Effects of stress on endophenotypes of suicide across species: A role for ketamine in risk mitigation

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ABSTRACT

Suicide is a leading cause of death and morbidity worldwide, yet few interventions are available to mitigate its risk. Barriers to effective treatments involve a limited understanding of factors that predict the onset of suicidal thoughts and behaviors. In the context of suicide risk, stress is a precipitating factor that is largely overlooked in the literature. Indeed, the pathophysiology of stress and suicide are heavily interconnected, underscoring the need to target the stress system in suicide prevention. In this review, we integrate findings from the preclinical and clinical literature that links stress and suicide. We focus specifically on the effects of stress on underlying biological functions and processes associated with suicide, allowing for the review of research using animal models. Owing to the rapid anti-suicidal effects of (*R,S*)-ketamine, we discuss its ability to modulate various stress-related endophenotypes of suicide, as well as its potential role in preventing suicide in those with a history of chronic life stress (e.g., early life adversity). We highlight future research directions that could advance our understanding of stress-related effects on suicide risk, advocating a dimensional, endophenotype approach to suicide research.

1. Introduction

Suicide is a leading cause of death worldwide and a major threat to public health. In 2016, almost 10 million American adults reported suicidal thoughts, and 1.3 million people attempted suicide (Substance Abuse & Mental Health Services Administration, 2017). Despite increasing rates of suicide (Stone et al., 2018), few interventions have been established to mitigate its risk. Indeed, a 10-year systematic review revealed very little progress in the pursuit of effective suicide prevention strategies (Zalsman et al., 2016). Barriers to effective interventions include our limited understanding of the risk factors or endophenotypes—broadly defined as quantifiable measures of underlying biological processes and functions—that contribute to suicidal thoughts and behaviors. In this context, stress has a profound impact on several endophenotypes of suicide in humans and animals, necessitating careful consideration of its role as a precipitating factor for suicide risk. Although chronic stress has been well characterized as a robust predictor of major depressive episodes (e.g., Kendler et al., 1999), few articles have reviewed its connections with the pathophysiology of suicidal behavior.

Overlapping mechanisms between the pathophysiology of stress and candidate endophenotypes of suicide (see Table 1) underscore the importance of targeting the stress system in suicide prevention. Presently, however, insights into the neurobiological underpinnings of suicide may be hindered by the inability to successfully model suicidal behaviors in animals. In fact, many dimensions involved in the act of killing oneself cannot be ascertained using animal models (e.g., deliberate intent, conscious planning, or awareness of the definitive consequences of the act). An endophenotype approach to suicide research—that is, the study of disruptions in underlying processes linked to suicide— can incorporate animal research to better understand the factors that contribute to its onset. Towards this end, animal models could be used to understand distinct components implicated in suicidal behaviors.

This review integrates findings from the preclinical and clinical literature that link chronic stress exposure and suicide. Various biological and behavioral consequences of chronic stress that may contribute to suicidal behaviors are reviewed from a translational neuroscience perspective. Specifically, we highlight the effects of stress on several biomarkers associated with suicide in humans, reviewing how these

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Table 1
Summary of overlapping mechanisms associated with suicide and stress, as well as therapeutic effects of ketamine within each endophenotype.

Endophenotype	Suicide	Chronic stress	Effects of Ketamine
HPA dysregulation	• Adrenal hypertrophy in suicide decedents (Szigethy et al., 1994) • GR downregulation and DST non-suppression linked to death by suicide (Coryell and Schlesser, 2001; Pandey et al., 2013; Pérez-Ortiz et al., 2013) • Lower baseline CORT (Melhem et al., 2016) and blunted CORT reactivity (O'Connor et al., 2017) in suicide attempters • Reduced hippocampal GR expression in suicide decedents with a history of abuse (Labonte et al., 2012)	*Chronically stressed animals:* • Sustained adrenal hypertrophy (Mizoguchi et al., 2008; Ulrich-Lai et al., 2006) • DST non-suppression (Mizoguchi et al., 2001) • Reduced basal CORT levels and blunted stress reactivity (Lovallo et al., 2012; Miller et al., 2007) *ELS-exposed animals and humans:* • Blunted HPA activity in adulthood, indexed by reduced CORT and ACTH responses (Bunea et al., 2017; O'Connor et al., 2018; Perry et al., 2019), with exceptions (e.g., Heim et al., 2000)	• Rapid reversal of DST non-suppression in humans that coincided with improved depressive symptoms (Ostroff and Kothari, 2015) • Normalized CORT levels and restored GR expression in the hippocampus of chronically stressed mice (Wang et al., 2019) • Acutely but significantly increased salivary and plasma CORT secretion within an hour of infusion (Hergovich et al., 2001; Khalili-Mahani et al., 2015)
Inflammation	• Elevated CRP levels in people with suicidal tendencies (i.e., SI, suicide attempts, or death by suicide; Chen et al., 2020) • Depressed individuals with high CRP were twice as likely to attempt suicide (Oh et al., 2020) • Higher plasma kynurenine levels in MDD patients with a history of suicide attempts (Sublette et al., 2011) • Elevated CSF quinolinic acid in suicide attempters that decreased within six months of the attempt (Erhardt et al., 2013) • Plasma IL-6 and IL-1B were robustly associated with suicide (Black and Miller, 2015) • IL-6 exerted largest impact on suicide risk compared to other inflammatory markers (Thomas et al., 2021)	*Chronically stressed animals:* • Elevated kynurenine and quinolinic acid levels in plasma and brain (Chen et al., 2013; Fuertig et al., 2016) • Quinolinic acid inhibitor rescued depressive-like behaviors (Chen et al., 2013) *Humans and rodents:* • Low-grade systemic inflammation following chronic stress (e.g., elevated plasma CRP levels) (Clougherty et al., 2010; Gouin et al., 2012, 2016) • Plasma IL-6 levels elevated after chronic stress (Carpenter et al., 2010; Himmerich et al., 2013; Kiecolt-Glaser et al., 2003) • Immunological challenges that elevate inflammatory markers produced depressive-like behaviors (DellaGioia and Hannestad, 2010; Depino, 2015)	• Suppressed proinflammatory cytokine production and CRP levels without impacting anti-inflammatory cytokine levels (Kawasaki et al., 1999; Takenaka et al., 1994) • Disrupted the kynurenine pathway, suppressing the release of proinflammatory cytokines relevant to suicide risk (e.g., TNF-α, IL-6, IL-1β; Kopra et al., 2021) • Reduced serum proinflammatory cytokines, suppressed hippocampal microglial activation, and downregulated the proinflammatory cytokine-promoting TLR4/p38 pathway in the hippocampus (Tan et al., 2017) • Attenuated hippocampal IDO and the KYN/TRP ratio (Wang et al., 2015) • Antidepressant effect predicted by its modulation of IL-6 (Yang et al., 2015)
Serotonin	• Decreased 5-HIAA expression in CSF of suicide attempters (Hoertel et al., 2015) • Reduced DRN neurons expressing SERT mRNA in decedents (Arango et al., 2001) • SERT binding selectively reduced in the ventral PFC (Mann et al., 2000; Underwood et al., 2012) and dorsolateral PFC (Austin et al., 2002) of decedents • Upregulated 5-HT2A in the PFC of decedents (Stanley and Mann, 1983; Arora and Meltzer, 1989; Arango et al., 1990; Pandey et al., 2002)	*Chronically stressed animals:* • Decreased 5-HIAA (Ahmad et al., 2010) and increased 5-HT2A expression (Dwivedi et al., 2005) in the frontal cortex • Elevated 5-HT2A expression in the frontal cortex of learned helplessness rats (Dwivedi et al., 2005) • Decreased 5-HT levels in the PFC (Liu et al., 2013), with exceptions (Venzala et al., 2013; Xu et al., 2016) *ELS-exposed animals:* • Lower CSF 5-HIAA concentrations that persisted into adulthood (Higley et al., 1996; Shannon et al., 1995) • Reduced SERT mRNA expression in the adult DRN (Bravo et al., 2014)	• Increased extracellular serotonin (Lindefors et al., 1997) • Inhibited serotonin clearance via SERT and the PMAT (Bowman et al., 2020) • Promoted 5-HT synthesis by suppressing the IDO/kynurenine pathway (Capuron et al., 2002) • Increased medial PFC serotonin levels, which is directly associated with antidepressant-like behaviors in animals (Pham et al., 2017)
Despair/ helplessness	• Depressed mood predicted suicidal behaviors (Hall et al., 1999; Large et al., 2011) • Suicide attempters significantly more likely to report hopelessness and helplessness (Furr et al., 2001) • Learned helplessness predicted suicidality (SI, intention, and attempts) (Aslam and Bano, 2019; Seyakhane et al., 2021)	*Chronically stressed animals:* • Behavioral despair and learned helplessness induced by chronic stress (e.g., Gonzalez et al., 1990; Molina et al., 1994; Prince and Anisman, 1984) *Repeated life stress in humans:* • Potent predictor of hopelessness (Bonner and Rich, 1991; Dixon et al., 1993; Lew et al., 2019; Violanti et al., 2016)	• Reduced self-reported hopelessness within 40 min of infusion (Burger et al., 2016; DiazGranados et al., 2010) • Reduced stress-induced immobility in forced swim (Fitzgerald et al., 2019; Wang et al., 2019) and tail suspension (Koike et al., 2011) tests in rats
Anhedonia	• State anhedonia associated with acute suicide risk (i.e., within one year) (Fawcett et al., 1990; Yang et al., 2020a) • Reduced pleasure capacity associated with acute SI and motivational deficits associated with longer-term SI (Yang et al., 2020b) • Loss of interest robustly predicted SI (Winer et al., 2014) and lifetime suicide attempts (Sagud et al., 2020)	*Chronically stressed animals:* • Reductions in reward learning (Der-Avakian et al., 2017; Lamontagne et al., 2018) *Repeated life stress in humans:* • Correlated positively with state anhedonia in adolescents (Yang et al., 2020d) • Moderated relationship between state anhedonia and SI (Yang et al., 2020d) • Loss of interest in trauma-exposed individuals who attempted suicide (Legarreta et al., 2015) • Childhood maltreatment associated with reduced striatal response to reward cues (Dillon et al.,	• Produced anti-anhedonic effects that contributed to reductions in suicidal thoughts independently of other depressive symptoms (Ballard et al., 2017) • Anti-inflammatory properties promoted mesolimbic dopamine synthesis by inhibiting kynurenine-induced oxidative stress (Stanton et al., 2019) • Improved anticipatory anhedonia by modulating affective networks, for example, by reversing over-activity of the subgenual ACC (Alexander et al., 2019) • Rapidly restored stress-induced reward dysfunction while restoring synaptic proteins, spine number, and the frequency/amplitude of synaptic

