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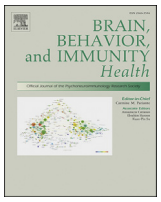

Psychoneuroimmunology: The new frontier in suicide research

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ABSTRACT

Elucidating complex, multifactorial phenomena like suicide and suicidal behaviors (SSB) require multidisciplinary fields such as Psychoneuroimmunology (PNI). Indeed, our appreciation of the bidirectional communication channels between the brain and the rest of the body with its immune arsenal as the key player has positioned PNI as a promising field of research. We now know that major psychiatric, behavioral, and somatic disorders related to SSB accompany neuroimmune dysregulation. These disorders range from depression, emotional dysregulation, atopy, and epilepsy to certain viral and parasitic infections. By utilizing epidemiological, genetic, microbial, and molecular approaches, the PNI research community has excogitated novel biomarker candidates and pathways in support of SSB risk stratification at individual level. This remarkable progress in just two previous decades shall, if successful, help implement personalized prevention and treatment strategies, using PNI-assisted tools. The aims of this narrative review and opinion piece are to summarize important discoveries concerning the role of neuroimmune activation in SSB and to highlight important future directions for the field. Major caveats of the findings concerning methodological approaches, clinical reality of frequent comorbid psychopathology, and novel molecular targets are presented. Finally, this review calls on the PNI research community for increased attention towards factors that promote resilience to suicide, while accepting "consciousness" under its wing. Thus, PNI represents the new frontier in suicide research. Future breakthroughs in this discipline shall bring us closer to understanding the biological substrates of qualia i.e., subjective, and experiential meanings of life and death.

1. Introduction

Contrary to popular belief, the age standardized suicide rate between 1990 and 2016 *decreased* by 33% in the world (Naghavi, 2019). There is, however, no ground for complacency because approximately 800,000 deaths occurred by suicide in 2016 alone (World Health Organization, 2019a). Suicide rates have remained stably high in Eastern Europe, and worryingly increased in some countries in high income Asia pacific region, central Latin America, Western sub-Saharan Africa and the USA (Naghavi, 2019; Hedegaard et al., 2020). It is estimated that more than 20 other persons may have attempted suicide for each adult who died by suicide (World Health Organization, 2019b). Clearly, suicide and other self-harm behaviors are likely to be heavily underreported. The great majority of suicides occur in the context of psychiatric disorders (Cavanagh et al., 2003), and more than one in four suicides would be preceded by a mental health service utilization the same year (Walby et al., 2018). Thus, patients in mental health services are crucial targets for suicide interventions. However, given the complex etiology, unreliable pathways leading to impulsive and non-impulsive suicide attempt, and limited understanding of the pathomechanism, suicide is hard to predict. Following the recognition of suicidal behavior disorder as a distinct condition for further study in the DSM-5 (American Psychiatric Asso, 2013), there has been a surge in interest to identify biomarkers. Novel biomarkers should, ideally, not just represent a proxy for an underlying disease process with a suicidal symptom, but also help stratify risk, predict future suicidal behavior, monitor treatment progress, and identify intervention targets regardless of psychopathologies. PNI research community has joined this nascent but needed field by leveraging the knowledge of neuroimmune interactions in the maintenance of mood and behavioral flexibility. This short review revisits the major PNI findings relevant to suicide and suicidal behavior (SSB) in conjunction with related disorders and as a stand-alone entity. Finally, future directions are proposed highlighting resilience, comorbidity and novel biomarker classes. (see Fig. 1)

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Fig. 1. Sudan Prasad Neupane MBBS, MPhil, PhD. Dr. Neupane is a scientist at the National Center for Suicide Research and Prevention at the Faculty of Medicine, University of Oslo. He is also a senior scientist at the Oral Health Center of Expertise in Rogaland, Stavanger, Norway. While working as a clinician in the high hills of Dolakha in Nepal, he encountered families in which alcohol use disorder, depression, anxiety and suicidal behavior were congregated. Curious about the mechanisms underlying the comorbid psychopathology, he joined the labs of Drs Jørgen G. Bramness and Lars Lien at the University of Oslo and conducted a series of epidemiological and experimental studies among individuals exposed to alcohol. His works have focused on characterizing the comorbid phenotypes of depression, anxiety, PTSD and suicidal behavior in chronic heavy drinking through circulating cytokines, chemokines, hormones, neurotoxins, neurotrophic factors as well as gut microbiota biomarkers. In 2015, he earned his doctorate in Addiction Medicine and Psychoneuroimmunology from the University of Oslo. Dr. Neupane spent a year as a visiting Fulbright scholar at the Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, NC, USA where he worked with Dr. Fulton T. Crews investigating the role of non-coding elements of the genome, the miRNA and lncRNAs, in regulating the alcohol-induction of neuroimmune signaling. Dr. Neupane is passionate about the inextricable unity of mind and body. His current work focusses on understanding the neuroimmune correlates and the consequences of peripheral immune activation on mood and addictive/self-harm behaviors.

