MedCrave
Step into the World of Research

Journal of Neurology & Stroke

Review Article

Open Access

CrossMark

Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis

Abstract

Suicidal thoughts and actions occur due to a dynamic interaction of biological vulnerability, exposure to stress, psychological processes, and social context. This paper reviews neurobiological domains linked to suicidal thoughts and behavior, with a focus on monoaminergic signaling, HPA-axis dysregulation, neuroinflammation, neurotrophic and synaptic-plasticity pathways, large-scale brain networks, and genetic-epigenetic vulnerability. A range of post mortem and neuroimaging findings, as well as molecular, genetic and clinical findings have shown that serotonergic functioning is altered, prefrontal limbic connectivity is disrupted, there is atypical cortisol responsivity, inflammatory activation and reduced neurotrophic signaling. Nevertheless, these findings are heterogeneous and not specific to suicidal phenotypes; many also occur in the context of major depressive disorder, trauma-related disorders, chronic stress and other psychiatric disorders. Changes related to a crisis may be measured during a situation, but "what is most important is the timing, context, situation". According to current evidence, multidimensional risk assessment should integrate biological findings with clinical, psychological, and social information, and isolated biomarkers should not be used clinically. It is essential to carry out prospective, longitudinal, multimodal studies that feature well-matched psychiatric comparison groups. Doing so will help researchers make the distinction between trait vulnerability and state-dependent crisis markers. Furthermore, scientists must begin to determine whether biomarker combinations can contribute to precision prevention in an ethical and dependable manner.

Keywords: Suicidal ideation, suicide, neurobiology, serotonin, HPA axis, neuroinflammation, BDNF, brain networks, epigenetics, biomarkers

Volume 16 Issue 4 - 2026

Ahed J Alkhatib
Department of Legal Medicine, Toxicology and Forensic Medicine, Jordan University of Science & Technology, Jordan
ajalkhatib@just.edu.jo (retired)

Correspondence: Ahed J Alkhatib, Department of Legal Medicine, Toxicology and Forensic Medicine, Jordan University of Science & Technology, Jordan, Tel 009627959051145

Received: July 07, 2026 | **Published:** August 19, 2026

Introduction

Suicide is a global public health challenge that transcends class, race, sex, and age.[1] The World Health Organization reports nearly 700 thousand deaths yearly, with many more attempting and contemplating suicide.[1] Efforts to understand and address suicide have expanded exponentially; yet progress remains insufficient, particularly in low- and middle-income countries.[2] Provoking suicidal thoughts can be mere exposure to violence or hearing of another's suicide.[3] Thus the importance of understanding suicide, especially considering forthcoming environmental catastrophes, is amplified.[4] Nearly all self-inflicted deaths have a detectable cause.[5] Epidemiological, sociological, psychological, medicinal, and neurobiological approaches have been deployed to understand suicidal behavior and communicate preventive procedures.[6] Nevertheless, this article concentrates solely on neurobiological aspects.

Neurobiological alterations in suicidal individuals continue to be a matter of intense scholarly interest.[7] Direct measurements of biological parameters in living humans or post-mortem examinations of human tissues have provided insights into the neurobiology of suicide.[8] A vast number of candidate molecules, pathways, circuits, and networks has been identified; however, a comprehensive, cross-parameter understanding of the neurobiological factors underpinning suicidal ideation, expression, and repetition remains elusive.[9] Furthermore, a growing understanding of other neuropsychological phenomena—including other- or auto-aggressive behavior, impulsive aggression, and self-harming behavior—might intensify a cascade of neurobiological events culminating in suicidal acts.[10] Given this similar background, disentangling the neurobiological underpinnings of suicidal thoughts and actions presages elucidating these other conditions and encourages cross-pollination among rich, diverse research programs abreast other neurobiological factors.[11]

Disparate neurobiological factors govern the distinct short- and long-time scales over which suicidal actions are contemplated and performed.[12] Consistent, sustained alterations build negative emotional backgrounds and psychological pain over weeks, months, and often years.[13] More acute neurobiological alterations conducive to suicidal decision-making or self-harming behavior unfold within seconds to minutes and emerge temporally close to acts themselves.[14] Concurrently, developmentally-related factors such as the proximity of suicide and differences between grandchildren or great-grandchildren of individuals who attempted suicide shed enriched light on neurobiological factors contributing to the suicidal decision continuum.[15]

Neurobiological architecture of suicidal thoughts

Suicidal thoughts and behavior continue to be pervasive and pressing mental health issues, notwithstanding the increasing availability of effective treatments and preventive measures.[16] An estimated 7% of adults worldwide experienced suicidal ideation in 2021,[2] while close to 700,000 people died by suicide that same year.[2] Suicide was the global leading cause of death in young people aged 15 to 29 in 2021, affecting approximately 1.7 million adolescents aged 10 to 19.[17] Some individuals who experience such dysfunctional thoughts do not endorse criteria for a mental disorder.[18] This widespread nature of suicidal ideation across age and clinical status,

however, underscores the need for additional research into identifying and monitoring its underlying biological drivers.[19]

Neurobiological investigations have historically focused on suicide—the ultimate act of self-harm—rather than suicidal ideation per se.[20] Nevertheless, suicidal thoughts have been found to act as the earliest detectable indicator of an impending suicide attempt and as a robust predictor of attempted suicide across gender and culture.[21] Neurobiological understanding of suicidal behavior more generally thus stands to elucidate suicidal thoughts specifically.[22] The present evidence-based synthesis, therefore, concentrates on examining the neurobiological architecture of suicidal thoughts in greater detail while acknowledging other components of this framework relevant to the broader construct of suicidal behavior.[23]

Each of the five key neurobiological factors implicated in the suicidal behavior framework advanced by Aydin et al.[2]—disruption of serotonergic, noradrenergic, and dopaminergic systems; dysregulation of the hypothalamic-pituitary-adrenal axis; neuroinflammation and immune response; and perturbation of neurotrophic factors supporting synaptic plasticity—exhibits a well-established relationship with suicidal ideation. Beyond those five factors, Vargas-Medrano et al.[1] highlight an additional neurobiological component—structural changes in brain circuits and networks—that has been consistently associated with adolescent suicidal behavior and lends further insight into the architectures underlying suicidal thoughts.[1] This perspective points to the brain networks associated with suicidal ideation, namely the default mode network, salience network, emotion regulation and control network, and frontostriatal network.[1] First, the default mode network facilitates self-referential thinking, social cognition, and rumination, all of which are amplified by suicidal thoughts (24). Second, the salience network is activated by negative events and enhances emotional awareness and decision-making, underscoring the role of this circuit in modulating the attentional bias for negative stimuli observed in individuals with suicidal ideation.[25] Third, the impulse control and emotion regulation network is involved in suicidal ideation, through impaired control of the emotional decision-making process, and susceptibility to environmental modulation also occurs in the frontostriatal network (Table 1, Figure 1).[25]

Table 1 Neurobiological domains implicated in suicidal ideation and behavior

Domain	Representative abnormalities	Relevance to ideation/behavior	Specificity and interpretative caution
Monoaminergic systems	Serotonergic disturbance; noradrenergic stress activation; inconsistent dopaminergic findings.	Associated with mood regulation, aggression, impulsivity, and vulnerability to suicidal thoughts.	Results differ by tissue, diagnosis, and type of medication exposure, and definition of phenotype and are not suicidal behavior specific.
HPA-axis dysregulation	Altered cortisol reactivity, stress feedback changes, hippocampal involvement.	Links early adversity and chronic stress to acute suicidal vulnerability.	It remains difficult to disentangle state versus trait effects and exposure to depression or chronic stress causes similar HPA-axis changes.
Neuroinflammation	Cytokine activation, glial signaling, immune-pathway genetic signals.	May amplify psychological pain, sickness behavior, and stress sensitivity.	Inflammatory markers are nonspecific and are dependent on psychiatric, medical, behavioral and treatment factors.
Neurotrophic/plasticity factors	Reduced BDNF and altered neurotrophin signaling under stress.	Suggests impaired adaptive remodeling in cortico-limbic circuits.	Less serum BDNF may not limit the functionality of neural systems, which reduced levels overlap with depression.
Brain networks	Altered default mode, salience, frontostriatal, and prefrontal-limbic connectivity.	Supports rumination, negative salience, impaired control, and transition from ideation to action.	The imaging abnormalities mimic those of mood and stress-related disorders and require prospective, externally validated standardization.
Genetic/epigenetic factors	Familial liability, polygenic contribution, stress-responsive methylation changes.	May condition sensitivity to adversity and persistence of risk across development.	No one genetic or epigenetic marker is sufficient clinically: the effects are small, polygenic and context dependent.

