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ORIGINAL RESEARCH

Intrinsic Links Between Non-Suicidal Self-Injury and Sleep Quality and Cytokines: A Network Analysis Based on Chinese Adolescents with Depressive Disorders

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Background: Non-suicidal self-injury (NSSI) in adolescents has a complex etiology and a wide range of negative consequences. This study aimed to assess the interactions between NSSI and sleep quality and cytokines and explore the association of these factors with cognitive flexibility.

Methods: A cross-sectional survey was conducted from January 2022 to September 2024 in Qingdao, China. Adolescent Non-Suicidal Self-Injury Assessment Questionnaire, Pittsburgh Sleep Quality Index, and Wisconsin Card Sorting Test 128 card version were used to assess the NSSI, sleep quality, and cognitive flexibility. Levels of 12 serum cytokines were measured. Network analysis was performed by R software (version 4.4.1) to identify the central nodes and bridging symptoms of the network and all nodes' association with cognitive flexibility.

Results: A total of 337 adolescents with depressive disorders were included in the study. In the NSSI-Sleep Quality-Cytokines Network "Intentional scratches", "IL-12p70", and "Intentionally hitting oneself with fists or harder objects" were central nodes in the network. Furthermore, sleep-related variables such as "Sleep disturbance" and "Sleep duration" were identified as bridge symptoms. No direct association between NSSI and cognitive flexibility was observed.

Limitations: The cross-sectional design, reliance on self-reported data, and restricted geographic sample limit the ability to establish causal relationships and generalize the findings.

Conclusion: IL-12p70 plays a significant role in the development of NSSI among adolescents with depressive disorders. Sleep problems facilitate the interaction between NSSI and cytokines. Cognitive flexibility may be related to NSSI through indirect pathways.

Keywords: non-suicidal self-injury, sleep quality, cytokine, cognitive flexibility, network analysis

Introduction

Non-suicidal self-injury (NSSI) is the deliberate self-injury of body tissues without suicidal intent.[1] Due to its potentially serious consequences for mental health and adolescent well-being, NSSI has become a major public health issue of global concern. Research in recent years has highlighted the increasing prevalence of NSSI in Chinese adolescents, reflecting broader global trends.[2] The prevalence of NSSI varies widely across studies, but a systematic review suggests that approximately 13–29% of adolescents are likely to engage in NSSI at some point during adolescence.[3] NSSI is influenced by individual factors (eg, emotion regulation, impulsivity), family dynamics (eg, parental relationships, family pressures), and broad sociocultural factors (eg, academic pressures, peer relationships).[4,5] Although NSSI is not

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equivalent to suicidal behavior, it can lead to severe psychological distress and increased risk of subsequent suicidal ideation and suicidal behavior.[6]

Sleep disorders, such as insomnia and poor sleep quality, disrupt emotion regulation processes, making it more difficult for adolescents to manage distressing emotions effectively.[7] Sleep deprivation impairs prefrontal cortex functioning, weakening cognition control and emotion regulation.[8] The Transactional Model of Stress and Coping emphasizes the dynamic interplay between stressors, coping mechanisms, and outcomes.[9] Sleep disorders can be a stressor that challenges the adolescent's coping resources, leading to maladaptive coping strategies such as NSSI.[10] Engaging in NSSI may further disrupt sleep patterns, thus creating a vicious cycle. In addition, immune system activation can significantly impact mood and behavior. Cytokines, as small soluble proteins secreted by immune cells (eg, macrophages, T-cells) and glial cells in the central nervous system, are critical mediators of inflammatory responses and neuroimmune communication.[11] These signaling molecules can be categorized into pro-inflammatory cytokines (eg, IL-2, IL-12, IFN-γ, TNF-α) and anti-inflammatory cytokines (eg, IL-4, IL-10), which collectively regulate both peripheral and central nervous system functions.[12,13] New evidence suggests that cytokines are not only involved in immune defense, but also regulate neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity through complex bidirectional communication between the immune system and the nervous system, which in turn affects brain function and psychological processes.[14] The relevance of cytokines to sleep physiology has been extensively studied. Pro-inflammatory cytokines such as IL-6 and TNF-α exhibit circadian rhythmicity and play dual roles in sleep regulation: physiological levels facilitate normal sleep-wake cycles, while elevated concentrations disrupt sleep architecture.[15] Mechanistically, these cytokines interact to inhibit melatonin synthesis and alter dopamine/5-hydroxytryptamine (5-HT) metabolism in the prefrontal cortex - processes particularly evident in populations with psychiatric comorbidities.[16,17] A cross-sectional study showed that salivary IL-6 levels were increased in adolescents with severe sleep debt of ≥2h compared to those with normal work schedules. Cytokines such as IL-6, IL-8, and IL-10 were more significantly correlated with sleep duration compared to bedtime.[18] In the context of NSSI, cytokines dysregulation may create a neurobiological vulnerability through multiple pathways. First, cytokines mediate intermediate phenotypes of self-injurious behavior, ie despair, aggression, and hostility.[19] Cytokines reduce the availability of 5-HT, which in turn allows tryptophan (Trp) to synthesize neurotoxic metabolite.[20] This neurochemical change impairs impulse control and emotional stability. Second, cytokines regulate neuroplasticity through synaptic pruning and phagocytosis, which leads to alterations in brain structure and function.[21] Specifically, cytokine-induced changes may lead to limbic system inhibition, which can increase impulsive behavior.[22,23] Previous research suggests that participants who self-injure or commit suicide experience changes in brain region circuits associated with emotional processing tasks.[24] Additionally, brain electrophysiology evidence suggests that elevated levels of TNF-α in individuals with NSSI are associated with increased frontal Theta power,[23] which is a neural marker associated with suicidal ideation.[25] Together, these findings suggest that cytokines dysregulation may contribute to NSSI susceptibility through interrelated neural structural, and functional mechanisms, ultimately disrupting neural circuits that are critical for emotion regulation and behavioral control. Therefore, to effectively intervene with NSSI and mitigate its long-term effects on mental health, it is crucial to understand the mechanisms behind the interaction of NSSI with sleep and cytokines. As a widely used measure of cognitive functioning, the Wisconsin Card Sorting Test (WCST) reflects multiple cognitive dimensions such as cognitive flexibility, abstract reasoning, cognitive persistence, and working memory.[26] Self-injurious behavior and insomnia are both associated with cognitive functioning. For example, it was found that persistent errors on the WCST predicted suicidal ideation and suicidal behavior.[27,28]