2. Neuroimmune dysregulation in suicide, suicidal behavior and associated conditions

2.1. Somatic immune-inflammatory conditions and suicidal behavior

Epidemiological investigations have revealed that individuals with suicidal behavior have increased rates of somatic conditions that are clearly attributable to chronic inflammation, autoimmune dysfunction and atopy. For example, systemic lupus erythematosus, osteoarthritis, rheumatoid arthritis and fibromyalgia are associated with elevated risks of suicidal ideations, attempts and suicides (Li et al., 2018). Asthmatic patients also clearly carry increased risk for SSB, particularly in the context of the seasonal peaks of tree pollen (Qin et al., 2013). A meta-analysis of 15 studies further confirmed that patients with atopic dermatitis compared to persons without atopy had a greatly elevated risks of suicidal ideation and suicide attempts (44% and 36% increased odds, respectively), although reports on suicides were less consistent (Sandhu et al., 2019). Of particular relevance are exaggerated suicide risks in epilepsy and migraine. Arguably, SSB may result from frustrations with repeated seizures, or migraine attack, prolonged medication and associated social stress caused by these debilitating conditions. However, a study of 3700 patients with epilepsy showed an increased prevalence of suicide attempts among patients compared to healthy controls even *before* the diagnosis of epilepsy was made suggesting an underlying pathomechanistic link (Hesdorffer et al., 2012). Similarly, migraine is documented to increase the odds of suicide attempts (Pei et al., 2020). Moreover, Asian populations with migraine carried an increased risk of suicidal ideation (Friedman et al., 2017). It is no surprise that neurogenic neuroinflammation in migraine (Edvinsson et al., 2019) and seizures (Vezzani et al., 1999) may share pathological parallels with SSB.

Apart from these conditions, peripheral infections with neuroinflammatory components such as the HIV-AIDS and neuroborreliosis are known to increase neuropsychiatric symptoms (Brundin et al., 2017). A case with particular interest is *Toxoplasma gondi* infection. The parasite resides in intracellular cysts in glia and neurons in areas of particular relevance for suicidal behavior, i.e., prefrontal cortex and amygdala (McConkey et al., 2013). Following numerous reports of rodents showing potentially lethal feline attraction upon Toxoplasma infection through mechanisms not yet clear, associations of toxoplasmosis with multiple psychiatric conditions have been studied (Martinez et al., 2018a; Bak et al., 2018). Among a Korean sample of suicide attempters, *T. gondi* infection was associated with higher ratings on depression, anxiety, suicide severity and lethality, but not impulsivity (Bak et al., 2018). Moreover, a strong pleasantness to cat urine odor was found among men, but not women infected with the parasite showing gender dependent effect on possibly infectious origins of suicidal behavior (Flegr et al., 2011). Together, the above findings suggest that peripheral as well as CNS immune insults likely drive neuroinflammation that have a potential to exacerbate suicidal behavior in conjunction with psychiatric and somatic comorbidities of chronic nature.

