



eBRAIN-Health

Public report D6.2

Catalogue of multi-scale principles of brain dynamics in dementia

Project number	101058516
Project title	eBRAIN-Health - Actionable Multilevel Health Data
Submission date	July 2025
Authors	Leon Stefanovski, Konstantin Bülau, Leon Martin, Petra Ritter (CHARITE)
Dissemination level	Public (PU)
Public project website	https://ebrain-health.eu



Funded by
the European Union

Table of content

1. eBRAIN-Health	3
2. eBRAIN-Health consortium	3
3. Introduction	4
4. Partners involved	5
5. Description of work performed	5
5.1. NeuroMMSig – a Knowledge Graph of the mechanisms in Alzheimer’s Disease	5
5.2. TVBase: A Semantic Mapping Tool for Brain-Related Concepts	5
5.3. Deriving a network of dynamics by applying multi-layer graph theory	6
6. Results	6
6.1. Analysis of five main transmitter systems in Alzheimer’s Disease.....	6
6.2. Cholinergic mechanism in Alzheimer’s Disease	8
6.3. Dopaminergic mechanisms in Alzheimer’s Disease	11
6.4. Serotonergic mechanisms in Alzheimer’s Disease	13
6.5. Glutamatergic mechanisms in Alzheimer’s Disease.....	15
6.6. GABAergic mechanisms in Alzheimer’s Disease	18
6.7. Multi-layer subgraphs	21
7. Conclusion, next steps	21
Acknowledgements	22

1. eBRAIN-Health

The Project eBRAIN-Health will deliver a distributed research platform for modeling and simulating complex neurobiological phenomena of human brain function and dysfunction in a data protection compliant environment. It will provide thousands of multilevel virtual brains from patients and healthy human controls for research and innovation. Brain data from multiple sources will be pre-processed. Solving the societal grand challenge of dementia is a big task. Yet it appears feasible in a collective approach. Therefore, we will build an interdisciplinary digital twin for dementia for modeling and simulating complex phenomena at the service of research infrastructure communities. eBRAIN-Health-Cloud will offer end-to-end services for personalized complex brain modeling and simulations in distributed e-infrastructures with data protection by design and by default and simulation-ready human multiscale brain data that range from molecular (genomics, proteomics, metabolomics) and cellular to electrophysiology and imaging to behavioural, clinical, life-style and environmental data as well as data from wearables. Brain data are pre-processed and annotated such that they all relate to a common reference 3D brain space. eBRAIN-Health-Cloud constitutes a blend of three large-scale research programs: the FET Flagship Human Brain Project with its EBRAINS Research Infrastructure, the EOSC project Virtual Brain Cloud with its Virtual Research Environment for sensitive data and the H2020 project AI-MIND with intelligent tools for dementia risk estimation. The project will have synergies to topics of the Digital Europe Program, such as artificial intelligence, cybersecurity and supercomputing and the Health Data Space.

eBRAIN-Health-Cloud offers a next generation clinical research infrastructure and creates an open yet protected space for groundbreaking digital health innovation by the research infrastructure communities comprising academia and the private sector.

2. eBRAIN-Health consortium

- CHARITE – Universitaetsmedizin Berlin, Germany
- EBRAINS, Belgium
- Forschungszentrum Juelich GmbH, Germany
- Stichting Radboud Universiteit, Netherlands
- Universidad Pompeu Fabra, Spain
- OSLO Universitetssykehus, Norway
- tp21 GMBH, Germany
- Fraunhofer Gesellschaft zur Foerderung der Angewandten Forschung eV, Germany
- INDOC RESEARCH EUROPE gGmbH, Germany
- Universitaet Wien, Austria
- Universidad Complutense de Madrid, Spain
- EODYNE Systems SL, Spain
- ATHENA – Research and Innovation Center, Greece
- University of Oslo, Norway
- Universita degli Studi di Roma la Sapienza, Italy
- Alzheimer Europe, Luxembourg
- Institute National de Recherche en Informatique et Automatique, France
- Centre Hospitalier Universitaire Vaudois, Switzerland
- The University of Edinburgh, United Kingdom

[Find the partners on our website](#)

3. Introduction

Dementia has emerged as a critical global health concern, with its prevalence steadily increasing due to aging populations and improved diagnostic capabilities. It is estimated that over 55 million people worldwide are currently living with dementia, a number projected to nearly triple by 2050, placing significant burdens on healthcare systems and caregivers alike (World Health Organization, 2021). The rising prevalence underscores the urgent need for comprehensive strategies in diagnosis, treatment, and long-term care planning. Recent research highlights not only the growing incidence but also the socio-economic and emotional impact of the disease, prompting intensified scientific and policy-oriented responses (Livingston et al., 2020; [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6)).

In parallel to the growing complexity of neurodegenerative disorders like dementia, there is an emergent rise in the development and application of advanced knowledge technologies and large language models (LLMs). These tools are crucially changing the way how biomedical data is integrated, interpreted, and applied in both research and clinical contexts. Biomedical ontologies and knowledge graphs, such as the Uberon ontology for anatomical structures (Mungall et al., 2012; <https://doi.org/10.1186/2041-1480-3-36>), and domain-specific platforms like NeuroMMSig for multimodal mechanistic signatures of neurological disorders (Domingo-Fernández et al., 2017; <https://doi.org/10.1093/database/bax003>), are enabling a systematic representation and querying of complex biological information. Additionally, OMICS-based resources like STRING (Szklarczyk et al., 2021; <https://doi.org/10.1093/nar/gkab1114>), which provides high-confidence protein-protein interaction networks, and the Gene Ontology (Ashburner et al., 2000; <https://doi.org/10.1038/75556>), which offers structured vocabularies for gene functions, become inevitably foundational to computational modeling and hypothesis generation in dementia research. Combined with the reasoning capabilities of LLMs, these structured resources are enhancing the scalability and precision of knowledge discovery, paving the way for more personalized and mechanistically informed approaches to neurodegenerative disease management.

Building on these advances, The Virtual Brain adapter of semantics (TVBase) introduces a novel approach to bridging large-scale biomedical literature with brain modeling. TVBase is a literature-mining-based semantic brain mapping tool that generates spatially explicit brain maps based on any user-defined semantic query. Leveraging the vast corpus of over 36 million scientific articles indexed in PubMed (National Library of Medicine, 2022), TVBase enables researchers to uncover and visualize the neuroanatomical correlates of complex biomedical concepts through automated text mining and 3D mapping. This integration of semantic search with an anatomical ground truth provides a powerful platform for hypothesis generation, comparative analysis, and data contextualization in neuroscience. By grounding literature-derived knowledge in spatial brain representations, TVBase significantly enhances the interpretability of large-scale data and supports multimodal research efforts in complex conditions such as dementia.

In this report, we use TVBase to map the entities from a domain-specific knowledge graph—NeuroMMSig—onto anatomical brain structures, creating semantically enriched, spatially grounded representations of Alzheimer’s disease mechanisms. This process results in multi-layer graphs that combine literature-derived semantic mappings with curated mechanistic data, enabling in-depth exploration of complex pathophysiological pathways. These enriched graphs offer additional layers of information beyond traditional static knowledge representations, supporting hypothesis-driven analysis and discovery. Furthermore, the resulting brain maps can be integrated into dynamic brain

simulation platforms, such as The Virtual Brain, allowing for multimodal simulations that bridge molecular, structural, and functional perspectives—ultimately advancing our understanding of Alzheimer’s disease through a systems neuroscience lens.

4. Partners involved

CHARITE, SCAI

5. Description of work performed

5.1. NeuroMMSig – a Knowledge Graph of the mechanisms in Alzheimer’s Disease

NeuroMMSig is a publicly available web server and knowledgebase designed to support mechanistic interpretation and enrichment of multiscale data in neurodegenerative disease research. It encodes manually-curated, disease-specific pathophysiological mechanisms—principally focusing on Alzheimer’s disease, Parkinson’s disease and epilepsy—using the Biological Expression Language (BEL, REF) to capture causal relationships, and allows users to submit molecular, imaging or clinical features to retrieve ranked “mechanistic subgraphs” that best explain the input data in the context of a chosen disease (Domingo-Fernández et al., 2017; doi:10.1093/bioinformatics/btx399). Leveraging dedicated algorithms, NeuroMMSig implements mechanism-enrichment by comparing multimodal signatures, a paradigm first articulated in the mechanism-based taxonomy framework for neurodegenerative disorders (Hofmann-Apitius et al., 2015; doi:10.3390/ijms161226148).

