Graph-Theoretical Analysis of the Gut-Microbiome-Brain Axis: Identifying Mediators of Suicidal Ideation

Petr Chalupský[1][0009−0004−6138−085X], Shivam Kumar[1][0009−0005−6766−6565], Valeria Epelbaum[1,2][0009−0000−6889−1055], Valeria Krzhizhanovskaya[1,2][0000−0002−8247−129X], and Vivek M. Sheraton[1][0000−0002−6577−6016]

[1] University of Amsterdam, Amsterdam, The Netherlands
[2] Centre for Urban Mental Health, University of Amsterdam, The Netherlands
petr.chalupsky@student.uva.nl, s.kumar@uva.nl, v.epelbaum@uva.nl, v.krzhizhanovskaya@uva.nl, v.s.muniraj@uva.nl

Abstract. Despite emerging evidence linking the gut microbiome to suicidal ideation, their complex interplay is typically analyzed through pairwise correlations, leaving the systemic cascade poorly understood. To overcome this limitation and map the directional, multi-step mechanisms of this system, we formalized the gut-brain-SI axis as a directed causal knowledge graph. By systematically extracting causal links from empirical scientific literature to curate metabolic pathways across the vagus nerve, hypothalamic-pituitary-adrenal axis, and systemic circulation, we build a network comprising 41 nodes and 87 edges. Topological analysis revealed a highly structured but sparse architecture characterized by four distinct functional modules. Within this framework, we identified specific nodes responsible for systemic perturbation. Intestinal permeability demonstrated the maximum reach efficiency, acting as the primary upstream catalyst for dysbiosis. Conversely, neuroinflammation emerged as the dominant integration hub, exhibiting the highest degree centrality and betweenness centrality before propagating signals to psychiatric endpoints. These quantitative findings highlight potential topological mediators that could translate localized physiological alterations into suicidal ideation vulnerability. Ultimately, this static causal graph establishes the structural foundation required for future in silico system dynamics modeling of targeted microbial interventions.

Keywords: Gut-Brain Axis · Suicidal Ideation · Gut Microbiome · Neuroinflammation · Network Analysis · Causal Loop Diagram.

1 Introduction

Suicide is one of the leading causes of death, especially in young adults[5]. Although emerging research on the gut-brain axis suggests a link between suicidal ideation (SI) and alterations in the gut microbiome, their interplay is not yet well

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understood. We address this critical gap by conceptualizing the gut-microbiome-brain axis as a computational topological problem. Rather than observing isolated biological markers, we construct a directed causal network to map the signaling architecture between gut dysbiosis and psychiatric vulnerability. By applying rigorous graph-theoretical metrics to this complex system, we aim to construct a formal hypothesis framework for the systemic bottlenecks and critical hubs that translate physiological alterations into suicidal ideation, providing a structural foundation for future targeted interventions. This network will serve as a foundation for future computational models.

1.1 Background and Computational Motivation

Traditional suicide research often conceptualizes suicidal ideation (SI) through psychological frameworks, but recent neurobiological accounts emphasize a stress-diathesis model where environmental stressors interact with a trait-like biological vulnerability [32,45]. This diathesis is linked to dysregulation of serotonergic neurotransmission, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, and neuroinflammatory processes, including activation of the kynurenine pathway, nitro-oxidative stress, and reduced neurotrophic support such as decreased brain-derived neurotrophic factor (BDNF) [45,48,36,46]. These abnormalities are thought to impair cognitive control of mood, increase pessimism and reactive aggression, and amplify emotional pain and hopelessness, thereby fostering SI and, in some individuals, SA [45,13]. Large-scale microbiome-wide association studies underscore this diathesis, demonstrating that specific taxa are significantly associated with depressive symptoms. Notably, these bacteria are implicated in the synthesis of critical neuroactive metabolites, including glutamate, butyrate, serotonin, and gamma-aminobutyric acid (GABA) [38].

