Suicide as a Systemic Disorder

19

Aiste Lengvenyte, Emilie Olié, and Philippe Courtet

19.1 Introduction

Suicide, broadly defined as the intentional termination of one's own life, is a complex phenomenon, which affects human societies worldwide. Despite increasing efforts to reduce this burden, suicide rates remain as high as ever, and in some Western countries are even growing. Suicide transcends common disciplines. It is driven by intricate interactions between genetic predisposition and environment. Accumulating evidence indicates that the alteration of the immune system is of paramount importance to the pathophysiology of suicidal behaviours (SB) [1]. In this chapter, we will overview the current evidence for the role of inflammation in the pathway from health to suicide.

19.2 Suicide and Inflammation: Epidemiological and Clinical Findings

Recent analyses of large-scale registry data contributed significantly to the increasing appreciation of the innate immunity involvement in the pathway from health to suicide. Data from Danish registries showed the dose-dependent long-term increase in SB risk following infections treated with anti-infective agents for up to 5 years. Moreover, the risk was the highest for individuals treated with broad-spectrum antibiotics and requiring hospitalization [2]. Another large-scale sero-epidemiological case-control study from Denmark also showed a specific association between

A. Lengvenyte · E. Olié · P. Courtet (✉)
Department of Emergency Psychiatry and Acute Care, CHU Montpellier, Montpellier, France

University of Montpellier, Montpellier, France

FondaMental Foundation, Créteil, France
e-mail: e-olie@chu-montpellier.fr; philippe.courtet@umontpellier.fr

M. Berk et al. (eds.), *Immuno-Psychiatry*, https://doi.org/10.1007/978-3-030-71229-7_19

herpes simplex virus type 1 infection and suicide attempt or suicide in an otherwise healthy population [3].

Accordingly, medical conditions whose core feature is immune system dysfunction, such as systemic lupus erythematosus [4], multiple sclerosis [5], and asthma [6] have also been consistently associated with SB. An inflammatory response to increased air pollen counts in sensitized individuals could also serve as a putative explanation for increased suicide occurrence in spring season [7]. Indeed, intranasal corticosteroids have been shown to reduce suicide risk [8]. Though allergic conditions consist of various immune responses in the periphery with unknown effects on the central nervous system (CNS), supporting evidence for the peripheral inflammation and CNS function has been provided by tumour necrosis factor (TNF)-α inhibitors trials. Apart for some studies demonstrating the causal relationship between the induced inflammation and subsequent onset of depression [9], suicidal ideation and attempts have also been documented in previously psychiatrically healthy patients with multiple sclerosis following treatment with interferon-β [10]. Seasonal changes in vitamin D, which contributes to immune function via T-helper system promotion, concentration might also add to this connection, as deficiency in vitamin D has been associated with both higher levels of inflammatory cytokines in blood and suicide attempt history [11].

Substantial evidence also links the presence of infectious agents in the CNS with SB risk, very likely at least partly via increased neuroinflammation. Studies have consistently confirmed the association between seropositivity to *Toxoplasma gondii* and cytomegalovirus, common conditions in worldwide populations causing chronic low-grade inflammation and increased SB risk [12].

19.3 Peripheral Inflammation Markers and Suicide

A mounting number of studies detected inflammatory marker changes in the blood of suicidal subjects. Suicide attempt history in psychiatric patients has been related to higher neutrophil to lymphocyte ratio [13]. Furthermore, meta-analytical evidence demonstrated increased interleukin (IL)-1β and IL-6 in in-vivo blood levels and decreased in-vitro IL-2 levels in suicidal patients compared to both non-suicidal patients and healthy controls [14]. Another meta-analysis confirmed lower IL-2 plasma levels in suicidal patients, also adding that these subjects had lower IL-4 and higher TNF-β plasma levels than healthy controls, but not psychiatric patients [15].

Contrary to cytokines, C-reactive protein (CRP) has a sufficiently long half-life and is widely measured in everyday clinical practice, supporting its applicability in clinical research. A study that measured fasting high sensitivity CRP (hs-CRP) in depressed patients found a direct dose-dependent relationship between hs-CRP and suicide attempt history, and low-grade inflammation (hs-CRP > 3 mg/L) compared to those with low levels of hs-CRP (<1 mg/L), even after exclusion of patients with chronic diseases and high CRP levels (>10 mg/L). Meanwhile, suicidal ideation was not related to hs-CRP levels in this study, suggesting that inflammatory changes may serve as a trait, but not state, markers for suicidal vulnerability in depressed

patients [16]. Accordingly, two recent studies with bipolar disorder and unipolar depression patients reported a positive link between high serum CRP levels (>3 mg/L) and suicide attempt history compared to those with low levels of CRP [17, 18], though the study in depressed people found that the existence of physical illness could explain this relationship [18]. A study in youth observed distinct inflammatory profiles in suicide attempters compared to suicide ideators and healthy controls, as suicide attempters had higher CRP, TNF-α mRNA, and lower glucocorticoid receptor mRNA levels [19]. In a study of women with depression and anxiety diagnoses, the biological profile of patients assessed to be at increased suicide risk, the biological cluster containing increased levels of IL-6, lymphocytes, monocytes, white blood cell count, and polymorphonuclear leukocyte count significantly impacted suicide risk, while the cytokine IL-8 was independently and negatively associated with increased suicide risk [20].

