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THE NEUROBIOLOGY OF SUICIDAL IDEATION: AN INTEGRATIVE REVIEW

LA NEUROBIOLOGÍA DE LA IDEACIÓN SUICIDA: UNA REVISIÓN INTEGRADORA

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The neurobiology of suicidal ideation: an integrative review

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ABSTRACT

Introduction: The research question guiding this study is: What are the main neurobiological mechanisms associated with suicide, and how can pharmacological interventions influence these mechanisms to reduce suicidal ideation and behavior? The objective of this integrative review is to synthesize the evidence on the relationship between neurobiological factors and suicidal ideation, using a meta-analysis approach to quantitatively evaluate the available data. Methodology: The search was refined to include only free access articles, totaling sixty-seven studies, and clinical studies addressing the issue, resulting in seven articles analyzed. Inclusion criteria included the selection of empirical studies that evaluated the relationship between neurobiological factors and SI, ensuring that the research focused on direct evidence on the topic. Results and Discussion: Deficits in the excitation-inhibition balance in the anterior insula are associated with suicide risk, which is different from symptoms of depression. Therefore, it is suggested that SI may have distinct neurobiological underpinnings from depression, indicating a specific psychopathological effect. The model suggests that the interaction between neurotransmitters and hormones, as well as the social and environmental context (represented by the error ∈), may contribute to the risk of SI, and the sum of the influences of these factors can be used to predict risk dynamically over time. Conclusion: This model represents an advance in the understanding of suicidal ideation and in the development of prevention and intervention strategies. Continued research is essential to reduce the impact of suicide on society.

***Keywords*:** prevention, suicide, depression

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La neurobiología de la ideación suicida: una revisión integradora

RESUMEN

Introducción: La pregunta de investigación que guía este estudio es: ¿Cuáles son los principales mecanismos neurobiológicos asociados al suicidio y cómo pueden las intervenciones farmacológicas influir en estos mecanismos para reducir la ideación y el comportamiento suicida? El objetivo de esta revisión integrativa es sintetizar la evidencia sobre la relación entre los factores neurobiológicos y la ideación suicida, utilizando un enfoque de metaanálisis para evaluar cuantitativamente los datos disponibles. Metodología: La búsqueda se refinó para incluir únicamente artículos de libre acceso, totalizando sesenta y siete estudios, y estudios clínicos que abordaran el tema, resultando en siete artículos analizados. Los criterios de inclusión comprendieron la selección de estudios empíricos que evaluaran la relación entre factores neurobiológicos y la ideación suicida (IS), asegurando que la investigación se centrara en evidencia directa sobre el tema. Resultados y Discusión: Los déficits en el equilibrio de excitación-inhibición en la ínsula anterior se asocian con el riesgo de suicidio, lo cual es diferente de los síntomas de depresión. Por lo tanto, se sugiere que la IS puede tener bases neurobiológicas distintas a la depresión, lo que indica un efecto psicopatológico específico. El modelo sugiere que la interacción entre neurotransmisores y hormonas, así como el contexto social y ambiental (representado por el error ∈), puede contribuir al riesgo de IS, y la suma de las influencias de estos factores puede utilizarse para predecir el riesgo de manera dinámica a lo largo del tiempo. Conclusión: Este modelo representa un avance en la comprensión de la ideación suicida y en el desarrollo de estrategias de prevención e intervención. La investigación continua es esencial para reducir el impacto del suicidio en la sociedad.

***Palabras clave*:** prevención, suicidio, depresión

A neurobiologia da ideação suicida: uma revisão integrativa

RESUMEN

Introducción**:** La pregunta de investigación que guía este estudio es: ¿Cuáles son los principales mecanismos neurobiológicos asociados al suicidio y cómo pueden las intervenciones farmacológicas influir en estos mecanismos para reducir la ideación y el comportamiento suicida? El objetivo de esta revisión integrativa es sintetizar la evidencia sobre la relación entre los factores neurobiológicos y la ideación suicida, utilizando un enfoque de metaanálisis para evaluar cuantitativamente los datos disponibles. Metodología**:** La búsqueda se refinó para incluir únicamente artículos de libre acceso, totalizando sesenta y siete estudios, y estudios clínicos que abordaran el tema, resultando en siete artículos analizados. Los criterios de inclusión comprendieron la selección de estudios empíricos que evaluaran la relación entre factores neurobiológicos y la ideación suicida (IS), asegurando que la investigación se centrara en evidencia directa sobre el tema. Resultados y Discusión**:** Los déficits en el equilibrio de excitación-inhibición en la ínsula anterior se asocian con el riesgo de suicidio, lo cual es diferente de los síntomas de depresión. Por lo tanto, se sugiere que la IS puede tener bases neurobiológicas distintas a la depresión, lo que indica un efecto psicopatológico específico. El modelo sugiere que la interacción entre neurotransmisores y hormonas, así como el contexto social y ambiental (representado por el error ∈), puede contribuir al riesgo de IS, y la suma de las influencias de estos factores puede utilizarse para predecir el riesgo de manera dinámica a lo largo del tiempo. Conclusión**:** Este modelo representa un avance en la comprensión de la ideación suicida y en el desarrollo de estrategias de prevención e intervención. La investigación continua es esencial para reducir el impacto del suicidio en la sociedad.