Systematic reviews and meta-analyses show that inflammatory markers (e.g., IL-6, TNF-α, CRP) and broader immune-oxidative stress profiles are elevated in both recent SI and recent SA, with larger effect sizes for SA than SI, suggesting more pronounced biological perturbation among attempters [46,11,2]. Similarly, observational studies in young adults report that higher inflammatory markers and stress scores, together with lower BDNF, are associated with greater suicide risk and suicidal ideation [48,36,13]. Collectively, neurobiological models thus link SI to interacting changes in neuroinflammation, neurotoxicity, monoamine systems (particularly serotonin), HPA-axis stress responsivity, and neuroplasticity [32,13]. However, current evidence remains largely correlational and operates at a relatively high level of abstraction, which makes it challenging to understand how physiological alterations translate into particular suicidal thoughts, desires or intentions in real time.

Translating this complex biological diathesis into a predictive computational framework requires moving beyond pairwise observational studies. While existing reviews successfully establish isolated correlations—such as the link between elevated inflammation and suicidal ideation—they cannot capture the directional, multi-step systemic cascade. To map this structural architecture, the gut-brain-SI axis must be formalized as a directed knowledge graph. By structuring these

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physiological markers as nodes and their interactions as directed edges based on current evidence, this approach provides a meta-analytic topological map. Applying graph-theoretical metrics allows us to quantitatively identify the systemic bottlenecks, upstream catalysts, and neglected mechanistic pathways (e.g., missing biological feedback loops) that traditional clinical observations and narrative reviews fail to capture.

1.2 The Gut-Brain Axis

The gut microbiome communicates with the central nervous system (CNS) via the gut-brain axis, a complex bidirectional signaling network [12]. The gut is extensively innervated by the enteric nervous system (ENS), which controls gut motility and fluid secretion [16]. Intestinofugal neurons, whose cell bodies reside in the ENS, project axons to the sympathetic prevertebral ganglia. Additionally, the ENS interacts with the CNS through extrinsic primary afferent neurons following spinal and vagal afferent routes [16].

The vagus nerve provides further innervation, with vagal afferents detecting motion (i.e., tension, stretch) and small molecules such as gut hormones and neurotransmitters [3]. These signaling molecules are released by enteroendocrine cells (EECs), which can be stimulated by bacterial metabolites like short-chain fatty acids (SCFAs) [29]. Other metabolites, such as kynurenine and tryptophan, can cross the intestinal barrier, enter the circulation, and traverse the blood-brain barrier [15,8].

A critical non-neuronal component of the axis is the HPA axis, which coordinates the neuroendocrine stress response. Studies in germ-free (GF) mice subject to restraint stress have demonstrated a hyperresponsive HPA axis, suggesting that the gut microbiome plays a regulatory role in stress signaling [44]. Moreover, the HPA axis can be activated by pro-inflammatory cytokines released in response to bacterial antigens [55].

2 Methodology

2.1 Scope and Simplifying Assumptions

The interaction between the gut microbiome and suicidal ideation (SI) is complex, involving feedback loops between diet, microbial composition, the gut-brain axis, and neurobiology. Each component presents its own layer of complexity; for instance, the human gut microbiome comprises thousands of bacterial species interacting within a host-specific environment defined by pH, motility, and location [43]. A fundamental challenge lies in the mechanistic modeling of subjective experiences; the understanding of precise translation of physiological changes into specific thought patterns, such as SI, remains incomplete [40].

To construct a tractable model, we applied several simplifying assumptions. Regarding behavioral feedback, we treated diet as an exogenous variable. While the gut-brain axis functions bidirectionally and mood disorders frequently alter

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dietary habits, we omitted this reverse causality to constrain network complexity and maintain the tractability required for subsequent computational modeling. To further reduce complexity, age, sex, and short-term interventions (e.g., antibiotics, NSAIDs, antipsychotics) from the core model.