Table 1 (*continued*)

Endophenotype	Suicide	Chronic stress	Effects of Ketamine
		2009; Birn et al., 2017; Hanson et al., 2015) as well as blunted reward learning (Dennison et al., 2019; Pechtel et al., 2013) in adulthood	currents in layer V PFC pyramidal neurons (Li et al., 2011) • Attenuated exaggerated neuronal burst firing in the lateral habenula (Yang et al., 2018)
Sleep disturbances	• Sleep disturbances increased risk for SI, suicide attempts, and death (Bernert et al., 2015; Liu et al., 2020) • Nocturnal cognitive hyperarousal predicted first-time SI, and suicide risk was highest when hyperarousal co-occurred with insomnia (Kalmbach et al., 2021)	*ELS-exposed humans:* • Childhood adversity strongly associated with sleep disorders in adulthood (Alter et al., 2021; Bader et al., 2007; Kajeepeta et al., 2015) • Hyperarousal was prevalent, perhaps reflecting overactive preparedness (Barlow, 2004; Palagini et al., 2015)	• Reduced SI by reducing insomnia, sleep restlessness, early morning waking, and nocturnal wakefulness (Rodrigues et al., 2021; Vande Voort et al., 2016) • Increased plasma BDNF levels proportionally to enhanced slow-wave activity during non-REM sleep in those with TRD (Duncan et al., 2017)
Impulsivity	• Impulsive behavior predicted suicidality, particularly among suicide attempters (Brent et al., 2003; Mann et al., 2000) • Trait impulsivity linked to higher risk for suicide attempt (Mann et al., 2000) • Trait impulsivity predicted long-term suicide risk; state impulsivity predicted proximal risk for self-harm or suicide (Liu et al., 2017)	*Chronically stressed animals:* • Long-term deficits in impulse control (Comeau et al., 2014; Sanchís-Ollé et al., 2019) *ELS-exposed humans:* • High impulsivity and suicide attempts (Brodsky et al., 2001) • Suicide decedents with impulsive traits were more likely to have a history of childhood abuse and a stressful life event up to a week prior to death (Zouk et al., 2006)	• Modulated inhibitory control networks in those with TRD, which predicts antidepressant outcomes (Sahib et al., 2020) • Reduced impulsive aggression in socially isolated mice (Chang et al., 2018) • Improved impulse control in a serial choice task 24 h after administration (Davis-Reyes et al., 2021)

Abbreviations: ACC: anterior cingulate cortex; ACTH: adrenocorticotropic hormone; BDNF: brain-derived neurotrophic factor; CORT: cortisol or corticosterone; CRP: C-reactive protein; DRN: dorsal raphe nucleus; DST: dexamethasone suppression test; ELS: early life stress; GR: glucocorticoid receptor; HPA axis: hypothalamic-pituitary-adrenal axis; IDO: indoleamine 2,3-dioxygenase; IL-6: interleukin-6; IL-1β: interleukin-1beta; KYN/TRP: kynurenine/tryptophan; MDD: major depressive disorder; PFC: prefrontal cortex; PMAT: plasma membrane monoamine transporter; SERT: serotonin transporter; SI: suicidal ideation; TNF-α: tumor necrosis factor alpha; TRD: treatment-resistant depression.

systems are understood from a mechanistic level in animals. We then propose a potential role for the glutamatergic modulator racemic (*R,S*)-ketamine (hereafter referred to as ketamine) in ameliorating stress-related impacts on each endophenotype discussed in the review. Although others have shown long-term benefits of traditional antidepressants in restoring chronic stress pathology (e.g., selective serotonin reuptake inhibitors (SSRIs); Surget et al., 2011), these treatments are associated with significant delays in treatment response (weeks to months). Lithium, a commonly used anti-suicidal agent, counteracts some stress-related pathologies associated with suicide (Beurel and Jope, 2014), but similarly requires long-term administration to achieve these effects (Tondo and Baldessarini, 2018). This delay in treatment response impedes the successful deterrence of imminent suicidal intentions or behaviors, necessitating alternative agents, like ketamine, that potentially offer rapid therapeutic benefits. We offer a timely and novel discussion of recent findings from human and animal research demonstrating rapid-acting mechanisms via which ketamine effectively rescues stress-induced pathologies linked to suicide risk. We also discuss important controversies underlying ketamine's effects in this context.

Throughout the review, sex differences and developmental trajectories that promote maladaptive responses to stress are highlighted. Finally, the review discusses the benefits of a dimensional, Research Domain Criteria (RDoC)-focused approach to studying the impact of stress on suicide risk.

2. Neuroendocrinology of stress

The biological stress response is characterized by interconnecting systems that counteract threats to homeostasis. Neuroendocrine responses to these threats, which are triggered by environmental stressors, are primarily regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Briefly, stressors activate the HPA axis, prompting a biological cascade that results in adrenal cortical release of glucocorticoid hormones (i.e., corticosterone in rodents; cortisol in humans; henceforth, CORT). CORT plays a critical role in regulating the sympathetic "fight-or-flight" response, promoting proinflammatory cytokine release (Pariante and Lightman, 2008). The immune response is an evolutionarily

adaptive sequela to acute stress, given the increased likelihood of physical injury (and, thus, infection) following an encounter with a threat (Avitsur et al., 2002). In the short term, the stress response promotes survival while mobilizing and allocating bodily resources needed to respond to acute threat (McEwen and Seeman, 1999). Once the threat, or stressor, is no longer present, glucocorticoid and cytokine release is attenuated by negative feedback inhibition, owing to CORT's affinity to glucocorticoid receptors (GRs), primarily in the hippocampus (Pariante and Lightman, 2008).

The stress response becomes maladaptive when stressors persist for long periods of time (i.e., chronic stress), resulting in sustained activation of the HPA axis. Prolonged hyperresponsiveness of the HPA axis begets glucocorticoid insufficiency, characterized by compensatory GR downregulation (Paskitti et al., 2000) and blunted GR-mediated signal transduction (Mizoguchi et al., 2001) in the hippocampus. Due to blunted negative feedback regulation of the HPA axis, aberrant CORT and cytokine signaling ensues. These maladaptive responses characterize the pathophysiology of several mental disorders, including depression, highlighting the impact of chronic stress in psychopathology. The following sections review the interconnections and overlapping mechanisms between suicide and chronic stress pathophysiology and note differential effects across development.

3. Stress as a risk factor for suicide

3.1. HPA dysregulation

HPA axis abnormalities have been identified as robust predictors of suicide. For instance, adrenal hypertrophy was reported in autopsies of suicide decedents but not in sudden death controls (Szigethy et al., 1994), implicating HPA hyperactivity in the pathophysiology of suicide. In animals, chronic stress similarly produced adrenal hypertrophy (as indexed by elevated adrenal gland weight) (Mizoguchi et al., 2001; Ulrich-Lai et al., 2006). Due to sustained HPA hyperactivity, hypertrophy can persist long after the termination of stress (Mizoguchi et al., 2008). While adrenal enlargement associated with suicide deaths does not necessarily inform causal attributions between stress and suicide,

adrenal hypertrophy is typically associated with HPA dysregulation, which predicts suicidal behaviors (Coryell and Schlesser, 2001). In this context, various conditions associated with elevated suicide risk (e.g., mood disorders, schizophrenia) are also associated with HPA dysregulation marked by reduced hippocampal GR expression. GR downregulation is a compensatory response to HPA hyperactivity (McGowan et al., 2009), whereby prolonged elevations in adrenal CORT secretion lead to GR downregulation, diminishing the efficacy of negative feedback systems that regulate HPA activity. Postmortem studies found that GR expression was substantially reduced throughout the brains of those who died by suicide (Pandey et al., 2013; Pérez-Ortiz et al., 2013), implicating a link between suicide and impaired negative feedback regulation in the HPA axis. Towards this end, non-suppression in the dexamethasone suppression test (DST), a biomarker of impaired GR functioning, was found in chronically stressed animals (Mizoguchi et al., 2001) and has also been linked to a 14-fold increase in the probability of eventual suicide in humans (Coryell and Schlesser, 2001). Indeed, among those with major depressive disorder (MDD), DST non-suppressors were more likely to be hospitalized or die by suicide relative to suppressors, with significantly more suicidal events (i.e., suicide attempts, hospitalizations, and deaths) among non-suppressors (Yerevanian et al., 2004). Drugs that block GRs (e.g., mifepristone) could potentially mitigate suicide risk, owing to their ability to upregulate GRs and acutely restrain hypercortisolism through enhanced HPA negative feedback (McQuade and Young, 2000). Although this has yet to be directly studied in the context of suicide, mifepristone rapidly restores several chronic stress-induced afflictions in animals (e.g., hippocampal neurogenesis; Oomen et al., 2007).