2.2. Inflammatory signatures of suicide and suicidal behavior

In addition to immune-inflammatory insults as described above, the immune system engages its innate and adaptive arsenals in response to psychosocial stressors (Miller and Raison, 2008; Leonard, 2010). The innate immune cells, mainly consisting of macrophages, monocytes, granulocytes, dendritic cells, and Natural Killer (NK) cells provide the first-line of defense by recognizing and responding to pathogenic and other danger signals. The pathogen-specific B cells that produce antibodies and T cells, including the helper, memory, cytotoxic and regulatory T cell subsets, mediate the acquired immune response and these cells are found altered in depression and suicidal behavior (Ucuz and Kayhan Tetik, 2020; Martinez-Botia et al., 2020). The immune response is orchestrated in a tightly-regulated fashion by engaging innate and adaptive components and is dependent on the pro and anti-inflammatory messenger molecules, the cytokines, produced in the CNS and the periphery. Moreover, pro-inflammatory cytokines can activate the hypothalamic-pituitary-adrenal axis (HPA axis) causing cortisol release. Depression is associated with hyperactive HPA axis and glucocorticoid resistance (Zunszain et al., 2011). Finally, the pro-inflammatory cytokines TNF-α (tumor necrosis factor –α) and IFN-γ (interferon -γ) can activate the kynurenine pathway of tryptophan metabolism by inducing the rate limiting enzyme indolamine 2,3-dioxygenase (O'Connor et al., 2009). This diverts tryptophan away from serotonin synthesis and results in accumulation of potentially neurotoxic metabolites such as quinolinic acid and anthranilic acid, which may contribute to excitotoxicity in SSB (Maes et al., 2007). Thus, psychiatric illness is related to a sophisticated immune response system through the interactions with inflammatory messenger molecules, endocrine stress hormones, neurotransmitter systems, and downstream metabolites (Leonard, 2010; Miller et al., 2009; Halaris et al., 2019).

In 1991, R.S Smith proposed the “macrophage theory of depression” implicating the inflammatory products of macrophage responsible for depression (Smith, 1991). Two decades later Torres-Platas and

colleagues demonstrated that low-grade cerebral neuroinflammation induced by circulating monocytes recruited centrally may lead to depression and suicide (Torres-Platas et al., 2014). The levels of the pro-inflammatory cytokines interleukin (IL)-1β and IL-6 were reported higher in the blood samples of patients with suicide attempts compared with the levels in both patients without suicidal attempts and healthy control subjects (Black and Miller, 2015). IL-2, another pro-inflammatory cytokine was reduced in plasma samples (Ducasse et al., 2015a) of suicidal subjects as well as in-*vitro* production by stimulated peripheral blood mononuclear cells of suicidal patients compared to patient or healthy control subjects (Black and Miller, 2015). Among anti-inflammatory cytokines, plasma IL-4 levels were reduced while transforming growth factor (TGF)-β levels were increased (Ducasse et al., 2015b). In the CSF, suicide attempters showed higher IL-6 and quinolinic acid levels, but lower kynurenic acid, endotaxin1, MCP (monocyte chemoattractant protein) -1,4, MIP-1β (macrophage inflammatory protein-1β) and TARC (thymus and activation-regulated chemokine) levels regardless of psychiatric diagnosis (Enache et al., 2019). Protein and mRNA expression of corticotropin-releasing factor (CRF), CRF receptors and CRF binding protein as well as IL-6 were shown altered in the postmortem samples of pre-frontal cortex and central amygdaloid nucleus but not in the hippocampus of teenage suicide subjects (Pandey et al., 2012, 2019a). These findings were further confirmed in a recent meta-analysis showing higher IL-1β, IL6, TNF-α, TGF-β, VEGF (vascular endothelial growth factor), and kynurenic acid and lowered IL-2, IL-4, and IFN-γ levels in specific brain regions of suicidal subjects (Serafini et al., 2020). IL-6 levels has been consistently shown in the blood, cerebrospinal fluid (CSF) and brain tissue of suicide attempters (Ganança et al., 2016), making IL-6 a distinct cytokine marker for suicide (Black and Miller, 2015). Indeed, IL-6 levels in CSF were the highest in more violent suicide attempters (Lindqvist et al., 2009). These promising correlative findings would support evaluation of cytokine biomarkers if they proved helpful in predicting SSB.

Isung et al. (2012) measured plasma cytokines of 58 middle-aged suicide attempters and followed them for an average of 13 years. Of the 7 subjects who died by suicide, low levels of a single cytokine i.e, vascular endothelial growth factor was predictive of suicide (Isung et al., 2012). Among US military personnel suicide deaths (N = 800), lower levels of docosahexaenoic acid during the preceding year predicted suicide deaths when compared with matched controls (Lewis et al., 2011). Some preclinical models of social defeat show similarly increased expressions of brain inflammatory cytokines (Audet et al., 2011; Powell et al., 2009), but further longitudinal studies with biomarker candidates predicting SSB are clearly needed. Unfortunately, prediction models so far have been weak, and any observed prospective associations between biological risk factors and SSB seem to be accounted for by publication bias (Chang et al., 2016).