5.2. TVBase: A Semantic Mapping Tool for Brain-Related Concepts

TVBase represents an innovative tool for visualizing the association between semantic concepts and brain anatomy within a standardized 3D framework. While the software can be accessed programmatically as a Python library, it also includes an intuitive graphical user interface (GUI), enabling broad applicability across both research and clinical domains. At its core, TVBase links neuroanatomical terms with their spatial representations aligned in a canonical brain template, thereby enabling the construction of semantic brain maps based on biomedical literature indexed in PubMed.

The system queries concept frequencies and their anatomical co-occurrences using the SCAIView literature mining platform (DOI: 10.3233/SHTI180299), leveraging the Uberon anatomy ontology for brain structure references (DOI: 10.1186/2041-1480-3-27). A modified Kullback-Leibler divergence metric is used to quantify the relevance of each anatomical term to a given concept (e.g., assessing the relevance of the “hippocampal formation” in relation to “memory”).

To ensure anatomical accuracy, the mapping between Uberon terms and the Human Connectome Project (HCP) Glasser brain parcellation (DOI: 10.1038/nature18933) underwent multi-step manual curation.

TVBase supports both free-text input and standardized vocabularies covering genes, proteins, functions, and biological processes. Outputs are compatible with widely used volumetric templates such as MNI-152 (DOI: 10.1016/j.neuroimage.2011.07.013) and surface-based models like fsaverage (DOI: 10.1016/S1053-8119(99)90396-2, DOI: 10.1016/j.neuroimage.2012.01.021) and fsLR

(DOI: 10.1016/j.neuroimage.2013.05.039). Generated maps can be translated into more than 46 different anatomical parcellation schemes (DOI: 10.1038/s41592-021-01185-9).

The software will be openly available and further offers API access and is compatible with the Virtual Brain simulation platform (www.thevirtualbrain.org).

Validation efforts involved comparing 8121 TVBase-generated maps with established knowledge sources. Each concept was supported by an average of 2,170 scientific publications and linked to 345 distinct anatomical terms from the Uberon ontology, confirming the robustness and granularity of the semantic-anatomical associations.

The framework of TVBase is described in detail in a publication that at the time of this report is under review.

5.3. Deriving a network of dynamics by applying multi-layer graph theory

To investigate the structural and functional modularity within NeuroMMSig-derived molecular signatures, we applied the Infomap algorithm (DOI: 10.1103/PhysRevE.70.056131) for community detection across both monoplex and multilayer network configurations. Three layers of a multi-layer graph were considered: (1) a monoplex network comprising only the original links from NeuroMMSig, (2) an additional layer integrating the connections with spatial similarity measures from TVBase, and (3) another additional layer that additionally incorporates weighted spatial similarity derived from large language model (LLM)-weighted TVBase maps. In these networks, edge weights reflect the probability of a random walker transitioning between nodes, and Infomap optimizes community structure by minimizing the map equation to retain information flow within modules—thereby highlighting biologically coherent clusters. To harmonize interpretations across network layers, we standardized edge weights using statistical transformations. Spatial similarity in the TVBase layer was treated as a repulsive feature, implying decreased likelihood of co-functionality, while negative correlations in the LLM-weighted layer were interpreted cautiously; only positive TVBase similarities and absolute values from LLM-derived maps were retained to avoid biologically implausible negative edge weights. The influence of integrating spatial data was assessed by comparing the steady-state node flow—i.e., the long-term probability of random walker visitation—across monoplex and multilayer networks. Significant shifts in node prominence indicated that spatial co-localization can recontextualize molecular interactions beyond direct connections from within NeuroMMSig. All network analyses were conducted using the Infomap Python package, with visualization facilitated by pymnet and the Arena3D web platform (Kokoli et al., 2023).

6. Results

6.1. Analysis of five main transmitter systems in Alzheimer's Disease

To explore how spatial embedding influences molecular mechanisms of neurotransmission in Alzheimer's disease, we mapped each concept within five neurotransmitter-related subgraphs from NeuroMMSig—specifically, those centered on acetylcholine, dopamine, GABA, glutamate, and serotonin. These subgraphs were derived from curated mechanistic signatures associated with Alzheimer's pathology. For each subgraph, we enriched the original network by adding two additional layers based on spatial similarity. The first layer utilized spatial similarity scores derived from TVBase. The second layer integrated a large language model (LLM)-enhanced version of the TVBase map,

refining spatial relationships based on semantically enriched concept embeddings. This yielded five multilayer networks, each representing a distinct neurotransmitter system within a spatial-functional framework. In the following sections, we provide a detailed analysis of each multilayer network, highlighting how spatial organization modulates the functional modularity and network prominence of individual mechanisms involved in Alzheimer's disease.

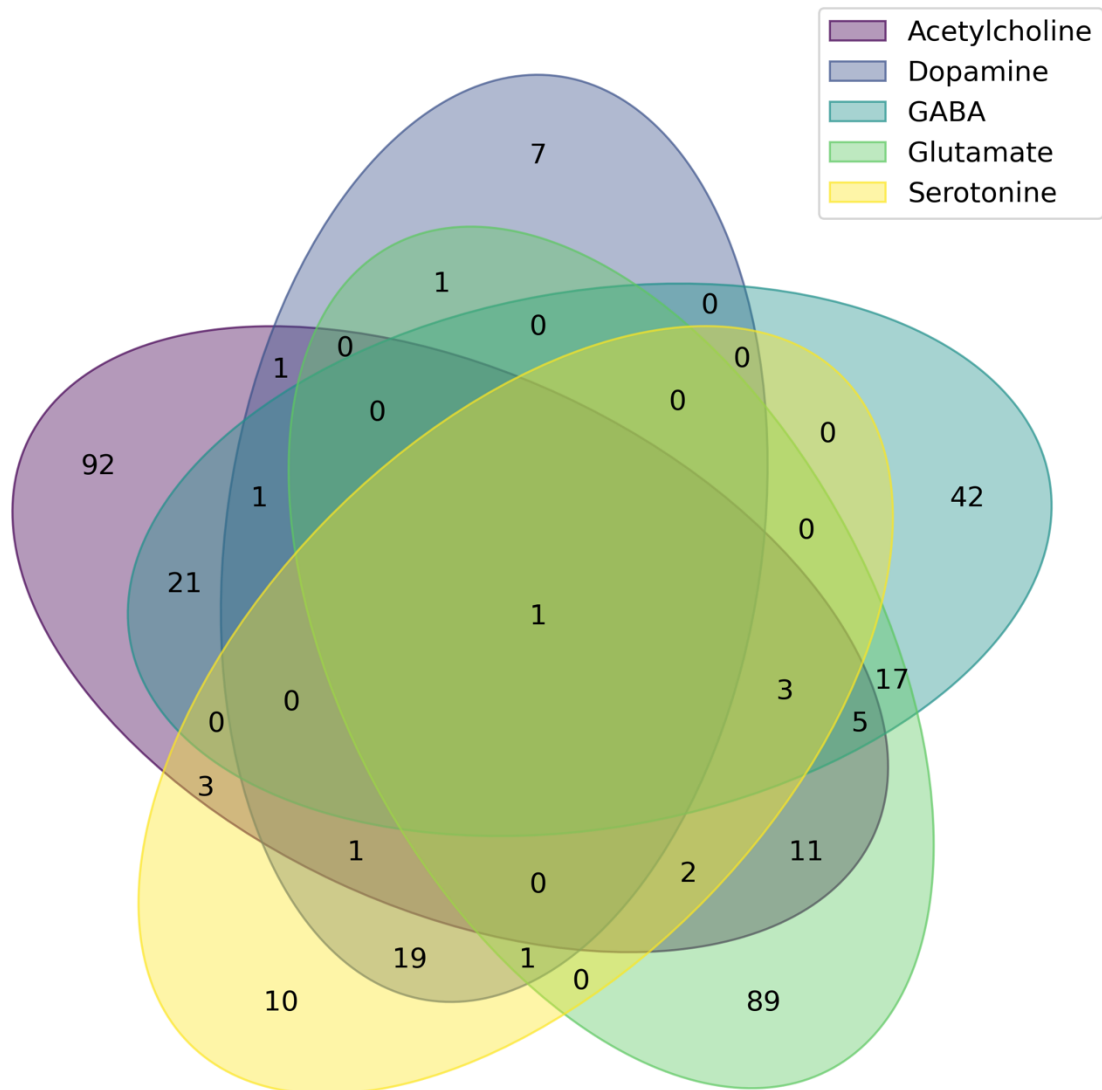


Figure 1. Venn diagram showing the overlap of mechanistic concepts among the five neurotransmitter-related subgraphs (acetylcholine, dopamine, GABA, glutamate, and serotonin) in NeuroMMSig. Each section indicates the number of shared or unique entities, highlighting the extent of molecular convergence and specificity across neurotransmitter systems implicated in Alzheimer's disease.