19.4 From Systemic Inflammation to Central Nervous System Changes

Several lines of evidence converge on the link between peripheral and central inflammation and its effects on brain structure and function. Possibly due to their short half-life, cytokine levels in the periphery do not reflect their levels in the CNS. Peripheral and central inflammation are nevertheless tightly linked. In a study with depressed patients, plasma CRP levels were related to cerebrospinal fluid (CSF) CRP levels, which, in turn, were linked to CSF cytokine receptors [21]. Different mechanisms have been proposed to link immune system and brain function changes that can mediate suicidal behaviours. Firstly, systemic inflammation and neuroinflammation cause blood-brain barrier (BBB) lesions, including changes of BBB permeability [22]. An increase in blood-brain barrier (BBB) permeability impairs synaptic transmission and neuronal functioning [23]. Interestingly, changes in blood levels of S100B, a protein biomarker of BBB permeability, were found in adolescents with suicidal ideation in comparison to healthy controls [24]. Altogether, it is hypothesized that BBB permeability may have an impact on the communication between peripheral inflammation and the brain [25], and may play a role in suicidal physiopathology.

Systemic inflammation is also proposed to affect the body's interoceptive systems. Following the immune activation, circulating inflammatory mediators activate visceral autonomic afferents, humoral, and cellular interoceptive pathways in parallel that then communicate the changes in immune state to the brain. When inflammation is severe, chronic, occurs during critical developmental period, or on a background of other chronic brain exposures, prolonged activation of interoceptive pathways can precipitate long-standing maladaptive neurobiological and behavioural changes [26]. Systemic inflammation has been demonstrated to alter the microstructure of the insular cortex, which is implicated in representing internal physiologic states including inflammation, also linking it to subjective fatigue [27]. Moreover, in accordance with the stress-diathesis model of suicide, interoceptive

pathways activation has been linked to the stress sensitization. For example, direct monocyte trafficking to brain, a cellular interoceptive pathway, increases significantly following severe stress, and possibly serves as a mechanism for amplifying behavioural stress responses when stress is repetitive or prolonged [28]. Self-reported interoceptive deficits, or the inability to effectively and accurately monitor the physiological state of the body, have been linked to both suicidal ideation and suicide attempts [29, 30], and are more pronounced in the extreme end of the suicidal continuum [30]. Indeed, in a large multiple sample study, self-reported interoceptive deficits in adult participants were associated with suicide attempts history, but not suicidal ideation [31].

19.5 Central Inflammation and Suicide

While normal brain function requires low levels of inflammatory cytokines, when inflammation surpasses brain adaptive capacity, elevated cytokine levels result in anatomical and functional damage, entailing maladaptive neurobiological and behavioural changes. Cerebrospinal fluid (CSF) levels of IL-6 are increased in suicide attempters regardless of their psychiatric diagnosis [32], and IL-1β and IL-6 levels in both CSF and post-mortem brain samples have been linked to suicidality in patients with psychiatric disorders [14]. Consistently, a human post-mortem study found a significant increase in the complement system, which plays a critical role in inflammation, component 3 expression in the prefrontal cortex of depressed suicide subjects [33]. Another putative neuroinflammation marker found in patients with suicidal ideation, the translocator protein (TSPO), reflecting microglial activation. A post-hoc analysis of a small sample of depressed patients demonstrated that TSPO was increased in individuals with suicidal thoughts compared to those without suicidal thoughts, who were not different from healthy controls, most robustly in the anterior cingulate cortex and insula [34].

Compelling evidence comes from studies examining the relationship between conditions directly causing neuroinflammation and glial activation in the brain, such as traumatic brain injury [35] and concussion [36], and SB. Microglia and macrophages belong to the innate immune system and are highly reactive to alterations in homeostasis. Upon the recognition of environmental stressors, they morph into active phenotypes and induce the transcription of the inflammasome [37]. In the face of repetitive environmental challenges, microglia and macrophages are primed for amplified and persistent inflammatory responses. This chronic neuroinflammation might increase susceptibility to new stressors, serving as a neurobiological mediator within the stress-diathesis model of suicide. Indeed, individuals with traumatic brain injury history have been demonstrated to have significantly higher TNF-α levels than healthy controls, which were associated both with disinhibition and suicidal ideation up to 12 months after the injury [38]. Several post-mortem studies found higher microglia priming, demonstrated by overactive de-ramification, in the anterior cingulate cortex of suicide descendants compared to subjects that died from other causes [39, 40].

