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Neuroscience PERSPECTIVE

The Innovation Life

Neurexins, latrophilins, and teneurins: Trans-synaptic signalling modules for synapse specification and organisation

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Received: January 12, 2026; Accepted: June 26, 2026; Published Online: June 30, 2026; https://doi.org/10.59717/j.xinn-life.2026.100274

Citation: Gao E. Y. and Lv X. (2027). Neurexins, latrophilins, and teneurins: Trans-synaptic signalling modules for synapse specification and organisation. *The Innovation Life* **5**:100274.

Synapse specification and organisation rely on coordinated trans-synaptic interactions that couple molecular recognition to the assembly of pre- and postsynaptic compartments. While neurexins and cerebellin-mediated pathways have long been recognised as core determinants of synaptic identity, recent studies have identified latrophilins (LPHNs) as important organisers of defined excitatory pathways. In particular, the formation of teneurin-latrophilin-FLRT complexes has emerged as a key mechanism contributing to synaptic specificity in selected hippocampal and cortical circuits. Accumulating evidence further indicates that alternative splicing of LPHN3 configures intracellular signalling logic rather than merely modulating extracellular adhesion, thereby biasing the maturation of trans-synaptic contacts toward functional synapses. Here, we review recent advances that redefine latrophilin-dependent complexes as dynamic, signal-transducing synaptic modules linking molecular recognition to nanoscale synaptic organisation.

INTRODUCTION

The formation of precise synaptic connections is fundamental for neural circuit assembly and function. Among the molecular systems governing synapse specification, neurexins and their postsynaptic partners have long been recognised as central determinants of synaptic identity. Neurexins regulate excitatory synapse formation and constraint, whereas teneurins and latrophilins (LPHNs), a family of adhesion G protein–coupled receptors, contribute to trans-synaptic organisation in hippocampal and cortical circuits.[1] Unlike classical synaptic adhesion molecules such as neurexins or cadherins, latrophilins belong to the adhesion GPCR (aGPCR) family and function primarily as signalling receptors that couple trans-synaptic recognition to intracellular pathways controlling synapse stabilization.

Latrophilins interact with teneurins and FLRTs to form tripartite complexes that promote pathway-specific connectivity and synaptic stability. Latrophilins function as signalling hubs shaped by alternative splicing and neuronal activity. However, an adhesion-centric view of synapse specification does not explain how molecular recognition is translated into signalling that determines synaptic stability and function.

NEUREXIN- AND CEREBELLIN-MEDIATED PATHWAYS IN SYNAPSE SPECIFICATION

Neurexins constitute a central molecular system governing synapse specification by engaging diverse postsynaptic partners and generating molecular diversity through extensive alternative splicing.[2] Cerebellins further refine this framework by bridging presynaptic neurexins to postsynaptic glutamate receptor complexes, thereby stabilising defined synaptic connections. Within this broader recognition system, latrophilins represent a distinct class of organisers that operate through signalling-dependent molecular logic. Acting primarily postsynaptically, latrophilins engage presynaptic teneurins to stabilise specific afferent inputs, adding an additional signalling-dependent layer to neurexin-based synaptic recognition.[3]

TENEURINS AND THE TENEURIN–LATROPHILIN–FLRT COMPLEX

Teneurins are large type II transmembrane proteins that are highly conserved across species and enriched at synapses. Presynaptic teneurins, particularly teneurin-3 and teneurin-4, exhibit spatially organised distributions within hippocampal circuits and contribute to pathway-specific trans-synaptic recognition, positioning them to engage postsynaptic latrophilin-dependent adhesion complexes.[4]

Latrophilins bind teneurins with high affinity and can simultaneously associate with fibronectin leucine-rich repeat transmembrane proteins (FLRTs), forming tripartite teneurin–latrophilin–FLRT complexes that bridge pre- and postsynaptic membranes. Structural analyses indicate that teneurin extracellular domains mediate this interaction and that autoproteolysis exposes surfaces critical for complex formation. Super-resolution imaging studies suggest that latrophilin-dependent complexes are enriched at peri-PSD nanodomains rather than confined to PSD cores or extrasynaptic regions. In hippocampal CA1 pyramidal neurons, LPHN2 and LPHN3 occupy distinct dendritic domains and selectively regulate distinct presynaptic inputs across hippocampal and cortical circuits, consistent with cell-type- and pathway-specific deployment across these circuits.