Furthermore, we limited our scope to the neurobiological drivers of SI, specifically neuroinflammation, neurotoxicity, and serotonin dysregulation. While psychological factors are critical to the suicidal process, quantifying their direct systemic impact (e.g., the exact physiological weight of thwarted belongingness) remains highly challenging. To reduce complexity and ensure connections between nodes remain quantifiable for computational modeling, these variables remain outside the purview of this initial physiological model. Among psychiatric comorbidities, we prioritized mood disorders (Major Depressive Disorder and Bipolar Disorder). We excluded Schizophrenia due to its distinct neurobiological profile [34], and Autism Spectrum Disorder (ASD), which is characterized by specific microbial signatures such as the overgrowth of *Clostridium* species and elevated production of p-cresol [18,24]. Finally, confounding conditions such as Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disease (IBD), and autoimmune disorders were excluded to isolate the gut-brain-SI axis.

2.2 Variable Selection and Database Curation

We conducted a review of scientific literature on the gut microbiome, diet, the gut-brain axis, and suicidal ideation. Our search identified over a hundred variables playing a key role in the gut-brain axis. These variables were prioritized based on relevance, and we focused on three main modes of interaction between the gut microbiome and the brain: the vagus nerve, the HPA axis, and the bloodstream [12]. Gut bacteria produce metabolites that activate the vagus nerve either directly or through enteroendocrine cells [12,51]. Bacterial antigens can trigger an immune response, leading to the secretion of pro-inflammatory cytokines and ultimately the activation of the HPA axis [4]. Lastly, specific metabolites, such as kynurenine and tryptophan, can cross the epithelial barrier, enter the bloodstream, and traverse the blood-brain barrier [15,8].

Initial modeling at the taxonomic level of phyla proved too coarse. While literature suggests effects from phyla composition (e.g., the *Firmicutes*/*Bacteroidetes* ratio), evidence is often mixed [19,35]. In reality, significant functional differences occur at the genus or even species level [6,37]. As the gut is host to thousands of species, we limit ourselves to genera, specifically those that are most relevant to the gut-brain axis based on metabolite production. We identified eight key metabolites: histamine, BCAA, GABA, catecholamines, SCFA, tryptophan, kynurenine, and serotonin [12,14,31].

Based on this selection, we matched metabolites to producing genera (see Table 1). To characterize the substrate consumption of these genera, we queried the BacDive database [41]. We identified relevant samples using a boolean search strategy requiring a match for both host and isolation source. Specifically, a sample was included only if it contained at least one keyword identifying the host ("human", "homo sapiens", "patient", "infant", "child", "adult", "volunteer",

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"subject") AND at least one keyword identifying the source ("feces", "faeces", "stool", "fecal", "meconium", "rectal").

Table 1. Characteristics and Metabolite Production Profiles of Selected Gut Bacterial Genera. A summary of the filtered bacterial genera incorporated into the causal network, detailing their taxonomic phylum, Gram stain classification, and primary production of neuroactive and immunomodulatory metabolites (e.g., short-chain fatty acids, GABA, tryptophan). Bold text indicates genera specifically retained after filtering for macronutrient substrate consumption using the BacDive database.