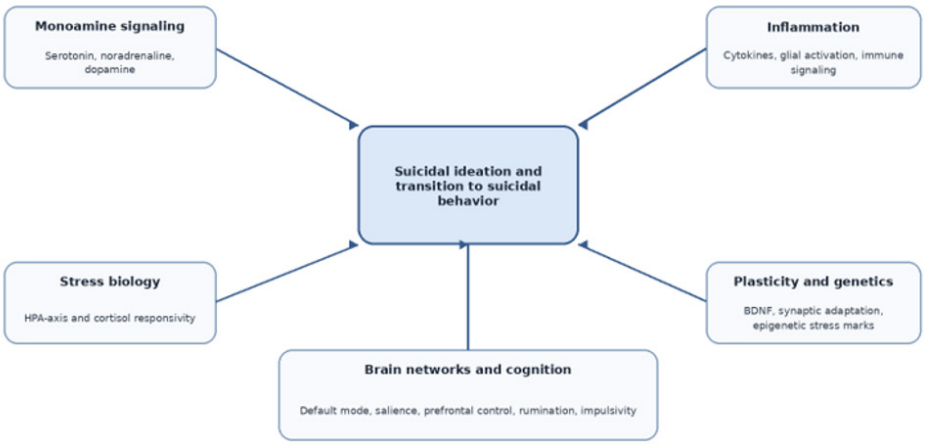

Figure 1 Integrated neurobiological architecture connecting biological domains with suicidal ideation and behavior

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

Serotonergic system disturbances

An abundance of evidence involves deficiency in serotonergic neurotransmission in the neurobiological circuit involving suicidal thinking.[26] In individuals who have attempted suicide, levels of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of 5-HT, are low in the CSF. These levels are confined to the suicidal subgroup among subjects with major depressive disorder.[26] The postmortem human brain literature shows that 5-HIAA and other indirect markers of serotonergic function, especially in brainstem nuclei, were consistently lower than controls in samples of suicide decedents suffering from psychiatric disorder, especially mood and psychotic disorder.[2] Similar findings come from independent studies of 5-HT1A receptor levels in the brains of suicide decedents with major depression, which show lower levels of receptor availability, primarily in the prefrontal cortex and hippocampus: two regions that are critical in emotion regulation and self-referential thought.[27]

Genetic studies have also supported an association between serotonergic dysfunction and major depressive disorder-related suicide risk by relating the presence of functional 5-HT transporter (5-HTT) gene promoter and 5-HT1A receptor polymorphisms to termination of life in major depression.[28] Because the association of genetic variants related to the 5-HTT system with suicidal phenotypes has been documented in other clinical and experimental populations, parallel investigations of candidate genes involved in additional biogenic amine pathways, including noradrenalin and dopamine systems, have been initiated.[29]

Noradrenergic and dopaminergic pathways

There is a lack of complete understanding of the neurobiology of suicidal behaviour. According to a number of familial, twin and adoption studies, there is a heritable contribution that is at least in part independent from a current psychiatric diagnosis. Furthermore, clinical studies link suicidal behaviour with aggression and impulsivity.[30–33] As a possible contributing factor to stress-related vulnerability, noradrenergic dysfunction and changes concerning the locus coeruleus have been investigated.[34]

Suicide has also been associated with noradrenergic transmission, due to lower levels of noradrenaline in the brain stem.[2] A rise in the activity of LC noradrenergic transmission might be associated with stress and other developmental risk factors which may indicate a shift to suicide behaviour.[5] Changes in noradrenergic activity have been shown in postmortem brains, CSF and plasma levels and experimental animal models using suicidal models.[8] Due to its expected relationship with suicidal behavior,[35] the locus coeruleus has been heavily investigated. Research involving this nucleus has generated conflicting results; low noradrenaline (NA) levels and high α2-adrenergic receptor densities in suicide victims have been observed but also decreased β1-adrenergic and 5-HT2 receptor binding sites and GABAA receptor subunit alterations have been reported.[36] Compelling evidence shows that short-term adjustments of this system commonly occur across various models of individual vulnerability to stress-inducible behavioral changes.[37]

The evidence supporting dopamine's involvement is less reliable than that involving serotonin and norepinephrine. Although some postmortem research has not detected differences in cortical and subcortical dopamine levels in suicide decedents versus controls, studies have found associations involving striatal D2 receptors in some clinical groups (26,38-40). Dopaminergic findings may thus be considered transient and phenotype-dependent, rather than interpretative evidence of a single decisive mechanism.[41]

Hypothalamic-pituitary-adrenal axis dysregulation

The HPA axis is an essential neuroendocrine system that responds to stress. Following activation, the blood levels of glucocorticoids will rise. In humans, cortisol is the main glucocorticoid that rises.[41] These hormones terminate activity through feedback inhibition. Human studies performed postmortem have shown, irrespective of psychiatric diagnosis, that the HPA axis is impaired in suicide decedents; dysregulation has also been linked to receiving treatment with antidepressants.[42] As a result, extensive changes in the hippocampus, which is involved in HPA-axis assessment of stress and feedback control, were noted in suicide.[43] Cortisol has been the most studied mediator of stress response concerning suicidal behavior.[44] Dysregulation of the hypothalamic-pituitary-adrenal axis is linked with suicide ideation, attempt, and completion, as well as increased risk for mood, psychotic, and personality disorders.[42] Cortisol responses to stress are blunted in suicide attempters, most likely due to either signaling dysfunction of the HPA axis or impairment of the CNS to cortisol.[45] Previous traumatic experiences are associated with weakened reactivity of the HPA axis to any further stress. Furthermore, the HPA axis modifications are related to childhood and adult trauma history. According to a research study,[46] women who were sexually or physically abused during childhood, showed inhibition of the pituitary-adrenal response.