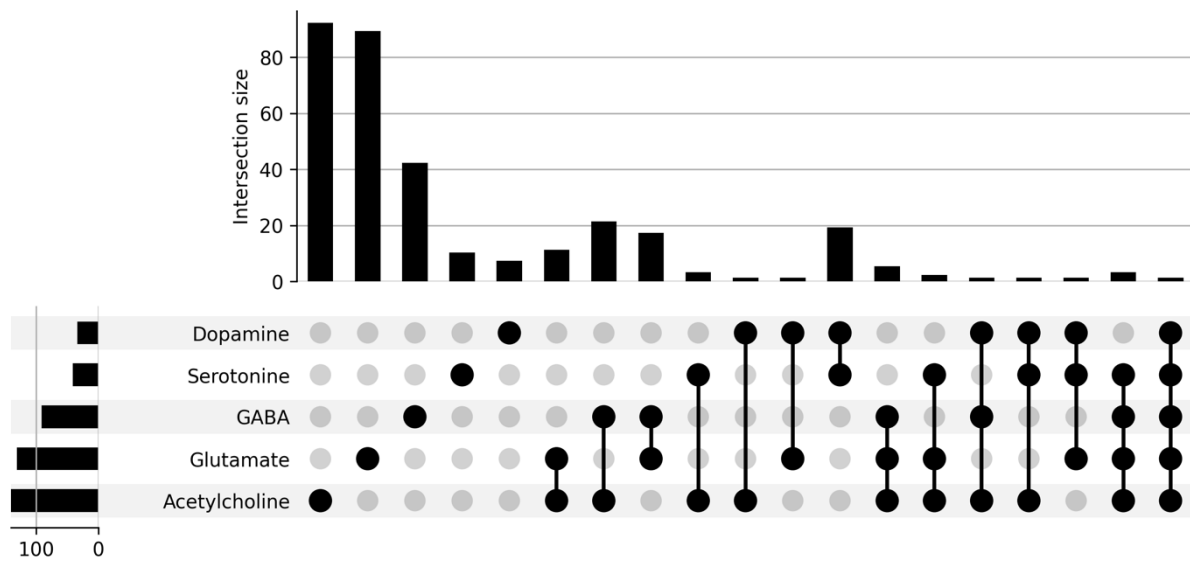


Figure 2. Intersection size plot depicting the number of shared entities between combinations of the five neurotransmitter-related NeuroMMSig subgraphs: acetylcholine, dopamine, GABA, glutamate, and serotonin. The plot highlights both pairwise and higher-order overlaps, illustrating the degree shared components among neurotransmitter mechanisms involved in Alzheimer’s disease.

6.2. Cholinergic mechanism in Alzheimer’s Disease

The acetylcholine subgraph in NeuroMMSig captures the molecular interactions and pathways associated with acetylcholine signaling, a key neurotransmitter system implicated in cognitive function and memory. Dysregulation of acetylcholine signaling is a hallmark of Alzheimer’s disease, contributing to synaptic dysfunction and neurodegeneration. This subgraph integrates e.g. protein-protein interactions, receptor dynamics, and enzymatic processes involved in acetylcholine synthesis, release, and degradation, providing a focused framework to study its mechanistic role in Alzheimer’s pathology.

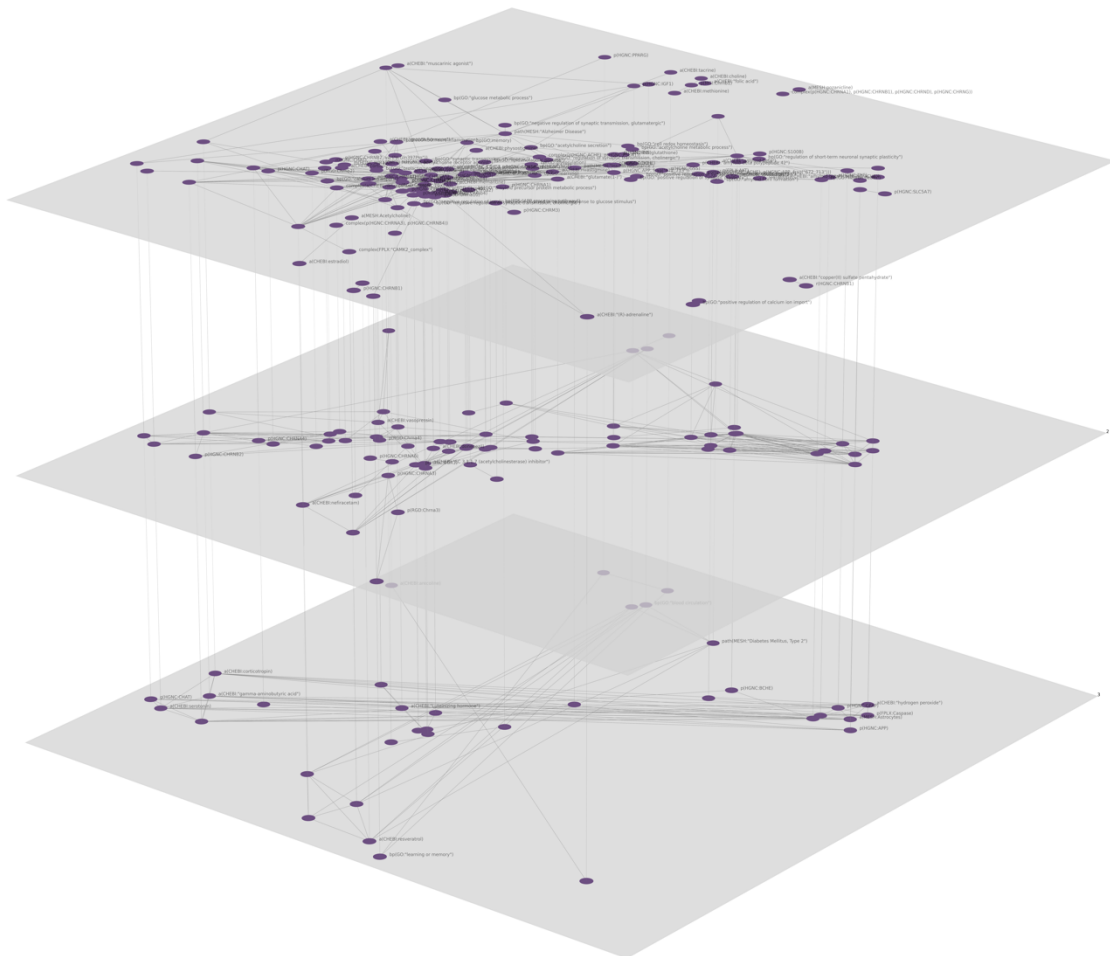


Figure 3. Multilayer network representation of the acetylcholine-related molecular mechanism in Alzheimer's disease. The first layer depicts interactions derived from NeuroMMSig. The second layer shows spatial similarity relationships between semantic maps based on TVBase. The third layer incorporates spatial associations refined by large language model (LLM)-enhanced TVBase embeddings. This multilayer approach integrates molecular interactions with spatial co-localization and semantic enrichment, enabling comprehensive analysis of network modularity and functional organization.

