PSYCHONEUROIMMUNOLOGY OF SUICIDE AND SUICIDAL BEHAVIOR

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ABSTRACT

Elucidating complex, multifactorial phenomena like suicide and suicidal behaviors (SSB) require multidisciplinary fields such as PNI. 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 lecture is 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 integrating and utilizing nondual traditions of the East into such investigations.

INTRODUCTION

Although the age standardized suicide rate between 1990 and 2016 *decreased* by 33% in the world, approximately 800,000 deaths occurred by suicide in 2016 alone. Suicidal behavior disorder is proposed as a distinct condition for further study in the DSM-5 leading to a surge in interest to identify biomarkers relevant to suicide. PNI research has a potential to examine suicide-specific neuroimmune biomarkers.

NEUROIMMUNE DYSREGULATION IN SUICIDE, SUICIDAL BEHAVIOR AND ASSOCIATED CONDITIONS

Somatic immune-inflammatory conditions and suicidal behavior

Somatic immune-inflammatory conditions including systemic lupus erythematosus, osteoarthritis, rheumatoid arthritis and fibromyalgia, asthma, epilepsy and migraine, HIV infection are associated with increased suicidal behavior.
Toxoplasma gondi infection is an interesting case for suicide PNI research. Both animal and human studies indicate associations between toxoplasmosis and suicidal behavior.

Inflammatory signatures of suicide and suicidal behavior

Suicidal behavior is suggested to accompany alterations in a tightly regulated system of immune response mechanism through the interactions with inflammatory messenger molecules, endocrine stress hormones, neurotransmitter systems, and downstream metabolites. Among other metabolites, inflammatory cytokines such as IL-6, IL-2, TNF-alpha, VEGF, IL-1B, IFN-gamma and DHEA are implicated.

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, CCL-2, 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. Most studies indicate symptom severity as an indicator for suicidal behavior in the background of psychiatric pathologies and associated neuroimmune changes.

Neuroimmune dysregulation in suicidal behavior independent of other pathologies

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 partly because SSB is neither clinically (reliably) predictable nor a valid suicidal endophenotype is currently described. However, some findings indicate high CRP, IL-6 rise, microgliosis, higher memory T helper cells to be specific to suicidal behavior.

FUTURE DIRECTIONS FOR RESEARCH

Methodological considerations

PNI research on suicidology is a nascent field. Most studies have small sample size and are underpowered. Heterogeniety in terms of sampling and analytical protocols. Important confounders need to be accounted for: sex, age, diurnal/seasonal variation, medication, ethnic/genetic and sociocultural differences, physical activity, somatic diseases, food intake, and environmental pollutants.
More studies are needed with inclusion rather than exclusion of comorbid conditions.
PNI on 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, intergenerational and societal trauma are important areas for research.
Endophenotype approach independent of depression in suicidal behavior are useful; recommended endophenotypic approaches are aggressive/impulsive trait, emotional regulation disorders, cortisol social stress response, serotonergic neurotransmission as well as second messenger systems. Longitudinal studies with the role of neuroimmune biomarkers are sorely needed.

Novel molecular targets

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?
Novel molecular targets: non-coding RNAs (miRNA, lncRNA) measured in exosomes.TLRs, calcium ion channel genes and cytokine genes. Role of gut microbiome and Polygenic risk estimations.

Greater focus on Resilience

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.
The mechanism for how 'qualia', the subjective experiences relate to neuroimmune physiology is unknown. PNI resilience research should emphasize/prioritize on this area. Mindfulness, spirtuality, consciousnes- based non-dual eastern traditions are useful areas to examine how neuroimmune resolution/recovery may support healing and suicide prevention.

CONCLUSION

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. Novel interventions at molecular levels should be combined with investigations on psychedelic substances, music, hyperthermia, intermittent fasting, mindfulness and compassion meditation as potential interventions in depression and SSB.

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