HPA abnormalities have been differentially characterized in suicidal ideation (SI) versus suicide attempt, particularly with respect to CORT transmission. Those with high levels of SI have tended to show enhanced HPA reactivity, marked by elevated CORT output (Giletta et al., 2015; Shalev et al., 2019). Compared to those with continuous periods of SI, those with brief and fleeting SI showed HPA hyper-responsiveness (i.e., greater CORT response) to an acute social stressor (Rizk et al., 2018). In contrast, those who attempted suicide had substantially lower baseline CORT (Melhem et al., 2016), with levels reaching their lowest point within one year of the attempt (O'Connor et al., 2017). This divergence implicates dynamic alterations in CORT output that appear at various stages along the continuum of suicide risk, with lower transmission occurring more proximal to an attempt. Hair CORT concentrations, which capture CORT levels in the prior two to three months, were lower in suicide attempters than in those with SI (Melhem et al., 2017), further highlighting the possibility that blunted CORT transmission precedes suicide attempt. Critically, low CORT output is also a long-term consequence of chronic stress. Although chronic stress reliably *increases* CORT transmission during and immediately after exposure (i.e., hypercortisolism), HPA activity becomes suppressed over time, resulting in stark *reductions* in basal CORT levels (i.e., hypocortisolism) (Miller et al., 2007). Put differently, CORT secretion decreases with time elapsed since chronic stress exposure. The negative correlation between the time since adversity and HPA activity can be explained by a compensatory self-adjustment process intended to counteract the persistently elevated CORT levels accrued during stress exposure (Fries et al., 2005). Essentially, hypocortisolism reflects an "over-adjustment" that occurs in pursuit of homeostatic restoration after stress (Fries et al., 2005). The process, which likely involves increased sensitivity to the negative feedback of glucocorticoids within the HPA axis (Heim et al., 2000), is therefore a failed attempt to protect the organism from the deleterious effects of hypercortisolism.

Evidence from animal and human studies converge on the potential contribution of early life stress (ELS) as a specific risk factor for suicide. Relative to those who died by suicide with no history of childhood abuse, those with a history of abuse showed reduced hippocampal GR expression (Labonte et al., 2012), denoting impaired negative feedback regulation. Relatedly, the *FKBP5* gene, which modulates GR signaling,

interacts with childhood trauma to increase risk of suicide attempt (Roy et al., 2010). Homozygous carriers of the *FKBP5* allele show deficits in hormonal recovery (i.e., CORT output) following psychosocial stress (Ising et al., 2008), further implicating this genetic contribution to suicide risk after stress exposure. Furthermore, rats that underwent chronic stress during rearing showed blunted HPA activity in later life, particularly indexed by reduced CORT and adrenocorticotropic hormone (ACTH) response (Perry et al., 2019). In humans, a similar relationship exists between ELS and blunted CORT response, with maximal effects emerging in adulthood (Bunea et al., 2017). Blunted stress reactivity has similarly been observed among those with persistent childhood trauma (O'Connor et al., 2018) and those with any lifetime adversity (Lovallo et al., 2012). Notably, the time-lag between ELS and CORT depletion remains unpredictable, with large individual variability in the onset and manifestation of the associated psychopathology (if any emerge at all). Stress reactivity, which is a response to an acute stressor, could be a promising biomarker (e.g., indexed by changes in CORT transmission) for predicting the onset of a suicide crisis. Indeed, lower CORT output is observed in response to an acute stressor among those who attempted suicide within the past year compared to those with a more distant history of attempt (O'Connor et al., 2017). Among attempters, lower CORT responsiveness to an acute stressor has also been associated with higher SI at one-month follow-up (O'Connor et al., 2017), suggesting that reduced stress reactivity might predict an imminent suicide crisis. These findings highlight the need to identify pharmacological interventions that rapidly restore HPA axis functioning in those with a recent history of suicide attempt. Interestingly, differential CORT reactivity patterns were recently identified among various subtypes of suicide attempters; for instance, attempters with high levels of impulsive aggression had increased CORT response to acute stress (Stanley et al., 2019).

It should be noted that contrasting findings have also been reported, with *elevated* CORT responses to acute stress observed in women with a history of childhood abuse (Heim et al., 2000). Further research is needed to understand the various factors that contribute to either hypo- or hyperactivity of the HPA axis, as well as specific developmental trajectories that predict divergent reactivity patterns. With respect to the latter, recurring psychological distress might determine reactivity patterns after ELS. Evidence suggests that *blunted* CORT reactivity may occur in ELS-exposed individuals with recurrent adulthood stress, but that *elevated* CORT reactivity occurs in those without a history of stress in adulthood (Goldman-Mellor et al., 2012). Preclinical models could help capture divergent CORT reactivity patterns when stress is administered at various developmental timepoints.

3.2. Inflammation

HPA axis alterations, particularly glucocorticoid resistance, have been associated with disruptions within inflammatory signaling pathways. Indeed, chronic stress-induced glucocorticoid resistance (e.g., hypocortisolism or GR downregulation) has been linked to a failure to regulate the immune response (Cohen et al., 2012), leading to persistent low-grade inflammation. Normally, CORT binds to GRs on immune cells to suppress the inflammatory cascade (thereby restraining proinflammatory cytokine release). Glucocorticoid resistance precludes this regulatory response, leading to hyperinflammation. Elevated inflammatory markers have been associated with various psychopathologies, including heightened immune response *preceding* the onset of depression (Dowlati et al., 2010; van den Biggelaar et al., 2007). In support of a potential causal link between inflammation and depression, immunological challenges that elevate inflammatory markers produced depressive-like behavior in rodents (Depino, 2015) and non-depressed humans (DellaGioia and Hannestad, 2010). As an important caveat, less research has explored the link between inflammation and suicide, limiting the ability to infer causality. While elevated plasma cytokine levels (e.g., interleukin (IL)-6) have been strongly associated with SI (e.

g., O'Donovan et al., 2013) and suicide attempt (e.g., Janelidze et al., 2011), other immunobiological factors (e.g., IL-8) were found to be reduced in those with suicidal thoughts and behaviors (Keaton et al., 2019). C-reactive protein (CRP), an acute-phase protein found in plasma, is an inflammatory biomarker used as an index for infection or inflammation in the periphery. A recent meta-analysis found that CRP levels were substantially elevated in people with suicidal tendencies (i. e., SI, suicide attempt, or death by suicide) (Chen et al., 2020), underscoring the ways that inflammation may predict suicide risk; other studies also found increased CRP concentrations in those with suicidal thoughts and behaviors (Oh et al., 2020; Yang et al., 2016). Another study found that depressed individuals with high CRP levels were 1.9 times more likely to attempt suicide than those with low CRP levels (Oh et al., 2020), a finding particularly relevant to the discussion of stress as a predictor for suicide given that chronic stress promotes low-grade systemic inflammation (Rohleder, 2019). In particular, elevated plasma CRP levels have been identified in both stress-exposed humans (e.g., family caregivers) (Gouin et al., 2012, 2016) and rodents (e.g., chronic social stress) (Clougherty et al., 2010). Some studies suggest that this finding may be most pronounced in women than in men (Shivpuri et al., 2012), but further work is needed to elucidate the underpinnings of these sex differences.

Disruptions in kynurenine signaling underlie both suicide and chronic stress pathology, further highlighting a potential mechanistic link between the two. Indeed, mounting evidence suggests that specific dysregulation within the kynurenine pathway promotes suicidal behaviors (Bryleva and Brundin, 2017). Higher plasma kynurenine levels have been found in MDD patients with a history of suicide attempts compared to MDD patients with no history of attempts or non-depressed controls (Sublette et al., 2011). Preclinical research similarly identified increased kynurenine levels in the plasma and brain (amygdala, hippocampus) of chronically stressed mice (Fuertig et al., 2016) that was reversed by blocking indoleamine 2,3-dioxygenase (IDO), an enzyme that catalyzes the conversion of tryptophan to kynurenine (Fuertig et al., 2016). The adverse effects associated with hyperactive kynurenine signaling likely involve decreased neuroprotective factors (e.g., brain derived neurotrophic factor (BDNF)) and increased quinolinic acid, a neuroexcitotoxic metabolite that acts as an N-methyl-D-aspartate (NMDA) receptor agonist. In particular, kynurenine metabolites, which are elevated in those with a lifetime history of suicide attempt (Sublette et al., 2011), might elicit suicidal behaviors by affecting glutamate signaling. Quinolinic acid, for instance, may cause neurotoxicity (e.g., axonal degeneration) via the increased release and disrupted reuptake of glutamate (Guillemin, 2012). Elevated quinolinic acid has been found in the CSF of suicide attempters, with levels decreasing within six months of the attempt (Erhardt et al., 2013). Preclinically, elevated quinolinic acid levels were found in chronically stressed rats (Chen et al., 2013), and these increases were accompanied by increased IDO expression in the frontal cortex (Martín-Hernández et al., 2019). Chronic stress not only increased quinolinic acid and glutamate in the hippocampus, it also upregulated expression of NMDA receptor subunits NR2B and mGluR1 (Chen et al., 2013). Critically, intrahippocampal microinfusions of a quinolinic acid inhibitor reduced NR2B and mGluR1 expression and rescued depressive-like behaviors (e.g., sucrose preference; Chen et al., 2013). Notably, the expression of these NMDA receptor subunits was higher in the dorsolateral prefrontal cortex (PFC) of those who died by suicide (Gray et al., 2015). Although direct causal attributions between stress-induced inflammation and suicide are difficult to infer, these findings suggest that pharmacological modulation of the kynurenine pathway could be important for future suicide research.

