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Structural and Functional Bioinformatics of Neurexin: A Step Towards Understanding Neurodevelopmental Disorders

Esma Zajimović

zajimovic95@gmail.com

International university of Sarajevo https://orcid.org/0009-0001-8063-5027

Research Article

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Abstract

Neurodevelopmental disorders represent one of the most prevalent challenges in today's society with their origins often linked to critical process underlying nervous system development. The proteins that regulate these essential processes are vulnerable to mutations, which can disrupt normal function and contribute to the development of these disorders. Synaptogenesis, the formation of synapses, plays a pivotal role in neural development and functioning. Dysregulation of the genes responsible for proteins that facilitate synapse formation can lead to neurodevelopmental disorders. To explore the current understanding of this process and to refine research inquiries, a comprehensive literature review was conducted. Additionally, bioinformatical modeling was performed to understand the function of Neurexin, protein that plays important role in synapse formation process. Bioinformatical modeling included steps as determining 3D structure of protein, which is essential for understanding protein's function, identifying proteins it interacts with and finally molecular docking with largest proteins it interacts with. Each of these proteins has the capacity of serving as potential target for drug development. Advancing our knowledge in this field holds promise for the development of improved therapeutic strategies for various neurological diseases and conditions. Continued investigation into synaptogenesis could significantly enhance treatment options and outcomes for affected individuals.

1. Introduction

1.1 Synaptogenesis as the fundamental feature of nervous system

Synaptogenesis is the process of forming new synapses. (Qi C.,2022). Synapses are the basic units for information storage and processing. These are the points at which neurons communicate with each other.(Sudhof TC, 2021). Commmunication occurs as neurotransmitters are sent to synaptic cleft. Signal is initiated by presynaptic neurons and received by postsynaptic neurons by receiving it through dendrites(T.M.Sanderson, 2020). The development of specific structures at the sending (presynaptic) and receiving (postsynaptic) neurons is part of the process of synapse formation,as illustrated by Figure 1.(Stephen D. Glasgow,2019) Any axonal or dendritic modification can influence synaptogenesis, which may interfere with neural development(Qi C.,2022).Homeostasis of nervous system is maintained by neural networks(RC Vergara,2019). To form neural networks for learning, cognition, emotion, and behaviour, synapse formation is crucial (Daniel A Colon Ramos,2020).

Genes that regulate the expression of proteins that modulate synaptogenesis are susceptible to mutations. In case of dysregulation, neurodevelopmental disorders occur. Studies from the previous decade support this relationship between gene regulation and the onset of mental disorders.

1.2 Molecular Mechanisms of Synaptogenesis

The two forms of synapses that coexist in the nervous system are chemical and electrical synapses. Communication between these two forms of synapses is crucial for maintaining homeostasis of the nervous system (K. Koga, 2015). Electrical synapses and chemical synapses differ in the way they

transmit signals. To ensure fast, bidirectional communication, electrical synapses utilize the flow of ions through gap junctions. Chemical synapses are responsible for slower unidirectional signal transduction through neurotransmitters (Alberto E Perenda,2015). Electrical synapses are mainly found in smaller and faster neural circuits, while chemical synapses perform more complex processing because of their plasticity, specificity, and modulation (S, Jabeen, 2018). Three compartments make up the synapse. These are: pre-synaptic terminal, synaptic cleft, and post-synaptic compartment (AA Cole,2023).

1.3 Key proteins and signalling pathways

Every process in organism is result of coordinated action of different proteins. Process of the Synapse formation is driven by the action of numerous proteins, primarily Cell- Adhesion Molecules(CAMs) and scaffold proteins (Qi et.al ,2022). Besides these two types of proteins, a large number of other proteins participate in this interplay, as the literature suggests.Among them are: Synaptophysin,SNAP25, Synapsins, Neuroligins and Neurexins, PSD -95 and BDNF.

Their functions are summarized in Table 1

1.4 Developmental and Experience-Dependent Synapse Formation

Synapse formation is crucial for development; it is a continuous process that occurs throughout an organism's life. It follows adulthood and is responsible for neuroplasticity, which is the ability of the brain to reorganize itself through alternative neural pathways.(Fuchs,2014).There was a belief that the majority of synapses form during the first trimester of pregnancy, but recent discoveries suggest that synaptogenesis is the most rapid later on in pregnancy, as in the third trimester (ME Thomason, 2021). Besides the developmental aspect of synaptogenesis, new neural pathways form in response to learning new skills. The significance of this capability is best observed during the recovery after brain injury.

