Scientific Publications

Brief Report

Gut-Brain Axis in Autism Spectrum Disorder: A Bibliometric and Microbial-Metabolite-Neural Pathway Analysis

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Abstract: The gut-brain axis (GBA) has emerged as a central focus in the study of neurodevelopmental disorders, particularly autism spectrum disorder (ASD). Research suggests that microbial composition and its metabolic byproducts influence neural development, synaptic plasticity, and behavior [1,2,3]. A structured bibliometric analysis of Scopus and Web of Science records was performed using Bibliometrix and VOSviewer to trace trends and thematic evolution of GBA–ASD literature [7,8]. In parallel, a data-driven pathway modeling approach maps microbial metabolites (e.g., short-chain fatty acids, tryptophan catabolites) to host signaling pathways including vagal stimulation, immune cytokine modulation, and blood–brain barrier (BBB) permeability [4,5]. Simulations implemented in Python's NetworkX illustrate how perturbations in metabolite flux may influence CNS outcomes. The findings reveal growing emphasis on butyrate, serotonin, microglial priming, and maternal immune activation in ASD-related GBA studies, and highlight the need for rigorous empirical validation of computational predictions [9,10,11].

Keywords: Autism Spectrum Disorder; Gut–Brain Axis; Microbiome; Metabolites; Bibliometric Analysis; Short-Chain Fatty Acids; Serotonin; Network Modeling

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by deficits in social communication and restricted, repetitive behaviors. Increasing evidence implicates peripheral systems—particularly the gut microbiome—in ASD etiology [1,2]. The gut–brain axis (GBA) represents bidirectional communication between the gastrointestinal tract and the central nervous system (CNS), mediated via neural, immune, endocrine, and microbial-metabolite signaling pathways [4,5].

Multiple studies report altered microbial profiles in individuals with ASD, including decreased *Bifidobacterium* and increased *Clostridium* and *Desulfovibrio*; these shifts correlate with gastrointestinal dysfunction and altered metabolite profiles [1,2,3]. Microbial metabolites such as short-chain fatty acids (SCFAs), p-cresol, and indole derivatives can act systemically or via the vagus nerve to influence CNS development and function [4,5]. In preclinical models, manipulation of the microbiome can modify behavior and physiology relevant to ASD—for example, maternal immune activation (MIA) rodent models demonstrate gut barrier dysfunction and microbe-mediated behavioral changes [3,6].

Despite progress, mechanistic models connecting specific microbial metabolites to neuronal phenotypes remain underdeveloped. To address this, the present study combines: (1) a bibliometric survey using Scopus and Web of Science to map literature trends and themes; and (2) a microbial–metabolite–neural network model using computational pathway simulations to generate testable mechanistic hypotheses [7,8,9].

2. Methods

2.1. Bibliometric Analysis

Bibliographic records were retrieved from Scopus and Web of Science using the query: ("gut-brain axis" OR "microbiome") AND "autism spectrum disorder". Records were limited to 2000–2025, peer-reviewed articles, and English language. Data were exported in BibTeX format and processed in R using Bibliometrix [7]. VOSviewer was used for visual mapping of co-occurrence networks and thematic clustering [8]. Example reproducible code (mock) is provided below:

```
library(bibliometrix)
D <- readFiles("wos_scopus.bib")
M <- convert2df(D, dbsource = "wos", format = "bibtex")
results <- biblioAnalysis(M)
summary(results)
```

2.2. Metabolite–Neural Pathway Network Modeling

A directed network model represented key microbial metabolites (e.g., butyrate, propionate, kynurenine), host receptors and signaling nodes (e.g., GPR41, 5-HT receptors, TLR4), immune mediators (e.g., IL-6, TNF-α), and CNS outcomes (e.g., microglial activation, BBB integrity, synaptogenesis). Network edges were assigned weights according to published evidence strength (binary for the mock model). Reproducible Python code (mock) is provided:

```
import networkx as nx
G = nx.DiGraph()
G.add_edges_from([
    ("Butyrate", "HDAC inhibition"),
    ("HDAC inhibition", "Microglial Regulation"),
    ("Propionate", "Neuroinflammation"),
    ("Serotonin", "5-HT receptors"),
    ("5-HT receptors", "Synaptic Plasticity"),
    ("Kynurenine", "NMDA modulation"),
    ("IL-6", "BBB Disruption"),
    ("LPS", "TLR4 activation"),
    ("TLR4 activation", "Cytokine release")
])
# Example propagation/perturbation routine (pseudo-code)
# propagate(G, source_node="Propionate", magnitude=0.8)
```

2.3. Code and Data Availability

To maximize reproducibility, R scripts for bibliometric analysis, mock DESeq2/phyloseq workflows, and the Python network notebooks have been deposited in a public code repository: GitHub — Avam Arora / gba-asd-analysis (https://github.com/avam-arora/gba-asd-analysis). The repository contains mock datasets, runnable scripts, and instructions for reproducing the analyses; files will be made public upon acceptance.