Certain proinflammatory cytokines that activate the kynurenine pathway, like interferon (IFN)-γ, IL-1B, and IL-6, are elevated in people with suicidal tendencies, mirroring the proinflammatory patterns reliably observed following chronic stress. A meta-analysis found dissociable patterns of cytokine and chemokine levels in suicidal (i.e., active SI, history of suicide attempt, or suicide death) versus non-suicidal

individuals (Black and Miller, 2015). Specifically, plasma IL-6 and IL-1B were robustly associated with suicide risk (Black and Miller, 2015). Another recent meta-analysis of stress mediators in suicide (Thomas et al., 2021) found that IL-6 had the largest impact on suicide risk of all the mediators (e.g., CORT, IFN-γ, tumor necrosis factor (TNF)-α). This is particularly interesting given the role of IL-6 in chronic stress pathology. Indeed, relative to other inflammatory markers, plasma IL-6 levels were found to be particularly elevated in humans (Carpenter et al., 2010; Kiecolt-Glaser et al., 2003) and animals (Himmerich et al., 2013) exposed to chronic stress. In psychiatrically healthy adults, plasma IL-6 levels were related to volumetric decreases of the hippocampus and amygdala, which are critical in regulating the stress response (Ironside et al., 2020). Collectively, these findings suggest that pre-existing hypercytokinemia, particularly elevated IL-6 transmission, could predict suicidal behaviors. Interestingly, IL-6 levels were also significantly higher in the cerebrospinal fluid (CSF) of recent suicide attempters compared to healthy controls (Lindqvist et al., 2009), and elevated IL-6 and IL-1B levels were found in the postmortem PFC of those who died by suicide (Pandey et al., 2012; Tonelli et al., 2008).

Microglia and astrocytes produce cytokines, suggesting that elevated cytokine transmission originates in the central nervous system (CNS). Some, however, have postulated that the association between inflammation (e.g., elevated levels of CRP, kynurenine, or cytokines) and suicidal behaviors is mediated by elevated permeability of the blood-brain barrier (BBB). This would allow peripheral inflammation to be trafficked into the CNS (Hsuchou et al., 2012). In an early study, 16 of 90 (18%) suicide attempters had compromised blood-CSF barriers, defined as an increased CSF/serum albumin ratio (Bayard-Burfield et al., 1996). More recent studies found elevated levels of S100B, a biomarker of BBB function, in those with SI (Falcone et al., 2010), as well as dysregulated cell adhesion signaling (e.g., CD44) in suicide attempters (Ventorp et al., 2016). These findings are particularly salient in the context of potential stress-related impacts on suicide risk, given that chronic stress promotes molecular adaptations to the BBB that foster neuroinflammation. Indeed, rodent studies found stress-induced increases in BBB permeability that led to depressive phenotypes (e.g., Dudek et al., 2020). Additional research is needed to uncover the precise mechanisms that could link suicide and stress-induced changes in BBB morphology, particularly in suicide-related brain regions (e.g., ventrolateral and dorsolateral PFC) that might be particularly impacted by neuroinflammation.

3.3. Serotonin

Abnormalities in serotonergic signaling have long been associated with suicidal behaviors, particularly reduced concentrations of extracellular 5-HT and its metabolite, 5-HIAA (Mann et al., 1989). Altered serotonin transporter (SERT) levels and 5-HT1A and 5-HT2A receptor expression have also been associated with suicide, but these might be more appropriately interpreted in the context of general reductions in 5-HT functioning (Purselle and Nemeroff, 2003). Of note, because dysfunctional 5-HT neurotransmission also underlies the pathophysiology of depression (Owens and Nemeroff, 1994), whether 5-HT deficits contribute to suicide risk independently of depression should be carefully considered.

Early studies found that CSF 5-HIAA levels predicted acute suicide risk among those with a lifetime history of suicide attempts (Nordström et al., 1994), warranting consideration of factors that might modulate serotonin transmission in those with high suicide risk. Building on this work, a recent meta-analysis found that suicide attempters had decreased 5-HIAA expression in the CSF (Hoertel et al., 2015), a finding that was not uniquely associated with violent methods as previously thought (Mann, 2003). In this context, early-life adversity might be an important factor that disrupts serotonin signaling in later life. For example, maternal separation reduced SERT mRNA expression in the adult rat dorsal raphe nucleus (DRN) (Bravo et al., 2014), and another

study found a 54% reduction in DRN neurons expressing SERT mRNA in suicide decedents (Arango et al., 2001). In classic non-human primate studies of peer-only rearing (a form of ELS), parentally neglected animals exhibited lower CSF 5-HIAA concentrations than mother-reared animals that persisted into adulthood (Higley et al., 1996; Shannon et al., 1995). Interestingly, other studies found that these animals were also more likely to exhibit deficits in impulse control (Higley et al., 1991) (see Section 3.5). Opposing findings were reported in studies using different ELS paradigms (e.g., variable foraging demand) (Coplan et al., 2014), implicating differential variations in 5-HT neurotransmission based on the ELS experience. Taken together, this evidence further supports the notion that specific forms of chronic stress (e.g., parental neglect versus environmental unpredictability) might differentially predict suicide risk based on distinct patterns of serotonergic activity in adulthood.

Altered 5-HT signaling in the PFC is particularly salient in the context of stress and suicide. Chronically stressed rodents, for instance, showed decreased 5-HT levels in the PFC (Liu et al., 2013), though some replication attempts were unsuccessful (Venzala et al., 2013; Xu et al., 2016). Chronic stress also decreased 5-HIAA levels (Ahmad et al., 2010) and increased 5-HT2A expression (Dwivedi et al., 2005) in the frontal cortex of rats. With respect to the latter, repeated (but not acute) stress exposure led to elevated 5-HT2A expression in the frontal cortex of rats, but only in those that developed learned helplessness in response to inescapable shock (Dwivedi et al., 2005). This is particularly interesting given that learned helplessness is considered a suicide trait-related behavior in animals, specifically a proxy for hopelessness (Malkesman et al., 2009), and several lines of research showed upregulated 5-HT2A in the PFC of individuals who died by suicide (Stanley and Mann, 1983; Arora and Meltzer, 1989; Arango et al., 1990; Pandey et al., 2002). Relatedly, SERT binding was selectively reduced in the ventral PFC (Mann et al., 2000; Underwood et al., 2012) and dorsolateral PFC (Austin et al., 2002) of suicide decedents, whereas widespread reductions in SERT binding were seen throughout the PFC of non-suicidal individuals with MDD (Mann et al., 2000). These findings implicate specific reductions in serotonergic innervation of the PFC in suicide that might increase suicide risk via impaired decision-making and impulse control (Mann and Currier, 2010). Importantly, SERT polymorphisms (e. g., in *5-HTTLPR*) have been shown to modulate the relationship between ELS and suicide risk (Benedetti et al., 2014), complicating the link between stress and suicide. Specifically, stressful life events predicted SI and attempts in carriers of the short (but not long) allele of *5-HTTLPR* (Benedetti et al., 2014; Caspi et al., 2003).[1] Of relevance, short allele carriers with a history of emotional neglect also developed smaller hippocampal volumes, with larger volumes observed in long allele carriers (Frodl et al., 2010). Thus, genotypical diatheses involving the 5-HT system might determine the magnitude of suicide risk conferred by chronic stress. As a caveat to this research, several recent studies have failed to show significant associations between the *5-HTTLPR* polymorphism and childhood trauma (Fratelli et al., 2020; Özçürümez et al., 2019). Future research should examine whether these polymorphisms serve any neuroprotective functions against suicide pathophysiology.

3.4. Clinical risk factors

3.4.1. Despair/helplessness
Depressed mood, which is characterized by persistent feelings of despair and low positive affect, predicts suicidal behaviors (Hall et al., 1999; Large et al., 2011) even among those who do not meet criteria for MDD in the year prior to SI or suicide attempt (Bethell and Rhodes, 2007). In a survey of 1455 college students, hopelessness was the most frequently cited factor that contributed to SI (Furr et al., 2001). Indeed, suicide attempters were significantly more likely to report hopelessness and helplessness relative to non-attempters (Furr et al., 2001), further highlighting the contribution of these depressive traits to suicide risk (although the relationship between hopelessness and suicide might be weaker than previously reported (Ribeiro et al., 2018)). Furthermore, recent research points to learned helplessness as another significant predictor of suicidality (ideation, intention, and attempt) (Aslam and Bano, 2019; Seyakhane et al., 2021).

For decades, repeated life stress has been identified as a potent predictor of hopelessness (Bonner and Rich, 1991; Dixon et al., 1993). Schotte and Clum (1987) proposed a diathesis-stress-hopelessness model of suicide, whereby deficits in social problem-solving mediate the relationship between stress and suicide. Their model was based on the finding that those with high levels of life stress and poor interpersonal problem-solving also had the highest levels of hopelessness and suicidal thoughts and behaviors (Schotte and Clum, 1982). More recently, repeated stressors were associated with hopelessness among police officers (Violanti et al., 2016) and university students (Lew et al., 2019). Moreover, hopelessness and SI were higher among war veterans with subthreshold post-traumatic stress disorder (PTSD) compared to those without PTSD (Jakupcak et al., 2011), implicating major life stressors (particularly traumatic events) in the relationship between hopelessness and suicide.

Relatedly, early preclinical studies reported behavioral despair among chronically stressed rodents (e.g., Gonzalez et al., 1990; Molina et al., 1994; Prince and Anisman, 1984), whereby immobility—a proxy for hopelessness—was increased during aversive situations (e.g., forced swim or tail suspension tests) (Cryan et al., 2005). SSRI treatment reversed chronic stress-induced despair (Cryan et al., 2005), suggesting that reduced 5-HT signaling could underlie this endophenotype; however, it should be noted that other compounds, like (*R,S*)-ketamine, produce similar effects (Fitzgerald et al., 2019). Importantly, recent attempts to replicate these findings have failed (e.g., Suvrathan et al., 2010). Some have also raised concerns about the validity of these paradigms in assessing depressive-like behaviors, arguing that they might more appropriately evaluate stress-coping strategies (Commons et al., 2017; Cryan et al., 2005). Thus, animal models of despair need to be refined in order to foster cross-species translational pursuits of stress-related suicide pathology.