Neuroinflammation and immune signaling

Neuroinflammation and abnormalities in immune signaling systems are increasingly implicated in the neurobiological mechanisms underlying suicidal behavior.[47] Biochemical studies in cerebrospinal fluid and post-mortem brain tissues reveal elevated levels of proinflammatory cytokines and chemokines in individuals who died by suicide.[48] Complementing these findings, large-scale genetic analyses support a polygenic model in which a common genetic risk architecture links both suicide attempts and major psychiatric disorders, with several risk variants associated with distinct immune pathways.[49] Empirical meta-analyses conducted on studies in suicide attempters and completers confirm elevated levels of multiple inflammatory cytokines, including interleukin-6, a pleiotropic proinflammatory cytokine implicated in multiple pathogenic processes.[50] Anomalous immune activity and dysregulated inflammatory signaling systems thus represent a potentially critical neurobiological substrate of increased suicide risk.[51]

At a cellular level, the innate immune response to injury, stress, and inflammation is mediated by the activation of glial cells and the release of proinflammatory cytokines, chemokines, and other inflammatory mediators.[52] Extensive evidence identifies such neuroinflammatory processes as essential players in the pathophysiology of major mental disorders associated with an increased risk of suicidal behavior, including mood disorders, schizophrenia, post-traumatic stress disorder, and substance use disorders.[53] Meta-analyses of biochemical studies demonstrate the presence of altered concentrations of proinflammatory cytokines in the plasma and serum of patients with major depression, anxiety disorders, post-traumatic stress disorder, and psychosis, conditions that are also strongly linked to suicidal behavior.[54] Cortical and peripheral alterations of proinflammatory cytokines, such as IL-1α, IL-1β, TNF-α, and IL-6, have been identified in post-mortem studies of depressed individuals, and the detection of multiple inflammatory markers has been observed in both the cerebrospinal fluid and post-mortem brains of suicides.[55]

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

Neurotrophic factors and synaptic plasticity

Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), have emerged as significant contributors to the neurobiological understanding of suicidal behavior and ideation.[56] During major stressors associated with increased suicide risk, BDNF levels and its expression within the brain are reduced.[2] Furthermore, low concentrations of BDNF are documented in patients suffering from mood and anxiety disorders, which are also associated with elevated suicide rates.[26] Neurotrophins actively regulate the genesis (neurogenesis), development (dendritic branching) and survival (apoptosis) of neurons and glial cells in several brain regions, particularly in the cerebral cortex and limbic system.[57] Specific neurotrophic and growth factors have been reported to stimulate cellular processes involved in neuronal plasticity and to modulate neurobiological changes associated with chronic stress and antidepressant treatment.[58] BDNF has emerged as a pivotal factor that is highly relevant to the neurobiology of suicide and affects the pathophysiology of other psychiatric disorders accompanying suicidal behavior.[59]

Time-dependent neurobiological variability

Sustained suicidal ideation may arise from chronically changed brain activity or structure, while transient thoughts might reflect dynamic neurobiological fluctuations independent from longer-lasting alterations.[60] Neurobiological processes underlying the acute experience of suicidal thoughts may differ among individuals; therefore, suicidal ideation and behaviour observed in certain individuals might not represent the same underlying neurobiological patterns observed in clinical populations.[61]

The neurobiological processes associated with suicidal behaviour evolve throughout the human lifespan, and age distribution is an important issue in suicide research.[62] These factors highlight the need for differentiated study of adolescent and adult populations, as well as consideration of vulnerable time periods such as early childhood, adolescence and late life.[63]

Acute versus chronic states

Analysis of neurobiological correlates of suicidal ideation should look for temporal dimensions. An acute crisis can appear suddenly over several hours to days, with sudden changes in emotional state, response to stress, cognition, sleep and inhibition. The changes that depend on the state may exist alongside more stable vulnerabilities, including more frequent rumination, altered stress system regulation, altered reward processing and persistent network-level alterations.[2,60,61] Given that most studies rely on single assessments, it remains difficult to determine whether a measured change preceded the crisis, occurred during it, or is a result of treatment and recovery.

Chronic vulnerability may last for weeks or years, and the timing of the stressor may be influenced by earlier episodes, early adversity, another psychiatric illness and repeated exposure. Momentary assessment and repeated biological sampling are thus particularly useful for distinguishing relatively stable traits from short-lives fluctuations and detecting within-person changes that come before worsening ideation.[64–68] A clinically meaningful temporal model is expected to link developmental vulnerability, chronic background risk, acute state change, and outcome without assuming a one pathway serves every stage in the same way (Figure 2).

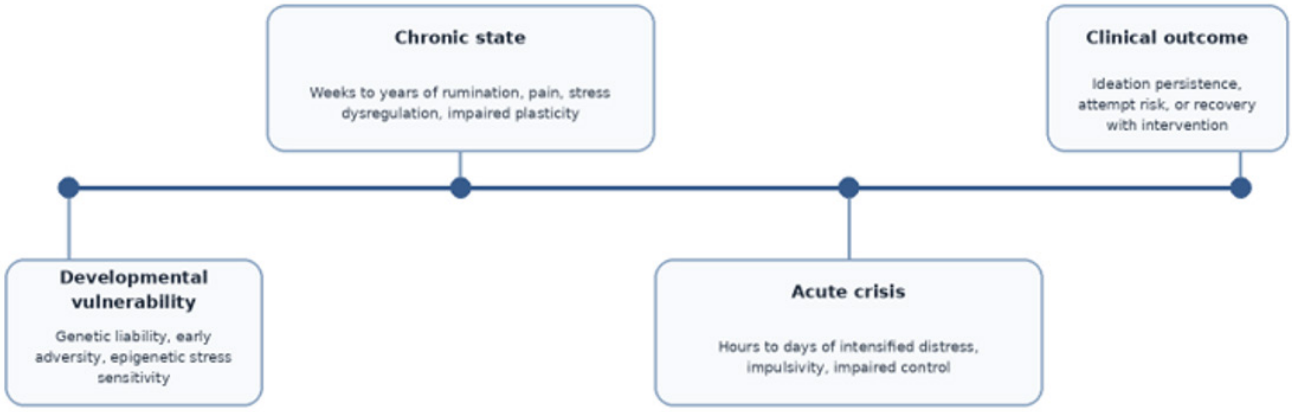

Figure 2 Temporal and developmental model distinguishing vulnerability, chronic state, acute crisis, and clinical outcome

Developmental considerations

At present, researchers are interested in how suicidality might change as the adolescent grows, a time of increased risk for suicidal thoughts and behavior.[69] It is thought that alterations in serotonergic functioning and certain brain morphometric changes detectable with neuroimaging contribute to this increased risk.[70] Reshaping in the frontal cortex may also be more likely to trigger suicidal behavior in late adolescence than childhood and early adulthood; an increasing volume of research suggests these alterations are relatively state traits that confer risk for suicidal behavior.[2]

The searches into the adolescents have shown differences in terms of inflammatory and transcriptomic among the individuals who have depression, nonsuicidal self-injury, or suicide attempt. However, findings are preliminary and differ by phenotype and sample characteristics.[71,72] Childhood maltreatment may affect stress-sensitive brain areas via epigenetic modifications, but the issue of tissue specificity and causation is enigmatic. Genetic variants studied for their potential contribution to differences between people in sensitivity to stress include 5-HTTLPR, CRHR1, CRHR2, CRHBP, and BDNF Val66Met.[1]

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

Brain networks involved in suicidal ideation

Changes in connections between large networks in the brain might be a cause of suicidal ideation. More specifically, these connections affect the Default Mode Network, Salience Network and Cognitive Control Network.[74] People who think about suicide show increased interactions between brain networks related to mind-wandering and emotional situations. This correlates with negative thinking[71–73] and thinking about negative life events.[74] Another study suggested an enhanced resting-state connection between the default and salience networks in depressed people with suicidal ideation. This appears crucial for rumination as highlighted.[76] Neuroimaging done on major depressive disorder patients who previously attempted suicide showed that the whiteness of the frontal and subcortical areas was less.[74]

Default mode network and rumination

Neuroimaging studies have found that the default mode network (DMN) is involved in ruminative, self-referential thinking.[77] The act of ruminating is a repetitive and passive focus on one's internal cues, thoughts, or feelings which may be distressing.[78] Reflective rumination is a thought process about the causes of negative mood, while brooding is dwelling on failure.[79] Thus, brooding is thought to precipitate suicidal thoughts more than reflection does, especially in mild to moderate major depressive episodes.[80] When brooding, a person will have a cycle of ruminative thoughts and fail to focus on external, present-moment stimuli. Rather, they will be focused on their past failures, lost opportunities, and painful losses.[81] Those who suffer from the melancholic type of depression and who reflect on their own emotional pain report higher rates of suicidal ideation, and ruminative brooding is a predictor of increased suicidal thought amongst adolescent and young adult samples.[82]