2.3. Suicidal behavior as part of neuropsychiatric disorders: neuroimmune correlates

PNI findings in SSB are largely an extension of studies on depression. Numerous studies have shown clearly elevated levels of IL-6, TNF-α, IL-10, the soluble IL-2 receptor, MCP-1, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 and reduced IFN-α levels in patients with depression (Köhler et al., 2017). Increasingly insightful evidences are mounting in the PNI of bipolar affective disorder, schizophrenia, alcohol use disorder and posttraumatic stress disorder, and to some extent on personality disorders, eating disorders and adjustment disorders, all of which confer substantially elevated risks for SSB (Too et al., 2019). The evidence of immune dysregulation in the pathophysiology across the heterogeneous spectrum of psychiatric disorders (Dantzer, 2017) may also indicate that suicide endophenotype related to immune dysregulation is plausible (Isung et al., 2014). Recently, a large genome-wide association data suggested genetic overlap between C-reactive protein (CRP) and depression, and that upregulated IL-6 signaling could be a potential causal factor for suicidality (Kappelmann et al., 2020). The case of IL-6 is attractive since IL-6 has been suggested as a useful marker for identifying the onset of depression (Khandaker et al., 2014) as well as differentiating depressed patients with and without suicidal tendency (Enache et al., 2019; O'Donovan et al., 2013). Impulsivity and IL-6 correlated directly in the blood of suicide attempters, whereas CSF IL-6 levels correlated positively with monotony avoidance, prompting the authors to conclude that neuroinflammation hypothesis of SSB lends partial support through associations of inflammatory cytokine with impulsivity (Isung et al., 2014).

Alcohol use disorder is among the most important risk factors for suicide. We and others have shown its immune modulating properties through activation of peripheral and central neuroimmune signaling (Crews and Vetreno, 2016; Szabo and Saha, 2015; Neupane et al., 2016). The same cytokines that are involved in neuroimmune pathologies of depression and suicide behavior are altered in alcohol use disorders either causally or as epiphenomena (Neupane, 2016). We have reported involvement of dysregulated peripheral cytokine, tryptophan and kynurenine as well as brain-derived neurotrophic factors in depression comorbid with alcohol use disorder (Neupane et al., 2014, 2015a, 2015b). Furthermore, we demonstrated that inflammatory response in substance use disorder was contingent to trauma (Toft et al., 2018), gut microflora (Bjørkhaug et al., 2020) and anxiety (Martinez et al., 2018b). From our own investigation among men with alcohol use disorder, the levels of IL-17, TNF-α and Eotaxin (out of a panel of 27 cytokines) were lower in patients with suicidal ideation, suicidal plans and history of suicidal attempts (unpublished data). Suicidal behavior was closely associated with PTSD in the sample (Neupane et al., 2017), but these cytokine changes were specific to the sample with history of suicide attempt.

2.4. Neuroimmune dysregulation in suicidal behavior independent of other pathologies

Most suicidal behaviors occur in the context of one or more psychiatric conditions. However, a psychiatric diagnosis is neither essential nor sufficient for suicidal behavior to be present. Evidence from psychological autopsy studies in the Western countries consistently show that about 10% of individuals who die by suicide do not present an identifiable psychiatric disorder before death (World Health Organization, 2019b; Cavanagh et al., 2003). In China, India and Indonesia, the rates varied between 20 and 70% (Phillips et al., 2002; Knipe et al., 2019). In the US more than 80% adolescents with suicidal behavior had received some form of mental health treatment (Gili et al., 2019). Even in the most common psychiatric predictors of suicide i.e, severe depression, borderline personality disorder and psychotic or bipolar disorders the suicide deaths occur in a small minority, under 5% (Álvarez-Tomás et al., 2019). Lifetime suicide attempts are reported in less than 50% patients with these disorders (Dong et al., 2019), and half of individuals below 35 years of age who died by suicide had a personality disorder indicating emotional regulation disorder as a more common psychopathology (Paris, 2019). With these nuances in place, we can conclude that although suicidal behavior most commonly accompanies psychiatric disorders, it is not an intrinsic dimension of any single disorder. As stated under Introduction, it may therefore be relevant to address suicidal behavior as a stand-alone diagnosis. This standpoint leads to an important question, namely, given that a range of psychiatric disorders are associated with immune dysregulation - how will we know if a particular biomarker is specific to SSB as opposed to being a more general marker of psychopathology?