Network analysis has emerged as a powerful framework for understanding the intricate relationships within psychological phenomena in recent years. By conceptualizing psychological attributes and behaviors as nodes and their connections as edges, network analysis offers a new approach to studying the complex dynamics of human cognitive, emotional, and social behaviors, moving beyond traditional linear models to focus on the interconnections and interactions between variables.[29] The central nodes and bridge symptoms as core concepts of network analysis provide unique insights into the structure and dynamics of symptom interactions. As key nodes in the network, typically characterized by high connectivity or influence, central nodes influence the flow of information throughout the system, and these nodes are critical for understanding which symptoms may be key factors in maintaining or exacerbating a state of dysregulation.[30]

On the other hand, bridging symptoms are connectors between different symptom clusters or modules in the network and help to elucidate potential pathways of symptom transmission and consolidation.[31] By identifying and analyzing bridging symptoms, it is possible to gain a deeper understanding of the mechanisms underlying symptom relationships and the overall architecture of the psychopathology network.

To date, no studies have performed network analysis to explore the link between adolescent NSSI and sleep quality, and network analysis studies of adolescent NSSI have often ignored biologically objective indicators. This study is the first to use network analysis to construct a network of relationships between adolescent NSSI, sleep quality, and cytokines. While identifying central nodes and bridge symptoms, nodes closely related to cognitive flexibility were identified to inform the development of targeted interventions for adolescent NSSI.

Methods

Study Design and Participants

This investigation was conducted from January 2022 to September 2024 in Qingdao, China. Convenience sampling was used to recruit study participants at Qilu Hospital of Shandong University (Qingdao). All participants participated in this study on a voluntary and anonymous basis. According to the National Health and Medical Research Council guidelines, a parent or legal guardian of the participants provided informed consent, with the participant's assent. The diagnosis was made by two physicians at the level of attending and above, referring to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), using a structured clinical interview, and psychometric measures and blood samples were completed. Participants were required to meet the following criteria: 1) meet the DSM-5 diagnosis of depressive disorders; 2) 6–18 years of age, regardless of gender; 3) not taking medication in the last month, not receiving electroconvulsive, transcranial magnetic stimulation, and other related treatments; 4) no diagnosis of neurological disorders, immune disorders, and other disorders that would affect the serum cytokine levels; and 5) able to comprehend the content of the survey and non-color-blind. According to the Declaration of Helsinki, the study protocol was approved by the Ethics Committee of Qilu Hospital of Shandong University (Qingdao).

Measures

Assessment of Non-Suicidal Self-Injury

The Adolescent Non-Suicidal Self-Injury Assessment Questionnaire (ANSAQ) is divided into 2 sub-questionnaires: behavioral and functional.[32] The behavioral questionnaire was used in the study to assess the frequency of NSSI in adolescents. The behavioral questionnaire consists of 12 entries divided into 2 dimensions of self-injurious behavior with/without visible tissue damage. A 5-point Likert scale is used, with each entry containing 5 options: "no, occasionally, sometimes, often, always", and a score range of 0–4. Higher scores indicate a higher frequency of NSSI, and the Cronbach coefficient for this scale in this study was 0.889. The diagnosis of NSSI was determined by a structured clinical interview concerning DSM-5 diagnostic criteria (at least 5 occurrences in the past year).[32,33]

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a commonly used tool for assessing sleep quality and was first developed by the Sleep Research Centre at the University of Pittsburgh.[34] The scale assesses subjects' sleep problems related to the past month through self-assessment. The PSQI covers "Subjective sleep quality", "Sleep latency", "Sleep duration", "Sleep efficiency", "Sleep disturbance", "Use of sleep medication", and "Daytime dysfunction" 7 factors comprising 19 questions. Each factor is scored on a scale ranging from 0 to 3, and the total score ranges from 0 to 21, with higher scores indicating poorer sleep quality. The Chinese version of the PSQI is also widely used,[35] and the Cronbach coefficient for the scale in the present study was 0.885.

Wisconsin Card Sorting Test 128 Card Version

The WCST 128 card version is a psychological testing tool designed to assess an individual's cognitive flexibility, executive function, and attentional control.[26] The cards in the test differ in three dimensions: color (red, blue, yellow, green), shape (circle, triangle, star, cross), and number (one, two, three, four). In each test, participants were required to

choose one of the four stimulus cards to match with the response card. Participants received "correct" or "incorrect" feedback after each matching choice. Participants used the feedback to adjust their strategy and recognize the rules of matching. After ten consecutive correct matches, ie, "completing a category" the matching rules are changed without notice, and the participant is required to recreate the matching rules for the next category, and the test is terminated after six categories or 128 tests. The results of the test include the "Total errors", "Perseverative responses", "Perseverative errors", "Non-perseverative errors", etc. "Perseverative errors", as an indicator of cognitive flexibility, reflect the ability of an individual to adapt to new cognitive tasks or changes in rules.[28]

Biochemical Measurements

Between 7:00 and 9:00 AM, 5 mL of EDTA anticoagulated whole blood was obtained from the study subjects via venipuncture of the forearm. The samples were centrifuged at 3500 rpm for 8 minutes. The serum was dispensed and stored at −80°C until batch analysis. Following the manufacturer's instructions, a 12-Cytokines Assay Kit (Raisecare, Qingdao, Shandong, China) was used to measure the levels of 12 cytokines in the serum samples by multiplex bead-based flow immunofluorescence assay: TNF-α, IFN-α, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, and IL-17. Detection and data analysis were performed using BD FACSDiva and Vigene Tech software.