Early models proposed that alternative splicing of latrophilins primarily regulated extracellular binding properties. However, recent evidence suggests that, for the experimentally tested LPHN3 splice variants, splicing-dependent changes predominantly alter intracellular signalling competence rather than ligand affinity.[5]

LATROPHILINS AS SIGNAL-TRANSDUCING SYNAPTIC ORGANISERS

Among latrophilins, LPHN3 has been most extensively studied due to its strong association with defined excitatory circuits and neurodevelopmental disorders. Loss-of-function analyses suggest that disruption of *LPHN3* compromises synaptic stability and reduces synapse number without broadly affecting neuronal viability, supporting a selective role in synaptic organisation.[5]

Recent work indicates that alternative splicing of LPHN3 functions as a regulatory mechanism that biases intracellular signalling output. Inclusion of exon 31 biases LPHN3 coupling toward $G\alpha_s$, whereas exclusion favours coupling to $G\alpha_{12/13}$. These findings suggest that exon-31-dependent splicing determines the intracellular coupling logic of LPHN3, rather than acting as a context-dependent on–off switch for synapse formation.

Gαs-coupled isoforms preferentially promote excitatory synapse formation. Mechanistically, these isoforms operate through a convergent pathway involving cAMP–PKA signalling, which is known to regulate phosphorylation of postsynaptic scaffold components such as PSD-associated proteins, thereby promoting scaffold recruitment and stabilization. PKA-dependent phosphorylation of scaffold proteins may facilitate condensate-like assembly. Direct molecular links between PKA signalling and postsynaptic scaffold phase separation remain unresolved, but available evidence supports its role in scaffold recruitment and stabilization. In contrast, RhoA signalling is more commonly associated with cytoskeletal remodeling and may not directly support postsynaptic scaffold condensation under the tested conditions. Forced switching of splicing toward the $G\alpha_{12/13}$-coupled mode phenocopies LPHN3 deletion, supporting a model in which splicing-dependent signalling logic is required for efficient synaptogenesis rather than acting as a purely modulatory feature.[5] Adhesion GPCRs have been implicated in synaptic function beyond latrophilins(Figure 1).[6]