1.5 Biological significance of Neurexin

Neurexins belong to the large family of presynaptic cell adhesion molecules(CAM's). Together with postsynaptic Neuroligins, they regulate both the excitatory and inhibitory aspects of neural activity (C.Reissner, 2013).To define synaptic boundaries and ensure proper alignment of synaptic machinery, neurexins physically link presynaptic and postsynaptic membranes (Boxer EE, 2022) .The aim of this study is to perform predictive modelling ,analyze protein-protein interactions of molecules that participate in the process of synapse formation, understand genetic variabilityand perform pathway analysis. These steps are necessary for understanding how neurexin-related mechanisms influence neurodevelopmental disorders. Researches like this pave the way into developing gene therapy, integrating personalized medicine approaches, drug development or combined targeting of proteins incluuded in this study.

Note- Figure 2 adapted from

1. (Tossio P. et.al,2022.) 2. (Sudhof T.C.,2004.) 3. (Scheiffele P. et.al,2000.) 4.(Wu Q.,2017) 5. (Sasi M.,2017)

2. Research method

2.1 Literature review:

To be able to understand current knowledge and define research questions, literature that covered designated keywords was systematically and carefully reviewed. Mainly reviewed literature was found on PubMed Central database

2.2 Data Collection

2.2.1 Identification of Proteins of Interest

2.3 Initially, we defined a specific list of proteins relevant to our research, focusing on those implicated in synaptogenesis mechanisms.

2.4 Selection of Databases

- We utilized established and reputable databases for comprehensive data retrieval:
- **UniProt**: This database provides extensive protein sequence and functional information, including detailed annotations on biological functions, localization, and interactions.
- **Protein Data Bank (PDB)**: A structural database offering 3D representations of proteins, which is vital for understanding the structure-function relationships pertinent to the proteins of interest.
- **Accession ID Collection**

We systematically gathered the accession IDs for the targeted proteins from both databases. The process involved:

- Conducting searches in UniProt and PDB for each protein, ensuring accuracy in the retrieval process.
- Compiling accession IDs alongside pertinent details about each protein's function, including its role in the process of synapse formation.
- **Data Structuring**

The collected data was organized in a relational format, such as a database or a structured spreadsheet. Each entry included:

- Accession ID
- Protein Name
- Function

- Additional Relevant Information (e.g., known pathways, interaction partners)

2.5 Retrieving Target protein: Experimentally determined structure of target Neurexin protein was retrieved from UniProt database. UniProt: UniProtKB: Homepage accessed on January,7th, 2026.Determined structure with UniProt ID: Q9ULB1 consists of alpha and beta sheets of 1712 amino acids.

2.6 Interactome assessment: To identify and illustrate proteins that interact with Neurexin, STRING server was used. Interactome builder was set to show no more than 20 interactions in first shell while the second shell was set to show no more than five interactions in high confidence (0.700)

2.7 Molecular Docking: to predict the preferred orientation and binding affinity of ligand molecule to protein we performed molecular docking of Neurexin with BDNF and Synaptophysin with Neurexin. Since both of ligand molecules belong to large protein families, it was not possible to use single.pdb file as the basis for docking. Alpha Fold server was chosen because of the possibility to approach docking from genomic sequence.

2.8 Synaptophysin-Neurexin docking

2.8.1. Target Protein Preparation:

Fasta sequence of Synaptophysin (Homo sapiens) was retrieved from NCBI (National Center for Biotechnology Information)

2.8.2 Ligand 1 Protein Preparation:

Fasta sequence of Neurexin (Homo sapiens) was retrieved from NCBI database.

2.9 Synaptophysin-BDNF docking

2.9.1 Ligand 2 Protein Preparation

Fasta sequence of BDNF(Homo Sapiens) was retrieved from NCBI database.

2.10 Predicting 3D structure of Synaptophysin, BDNF and Neurexin

For the purpose of 3D structure determination of designated proteins, the Swiss- model server was used. As a template for prediction genomic sequence was used. Genomic sequences were retrieved from UniProt database.

3. Results

3**.2. Data Collection** To asses data about proteins involved in regulating synaptogenesis we listed their PDB and UniProt accession ID’S as shown in Figure3

Experimentally determined structure of Neurexin that was retrieved from UniProt database is depicted in Figure 3.

3.3 Interactome prediction

Interaction of Neurexin with other proteins is illustrated by Figures 4 and 5

3.4 Molecular Docking

To analyze the nature of Neurexin's interaction with other proteins two molecular dockings were done. Molecular docking was performed with BDNF (Brain Derived Neurotrophic Factor) and Synaptophysin.