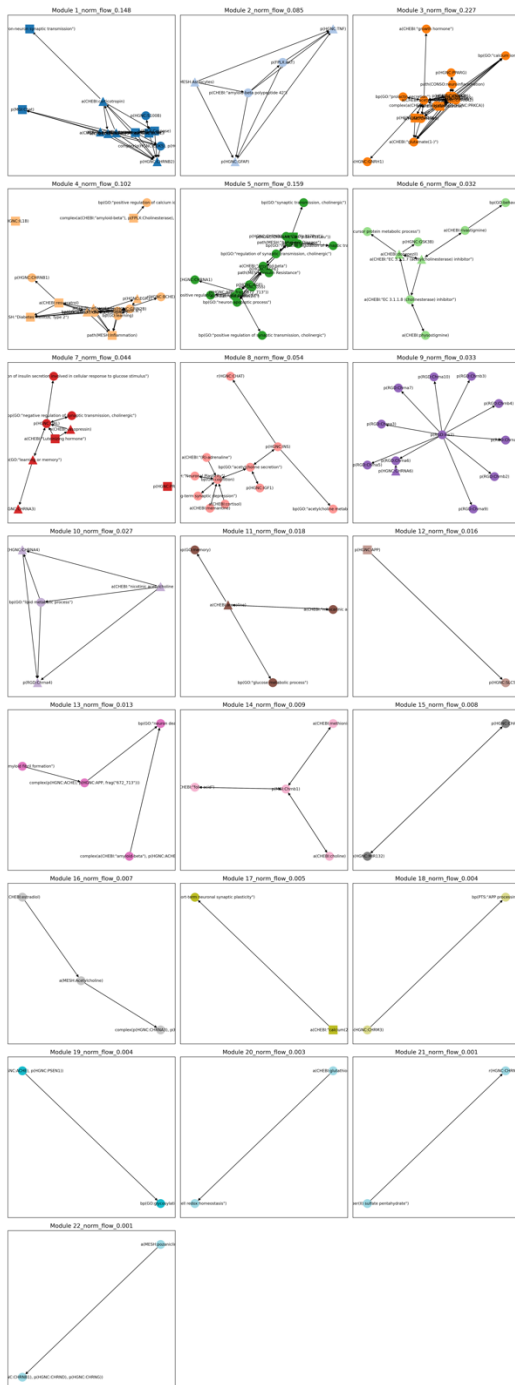


Figure 4. Community modules identified by flow-based Infomap analysis of the multilayer NeuroMMSig subgraph related to acetylcholine signaling in Alzheimer's disease. Modules represent clusters of entities with high intra-community flow, integrating interactions with spatial similarity layers from TVBase and LLM-enhanced TVBase maps. This modular decomposition reveals biologically relevant functional groupings influenced by both molecular connectivity and spatial co-localization.

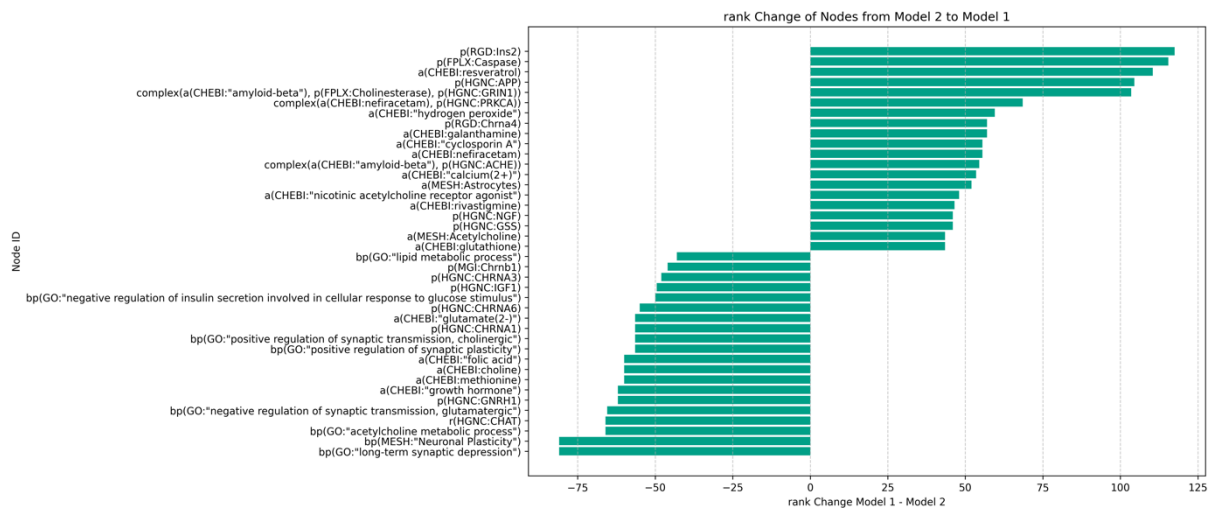


Figure 5. Ranking of entities within the NeuroMMSig acetylcholine subgraph based on flow analysis across network configurations. The plot compares node prominence in the original NeuroMMSig layer and after adding spatial similarity layers from TVBase and LLM-enhanced TVBase. Integration of spatial and semantic information alters the relative importance of entities, highlighting concepts whose functional roles are modulated by brain spatial organization and enriched semantic context.

6.3. Dopaminergic mechanisms in Alzheimer’s Disease

The dopamine subgraph in NeuroMMSig represents the molecular networks involved in dopamine signaling pathways, which play crucial roles in reward, motivation, and motor control. Alterations in dopamine neurotransmission have been linked to cognitive decline and neuropsychiatric symptoms observed in Alzheimer’s disease. This subgraph encompasses protein interactions related to dopamine synthesis, receptor signaling, and downstream effectors, offering insights into dopamine’s contribution to Alzheimer’s pathology.