REGULATION OF LPHN3 ALTERNATIVE SPLICING

Although the functional consequences of LPHN3 alternative splicing are

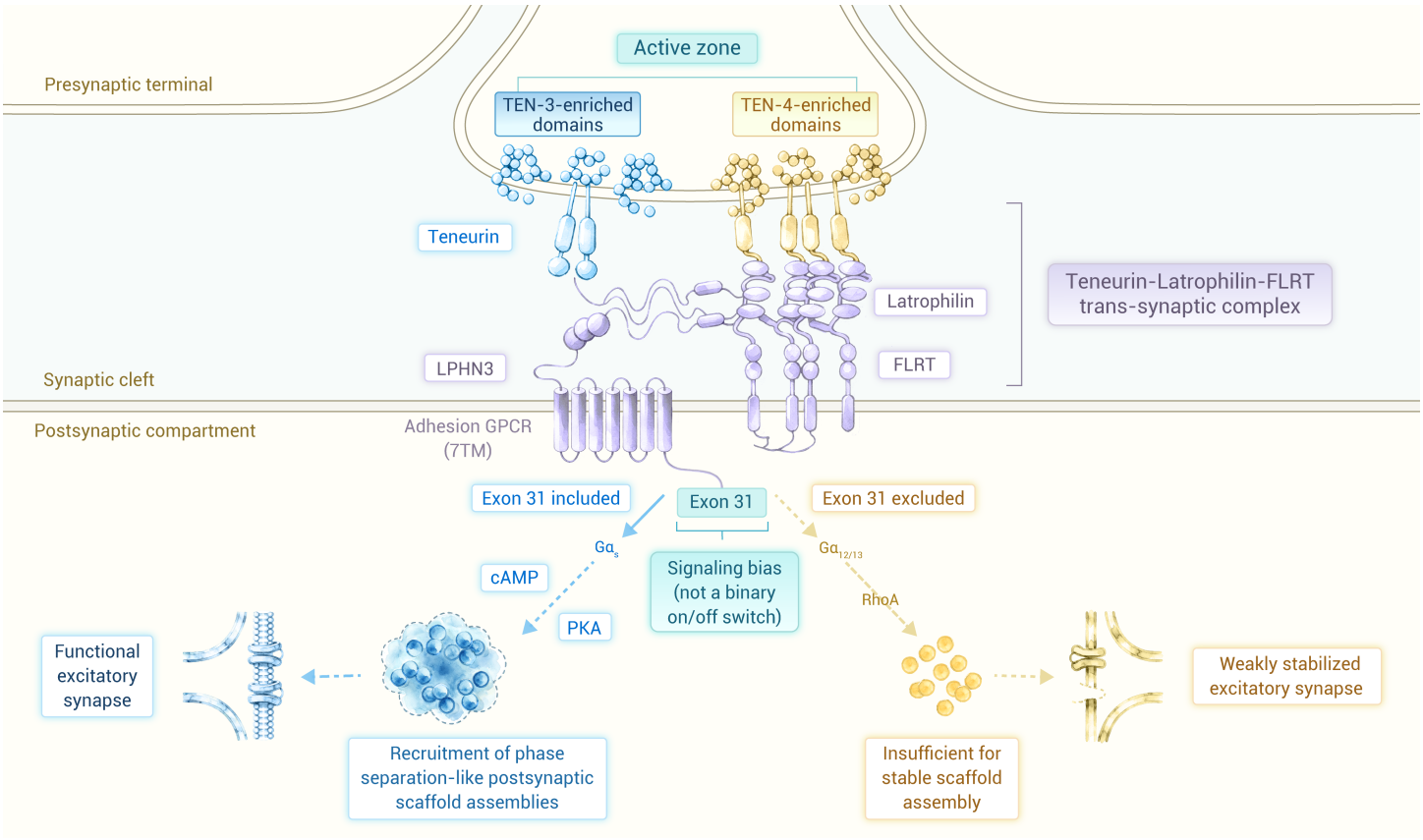

Figure 1. Alternative splicing of latrophilin-3 biases trans-synaptic signalling logic to control excitatory synapse specification Presynaptic TEN-3 and TEN-4 engage postsynaptic latrophilin and FLRT to form a Teneurin–Latrophilin–FLRT adhesion complex. LPHN3 exon 31 inclusion biases signalling toward $G\alpha_s$–cAMP–PKA, promoting postsynaptic scaffold assembly and functional excitatory synapse formation, whereas exon 31 exclusion favors $G\alpha_{12/13}$–RhoA signalling and weaker scaffold stabilization. The inset depicts a reconstitution system demonstrating that teneurin, latrophilin, and FLRT are sufficient to organize aligned synaptic assemblies.

now increasingly clear, the molecular mechanisms that regulate exon choice remain largely unexplored. As with other synaptic adhesion molecules, alternative splicing of latrophilins is likely controlled by a combination of cis-regulatory elements and trans-acting RNA-binding proteins (RBPs) whose expression and activity vary across development and neuronal state. Developmental regulation of splicing could bias latrophilin signalling competence during defined windows of synaptogenesis, thereby tuning the probability that nascent trans-synaptic contacts mature into stable excitatory synapses. In pathological contexts, genetic variation affecting splicing regulatory elements or dysregulation of RBPs could shift the balance of LPHN3 isoforms toward signalling modes that fail to support postsynaptic scaffold assembly, offering a mechanistic link between disease-associated variants and synaptic vulnerability. Elucidating how splicing regulation interfaces with trans-synaptic signalling thus represents a critical next step toward understanding how latrophilins contribute to circuit development and plasticity.[5,7] In addition to transcript-level regulation, LPHN3 function may also be shaped by post-translational processing; for example, extracellular proteolytic cleavage has been proposed as a potential mechanism that could regulate receptor availability or signalling competence.