Available evidence for suicide-specific biomarkers is inconclusive (Black and Miller, 2015; Ganança et al., 2016; Lindqvist et al., 2009), partly because SSB is neither clinically (reliably) predictable nor a valid suicidal endophenotype is currently described. In a carefully designed study, Steinar et al. (Steiner et al., 2008) measured microglial activation in patients with schizophrenia and affective disorders who died by

suicide and compared with patients dying by other causes and healthy people with non-suicidal sudden deaths. Results showed that microgliosis was specific to suicide-samples independent of schizophrenia or affective disorder (Steiner et al., 2008). Moreover, a principal component analysis of 20 CSF biomarkers among a heterogenous group of 124 psychiatric patients with suicide attempt suggested that suicidal behaviors may be clustered into different combinations of biomarkers within the immune system, monoamine neurotransmitter system and HPA axis (Lindqvist et al., 2011). Recently, memory T helper cells were shown distinguishably higher in depressed patients with high risk for suicide (Schiweck et al., 2020). Such innovative studies will help to identify neuroimmune-based biomarker candidates of SSB exclusive of other conditions.

3. Future directions

Neuroimmunology of suicide is a nascent field. Nonetheless, research in the past decade alone has generated a considerable amount of data supporting the contribution of immune dysregulation in suicide and suicide behavior. The rapid progress in the understanding of the neuroimmune contributions to SSB comes with numerous caveats and hazy ideas as to where the future of this field should be heading. The following sections highlight three major areas for future PNI endeavors in Suicidology: addressing comorbid pathology, continuing the search for novel molecular biomarkers, and prioritizing resilience.

3.1. Methodological considerations

Cytokines, chemokines, toll-like receptors along with their agonists are a proxy for tightly regulated pathways. Small changes in their levels over time may have far-reaching consequences. However, clinical data published on suicides often lack adequate sample size rendering the analyses underpowered. Additionally, there is a large heterogeneity in the type of biological specimens and assay techniques making comparisons across studies challenging. A large number of potential confounders of immune parameters exist: sex, age, diurnal/seasonal variation, medication, ethnic/genetic and sociocultural differences, physical activity, somatic diseases, food intake, and environmental pollutants. Moreover, the designs of these studies are challenged by the important variable *comorbidity*.

Most investigators tend to exclude patients with comorbid disorders in search of a 'purely homogenous' isolated disorder. As patients with SSB typically have multiple disorders, this approach may not only be unrealistic but an error of the first order simply because of the interactions between biological factors as well as the multiple associated psychopathologies. This concern is of particular relevance in comorbid alcohol use disorder and major depression (Neupane, 2016). Comorbid disorders are not only real mix of conditions accentuating suicide risk, but they may also falsely show attenuated neuroimmune response (Neupane et al., 2014). Notably, the use of cytokines such as IFN-α and IL-2 in treatment of hepatitis and several malignancies often follows neuropsychiatric adverse effects including depression and SSB, particularly in patients with comorbid psychopathology (Raison et al., 2005). Between-person variations in the inflammatory profile may be due to adverse life events including in utero and early life exposure of infections, drugs or violence, verbal or emotional abuse, or neglect during childhood (Hartwell et al., 2013). These exposures can result in early-age priming of brain neuroimmune signaling leading to inflammatory activation that can last for a long time (Qin et al., 2008) and potentially contribute to neuroimmune changes related to depression and suicidal behavior. As an example, we found that symptom improvement of PTSD with treatment did not follow reductions in cytokine release (Toft et al., 2018). Such insights are only obtainable through the inclusion of comorbid samples in PNI investigations. Selective exclusion of study sample may also be ethically questionable and should rather be compensated by larger samples and preferably subgroup analyses. Eventual inclusion of SSB as a distinct disorder in the classification systems will encourage more inclusive samples in future investigations.