Statistical Analyses

Network Estimation

We constructed graphical Gaussian models (GGMs) to examine the relationship between NSSI, sleep quality, and cytokines. The models were created in this study using R (version 4.4.1) as well as the qgraph (version 1.9.8) software packages,[36] qgraph is commonly used for network analysis and visualization in psychological and clinical research. The network models included all items of the ANSAQ, PSQI, and cytokines measure (IL-12p70, IL-6, TNF-α, etc). Pairwise correlations between items were estimated using Spearman's rank correlation coefficient. The Extended Bayesian Information Criterion Graphical Lasso (EBICglasso) algorithm was then applied to convert the correlation matrix into a partial correlation network to construct network edges. When constructing such networks with many variables, it's important to manage the risk of spurious or irrelevant correlations. To reduce spurious correlations and improve the stability and reliability of the network model, the least absolute shrinkage and selection operator (LASSO) was applied to the inverse covariance matrix estimation, shrinking small partial correlations to zero to achieve sparse network structures.[37] LASSO is a form of regularization that minimizes overfitting by imposing a penalty on the absolute size of the coefficients, effectively shrinking some coefficients to zero. This process helps identify the most important relationships and reduces the risk of including noise in the model ensuring that the model generalizes well to new data. To further refine the network and improve its interpretability, the Extended Bayesian Information Criterion (EBIC) was employed, with the hyperparameter γ set to 0.5.[38] EBIC is a model selection criterion that balances the fit of the model with its complexity, encouraging the inclusion of relevant edges while pruning weaker, less meaningful correlations, ensuring that the resulting network is both statistically robust and interpretable, focusing on the most influential relationships. The visualization consists of edge colors that reflect the direction of the correlation: positive correlations are shown in blue, and negative correlations are in red. Secondly, edge thickness represents the absolute strength of partial correlations, while node proximity in the layout is determined by the Fruchterman-Reingold algorithm to minimize overlapping. Through this graphical representation, the interconnections between variables can be visualized.

Network Centrality and Stability Analysis

Centrality indices allow the identification of nodes that have significant influence in the network, leading to a better understanding of the structure and function of the network.[39] Commonly used centrality indices include strength, closeness, betweenness, and expected influence (EI). Among them, closeness and betweenness estimates are not always reliable;[36] EI is more applicable to network models with both positive and negative correlations than the other three.[39] To quantify the importance of nodes, we calculated the EI by using R packages qgraph (version 1.9.8), where a larger EI suggests that a node occupies a more influential position in the network and is more closely connected to other nodes. In addition, in this study, bridge EI was calculated by R packages networktools (version 1.5.2) as a key indicator for identifying bridge symptoms, and

the 80th percentile of the bridge EI value was used as the critical value.[40] In the network model, bridge symptoms with high EI play a key role in connecting different symptom groups and can maintain network connectivity and information flow. Removing these bridging symptoms may result in the network splitting into isolated subgroups, thereby weakening the overall structure and function of the network. To quantify the stability and reliability of constructing network EI, we used R packages bootnet (version 1.6.0) to perform a bootstrap difference test to explore whether there are statistical differences between the EI of the nodes; the Correlation Stability Coefficient (CS-C) was calculated to EI stability was assessed.[36] CS-C denotes the maximum reducible proportion of the original dataset, ie, the correlation between the original centrality index and the centrality index of its progressively reduced subset is at least 70% at a 95% confidence level. The minimum threshold for the CS-C is 0.25 to ensure a confident interpretation of the centrality indexes, with 0.25–0.5 denoting moderately stable, and greater than 0.5 denoting high stability.[36] Finally, we identified items directly associated with "Perseverative errors" in ANSAQ, PSQI, and cytokines by using the "flow" function in the R packages qgraph (version 1.9.8).[41]

Results

A total of 337 adolescents (209 females and 128 males) were included in this study. The actual adolescents who participated in the study ranged in age from 12–18. The mean age of the participants was 15.34 ± 1.75 years, with a mean ANSAQ score of 9.24 ± 9.14. Among the participants, 270 (80.11%) lived in urban areas, 141 (41.84%) were only children, and 213 (63.20%) were diagnosed with NSSI. Descriptive statistics for all adolescents are shown in Table 1.

Table 1 Descriptive Statistics for the 337 Adolescents

Variables	Mean±SD or n (%)
Age, years	15.34±1.75
Height, cm	169.42±8.67
Weight, kg	61.74±16.12
Gender	
Male	128(37.98)
Female	209(62.02)
Residence	
Urban	270(80.12)
Rural	67(19.88)
Only child	
Yes	141(41.84)
No	196(58.16)
Education level	
Primary School	13(3.86)
Junior High School	138(40.95)
Senior High School	166(49.26)
University and over	20(5.93)
ANSAQ	9.24±9.14
PSQI	9.80±3.89
Perseverative Errors	17.21±12.42
TNF-α	1.89±1.78
IFN-α	1.86±1.19
IFN-γ	5.41±6.81
IL-1β	6.73±10.84
IL-2	2.23±2.47
IL-4	0.86±0.86
IL-5	2.08±2.02

(*Continued*)

Table 1 (Continued).

