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MOOD DISORDERS (E BACA-GARCIA, SECTION EDITOR)

Environmental Stressors May Drive Inflammation and Alter Neurocircuitry to Promote Suicidal Behavior

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Abstract

Suicide morbidity and mortality are serious public health problems, accounting for over 40,000 deaths annually and over $10 billion in combined medical and work loss costs. Suicidal behavior is the outcome of a complex causal web of distal and proximal risk processes that includes a range of interacting environmental and biological determinants. We review current understanding of risk and protective factors, including recent findings on inflammatory processes, discuss recent research on environmental risks for suicidal behaviors with a focus on economic stress, and examine potential mechanisms by which external factors and internal processes such as inflammation might contribute to pathways leading to suicidal behavior. We propose a model that links changes in the default network or resting state of brain activity with corresponding changes in brain structure and function, which in turn may be influenced by diverse inflammatory mediators, and suggest a potential framework that highlights multidisciplinary opportunities for further research.

Keywords Suicidal behavior · Neuroinflammation · Stress · fMRI · Default network · Unemployment

Introduction

Suicide mortality and morbidity convey substantial personal, societal, and economic costs. In addition to the emotional toll suffered by families and loved ones, combined medical and work loss costs resulting from suicide deaths amount to an estimated $51 billion [1]. Nonfatal self-inflicted injuries account for nearly 500,000 emergency department (ED) visits [1], over 160,000 hospitalizations [2], and $10.4 billion in combined medical and work loss costs [1].

Suicide is defined by the Institute of Medicine (IOM) as "death caused by self-directed injurious behavior with any intent to die as a result of the behavior" [3]; a *suicide attempt* is defined as a "non-fatal self-directed potentially injurious behavior with any intent to die as a result of the behavior" [3]. Three essential elements distinguish death by suicide from nonsuicidal fatalities, and all three criteria must be present in order for an act to be considered suicide: (1) the act or injury is self-inflicted, (2) the act is intentional, and (3) the outcome of the act is death [4, 5]. Like suicide, a suicide attempt is also self-directed and intentional. Although a suicide attempt is not fatal, it includes the desire to die at some nonzero level and the individual's expectation that the outcome of the act will be death [4–6]. These features distinguish a suicide attempt from nonsuicidal self-injury or violence (NSSI). While both are self-directed and intentional, NSSI does not include either the desire to die or expectation of death [5].

Suicide mortality and morbidity are serious, but preventable, public health problems. A better understanding of the risks and antecedents that lead to suicide can potentially save tens of thousands of lives. The goal of this review is to briefly

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summarize current understanding of risk and protective factors, including recent findings on inflammatory processes, discuss recent research on environmental risks for suicidal behaviors with a focus on economic stress, and suggest a potential framework that highlights multidisciplinary opportunities for further research.

Mortality

The 2017 age-adjusted death rate from suicide (intentional self-harm) [7] in the USA was 14 per 100,000, an increase of 33% since 1999 (10.5 per 100,000) [8]; indeed, increased suicide rates are considered an important contributor to the recent alarming decline in US life expectancy [9]. Suicide was the tenth leading cause of death, accounting for about 1.6% of total deaths in 2017, with rates among whites 2.5 times higher than rates among blacks [8, 10]. Although suicide mortality rates are nearly four times greater among men than among women regardless of race, ethnicity, or age, between 1999 and 2017, rates among women increased by 53% compared with a 26% increase among men [8]. Suicide rates are generally higher among older age groups, with the highest rates found among men 75 years of age and older [8]. US suicide rates vary widely across geographic areas, with consistently higher rates reported in Western and Mountain states [10] and in rural counties [8].

Morbidity

Overall lifetime prevalence of nonfatal suicide attempts in the general population ranges from 1.1 to 5.0% [11–15], with 12-month prevalence estimates ranging from 0.2 to 1.7% [13, 16–20]. Limited reports of incidence of nonfatal suicidal behaviors among adults show annual incidence estimates from 149/100,000 person-years to 190/100,000 person-years [19, 20].