Salience and emotion regulation networks

Over-activity in the control network identified in the fMRI scans of participants, with pre-occupation or non-verbal responsive injury, signaling dual impact of injury on the willingness to err and the psychological stability.[41] Individuals suffering from major depressive disorder (MDD) exhibited a change in rs-FC within these networks. Alterations in rs-FC have been recognized as potential biomarkers of suicide risk.[83] According to a study,[84] the salience network of patients who attempted suicide in the past connected less well with the default mode and executive control networks. Moreover, the angular gyrus is an important node of the salience network and has abnormal rs-FC with regions in the superior parietal lobule, inferior frontal gyrus, and dorsolateral prefrontal cortex, all of which relate to higher suicide risk.[85] When internal communication breaks down, people begin to make poor decisions, eventually leading them to self-harm.[84]

Prefrontal control and impulsivity

Suicide appears to be an impulsive act, but the consensus on the relationship between the two is disputed.[86] There are mixed currents of evidence regarding the role of impulsivity in engaging in suicidal ideation, particularly in situations requiring immediate decision making.[87] Various types of impulsivity possibly have a differential modulating effect on the relationship: impulsive, unplanned suicide attempts are usually less lethal, frequently comorbid with substance use and low level of education; whereas more deliberated attempts continue to remain modulated by impulsive decision-making oriented towards terminating acute suffering.[86] Involuntary brain circuits linked to impulsive choices and aggression have also been linked to the intensity of suicidality behavior. As a result, high-risk clinical populations ought to receive psychoeducation to reduce the level of impulsivity.[88]

The individual difference in impulsive choice is correlated with activation in neural systems associated with the valuation of distant rewards, and the control of reward-directed behavior that follows these valuations.[89] According to,[90] the representation of delayed reward value in the striatum is controlled by the prefrontal cortex. Activation control in areas involved in reward valuation appears as an underlying mechanism of self-control when making consumer-choice decisions.[91] Current models of impulsivity posit that prefrontal control of emotion-driven behavior could underlie the connection between mechanisms that modulate impulsivity and suicidal thoughts and acts. Suicidal actions are also associated with the functional organization of self-referential cognition.

Genetic and epigenetic contributions

According to some estimates, the heritability for suicidal behavior would be between 36% and 63% for both ideation and attempts. Importantly, the estimates in the lower range are for very specific highly lethal forms such as hanging, self-immolation and carbon monoxide poisoning.[92] Research on twins indicates that death by suicide is significantly more heritable (73%) than suicidal thoughts (46%). This suggests that the onset of suicidal thoughts is related to adversity, becoming a victim, losing loved ones and other personal tragedy, whereas familial neurobiological factors are more pertinent for death by suicide.[2] According to a study referenced in 93, genome-wide association studies on suicide-related traits provide slight significance on common variant contributions to suicide thoughts and behaviors, and polygenic risk scores can enhance discrimination. Changes that regulate the expression of stress-responsive genes have been documented in tissue samples from suicide victims and in animal models of frequent depressive behaviors.[94]

Heritability and common variants

Family and twin research support a heritable component of suicidal thoughts and behaviors, although estimates differ according to phenotype, population, and method.[92,95–99] The early candidate-gene studies focused on serotonergic and stress-response pathways including 5-HTT, 5-HT1B, TPH1, MAOA, HPA-axis genes, and BDNF. Nonetheless, individual variants tend to show small and inconsistent effects, which have not led to clinically useful prediction. New genome-wide approaches suggest that schizophrenia may share common architecture with autism. Findings derived from genetic research are to be interpreted probabilistically; they confer susceptibility that interacts with developmental and environmental exposures not deterministically as a single-gene mechanism.

Epigenetic modifications in stress-responsive genes

One possible pathway through which adversity and chronic stress can lead to changes in the expression of genes involved in stress responsivity, neuroplasticity, immune signalling, and brain development is epigenetic mechanisms. Postmortem brain tissue and peripheral samples have been studied to report DNA-methylation and gene-expression differences associated with suicide-related phenotypes; however, results differ according to tissue, age, diagnosis, medication exposure and analysis.[94,97,101–105] Since epigenetic patterns are dependent on cell types and context, peripheral changes should not be assumed to be representative of the brain and cross-sectional data cannot inform whether observed changes are causes, consequences, or correlates of illness. Before epigenetic markers can aid in

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

personalized risk assessment, validation must occur in longitudinal, well-established cohorts.

Interaction with psychosocial and environmental factors

Suicidal behavior is influenced by psychosocial and environmental conditions.[1] Risk may increase due to damage or loss, chronic stress, substance use and pain syndrome.[106] Socioeconomic status and cultural context affect vulnerability.[2]

Stressful life events trigger nearly 30% of suicides, with the loss of love and other trauma having a significant role.[107] Occurrence of suicidal thought during life is positively related to sexual abuse.[108] Almost every person who died through suicide has suffered chronic stress, and the role of chronic pain in suicide remains uncertain although chronic pain people are more likely to have endorsed it.[109]

Trauma, loss, and chronic stress

Experiencing trauma, loss, and chronic stressors could affect individual suicide risk, due to the cumulative impact of those on the HPA axis, autonomic regulation, inflammatory signaling, sleep, and prefrontal-limbic control. Altered cortisol responsiveness and stress-sensitive epigenetic processes are linked with early adversity whereas repeated exposure to stress may confer allostatic overload and limited recovery from subsequent challenges.[43,46,63,100,106–110] These processes are not deterministic in nature but probabilistic, with exposure not generating the same biological response every time; and effects are modified by timing of development, psychiatric co-morbidity, social support, coping resources and treatment. We need more studies that observe the same people over time to see if changes happened before worsening ideation. Or whether changes are due to the effects of distress that happened.

Substance use and pain syndromes

Chronic pain is another major risk factor for suicidal thoughts and actions. On the whole, nearly one in six has chronic pain; it is nonetheless associated with increased risk of suicide. Indeed, people who seek or obtain physician-assisted death often have complex psychopathology, characterized by suicidal ideation.[111] A range of psychological factors are responsible for suicidality in chronic pain, including psychiatric morbidity, sleep disturbance, undiagnosed mood disorder.[112] Gaining access to lethal means appears to be a strong suicidality facilitator. Moreover, substance use (especially alcohol misuse) longitudinally increases suicidal behavior risk and is thought to further increase risk in chronic pain populations.[112]

Socioeconomic and cultural contexts

Socioeconomic and cultural factors can influence exposure to stressors, access to care, social connectedness, stigma and the meaning or disclosure of suicidality. These contextual influences may interact with neurobiological vulnerability through chronic stress, sleep disturbance, substance use, decreased treatment access or social withdrawal.[1,2,113] Nonetheless, associations at the population level must not be read as resulting from individual biological mechanisms. Cross-cultural studies should be conducted with locally validated measures, taking into account differences in reporting, service availability and refraining from assuming that identified biomarkers have the same meaning or predictive value in a different social context.

Implications for risk assessment and intervention

Stress responsivity, affect regulation, rumination, inhibitory control, suicidal ideation and behaviour could all be linked via neurobiological work. The findings could help generate new hypotheses, enhance phenotypic stratification, and pinpoint future preventive research targets.[59,61,114] Nonetheless, they cannot substitute for the direct clinical assessment of current ideation, previous behavior, psychiatric symptoms, psychological stressors, access to care, and protective factors. The best translation framework should be more integrative than biomarker-led.Among the candidate measures are cortisol responsivity, inflammatory signaling, neurotrophic factors, genetic or epigenetic profiles, and prefrontal–limbic and large-scale brain network connectivity.[10,12,41] Currently, the best use of these measures is for testing mechanisms and characterizing groups rather than classifying individual patients. To interpret structural brain variations, one should pay heed to phenotype definitions, psychiatric diagnosis, medication exposure, physical health, tissue source, the developmental stage, and the interval between assessment and the clinical state studied (Table 2).

