Leveraging Graph Theory to Highlight Key Neurological Mediators of TBI Potentiated Suicidal Ideation

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Background

- Concussive brain injuries are known risk factors driving suicide in military and civilian populations.
- Though elements of neurophysiology have been implicated, basic changes in neurotransmission and neuro-inflammatory networks remain poorly understood.

Objective

Highlight key neurological mediators of TBI and blast potentiated stress response in suicidal ideation (SI) by applying graph theory to a mechanistically-informed signaling network derived using automated text mining of documented regulatory interactions.

Methods

- Automated text-mining of >**4,200 peer-reviewed publications** using Pathway Studio interface to the Elsevier Knowledge Graph (Elsevier BV, Amsterdam) extracted a network of **34 functionally related constructs**.
- The network described the interactions of mood (Profile of Mood States (POMS)) and depression scores (Hamilton Depression Rating Scale (HAM-D)), severity of traumatic brain injury (TBI) (MESH M0480881) and SI (Columbia-Suicide Severity Rating Scale (C-SSRS)), through key neurotransmission, neuro-immune and endocrine mediators in response to psychological stress and concussive blast injury.
- Information flow through the **149 documented regulatory interactions** was analyzed using graph theoretical metrics such as *betweeness* centrality and shortest path length.

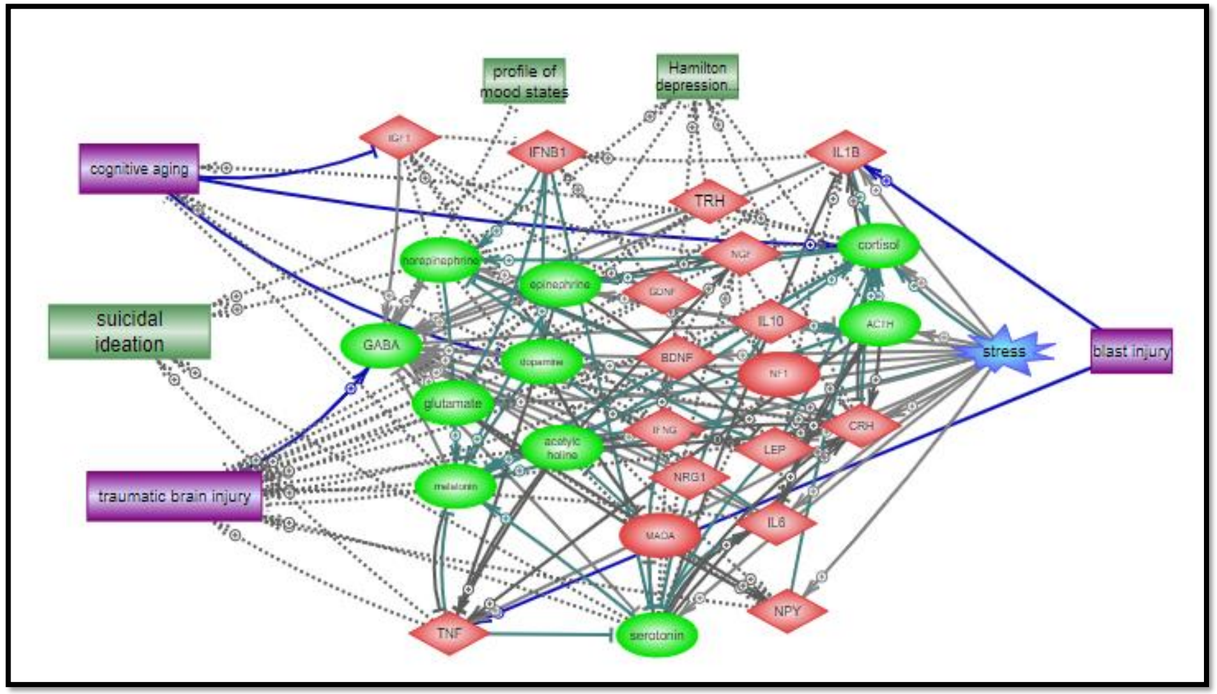

Figure 1. *Shared regulation of stress and blast injury*. A mechanistically-informed regulatory network describing the propagation of stress and response to blast injury through core neurotransmitters and neuroinflammatory markers

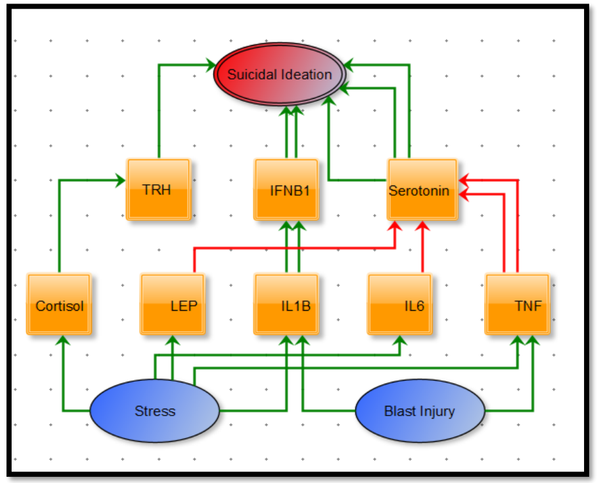

Figure 2. *Shortest paths sub-network*. Shortest paths through the network in Figure 1 linking blast injury and/ or stress to suicidal ideation (SI) through 2 cascading intermediate mediators. The effects of stress and blast injury in exacerbating SI are jointly compounded in a cascade involving IL1B and IFNB1. This aggravating SI competes with a counteracting cascade involving downregulation of serotonin by TNF.

Results

- Inhibitory neurotransmitter **GABA** exerted the highest control over information flow (betweeness centrality), followed by serotonin, cortisol and cognitive aging (MESH D003072; M0004723).
- Interestingly **serotonin and cortisol** both also served as mediators in the joint transmission of stress and blast injury towards increased SI.
- While GABA, and to a lesser extent cognitive aging, played a central role in controlling neurotransmission overall, neither *directly* mediated SI.
- Paths driving SI were instead dominated by inflammatory mediator **IL-1B**, a driver of sickness behavior, and demyelination effector **IFNB1**, associated with multiple sclerosis (MS), both acting in a sequential cascade.
- This aggravating effect is offset by *competing* downregulation of **serotonin**
- The most direct mediator remained inflammatory cytokine **TNF**, offering a *single* nucleating point for stress and blast injury in exacerbating SI.

Conclusion

This network analysis suggests that select neuroinflammatory mediators may serve as *direct integrators* of exposure to psychological and physical stressors in exacerbating suicidal drive and that genetic and/or epigenetic factors may discriminate between available competing signaling cascades.

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