'self inflicted injuries':ab,ti OR 'self inflicted injury':ab,ti OR 'self injury':ab,ti OR...
'self mutilation':ab,ti OR 'self wounding':ab,ti OR 'self-harming':ab,ti OR 'self-inflicted harm':ab,ti OR 'self-inflicted mutilation':ab,ti OR 'self-inflicted wound':ab,ti OR 'self-inflicted wounding':ab,ti OR 'self-injuring behavior':ab,ti OR 'self-injuring behaviour':ab,ti OR 'self-injurious behavior':ab,ti OR 'self-injurious behaviour':ab,ti OR 'self-mutilation':ab,ti OR 'selfharm':ab,ti OR 'selfinflicted injury':ab,ti OR 'selfinflicted wounds':ab,ti OR 'selfinjuring behavior':ab,ti OR 'selffinjuring behaviour':ab,ti OR 'selffinjurious behavior':ab,ti OR 'selffinjurious behaviour':ab,ti OR 'selfinjury':ab,ti OR 'selfmutilation':ab,ti OR 'non suicidal self injury':ab,ti OR 'non suicidal self-injury':ab,ti OR 'non suicidal self injuries':ab,ti OR 'non suicidal self injuries':ab,ti OR 'NSSI':ab,ti) AND ('depression'/exp OR 'central depression':ab,ti OR 'clinical depression':ab,ti OR 'depressive disease':ab,ti OR 'depressive disorder':ab,ti OR 'depressive episode':ab,ti OR 'depressive illness':ab,ti OR 'depressive personality disorder':ab,ti OR 'depressive state':ab,ti OR 'depressive symptom':ab,ti OR 'depressive syndrome':ab,ti OR 'mental depression':ab,ti OR 'parental depression':ab,ti)

PsycINFO (through OVID):
AND (exp Major Depression/ OR Depressive Disorder.ab,ti. OR Depressive Disorders.ab,ti. OR Disorder, Depressive.ab,ti. OR Disorders, Depressive.ab,ti. OR
Neurosis, Depressive.ab,ti. OR Depressive Neuroses.ab,ti. OR Depressive Neurosis.ab,ti. OR Neuroses, Depressive.ab,ti. OR Depression, Endogenous.ab,ti. OR Depressions, Endogenous.ab,ti. OR Endogenous Depression.ab,ti. OR Endogenous Depressions.ab,ti. OR Depressive Syndrome.ab,ti. OR Depressive Syndromes.ab,ti. OR Syndrome, Depressive.ab,ti. OR Syndromes, Depressive.ab,ti. OR Depression, Neurotic.ab,ti. OR Depressions, Neurotic.ab,ti. OR Neurotic Depression.ab,ti. OR Neurotic Depressions.ab,ti. OR Melancholia.ab,ti. OR Melancholias.ab,ti. OR Unipolar Depression.ab,ti. OR Depression, Unipolar.ab,ti. OR Depressions, Unipolar.ab,ti. OR Unipolar Depressions.ab,ti.)

Web of Science
TS=(self-injurious behavior OR Behavior, Self-Injurious OR Self Injurious Behavior OR Self-Injurious Behaviors OR Intentional Self Injury OR Intentional Self Injuries OR Self Injury, Intentional OR Intentional Self Harm OR Self Harm, Intentional OR Nonsuicidal Self Injury OR Nonsuicidal Self Injuries OR Self Injury, Nonsuicidal OR Deliberate Self-Harm OR Deliberate Self Harm OR Self-Harm, Deliberate OR Self-Injury OR Self Injury OR Non-Suicidal Self Injury OR Non Suicidal Self Injury OR Non-Suicidal Self Injuries OR Self Injury, Non-Suicidal OR Self Harm OR Harm, Self OR Self-Destructive Behavior OR Behavior, Self-Destructive OR Self Destructive Behavior OR Self-Destructive Behaviors OR NSSI) AND TS=(Depressive Disorder OR Depressive Disorders OR Disorder, Depressive OR Disorders, Depressive OR Neurosis, Depressive OR Depressive Neuroses OR Depressive Neurosis OR Neuroses, Depressive OR Depression, Endogenous OR Depressions, Endogenous OR Endogenous Depression OR Endogenous Depressions OR Depressive Syndrome OR Depressive Syndromes OR Syndrome, Depressive OR Syndromes, Depressive OR Depression, Neurotic OR Depressions, Neurotic OR Neurotic Depression OR Neurotic Depressions OR Melancholia OR Melancholias OR Unipolar Depression OR Depression, Unipolar OR Depressions, Unipolar OR Unipolar Depressions)

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SinoMed:

Wanfang Data:
(主题: ("自我伤害行为" OR "自残" OR "自伤" OR "自我伤害" OR "自我毁灭" OR "自毁" OR "NSSI")) AND (主题: ("抑郁" OR "抑郁症" OR "情绪抑郁" OR "抑郁症状" OR "抑郁综合征" OR "抑郁障碍" OR "抑郁症, 神经官能性" OR "神经官能性抑郁症" OR "忧郁症" OR "单相抑郁症" OR "抑郁性神经症" OR "抑郁性内因性" OR "内因性抑郁症" OR "内因性抑郁症状" OR "抑郁症, 更年期" OR "抑郁症, 产后" OR "抑郁症, 难治性" OR "忧郁")

VIP Databases:
(K=自我伤害行为 OR T=自我伤害行为 OR R=自我伤害行为 OR K=蓄意自我伤害 OR T=蓄意自我伤害 OR R=蓄意自我伤害 OR K=自毁行为 OR T=自毁行为 OR R=自毁行为 OR K=自残 OR T=自残 OR R=自残 OR K=自我伤害 OR T=自我伤害 OR R=自我伤害 OR K=NSSI OR T=NSSI OR R=NSSI) AND (K=抑郁 OR T=抑郁 OR R=抑郁 OR K=忧郁 OR T=忧郁 OR R=忧郁 OR K=抑郁综合征 OR T=抑郁综合征 OR R=抑郁综合征 OR K=抑郁障碍 OR T=抑郁障碍 OR R=抑郁障碍 OR K=单相抑郁症 OR T=单相抑郁症 OR R=单相抑郁症 OR K=内源性抑郁症 OR T=内源性抑郁症 OR R=内源性抑郁症 OR K=忧郁症 OR T=忧郁症 OR R=忧郁症 OR K=情绪抑郁 OR T=情绪抑郁 OR R=情绪抑郁 OR K=抑郁症状 OR T=抑郁症状 OR R=抑郁症状 OR K=神经官能性抑郁症 OR T=神经官能性抑郁症 OR R=神经官能性抑郁症 OR K=内因性抑郁症 OR T=内因性抑郁症 OR R=内因性抑郁症 OR K=抑郁性
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