Table 2 Translational implications for risk assessment and intervention

Assessment layer	Useful indicators	Clinical/research value	Limitation
Clinical phenotype	Ideation severity, previous attempt, impulsivity, rumination, psychiatric comorbidity.	Anchors biological findings to observable risk and treatment need.	Self-report fluctuates and may be influenced by stigma or concealment.
Biological markers	Cortisol response, inflammatory markers, BDNF-related measures, genetic/epigenetic profiles.	Can refine mechanistic hypotheses and future stratified prevention models.	Exploratory and nonspecific; insufficient alone for individual prediction or clinical disposition.
Neuroimaging	Prefrontal-limbic, default mode, salience, and control-network connectivity.	Maps biological substrates of rumination, affect regulation, and impulse control.	Overlap with depression and stress-related disorders, together with cost, availability, and reproducibility, limits routine clinical use.
Temporal context	Acute crisis markers versus chronic vulnerability indicators.	Helps distinguish immediate intervention needs from long-term prevention planning.	Requires longitudinal designs and repeated measurement.
Psychosocial context	Trauma, loss, chronic stress, substance use, chronic pain, socioeconomic stressors.	Explains how environmental exposure interacts with biological susceptibility.	Contextual variables are complex and may be difficult to quantify consistently.

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

Biomarker candidates and limitations

Research incorporating genomic, inflammatory, and neuroimaging data has yielded numerous candidate biomarkers related to neurogenesis, apoptosis and stress reactivity (AP), as well as prefrontal-limbic structure and function, serotonin (5-HT) transmission, and epigenetic regulation.[26,115–119] However, there is uneven replication and generally modest effect sizes and many studies use small or diagnostically heterogeneous samples. Tests that look at BDNF and cytokines in the blood, cortisol in saliva, gene-expression patterns and so on provide informative results at the group level, but they measure the central nervous system processes only indirectly, and they often overlap with major depressive disorder and other stress-related conditions. Studies over a long-term period must compare individuals with the same psychiatric diagnosis but with different suicidality trends to provide evidence for incremental validity.

Specificity, confounding, and clinical validity of candidate biomarkers

A major restriction of the current literature on biomarkers is lack of specificity. Major depressive disorder, trauma-related conditions, chronic stress, psychosis, substance-use, and several medical illnesses[26,42-59,74–85,116–119] have been associated with altered serotonin signaling, atypical cortisol responsivity, inflammatory activation, lower BDNF, and prefrontal-limbic or large-scale network abnormalities. A group difference is not by itself sufficient to show that a marker is specific to suicidal ideation and/or predicts transition from ideation to behavior, and/or adds value to established clinical variables.

Confounding factors included diagnosis and severity of the most pronounced diagnosis, medication exposure (antidepressants, psychotropic medications, and other drugs), sleep, smoking, body composition, infection, chronic disease, substance use, age, sex, and timing and locus of biological sampling. Factors such as agonal processes and the quality of tissue may affect the postmortem findings, whereas peripheral measures may not necessarily reflect the CNS. Next studies should compare psychiatric groups with suicidal ideation and behavior. The other psychiatric group should not have these ideation and behavior. The measures must be repeated. Also, the measures must be within the person. Next, the outcome must be predefined. Also, the study must test whether multimarker models provide an increment and externally validated prediction. There should not be determined of individual risk or clinical disposition based on isolated biomarkers until such evidence is available.

Ethical considerations in neurobiological research

Suicide has been a critical global public health issue for decades since not enough is known about the neurobiology of suicide which prevents the development of more effective prevention.[2] Ethical justification for research on the neurobiology of suicidal ideation can be derived from the risk-benefit ratio of the study protocols including informed consent procedures, protection of privacy, appropriate clinical referral pathways, and deterrence against the stigmatizing and deterministic interpretation of study findings. Ethical translation also requires clear statements that candidate biomarkers are investigational and not meant to independently determine an individual's future behavior.[119,120]

Conclusion

Suicidal thinking and acts are linked with changes in a variety of monoaminergic domains. All the evidence points toward a distributed and context-dependent model, in which biological vulnerability combines with developmental stage, psychopathological disease, adversity and current stress. No single pathway or biomarker can explain the onset, development, or escalation of suicidal thoughts.

The limitations of interpretation arise from the heterogeneity in the definition of phenotypes, a cross-sectional design, small samples, medication and medical confounding, reliance on peripheral measures, and the prevalence of postmortem or diagnostically mixed studies. Several other important psychiatric conditions such as major depressive disorder, trauma-related conditions as well as chronic stress show similar changes. As such, current biomarkers have mechanistic value but insufficient specificity and prediction for independent clinical use. Future ready design studies with longitudinal repeated-measures, comparison groups with well-matched psychiatry samples, multimodal inclusion and transparency, explicit differentiation of chronic vulnerability from acute crisis. The assessment of clinical risk should continue to be based not only on biological evidence but also, directly, on psychological, social and clinical factors.

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Vargas-Medrano J, Diaz-Pacheco V, Castaneda C, et al. Psychological and neurobiological aspects of suicide in adolescents: Current outlooks. *Brain, behavior, & immunity-health*. 2020;7:100124.
2. Aydın M, Hacımusalar Y, Hocaoğlu Ç. Neurobiology of suicidal behaviour. current approaches in psychiatry. *Psikiyatride Guncel Yaklasimlar*. 2019;11(5).
3. Schaffer KB, Dandan T, Bayat D, et al. Self-inflicted injury and the older trauma patient: a 20 year review of suicide attempts and outcomes. *European geriatric medicine*. 2022;13(1):119–25.
4. Bhagat AK, Kumar S, Ankur C, et al. Fatal suicidal cut-throat wound in a patient with double valve replacement: interplay of cardiac dysfunction and self-harm. *Cureus*. 2025;17(5).
5. Simonit F, Da Broi U, Giudici F, et al. Autopsy findings in fire deaths in relation to manner of death: Analysis of autopsy records in Friuli, Italy (1993–2020). *Legal Medicine*. 2024;67:102372.
6. Baldino G, Tarzia P, Roccuzzo S, et al. Multiple suicidal gunshot wounds. case reports and mini-review of literature. *La Clinica Terapeutica*. 2024;175(4).
7. Ren N, Zheng S, Zhou Y, et al. The prospect of suicide biomarkers: from neurobiology to precision prevention. *Frontiers in Psychology*. 2026;17:1757838.
8. Lee SE, Shin H, Kim G, et al. Pain-related gray matter volume reductions in unmedicated individuals with nonsuicidal self-injury: a voxel-based morphometry study. *PsyArXiv*. 2022.
9. Rodrigues FD, Rodrigues MA, da Silva AP. The neurobiology of suicidal ideation: an integrative review. *Ciencia Latina: Revista Multidisciplinar*. 2025;9(4):6205–6229.
10. Westlund Schreiner M, Manuele SJ, Washburn JJ, et al. White matter and impulsivity are prospectively associated with non-suicidal self-injury in youth: evidence for sex differences. *Neuropsychopharmacology*. 2026:1–8.
11. Hercher C. An investigation of the cellular and molecular landscape of the human cerebellum: implications for depression and suicide, 2026.