Bacteria	**Phylum**	**Metabolite Production**	**Gram Stain**	**References**
Agathobacter	Firmicutes	SCFA	Gram-positive	[30]
Akkermansia	Verrucomicrobiota	SCFA	Gram-negative	[28]
Anaerostipes	Firmicutes	SCFA	Gram-positive	[28]
Bacillus	Firmicutes	tryptophan	Gram-positive	[27]
Bacteroides	Bacteroidetes	SCFA, GABA, catecholamines	Gram-negative	[28,52,33]
Bifidobacterium	Actinobacteria	SCFA, GABA	Gram-positive	[50,53]
Blautia	Firmicutes	SCFA	Gram-positive	[28]
Clostridium	Firmicutes	SCFA, BCAA	Gram-positive	[50,39]
Coprococcus	Firmicutes	SCFA	Gram-positive	[28]
Enterococcus	Firmicutes	GABA, catecholamines	Gram-positive	[22,42]
Eubacterium	Firmicutes	SCFA	Gram-positive	[28]
Faecalibacterium	Firmicutes	SCFA	Gram-variable	[28]
Lacticaseibacillus	Firmicutes	GABA	Gram-positive	[17,25]
Lactiplantibacillus	Firmicutes	GABA, BCAA, tryptophan	Gram-positive	[17,49,9,25]
Lentilactobacillus	Firmicutes	GABA	Gram-positive	[25]
Levilactobacillus	Firmicutes	GABA	Gram-positive	[25]
Ligilactobacillus	Firmicutes	GABA	Gram-positive	[25]
Parabacteroides	Bacteroidetes	GABA	Gram-negative	[42]
Prevotella	Bacteroidetes	SCFA, BCAA	Gram-negative	[28,21]
Pseudomonas	Proteobacteria	kynurenine	Gram-negative	[26]
Roseburia	Firmicutes	SCFA	Gram-variable	[28]
Ruminococcus	Firmicutes	SCFA	Gram-positive	[50]
Veillonella	Firmicutes	SCFA	Gram-negative	[50]
Phascolarctobacterium	Firmicutes	SCFA	Gram-negative	[28]

We categorized substrates into macronutrient groups: simple sugars, complex carbohydrates, protein, fats, and other. Due to inconsistent sample sizes, we applied an empirically derived cutoff, retaining genera with more than 5 hits and an overall percentage of hits more than 10% for a given macronutrient to minimize false positives. This process yielded 6 genera. We removed histamine, BCAAs and serotonin from the model as the selected genera were not found to produce them.

Research has shown an association of *Veillonella* and *Phascolarctobacterium* with suicidal ideation [1,7]. As an opportunistic gut pathogen typically found in the oral cavity, *Veillonella* lacks the capacity to utilize simple sugars, depending instead on lactic acid cross-feeding [54]. Similarly, *Phascolarctobacterium* is a specialized cross-feeding bacterium that consumes succinate [47]. Given their reported implications in suicidal ideation, both genera were incorporated into the model.

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2.3 Network Construction

Following variable selection and pathway identification, we conducted a targeted literature search to establish causal links. We qualitatively graded the evidence for each interaction on a four-point scale:

1. Assumption (theoretical link only)
2. Association (correlational evidence)
3. Possible Causality (suggested by mechanisms but not definitively proven)
4. High Evidence of Causality (established mechanism)

This process yielded a directed weighted network comprising 41 nodes and 87 edges.

2.4 Topological Metrics

We performed Network analysis using NetworkX (version 3.5) [20]. We evaluated the structural properties of the graph through five primary metrics: betweenness centrality, PageRank, Shannon entropy, modularity, and reach efficiency. To assess network robustness, we conducted a node vulnerability analysis by measuring the decrease in global efficiency when an individual node was removed from the base topology.

Betweenness centrality identifies the critical systemic bottlenecks through which localized signals must pass to propagate across the network. The betweenness centrality of a node i is calculated as:

$$g(i) = \sum_{s \neq i \neq t} \frac{\sigma_{st}(i)}{\sigma_{st}}, \tag{1}$$

where σ_{st} is the total number of shortest paths from node s to node t and $\sigma_{st}(i)$ is the number of shortest path from s to t that pass through node i.

PageRank highlights the ultimate topological sinks within the directed graph, identifying which nodes act as the primary downstream endpoints of cascading physiological failures. The PageRank (PR) of a node p_i is given by the expression:

$$PR(p_i) = \frac{1-d}{N} + d \sum_{p_j \in M(p_i)} \frac{PR(p_j)}{L(p_j)}, \tag{2}$$

where $L(p_j)$ denotes the number of outgoing links from node p_j, d is the damping factor (set to 0.85), N is the total number of nodes, and $M(p_i)$ is a set of nodes that link to node p_i.