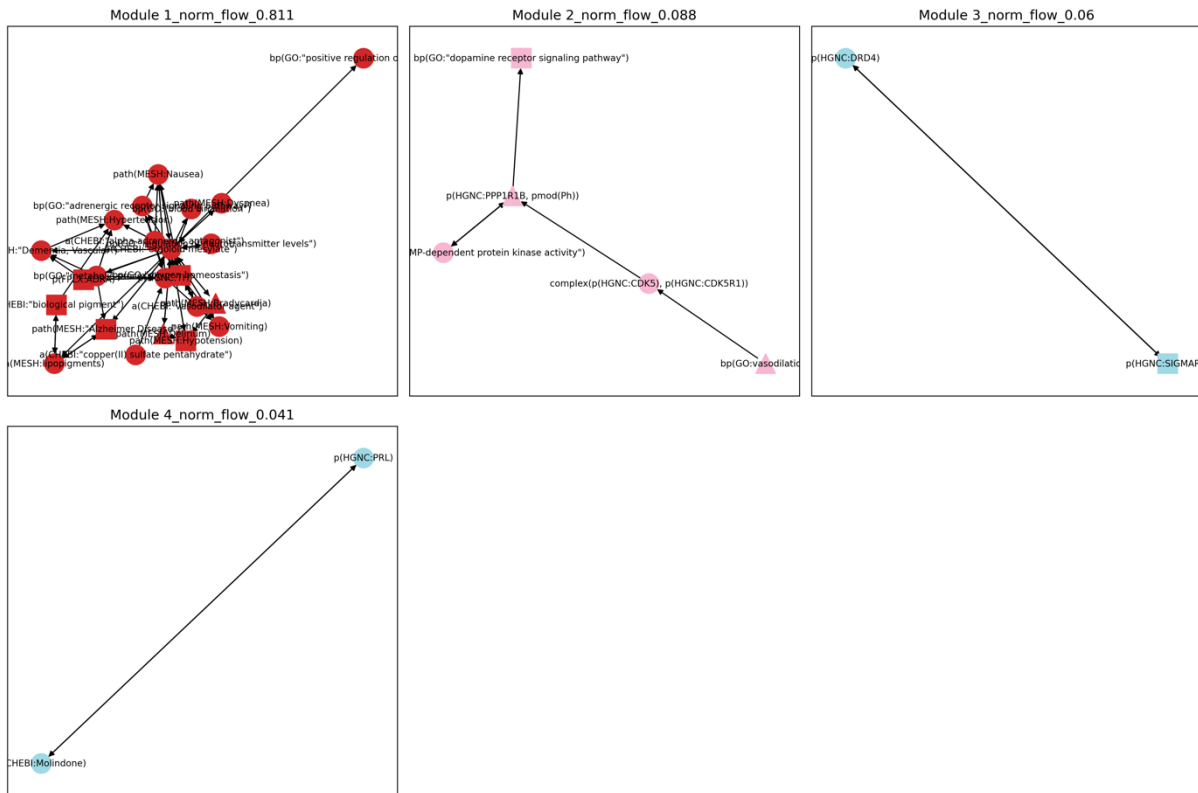


Figure 7. Community modules identified by flow-based Infomap analysis of the multilayer NeuroMMSig subgraph related to dopamine signaling in Alzheimer's disease. Modules represent clusters of entities with high intra-community flow, integrating interactions with spatial similarity layers from TVBase and LLM-enhanced TVBase maps. This modular decomposition reveals biologically relevant functional groupings influenced by both molecular connectivity and spatial co-localization.

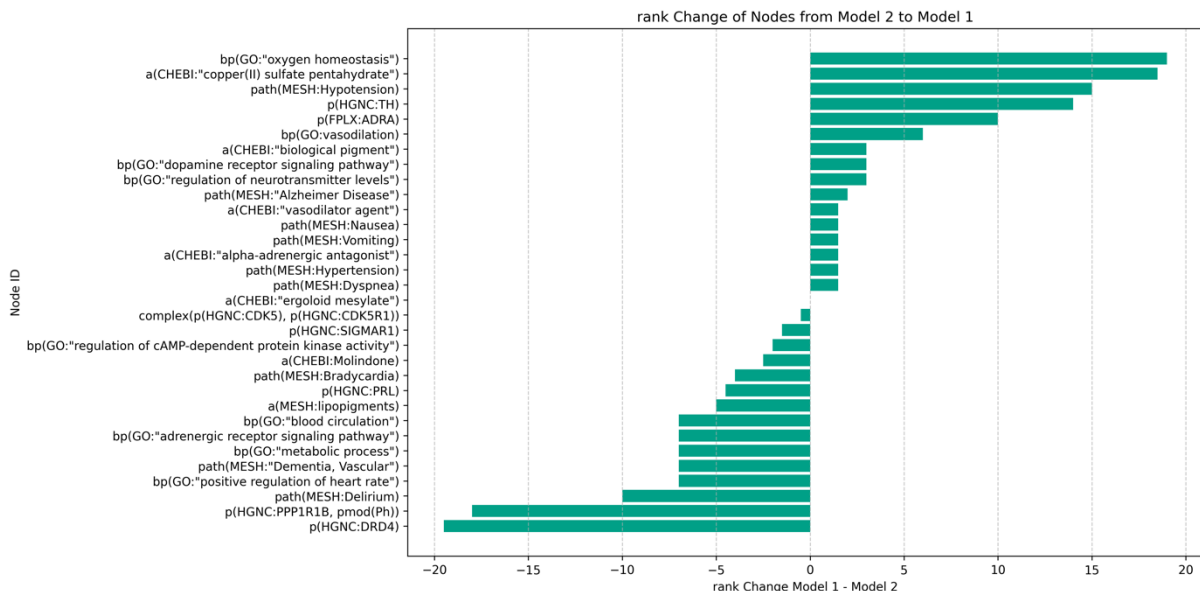


Figure 8. Ranking of entities within the NeuroMMSig dopamine subgraph based on flow analysis across network configurations. The plot compares node prominence in the original NeuroMMSig layer and after adding spatial similarity layers from TVBase and LLM-enhanced TVBase. Integration of spatial and semantic information alters the relative importance of entities, highlighting concepts whose functional roles are modulated by brain spatial organization and enriched semantic context.

6.4. Serotonergic mechanisms in Alzheimer's Disease

The serotonin subgraph captures the complex molecular mechanisms governing serotonin signaling, a neurotransmitter system implicated in mood regulation, cognition, and neuroplasticity. Serotonergic dysfunction is frequently observed in Alzheimer's disease, influencing behavioral symptoms and disease progression. This subgraph details interactions among proteins responsible for serotonin synthesis, receptor activity, and transport, providing a focused perspective on serotonin's role in Alzheimer's-related neural changes.

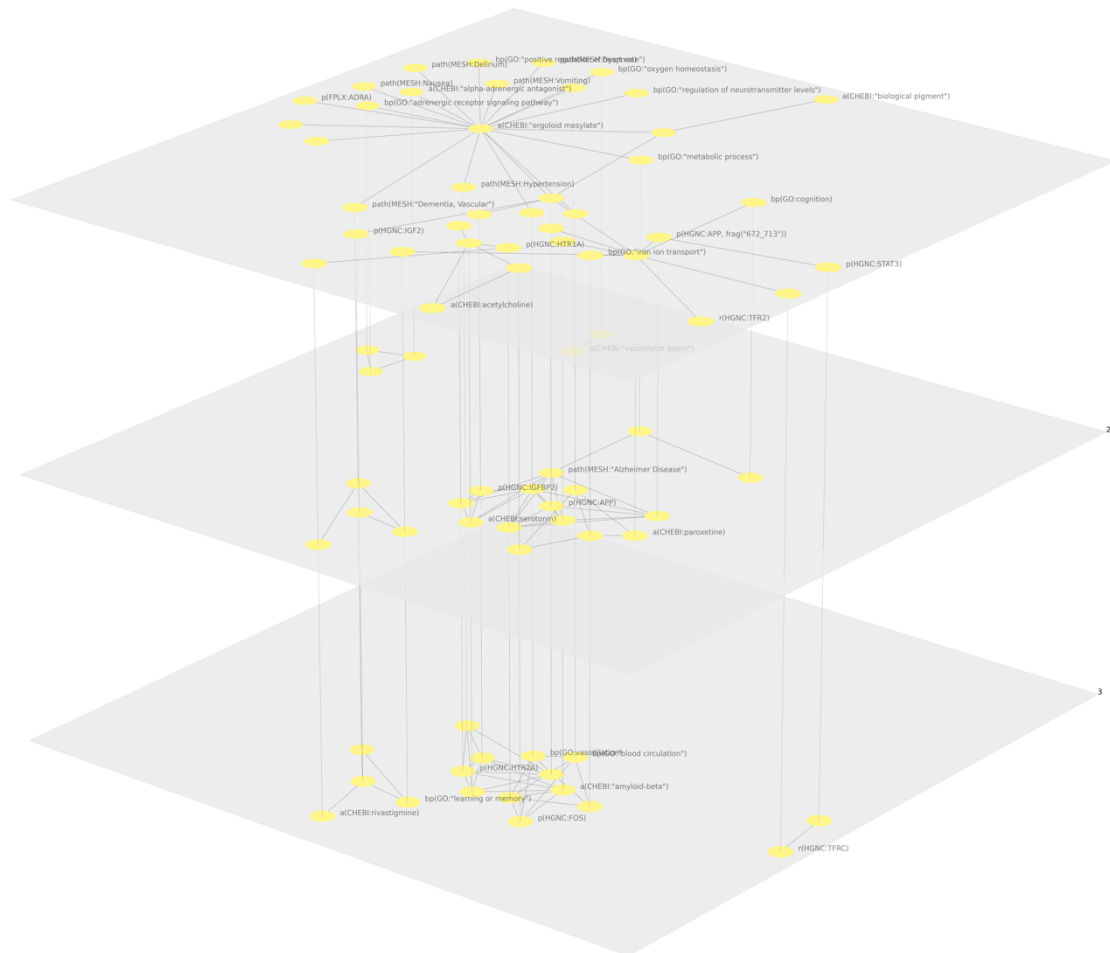


Figure 9. Multilayer network representation of the serotonin-related molecular mechanism in Alzheimer's disease. The first layer depicts interactions derived from NeuroMMSig. The second layer shows spatial similarity relationships between semantic maps based on TVBase. The third layer incorporates spatial associations refined by large language model (LLM)-enhanced TVBase embeddings. This multilayer approach integrates molecular interactions with spatial co-localization and semantic enrichment, enabling comprehensive analysis of network modularity and functional organization.