12. Susanti I, Saputra NI, Budiyanti L, et al. Nursing care for a patient with a risk of suicide due to depression using the solution-focused brief therapy approach: case study. *OBM Neurobiology*. 2025;9(4):1-1.
13. Li LM, Carson A, Dams-O'Connor K. Psychiatric sequelae of traumatic brain injury—future directions in research. *Nature Reviews Neurology.* 2023;19(9):556–571.
14. Surjan J, Grossi JD, Del Porto JA, et al. Efficacy and safety of subcutaneous esketamine in the treatment of suicidality in major depressive disorder and bipolar depression. *Clinical drug investigation.* 2022;42(10):865–873.
15. Poon JA, Zelaya DG, Rajasankar V, et al. Childhood threat and deprivation and links to mental health behaviors and health risk behaviors among young sexual minority men: the differential roles of mindfulness and emotion regulation. *Int J Environ Res Pub Health.* 2026;23(5):609.
16. Nouri E, Moradi Y, Moradi G. The global prevalence of suicidal ideation and suicide attempts among men who have sex with men: a systematic review and meta-analysis. *Eur J Med Res.* 2023;28(1):361.
17. World Health Organization. Suicide worldwide in 2021: global health estimates. World Health Organization; 2025.
18. Ivey-Stephenson AZ. Suicidal thoughts and behaviors among adults aged≥ 18 years—United States, 2015–2019. MMWR. Surveillance Summaries. 2022;71.
19. Lee S. Passive suicidal ideation in older adults from 12 European countries. *J Population Ageing.* 2023;16(1):137–154.
20. Sher L, Oquendo MA. Suicide: an overview for clinicians. *Medical Clinics.* 2023;107(1):119–130.
21. Swamy RD. Analysis of suicide ideation documents posted on Twitter using an NLP classifier (Doctoral dissertation, Dublin, National College of Ireland).
22. Kurniawan D, Fitriawan AS, Susanti BAD. et al. Predictors of suicidal behaviors among school-going adolescents: a cross sectional study in Indonesia. *Middle East Curr Psychiatry.* 2024;31:39.
23. Hassan E, Bhatnagar R, Abd El-Hafeez T, et al. Detection of suicide and depression for early intervention and initiative-taking mental healthcare. In: 2025 7th International Conference on Signal Processing, Computing and Control (ISPCC) 2025 Mar 6 (pp. 99-104). IEEE.
24. Hakopian N. Effects of Repetitive Negative Thinking on default mode network connectivity and working memory in co-occurring anxiety and depression (Doctoral dissertation, Palo Alto University), 2024.
25. Dimopoulos A. Neural mechanisms of cognitive behavioral therapy for depression: A multimodal systematic review. *Undergraduate Research in Natural and Clinical Science and Technology Journal*. 2026:1–9.
26. Costanza A, D'Orta I, Perroud N, et al. Neurobiology of suicide: do biomarkers exist?. *Int J Legal Med*. 2014;128(1):73–82.
27. Ganesh KA, Verma AK, Sinha SS, et al. Neurotransmitter dysregulation in depression, anxiety, and suicidality: from synaptic dysfunction to cellular pathogenesis. *Psychiatry Res*. 2026:117120.
28. Lee JL. A comparison of genetic versus non-genetic contribution of serotonin to suicide. *Science Insights*. 2023;43(1):995–1002.
29. Tatayeva R, Tussupova A, Nursafina A, et al. A Study of candidate genes associated with suicide attempts in the Kazakh population in astana, Kazakhstan. *Int J Molecular Sci*. 2026;27(5):2294.
30. Spencer AE. Genetic vulnerability for preadolescent suicidal thoughts and behaviors. *Biological Psychiatry*. 2022;92(3):e17–e18.
31. Artés C, Porras-Segovia A, Ruiz-Veguilla M, et al. Designing interventions guided by digital phenotype and pharmacogenetics in Spain for suicidal behaviour based on retrospective data: the multicentre SMARTomicS study protocol. *BMJ open*. 2026;16(5):e106685.
32. Alrfooh A, Casten LG, Gringer Richards J, et al. Investigating the relationship between DNA methylation, genetic variation, and suicide attempt in bipolar disorder. *Archives of suicide research.* 2026;30(1):203–223.
33. Tonkuş MB, Çalışkan BB, Alagöz E. The relationship between suicide and hopelessness in young adults aged 18-30: A systematic review. *J Psychiatric Nursing/Hemşireleri Derneği.* 2022;13(3):253.
34. Lee E, van Dijk MT, Kim BG, et al. Polygenic scores for psychiatric traits mediate the impact of multigenerational history for depression on offspring psychopathology. *Molecular Psychiatry.* 2026;31(2):1074–1084.
35. Yamamoto M, Hirakata H, Toda K. Neural signaling mechanisms in depression: bridging classical monoamine hypotheses, animal models, and emerging antidepressant strategies. *Frontiers in Cell and Developmental Biology.* 2026;14:1777975.
36. Szynkarek A, Tyrybon W, Karcz M, et al. Restorative or disruptive? effects of antidepressants on sleep architecture in depression: A. Szynkarek et al. *CNS drugs*. 2026:1–5.
37. Korukonda A, Weinshenker D. A new hope: locus coeruleus-norepinephrine system at the nexus of neuropsychiatric symptoms. *Molecular Psychiatry*. 2026:1–3.
38. Duval F, Mokrani MC, Danila V, et al. Dopamine function and hypothalamic-pituitary-thyroid axis activity in major depressed patients with suicidal behavior. *Brain sciences.* 2022;12(5):621.
39. Kumar P, Rai S, Joshi A. Role of functional foods and nutraceuticals for depression, post-traumatic stress disorder, and suicidal behaviors. In: Nutraceutical fruits and foods for neurodegenerative disorders 2024;101–122.
40. Roy B, Ochi S, Dwivedi Y. Potential of circulating miRNAs as molecular markers in mood disorders and associated suicidal behavior. *Int J Mol Sci.* 2023;24(5):4664.
41. López JF, Vazquez DM, Chalmers DT, et al. Regulation of 5-HT Receptors and the Hypothalamic-Pituitary-Adrenal Axis: Implications for the Neurobiology of Sucide. *Annals of the New York Academy of Sciences.* 1997;836(1):106–134.
42. O'Connor DB, Green JA, Ferguson E, et al. Cortisol reactivity and suicidal behavior: Investigating the role of hypothalamic-pituitary-adrenal axis responses to stress in suicide attempters and ideators. *Psychoneuroendocrinology.* 2017;75:183–191.
43. Gartland N, Rosmalen JG, O'Connor DB. Effects of childhood adversity and cortisol levels on suicidal ideation and behaviour: Results from a general population study. *Psychoneuroendocrinology.* 2022;138:105664.
44. Wang YF, You GY, Han T, et al. Network analysis of comorbid depression, suicidality and biomarkers on HPA axis among mood disorder patients to psychiatric emergency services. *Translational psychiatry*. 2023;13(1):203.
45. Duval F, Mokrani MC, Danila V, et al. Hypothalamic-prolactin axis regulation in major depressed patients with suicidal behavior. *Psychoneuroendocrinology*. 2023;151:106050.
46. Orlandi M, Marazzi F, Morandi C, et al. Biomarkers Identifying Tendency to Suicide (BITS): detection of biomarkers in adolescents with suicidal ideation or suicidal behavior for early prevention or intervention. A prospective cohort study. *Frontiers in Human Neuroscience.* 2026;20:1721827.
47. Behera C, Gupta S, Shelton R, et al. Inflammation and treatment strategies for suicidal behavior. *The World Journal of Biological Psychiatry*. 2026;27(5):403–423.
48. Sha Q, Fu Z, Escobar Galvis ML, et al. Integrative transcriptome-and DNA methylation analysis of brain tissue from the temporal pole in suicide decedents and their controls. *Molecular psychiatry.* 2024;29(1):134–145.