Modularity measures functional compartmentalization, revealing the extent to which the system segregates into distinct, dense local pathways rather than operating as a globally entangled whole. Modularity can be defined as:

$$Q = \frac{1}{2m} \sum_{ij} \left(A_{ij} - \gamma \frac{k_i k_j}{2m} \right) \delta(c_i, c_j), \tag{3}$$

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where m is the number of links, A is the adjacency matrix of network G, k_i is the degree of node i, γ is the resolution parameter (set to 1), and $\delta(c_i, c_j)$ is Kronecker delta (1 if node i and node j are in the same community) [10].

In the context of this static knowledge graph, Shannon entropy was adapted to quantify the diversity and distribution of empirical evidence supporting a given node, rather than representing biological signal entropy. Therefore, a higher entropy score indicates a node supported by a broad, evenly distributed foundation of literature across multiple incoming or outgoing pathways, whereas a lower score suggests a hub reliant on isolated or less robustly evidenced connections. The Shannon entropy of a node (H_i) is calculated as follows:

$$H_i = -\sum_{j \in N_i} p_{ij} \log_2 p_{ij}, \tag{4}$$

where p_{ij} is the normalized weight (based on qualitatively graded evidence) of an edge between node i and j, and N_i is the set of neighbors connected to node i.

Reach efficiency of node i is defined as:

$$RE(i) = \frac{N_k(i)}{n_{out}(i)}, \tag{5}$$

where $N_k(i)$ is the number of nodes within k steps of node i and $n_{out}(i)$ is the out degree of node i

3 Results

3.1 Network Architecture and Critical Hubs

The causal knowledge graph (Figure 1) exhibits a sparse architecture with a density of 0.053 (Figure 2). This sparsity, combined with a low average clustering coefficient (0.058), likely reflects the current limitations of available empirical literature rather than a true biological absence of dense feedback loops. Despite this low density, the network is highly structured; the modularity score of 0.4634 confirms a strong division into four distinct communities: the gut compartment, kynurenine pathway, inflammatory pathway, and a neurobiological compartment. This partitioning based on the Clauset-Newman-Moore greedy modularity maximization offers an alternative view to our initial theoretical division (intake, gut, gut-brain axis, brain).

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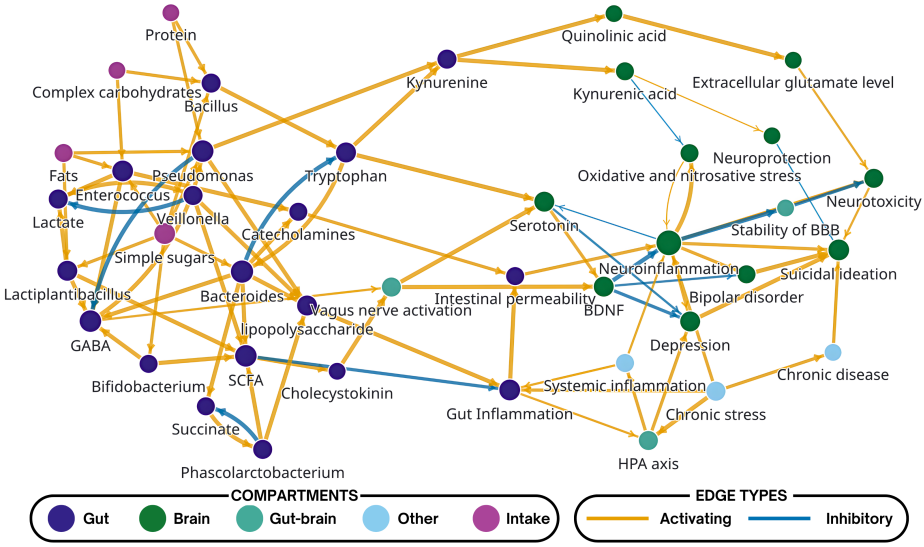