Variables	Mean±SD or n (%)
IL-6	2.28±2.33
IL-8	1.56±4.45
IL-10	1.76±1.23
IL-12p70	1.02±0.38
IL-17	4.50±5.32

Abbreviations: ANSAQ, Adolescent Non-Suicidal Self-Injury Assessment Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

Network Structure

Figure 1 depicts the structure of the NSSI-sleep quality-cytokines network. 149 (32.04%) of the 465 edges had non-zero weights, suggesting partial interconnectivity among the 3 symptom communities. The 10 most strongly correlated edges in the overall network of relationships were distributed within each community (ie, 5 edges in the cytokines community, 3 edges in the NSSI community, and 2 edges in the sleep quality community). The edge between CK7 ("IL-5") and CK11 ("IL-12p70") represented the strongest association edge within the cytokines community (weight=0.295), followed by the edge between CK1 ("TNF-α") and CK6 ("IL-4") (weight=0.289), the edge between CK1 ("TNF-α") and CK2 ("IFN-α") (weight=0.276), the edge between CK4 ("IL-1β") and CK9 ("IL-8") (weight=0.246), and the edge between CK1 ("TNF-α") and CK11 ("IL-12p70") (weight=0.223). In the NSSI community, the edge weight between NSSI1 ("Intentional pinching") and NSSI2 ("Intentional scratches") was the strongest (weight=0.423), followed by the edge between NSSI6 ("Intentionally stabbing yourself") and NSSI7 ("Intentionally cutting yourself") (weight=0.249), and the edge between NSSI4 ("Intentionally hitting hard objects with fists") and NSSI5 ("Intentionally hitting oneself with fists or harder objects") (weight=0.216). In the sleep quality community, the connection between PSQIA ("Subjective sleep quality") and PSQIB ("Sleep latency") was the strongest (weight=0.350), followed by the edge between PSQIA ("Subjective sleep quality") and PSQIE ("Sleep disturbance") (weight=0.274). In the interaction edges between NSSI, sleep quality, and cytokines, the edge

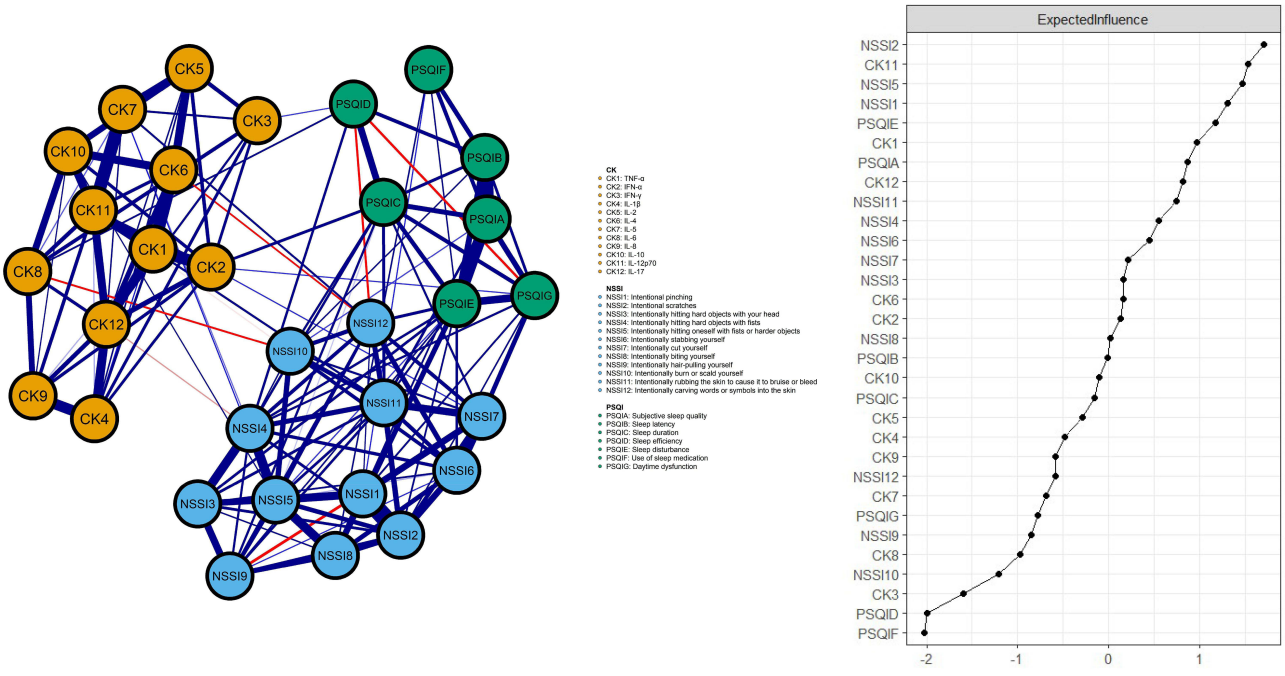

Figure 1 Network structure and expected impact of NSSI-sleep quality-cytokines network in adolescents with depressive disorders (Blue edges indicate positive correlations and red edges indicate negative correlations).

between PSQIE ("Sleep disturbance") and NSSI8 ("Intentionally biting yourself") (weight=0.106) was the strongest, followed by the connection between PSQIG ("Daytime dysfunction") and NSSI7 ("Intentionally cutting yourself") (weight=0.092), the connection between PSQIC ("Sleep duration") and NSSI11 ("Intentionally rubbing the skin to cause it to bruise or bleed") (weight=0.053), the connection between PSQIE ("Sleep disturbance") and NSSI12 ("Intentionally carving words or symbols into the skin") (weight=0.053), and the connection between PSQIC ("Sleep duration") and CK2 ("IFN-α") (weight=0.052).

Across the network, NSSI2 ("Intentional scratches") had the highest EI, followed by CK11 ("IL-12p70"), NSSI5 ("Intentionally hitting oneself with fists or harder objects"), NSSI1 ("Intentional pinching") and PSQIE ("Sleep disturbance"), five symptoms that were central to understanding the NSSI-sleep quality-cytokines interactions in adolescents with depressive disorders. In contrast, CK3 ("IFN-γ"), PSQID ("Sleep efficiency"), and PSQIF ("Use of sleep medication") were located at the edge of the network and had a low influence on the overall relational network (Figure 1). In terms of bridge EI, PSQIE ("Sleep disturbance") and PSQIC ("Sleep duration"), were the most critical bridging symptoms linking NSSI, sleep quality, and cytokines, followed by PSQIG ("Daytime dysfunction") and NSSI11 ("Intentionally rubbing the skin to cause it to bruise or bleed") and NSSI4 ("Intentionally hitting hard objects with fists") (Figure 2).