Palabras clave: prevención, suicidio, depresión

INTRODUCTION

Suicide is a public health issue, responsible for millions of deaths annually. According to Alves et al. (2024), between 2011 and 2022, Brazil observed a 6% increase per year in suicide rates among young people and a 29% annual growth in reports of self-harm among people aged 10 to 24. The rates were higher than those recorded in the general population, where suicide rates increased by 3.7% per year and self-harm rates by 21% per year.

Thus, there was a need to better understand risk factors to predict symptoms and develop effective interventions for suicidal ideation (SI), a phenomenon influenced by biological, psychological, and social factors (Berardelli et al., 2020; O'Connor et al., 2016). The investigation of the mechanisms underlying this network led to the study of the neurobiology of suicide, focusing on the interaction between neurotransmitters and stress-related hormones, such as serotonin, dopamine, GABA and norepinephrine, which act on neural circuits responsible for emotional regulation and impulsivity (Abram et al., 2022; Genis-Mendoza et al., 2022).

In this context, the research question guiding this study is: What are the main neurobiological mechanisms associated with suicide, and how can pharmacological interventions influence these mechanisms to reduce suicidal ideation and behavior? The objective of this integrative review is to synthesize the evidence on the relationship between neurobiological factors and suicidal ideation, using a meta-analysis approach to quantitatively evaluate the available data. Studies that investigate the role of neurotransmitters, cortisol, and neural circuits in vulnerability to suicidal behavior will be analyzed.

This article seeks to integrate these findings, which highlight the importance of neurotransmitters in regulating mood and impulsivity, as well as the effects of cortisol on vulnerability to suicide, into a model that helps identify individuals at risk (Gilbert et al., 2020; Zhang et al., 2018). It is known that the construction of mathematical formulas allows the quantification of synaptic intensity and interactions between neurotransmitters, based on parameters such as the number of molecules released and receptor density, contributing to the understanding and intervention in SI (Bazenkov et al., 2018; Avery & Krichmar, 2017).

Brain Activity in Depression and Anxiety

Scientific studies have focused on the brain structures and circuits that engage in depression and anxiety. Brain activity in people with depression and anxiety involves a network of subcortical and cortical regions associated with emotional regulation, threat processing, and stress response.

The amygdala is a structure frequently associated with depression and anxiety, where it acts in the regulation of emotions and in the processing of threats. It has been shown that the amygdala presents increased activity in individuals with depression and anxiety, especially in response to negative stimuli. The elevation is related to the increase in symptoms of fear and rumination, which are factors that intensify anxiety. In patients who present only with depression, amygdala hyperactivity may be less prominent, indicating differences in the involvement of this structure between the two disorders (Hou et al., 2023).

The prefrontal cortex (PFC), particularly the dorsolateral prefrontal cortex (DLPFC), associated with cognitive control and emotional regulation, and the ventromedial prefrontal cortex (VMPFC), more closely related to the evaluation of rewards and punishments. Individuals with depression often exhibit reduced activity in the DLPFC, which contributes to difficulties in regulating negative emotions and increased emotional reactivity. Furthermore, dysfunction in the VMPFC can lead to excessive negative appraisals of experiences and thoughts, resulting in rumination and pessimism (Ionescu et al., 2013).

The anterior cingulate cortex (ACC) engages in the modulation of affect and behavior. Neuroimaging studies indicate that the ACC of individuals with depression often presents reduced functional connectivity with other cortical regions, associated with decreased gray matter volume. This alteration tends to be related to difficulty suppressing negative emotions and coping with stress. Decreased connectivity between the ACC and the PFC compromises cognitive control over emotional responses (Zhang et al., 2018).

The hippocampus, known for its role in memory and stress regulation, is commonly observed in patients with depression to have a reduction in volume attributed to chronic stress and excess cortisol. This change is related to memory deficits and difficulty processing current information, which can intensify feelings of hopelessness (Tozzi et al., 2024).

In contrast, connectivity between the PFC and the amygdala is present in patients with anxiety, presenting hyperconnectivity between both regions, which is related to constant vigilance and amplification of fear responses. In depression, connectivity is reduced, contributing to apathy, and reduced emotional reactivity (Hou et al., 2023).

Tozzi et al. (2024) propose a personalized approach to identify depression and anxiety biotypes, based on specific brain connectivity patterns. It is noted that the brain circuits involved vary between individuals, suggesting that personalized assessment of neural networks may be essential to develop more effective treatments.

Relationships between Stress, HPA Axis and Suicidal Ideation

The hypothalamic-pituitary-adrenal (HPA) axis regulates the stress response, and its alterations can impact mental health. Hyperactivity or hyporesponsiveness of the HPA axis is associated with psychiatric conditions, such as depression and anxiety, which may precede suicidal behavior.

For Genis-Mendoza et al. (2022), elevated cortisol levels are related to suicide risk, since individuals who attempted suicide had significantly higher cortisol levels compared to healthy controls. The results indicate that HPA axis dysregulation, reflected by elevated cortisol levels, may be a risk marker for suicidal behaviors. Furthermore, chronic stress is associated with mental health, and elevated cortisol can aggravate symptoms of depression and anxiety, increasing vulnerability to suicide.