Little is known for the ethnic differences in suicide risk and relative contribution of potentially inflammatory insults due to acculturative stress, genetic variability, adverse early life events among minority populations (Wyatt et al., 2015). The differences across generations of immigrants make an interesting case for environmental factors including the contribution of microbial load and diversity within (the gut) and in the physical environment. Indeed, burgeoning work on the role of gut microbiome in the risk and resilience for psychiatric conditions (Dinan and Cryan, 2017), including ours (Bjørkhaug et al., 2020), has expanded to suggest that immune signals through altered populations of gut microbiome and disruption of the gut barrier function may contribute to suicidal behavior (Ohlsson et al., 2019). Furthermore, we now know the putative roles of immune dysfunction on intergenerational transmission of psychopathology (Plant et al., 2016). A relevant question is whether future generations of the immigrants assume the suicidal risk carried by the local population, and if so what the neurobiological correlates for the same are. Given the gender-disparity in suicide attempt and suicides and sex-differences in neuroimmune response, disaggregation by sex should a norm in these analyses. Clearly, well-powered longitudinal studies are necessary, as evidenced by a failure to model longitudinal association between cytokines and SSB (Chang et al., 2016). Surprisingly few studies have examined possible endophenotype exclusive of depression in SSB; recommended endophenotypic approaches are aggressive/impulsive trait, emotional regulation disorders, cortisol social stress response, serotonergic neurotransmission as well as second messenger systems (Mann et al., 2009).

3.2. Novel molecular targets

Given the complex multifactorial gene-environment interaction in suicidality, identifying and utilizing specific biomarkers is challenging. Multiple studies suggest IL-6 is a potential biomarker candidate for SSB in depression (Enache et al., 2019; O'Donovan et al., 2013). However, a pleiotropic immune marker such as IL-6 and other cytokines showing small group differences are unlikely to be implementable. Another layer of complexity involves heritability in SSB. Unfortunately, studies that have targeted serotonergic, dopaminergic and GABAergic neurotransmitter systems, HPA axis, cytokine networks and neurotrophins have yielded either small effects or conflicting results in terms of endophenotyping (Mann et al., 2009). Very specific self-harm phenomena such as dying from overworking, termed *Karoshi* in Japan and *guolaosi* in China can provide useful biomarker candidates. Are subjects who die by these phenomena inherently inflamed, and if so, is inflammation reduction effective in these situations?

More recently, newer promising biomarker candidates are established. Using postmortem brain samples (Pandey et al., 2019b), observed overexpressed protein or mRNA of TLR2-4,6,10 in the prefrontal cortex of depressed suicide decedents. Recent genetic studies have supported involvement of immune-related pathways in suicide (DiBlasi et al., 2020; Policicchio et al., 2020). Polygenic risk estimations are undergoing. Upon replication, confirmed genetic associations will provide molecular basis of SSB. Previously deemed 'junk DNA', non-coding RNAs including microRNA and long non-coding RNA (lncRNA) have been, more recently, implicated in SSB (Yoshino and Dwivedi, 2020). Neuronal vesicular release into the circulation makes many such non-protein coding genes and their regulator molecules biomarker candidates for prediction of suicide risk. We discovered that one such lncRNAs the MALAT-1, that regulates synaptic proteins by modulating alternative pre-messenger RNA splicing, was found elevated in the postmortem brain samples from alcohol-related deaths (Neupane et al., 2019). Other groups have confirmed the role of multiple miRNAs including the putative BDNF regulator miRNA-132 and mi-182 (Yoshino and Dwivedi, 2020; Roy et al., 2017). Whole exome sequencing detected calcium ion channel genes and TGF-β signaling pathway in suicide (Tombacz et al., 2017)

whereas epigenetic switching of TNF-α gene (Wang et al., 2018) was also observed in SSB. These novel molecules may provide more proximal bioswitches relevant in SSB prediction and treatment monitoring. Imaging studies and pharmacoimmunogenetic approaches are newer addenda to the search.