3.4.2. Anhedonia
Anhedonia, which reflects diminished interest or pleasure in previously rewarding activities, has a complex relationship with suicide risk. Specifically, the level of suicide risk in those with anhedonia depends on the severity, stability (state or trait), and type (consummatory or motivational) of anhedonic experience. These complex interactions have been reviewed elsewhere (see Bonanni et al., 2019; Loas, 2014). Briefly, acute suicide risk (i.e., within one year) is particularly high when anhedonia is severe and onset is acute (i.e., state rather than trait anhedonia) (Fawcett et al., 1990; Yang et al., 2020a). Indeed, trait-like anhedonia confers a low suicide risk and is sometimes unrelated to suicide (Loas, 2007), perhaps reflecting reduced sensitivity to fluctuations in subjective hedonic experiences that would otherwise trigger a suicide crisis. Furthermore, few studies have evaluated the distinction between consummatory and motivational anhedonia in relation to suicide risk. A recent longitudinal study found that reduced pleasure capacity (consummatory) was associated with acute SI (within one year) whereas motivational deficits were associated with longer-term SI (Yang et al., 2020b). Some studies found that a loss of interest robustly predicted SI (Winer et al., 2014), implicating motivational-related deficits in suicide. Interestingly, a loss of interest in *people* (social anhedonia)

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[1] Notably, rodents do not harbour the orthologue of the human *5-HTTLPR* polymorphism. Heterozygous SERT knockout rodents are typically used as the homologous animal model, given similarities to the human *5-HTTLPR* short allele carrier. In these studies, SERT knockout rodents showed increased depressive phenotypes following ELS compared to their wildtype counterparts (e.g., Carola et al., 2008), but the literature is very mixed (for a comprehensive review, see Houwing et al., 2017).

was uniquely associated with recent SI (Yang et al., 2020c) and with lifetime suicide attempts (Sagud et al., 2020).

Very few studies have explored the relationship between anhedonia, stress, and suicide. In one recent study, Yang et al. (2020d) found that the number of stressful life events in the past year correlated positively with state anhedonia in adolescents, and state (not trait) anhedonia was specifically associated with higher SI. Interestingly, they found that academic stressful events moderated the relationship between state anhedonia and SI, such that those with anhedonia were at increased risk for SI when experiencing high academic stress (Yang et al., 2020d). Other studies have focused on war veterans with PTSD, showing that the relationship between trauma and SI was mediated by anhedonia (Blais and Geiser, 2019). Relatedly, those who had attempted suicide were more likely to report diminished interest in (pre-traumatic) activities (Legarreta et al., 2015). These findings suggest that reducing stress- or trauma-related anhedonia, particularly diminished interest, might be critical in mitigating suicide risk.

Diminished interest, or motivational anhedonia, is particularly relevant to suicide risk, suggesting that aberrant dopaminergic signaling might underlie the relationship between stress and suicide. In both humans and animals, the mesocorticolimbic dopamine pathway is robustly impacted by chronic stress (for a comprehensive review, see Pizzagalli, 2014). ELS might be especially predictive of dysfunctional reward processing patterns linked to suicide. Childhood maltreatment, for instance, was associated with reduced striatal response to reward cues (Dillon et al., 2009; Birn et al., 2017; Hanson et al., 2015) as well as with blunted reward learning (Dennison et al., 2019; Pechtel et al., 2013) in adulthood. In rodents, ELS impaired pleasure-reward functional connectivity (Bolton et al., 2018) and reduced motivation to pursue reward (Leventopoulos et al., 2009). Given the association between acute (state) anhedonia and suicide (Fawcett et al., 1990; Yang et al., 2020a), it is also imperative to examine the effects of adulthood stress on reward processing. Laboratory stress paradigms in humans found that acute stress challenges (e.g., simulated peer rejection) reduced striatal activation in anticipation and response to reward (Kumar et al., 2014; Oei et al., 2014). Acute stressors also reduced anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) activation in a probabilistic reward task (Bogdan et al., 2011). Generally, preclinical studies have noted reductions in reward learning after *chronic* stress (e.g., Der-Avakian et al., 2017; Lamontagne et al., 2018, 2022). Of relevance to suicide risk, one study found that rats bred for learned helplessness showed diminished reward processing after acute stress exposure compared to non-helpless rats (Enkel et al., 2010). This suggests that stress interacts with a predisposition for helplessness to induce anhedonic-like behaviors. Thus, interactions between stress and reward pathways might be critical in establishing targeted interventions to reduce suicide risk.

3.4.3. Sleep disturbances

Sleep disturbances have been identified as important risk factors for SI, suicide attempt, and suicide death (Bernert et al., 2015; Liu et al., 2020) that may occur independently of depression (Pigeon et al., 2012). Among several factors that regulate sleep, the arousal system is particularly relevant in the context of suicide risk. Hyperarousal is characterized by wakefulness, high-frequency EEG rhythms, and increased global brain metabolism during both sleep and wakefulness (Bonnet and Arand, 2010). In a recent study of women with mild to moderate depression, nocturnal cognitive hyperarousal predicted first-time SI, and suicide risk was highest when hyperarousal co-occurred with insomnia (Kalmbach et al., 2021). Thus, interventions that remediate sleep disturbances, particularly hyperarousal, could help reduce suicide risk. In this context, reductions in nocturnal wakefulness differentiated those with SI who had an anti-suicidal response to ketamine compared to those without an anti-suicidal response (Vande Voort et al., 2016), further highlighting a mechanistic link between disrupted sleep and suicide.

Childhood adversity is strongly associated with sleep disorders in adulthood (for a systematic review, see Kajeepeta et al., 2015). For instance, some studies found dissociable sleep patterns among those with insomnia who had adverse childhood experiences versus those who did not (Bader et al., 2007). Specifically, those with ELS had more awakenings and increased movement during sleep, as well as reduced sleep efficiency, compared to those without ELS (Bader et al., 2007). These differential sleep patterns may ultimately be relevant to the neurobiological underpinnings of stress-related insomnia and suicide, but this has yet to be investigated. Nevertheless, emerging research points to a specific role for ELS-related sleep disruptions in suicide risk. For instance, childhood trauma was associated with poor sleep quality among veterans with and without MDD; specifically, among those with MDD, childhood trauma was directly associated with increased suicide risk (Alter et al., 2021). Relatedly, among adolescent inpatients admitted for suicidal thoughts or behaviors, an association between suicide attempt and childhood trauma (bullying followed by sexual abuse and loss) was explained by poor sleep quality (King et al., 2021). Although the relationship between stress-related sleep disruption and suicide is not uniquely associated with early adversity (see Healy and Vujanovic, 2021; Liu et al., 2019), ELS might play a critical role in a vulnerability toward hyperarousal, which could then contribute to insomnia (Palagini et al., 2015). Indeed, hyperarousal is prevalent among those with ELS or trauma, perhaps reflecting an overactive preparedness to cope with potential negative events in the future (Barlow, 2004; Palagini et al., 2015).

From a neurobiological perspective, dysregulated HPA activity could enhance susceptibility to hyperarousal-induced insomnia, given that dynamic fluctuations in stress hormones (CORT, ACTH) are essential for sleep regulation (Han et al., 2012). Importantly, the relationship between the neurobiology of stress and sleep is bidirectional. That is, insomnia could affect stress-related endocrinology (e.g., elevated evening CORT release) (Basta et al., 2007) and stress responses could influence sleep patterns (Åkerstedt, 2006). With respect to the latter, stress-exposed animals developed sleep disturbances that resemble stress-induced insomnia in humans (Kant et al., 1995), namely increased sleep latency and high-frequency EEG activity in non-REM sleep (Cano et al., 2008). In support of a hyperarousal model of insomnia, these animals showed activation of both sleep-promoting systems (e.g., ventrolateral preoptic nucleus) and arousal systems during sleep (Cano et al., 2008), likely due to competing homeostatic and circadian pressures. Interestingly, lesions to the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BST) restored non-REM and REM sleep in these animals (Cano et al., 2008). This is likely due to their projections to structures involved in autonomic arousal. Given the contribution of the CeA-BST in mediating stress and arousal responses, these might be important targets for suicide research in the context of sleep.

3.5. Impulsivity

Impulsivity is characterized by an inability to inhibit actions, often leading to rapid and unplanned reactions to events with little consideration of the negative consequences to oneself or others. Suicide is not always associated with impulsive behavior, but many studies identify impulsivity as a critical risk factor for suicide, particularly among attempters (Brent et al., 2003; Mann et al., 2000). In contrast, non-impulsive suicide is associated with higher measures of persistence and self-directedness (Zouk et al., 2006). Impulsivity is thought to predispose those with SI to act on these thoughts (Kim et al., 2003), making this trait particularly important in determining suicide risk. Indeed, independent of psychiatric diagnosis, those with trait impulsivity are at higher risk for suicide attempt (Mann et al., 2000).

Individuals with a history of chronic stress, particularly childhood maltreatment, have significantly higher impulsivity and are more likely to make a suicide attempt compared to those without a history of stress

(Brodsky et al., 2001). According to a diathesis-stress model of suicide (Mann et al., 2000), life stress might act as a catalyst for suicide in those with high trait impulsivity. This might be a consequence of interactions between impulsive behaviors and reactions to stress. In this context, suicide decedents with impulsive traits were significantly more likely than their non-impulsive counterparts to have a history of childhood abuse and to have had a stressful life event up to a week prior to death (Zouk et al., 2006). This further highlights the role of stress as a potential antecedent to suicide among those with impulsive traits.