However, a meta-study identified associations between cortisol levels and suicide attempts, but did not find a significant overall effect of suicidal group on cortisol levels. Such variation suggests that the relationship between cortisol and suicide is influenced by individual factors, such as psychiatric comorbidities and stress history (O'Connor et al., 2016).

Berardelli et al. (2020) highlight that HPA axis activity is linked to suicide risk, regardless of the presence of psychiatric conditions. It is therefore suggested that HPA axis dysregulation is a risk factor that manifests itself in different clinical contexts.

Furthermore, there is evidence of a blunted HPA axis response in individuals who have attempted suicide. Melhem et al. (2016) found that these individuals had reduced total cortisol production in response to stressors, in contrast to elevated cortisol levels observed in other contexts. This indicates altered HPA axis reactivity, suggesting that stress response patterns may vary among at-risk individuals.

Neurotransmitter Interaction and Implications in Suicidal Ideation

The interaction of neurotransmitters, such as serotonin, dopamine, and glutamate, influences neural circuits and regulates behaviors. Dysfunction of these systems may be related to psychiatric disorders, such as depression and anxiety, which are risk factors associated with suicidal behaviors.

Dopamine and serotonin are associated with impulsive-aggressive behaviors, and both, together with their respective receptors, are targets of treatments, since antagonists of these receptors have been shown to reduce such behaviors in humans. Brexpiprazole modulates the activity of the serotonergic and dopaminergic systems, functioning as a partial agonist at serotonin 5-HT1A and dopamine D2 receptors, in addition to acting as an antagonist at serotonin 5-HT2A receptors (Liebe et al., 2018).

Computational models have allowed the simulation of interactions between neurotransmitters by representing the activation of different neurotransmitter receptors and the impact on neural circuits (Gandolfi et al., 2021). Furthermore, personalized brain models are being developed in suicide research to integrate multimodal neuroimaging data and information on neurotransmitter receptors, allowing for more accurate prediction of individual responses to neurotransmitter activity. In this sense, neurobiological responses to stress and risk factors may vary between individuals, impacting susceptibility to SI, so personalization is necessary (Khan et al., 2022).

From this perspective, the interaction of neuromodulatory systems and the influence on brain function offers new perspectives for therapeutic interventions (Avery & Krichmar, 2017). Discrete modeling of neuronal interactions contributes to the analysis of the mechanisms underlying the neurobiology of suicide, focusing on non-synaptic interactions between neurons mediated by chemical agents (Bazenkov et al., 2018).

Hansen et al. (2022) created a three-dimensional normative atlas that maps neurotransmitter receptors and transporters in different systems to investigate interactions between neurotransmitters, brain structure and behavior, as well as to serve as a reference for future investigations on SI.

The dynamic coupling structure between neuronal and neurotransmitter systems needs to be considered (Kringelbach et al., 2020), since data-driven models that analyze neurotransmission at cerebellar synapses provide information about specific brain regions involved in SI (Masoli et al., 2022).

Serotonin

Serotonin release during an action potential is a process influenced by factors such as calcium dynamics and vesicle content. Studies indicate that a single action potential can result in the release of many serotonin molecules, often in the tens of thousands. This process occurs through exocytosis, in which serotonin-containing vesicles fuse with the plasma membrane. In pancreatic beta cells, for example, a single action potential can release approximately 13,310 serotonin molecules from the vesicles (Hatamie et al., 2021).

However, the release depends on calcium ions (Ca^{2+}), which function as intracellular messengers; increased neuronal activity elevates Ca^{2+} levels, facilitating the release of serotonin (Héry & Ternaux, 1980). In beta cells, each vesicle contains approximately 39,317 serotonin molecules, and approximately one-third of this amount is released during an exocytosis event (Hatamie et al., 2021).

Furthermore, in some neurons, a sequence of action potentials can sustain serotonin release for prolonged periods, demonstrating a feedback mechanism that increases the efficiency of release (Leon-Pinzon et al., 2014). Although these data demonstrate a significant release of serotonin, it is important to highlight that not all the serotonin stored in the vesicles is released, suggesting a specific regulation of this neurotransmitter dynamic.

Dysfunctions in serotonin dynamics, such as inadequate release or reduced action, contribute to impulsive behaviors and feelings of hopelessness. Low serotonin levels have been observed in individuals at risk for suicide, and the interaction with other neurotransmitters, such as dopamine and norepinephrine, influences impulsivity and decision-making. Changes in serotonin in response to stressors or trauma increase the risk of suicidal thoughts, linking neurochemical imbalances to the development of SI.

Dopamine

Through tonic and phasic firing of neurons, dopamine is released in the brain, being an important mediator for understanding neurological functions and disorders. Dopaminergic neurons in the ventral midbrain exhibit tonic firing, producing low levels of extrasynaptic dopamine, and phasic bursts that can saturate dopamine uptake transporters, resulting in high transient concentrations (Shashaank et al., 2023).