3.3. Greater focus on resilience

In contrast to the extensive work on etiopathogenesis of mental illness, investigations of protective factors that help sustain mental health and wellbeing are relatively scarce. Work on immunological protective factors conferring resilience, i.e., the ability to adapt and swiftly recover after experiencing adversities, appears to be an area of research that requires more focus (Davydov et al., 2010). Thus, the work on resilience also provides a novel area of research in the PNI of Suicidology. Surprisingly, Chang et al. (2016) could identify no more than one study reporting the size of the protective effect of a biological factor on SSB, precluding a meta-analytic review of the topic. Paradoxically, we know little about the biological factors that contribute to the desire of the vast majority of people to keep living rather than the factors that may contribute to the situation around relatively few suicide events. It is noteworthy here that even in the presence of the most common psychiatric risk factors, about 95% people do not die by suicide (Álvarez-Tomás et al., 2019).

Resilience enhancement is an integral component of primary suicide prevention. The strategies include life skills enhancement, parenting programs, reducing exposure to drugs and trauma/violence, reducing social inequities and re-establishing community ties (Caldwell, 2008). An example of how enhancing the health of apparently low risk populations can contribute to reduction in the total disease burden in the society can be gained from the alcohol research. It is observed that reducing total alcohol consumption in the society, such as through restrictive policy measures will lead to reduced alcohol-related harms including suicide deaths (Razvodovsky, 2011). Thus, it is imperative that resilience enhancement receives greater attention as a strong primary prevention measure in the population but also in treatment of patient populations since this intervention is likely to reduce SSB burden in both groups (Sher, 2019). Thematically relevant resilience factors arising at the level of human consciousness are higher brain faculties including purpose, cognitive and emotional flexibility, spirituality and optimism. Future PNI research could therefore contribute more towards delineating the connections of resilience factors with human consciousness.

As highlighted by our PNI leaders (Kelley et al., 2020), there are advantages to harvest from the more holistic health perspective of the East. I opine that rigorous and advanced scientific methods that are standard in the West should be implemented to test relevant hypotheses that the diverse but rich wisdom traditions have to offer - be it in the form of mindful awareness, different forms of exercise or dietary practices. The 'consciousness-model' of the nondual eastern traditions may provide important conceptual insights into the pathological basis of mental illness and the mechanisms of change in therapy (Gendle, 2016). As an example, dialectal behavior therapy, an evidence-based SSB intervention is a product of rigorous Western behavioral science blended with the Eastern traditions of Zen Buddhism and mindfulness (Linehan et al., 1991). As we practice the deductive methods and keep dissecting and reintegrating the psychological, neurological and immunological slices in our experiments, we should continuously be reminded that our integrative approach is an appreciation of oneness of human experience, something that can be considered rested at consciousness. It is clear that we need to closely examine how such techniques as mindfulness-based practices bring back neuroimmune function to normalcy (Reive, 2019), and to know if there are specific populations that benefit more than others. For instance, religious attendance seem to reduce suicide risk in selected populations (Lawrence et al., 2016). However, the mechanism for how 'qualia', the subjective experiences relate to neuroimmune physiology is unknown. As a step in this direction, we examined if metacognitive beliefs were associated with anxiety (which they were), but cytokines did not moderate the association (Johnson et al., 2020).

4. Conclusions

Since neuroimmune activation has consequences to multiple chronic inflammatory conditions and general health, the role of PNI community would be to utilize the novel genetic, epigenetic, and neurochemical factors in demystifying how they relate to suicide and suicidal behavior and how resilience enhancement prevents SSB through neuroimmune mechanisms. The global expansion of the PNI research community over the recent decades is enabling investigation of the neuroimmune-based markers of SSB risk and resilience in a cross-cultural perspective. With the knowledge of the integrated bodily substrates, PNI proves to be the foremost science equipped with the possibility to sense the qualia i.e., subjective experience, a basis for the truth of everybody's life that also includes some individuals' desire to end their lives in the context of massive psychological pain. Excellent research departments across USA and Europe are increasingly dedicated to examining novel interventions at molecular levels, but also through the use of psychedelic substances, music, hyperthermia, intermittent fasting, mindfulness and compassion meditation as potential interventions in depression and SSB. One might wonder our healthy control group should perhaps come from deep meditators with their immune system at 'rest' and not from the apparently well-functioning stressed human. As highlighted in this manuscript, the PNI community stands ready to embrace both challenges and such novel openings.

Declaration of competing interest

The author declares that there is no conflicts of interest.

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