Network Stability

For the stability of the NSSI-sleep quality-cytokines network, the CS-C for EI was 0.672, which implied that the model exhibits a high degree of stability despite some variability (Figure 3). The network structure and its dynamics behaved with good reproducibility and predictability; the bootstrap difference test of variance showed that most comparisons between EI were statistically significant (Figure S1). The CS-C = 0.517 for bridged EIs was also suggestive of a highly stable network structure (Figure 3); however, the bootstrap difference test of variance showed that only a small number of bridge EI comparisons between nodes were statistically significant, eg, PSQIE ("Sleep disturbance"), PSQIC ("Sleep duration"), and PSQIG ("Daytime dysfunction") (Figure S2).

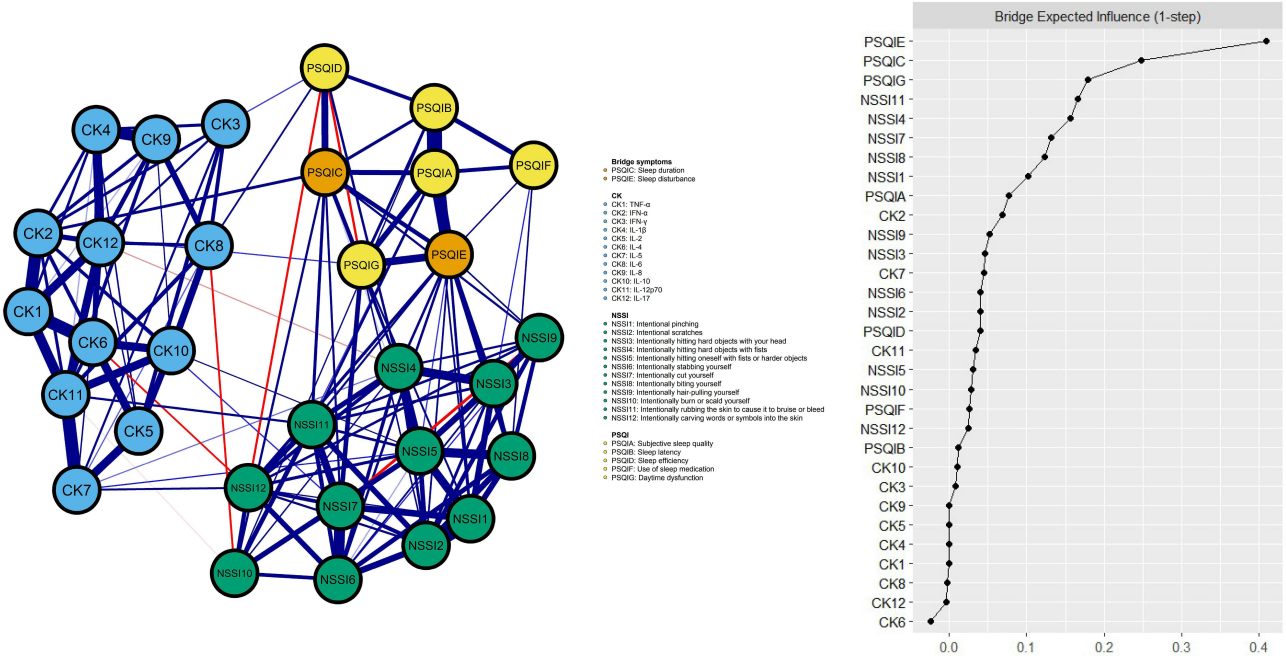

Figure 2 Network structure of NSSI-sleep quality-cytokines network showing bridge symptoms in adolescents with depressive disorders (Blue edges indicate positive correlations and red edges indicate negative correlations).

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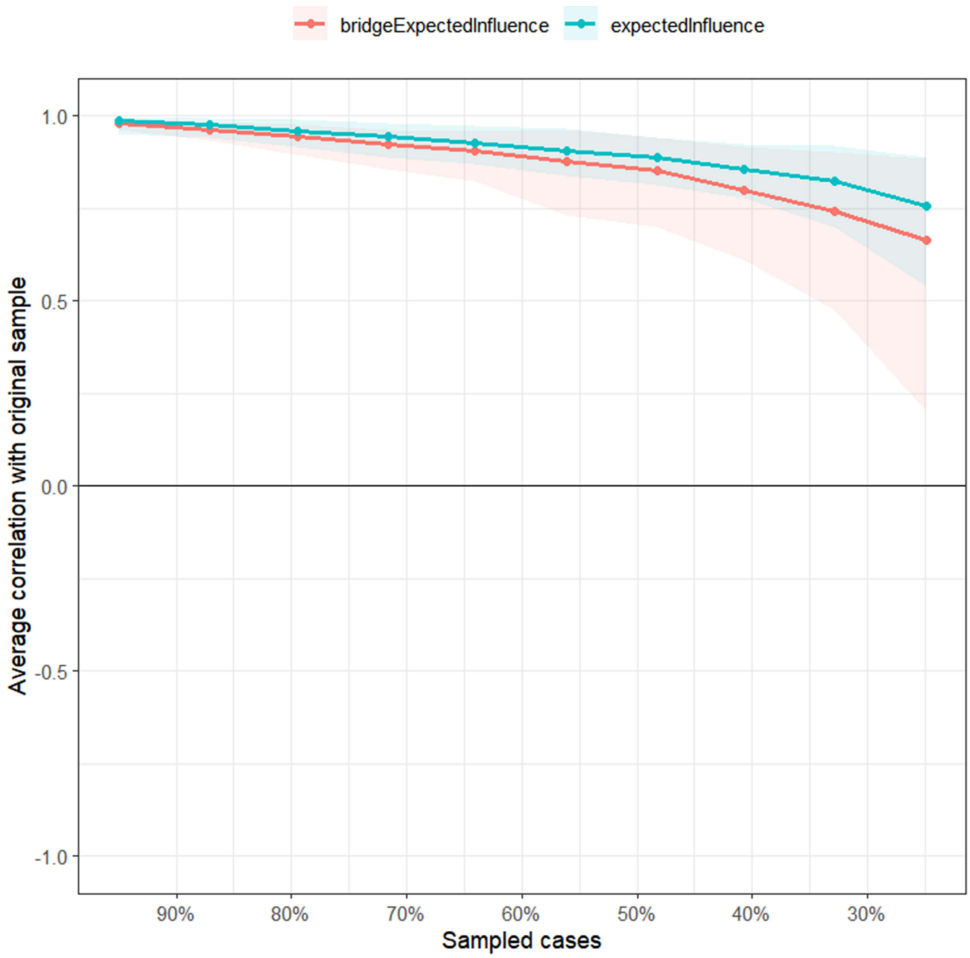

Figure 3 The stability of expected influence and bridge expected influence using case-dropping bootstrap of NSSI-sleep quality-cytokines network.