Several important questions remain open. Resolving this will require cell-type–specific transcriptomics combined with systematic perturbation of splicing regulators. In addition, while direct links between LPHN3 alternative splicing and behaviour have not yet been established, the present model suggests a plausible circuit-level mechanism. By biasing postsynaptic signalling logic and scaffold assembly, exon 31–dependent splicing is expected to influence synaptic stability and integration within specific excitatory circuits, which over development could shape circuit maturation and functional tuning. Addressing these questions will be essential for understanding how molecular diversity is translated into synaptic, circuit, and ultimately behavioural organization.

RECENT ADVANCES: RECONSTITUTION OF SYNAPTIC JUNCTION ASSEMBLY

In particular, reconstitution studies published recently demonstrate that teneurin–latrophilin complexes are sufficient to organise aligned pre- and postsynaptic molecular assemblies from defined components in a reductionist reconstitution system. These experiments show that trans-synaptic engagement of teneurins and latrophilins can nucleate synaptic junction assembly, coordinating presynaptic active zone components with postsynaptic scaffold condensates.[8]

These findings provide direct physical evidence that latrophilin-dependent complexes function as signalling and assembly platforms rather than static adhesion bridges. Together, these findings suggest a provisional model in which extracellular recognition, intracellular signalling, and mesoscale organisation are integrated processes, although further work is needed to confirm the generality of this mechanism.

IMPLICATIONS FOR CIRCUIT ORGANISATION AND DISEASE

Latrophilin-dependent synaptic organisation exhibits striking pathway specificity. In the hippocampus, LPHN3 preferentially affects Schaffer collateral synapse formation, with comparatively minor effects on entorhinal cortex inputs to CA1, indicating that distinct molecular codes govern different afferent pathways. Such specificity suggests that alternative splicing and signalling configuration of latrophilins contribute to circuit-level wiring rules.[2,4,9]

Beyond synapse formation per se, splicing-dependent signalling by latrophilin-3 provides a mechanistic framework linking molecular recognition to circuit-level organisation, while potential behavioural consequences remain indirect and context dependent. By biasing intracellular coupling toward $G\alpha_s$–cAMP–PKA signalling or $G\alpha_{12/13}$–RhoA pathways, alternative LPHN3 isoforms selectively stabilise or destabilise postsynaptic scaffold assembly at defined afferent inputs. In hippocampal circuits, such bias is predicted to

differentially weight Schaffer collateral versus entorhinal inputs to CA1 pyramidal neurons. Perturbations that shift LPHN3 splicing toward signalling-incompetent modes phenocopy LPHN3 loss of function at the synaptic level and may, over development, contribute to circuit-level alterations in information routing. Consistent with this view, pathway-specific synaptic deficits caused by disruption of trans-synaptic adhesion systems have been associated with cognitive changes in animal models, such as alterations in hippocampus-dependent learning or attentional processes. While these findings suggest a possible route by which molecular perturbations may influence behaviour, direct causal evidence remains limited and context-dependent.[2,5]

OUTSTANDING ISSUES AND UNRESOLVED QUESTIONS

Despite rapid progress in defining the molecular and signalling architecture of the teneurin–latrophilin–FLRT system, key issues regarding LPHN3 function remain unresolved.