There is almost no information on one of the major criteria for suicidal self-injuries, intent of suicidal behaviors. Evidence from a handful of studies of representative populations 15–54 years of age [12–15] indicates that the proportion of deliberate, self-inflicted injuries made with the intent to die is approximately two thirds of all nonfatal self-injuries, suggesting that suicide attempts are more common than NSSIs, although the latter are clearly nontrivial and need attention. The line between attempted suicide and NSSI is not sharply drawn, and it is likely that the two populations overlap. Limited findings from recent studies have shown that NSSI and suicide attempts share common characteristics and can co-occur [21–24], and more severe forms of NSSI such as cutting or burning are associated with increased risk for suicide attempts [21, 25].

In contrast to mortality rates from suicide, both lifetime and 12-month prevalence rates of nonfatal suicidal behaviors are higher among women than among men, across all age and racial/ethnic groups [11, 15–18, 26–29], but there appear to be no significant sex differences in more recent or incident suicidal ideation or behaviors among adults [13, 19, 20, 30]. Also, in contrast to suicide mortality, there is consistent evidence from multiple studies that both lifetime and recent rates for nonfatal suicidal behaviors and NSSIs are higher in younger age groups [11–13, 18–20, 24, 30–32].

Distal and Proximal Risks for Suicidal Behavior

A risk factor is a characteristic, variable, or hazard that increases the likelihood of development of an adverse outcome, is measurable, and precedes the outcome [33]. Risk can be distal or proximal. Distal risk factors encompass the underlying biological, interpersonal, and contextual vulnerabilities for suicidal behaviors and are considered necessary but not sufficient. Proximal risk factors are stressors or precipitating conditions or events that may closely precede suicidal behavior, but they are neither necessary nor sufficient [34, 35].

Suicidal behavior is the outcome of a complex causal web of both distal and proximal risk processes that includes a constellation of interacting environmental and biological determinants. Distal risk factors for suicide and suicidal behavior have been well established for individuals who die by suicide or make serious suicide attempts and who share many of the same risks [31]. The primary distal risk factors for suicidal behavior include psychopathology, comorbid mental, substance use, or physical disorders, selected endophenotypes, and familial contribution to risk [11–15, 26, 34, 36]. Familial studies of suicide have described a broad suicide phenotype that includes ideation, plans, and attempts, aggregates in families, and is heritable [37], but this observation is explained only in part by familial transmission of vulnerability to psychiatric disorders [37, 38]. Examination of potential intermediate phenotypes, or endophenotypes, for suicidal behavior has identified several that meet the endophenotype criteria [39] and are significantly associated with suicidal behaviors [36].

Distal risk factors can interact with proximal precipitants to produce a heavy burden of risk and unleash a cascade of behavioral and biological processes in a vulnerable person, leading to suicidal outcomes [34]. Proximal risk factors vary greatly by individual but can include, for example, serious perceived interpersonal problems, social problems, economic stress, or other socio-environmental risk factors. The overall burden of risk and its perceived impact on the individual may be more salient than the exact nature of a precipitating factor.

Economic Stress and Suicide

One example of proximal risk in the socio-environmental domain is economic stress. The worldwide economic recession in the early 2000s has drawn attention to the potential role of economic stress and unemployment as contributors to suicide deaths. There is substantial evidence that economic recession is associated with an increase in suicide rates in middle- and high-income countries [40•] and that rising unemployment during such periods is associated with a marked increase in suicides, particularly among males [40•, 41]. For example, the US suicide rate among working-age adults 16–64 increased from 12.9/100,000 in 2000 to 17.3/100,000 in 2016, an increase of 34% [42]. In a study of the impact of unemployment on suicide rates from 1979 to 2010, DeFina & Hannon [43•] showed that unemployment rates did not significantly impact suicide rates during the first half of the study period but had a highly significant effect during the second half, which corresponded with the recent recession. The impact of unemployment appears to differ by social and occupational group, with men and people in blue-collar jobs being particularly affected [40•, 42, 43•].

