News Release

Is There a Fundamental Design Principle of Neural Circuits? :
A Data-Driven Decoding of a Gene-Gradient–Encoded Brain Wiring Map

Key Points

- Analyzed the rules governing how neurons connect in the brain using real whole-brain datasets
- Developed a novel analytical framework, SPERRFY, that decodes a "gene-gradient–encoded brain wiring map" from connectome data and spatial gene expression profiles
- Demonstrated that this inferred wiring map can reconstruct actual brain connectivity patterns with high accuracy
- Suggested that both large-scale global connectivity and fine-scale local connectivity may be regulated by hierarchical gene-expression gradients
- Systematically identified candidate genes potentially involved in neural circuit formation, opening new avenues for research into brain development and neurological disorders

Summary

Professor Honda Naoki (Graduate School of Medicine, Nagoya University), together with Dr. Jigen Koike (Ph.D. Student, Hiroshima University) and colleagues, has developed a novel data-driven framework that reveals the wiring principles of the brain at the whole-brain scale.

The research integrates mouse whole-brain connectome data with spatial gene expression profiles and introduces a new analytical method named SPERRFY. This method extracts gene-expression gradients that best explain large-scale neural connectivity patterns. The resulting gradients can be interpreted as a "molecular wiring map" encoded by genes, specifying which brain regions are more likely to connect.

Using this wiring map, the researchers successfully reconstructed the actual neural connectivity structure of the mouse brain with high accuracy. Importantly, connectivity patterns that cannot be explained solely by physical distance were captured by the inferred gene-expression gradients.

These findings provide the first systematic framework linking molecular-level gene-expression gradients to whole-brain connectome architecture, offering a unifying perspective that bridges developmental molecular neuroscience and systems-level brain organization.

This study will be published in the Proceedings of the National Academy of

Sciences of the United States of America (PNAS) on March 3, 2026.

Research Background

Neural circuits in the brain are not formed randomly. During development, neurons extend axons toward specific targets, guided by molecular cues that provide spatial information. One of the foundational theories describing this mechanism is Sperry’s chemoaffinity theory, proposed in 1963, which suggests that neurons recognize their targets based on gradients of chemical molecules distributed across space.

Although molecular gradients have been experimentally validated in relatively simple systems such as the visual pathway, it has remained unclear how these molecular mechanisms scale up to explain the formation of complex whole-brain connectivity patterns, known as the connectome.

With the recent accumulation of large-scale connectome datasets and spatial transcriptomic data, it has become possible to revisit this classical theory from a data-driven systems-level perspective.

Research Results

(1) Extraction of a Gene-Encoded “Molecular Wiring Map”

The research team developed a new machine-learning-based analytical framework called SPERRFY. By integrating whole-brain mouse connectome data with spatial gene expression profiles, the method extracts combinations of gene-expression gradients that best explain connectivity patterns across brain regions.

These gradients encode spatial information that determines which brain regions are more likely to be connected. The inferred gradients can therefore be interpreted as a gene-encoded “molecular wiring map” of the brain.

(2) High-Accuracy Reconstruction of Neural Connectivity

Using the extracted molecular wiring map, the researchers reconstructed large-scale neural connectivity patterns in the mouse brain. The reconstructed connectivity showed high agreement with actual connectome data.

Notably, the model explained connectivity patterns that cannot be accounted for by simple physical proximity alone, indicating that gene-expression gradients provide essential information governing neural wiring.

(3) Hierarchical Control of Neural Wiring

Further analysis suggested that multiple gene-expression gradients operate at different hierarchical levels. Some gradients capture coarse, large-scale connectivity organization across the brain, while others regulate finer-scale local and inter-regional connectivity patterns.

This hierarchical structure implies that brain wiring is controlled not by a single molecular gradient, but by multiple layered gradients working in coordination.

(4) Systematic Identification of Candidate Genes

The study also identified genes whose spatial expression patterns align with the inferred wiring map. Several of these genes are known to be involved in axon guidance and neurodevelopment, supporting the biological validity of the framework.

Research Summary and Future Perspective

This study presents a general data-driven framework that links molecular gradients to whole-brain connectivity architecture, bridging developmental molecular mechanisms and large-scale neural systems organization.

As connectome and spatial transcriptomic datasets continue to expand across species—including humans and non-human primates—the SPERRFY framework can be applied to investigate conserved and species-specific wiring principles. This may provide new insights into brain evolution, developmental disorders, and neuropsychiatric diseases.

In the future, combining this computational framework with experimental validation may enable causal investigations into the molecular mechanisms governing neural circuit formation.

Publication

Jigen Koike, Ken Nakae, Riichiro Hira, Yuichiro Yada, Honda Naoki: A data-driven framework linking the connectome to spatial gene expression gradients inspired by chemoaffinity theory. Proceedings of the National Academy of Sciences of the United States of America (2026)

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