Flow Network of Perseverative Errors

The flow diagram illustrating connections of "Perseverative errors" with NSSI, sleep quality, and cytokines is shown in Figure 4. A total of 3 nodes were directly related to "Perseverative errors", and the rest were indirectly related to "Perseverative errors". Among them, CK8 ("IL-6") and PSQID ("Sleep efficiency") showed a direct positive correlation with "Perseverative errors", and CK9 ("IL-8") showed a direct negative correlation.

Discussion

To our knowledge, this was the first study to investigate the NSSI-sleep quality-cytokines relationship network in a population of adolescents with depressive disorders, while exploring the relationship between these factors and cognitive flexibility interactions. In the whole interaction network, "Intentional scratches", "IL-12p70", and "Intentionally hitting oneself with fists or harder objects" were the most central nodes, followed by "Intentional pinching" and "Sleep disturbance". Previous studies have confirmed that behaviors such as pinching and scratches, which are relatively easy to perform or easy to detect, are located at the core of the NSSI symptom network,[32] and that adolescents with depressive disorders are more inclined to choose these ways to quickly and easily release their internal painful experiences,[41] or to try to send distress signals through the traces of pinching and scratches, to wake up people around them and to avoid being abandoned.[42] The present study expands on previous research by showing that pinching, scratches, and hitting oneself with fists or harder objects are also central to the NSSI-sleep quality-cytokines network. This finding deepens the understanding of the NSSI in adolescents with depressive disorders and provides key clues for mental health interventions. Cytokines affect neuropsychiatric behavior through multi-pathway mechanisms, and their

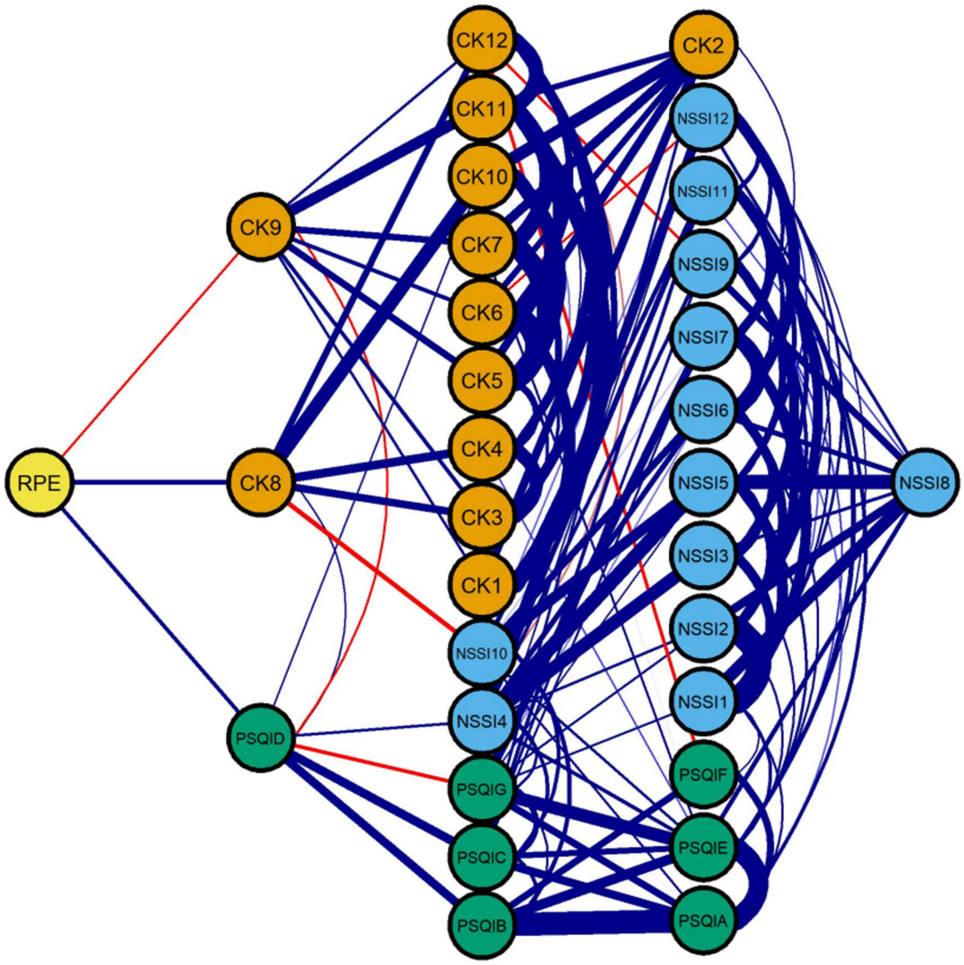

Figure 4 Flow network of perseverative errors (Blue edges indicate positive correlations and red edges indicate negative correlations).