Despite this work, the overall quality and strength of the evidence linking economic stress with suicide are limited [40•]. While there is no doubt that suicide rates increase with unemployment rates, the association is merely correlational. No causal inferences can be made because the available evidence comes from ecological studies, that is, the findings are based on aggregate data at the state, country, or regional level, and not on the experiences of individuals. Further, most studies linking suicide with unemployment have failed to take into account mental health, including substance use disorders, as a potential confounder in a hypothesized causal pathway between unemployment and suicide. Without individual-level data from well-characterized cohort studies, it is not possible to demonstrate whether a direct causal link may exist between becoming unemployed and subsequent suicidal behavior or death.

The issue is further complicated by the observation that chronic unemployment is associated with depression and mental illness, including substance use disorders [40•], but the population of persons who are both unemployed and depressed or mentally ill includes at least two subpopulations that may not be mutually exclusive. One group includes those who were previously healthy but become clinically depressed as a result of prolonged unemployment, mounting debts, possible loss of housing, other economic stress, and relationship strain [30, 40•, 44]; the other includes those who are chronically unemployed or underemployed because they have a mental and/or substance use disorder and have difficulty finding or maintaining employment. The latter group especially may be more vulnerable to suicidal behavior since they are more likely to be unemployed regardless of the economic situation, are more likely to have lower-level jobs and earn less money, are less likely to have stable employment, and are more likely to lose their jobs [44–46].

A recent meta-analysis of five population-based, retrospective cohort studies was conducted by Milner et al. [47••] in an effort to disentangle the unemployment-suicide relationship by controlling for the occurrence of mental disorders. The authors found that the overall relative risk for suicide of 1.58 was reduced by 37% to 1.15 after adjusting for a history of prior mental disorder. They also found that longer exposure to unemployment was associated with a higher risk of suicide death [47••].

Suicidal behavior can be an outcome of distal risk factors such as psychopathology and biological vulnerability that interact with more proximal risks such as economic stress, yet our understanding of potential mechanisms underlying both distal and proximal risks remains limited. The sheer length and diversity of the list of proximal risk factors present a challenge to researchers and highlight the need for a framework to explain our observations. The relationship between economic stress and suicide is only one example from a litany of exposures that needs to be consolidated. Other examples of possible proximal risk factors include, but are not limited to, arguments with a romantic partner, or with a friend, parent, employer, or co-worker; a humiliating experience; being the victim of discrimination and/or bullying; terminal illness, physical or sexual abuse, incarceration, living alone, availability of means such as firearms or poisons; intoxication with alcohol or other drugs; and perceived loss of independence. These are not trivial experiences; they are negative, stressful, and can be life-threatening, but many individuals experience similar stressors yet never become suicidal. It is reasonable to think that almost any stressful experience that has a powerful subjective impact could lead to suicide for some vulnerable individuals, but how this might happen is not yet well understood. What are the potential biological mechanisms by which greatly diverse, clinically observed, proximal exposures might interact with underlying distal risk processes to bring about suicidal behavior?

Biological Processes and Suicide

Investigations of post mortem brain tissue of individuals who died by suicide led to the identification of biological correlates of suicidal behavior (see Mann [48] for a review). Investigators have directed considerable attention to studies of serotonergic system dysfunction, which has been implicated in depression, hopelessness, and pessimism [48, 49] and has been independently linked with aggression and impulsivity [36, 48, 50]. Attention has also focused on the noradrenergic system; overactivity has been associated with severe anxiety, agitation, overactivity of the hypothalamic–pituitary–adrenal (HPA)

axis, and increased risk for suicide [48]. Evidence of HPA axis dysfunction in suicide suggests that a biological response to stressors such as poor interpersonal relationships, abuse, bullying or other proximal risk factors may help explain the contribution of such experiences to the overall burden of risk for suicide. Stressors such as these, especially early in life, are postulated to produce epigenetic changes as seen in post mortem suicide brain tissue, which alters glucocorticoid receptor expression and results in HPA axis dysfunction [51]. HPA axis dysfunction may increase an individual's risk for suicide by reducing their ability to modulate the inflammatory response and adapt to ongoing stressors [52].