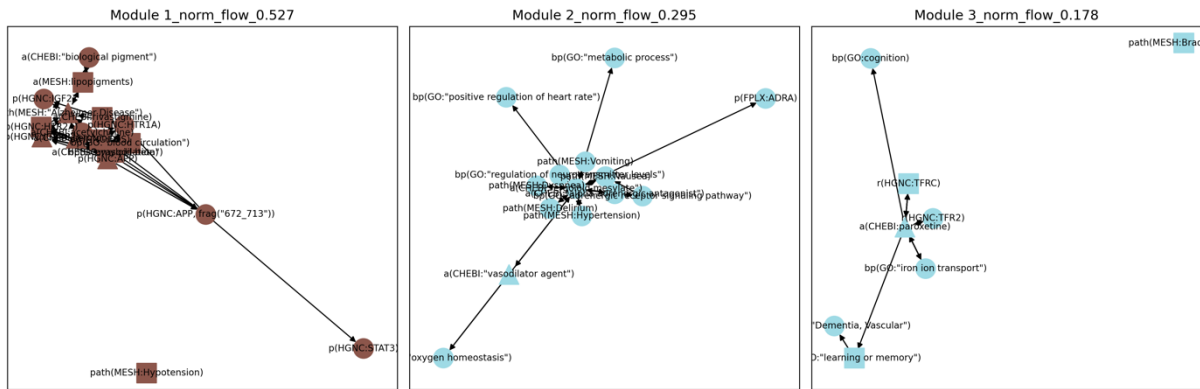


Figure 10. Community modules identified by flow-based Infomap analysis of the multilayer NeuroMMSig subgraph related to serotonin signaling in Alzheimer's disease. Modules represent clusters of entities with high intra-community flow, integrating interactions with spatial similarity layers from TVBase and LLM-enhanced TVBase maps. This modular decomposition reveals biologically relevant functional groupings influenced by both molecular connectivity and spatial co-localization.

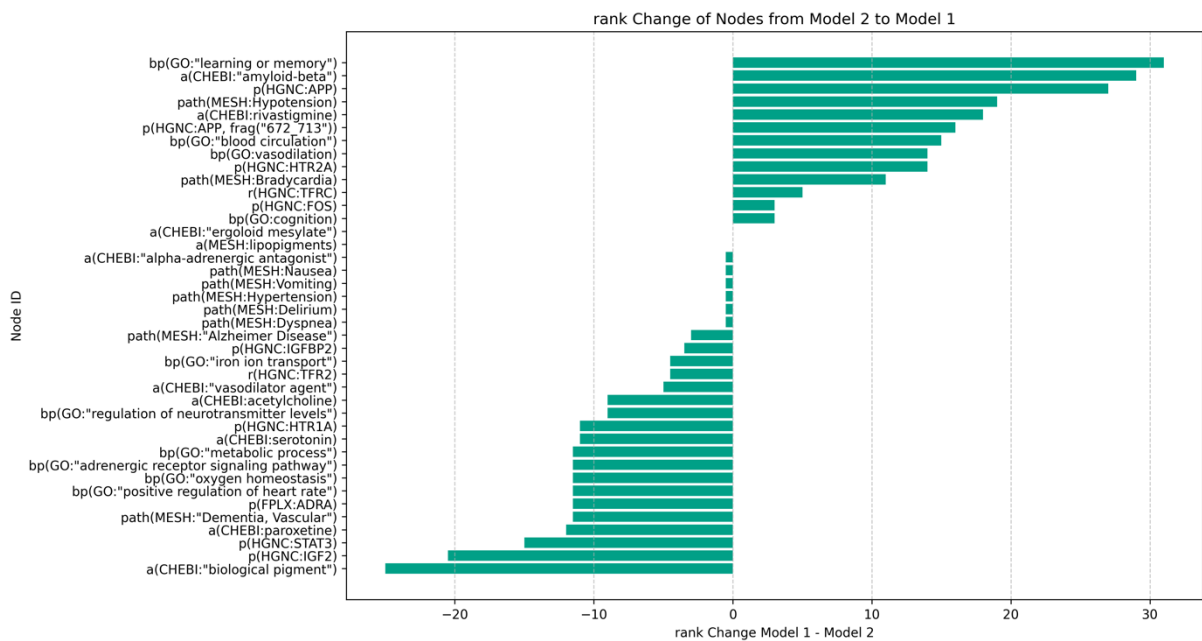


Figure 11. Ranking of entities within the NeuroMMSig serotonin subgraph based on flow analysis across network configurations. The plot compares node prominence in the original NeuroMMSig layer and after adding spatial similarity layers from TVBase and LLM-enhanced TVBase. Integration of spatial and semantic information alters the relative importance of entities, highlighting concepts whose functional roles are modulated by brain spatial organization and enriched semantic context.

6.5. Glutamatergic mechanisms in Alzheimer's Disease

The glutamate subgraph represents the excitatory neurotransmitter network critical for synaptic transmission, plasticity, and memory formation. Glutamatergic dysfunction, including excitotoxicity, is a well-established factor in Alzheimer's disease progression. This subgraph includes proteins related to glutamate release, receptor signaling, and clearance, enabling detailed analysis of glutamate's mechanistic involvement in Alzheimer's disease.