An important consideration in this discussion is whether impulsivity is an antecedent or a *consequence* of stressful or traumatic life events. Some have posited that those with high trait impulsivity might be more likely to engage in activities that predispose them to adverse circumstances, classifying it as a risk factor for trauma (e.g., PTSD) (Anestis et al., 2014; Braquehais et al., 2010). Other studies point to a causal role of stress in dysfunctional impulsive control. For instance, laboratory stress induction increased self-reported state impulsivity in a sample of women with no lifetime history of mental disorders (Cackowski et al., 2014). A recent study found similar results, showing that those with higher stress-induced increases in impulsivity also had higher stress-induced CORT release (Simon et al., 2021), highlighting a potential mechanism by which stress leads to poor impulse control. Corroborating this notion, hydrocortisone increased impulsive choice behavior 15 min (but not 195 min) after administration in healthy participants (Riis-Vestergaard et al., 2018). This suggests that acute stress may contribute to a transient impulsive state that could precede a suicide crisis. In fact, trait impulsivity was shown to predict long-term suicide risk, while state impulsivity predicted proximal risk for self-harm or suicide (Liu et al., 2017).

Preclinical research further sheds light on biosignatures of stress-induced impulsivity. In rodents, chronic stress during adolescence induced long-term deficits in impulse control into adulthood (Comeau et al., 2014; Sanchís-Ollé et al., 2019). This mirrors the increased impulsivity observed among suicide attempters with a history of ELS (Brodsky et al., 2001). PFC maturation is thought to be critical to the development of self-control (Casey, 2015), and high impulsivity has been uniquely linked to reduced cortical thickness in lateral PFC regions (Merz et al., 2018). Towards this end, the PFC is extremely sensitive to stress during early development (Romeo, 2017), particularly in adolescence (Caballero et al., 2016), pointing to PFC-dependent mechanisms that contribute to impulsivity in those with ELS. As mentioned previously, the serotonergic system also plays a role in impulsivity, particularly among ELS-exposed animals with low CSF 5-HIAA concentrations (Higley et al., 1996). Reduced serotonergic input to the ventral PFC, as indexed by a localized reduction in SERT binding in this region, is thought to underlie impairments in impulse control and behavioral inhibition, thereby increasing suicide risk (Mann et al., 2000). Indeed, post-mortem studies found that suicide and impulsive aggression were specifically tied to deficient SERT binding in the ventral PFC, not widespread deficits throughout the brain as seen in MDD (Mann et al., 2000; Seo et al., 2008).

4. Remediating stress-related endophenotypes of suicide: A potential role for ketamine?

The following section considers a role for ketamine treatment in restoring stress-related neurobiological and behavioral correlates of suicide. The effects of traditional antidepressant treatment (e.g., SSRIs) on chronic stress and stress-related disorders have been extensively reviewed in humans (Davidson, 2006) and rodents (Willner, 2017). Although several preclinical studies found that SSRIs had restorative effects on chronic stress pathology (e.g., Surget et al., 2011), their antidepressant response generally takes several weeks to manifest, posing major concerns for those with imminent suicidal thoughts and behaviors. Lithium has also been reviewed in the context of stress and suicide, specifically its effects on traits that predict suicidal behavior (see Beurel

and Jope, 2014). Lithium is particularly effective in mitigating negative effects of stress through its inhibition of glycogen synthase kinase-3 (GSK3), which could underlie its anti-suicidal properties. Indeed, some have linked GSK3 inhibition to reductions in stress-induced inflammation, aggression, impulsivity, and depression (Beurel and Jope, 2014), all of which have been discussed here as predictors of suicide. In addition to recent findings challenging the efficacy of lithium in reducing suicide-related events (see Katz et al., 2022), lithium requires long-term administration to reduce suicidal behavior and traits that predict suicide risk (e.g., impulsivity, aggression) (for a review, see Tondo and Baldessarini, 2018). Other modalities may also be of interest to this discussion, including brain stimulation (electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS)) or psychotherapy. However, antidepressant response times for these methods are also often slow (Duncan et al., 2017).

This discussion focuses exclusively on ketamine due to its established rapid-acting antidepressant effects, particularly on SI, as demonstrated in controlled clinical studies (e.g., Ballard et al., 2014). Preclinical studies have also extensively investigated ketamine's effects on stress-related endophenotypes (for a review, see Abdallah et al., 2016), allowing for cross-species analysis. Fewer clinical data exist for other rapid-acting compounds, like psychedelics or scopolamine (Duman et al., 2016; Witkin et al., 2019), but these drugs are certainly worth considering in future studies exploring the links between stress and suicide.

4.1. Neurobiology of ketamine's antidepressant effects

In the past decade, numerous studies demonstrated the rapid antidepressant (Berman et al., 2000; Zarate et al., 2006) and anti-suicidal (Ballard et al., 2014) properties of subanesthetic-dose ketamine, offering a novel therapeutic target for depression and suicide. Briefly, depression is associated with deficits in homeostatic plasticity (Turrigiano, 2012), specifically reduced prefrontal and hippocampal synaptic connectivity (Duman and Aghajanian, 2012; Kang et al., 2012). These alterations likely result from aberrant glutamatergic signaling and astroglial damage, causing elevated extracellular glutamate release. This promotes excitotoxicity as well as deficits in synaptic strength and dendritic branching (Krystal et al., 2013). Mammalian target of rapamycin complex 1 (mTORC1) pathway inhibition is implicated in depression, as is synaptic loss (Ota et al., 2014). Indeed, chronic stress is used as an animal model of depression by increasing mTORC1 inhibition in the PFC via the stress-induced protein, "regulated in development and DNA damage responses-1" (REDD1) (Ota et al., 2014). This mirrors elevated REDD1 levels in the postmortem dorsolateral PFC (DLPFC) of MDD patients (Ota et al., 2014), highlighting an important contribution of both glutamate and mTORC1 modulation in stress and depressive pathophysiology.

In contrast to traditional antidepressant treatments, subanesthetic-dose ketamine rapidly restores synaptic neuroplasticity, primarily owing to glutamatergic modulation through actions on the NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. One hypothesis postulates that ketamine preferentially blocks NMDA receptors on gamma aminobutyric acid (GABA)-ergic interneurons, transiently increasing glutamate release. This glutamatergic surge, particularly in the PFC, is thought to be critical to ketamine's antidepressant effects (Abdallah et al., 2015). Another hypothesis suggests that direct NMDA receptor blockade (via low-dose ketamine) inhibits eukaryotic elongation factor (eEF2) kinase, thereby de-suppressing BDNF and promoting synaptic plasticity (for a review, see Monteggia and Zarate, 2015). Ketamine also activates AMPA receptors while blocking extrasynaptic NMDA receptors, with increased AMPA signaling as a net effect (Koike et al., 2011). With the shift in balance of glutamate activation from NMDA to AMPA receptors comes increased BDNF expression, thereby enhancing plasticity (Autry et al., 2011). Critically, ketamine also stimulates mTORC1, which promotes

synaptic connectivity in the PFC. This process reverses chronic stress-induced synaptic damage (Li et al., 2011) and promotes the regrowth of dendritic spines within hours of administration (Li et al., 2010). Furthermore, opioid system activation might partially underlie ketamine's antidepressant properties. In a sample of ketamine-responsive patients with treatment-resistant depression, pre-infusion treatment with an opioid receptor antagonist (naltrexone) attenuated the antidepressant effects (Williams et al., 2018). Similar findings were recently reported in rodents, adding that the opioid system did not mediate the actions of ketamine but instead interacted with NMDA receptor signaling, achieving antidepressant effects (Klein et al., 2020). This might reflect a role of the endogenous opioid system in ketamine's antidepressant effects, particularly direct and/or indirect actions at the mu opioid receptor (Williams et al., 2018), but further research is necessary to substantiate these underlying mechanisms.

Some controversies have emerged surrounding the use of ketamine as an anti-depressant and anti-suicidal agent. This largely stems from studies examining long-term ketamine abuse (i.e., three times weekly for at least one year), which is linked to profound spatial memory impairments and hippocampal dysregulation (Morgan et al., 2014). At therapeutic doses, however, cognitive side effects, including memory impairments, dissipate within three days of infusion (Morgan et al., 2004). Indeed, six 0.5 mg/kg ketamine infusions over a 12-day period significantly *improves* visual and working memory and does not adversely impact executive functioning (Shiroma et al., 2014). Moreover, pre-infusion cognitive functioning predicts antidepressant response to ketamine (Shiroma et al., 2014), suggesting its clinical effects could be subserved by pro-cognitive effects. Anti-suicidal effects of ketamine could also be attributed to improved executive function capabilities, given the link between dysregulated executive functioning (e. g., impulsivity) and suicide risk (Lee et al., 2016). Relatedly, the preclinical literature points to diverging effects of ketamine based on dosage. In rats, high doses of ketamine (20–30 mg/kg), which fail to ameliorate stress-induced depressive symptoms (Donahue et al., 2014), inhibit astrocytic activation (Shibakawa et al., 2005)—a mechanism that likely underlies its analgesic properties (Mei et al., 2010). By contrast, lower doses that ameliorate CMS-induced depressive phenotypes (2–15 mg/kg) rapidly activate astrocytes and subsequently stimulate BDNF synthesis (Ardalan et al., 2020). In fact, blocking astrocyte activation precludes the antidepressant benefits of ketamine (but not scopolamine) (Wang et al., 2018), implicating an important role for astrocytic activation in ketamine's antidepressant effects. For these reasons, the following discussion focuses on studies that involve therapeutic uses of ketamine (0.4–0.8 mg/kg in humans; 2–15 mg/kg in rodents).