Neuroinflammation appears to be the unifying factor underpinning otherwise unrelated biological distinctions associated with mental illness and suicide [53••]. Recent findings suggesting that inflammatory processes have a role in suicide include associations between inflammation and depression and between infection (e.g., *Toxoplasma gondii* [53••]), peripheral cytokine levels, inflammatory metabolites, traumatic brain injury [54], vitamin D deficiency [55, 56], and higher risk for suicidal ideation and behaviors [57]. Neuroinflammation is associated with activation of microglia and production of inflammatory cytokines, which can influence HPA axis and neurotransmitter functioning as well as neurogenesis and neurodegeneration. Inflammatory cytokines can activate the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan, serotonin, and melatonin, and initiates the production of neuroactive and immunoregulatory metabolites, including kynurenine and quinolinic acid [58]. The influence of inflammatory cytokines on serotonin function could explain why serotonin deficits are often seen in suicide [36, 48].

Normally, circulating immune mediators are largely blocked by the blood–brain barrier (BBB). However, in certain situations, disruption of the blood–brain barrier plays a role in cellular damage in neurological disorders, including multiple sclerosis [59], traumatic brain injury, and even pain [60]. The exposure of the brain to increased blood flow also increases exposure to increased matrix metalloproteinases (MMPs), proteolytic enzymes that degrade all components of the extracellular matrix (ECM) when activated [61]. MMPs can further disrupt the BBB and break down myelin, an important component of the white matter tracts which are critical for optimal brain connectivity [62]. Excessive alcohol intake may also drive neuroinflammation [63•]. More detailed investigations of these processes have been reviewed elsewhere [53••, 64••, 65, 66••, 67, 68].

Brain Imaging

While the core neural networks involved in psychopathology and suicidal behavior are not yet fully understood, recent research using functional magnetic resonance imaging (fMRI) suggests how the brain may be altered to promote suicide [69]. For example, fMRI conducted during the resting state has associated vulnerability to suicidal behavior with abnormalities in fronto-limbic or fronto-parietal cerebellar pathways which appear during cognitive or emotionally salient tasks. In suicidal patients, fMRI data at a resting state showed greater relative coupling between the dorsal anterior cingulate cortex (dACC) and ventral posterior cingulate cortex (PCC) compared to control patients [70]. The dACC, a component of the limbic system, has also been shown to have relatively increased activation during emotional tasks in patients with a history of suicidal behavior.

The data suggest a model which may prove useful in driving multidisciplinary research. FMRI is based on the principal that when the activity of neurons increases, glutamate flux and cerebral blood flow increase. By extension, a change in cognitive response styles associated with suicide, which induces increased activity of some neurons, will induce a compensatory vasodilatation to increase blood flow to those neurons [71]. In addition to the established effect of this increased blood flow of supplying greater metabolic support for cellular functions, other effects may occur over time. As blood carries humoral messengers which can influence neurons, we hypothesize that localized increases in blood flow could cause a local exaggeration of this influence. Therefore, areas of the brain with increased neural signaling can be expected to experience an exaggerated influence from immunologically active molecules which could influence nerve function. The net effect is that altered cognitive processing patterns could affect structural changes in localized areas of the brain. If humoral messengers promote an exaggerated inflammatory signal, this could promote a localized inflammatory signal in the brain that could activate microglia and cause neurodegeneration, which, when persistent, could explain changes in the brain detected by structural imaging of individuals with suicidal behavior [72, 73]. It is unknown if depressive ruminations are associated with specific neural pathways, but if they are, excess inflammatory signaling induced in such pathways could lead to neuroanatomical changes noted with depression [74], creating a suicide-promoting cycle of dysfunctional neural circuitry. Psychotherapeutic interventions which minimize such ruminations (e.g., ketamine [75]) could drive neuroadaptations away from this dysfunctional cycle of brain activity and toward a normal pattern.