First, the extent to which LPHN3 signalling is required in vivo remains debated. While reconstitution and overexpression studies clearly demonstrate that LPHN3 coupling to Gαs–cAMP–PKA signalling is sufficient to promote synapse formation, it is less clear whether such signalling is uniformly necessary across brain regions and developmental stages. In particular, whether endogenous LPHN3 signalling operates as a permissive cue or as an instructive determinant of synaptic stability in vivo remains to be established. Moreover, the degree to which G-protein coupling bias is conserved across distinct neuronal populations is still largely unexplored.

Second, the causal role of alternative splicing in shaping LPHN3 function is not fully resolved. Although splicing-dependent signalling bias provides an attractive mechanistic framework, it remains unclear whether changes in LPHN3 splicing actively drive synaptic specification or instead reflect downstream consequences of developmental programs or neuronal activity states. Compensatory mechanisms, including redundancy among adhesion GPCRs or homeostatic regulation of intracellular signalling pathways, may further mask the functional impact of individual splice variants in vivo.

Third, the boundaries of extrapolating synaptic mechanisms to behaviour require careful consideration. Pathway-specific synaptic effects and circuit-level input weighting provide a plausible link between LPHN3 signalling and cognitive function; however, direct behavioural evidence remains limited and model dependent. Many reported behavioural phenotypes associated with trans-synaptic adhesion systems arise from broad genetic or circuit perturbations, complicating attribution to specific splicing or signalling mechanisms. As such, the relationship between LPHN3-dependent synaptic organisation and higher-order cognition should be regarded as context dependent rather than strictly causal.

Addressing these outstanding questions will require integrative approaches that combine isoform-specific genetic manipulations, circuit-resolved functional analyses, and behaviourally relevant paradigms. Such efforts will be essential for clarifying how splicing-dependent modulation of latrophilin signalling contributes to neural circuit development and function.[10] An additional perspective is that latrophilins may function as mechanosensitive adhesion GPCRs, although direct experimental evidence in synaptic contexts remains limited. Their large extracellular domains, which engage teneurins and FLRTs, may allow tension across the synaptic cleft to induce conformational rearrangements that expose tethered agonist elements and thereby regulate downstream G-protein coupling. In this framework, latrophilins would operate as mechanotransducing GPCR sensors supporting mechanosensory stabilization of synaptic architecture rather than directly converting force into ion flux like Piezo channels.

CONCLUSION

Synaptic specificity arises from coordinated trans-synaptic interactions integrating molecular recognition and intracellular signalling. Neurexin- and cerebellin-mediated pathways provide a foundational framework for synapse differentiation, while teneurin–latrophilin–FLRT complexes add a distinct, signalling-dependent layer of organisation. Emerging evidence indicates that alternative splicing of *LPHN3* configures intracellular signalling logic, enabling latrophilins to act as dynamic organisers of synaptic assembly rather than passive adhesion molecules. Consistent with this view, reconstitution-based studies published recently demonstrate that teneurin–latrophilin complexes are sufficient to drive synaptic junction assembly from defined molecular components under controlled reconstitution conditions, providing direct support for a model in which trans-synaptic adhesion is intrinsically coupled to signalling-dependent synapse organisation.[8] Defining how splicing-dependent signalling logic is regulated across development and activity states will be essential for understanding how synaptic specificity is established and maintained in complex neural circuits.

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FUNDING AND ACKNOWLEDGMENTS

This work received no specific funding. E.G. prepared this manuscript during his PhD training at the OIST and while serving as a research assistant at the USTC. We thank Prof. Thomas C. Südhof for helpful discussions at an early stage of this work. We thank Prof. Yukiko Goda for helpful discussions on an early draft of the manuscript. We thank Prof. Yuqian Ma for providing an academic environment and support during the preparation of this manuscript. We thank Ms. Xinxu Ma for her careful assistance with literature cross-checking and the refinement of schematic figures. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

E.G. conceived the review, performed the literature analysis, and wrote the manuscript. X.L. provided conceptual guidance, critically revised the manuscript, and supervised this work. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.