Fig. 1. Gut-Brain Axis Causal Knowledge Graph. A complete directed network representation illustrating the complex bidirectional communication between dietary intake, the microbiome, and mental health outcomes. The network comprises 41 nodes distributed across five functional compartments: Dietary Intake, Gut microbiome, Gut-brain interface, Brain outcomes, and Other regulatory factors. Edge formatting denotes relationship polarity and empirical support: activating, inhibitory, with thickness of lines representing the weight and strength of evidence drawn from literature review.

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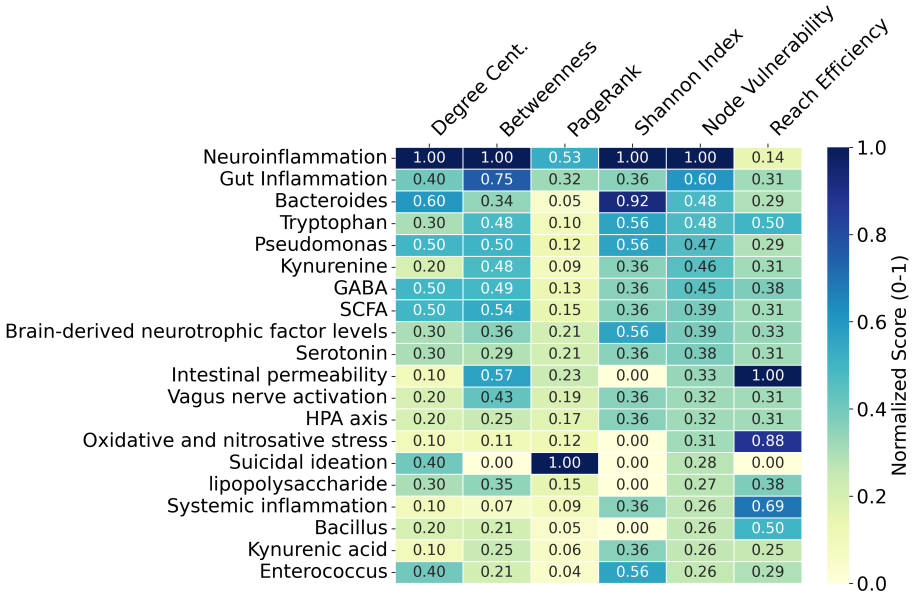

Fig. 2. Topological and centrality metrics of key gut-brain axis nodes. A heatmap displaying normalized scores (0-1) across six network metrics: Degree Centrality, Betweenness Centrality, PageRank, Shannon Index, Node Vulnerability, and Reach Efficiency. Darker blue shades indicate higher metric values.

Topological analysis of the network identifies distinct bottlenecks that dictate the flow of systemic perturbation. Neuroinflammation acts as the primary systemic hub, possessing the highest total degree (12.0) and betweenness centrality (0.089). This positions neuroinflammation as the dominant mediator through which peripheral signals are integrated before impacting psychiatric outcomes. Suicidal ideation represents the primary downstream consequence within the network, reflected by its peak PageRank value of 0.148.

Furthermore, intestinal permeability and oxidative stress exhibit the highest reach efficiency scores (8.0 and 7.0, respectively), indicating their capacity to propagate localized dysbiosis into widespread systemic cascades, identifying them as critical upstream drivers capable of triggering the gut-brain-SI axis.

To facilitate direct comparison across disparate topological metrics with varying scales, all raw node scores were independently normalized to a $[0, 1]$ range using Min-Max scaling.