Neuroimmune Interactions

Perhaps the most illustrative association of immune dysregulation and suicide is the association of allergy with suicide

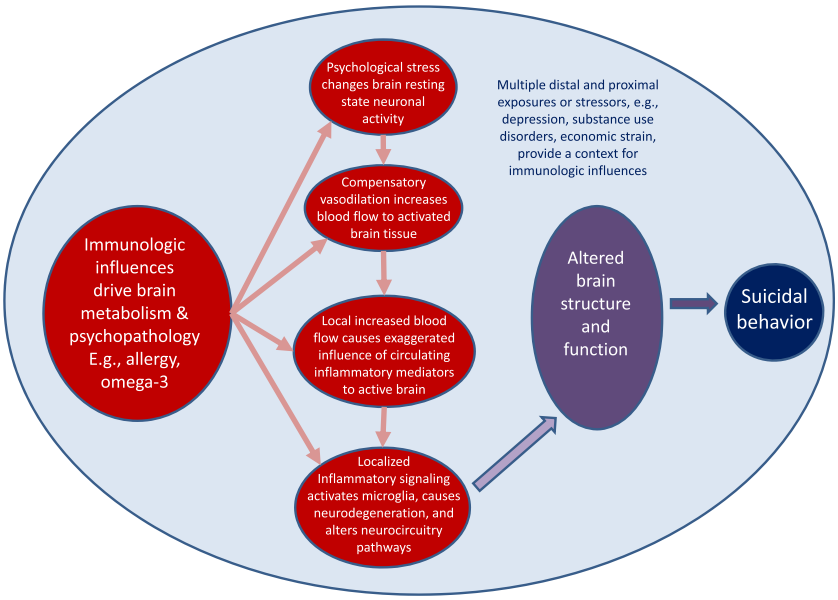

Fig. 1 Multiple distal and proximal stressors interact to initiate neurological changes and promote suicide

[76]. This is supported by studies demonstrating an increased risk of suicide in individuals with allergy and other disorders of immunity [77]. Allergy and immune dysfunction can be alleviated by a number of host factors; some of these, such as omega 3 fatty acids [78, 79], are themselves inversely associated with suicide [80•, 81].

Figure 1 illustrates how external stressors and neuroinflammation might alter neurocircuitry to promote suicidal behavior. Distal risks, such as underlying mental and substance use disorders and endophenotypes, and proximal risks, such as economic strain, interact with each other and provide a context for immunologic influences that drive brain metabolism and psychopathology. These in turn lead to changes in the brain's resting state neuronal activity. Compensatory vasodilation increases blood flow to the brain; local increased blood flow exaggerates the influence of circulating inflammatory mediators; localized signaling activates microglia and causes neurodegeneration and alters neurocircuitry pathways. These changes alter brain structure and function and may lead to suicidal behavior.

We theorize that chronic psychological stress could alter resting state activity of the brain, permitting immune mediators to influence neuronal structure and function at the site of altered activity, and creating a death-promoting cycle of neurocircuitry that leads to elevated risk for suicide in affected individuals. We propose that this mechanism could help explain the association of suicidal behavior with immunological dysregulation such as that seen in allergy, as well as that seen with inadequate exposure to anti-inflammatory factors such as omega-3 fatty acids [82, 83]. A potential mechanism of this nature suggests that public health efforts directed to improving immune function might work to normalize brain function when psychosocial risk is high. Recent work with soldiers to increase dietary omega-3 fatty acid intake suggests that this type of change is feasible and may produce an entirely new approach to suicide prevention [84].

Conclusion

While the accumulation of proximal stressors may add to the overall risk burden for suicidal behavior, the distal risk factors related to biology may present the greatest opportunities for the prevention of suicide [84, 85]. Research which combines imaging techniques with both psychological and dietary interventions could both test this hypothesis and help optimize public health interventions. Although the various disciplines which study suicide do not commonly synthesize their respective areas of expertise, it is precisely in the synthesis where prevention efforts may be the most productive.

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Compliance with Ethical Standards

Conflict of Interest Eve K. Mościcki and John C. Umhau declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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