PTSD, Depression and Anxiety: A Unifying Bio-behavioral Feedback Model

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Background

- Military suicide rates continue to increase, presenting with multifactorial complexities including PTSD, depression and anxiety.
- Protective factors connected with suicidal ideation (SI) that support resilience also influence depression and anxiety disorder symptoms that contribute to suicide risk.
- Conceptualizing suicide prevention as maintenance of an adaptive homeostatic resilience (R), mediated by highly integrated regulatory interactions, may elucidate how risk and protective qualities maladaptively equilibrate to promote suicidal behavior.

Objective

Identify potential regulatory mechanisms and mediators spanning multiple physiological systems that may support various co-morbidities in the context of SI.

Methods

- Suicidal behavior and SI (Columbia-Suicide Severity Rating Scale) served as nucleating points with Minnesota Multiphasic Personality Inventory-2-Restructured Form® (MMPI-2-RF®) elements: emotional distress, cognitive symptoms, behavioral problems, and somatization.
- Automated text-mining of >18,000 citations created a network of 59 functionally related constructs describing cognition (e.g., working memory), intelligence (WAIS-IV), autonomic function, brain activity (EEG, MRI perfusion) as well as endocrine (stress, sex, metabolic), immune (inflammatory, anti-inflammatory) and neurotransmission mediators, linked through 417 regulatory interactions, extracted with Pathway Studio interface (Elsevier, Amsterdam).
- Network dynamic response was constrained to reproduce partial descriptions of generalized anxiety disorder (GAD), depression and PTSD, conditions with high SI.

Results

- Regulatory kinetics were identified for 6 competing models where marker error was <5%.
- Dynamic stability required inclusion of 5 novel regulatory interactions, e.g., inhibition of inflammatory activator IGF1 by anti-inflammatory IL-10 and inhibition of spatial orientation by glutamate accumulation.
- Simulations predict that low resting levels of acetylcholine in the context of low serotonin, low norepinephrine, and low brain-derived neurotrophic factor, might increase SI risk.
- A more widespread departure from normal neurotransmitter levels would be required to elevate PTSD risk, with characteristic reduction in slow brain wave activity.

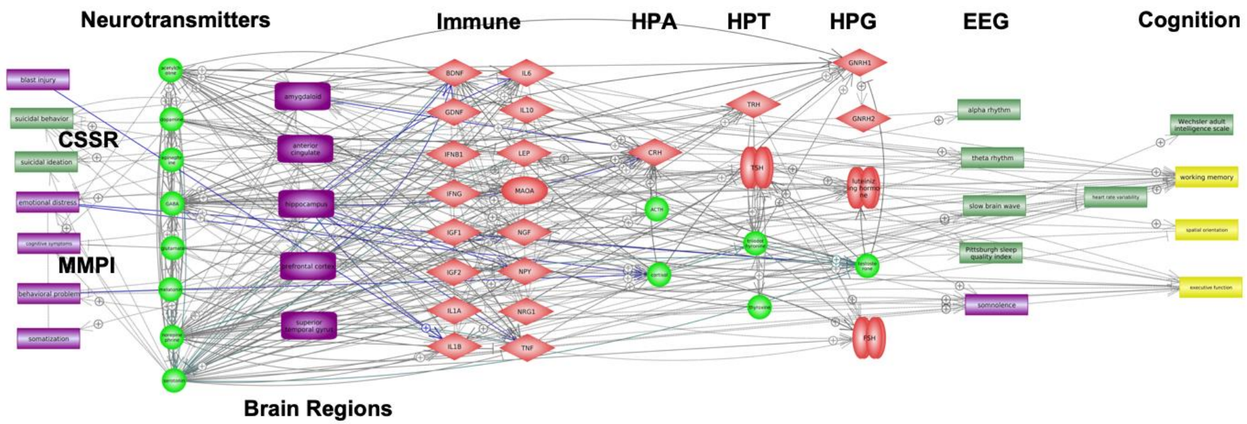

Fig. 1. *A preliminary network mode of SI and R behavior*. A literature-informed network of 59 elements (including blast injury insult) describing the bio-behavioral feedback regulation of suicidal ideation and behavior and elements of MMPI-2-RF, cognition and sleep with mediators of neurotransmission, brain anatomy and activity, as well as immune, endocrine and autonomic function linked through 417 activating and inactivating regulatory interactions documented across over 18,000 citations.

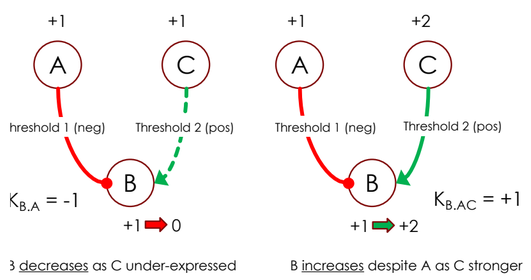

Fig. 2. *A simple decisional logic*. Regulatory input must exceed a perception threshold and is assessed in the context of competing signals

Results continued

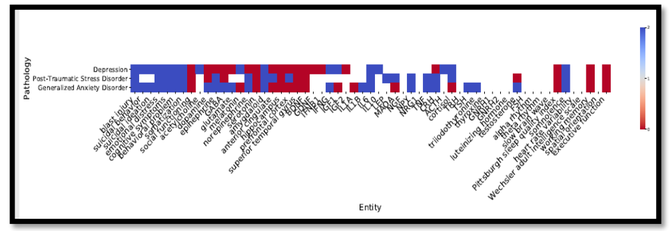

Fig. 3. *Qualitative reference profiles*. Relative up and down expression of markers in depression, PTSD and GAD

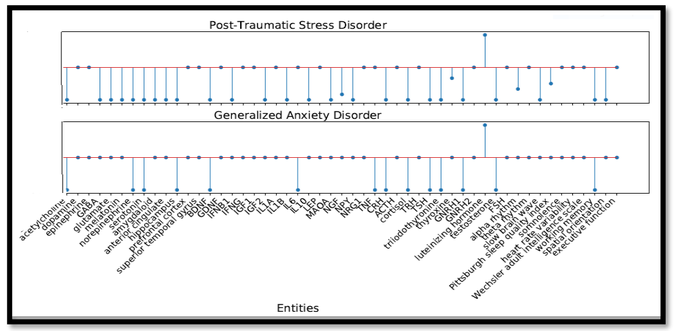

Fig. 4. *Predicted risk profiles*. Excursions in relative marker expression that decrease regulatory stability in favor of PTSD and GAD

Conclusion

Functional relationships extracted from literature suggest a circuitry that supports propagation of bio-behavioral feedback during an adaptive response to trauma and highlights excursions in baseline marker expression indicative of SI risk.

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