A study has demonstrated that, within the default mode network, which is crucial for the self-referential processes, IL-6 covaried positively with the connectivity of the subgenual anterior cingulate cortex and negatively with a region of the dorsal medial prefrontal cortex [41]. Increased default mode network activity has been observed in suicide attempters, especially in recent attempters [42]. Salience network, which is involved in coordinating the activation of executive control and default mode networks coherence, has been demonstrated to decrease in functional connectivity in response to increased plasma IL-6 and TNF-α concentration [43], and reduction in suicidal ideation is associated with increased salience network coherence [44].

Genetic and epigenetic changes have been proposed to take part in this complex relationship between inflammation and SB. A family-based analysis revealed a genetic overlap between IL-8 and risk for suicide attempt in females [45]. Postmortem studies demonstrated increased mRNA and protein levels of IL-1β, IL-6, TNF-α, lymphotoxin A, and certain Toll-like receptors, as well as decreased anti-inflammatory cytokine IL-10, and IL-1 receptor antagonist levels in the prefrontal cortex of depressed individuals who died by suicide compared with controls [46, 47]. In accordance, a study that used two different cohorts of brain samples revealed consistently increased TNF-α expression in the dorsolateral prefrontal cortex of all individuals who died by suicide regardless of psychiatric diagnosis [48].

19.6 Kynurenine Pathway

A growing body of evidence suggests that a putative pathway linking inflammation and SB is the dysregulation of the kynurenine pathway of tryptophan metabolism. Under normal circumstances, around 90% of tryptophan is metabolized via this pathway, raising the levels of cellular energy, while a fraction of tryptophan is converted to 5-HT and, subsequently, melatonin. In the brain, where tryptophan is transported via the BBB, the kynurenine pathway produces several neuroactive compounds, of which quinolinic acid and kynurenic acid are of particular importance. Increased levels of pro-inflammatory cytokines due to the inflammation induce the kynurenine pathway, preferentially generating cellular energy, in disadvantage of 5-HT production [49]. Chronic excess of pro-inflammatory cytokines continually up-regulates the expression of the enzymes that launch the kynurenine pathway hepatic tryptophan-2,3-dioxygenase (TDO) and extrahepatic indoleamine-2,3-dioxygenase (IDO), while in the brain-activated microglia and infiltrating monocytes and macrophages convert kynurenine into quinolinic acid. Quinolinic acid, synthesized mainly by activated microglia and brain-infiltrating macrophages, selectively agonizes *N*-methyl-*D*-aspartate (NMDA) receptors, inhibits glutamate uptake by astrocytes, and stimulates glutamate release, resulting in decreased brain-derived neurotrophic factor (BDNF) expression and ecotoxicity [50]. Moreover, it has pro-inflammatory and immunoregulatory properties. Meanwhile, astrocytes express the enzyme kynurenine aminotransferase essential to produce kynurenic acid, which, in contrast to quinolinic acid, exerts

neuroprotective properties via antagonism of NMDA and cholinergic α7 nicotinic receptors [51]. Preclinical evidence shows that chronic mild stress leads to increased IDO expression and increased levels of quinolinic acid in rats. Interestingly, antidepressants restored these effects [52].

Plasma level of kynurenine, the first metabolite produced along the kynurenine pathway, has been reported to be significantly elevated in depressed suicide attempters compared to non-suicidal patients [53]. Another study found a net decrease in plasma tryptophan levels and an increase in kynurenine/tryptophan ratio in suicidal adolescents with major depressive disorder, compared to non-suicidal individuals with major depressive disorder and healthy controls. Moreover, the kynurenine/tryptophan ratio was correlated with the severity of suicidal ideation [54]. Quinolinic acid levels in CSF have been demonstrated to be two to three times in suicide attempters compared to controls [55]. Moreover, in accordance with the inflammatory hypothesis, they positively correlated with IL-6 levels in CSF. Notably, quinolinic acid levels, though decreasing, remained increased at almost 2 years after the suicide attempt, and the magnitude of suicidal symptoms during the follow-up was related to fluctuations in cytokines and kynurenic acid, with direct relationship with the former and inverse with the latter, showing sustained dysregulation of the tryptophan-kynurenine pathway [56]. Post-mortem study demonstrated increased counts of quinolinic acid-reactive microglia cells in the subgenual anterior cingulate cortex and anterior midcingulate cortex in depressed suicide completers [57]. Moreover, the deficient activity of one kynurenine pathway enzyme has been linked to increased suicidal vulnerability [58]. Accordingly, a post-mortem study has demonstrated decreased 5-HT transporter and increased 5-HT1A and 5-HT2A binding in the neocortex of depressed suicide victims compared to healthy controls [59], suggestive of an adaptive response to low 5-HT availability in the brain, which could result from the kynurenine pathway hyperactivation. Involvement of the kynurenine pathway in the pathophysiology of suicide might also explain the specific rapid anti-suicidal effect of ketamine, an NMDA-antagonist [60].