induction of social withdrawal, pleasure deficit, and pain perception abnormalities are strongly associated with an elevated risk of self-injury behavior. At the level of molecular mechanisms, cytokines accelerate the metabolism of Trp to kynurenine (Kyn) through activation of indoleamine 2.3-dioxygenase (IDO), leading to accumulation of neurotoxic quinolinic acid, an imbalance that not only reduces prefrontal 5-HT synthesis[14] but also through activation of the N-methyl-D-aspartic acid receptors to enhance glutamatergic excitotoxicity, which in turn impairs mood regulation.[43] Meanwhile, chronic inflammatory states accelerate the degradation of dopamine and norepinephrine by upregulating monoamine oxidase activity, further exacerbating motivational deficits and pleasure deficits.[44] At the neuroendocrine level, cytokines activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to the sustained release of glucocorticoids, whereas chronic cortisol exposure triggers the failure of negative feedback regulation through the downregulation of hippocampal glucocorticoid receptors, resulting in the vicious circle of inflammation-hyperactivity of the HPA axis.[45] It is worth noting that IL-1 and IL-6 can also act directly on the central pain regulatory network and lower the pain threshold by enhancing the sensitization of dorsal horn neurons and inhibiting the function of the endogenous opioid system,[46] which may induce the nociceptive dissociation phenomenon of self-injury behavior. The difference from previous studies is that this research demonstrates for the first time the important role of IL-12p70 in the occurrence of NSSI. IL-12p70 is the active form of IL-12, a cytokine produced by monocytes and dendritic cells, which has been shown to play a key role in immune responses and inflammatory processes.[47,48] This factor is not only involved in the regulation of T-cell differentiation and maturation but is also closely associated with neuroinflammation in a variety of mental health states.[49,50] Previous studies have also suggested a prominent role of IL-12 in the conversion of Trp to Kyn and serum IL-12p70 levels were significantly elevated in patients with major depressive disorder (MDD)[51] and were

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significantly higher in patients with suicidal MDD than in non-suicidal MDD, suggesting its potential as a biomarker of self-injury.[52] In addition, IL-12p70 may impair synaptic plasticity by activating inflammatory responses in microglia of the central nervous system,[53,54] promoting the release of reactive oxygen species and nitric oxide.[55] IL-12 may upregulate the expression of brain chemokines (eg, CXCL10) through its effects on neurons and astrocytes,[56] which may mediate hippocampal neuronal damage and impair emotion regulation.[57] Meanwhile, the analgesic effect produced by brain chemokines[56] may reinforce the negative reinforcement mechanism of self-injury behavior. For those individuals experiencing both NSSI and depressive disorders, the clinical application of biologic or immunomodulatory therapies deserves further exploration. Combined with the results of this study, targeting IL-12, IL-12p70, and their associated inflammatory pathways may provide new ideas for the intervention of NSSI in adolescents. Animal experiments have shown that IDO inhibitors (eg, 1-methyltryptophan) can block inflammation-induced abnormalities in Trp metabolism, restore prefrontal 5-HT levels, and reduce depression-related behaviors.[58,59] Although no clinical trials have yet been conducted in humans, the research available suggests that such drugs may improve mood regulation by modulating the inflammation-activated Kyn metabolic Trp pathway. Supplementation with omega-3 fatty acids can be used as an adjunctive intervention, and their anti-inflammatory properties[60] may work by regulating the release of cytokines such as IL-12.[61,62] Clinical studies have demonstrated the ameliorative effects of omega-3 fatty acids on mood disorders in adolescents.[61] At subanesthetic doses, ketamine not only has a rapid antidepressant effect but also reduces the release of pro-inflammatory factors such as IL-12 by inhibiting microglia activation,[51] which has been found to significantly reduce suicide behavior and tendencies in adolescent patients in randomized controlled trials.[63] The monoclonal antibody ustekinumab against IL-12 has shown the potential to improve co-morbid depression/anxiety symptoms in the treatment of immune disorders, its intervention value for NSSI could be further validated in the adolescent population.[64,65] Future studies could target IL-12, and IL-12p70 to develop a multilevel clinical intervention strategy for NSSI.

Based on the identified bridging symptoms, "Sleep disturbance" and "Sleep duration" emerged as key mediating factors within this network, facilitating the interaction between NSSI and cytokines. In addition, "Daytime dysfunction" also shows higher bridge EI. Evidence from both animal and human studies suggests a bidirectional feedback loop between the immune system and sleep regulation. Specifically, cytokines, particularly IL-1 and TNF, have been identified as crucial regulators of sleep homeostasis and physiological sleep-wake behaviors.[66] Blocking the biological activity of IL-1 and TNF has been shown to reduce non-rapid eye movement (NREM) sleep, whereas enhancing their availability promotes both the quantity and intensity of NREM sleep.[67] A meta-analysis has revealed that elevated IL-6 levels are closely associated with poor sleep quality and insomnia complaints.[68] Furthermore, a cross-sectional study using the PSQI found that high levels of IL-1β, TNF-α, and IL-6 are linked to poor subjective sleep quality.[69] Notably, in our study, the bridging symptom "Sleep duration" exhibited a relatively high weight in its edge with IFN-α, which may suggest that different types of sleep disturbances have associations with distinct cytokines. Reduced sleep duration and poor sleep quality have been strongly linked to the incidence of self-injurious behavior, particularly among adolescents.[70] Based on the quality-stress theory of suicide,[71] sleep disturbances may impair emotional regulation and affect cognitive functioning and coping strategies, making individuals more prone to engaging in negative behaviors such as suicide or self-injury. Additionally, insufficient sleep can make individuals more vulnerable when coping with stress and negative emotions. The presence of daytime dysfunction can also increase the daily stress and psychological burden experienced by adolescents, impacting their social and academic performance, while simultaneously contributing to the accumulation of negative emotions. This creates a vicious cycle, further elevating the risk of NSSI. In summary, sleep quality issues, which act as bridge symptoms, may mediate the association between NSSI and cytokines, increasing the connectivity and flow efficiency of the entire network. Sleep quality is not only an independent risk factor in adolescent depressive disorders, but it also connects pathological states like NSSI through its interaction with inflammatory responses. Interventions targeting these bridge symptoms could reduce comorbidities and the overall severity of symptoms.[40] Cognitive Behavioral Therapy for Insomnia, as a first-line intervention for insomnia, has long-term treatment effects superior to medication[72] and can regulate various cytokines, including IL-1.[73,74] Home sleep environment interventions (eg, establishing a regular bedtime routine, limiting electronic device use) may enhance sleep regularity and improve sleep duration, and efficiency,[75] potentially reducing the risk of sleep problems associated with NSSI. For daytime

dysfunction, mindfulness-based stress reduction may simultaneously improve daytime alertness and sleep quality by enhancing emotion regulation and decreasing sympathetic excitability,[76] and this dual action may provide an effective intervention pathway to alleviate daytime dysfunction-related NSSI. Low-dose melatonin taken at bedtime has been shown to shorten sleep latency in children and adolescents,[77] and its antioxidant properties may indirectly regulate cytokines networks by reducing oxidative stress, providing a potential new direction for interventions in the co-morbidity of sleep disorders and NSSI. The combined application of these interventions may provide a more comprehensive solution for improving adolescent-associated NSSI behaviors through sleep quality targeting.