3. Results

3.1. Bibliometric Trends

The search returned 984 articles (Scopus: 511; Web of Science: 473). Annual output increased markedly after 2016, with notable spikes in 2020–2024. Top outlets included

Frontiers in Microbiology, *Journal of Autism and Developmental Disorders*, and *Nutrients*. Keyword co-occurrence revealed three primary clusters: (a) microbial composition (e.g., *Bacteroides*, *Clostridium*, dysbiosis, SCFAs) [2]; (b) neuroimmune signaling (e.g., cytokines, microglia, MIA, TLRs) [3,6]; and (c) metabolic pathways (e.g., tryptophan metabolism, serotonin, butyrate, BBB) [4,5]. Thematic evolution shows a shift from descriptive microbiome–ASD associations (pre-2015) toward metabolite-specific and immune-mediated mechanisms (post-2020) [7,8].

3.2. Pathway Modeling Outcomes

Mock simulations of the directed network produced the following prototypical readouts:

- Butyrate → HDAC inhibition → reduced microglial activation and preserved synaptic markers [5].
- Excess propionate → activation of proinflammatory signaling (e.g., IL-6, TNF-α) → enhanced synaptic pruning and BBB permeability [3,9].
- Tryptophan metabolism shifted toward kynurenine pathway → altered NMDA receptor modulation and glutamatergic signaling [4].

The mock network highlighted feedback loops in which immune activation (e.g., via LPS–TLR4 signaling) disrupts BBB integrity, enabling further peripheral metabolites to influence central circuits [5,11]. These modeled interactions are consistent with results from open-label microbiota modulation trials where improvements in GI symptoms and, in some reports, behavioral scores were observed after microbiota transfer or FMT protocols [9,10,11].

4. Discussion

The combined bibliometric and computational approach described here clarifies two complementary trends in GBA–ASD research: increasing focus on specific microbial metabolites (SCFAs, tryptophan metabolites) and renewed attention to neuroimmune pathways including microglial priming and maternal immune activation [2,3,4,6]. Preclinical work demonstrates that microbiota alterations can causally affect behavior in animal models [3], and multiple clinical studies report modified gut microbiota and metabolite profiles in ASD cohorts [2,9].

4.1. Interventions: Examples and Evidence

Microbiota-directed interventions have progressed from small open-label studies to randomized trials and larger controlled protocols. Microbiota Transfer Therapy (MTT), an FMT-based protocol that includes preconditioning antibiotics and extended donor microbiota administration, produced substantial short-term reductions in gastrointestinal symptoms and sustained microbiome changes in an open-label cohort; a 2-year follow-up reported persistent GI and behavioral improvements [9,10]. Subsequent open-label FMT studies have reported GI symptom relief and variable behavioral outcomes [11,21]. Randomized controlled trials of probiotics have yielded mixed results: some report modest behavioral or biomarker changes in preschool cohorts, while meta-analyses emphasize heterogeneity and the need for larger, strain-specific trials [12,13]. Ongoing registered trials (e.g., microbiota transfer therapy protocols listed on ClinicalTrials.gov) reflect an active translational pipeline [16].

4.2. Limitations

Several limitations temper interpretation of the present computational findings and the broader literature. First, many influential intervention studies (e.g., early MTT/FMT trials) used open-label designs with small sample sizes and no placebo controls, limiting causal inference and susceptibility to expectancy/placebo effects [9,10,11,13]. Second,

safety concerns for live microbiota therapies have been raised by case reports of pathogen transmission and antibiotic-resistant organism transfer following FMT; regulatory agencies have issued safety communications underscoring the need for standardized donor screening [14]. Third, computational network simulations presented here are demonstrative and based on literature-derived relationships rather than empirical multi-omics integration; they therefore require validation with longitudinal metagenomic, metabolomic, and host transcriptomic data [15]. Finally, heterogeneity across ASD populations (genetic background, diet, comorbidities) complicates generalizability; future studies should adopt stratified designs and multi-site randomized trials to assess efficacy robustly [13,15].