19.7 Inflammation as a Mediator Between Stress and Suicidal Behaviour

Stress, broadly referred to as the disruption of homeostatic balance by a stressor has been proposed to play a crucial role in increased SB susceptibility. Glucocorticoids, the end-products of the stress-response pathway, execute rapid anti-inflammatory action via a plethora of mechanisms, such as altered gene expression of pro-inflammatory cytokines [61], and protective action on the BBB [62]. Notably, glucocorticoids have a direct action on the brain, as their receptors are expressed by microglia [63]. However, this tight relationship between the stress-immune axes is highly susceptible to dysfunction, and excessive glucocorticoid release can contribute to increased inflammation by stimulating the release of IL-1β from microglia, which further contributes to activation of microglia and recruitment of monocytes into the brain.

Glucocorticoids and peripheral catecholamines facilitate inflammatory responses to future stimuli by stimulating monocytes to leave the bone marrow, down-regulating inhibitory receptors on microglia, and priming inflammatory responses mediated by peripheral monocytes or macrophages [64]. Pre-clinical studies show that stressors significantly increase microglial reactivity in the brains of experimental rodent models, which then contributes to altered behavioural responses [65]. Pro-inflammatory stress effects are also seen in clinical populations, as stress significantly increases the levels of circulating pro-inflammatory cytokines [66], possibly contributing to increased vulnerability when facing life challenges. Conversely, baseline peripheral inflammation modifies the prefrontal activity during social stress in patients having a history of depression but independently of suicidal status [67].

Inflammatory immune system dysregulation has also been proposed to act as a biological mediator linking SB and early life adversity. Solid evidence proves that early life adversity increases SB risk [68]. Early-life exposure to stress can trigger dysfunctional immune reprogramming, altering brain development, and increasing reactivity to stressors later in life. Pro-inflammatory state in adults, demonstrated by increased levels of such peripheral inflammation markers like CRP, IL-6, TNF-α [69], and soluble urokinase plasminogen activator receptor [70], has been consistently linked to early life adversity history. In accordance with the stress-diathesis model, unfavourable childhood environment has been associated with larger IL-6 stress responses in adulthood [71]. Increased levels of pro-inflammatory cytokines in depressed adolescent subjects with a childhood trauma history have been linked to inhibitory control deficits [72], behaviourally translating to impulsivity, which is linked to suicidality [73]. Interestingly, lithium, a proven anti-suicidal agent, is an inhibitor of the glycogen synthase kinase-3, which is activated in the brain by stress and promotes inflammation, as well as aggressive and depression-like behaviours in rodents [74].

19.8 Inflammation, Intermediate Phenotypes and Suicide

The increasing interest in the dimensional approach has led to a better understanding of certain behavioural dimensions that are implicated in suicidality. Anhedonia, a transdiagnostic positive valence symptom dimension, defined as the loss of pleasure or interest in previously rewarding stimuli, is independently related to increased suicidal ideation risk [75]. Convergent evidence suggests that inflammatory activation in response to physical, psychological or immunological stress disrupts mesolimbic reward functioning by interfering with dopamine synthesis, or via kynurenine-induced oxidative stress [76]. In animal models, chronic social stress led to immune activation and reduced the functioning of the ventral tegmental area-nucleus accumbens dopaminergic pathway, resulting in reduced reward-directed behaviours [77]. In humans, inflammation has been repeatedly linked to anhedonia [78] and related brain changes, such as the activation of the posterior cingulate cortex, prefrontal cortex, and basal ganglia regions, during reward processing [79].

Both increased glutamate levels in the basal ganglia and dorsal anterior cingulate cortex and anhedonia have been noted in depressed patients with serum CRP levels of 3 mg/L or higher, relative to those with CRP < 3 mg/L [80]. Another study identified that patients presenting a combination of elevated plasma CRP, basal ganglia glutamate levels, and greater severity of anhedonia also demonstrated lower regional homogeneity and impaired network integrity in the brain, supporting the link between peripheral inflammation, increased glutamate toxicity, and altered brain functionality [81]. Inflammation-induced neural responses to reward may provide insight into the sex gaps in suicide. For example, a functional magnetic resonance study that used an experimental inflammatory challenge found that endotoxin led to a reduced reward-related ventral striatum activity in anticipation of reward only in female participants [82]. Interestingly, anhedonia has also been linked to the ketamine's anti-suicidal effect [83].

Another intermediate phenotype, possibly linking inflammation and SB, is impulsivity. It has been linked to SB, especially the recent ones [73]. Increased anger and hostility have been observed in patients with hepatitis C that underwent IFN-α treatment [84]. In a sample with psychiatric inpatients, admitted because of suicide attempt or suicidal ideation, and healthy controls, TNF-α mRNA was associated with impulsivity and hopelessness [85]. Trait aggression and impulsivity have been proposed to mediate the relationship between *T.Gondii* infection and SB [86]. However, while some studies link immune system dysfunction to maladaptive decision-making patterns, characterized by impulsivity, present focus, and inability to delay gratification that can result in SB [87], other studies suggested that inflammatory profile and impulsivity both increase SB risk independently [88].