Cognitive flexibility is defined as the ability to alter decision-making behavior based on external feedback and changing environmental circumstances.[78,79] According to the diathesis-stress model,[28] cognitive inflexibility limits an individual's ability to solve problems when dealing with stress, thereby increasing the risk of suicidal ideation and suicidal behavior. Previous studies have found that depressed adolescents with NSSI exhibit poorer cognitive flexibility compared to those without NSSI,[80] but this study did not find a direct link between NSSI and cognitive flexibility. The underlying mechanisms for lacking a direct link between NSSI and cognitive flexibility may involve complex interactions at multiple levels. NSSI is more of an immediate and direct emotion regulation strategy than a long-term strategy based on problem-solving.[81] Its occurrence may rely more on rapid emotion regulation mechanisms than prefrontal-dominated cognitive control networks.[82] The immediate and direct character of this behavior may make it less dependent on complex cognitive strategies or flexible thinking patterns, thus weakening the direct predictive role of cognitive flexibility for NSSI. Neuroimaging studies suggest that adolescents with NSSI have significantly lower dorsolateral prefrontal activation when performing cognitive tasks.[83] In contrast, the amygdala (emotion-processing brain region) and ventral striatum (reward-related brain region) were better predictors of NSSI engagement,[84] suggesting that NSSI behaviors may rely more on immediate reward feedback or emotion regulation than on higher-order cognitive restructuring. In addition, previous studies have confirmed that cognitive dissonance is weakly associated with NSSI. NSSI may be influenced more by impulse control ability than cognitive flexibility.[81] Combined with the time frame of the biology of NSSI,[85] a range of distal and proximal influences, such as childhood maltreatment and autonomic functioning, may also have mediated or moderated the direct association of NSSI with cognitive flexibility. Finally, methodological limitations may also contribute to the lack of a direct link between cognitive flexibility and NSSI. Traditional cognitive flexibility measurement tools (eg, WCST) primarily assess rule-switching ability and may not adequately capture other cognitive characteristics associated with NSSI (eg, attentional bias toward negative stimuli). Future studies need to incorporate multilevel data analysis to further reveal the specific pathways of action between NSSI and cognitive flexibility. Overall, our findings offer a new perspective on understanding the complexity of NSSI and emphasize the importance of considering individual differences in cognitive interventions for self-injury.

Limitations

Despite providing some insights, this study has several limitations that need to be addressed in future research. First, as a cross-sectional study, we were unable to determine causal relationships among the variables. The cross-sectional design limited the observation of temporal changes, preventing us from revealing the dynamic interactions between these factors. Future longitudinal studies could incorporate multiple time-point assessments (eg, quarterly cytokine profiling and symptom tracking) could clarify the directionality of observed associations—for instance, whether elevated IL-12p70 precedes the onset of NSSI behaviors or emerges as a consequence of chronic sleep disturbance. Second, the data collection for NSSI and sleep quality relied on self-reported questionnaires, which may be subject to response biases such as social desirability bias and recall bias, potentially affecting the accuracy and reliability of the results. Additionally, several potential confounders (eg, socioeconomic status, family psychiatric history, and comorbid conditions like anxiety disorders or substance use) were not systematically controlled in the analysis. These factors may independently influence cytokine levels, sleep patterns, and NSSI risk, thereby confounding the observed network associations. Third, the data on cytokines were limited to serum samples, failing to reflect tissue-specific cytokine activity (eg, cerebrospinal fluid), which may restrict our comprehensive understanding of the role of cytokines in biological regulation. Finally, the study sample was confined to a specific geographic region among adolescents, which may limit the generalizability of the

findings. Future research should expand the diversity and geographic coverage of the sample to enhance the validity of the results. Integrating multimodal data sources (eg, actigraphy for objective sleep monitoring, structured clinical interviews for psychiatric comorbidities, and geospatial socioeconomic indices) would strengthen the robustness of causal inferences and network models.

Conclusion

This study explores the interactive relationships between NSSI, sleep quality, and cytokines in adolescents with depressive disorders through network analysis, providing new insights into how these variables interact. IL-12p70 has a potentially key role in regulating the connection between inflammation and mental health, particularly in the biological basis of NSSI. The centrality of IL-12p70 in the network may reflect its biological role in regulating Trp metabolism, impairing synapses, and mood regulation. Furthermore, sleep-related symptoms are not only associated with daily functional impairment but may also serve as critical pathways linking NSSI and biological markers. The strong association of sleep-related symptoms with NSSI may involve bidirectional inflammation-circadian rhythm regulation. Improving sleep quality may help reduce NSSI, which warrants special attention in intervention strategies. Finally, there is a lack of direct connection between NSSI and cognitive flexibility. Cognitive flexibility may operate through more complex indirect pathways or other psychological mechanisms related to NSSI behavior. This study deepens and expands the theoretical framework of neuroimmune by discovering the pivotal role of IL-12p70, revolutionizes the research methodology of NSSI by constructing an integrated network of biomarkers, and highlights the potential value of integrative interventions targeting sleep problems and immune responses in the treatment of NSSI, providing a theoretical basis for facilitating innovations in clinical practice.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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