Such bursts contribute to presynaptic plasticity, through mechanisms involving synuclein proteins, which regulate short-term facilitation and long-term depression of dopamine release (Shashaank et al., 2023). In addition to axonal release, dopamine is also released in a somatodendritic manner, from dendrites rather than the soma, as evidenced by techniques such as dopafilme (Beyene, 2022).

In this sense, a meta-analysis indicated that individuals with MDD tend to present greater dopamine release in the brain, as evidenced by a significant effect size ($g = 0.49$, $p = 0.030$), although the dopamine synthesis capacity does not show significant differences between patients with MDD and healthy controls ($g = -0.21$, $p = 0.434$). Furthermore, a lower availability of the striatal dopamine transporter (STT) was observed in patients with MDD, suggesting alterations in the dopaminergic system that may contribute to the pathophysiology of the disorder (Mizuno et al., 2023).

GABA

Advanced techniques have been developed to measure gamma-aminobutyric acid (GABA) concentrations, each with advantages and limitations. One study showed that untreated human astrocytes maintained an intracellular GABA level of 2.32 mM and released GABA into the extracellular medium, reaching levels of 0.70 mM after one hour, with this concentration being maintained for the following hours. However, the study did not provide specific quantitative measures of GABA release in the brain, focusing instead on the mechanisms of release from cultured human astrocytes (Lee et al., 2011).

Another study, with healthy volunteers, demonstrated that in vivo GABA concentrations measured in the occipital lobe were found to be 1.01 ± 0.36 micromole/cm³ for men and 1.16 ± 0.43 micromole/cm³ for women. These values were obtained using J-resolved two-dimensional magnetic resonance spectroscopy, a technique that allows quantification of GABA while minimizing overlap with other resonance peaks. Thus, it is suggested that these concentrations are comparable to those reported by other methods, indicating the usefulness of this technique to assess GABA levels in the brain (Ke et al., 2000).

Norepinephrine

One study noted that norepinephrine release is often estimated using the isotope dilution technique. For example, in the forearm, norepinephrine spillover rates can be altered by interventions such as sodium nitroprusside infusion and lower body negative pressure. Such interventions resulted in changes in

norepinephrine spillover and onset rates, the latter of which is considered an indicator of changes in neuronal release (Rongen et al., 2000).

In patients with primary hypertension, norepinephrine release into the cerebrovascular circulation was measured, revealing a mean cerebral norepinephrine spillover of 220 pmole/min, representing 9.1% of the total norepinephrine release into plasma (Esler et al., 1988).

Neurotransmitter Reuptake/Degradation Time

The reuptake and degradation of neurotransmitters, such as the serotonin transporter (SERT) and the dopamine transporter (DAT), are fundamental processes for maintaining neurotransmitter balance in the brain. These processes involve synthesis and degradation rates that can be influenced by factors such as pharmacological interventions. SERT turnover involves both its synthesis and degradation. Studies with the irreversible inhibitor RTI-76 have provided data on the recovery half-life of SERT, which is approximately 3.4 days, indicating a slow turnover rate. This process follows a standard model of protein synthesis and degradation, with a degradation rate constant of 0.0077 h^{-1} in the hippocampus (Vicentic et al., 1999).

Another study suggests that the recovery half-life of SERT is 2 to 3 days, like other synaptic proteins. In the case of DAT, the degradation and synthesis rates have also been studied with similar methodologies. The recovery half-life of DAT in the rat striatum and *nucleus acumbens* is approximately 2 days, with full restoration of binding observed 7 days after inhibition (Kimmel et al., 2000).

Therefore, it is suggested that DAT turnover occurs more rapidly than SERT, reflecting differences in their functions and regulation in neurotransmission. In the clinical setting, changes in SERT binding potential have been associated with treatment outcomes for depression. Patients who remit from depressive symptoms under escitalopram treatment show a significant decrease in SERT binding potential, suggesting that SERT availability may be a marker for treatment efficacy (Kimmel et al., 2000).

In addition to the biological turnover of SERT and DAT, it is also important to consider the environmental degradation of related compounds, such as the antidepressant sertraline. Photocatalytic degradation using zinc oxide nanoparticles has been shown to degrade sertraline in aqueous solutions,