19.9 Conclusion

The current suicide prevention, prediction, and treatment strategies, vastly based on heterogenous categorical constructs of mental disorders, are both overwhelmingly unspecific and unsatisfactory in their outcomes. In light of strengthening position of dimensional approach to mental disorders in medicine, reflected by the rise of such frameworks as the Research Domain Criteria, inflammation may be regarded as a transdiagnostic phenomenon, conferring to increased suicide risk. As described in this chapter, inflammatory changes are the common denominator in suicidal behaviours occurring throughout a range of ailments of varying severity. Peripherally, increased cytokines and CRP levels are detected in suicide attempters and completers, while microglia activation and kynurenine pathway activation seem to be involved centrally. Multiple biological bodily systems are implicated in this intricate relationship, spanning from subtle molecular to overt neuroanatomical alterations. Addressing the inflammatory pathways is a viable way to complement clinical and research practices by both serving as the heuristic in the assessment and intervention in suicidal behaviour risk, stratifying intervention options for susceptible individuals, and facilitating the development of novel specific therapeutic targets in suicide.

References

1. Courtet P, Giner L, Seneque M, Guillaume S, Olie E, Ducasse D. Neuroinflammation in suicide: toward a comprehensive model. World J Biol Psychiatry. 2016;17:564–86.
2. Gjervig Hansen H, Köhler-Forsberg O, Petersen L, Nordentoft M, Postolache TT, Erlangsen A, et al. Infections, anti-infective agents, and risk of deliberate self-harm and suicide in a young cohort: a Nationwide study. Biol Psychiatry. 2019;85:744–51.
3. Nissen J, Trabjerg B, Pedersen M, Banasik K, Pedersen OB, Sørensen E, et al. Herpes simplex virus type 1 infection is associated with suicidal behavior and first registered psychiatric diagnosis in a healthy population. Psychoneuroendocrinology. 2019;108:150–4.
4. Xie L-F, Chen P-L, Pan H-F, Tao J-H, Li X-P, Zhang Y-J, et al. Prevalence and correlates of suicidal ideation in SLE inpatients: Chinese experience. Rheumatol Int. 2012;32:2707–14.
5. Fredrikson S, Cheng Q, Jiang G-X, Wasserman D. Elevated suicide risk among patients with multiple sclerosis in Sweden. Neuroepidemiology. 2003;22:146–52.
6. Barker E, Kãlves K, De Leo D. The relationship between asthma and suicidal behaviours: a systematic literature review. Eur Respir J. 2015;46:96–106.
7. Qin P, Waltoft BL, Mortensen PB, Postolache TT. Suicide risk in relation to air pollen counts: a study based on data from Danish registers. BMJ Open. 2013;3:e002462.
8. Woo J-M, Gibbons RD, Qin P, Komarow H, Kim JB, Rogers CA, et al. Suicide and prescription rates of intranasal corticosteroids and nonsedating antihistamines for allergic rhinitis. J Clin Psychiatry. 2011;72:1423–8.
9. Raison CL, Borisov AS, Majer M, Drake DF, Pagnoni G, Woolwine BJ, et al. Activation of central nervous system inflammatory pathways by interferon-alpha: relationship to monoamines and depression. Biol Psychiatry. 2009;65:296–303.
10. Fragoso YD, Frota ERC, Lopes JS, Noal JS, Giacomo MC, Gomes S, et al. Severe depression, suicide attempts, and ideation during the use of interferon Beta by patients with multiple sclerosis. Clin Neuropharmacol. 2010;33:312–6.
11. Grudet C, Malm J, Westrin Å, Brundin L. Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood. Psychoneuroendocrinology. 2014;50:210–9.
12. Dickerson F, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C, et al. The association between immune markers and recent suicide attempts in patients with serious mental illness: a pilot study. Psychiatry Res. 2017;255:8–12.
13. Ekinci O, Ekinci A. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord J Psychiatry. 2017;71:574–80.
14. Black C, Miller BJ. Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients. Biol Psychiatry. 2015;78:28–37.
15. Ducasse D, Olié E, Guillaume S, Artéro S, Courtet P. A meta-analysis of cytokines in suicidal behavior. Brain Behav Immun. 2015;46:203–11.
16. Courtet P, Jaussent I, Genty C, Dupuy AM, Guillaume S, Ducasse D, et al. Increased CRP levels may be a trait marker of suicidal attempt. Eur Neuropsychopharmacol. 2015;25:1824–31.
17. Gan Z, Wu X, Liao Y, Wu Y, He Z, Yang Z, et al. The association between low-grade inflammation and the clinical features of bipolar disorder in Han Chinese population. Psychoneuroendocrinology. 2019;101:286–94.
18. Oh KY, Van Dam NT, Doucette JT, Murrough JW. Effects of chronic physical disease and systemic inflammation on suicide risk in patients with depression: a hospital-based case-control study. Psychol Med. 2019:1–9.
19. Melhem NM, Munroe S, Marsland A, Gray K, Brent D, Porta G, et al. Blunted HPA axis activity prior to suicide attempt and increased inflammation in attempters. Psychoneuroendocrinology. 2017;77:284–94.
20. Keaton SA, Madaj ZB, Heilman P, Smart L, Grit J, Gibbons R, et al. An inflammatory profile linked to increased suicide risk. J Affect Disord. 2019;247:57–65.

21. Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry. 2018;17:1310–4.
22. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun. 2017;60:1–12.
23. Librizzi L, de Cutis M, Janigro D, Runtz L, de Bock F, Barbier EL, et al. Cerebrovascular heterogeneity and neuronal excitability. Neurosci Lett. 2018;667:75–83.
24. Falcone T, Fazio V, Lee C, Simon B, Franco K, Marchi N, et al. Serum S100B: a potential biomarker for suicidality in adolescents? PLoS One. 2010;5:e11089.
25. Bargerstock E, Puvenna V, Iffland P, Falcone T, Hossain M, Vetter S, et al. Is peripheral immunity regulated by blood-brain barrier permeability changes? PLoS One. 2014;9:e101477.
26. Savitz J, Harrison NA. Interoception and inflammation in psychiatric disorders. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018;3:514–24.
27. Harrison NA, Cooper E, Dowell NG, Keramida G, Voon V, Critchley HD, et al. Quantitative magnetization transfer imaging as a biomarker for effects of systemic inflammation on the brain. Biol Psychiatry. 2015;78:49–57.
28. Wohleb ES, McKim DB, Sheridan JF, Godbout JP. Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. Front Neurosci. 2015;8:447.
29. Dodd DR, Smith AR, Forrest LN, Witte TK, Bodell L, Bartlett M, et al. Interoceptive deficits, nonsuicidal self-injury, and suicide attempts among women with eating disorders. Suicide Life-Threatening Behav. 2018;48:438–48.
30. Rogers ML, Hagan CR, Joiner TE. Examination of interoception along the suicidality continuum. J Clin Psychol. 2018;74:1004–16.
31. Hagan CR, Rogers ML, Brausch AM, Muehlenkamp JJ, Joiner TE. Interoceptive deficits, nonsuicidal self-injury, and suicide risk: a multi-sample study of indirect effects. Psychol Med. 2019:1–12.
32. Enache D, Pariante CM, Mondelli V. Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain Behav Immun. 2019;
33. Crider A, Feng T, Pandya CD, Davis T, Nair A, Ahmed AO, et al. Complement component 3a receptor deficiency attenuates chronic stress-induced monocyte infiltration and depressive-like behavior. Brain Behav Immun. 2018;70:246–56.
34. Holmes SE, Hinz R, Conen S, Gregory CJ, Matthews JC, Anton-Rodriguez JM, et al. Elevated translocator protein in anterior cingulate in major depression and a role for inflammation in suicidal thinking: a positron emission tomography study. Biol Psychiatry. 2018;83:61–9.
35. Madsen T, Erlangsen A, Orlovska S, Mofaddy R, Nordentoft M, Benros ME. Association between traumatic brain injury and risk of suicide. JAMA. 2018;320:580.
36. Fralick M, Sy E, Hassan A, Burke MJ, Mostofsky E, Karsies T. Association of Concussion with the risk of suicide. JAMA Neurol. 2019;76:144.
37. Herman FJ, Pasinetti GM. Principles of inflammasome priming and inhibition: implications for psychiatric disorders. Brain Behav Immun. 2018;73:66–84.
38. Juengst SB, Kumar RG, Arenth PM, Wagner AK. Exploratory associations with tumor necrosis factor-α, disinhibition and suicidal endorsement after traumatic brain injury. Brain Behav Immun. 2014;41:134–43.
39. Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N. Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. Brain Behav Immun. 2014;42:50–9.
40. Schnieder TP, Trencevska I, Rosoklija G, Stankov A, Mann JJ, Smiley J, et al. Microglia of prefrontal white matter in suicide. J Neuropathol Exp Neurol. 2014;73:880–90.
41. Marsland AL, Kuan DC-H, Sheu LK, Krajina K, Kraynak TE, Manuck SB, et al. Systemic inflammation and resting state connectivity of the default mode network. Brain Behav Immun. 2017;62:162–70.