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

49. Daray FM, Chiapella LC, Grendas LN, et al. Peripheral blood cellular immunophenotype in suicidal ideation, suicide attempt, and suicide: a systematic review and meta-analysis. *Molecular psychiatry*. 2024;29(12):3874-3892.
50. Omelchenko MA, Klyushnik TP, Obodzinskaya TE, et al. Neurobiological basis of suicidal behavior in adolescents. *Neuroscience and Behavioral Physiology*. 2026:1–6.
51. Iacob VT, Cămănaru EM, Moroșan AC, et al. Suicide and neuroinflammation. *Bulletin of Integrative Psychiatry*. 2023;1(4).
52. Serafini G, Parisi VM, Aguglia A, et al. A specific inflammatory profile underlying suicide risk? Systematic review of the main literature findings. *Int J Environ Res Public Health.* 2020;17(7):2393.
53. Shafi A, Akmal M, Sethi A, et al. A mechanistic insight of neuro-inflammation signaling pathways and implication in neurodegenerative disorders. *Inflammopharmacology.* 2026;34(1):309–318.
54. Kip E, Parr-Brownlie LC. Healthy lifestyles and wellbeing reduce neuroinflammation and prevent neurodegenerative and psychiatric disorders. *Frontiers in Neuroscience*. 2023;17:1092537.
55. Sălcudean A, Popovici RA, Pitic DE, et al. Unraveling the complex interplay between neuroinflammation and depression: a comprehensive review. *Int J Mol Sci.* 2025;26(4):1645.
56. Guillot CR, Kelly ME, Phillips NB, et al. BDNF and stress/mood-related interactions on emotional disorder symptoms, executive functioning, and deliberate self-harm. *J Psychiatric Res.* 2023;163:195–201.
57. De Simone S, Bosco MA, La Russa R, et al. Suicide and neurotrophin factors: A systematic review of the correlation between BDNF and GDNF and self-killing. *InHealthcare.* 2022;11(1):78.
58. Liu X, Li S, Yu Y, et al. Changes in plasma TPH2, GDNF, Trk-b, BDNF, and proBDNF in people who died by suicide. *Brain sciences.* 2023;13(7):1096.
59. Correia AS, Cardoso A, Vale N. BDNF unveiled: exploring its role in major depression disorder serotonergic imbalance and associated stress conditions. *Pharmaceutics*. 2023;15(8):2081.
60. Bhatt RR, Haddad E, Zhu AH, et al. Mapping brain structure variability in chronic pain: the role of widespreadness and pain type and its mediating relationship with suicide attempt. *Biological psychiatry.* 2024;95(5):473–481.
61. Diao Y, Huang Y, Guo M, et al. Disentangling individual heterogeneity reveals robust network and molecular signatures of major depressive disorder with suicidal ideation. *Translational Psychiatry.* 2026;273.
62. Sessa F, Polito R, Li Rosi G, et al. Neurobiology and medico-legal aspects of suicides among older adults: a narrative review. *Frontiers in Psychiatry*. 2024;15:1449526.
63. Torres-Berrío A, Bortolami A, Peña CJ, et al. Neurobiology of resilience to early life stress. *Neuropsychopharmacology.* 2026;51(1):29–45.
64. Spangenberg L, Spahn C, Serebriakova J, et al. Qualitative content analysis of reactivity effects and feasibility of ecological momentary assessments of suicide-related thoughts and behaviors in the long-term and in suicidal crises. *Frontiers in Psychiatry*. 2026;17:1744947.
65. Griffith JM, Brehm MV, James KM, et al. Momentary state anhedonia is associated with the quantity and quality of daily-life peer experiences among adolescents at varying risk for suicidal thoughts and behaviors. *Development and psychopathology.* 2026;38(1):502–511.
66. Macchia A, Löchner D, Montag C, et al. Fluctuations of dissociation and inner tension during inpatient dialectical behavior therapy: associations with self-injury and suicidal ideation. *Borderline Personality Disorder and Emotion Dysregulation.* 2026.
67. Iyanda O, Iyanda AE. When stress accumulates: interacting effects of childhood adversity, multidimensional victimization, and protective resources on adolescent suicidal behaviors. *Chronic Stress.* 2026;10:24705470261437060.
68. Leloup M, Notredame CE, Dubois J, et al "You feel like you're not alone": Exploring a sociotechnical assembly in suicide prevention. *Health.* 2026:13634593261433114.
69. Tursunmamat D, Liu X, Li Y, et al. A review of neurobiological and psychosocial mechanisms in adolescent non-suicidal self-injury. *Current Behavioral Neuroscience Reports*. 2026;13(1):11.
70. Gotlib IH, Uy JP, Buthmann JL, Pine DS. Psychobiological mechanisms underlying the association between early life stress and depression in adolescence. *Molecular Psychiatry*. 2026;31(2):1085–1094.
71. Zhou Z, Wang S, Yin J, et al. Whole blood transcriptome analysis in female adolescents with depression accompanied by nonsuicidal self-injury and suicide attempt. *Depression and Anxiety.* 2026;2026(1):6688695.
72. Podwalski P, Dawidowski B, Lipiński K, et al. Inflammatory biomarkers and white matter microstructure in borderline personality disorder: A cross-sectional study. *Psychoneuroendocrinology.* 2026:107816.
73. Kurt ZK, Taş Torun Y, Ibrahimkhanlı L, et al. The potential role of kynurenine pathway and inflammation in pediatric obsessive-compulsive disorder with and without major depressive disorder comorbidity. *Journal of Neural Transmission*. 2026:1–7.
74. Ishikawa K, Nemoto K, Shiratori Y, et al. Aberrant resting-state functional connectivity of major depressive disorder with higher risk of suicide. *Psychiatry and Clinical Neurosciences Reports*. 2022;1(3):e35.
75. Myung W, Han CE, Fava M, et al. Reduced frontal-subcortical white matter connectivity in association with suicidal ideation in major depressive disorder. *Translational psychiatry*. 2016;6(6):e835.
76. Zhang X, Wang R, Chen Y, et al. High-order segregation of brain functional networks in major depressive disorder patients with and without suicide. *The European Physical Journal Special Topics*. 2026;234(28):9219-9135.
77. Roberts H, Schreiner MW, Pocius S, et al. State rumination predicts inhibitory control failures and dysregulation of default, salience, and cognitive control networks in youth at risk of depressive relapse: Findings from the RuMeChange trial. Journal of affective disorders reports. 2024;16:100729.
78. Tang H, Xiong T, Shi J, et al. Global and reflective rumination are related to suicide attempts among patients experiencing major depressive episodes. *BMC psychiatry*. 2021;21(1):117.
79. Ou H, Baetens K, Xiao L, Deroost N. Trait and state rumination shape memory suppression: A think/no-think study. *Current Psychology.* 2026;45(6):658.
80. Sharma P, Raut R. Experiences of Suicide Attempt Survivors in Nepal: A Qualitative Study. *Journal of Manmohan Memorial Institute of Health Sciences*. 2026;11(1):2–2-6.
81. Akbulut ÖF, Pamuk K. Rumination, loneliness, task-oriented coping and mental well-being among university students: a serial mediation model. *Psychological Reports*. 2025:00332941251329788.
82. Tichenor SE, Palasik S, Yaruss JS. Understanding the broader impact of stuttering: Suicidal ideation. *American journal of speech-language pathology*. 2023;32(5):2087–2110.
83. Van Heeringen K, Bijttebier S, Desmyter S, et al. Is there a neuroanatomical basis of the vulnerability to suicidal behavior? A coordinate-based meta-analysis of structural and functional MRI studies. *Front Human Neurosci*. 2014;8:824.
84. Zobel SB, Bruno S, Torru P, et al. Investigating the path from non-suicidal self-injury to suicidal ideation: the moderating role of emotion dysregulation. *Psychiatry investigation*. 2023;20(7):616.
85. Xu H, Xu X, Chen Y, et al. The role of limited emotion regulation strategies on non-suicidal self-injury and suicide attempts among chinese adolescents: a network analysis. *Health Data Science.* 2026.