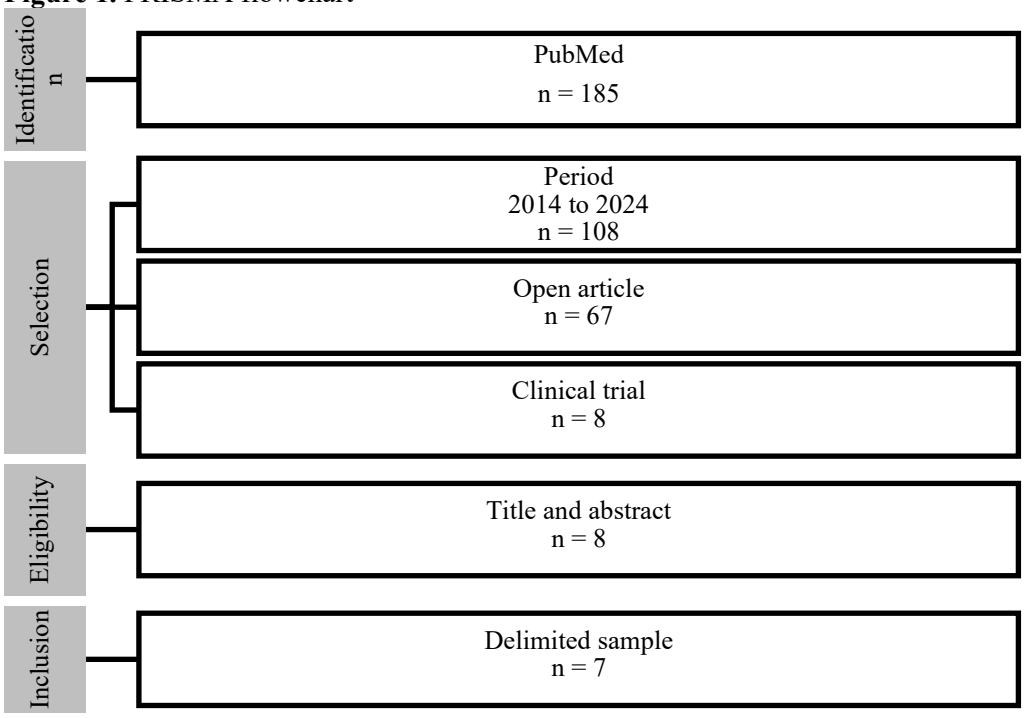
which may be useful in the environmental management of pharmaceutical pollutants (Mohamed et al., 2023).

METHODOLOGY

PubMed databases and other relevant repositories will be used to identify studies published between 2014 and 2024. The search will be conducted using controlled terms and keywords related to “suicidal ideation”, “neurotransmitters”, and “neurobiology”. The search strategy will include the use of *MeSH terms* such as “suicide”, "neurotransmitters", “neurobiology”, “depression”, “anxiety”, “neural circuits”. Additionally, if necessary, “suicidal ideation”, “biological factors”, “neurobiology of suicide” may be included.

The search was refined to include only free access articles, totaling sixty-seven studies, and clinical studies addressing the issue, resulting in seven articles analyzed. Inclusion criteria included the selection of empirical studies that evaluated the relationship between neurobiological factors and SI, ensuring that the research focused on direct evidence on the topic. Only studies published in English, Portuguese or Spanish were considered, ensuring data accessibility. In addition, only articles that contained quantitative data suitable for meta-analysis were included, aiming to obtain robust and significant results.

Figure 1. PRISMA flowchart



On the other hand, the exclusion criteria included the rejection of studies that did not present primary data or that focused on interventions without an analysis of neurobiological factors, since such studies did not directly contribute to the understanding of the relationship in question. Furthermore, systematic reviews or opinion articles that did not contain original data were also excluded, as they did not offer empirical evidence necessary for the proposed analysis.

RESULTS AND DISCUSSION

Myo-inositol levels are elevated in patients with psychotic depression in remission, indicating possible neurochemical alterations associated with the condition. Olanzapine, when administered continuously, can maintain creatinine levels in the dorsal anterior cingulate cortex (DACS), which suggests a stabilizing effect on brain regions involved in emotional and behavioral regulation (Tani et al., 2024).

However, pharmacological treatments such as brexpiprazole have also been shown to impact other areas, such as reducing activation of the right ventrolateral prefrontal cortex (dVLPFC) in patients with schizophrenia. Although brexpiprazole decreased activation in this region, improving stop signal reaction time (SRT), there was no worsening of psychiatric symptoms or increased impulsivity, which is promising for the control of impulsive behaviors (Van Erp et al., 2020).

In this context, ketamine emerges as a therapeutic alternative that, in a distinct way, acts quickly and effectively on glutamatergic neurotransmission, modulating neural circuits related to mood control and impulsivity, and may offer an additional effect in the treatment of refractory psychiatric disorders. The interaction between ketamine and the neurochemical mechanisms discussed, including the effect on regions such as the DACS and dVLPFC, may provide an integrated perspective on how different pharmacological agents influence brain activity and impulsive behavior.

The anterior insula is known to be active for SI, thus, ketamine can induce transient changes in the capacitance of the pyramidal cell membrane. Increased cortical excitability can improve SI through the effects of ketamine (Gilbert et al., 2020).

Ketamine models thalamic dysfunction in schizophrenia, in which N-methyl-D-aspartate receptor (NMDAR) signaling deficits contribute to the neurobiology of schizophrenia. Ketamine-induced dysconnectivity resembles thalamic dysconnectivity patterns in schizophrenia. Higher similarity

coefficients correlate with hallucination severity in schizophrenia. Pharmacological probes increase understanding of the pathophysiology of psychiatric conditions (Abram et al., 2022).

Ketamine normalizes frontostriatal connectivity in individuals with Treatment-Resistant Depressive Disorder (TRDD). Thus, it disrupts frontostriatal connectivity in healthy volunteers, and these effects occur independently of inflammatory processes. Ketamine has been shown to improve motivational symptoms in individuals with TRDD, and inflammatory markers do not influence the effects of ketamine (Mkrtchian et al., 2021).