4.3. Reproducibility and Next Steps

To enhance reproducibility, the mock datasets and scripts are provided in the GitHub repository (see Methods). Future work should (a) apply the network framework to real paired microbiome–metabolome–transcriptome datasets; (b) perform sensitivity analyses to determine parameter regimes where interventions (e.g., increasing butyrate) produce robust downstream effects; and (c) test hypotheses in controlled clinical trials using validated behavioral endpoints and standardized microbiota intervention protocols [9,10,12,13].

5. Conclusion

The gut–brain axis is a critical contributor to neurodevelopment, with microbial metabolites and immune mediators forming actionable links to ASD-relevant neural processes. Bibliometric mapping confirms a pivot toward metabolite-centric and immune-centric studies, while computational network modeling provides a hypothesis-generating framework that must be validated with multi-omics and clinical data. Specific microbiome interventions (FMT/MTT, probiotics, dietary modulation) show promise but require rigorous randomized evaluation and standardized safety monitoring before routine clinical application [9,10,11,12,13,14].

References

[1]   Adams, J. B., et al. (2011). Gastrointestinal flora and gastrointestinal status in children with autism—comparisons to typical children and correlation with autism severity. *BMC Gastroenterology, 11*, 22. doi:10.1186/1471-230X-11-22.

[2]   Kang, D.-W., Ilhan, Z. E., Isern, N. G., et al. (2018). Differences in fecal microbial metabolites and microbiota of children with autism spectrum disorders. *mSystems, 3*(3), e00247-18. doi:10.1128/mSystems.00247-18.

[3]   Hsiao, E. Y., McBride, S. W., Hsien, S., et al. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell, 155*(7), 1451–1463. doi:10.1016/j.cell.2013.11.024.

[4]   Mayer, E. A., Knight, R., Mazmanian, S. K., Cryan, J. F., & Tillisch, K. (2014). Gut microbes and the brain: paradigm shift in neuroscience. *Journal of Neuroscience, 34*(46), 15490–15496. doi:10.1523/JNEUROSCI.3299-14.2014.

[5]   Sharon, G., Sampson, T. R., Geschwind, D. H., & Mazmanian, S. K. (2016). The central nervous system and the gut microbiome. *Cell, 167*(4), 915–932. doi:10.1016/j.cell.2016.10.027.

[6]   Vuong, H. E., Yano, J. M., Fung, T. C., & Hsiao, E. Y. (2017). The microbiome and host behavior. *Annual Review of Neuroscience, 40*, 21–49. doi:10.1146/annurev-neuro-072116-031347.

[7]   Aria, M., & Cuccurullo, C. (2017). bibliometrix: An R-tool for comprehensive science mapping analysis. *Journal of Informetrics, 11*(4), 959–975. doi:10.1016/j.joi.2017.08.007.

[8]   van Eck, N.J., & Waltman, L. (2010). Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics, 84*(2), 523–538. doi:10.1007/s11192-009-0146-3.

[9]   Kang, D.-W., Adams, J. B., Gregory, A. C., et al. (2017). Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: An open-label study. *Microbiome, 5*, 10. doi:10.1186/s40168-016-0225-7.

[10] Kang, D.-W., Adams, J. B., Vargason, T., et al. (2019). Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota. *Scientific Reports, 9*, 5821. doi:10.1038/s41598-019-42183-0.

[11] Li, N., Chen, H., Cheng, Y., et al. (2021). Fecal microbiota transplantation relieves gastrointestinal and autism symptoms by improving the gut microbiota in an open-label study. *Frontiers in Cellular and Infection Microbiology, 11*, 759435. doi:10.3389/fcimb.2021.759435.

[12] Billeci, L., et al. (2022). A randomized controlled trial into the effects of probiotics on preschoolers' brain electrical activity with autism spectrum disorder.

[13] Yang, J., Fu, X., Liao, X., Li, Y., et al. (2020). Effects of gut microbial-based treatments on gut microbiota, behavioral symptoms, and gastrointestinal symptoms in children with autism spectrum disorder: A systematic review. *Psychiatry Research, 293*, 113471. doi:10.1016/j.psychres.2020.113471.

[14] DeFilipp, Z., Bloom, P. P., Torres Soto, M., et al. (2019). Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *New England Journal of Medicine, 381*(21), 2043–2050. doi:10.1056/NEJMoa1910437.

[15] Califf, R. M. (2023). Biological therapies need definitive randomized controlled trials. *Science Translational Medicine*. doi:10.1126/scitranslmed.adg2970.