4.2. Effects of ketamine on stress-related endophenotypes of suicide

Mounting evidence suggests that ketamine has rapid anti-suicidal properties. For instance, studies found that suicidal thoughts were substantially reduced within 24 h of a single intravenous ketamine infusion (0.5 mg/kg) (DiazGranados et al., 2010; Grunebaum et al., 2018; Price et al., 2009, 2014). While these effects may be mediated by reductions in depressive symptoms (Price et al., 2014), some research shows that ketamine reduces suicidal thoughts independently from depression (Ballard et al., 2014). This suggests that ketamine might remediate the endophenotypes of suicide discussed in this review (see Table 1). Indeed, preclinical studies found that ketamine restored chronic stress-induced pathologies linked to suicide (e.g., Fitzgerald et al., 2019). Thus, ketamine treatment might be of particular importance in reducing suicide risk.

4.2.1. Ketamine restores HPA functioning, GR-mediated feedback, and CORT production

Traditional antidepressants (e.g., SSRIs) usually take several weeks to exert their effects, with suicide attempts remaining high a month after treatment onset (Simon and Savarino, 2007). In contrast, ketamine exerts rapid anti-suicidal effects, likely owing to its unique ability to normalize aberrant HPA activity. In a recent study, a single intraperitoneal injection of ketamine normalized CORT levels and restored GR expression in the hippocampus of chronically stressed mice (Wang et al., 2019). These effects pertained exclusively to stress-susceptible mice (indexed by the social interaction test), suggesting that ketamine preferentially benefits those most vulnerable to stress. There is also preliminary evidence of rapid reversal of DST non-suppression post-ketamine in humans, an effect that coincided with improved depressive symptoms (Ostroff and Kothari, 2015). Given the link between suicide and hippocampal GR downregulation (Pandey et al., 2013; Pérez-Ortiz et al., 2013) and DST non-suppression (Coryell and Schlesser, 2001; Yerevanian et al., 2004), these effects could be critical to mitigating suicide risk.

NMDA and AMPA receptor modulation are also thought to be involved in regulating HPA response to stress (Pistovcakova et al., 2005; Zelena et al., 1999), making these candidate mechanisms by which ketamine—but not traditional antidepressants—might exert rapid antidepressant effects. Although emerging evidence highlights potential sex differences in ketamine's effects on HPA regulation after chronic stress (J. N. Johnston et al., 2021), more research is needed to understand the mechanisms underlying these findings. Interestingly, low-dose ketamine acutely but significantly increased salivary and plasma CORT secretion within an hour of infusion (Hergovich et al., 2001; Khalili-Mahani et al., 2015). Given the association between blunted CORT release and proximal suicide attempts (Melhem et al., 2016, 2017), ketamine might help prevent an active suicide crisis by rapidly mediating CORT transmission. However, as noted above, the causal link between CORT levels and suicide is poorly understood, and additional mechanistic studies into ketamine's anti-suicidal properties via CORT modulation are needed.

4.2.2. Anti-inflammatory properties of ketamine: normalizing the kynurenine pathway

Ketamine's ability to reduce hyperinflammatory response is well documented (De Kock et al., 2013; Kopra et al., 2021). For instance, ketamine was found to suppress proinflammatory cytokine production and CRP levels without impacting anti-inflammatory cytokine levels (Kawasaki et al., 1999; Takenaka et al., 1994). Of relevance to this discussion, ketamine was found to disrupt the kynurenine pathway, suppressing the release of proinflammatory cytokines relevant to suicide risk (e.g., TNF-α, IL-6, IL-1B) (Kopra et al., 2021). Notably, IL-6 has been identified as a unique predictive biomarker for ketamine's antidepressant effects (Yang et al., 2015), corroborating its distinct contribution to the pathophysiology of stress and suicide. In chronically stressed rodents, ketamine reduced serum proinflammatory cytokines, suppressed hippocampal microglial activation, and downregulated the proinflammatory cytokine-promoting TLR4/p38 pathway in the hippocampus (Tan et al., 2017). As mentioned previously, suicide is linked to elevated IDO (Bradley et al., 2015) and CSF quinolinic acid (Erhardt et al., 2013), making these inflammatory mediators particularly important for suicide prevention. In chronically stressed rats, low-dose ketamine attenuated hippocampal IDO and the kynurenine/tryptophan (KYN/TRP) ratio (Wang et al., 2015). There is also evidence of reduced levels of hippocampal quinolinic acid post-ketamine administration (Verdonk et al., 2019), likely reflecting downstream effects on IDO.

Among individuals with bipolar depression, ketamine significantly decreased IDO levels at 230 min, one day, and three days post-infusion (Kadriu et al., 2021). In this population, ketamine *increased* KYN levels one and three days after treatment and did not alter quinolinic acid levels (Kadriu et al., 2021). Thus, ketamine's effects on the kynurenine pathway are likely nuanced and might differentially affect distinct clinical populations. While the literature generally suggests that ketamine may help restrain hyperinflammatory mediators that characterize suicide, one important caveat is that it remains unknown whether

ketamine's anti-inflammatory properties may only exist when inflammation is abnormally high (Loix et al., 2011).

4.2.3. Ketamine promotes the synthesis of serotonin and increases prefrontal 5-HT signaling

Like SSRIs, ketamine robustly increases extracellular serotonin levels (Lindefors et al., 1997), but its rapid-acting effects make it more appealing than conventional antidepressants. Emerging evidence suggests that ketamine directly affects 5-HT signaling, particularly the inhibition of serotonin clearance via SERT and the plasma membrane monoamine transporter (PMAT) (Bowman et al., 2020). Ketamine also increased 5-HT levels indirectly by suppressing the IDO/kynurenine pathway that, when activated, converts tryptophan into kynurenine instead of 5-HT (Capuron et al., 2002). Thus, ketamine-induced reductions in the KYN/TRP ratio increase the 5-HT/TRP ratio, promoting serotonin synthesis.

In chronically stressed rats, ketamine blocked depressive-like behaviors, but not when animals were pretreated with a tryptophan hydroxylase inhibitor (Gigliucci et al., 2013). Extending these findings, studies found that ketamine specifically increased mPFC serotonin levels, a finding directly associated with antidepressant-like behaviors in animals (Pham et al., 2017). These findings are salient in the context of suicide, given its associations with aberrant 5-HT signaling within the PFC. Although fluoxetine produces similar effects on extracellular 5-HT in the mPFC, ketamine had more pronounced antidepressant effects that persisted for a longer period of time (Pham et al., 2017).

4.2.4. Impacts on clinical risk factors: ketamine improves mood, sleep, and reward processing

Among the most widely reported benefits of ketamine is its ability to rapidly improve depressive symptoms, which may underlie its anti-suicidal effects. In this context, ketamine reduced stress-induced immobility in the forced swim (Fitzgerald et al., 2019; Wang et al., 2019) and tail suspension (Koike et al., 2011) tests in rats, pointing to a reversal of despair and helplessness. These rapid antidepressant effects could be abolished by blocking AMPA receptors (Koike et al., 2011), suggesting that AMPA signaling is key to these behavioral outcomes. Similar findings have been observed in humans, with reductions in self-reported hopelessness reported within 40 min of ketamine infusion (Burger et al., 2016; DiazGranados et al., 2010). Improvements in hopelessness were also strongly associated with reduced SI (Price et al., 2014). Of note, decreased hopelessness might be associated with treatment optimism rather than with a direct effect of the drug, given that ketamine could be perceived as a promising alternative to traditional antidepressants. This may be particularly true for those with treatment-resistant depression.

Sleep improvements also mediate the effects of ketamine on SI, owing to reductions in insomnia, sleep restlessness, early morning awakening, and nocturnal wakefulness (Rodrigues et al., 2021; Vande Voort et al., 2016). Ketamine's sleep-improving effect is likely a multifactorial process involving the normalization of the circadian sleep/wake system. This could involve modulation of clock-gene related pathways, glutamatergic signaling, and BDNF expression (for a review, see Duncan et al., 2017). With respect to the latter, post-ketamine plasma BDNF levels increased proportionally to enhanced slow-wave activity during non-REM sleep in those with TRD (Duncan et al., 2017), corroborating earlier preclinical findings (Feinberg and Campbell, 1993). Synaptic strengthening and plasticity likely underlie these restorative effects on sleep, owing to ketamine-induced glutamatergic modulation.

Ketamine also has profound anti-anhedonic effects that contribute to its ability to reduce suicidal thoughts independently of other depressive symptoms (Ballard et al., 2017). Several mechanisms could underlie the pro-hedonic effects of ketamine that likely subserve associated reductions in suicide risk. For instance, ketamine's anti-inflammatory properties could restore mesolimbic dopamine synthesis by inhibiting

kynurenine-induced oxidative stress (Stanton et al., 2019). This is especially relevant considering the link between dopamine-mediated reward processing deficits (e.g., reduced interest) and suicide (Legarreta et al., 2015). Evidence also suggests that ketamine improves anticipatory anhedonia by modulating affective networks, for example, by reversing over-activity of the subgenual ACC, which has also been linked to suicide (Alexander et al., 2019). Interestingly, ketamine reverts stress-induced structural and functional deficits along the meso-corticolimbic reward pathway. In chronically stressed rats, acute ketamine treatment rapidly increased reward responsiveness while restoring synaptic proteins, spine number, and the frequency/amplitude of synaptic currents in layer V PFC pyramidal neurons (Li et al., 2011). These effects were blocked by mTOR inhibition (Li et al., 2010), suggesting that mTOR-dependent alterations in synaptic plasticity contributed to ketamine's anti-anhedonic effects. Similar findings have been reported in people with TRD, such that ketamine rapidly reduced anhedonic symptoms (Ballard et al., 2017) and modulated glucose metabolism along reward pathways (e.g., dorsal ACC (dACC), OFC) (Lally et al., 2015). Finally, ketamine attenuated exaggerated neuronal burst firing in the lateral habenula (LHb), the brain's "anti-reward center" (Yang et al., 2018), which might also play a role in its anti-anhedonic effects. Local LHb infusions of ketamine restored sucrose preference in rats exhibiting learned helplessness (Yang et al., 2018). This might be particularly relevant given the associations between anhedonia, helplessness, and suicide (Aslam and Bano, 2019; Seyakhane et al., 2021). Anhedonic symptoms are generally unresponsive to conventional antidepressants (Uher et al., 2012), likely reflecting dopamine-independent mechanisms associated with these drugs. Ketamine might therefore be a promising alterative for alleviating this endophenotype of suicide.