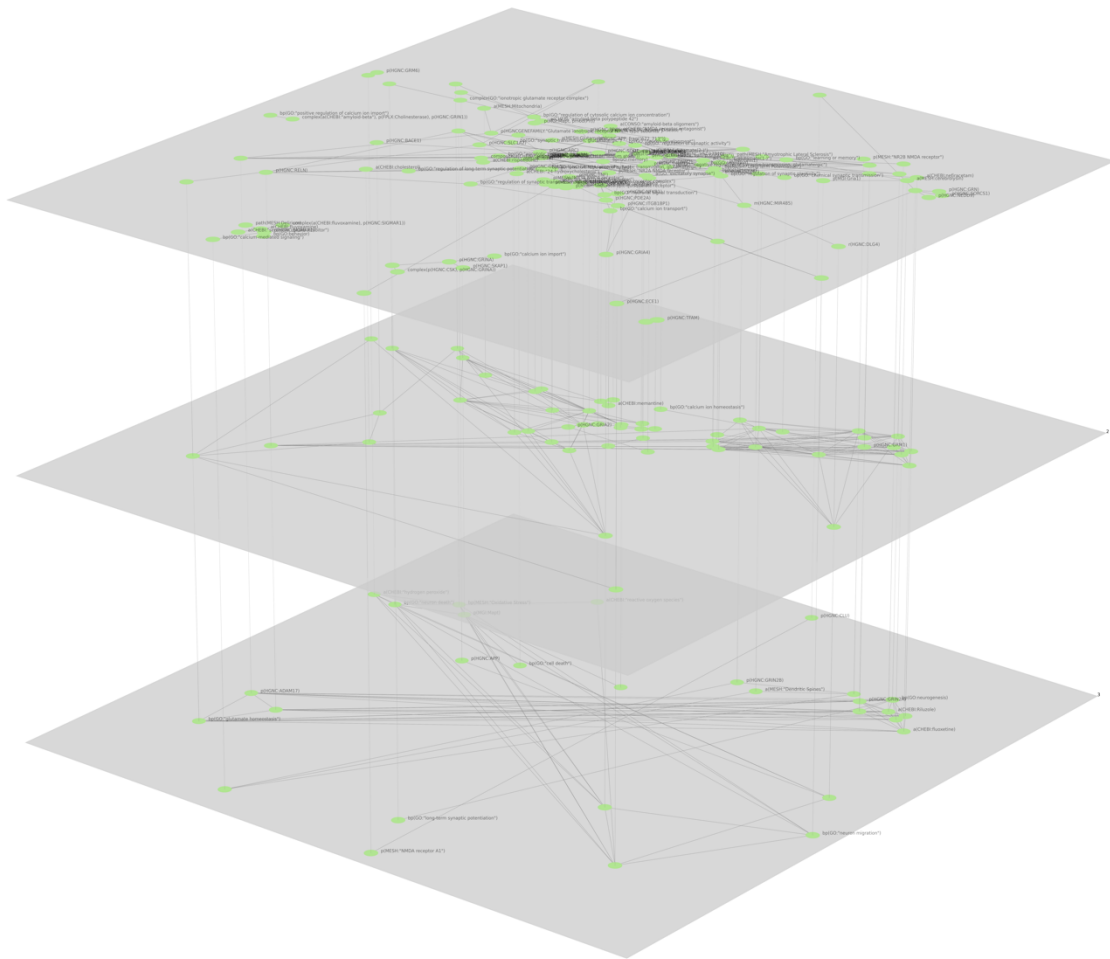


Figure 12. Multilayer network representation of the glutamate-related molecular mechanism in Alzheimer's disease. The first layer depicts interactions derived from NeuroMMSig. The second layer shows spatial similarity relationships between semantic maps based on TVBase. The third layer incorporates spatial associations refined by large language model (LLM)-enhanced TVBase embeddings. This multilayer approach integrates molecular interactions with spatial co-localization and semantic enrichment, enabling comprehensive analysis of network modularity and functional organization.

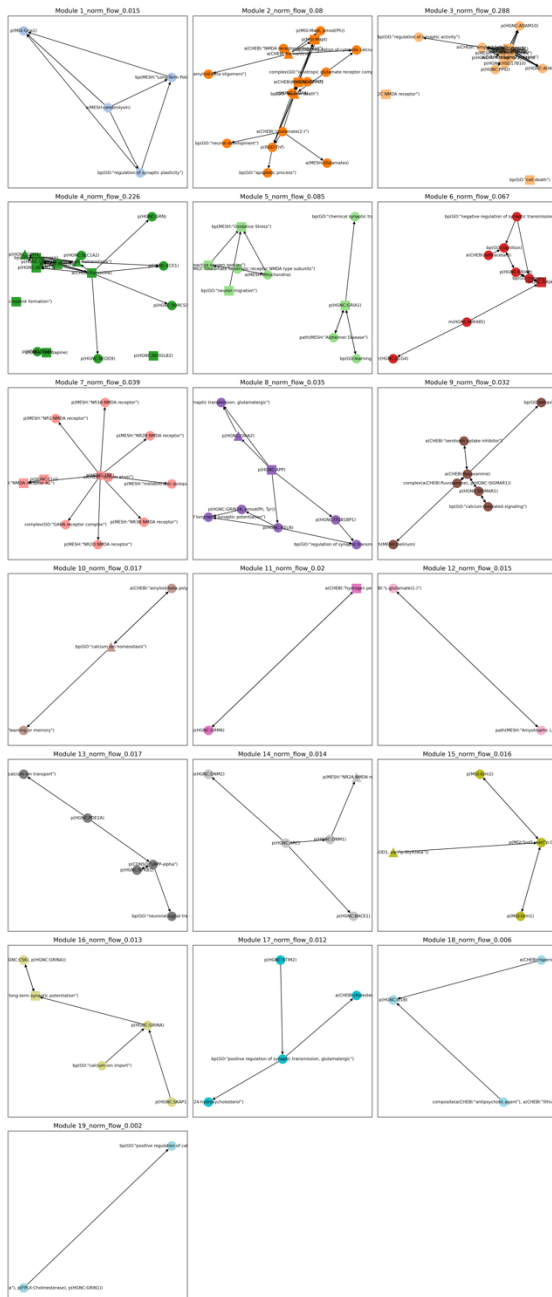


Figure 13. Community modules identified by flow-based Infomap analysis of the multilayer NeuroMMSig subgraph related to glutamate signaling in Alzheimer's disease. Modules represent clusters of entities with high intra-community flow, integrating interactions with spatial similarity layers from TVBase and LLM-enhanced TVBase maps. This modular decomposition reveals biologically relevant functional groupings influenced by both molecular connectivity and spatial co-localization.

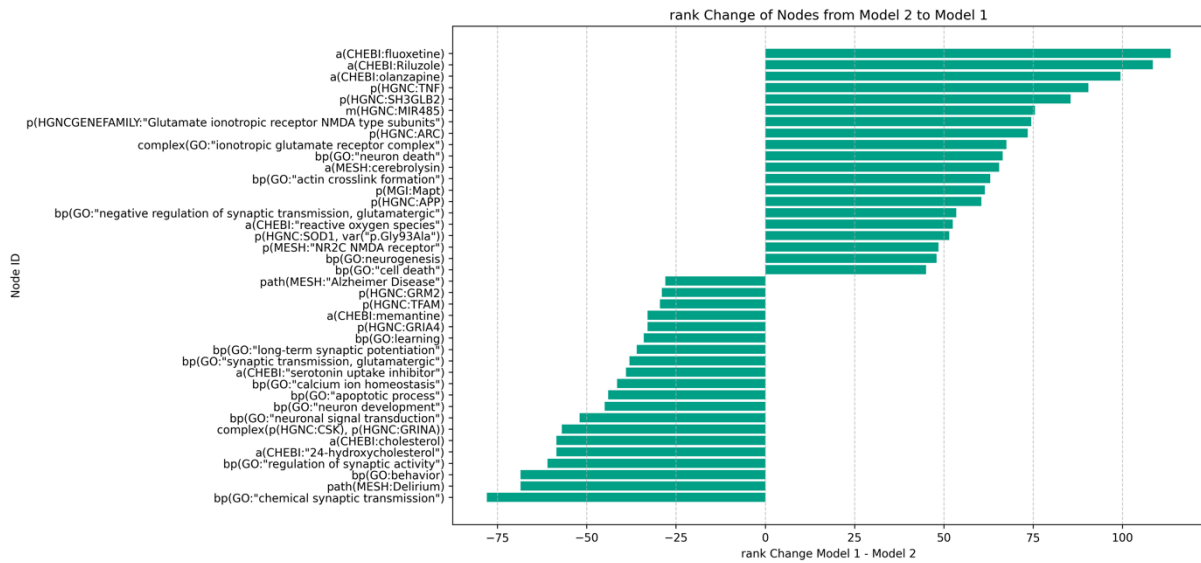


Figure 14. Ranking of entities within the NeuroMMSig glutamate subgraph based on flow analysis across network configurations. The plot compares node prominence in the original NeuroMMSig layer and after adding spatial similarity layers from TVBase and LLM-enhanced TVBase. Integration of spatial and semantic information alters the relative importance of entities, highlighting concepts whose functional roles are modulated by brain spatial organization and enriched semantic context.

6.6. GABAergic mechanisms in Alzheimer’s Disease

The GABA subgraph outlines the inhibitory neurotransmission network mediated by gamma-aminobutyric acid (GABA), essential for maintaining neuronal excitability balance. Disruption of GABAergic signaling contributes to synaptic imbalance and cognitive deficits in Alzheimer’s disease. This subgraph integrates protein-protein interactions involved in GABA synthesis, receptor function, and uptake, facilitating targeted exploration of GABAergic alterations in Alzheimer’s pathology.