However, ketamine alters emotional processing in Major Depressive Disorder (MDD), in which differential effects on task performance are observed between MDD and healthy volunteers. It is understood that emotional stimulus processing may serve as biomarkers for MDD, with participants with MDD demonstrating greater task accuracy than expected (Lundin et al., 2021).

Finally, ketamine acutely affects brain structures involved in attention processing, but the antidepressant effects of ketamine are affected by norepinephrine. However, genetic variations influence the physiological side effects of ketamine (Liebe et al., 2018).

Neurobiological Mechanisms

Psychotic Depression is a condition associated with a higher risk of suicide and mortality compared to depression without psychotic features. In patients with non-psychotic MDD, Magnetic Resonance Spectroscopy (MRS) studies have identified lower levels of choline, myo-inositol, and creatinine in the dorsolateral prefrontal cortex (DLPC) and ACC. When comparing the effects of the combination of sertraline with olanzapine and placebo in patients with Psychotic Depressive Disorder (PDD) in remission, a lower relapse rate was observed among those who continued with olanzapine. Neuroimaging analyses of the participants indicated changes in brain structure and functional connectivity, as well as in the levels of metabolites such as glutamate and N-acetyl aspartate. These results suggest that olanzapine treatment may influence the levels of certain metabolites, providing support for understanding the effects of antidepressants and antipsychotics on the symptoms and neurobiology of PDD (Tani et al., 2024).

Ketamine influences the *locus norepinephrine network coeruleus* (LC), providing elements to understand the neurobiological mechanisms related to depression and SI. In this sense, ketamine

administration generates changes in resting-state functional connectivity between the LC and thalamic nuclei, which may impact arousal regulation and emotional processing. The norepinephrine transporter (NET) genotype modulates the effects of ketamine on LC-thalamic connectivity, indicating that genetic factors influence treatment response and the mechanisms underlying SI. The findings suggest the involvement of norepinephrine pathways in the antidepressant effects of ketamine, connecting them to processes associated with suicidal thinking and behavior (Liebe et al., 2018).

Specific areas in the anterior insula associated with SI, differentiating it from other depressive symptoms. Thus, the anterior insula and anterior cingulate are part of the salience network, which engages in several psychiatric disorders. Dysregulation in signaling within the anterior insula and between it and other nodes of the salience network may affect suicide risk, suggesting a connection between this network and psychopathology. Furthermore, it has been observed that reduced connectivity in the glutamatergic receptor, of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type, between the insula and anterior cingulate, correlates with reduced depressive symptoms, indicating a relationship between neural connectivity and mood disorders (Gilbert et al., 2020).

Therapeutic Interventions

Gilbert et al. (2020) report that ketamine administration reduces the membrane capacitance of superficial pyramidal cells, the main sources of the magnetoencephalography (MEG) signal, suggesting a mechanism by which ketamine may influence SI and depressive symptoms. The effects on SI can manifest within a few hours and last up to a week, so they appear to act independently of the antidepressant effect of the substance. In addition, ketamine can induce spontaneous gamma synchrony in cortical networks, which contributes to the balance between excitation and inhibition in the brain.

From this perspective, ketamine is also considered in individuals with treatment-resistant MDD. To this end, it reduces depressive symptoms and SI within 24 hours of administration. The effects of the drug are associated with increased glutamate, which activates AMPA receptors, promoting synaptogenesis and synaptic potentiation. The rapid action of ketamine led to its approval for use in adults with treatment-resistant depression by regulatory authorities in the United States (Lundin et al., 2021).

Corroborating previous results, Liebe et al. (2018) emphasize that ketamine administration is indicated for the reduction of SI, acting on the modulation of neurotransmitter systems, especially norepinephrine.

The impact of a single dose of racemic ketamine on the *locus coeruleus* (LC) and its functional connectivity provides information on the antidepressant effects of the substance. The results indicate that changes in resting-state functional connectivity after ketamine administration contribute to the therapeutic effects in depression and IS.

On the other hand, treatment with brexpiprazole was associated with decreased activation of the VLPFC and improved RSP time, indicating an effect on the control of impulsive behaviors. Thus, no negative changes were observed in psychiatric symptoms or in the general functioning of treated patients, suggesting safety and tolerability of brexpiprazole. When evaluating its efficacy in reducing impulsivity, the results indicate that brexpiprazole may indirectly contribute to the prevention of SI and related behaviors in patients with schizophrenia (Van Erp et al., 2020).

Psychopathological Effects

Deficits in the excitation-inhibition balance in the anterior insula are associated with suicide risk, which is different from symptoms of depression. Therefore, it is suggested that SI may have distinct neurobiological underpinnings from depression, indicating a specific psychopathological effect. The findings indicate that ketamine treatment causes changes in the capacitance of the pyramidal cell membrane within the salience network, which is relevant for salience detection and switching between large-scale networks. This highlights the importance of gamma power as a biomarker for measuring synaptic homeostasis and dysregulation in psychiatric conditions, including those associated with SI (Gilbert et al., 2020).