4.2.5. Limited evidence for ketamine's effects on impulse control

Few studies have examined the therapeutic effects of subanesthetic-dose ketamine on impulsivity. Indeed, most preclinical studies found that active NMDA receptor blockade led to *impaired* impulse control (Benn and Robinson, 2014; Higgins et al., 2003; Smith et al., 2011), suggesting that ketamine might acutely produce unintended negative consequences on control. Challenging this notion, acute NMDA receptor blockade reduced impulsive aggression in socially isolated mice (Chang et al., 2018). Although these findings are not well characterized in humans, ketamine was found to modulate inhibitory control networks in those with TRD in a manner that predicted antidepressant outcomes (Sahib et al., 2020). This suggests that ketamine's effects on functional connectivity, as well as synaptic plasticity, could underlie long-term improvements in response inhibition. Supporting this hypothesis, a recent preclinical study found that low-dose ketamine improved impulse control in a serial choice task 24 h post-administration (Davis-Reyes et al., 2021). Although speculative, these findings suggest that ketamine may have delayed effects on impulsivity that might be related to its neuroplastic properties.

To date, few clinical studies have directly examined ketamine's effects on impulsivity. In a recent proof-of-concept trial (N = 18 depressed participants with SI), ketamine had no effect on self-reported impulsivity (indexed by the Barratt Impulsivity Scale; BIS) despite alleviating SI and improving hopelessness and pessimism (Domany et al., 2020). Future research is needed to confirm ketamine's potential effects on impulsivity. Such pursuits might focus on ketamine's ability to modulate aberrant glutamatergic activity and connectivity in the PFC, which characterize suicide risk.

5. Animal models of suicide

As mentioned at the outset, our understanding of the neural underpinnings of suicide are limited by an inability to model suicidal behaviors in animals. Although animal models of suicide, per se, do not exist, there is evidence of self-injurious behavior among animals experiencing highly stressful situations. Self-injury has been observed in

primates held in captivity, particularly those with ELS (Novak, 2003). Notably, these behaviors were not associated with externally directed aggression (Lutz et al., 2003). Furthermore, the risk of developing self-injury in monkeys was highest in response to early adversity and subsequent stress exposure (Tiefenbacher et al., 2005). Self-injury has also been linked to long-term central and peripheral disruptions in stress systems, namely blunted CORT responses to mild stress (Tiefenbacher et al., 2005). This is akin to GR insufficiency in DST non-suppressors, which is a predictor for suicide (Coryell and Schlesser, 2001).

At face value, these behaviors could resemble human characteristics linked to self-harm or suicidal thoughts and behaviors. However, it is important for researchers to avoid anthropomorphizing animals. For example, self-biting in primates rapidly lowers elevated heart rate (Novak, 2003), suggesting that it could be an effort to reduce arousal rather than an attempt to deliberately harm oneself. Relatedly, learned helpless behavior in rodents resembles the perception of futility in humans with hopelessness—that is, the recognition that one's efforts have no bearing on subsequent outcomes (Maier and Seligman, 2016). However, the interpretation of learned helplessness in rodents has been criticized (Cryan et al., 2005), given that immobility (or lack of struggle) might reflect an effort to conserve energy (perhaps pointing to *superior* coping strategies among these animals).

Rather than attempting to model suicide in animals, researchers should adopt a dimensional, endophenotype approach to research that focuses on transdiagnostic dimensions that predict suicide outcomes. Towards this end, animal models are critical for directly assessing the functional changes associated with stress on suicide-related endophenotypes. These studies also help infer causality through carefully controlled experimentation, which is rarely possible in human studies due to ethical constraints. Moreover, human studies focus largely on mental disorder diagnoses, particularly MDD, as risk factors for suicide. In addition to offering limited insights into mechanisms and processes involved in suicidality, this approach hinders the prospect for reverse translational research because it is impossible to develop single models of disease states, like MDD, in animals. In fact, such a model could not account for the enormous heterogeneity of unique presentations of symptom clusters observed in DSM-defined disorders (Cuthbert, 2014).

To overcome these challenges, the RDoC can be used to advance suicide research by promoting cross-species investigations of processes that predict suicidal thoughts and behaviors. This framework is especially useful considering the transdiagnostic nature of suicide, as well as the poor predictive power of self-report measures in this domain. Recent findings suggest that combining multiple units of analysis (e.g., subjective report and behavior) could enhance the ability to predict suicide (Nock et al., 2022). In this context, an RDoC approach would value cross-species behavioral assays of transdiagnostic risk factors discussed in this review. As an example, suicide could be examined within the Positive Valence Systems domain, perhaps targeting dysfunctional reward learning processes that predict suicide in humans. Using a cross-species task, like the probabilistic reward task (PRT; Pizzagalli et al., 2005), researchers could identify functional mechanisms that subserve reward learning in rodents and understand their relevance to suicide risk in humans. In effect, this endeavor will facilitate a better understanding of effective interventions that mitigate suicide risk. For a comprehensive review of RDoC applications to suicide research, see Glenn et al. (2017).

6. Future directions

This review has discussed promising new avenues for future suicide research based primarily on stress-related effects on endophenotypes of suicide, including the literature on endophenotypes that have been extensively studied in both animals and humans in stress and suicide research. Despite the breadth of the review, several additional biomarkers have not been discussed here, but will nevertheless be important to consider in future research. We refer the interested reader to a recent article that reviewed the last five years of research on suicide risk and discussed a number of novel biomarkers that may be relevant to this discussion (e.g., lipids, biometals, uric acid) (C. J. Johnston et al., 2021).

Notably, this review highlighted several instances where causality has yet to be established in the literature. In fact, much of the literature identifies associations between biomarkers and suicide, but few studies have established causal links between the two. As one recurring example, many clinical studies have shown associations between repeated life stress (particularly ELS) and increased suicide risk. The translational focus of the review sheds light on the importance of animal research on endophenotypes of suicide, given ethical constraints in both stress and suicide research. Indeed, many clinically relevant discoveries have been credited to animal research, mainly due to the limitations associated with human studies. In this context, cross-species translational research is needed to establish causal links between stress and suicide risk. Future studies should capitalize on established animal models of endophenotypes of suicide to determine the mechanisms by which stress acts as a precipitating and perpetuating factor in suicidality. Towards this goal, current gold-standard preclinical assessments (e.g., forced swim and sucrose preference tests) must be reconsidered, and perhaps refined, to optimize construct and face validity. The development of novel cross-species assays will help determine whether stress-related endophenotypes of suicide can be pharmacologically modulated, thereby informing treatments and interventions that could reduce suicide risk.

As discussed above, subanesthetic-dose ketamine profoundly restores stress-induced impairments in domains of functioning linked to suicide. Translational studies could systematically evaluate the restorative or prophylactic effects of ketamine on these domains to ascertain its mechanisms of action in reducing suicide risk. Towards this goal, studies might examine the restorative effects of ketamine in chronically stressed humans and animals, or perhaps whether it can prevent acute stress-induced dysfunction in those with ELS. Given that stress differentially affects neurobiological and behavioral correlates of suicide at various developmental periods, clinical trials should account for individual differences in prior stress experience in evaluating ketamine's anti-suicidal properties.

The current review highlights the heterogeneity of suicide, with dynamic changes in neurobiology and behavior along the continuum of suicide risk (e.g., differential CORT output patterns during periods of SI versus suicide attempt). Accordingly, future studies should move toward subtyping of suicidality (see Rizk et al., 2018) in order to identify specific characteristics that predict suicide risk. Carefully examining various suicide endophenotypes will play a critical role in any such endeavor. As an example, Stanley et al. (2019) recently identified a stress-responsive subgroup of suicide attempters with high impulsive aggression. Delineating these clinical characteristics will not only resolve paradoxical findings in the literature (e.g., Heim et al., 2000) but help characterize subgroups of people at high risk for suicide.

7. Conclusions

Chronic stress and suicide share several neurobiological underpinnings, offering a compelling case for stress-related antecedents in suicide risk. Recurring themes emerged in the current review that shed light on specific targets for intervention. ELS, for instance, predicts poor outcomes for most candidate endophenotypes of suicide in humans and animals. Indeed, childhood maltreatment is associated with higher risk of suicide attempt (and at an earlier age), independent of psychopathology (Hoertel et al., 2015). This highlights a critical need for early interventions for individuals who have experienced childhood adversity. Chronic, as opposed to acute, stress also exerts distinct effects in modulating endophenotypes of suicide. In a vacuum, acute stress exposure rarely elicits pathological outcomes. In the context of prior chronic stress exposure or underlying psychopathologies, however, acute stress could trigger imminent pathological reactions (Sousa,

2016). This review discussed instances where acute stress might predict an imminent suicide crisis with respect to stress reactivity, anhedonia, and impulsivity. Future research might examine the temporal dynamics of these effects, particularly the differential effects of stress at various points along the continuum of suicide risk (e.g., SI versus planning versus attempt). Finally, as reviewed above, ketamine acts on distinct components of stress pathophysiology that overlap with endophenotypes of suicide, in direct contrast to conventional antidepressants. Thus, ketamine treatment may be particularly effective for individuals who are susceptible to stress, perhaps most notably those with a prior history of prolonged stress exposure.

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