3.2 Feedback loops

The current network contains several feedback loops, including:

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- **Gut - HPA - Inflammation:** If persistent, gut inflammation leads to sustained hyperactivation of the HPA axis. This in turn fuels systemic inflammation, which increases gut inflammation. This loop is therefore reinforcing.
- **Neuroinflammation - Serotonin - BDNF:** Neuroinflammation leads to a decrease in serotonin levels, while serotonin under acute stress increases BDNF levels. BDNF then downregulates neuroinflammation, and overall, this loop is balancing.
- **GABA - Lactate - Succinate:** GABA, lactate, and succinate are consumed by their respective genera and the bacteria increase based on the amount of available metabolites, leading to balancing loops.
- **Oxidative Stress Cycle:** Neuroinflammation and oxidative/nitrosative stress feed into each other, creating a reinforcing loop.

The network currently lacks the density of feedback mechanisms that we would expect in a complex biological system, mostly due to the lack of evidence from existing literature.

4 Discussion

From Dysbiosis to Vulnerability The architectural analysis of the gut-brain network frames SI not as a psychological endpoint, but as the downstream consequence of a cascading neurobiological breakdown. The network topology identifies a clear, directional progression from localized gut dysfunction to systemic vulnerability.

Intestinal permeability and oxidative stress emerged as the primary upstream catalysts, exhibiting the highest reach efficiency scores within the network (8.0 and 7.0, respectively). This high reach efficiency suggests that a compromised epithelial barrier serves as the critical breach point, allowing localized dysbiosis to propagate outward. When permeability increases, bacterial metabolites and antigens, such as lipopolysaccharides, traverse into the systemic circulation.

This systemic leakage fuels the network's bottleneck: neuroinflammation. With the highest total degree (12.0) and betweenness centrality (0.089), neuroinflammation acts as the central integration hub where peripheral immune responses are translated into neurological disruption. While previous observational studies establish neuroinflammation as a correlate of psychiatric vulnerability, our network analysis formally maps its structural role as the requisite mechanistic bridge linking peripheral gut dysbiosis to the dysregulation of central nervous system targets [11,23]. By visualising the literature in this manner, the graph not only confirms heavily studied pathways but also exposes critical gaps in the current evidence base, highlighting where future empirical research can focus to complete our understanding of the systemic suicidal process.

Within our model, neuroinflammation drives the dysregulation of key neurotransmitters, leading to decreased serotonin availability and reduced levels of brain-derived neurotrophic factor. Concurrently, it amplifies neurotoxicity and oxidative stress, creating a reinforcing biological feedback loop. Ultimately, this sustained state of neuroinflammation and neurotoxicity erodes cognitive and

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emotional regulation, creating the biological diathesis required for SI. By identifying neuroinflammation as the mediator in this causal loop, our model suggests that vulnerability to SI is intertwined with the integrity of the gut barrier and the host's inflammatory response.

Limitations While this causal network provides a foundational mapping of the gut-brain-SI axis, several simplifying assumptions restrict its immediate clinical application. To maintain computational tractability, the current model faces various constraints. Strict inclusion criteria based on established mechanisms yielded a sparse architecture, underrepresenting the dense, multidirectional feedback loops typical of complex biological systems. Modeling the microbiome at the genus level masks functional and metabolic differences that occur at the species or strain level. The model treats diet as an exogenous variable and does not account for behavioral reverse causality, such as how the psychological burden of SI might alter dietary intake or gut motility. Incorporating this bidirectional interaction between psychiatric state and dietary habits is a primary objective for future expansions of this computational model. By controlling for demographic variables (e.g., age, sex) and excluding complex psychiatric comorbidities (e.g., Autism Spectrum Disorder, Schizophrenia), we significantly decrease the complexity of our model but at the same time decrease the specificity. We also do not include selective serotonin reuptake inhibitors, which can profoundly impact gut serotonin levels and are prevalent among individuals with SI. Advancing this static framework requires empirically quantifying bidirectional feedback mechanisms and expanding taxonomic resolution to capture host-specific metabolic variations.

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