Ketamine affects the brain's reward circuitry, including the striatum and VFP, modifying the functional connectivity between these regions, which are important for motivational behavior. In people with TDRT, ketamine increased functional connectivity within this circuit, while in healthy volunteers, the effect was the opposite. It is also suggested that inflammation may influence this process, since ketamine can act on dopaminergic function and the inflammatory response, affecting the functioning of the frontostriatal circuitry and motivational symptoms (Mkrtchian et al., 2021).

Finally, Liebe et al. (2018) identified that ketamine, by inhibiting the norepinephrine transporter, alters the concentration of this neurotransmitter in the synaptic clefts. This effect affects the functions of the *locus coeruleus* (LC), responsible for the release of norepinephrine in the brain, which participates in

the regulation of attention and vigilance. Ketamine administration modifies functional connectivity in brain networks, such as the alerting network, leading to a more distracted state of arousal. Furthermore, the genotype of the norepinephrine transporter influences the brain's response to ketamine, implying an interaction between the acute effects of the substance and the regulation of norepinephrine in the brain.

Mathematics Related to Suicidal Ideation

The neurochemical processes involving neurotransmitters such as serotonin, dopamine, GABA, and norepinephrine in the investigation of SI and the risk of tragic behaviors are understood. In this way, the interaction between these neurotransmitters, synaptic intensities and the mechanisms of synthesis, release and reuptake form the basis for modeling the neurophysiological processes that influence behavior.

In this sense, the formulas presented below seek to integrate such complexity, using parameters such as the quantity of neurotransmitters released, receptor density and reuptake time to estimate synaptic intensity and the correlation between neurotransmitters over time. The relationship between these intensities and factors such as cortisol, a hormone associated with stress, allows the construction of predictive models for the risk of SI, considering the biological aspects and environmental contexts that affect human behavior. The combination of these elements offers a more integrated view of the neurobiology of SI, contributing to the development of intervention strategies.

Basic Synaptic Strength Formula

This describes the intensity of synaptic signaling, that is, how much a neurotransmitter impacts communication between neurons. Thus, we have that the number of neurotransmitter molecules released ($N_{released}$) affects synapses during the transmission of a signal, as discussed in studies on the release of serotonin, dopamine, and other neurotransmitters. The density of receptors on the postsynaptic membrane ($R_{reception}$) determines the ability of the postsynaptic cell to respond to the neurotransmitter, and the availability of receptors, as shown in the variations in dopamine and serotonin, affects the effectiveness of signaling.

Furthermore, the receptor activation potential ($P_{potencial}$) refers to how well receptors can activate responses in the postsynaptic cell when stimulated, which can be influenced by factors such as the concentration of the neurotransmitter. Finally, the time it takes for the neurotransmitter to be reuptake

or degraded ($T_{reuptake}$) regulates the duration of action at the synapse, with reuptake being a critical process, as evidenced in serotonin and dopamine, which influences the levels of neurotransmitter available and, consequently, the intensity of signaling.

We have:

$$I_{synapse} = \frac{(N_{released} \times R_{reception} \times P_{potencial})}{T_{reuptake}}$$

Where:

$N_{released}$ = number of neurotransmitter molecules released.

$R_{reception}$ = density of receptors on the postsynaptic membrane.

$P_{potencial}$ = activation potential of receptors.

$T_{reuptake}$ = time of reuptake or degradation of the neurotransmitter.

This formula describes the impact of neurotransmitter on synaptic signaling and suggests that the interaction between these factors may directly influence behavior, including the risk of SI, by affecting how nerve signals are transmitted and interpreted.

Correlation between Neurotransmitters

The interaction between different neurotransmitters and the joint influence on the synaptic intensity of each one over time is seen in a way that delimits the relative contribution of each neurotransmitter (dopamine, GABA and norepinephrine) to serotonin signaling , represented by $\alpha_1, \alpha_2, \alpha_3$, respectively. Furthermore, the synaptic strength of serotonin ($I_{serotonine}(t)$), at a given time t, is influenced by the interaction with other neurotransmitters. Thus, the synaptic strengths of dopamine ($I_{dopamine}(t)$), GABA ($I_{GABA}(t)$) and noradrenalin ($I_{noradrenalin}(t)$) over time, as discussed, have a significant impact on the regulation of mood, emotions and behaviors, and the interaction between them can affect the predisposition to depressive states or SI .

We have:

$$I_{serotonine}(t) = \alpha_1 \cdot I_{dopamine}(t) + \alpha_2 \cdot I_{GABA}(t) + \alpha_3 \cdot I_{noradrenalin}(t)$$

Where:

$\alpha_1, \alpha_2, \alpha_3$ = coefficients that represent the mutual influence between neurotransmitters.

$I_{serotonine}(t)$, $I_{dopamine}(t)$, $I_{GABA}(t)$, $I_{noradrenalin}(t)$ = synaptic intensities of each neurotransmitter over time.

The inclusion of coefficients $(\alpha_1, \alpha_2, \alpha_3)$ allows us to model how changes in one neurotransmitter can affect others, so that variations in dopamine, GABA and norepinephrine can modulate serotonin activity and, consequently, the propensity to depressive states or SI .

Risk Model for Tragic Behaviors

To estimate the risk of tragic behaviors, such as SI, based on the interaction between neurotransmitters and hormones, the level of risk ($R(t)$)of tragic behaviors at a given time) is represented as a function of time and the synaptic intensities of the neurotransmitters.