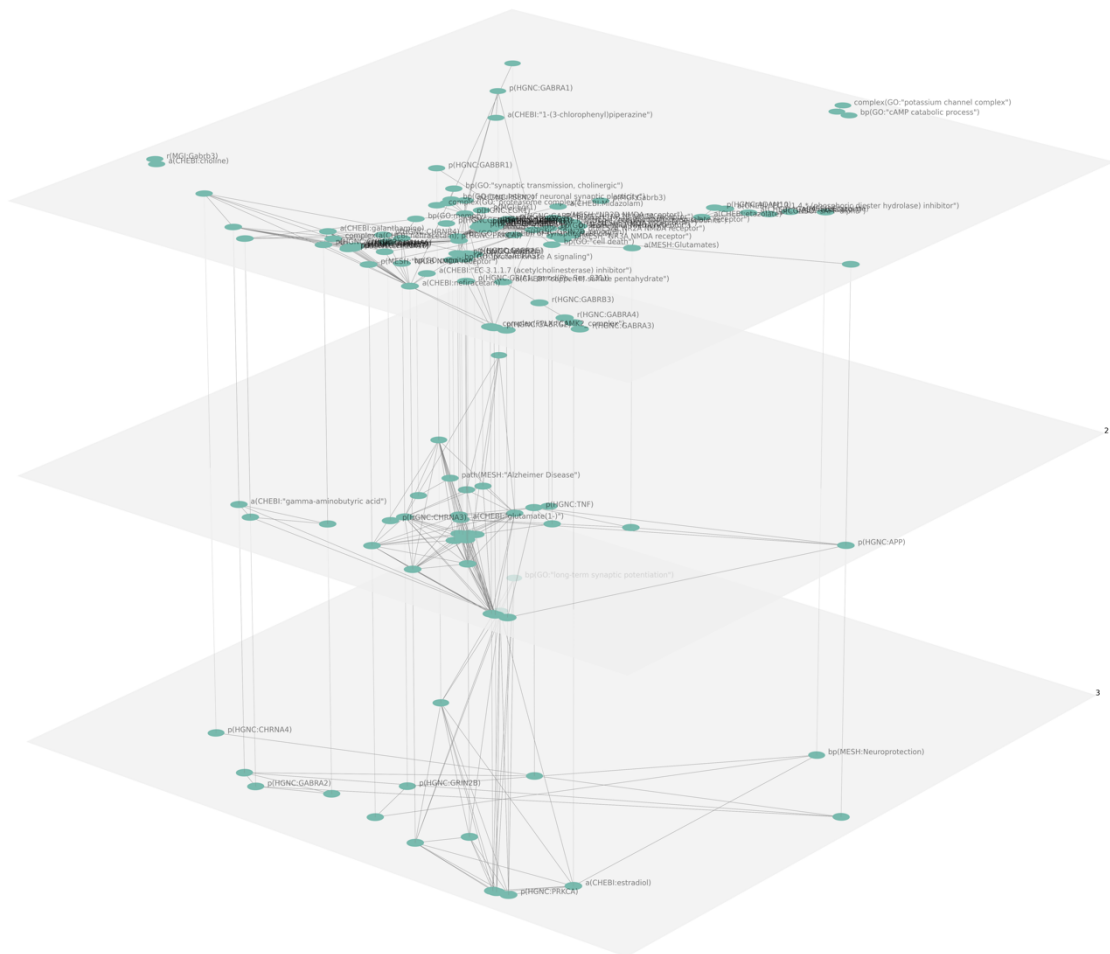


Figure 15. Multilayer network representation of the GABA-related molecular mechanism in Alzheimer's disease. The first layer depicts interactions derived from NeuroMMSig. The second layer shows spatial similarity relationships between semantic maps based on TVBase. The third layer incorporates spatial associations refined by large language model (LLM)-enhanced TVBase embeddings. This multilayer approach integrates molecular interactions with spatial co-localization and semantic enrichment, enabling comprehensive analysis of network modularity and functional organization.

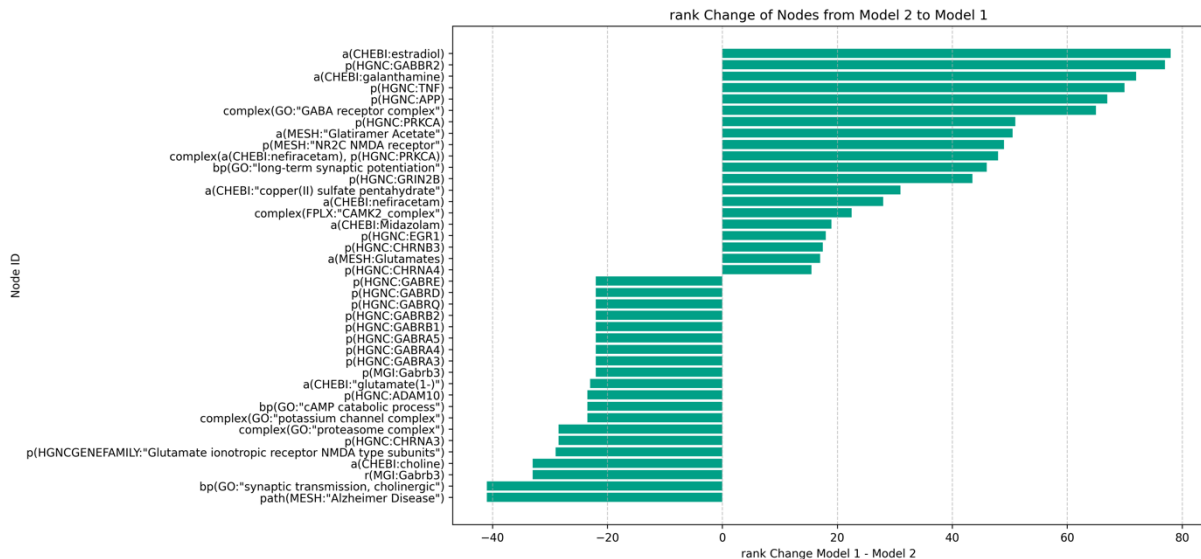


Figure 17. Ranking of entities within the NeuroMMSig GABA subgraph based on flow analysis across network configurations. The plot compares node prominence in the original NeuroMMSig layer and after adding spatial similarity layers from TVBase and LLM-enhanced TVBase. Integration of spatial and semantic information alters the relative importance of entities, highlighting concepts whose functional roles are modulated by brain spatial organization and enriched semantic context.

6.7. Multi-layer subgraphs

To support reproducibility and enable further analysis, the five neurotransmitter-related subgraphs extracted from NeuroMMSig—corresponding to acetylcholine, dopamine, GABA, glutamate, and serotonin mechanisms in Alzheimer's disease—are provided as a supplementary JSON file attached to this report. Each subgraph contains all three layers of the multi-layer graph. These files represent the foundational data used in the multilayer network construction and flow analysis presented in this study. Users can directly import the JSON file into standard network analysis tools for visualization or computational analysis.

```
multilayer_graph_Acetylcholine.json
multilayer_graph_Dopamine.json
multilayer_graph_GABA.json
multilayer_graph_Glutamate.json
multilayer_graph_Serotonine.json
```

7. Conclusion, next steps

This multilayer network analysis has revealed how integrating spatial information from TVBase and semantically enriched LLM-enhanced maps reshapes the functional prominence of molecular entities involved in neurotransmitter-related mechanisms in Alzheimer's disease. By incorporating spatial context into the protein interaction framework, we identified significant shifts in network flow for several biologically relevant entities. Notably, insulin signaling, caspase-mediated apoptosis, oxygen homeostasis, and HTR2A emerged as central hubs across multiple neurotransmitter systems, suggesting their integrative roles in disease progression. Additionally, pharmacological agents such as resveratrol, estradiol, fluoxetine, and riluzole were highlighted as modulators of these pathways, further underscoring their therapeutic potential.

These findings point toward a complex, spatially organized interplay of metabolic, genetic, and neurotransmitter systems in Alzheimer's disease. Looking forward, implementing the TVBase-derived spatial constraints in whole-brain simulations—such as those supported by The Virtual Brain platform—offers a promising path to integrate and validate these mechanistic insights. Such simulations could enable the construction of a holistic, biologically grounded model, capable of not only explaining but also predicting and modulating the dynamic systems-level behavior of Alzheimer's pathology. This approach will be instrumental in moving from static pathway analysis to spatially informed, multiscale modeling, ultimately advancing our ability to understand, intervene in, and control the mechanisms driving neurodegeneration.

Acknowledgements

The authors acknowledge the use of OpenAI's ChatGPT for assistance in language editing, which has been used in order to improve the clarity and readability of the manuscript. The content of this report lies in the sole responsibility of the authors.

Disclaimer

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101058516. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or other granting authorities. Neither the European Union nor other granting authorities can be held responsible for them.