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke*. 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

86. Da Silva AG, Malloy-Diniz LF, Garcia MS, et al. Cognition as a therapeutic target in the suicidal patient approach. *Frontiers in psychiatry*. 2018;9:31.

87. Valderrama J, Macrynikola N, Miranda R. Early life trauma, suicide ideation, and suicide attempts: The role of rumination and impulsivity. *Archives of suicide research.* 2022;26(2):731–747.

88. Zerekidze A, Bahlmann L, Petzold J, et al. Risk, reward, and suicide: how impulsivity and loss aversion influence decision-making in individuals who have attempted suicide. *Frontiers in Psychiatry*. 2026;17:1791411.

89. Brown VM, Wilson J, Hallquist MN, et al. Ventromedial prefrontal value signals and functional connectivity during decision-making in suicidal behavior and impulsivity. *Neuropsychopharmacology.* 2020;45(6):1034–1041.

90. Baldini V, Gnazzo M, Varallo G, et al. Beyond suicidal ideation: identifying high-risk university students through depression, sleep disturbance, and impulsivity—a cross-sectional secondary analysis. *Journal of Clinical Medicine*. 2026;15(9):3236.

91. Fisher-Fox L, Prestigiacomo CJ, Cyders MA. Urgency Theory in the context of broader emotion theories: a conceptual review. *Frontiers in psychiatry.* 2024;15:1403639.

92. Colbert SM, Monson ET, Andreassen OA, et al. Defining suicidality phenotypes for genetic studies: perspectives of the Psychiatric Genomics Consortium Suicide Working Group. *Molecular psychiatry.* 2025;30(12):6144–6154.

93. Colbert SM, O'Connell S, Edenberg HJ, et al. Suicidality phenotypes reflect both shared and distinct genetic factors. medRxiv. 2026:2026-05.

94. Ashley-Koch AE, Kimbrel NA, Qin XJ, et al. Genome-wide association study identifies four pan-ancestry loci for suicidal ideation in the Million Veteran Program. *PLoS genetics*. 2023;19(3):e1010623.

95. DiBlasi E, Shabalin AA, Monson ET, et al. Rare protein-coding variants implicate genes involved in risk of suicide death. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics.* 2021;186(8):508–520.

96. Murphy TM, Ryan M, Foster T, et al. Risk and protective genetic variants in suicidal behaviour: association with SLC1A2, SLC1A3, 5-HTR1B & NTRK2 polymorphisms. *Behavioral and Brain Functions*. 2011;7(1):22.

97. Mirza S, Docherty AR, Bakian A, et al. Genetics and epigenetics of self□injurious thoughts and behaviors: Systematic review of the suicide literature and methodological considerations. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 2022;189(7-8):221–246.

98. Abou Chahla MN, Khalil MI, Comai S, et al. Biological factors underpinning suicidal behaviour: an update. *Brain sciences.* 2023;13(3):505.

99. Gillespie NA, Su MH, Lannoy S, et al. Genetic overlap between DSM-IV major depressive disorder and suicidal behaviors: evidence from polygenic risk scores in young adult twins. *Behavior Genetics.* 2025;55(6):423–437.

100. Kimbrel NA, Ashley-Koch AE, Qin XJ, et al. Identification of novel, replicable genetic risk loci for suicidal thoughts and behaviors among US military veterans. *JAMA psychiatry*. 2023;80(2):135–145.

101. Yuan M, Yang B, Rothschild G, et al. Epigenetic regulation in major depression and other stress-related disorders: molecular mechanisms, clinical relevance and therapeutic potential. *Signal transduction and targeted therapy*. 2023;8(1):309.

102. Haghighi F, Xin Y, Chanrion B, et al. Increased DNA methylation in the suicide brain. *Dialogues in clinical neuroscience*. 2014;16(3):430–438.

103. González-Castro TB, Genis-Mendoza AD, López-Narváez ML, et al. Gene expression analysis in postmortem brains from individuals who died by suicide: A systematic review. *Brain sciences*. 2023;13(6):906.

104. Ceja Z, Van Velzen LS, Campos AI, et al. Recent breakthroughs in genetic and brain structural correlates of suicidal behaviors: a short review. Biological psychiatry. 2025;97(8):775–85.

105. Li QS, Shabalin AA, DiBlasi E, et al. Genome-wide association study meta-analysis of suicide death and suicidal behavior. *Molecular psychiatry.* 2023;28(2):891–900.

106. Shapovalova V. Post-Traumatic Stress Disorder: administration, clinical and pharmacological, organizational and legal, pharmaceutical management, recent case studies. *SSP Modern Pharmacy and Medicine*. 2024;4(1):1-8.

107. Gay M. Trait vulnerabilities and stressful life events: implications for youth suicide risk. *Vulnerable Children and Youth Studies*. 2025;20(1):92–110.

108. Li S, Wang X, Yu P, et al. Effects of stressful life events on suicide risk among orphaned and left-behind adolescents in China: The mediating roles of loneliness and subjective well-being. *Children and Youth Services Review*. 2024;161:107675.

109. Wheeler J, Mildred H, Broadbear JH, et al. Risk Factors associated with death by suicide in people diagnosed with borderline personality disorder in comparison with major depressive disorder: a descriptive study. *Journal of Psychiatric Research.* 2026;201:84–92.

110. Valderrama J. Stress and suicidal behavior: a cognitive, behavioral, and biological integrative approach. City University of New York; 2016.

111. Newton-John TR. Negotiating the maze: risk factors for suicidal behavior in chronic pain patients. *Current pain and headache reports.* 2014;18(9):447.

112. Baryshnikov I, Isometsä E. Psychological pain and suicidal behavior: A review. Frontiers in psychiatry. 2022 Aug 22; 13:981353.

113. Barzilay R, Moore TM, Calkins ME, et al. Deconstructing the role of the exposome in youth suicidal ideation: Trauma, neighborhood environment, developmental and gender effects. *Neurobiology of stress.* 2021;14:100314.

114. Tripathi N, Gupta G. Brain Mechanisms of Suicide: Neurocircuits and Inflammatory Triggers, 2025.

115. Niculescu AB, Levey DF, Phalen PL, et al. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. *Molecular psychiatry*. 2015;20(11):1266–1285.

116. Johnston JN, Campbell D, Caruncho HJ, et al. Suicide biomarkers to predict risk, classify diagnostic subtypes, and identify novel therapeutic targets: 5 years of promising research. *Int J Neuropsychopharmacol*. 2022;25(3):197–214.

117. Kim KY, Shin KY, Chang KA. Potential inflammatory biomarkers for major depressive disorder related to suicidal behaviors: a systematic review. *Int J Mol Sci*. 2023;24(18):13907.

118. Milic J, Jovic S, Sapic R. Advancing depression management through biomarker discovery with a focus on genetic and epigenetic aspects: a comprehensive study on neurobiological, neuroendocrine, metabolic, and inflammatory pathways. *Genes.* 2025;16(5):487.

119. Gal Z, Torok D, Gonda X, et al. New evidence for the role of the blood-brain barrier and inflammation in stress-associated depression: a gene-environment analysis covering 19,296 genes in 109,360 humans. *Int J Mol Sci.* 2024;25(20):11332.

120. Sobanski T, Peikert G, Kastner UW, Wagner G. Suicidal behavior-advances in clinical and neurobiological research and improvement of prevention strategies. *World journal of psychiatry*. 2022;12(9):1115.

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168. DOI: 10.15406/jnsk.2026.16.00666

Citation: Alkhatib AJ. Neurobiological factors underpinning suicidal ideation and suicide: an evidence-based synthesis. *J Neurol Stroke.* 2026;16(4):158–168.
DOI: 10.15406/jnsk.2026.16.00666