In addition, the coefficients $(\gamma_1, \gamma_2, \gamma_3)$ reflect the specific contribution of serotonin, dopamine, and cortisol to the risk of tragic behaviors. These variables are adjusted to understand how each neurotransmitter or hormone affects risk, based on evidence that serotonin and dopamine play critical roles in emotional regulation, while cortisol, a stress-related hormone, may increase vulnerability to such behaviors.

The synaptic intensities of serotonin ($I_{serotonine}(t)$) and dopamine ($I_{dopamine}(t)$) at time t are determinants for the risk of SI. As discussed, they act on emotional and behavioral states. Therefore, the concentration of cortisol ($C_{cortisol}(t)$) at time t reflects that the increase in cortisol, associated with stress, may be related to depressive states and a greater risk of SI.

To include environmental, social, or other non-directly controllable factors in mathematical modeling, the error or noise factor ($\in$) is important to capture variability in results that cannot be explained by neurotransmitters and hormones alone.

We have:

$$R(t) = \left(\gamma_1 \cdot I_{serotonine}(t)\right) + \left(\gamma_2 \cdot I_{dopamine}(t)\right) + (\gamma_3 \cdot C_{cortisol}(t)) + \in$$

Where:

$R(t)$= level of risk at a given time.

$\gamma_1, \gamma_1, \gamma_3$= parameters that represent the contribution of each neurotransmitter or hormone.

$I_{serotonine}(t)$, $I_{dopamine}(t)$ = synaptic intensities of serotonin and dopamine.

$C_{cortisol}(t)$= cortisol concentration.

$\in$ = error factor or external noise (environmental, social factors).

The model suggests that the interaction between neurotransmitters and hormones, as well as the social and environmental context (represented by the error $\in$), may contribute to the risk of SI, and the sum of the influences of these factors can be used to predict risk dynamically over time.

Risk Model for Tragic Behaviors: Critical Analysis and Perspectives

This article presents a mathematical model that seeks to estimate the risk of tragic behaviors, focusing on SI. In this sense, the model considers the dynamic interaction between biological factors, such as the neurotransmitters serotonin and dopamine, and the stress hormone cortisol, in addition to recognizing the influence of external factors, represented in the model as an error factor.

In this way, the model stands out for integrating distinct levels of analysis, combining biological factors (neurotransmitters and hormones), psychological factors (mood and emotions) and social factors (represented by the error factor). In this holistic perspective, the aim is to contribute to a more complete understanding of SI, going beyond reductionist views that focus only on a single aspect.

Therefore, the inclusion of multiple components and their interactions highlight the complexity of SI, demonstrating that this phenomenon cannot be explained by a single cause, but rather by the convergence of several factors. Thus, this perspective demystifies the idea that suicide is a simple or easily predictable problem.

Therefore, despite its limitations, the model serves as an important guide for future research. By highlighting the interaction between neurotransmitters, hormones, and contextual factors, it encourages the search for more accurate and effective biomarkers to identify individuals at risk.

Regarding the limitations of the model, one of the main ones is the difficulty of accurately measuring the components in real time. Obtaining reliable measurements of the synaptic activity of neurotransmitters and the precise influence of each factor in the individual context still represents a significant challenge for research.

The next steps in the research aim to encompass other individual variables in the response to neurotransmitters, hormones, and environmental factors, since the model, in its current form, cannot do so. Genetic factors, life experiences, personality traits and other individual aspects influence the way

each person responds to these elements, making universal application of the model a challenge. Finally, like all models, this one offers a simplified representation of a complex phenomenon.

CONCLUSIONS

This article discusses the importance of a multidimensional approach in the analysis of SI, showing that the interaction between neurotransmitters such as serotonin, dopamine, GABA, and norepinephrine has a direct impact on impulsive behaviors and emotional processing. Models that consider the influence of cortisol and external factors, such as the social environment and life history, offer a detailed view of the risk and protective factors related to suicide. However, challenges remain, such as the difficulty in accurately measuring these components in real time and adapting models to consider genetic variations and specific environmental influences.

Advances in neuroimaging techniques and the use of biomarkers to assess SI offer possibilities for the prevention and treatment of suicidal behavior. Models such as the one presented in this study, which highlight the interaction between biological and psychological factors, contribute to an understanding of SI, recognizing the complexity of the neurobiological mechanisms involved. However, continued research is essential to improve the ability to identify individuals at risk and develop interventions that consider the interactions between neurobiological and psychosocial factors.

Thus, this article presented a mathematical model that integrates biological, psychological, and social factors to estimate the risk of SI. Considering the interaction between neurotransmitters, such as serotonin and dopamine, the hormone cortisol, and contextual factors, the model seeks to contribute to the understanding of this phenomenon. Despite the advances, the model has limitations, especially regarding obtaining accurate and real-time measurements of its components. Future research is needed to validate the model in different populations and improve its predictive capacity. This model represents an advance in the understanding of suicidal ideation and in the development of prevention and intervention strategies. Continued research is essential to reduce the impact of suicide on society.

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