42. Malhi GS, Das P, Outhred T, Bryant RA, Calhoun V, Mann JJ. Default mode dysfunction underpins suicidal activity in mood disorders. Psychol Med. 2019:1–10.
43. Labrenz F, Ferri F, Wrede K, Forsting M, Schedlowski M, Engler H, et al. Altered temporal variance and functional connectivity of BOLD signal is associated with state anxiety during acute systemic inflammation. NeuroImage. 2019;184:916–24.
44. Schwartz J, Ordaz SJ, Ho TC, Gotlib IH. Longitudinal decreases in suicidal ideation are associated with increases in salience network coherence in depressed adolescents. J Affect Disord. 2019;245:545–52.
45. Knowles EEM, Curran JE, Göring HHH, Mathias SR, Mollon J, Rodrigue A, et al. Family-based analyses reveal novel genetic overlap between cytokine interleukin-8 and risk for suicide attempt. Brain Behav Immun. 2019;
46. Pandey GN, Rizavi HS, Zhang H, Bhaumik R, Ren X. Abnormal protein and mRNA expression of inflammatory cytokines in the prefrontal cortex of depressed individuals who died by suicide. J Psychiatry Neurosci. 2018;43:376–85.
47. Pandey GN, Rizavi HS, Bhaumik R, Ren X. Innate immunity in the postmortem brain of depressed and suicide subjects: role of toll-like receptors. Brain Behav Immun. 2019;75:101–11.
48. Wang Q, Roy B, Turecki G, Shelton RC, Dwivedi Y. Role of complex epigenetic switching in tumor necrosis factor-α upregulation in the prefrontal cortex of suicide subjects. Am J Psychiatry. 2018;175:262–74.
49. Schwieler L, Larsson MK, Skogh E, Kegel ME, Orhan F, Abdelmoaty S, et al. Increased levels of IL-6 in the cerebrospinal fluid of patients with chronic schizophrenia--significance for activation of the kynurenine pathway. J Psychiatry Neurosci. 2015;40:126–33.
50. Tavares RG, Tasca CI, Santos CES, Alves LB, Porciúncula LO, Emanuelli T, et al. Quinolinic acid stimulates synaptosomal glutamate release and inhibits glutamate uptake into astrocytes. Neurochem Int. 2002;40:621–7.
51. Borsini A, Zunszain PA, Thuret S, Pariante CM. The role of inflammatory cytokines as key modulators of neurogenesis. Trends Neurosci. 2015;38:145–57.
52. Martín-Hernández D, Tendilla-Beltrán H, Madrigal JLM, García-Bueno B, Leza JC, Caso JR. Chronic mild stress alters kynurenine pathways changing the glutamate neurotransmission in frontal cortex of rats. Mol Neurobiol. 2019;56:490–501.
53. Sublette ME, Galfalvy HC, Fuchs D, Lapidus M, Grunebaum MF, Oquendo MA, et al. Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. Brain Behav Immun. 2011;25:1272–8.
54. Bradley KAL, Case JAC, Khan O, Ricart T, Hanna A, Alonso CM, et al. The role of the kynurenine pathway in suicidality in adolescent major depressive disorder. Psychiatry Res. 2015;227:206–12.
55. Erhardt S, Lim CK, Linderholm KR, Janelidze S, Lindqvist D, Samuelsson M, et al. Connecting inflammation with glutamate agonism in suicidality. Neuropsychopharmacology. 2013;38:743–52.
56. Bay-Richter C, Linderholm KR, Lim CK, Samuelsson M, Träskman-Bendz L, Guillemin GJ, et al. A role for inflammatory metabolites as modulators of the glutamate N-methyl-d-aspartate receptor in depression and suicidality. Brain Behav Immun. 2015;43:110–7.
57. Steiner J, Walter M, Gos T, Guillemin GJ, Bernstein H-G, Sarnyai Z, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflammation. 2011;8:94.
58. Brundin L, Sellgren CM, Lim CK, Grit J, Pålsson E, Landén M, et al. An enzyme in the kynurenine pathway that governs vulnerability to suicidal behavior by regulating excitotoxicity and neuroinflammation. Transl Psychiatry. 2016;6:e865.
59. Underwood MD, Kassir SA, Bakalian MJ, Galfalvy H, Dwork AJ, Mann JJ, et al. Serotonin receptors and suicide, major depression, alcohol use disorder and reported early life adversity. Transl Psychiatry. 2018;8:279.

60. Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, Feder A, et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. Am J Psychiatry. 2018;175:150–8.
61. Sorrells SF, Sapolsky RM. An inflammatory review of glucocorticoid actions in the CNS. Brain Behav Immun. 2007;21:259–72.
62. Salvador E, Shityakov S, Förster C. Glucocorticoids and endothelial cell barrier function. Cell Tissue Res. 2014;355:597–605.
63. Sierra A, Gottfried-Blackmore A, Milner TA, McEwen BS, Bulloch K. Steroid hormone receptor expression and function in microglia. Glia. 2008;56:659–74.
64. Johnson JD, Barnard DF, Kulp AC, Mehta DM. Neuroendocrine regulation of brain cytokines after psychological stress. J Endocr Soc. 2019;3:1302–20.
65. Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. Psychopharmacology. 2016;233:1637–50.
66. Marsland AL, Walsh C, Lockwood K, John-Henderson NA. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. Brain Behav Immun. 2017;64:208–19.
67. Conejero I, Jaussent I, Cazals A, Thouvenot E, Mura T, Le Bars E, et al. Association between baseline pro-inflammatory cytokines and brain activation during social exclusion in patients with vulnerability to suicide and depressive disorder. Psychoneuroendocrinology. 2019;99:236–42.
68. Angelakis I, Gillespie EL, Panagioti M. Childhood maltreatment and adult suicidality: a comprehensive systematic review with meta-analysis. Psychol Med. 2019;46:1–22.
69. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry. 2016;21:642–9.
70. Rasmussen LJH, Moffitt TE, Eugen-Olsen J, Belsky DW, Danese A, Harrington H, et al. Cumulative childhood risk is associated with a new measure of chronic inflammation in adulthood. J Child Psychol Psychiatry. 2019;60:199–208.
71. Lockwood KG, John-Henderson NA, Marsland AL. Early life socioeconomic status associates with interleukin-6 responses to acute laboratory stress in adulthood. Physiol Behav. 2018;188:212–20.
72. Peters AT, Ren X, Bessette KL, Goldstein BI, West AE, Langenecker SA, et al. Interplay between pro-inflammatory cytokines, childhood trauma, and executive function in depressed adolescents. J Psychiatr Res. 2019;114:1–10.
73. Liu RT, Trout ZM, Hernandez EM, Cheek SM, Gerlus N. A behavioral and cognitive neuroscience perspective on impulsivity, suicide, and non-suicidal self-injury: meta-analysis and recommendations for future research. Neurosci Biobehav Rev. 2017;83:440–50.
74. Beurel E, Jope RS. Inflammation and lithium: clues to mechanisms contributing to suicide-linked traits. Transl Psychiatry. 2014;4:e488.
75. Ducasse D, Loas G, Dassa D, Gramaglia C, Zeppegno P, Guillaume S, et al. Anhedonia is associated with suicidal ideation independently of depression: a meta-analysis. Depress Anxiety. 2018;35:382–92.
76. Stanton CH, Holmes AJ, Chang SWC, Joormann J. From stress to anhedonia: molecular processes through functional circuits. Trends Neurosci. 2019;42:23–42.
77. Bergamini G, Mechtersheimer J, Azzinnari D, Sigrist H, Buerge M, Dallmann R, et al. Chronic social stress induces peripheral and central immune activation, blunted mesolimbic dopamine function, and reduced reward-directed behaviour in mice. Neurobiol Stress. 2018;8:42–56.
78. Freed RD, Mehra LM, Laor D, Patel M, Alonso CM, Kim-Schulze S, et al. Anhedonia as a clinical correlate of inflammation in adolescents across psychiatric conditions. World J Biol Psychiatry. 2018:1–11.
79. Bradley KA. Stern ER. Xie H, Kim-Schulze S, Gabbay V. Relationships between neural activation during a reward task and peripheral cytokine levels in youth with diverse psychiatric symptoms. Brain Behav Immun: Alonso CM; 2019.

80. Haroon E, Woolwine BJ, Chen X, Pace TW, Parekh S, Spivey JR, et al. IFN-alpha-induced cortical and subcortical glutamate changes assessed by magnetic resonance spectroscopy. Neuropsychopharmacology. 2014;39:1777–85.
81. Haroon E, Chen X, Li Z, Patel T, Woolwine BJ, Hu XP, et al. Increased inflammation and brain glutamate define a subtype of depression with decreased regional homogeneity, impaired network integrity, and anhedonia. Transl Psychiatry. 2018;8:189.
82. Moieni M, Tan KM, Inagaki TK, Muscatell KA, Dutcher JM, Jevtic I, et al. Sex differences in the relationship between inflammation and reward sensitivity: a randomized controlled trial of endotoxin. Biol Psychiatry Cogn Neurosci Neuroimaging. 2019;4:619–26.
83. Ballard ED, Wills K, Lally N, Richards EM, Luckenbaugh DA, Walls T, et al. Anhedonia as a clinical correlate of suicidal thoughts in clinical ketamine trials. J Affect Disord. 2017;218:195–200.
84. Bezemer G, Van Gool AR, Fekkes D, Vrolijk JM, Hansen BE, Janssen HLA, et al. Psychiatric side effects and fluctuations in serotonergic parameters in the treatment of chronic hepatitis C infection. Neuropsychobiology. 2012;65:126–32.
85. Chang HB, Munroe S, Gray K, Porta G, Douaihy A, Marsland A, et al. The role of substance use, smoking, and inflammation in risk for suicidal behavior. J Affect Disord. 2019;243:33–41.
86. Cook TB, Brenner LA, Cloninger CR, Langenberg P, Igbide A, Giegling I, et al. "Latent" infection with toxoplasma gondii: association with trait aggression and impulsivity in healthy adults. J Psychiatr Res. 2015;60:87–94.
87. Gassen J, Prokosch ML, Eimerbrink MJ, Proffitt Leyva RP, White JD, Peterman JL, et al. Inflammation predicts decision-making characterized by impulsivity, present focus, and an inability to delay gratification. Sci Rep. 2019;9:4928.
88. Cáceda R, Griffin WST, Delgado PL. A probe in the connection between inflammation, cognition and suicide. J Psychopharmacol. 2018;32:482–8.