Results we obtained are shown in figures 6a and 6b

3.5 3D Structure Prediction

The structures of Synaptophysin, Neurexin and BDNF predicted by Swiss model are shown in figures 7a,7b and 7c

4. Discussion

Understanding the critical importance of accurately regulating synaptogenesis has underscored the need for further research into the gene regulation of this process. Investigating how gene dysregulation or disruptions during synaptogenesis contribute to the onset of neurodevelopmental disorders, such as autism, ADHD, intellectual disability, cerebral palsy, and specific learning disorders, is essential. Future research could focus on analyzing and understanding the interaction sites of proteins involved in regulating synaptogenesis. These interaction sites are particularly susceptible to mutations and could serve as potential drug targets for developing pharmacological interventions aimed at optimizing synaptogenesis. Since brain injuries are a leading cause of disability and, in severe cases, death worldwide, future research should prioritize enhancing the recovery processes that follow primary interventions. Once the brain is injured, it often compensates by forming alternative neural pathways through new synapse formation. Combining such pharmacological approaches with traditional rehabilitation methods could potentially reduce the burden of brain injuries and improve recovery outcomes. While initial treatments, such as those performed after a stroke, aim to address immediate life-threatening issues, many individuals continue to experience long-term consequences, such as loss of mobility and independence. Therefore, advancing strategies to support and accelerate recovery in the later stages is crucial to improving quality of life for those affected by brain injuries. After conducting preliminary research using bioinformatics tools, the next step involves translating these findings into laboratory experiments aimed at developing gene therapies or novel drugs. Advances in these areas pave the way for integrating personalized treatment options, enabling more effective and tailored approaches to treating a wide range of diseases.

Structure of protein determines its function, so any determined structure should be observed through its biological significance.Neurexin belongs to large family of cell adhesion molecules(CAM's) which are essential for synaptic development and facilitating communication betweeen neurons. Neurexins typically contain several structural domains, LNS domains and EGF-like domains.These domains are organized in a way that allows them to bridge synaptic cleft, which contributes to their role.

Interaction sites of proteins are particularly interesting to study, because these sites are vulnerable to mutations and may serve as potential targets for drug development. Interactome we built confirmed the significance of interactions Neurexins makes. This significance is illustrated by its role in overall synapse formation process.

Molecular docking was performed to predict and analyze binding between target protein (Neurexin) and ligand molecules for the purpose of understanding the nature of interaction between proteins that are crucial for Neuroplasticity. We have performed docking with Neurexin and BDNF.

Molecular docking of Neurexin with BDNF

According to previous research BDNF and Neurexin are co-dependent. BDNF is a secreted signaling molecule that regulates differentiation growth and development of neurons through synaptogenesis which is crucial for regulated neuroplasticity. In contrast, Neurexin is presynaptic CAM that binds to postsynaptic Neuroligins. This binding is characterized by their extracellular domains interacting through various molecular mechanisms. This explains why these proteins don’t dock fully.

Molecular Docking of Synaptophysin with Neurexin

These two molecules dock indirectly too, because they interact through intermediary protein called Synaptotagmin. This interaction occurs during development and stabilization of presynaptic terminal in neurons. Neurexins are synaptic adhesion molecules, while Synaptophysin is the molecule found within the membrane of synaptic vesicle itself.

Limitations to the study: Predicted models may be different from naturally occuring protein structures.Interactions derived by STRING are predicted interactions, not experimentally confirmed. Docking presented here does not illustrate real cellular environment.This is preliminary study which requires further experimental validation.

Future perspectives: The future perspectives of bioinformatical modeling of Neurexin are promising.and could significantly advance our understanding of neurobiology and related fields

CONCLUSION

Synapse formation serves as the fundamental blueprint for the human brain's remarkable ability to adapt to new environments and experiences throughout life. The insights gained from current research on

synaptogenesis present a promising pathway to address various diseases that afflict our modern society, including neurodevelopmental disorders, age-related cognitive decline, and brain injuries.

By harnessing our understanding of the molecular and genetic mechanisms underlying synapse formation, we have the potential to develop targeted therapies that not only promote the rate of synaptogenesis but also enhance the quality and efficacy of synaptic connections. Such tailored treatments could revolutionize our approach to neurological health, offering new avenues for recovery and rehabilitation.

Furthermore, advancing our strategies in this area could significantly alleviate the societal burden associated with brain injuries and related conditions. As we strive for breakthroughs in neuroscience, fostering collaboration among researchers, clinicians, and policymakers will be essential to translate these scientific discoveries into practical, effective treatment solutions. In doing so, we can aspire to build a future where the challenges posed by neurological impairments are met with innovative, personalized medical interventions that enhance individual well-being and societal health as a whole.

References

1. *Qi C, Luo LD, Feng I, Ma S. Molecular mechanisms of synaptogenesis. Front Synaptic Neurosci. 2022 Sep 13; 14:939793. doi: 10.3389/fnsyn.2022.939793. PMID: 36176941; PMCID: PMC9513053.*
2. *Südhof TC. The cell biology of synapse formation. J Cell Biol. 2021 Jul 5;220(7):e202103052. doi: 10.1083/jcb.202103052. Epub 2021 Jun 4. PMID: 34086051; PMCID: PMC8186004.*
3. *Sanderson TM, Georgiou J, Collingridge GL. Illuminating Relationships Between the Pre- and Post-synapse. Front Neural Circuits. 2020 Apr 2;14:9. doi: 10.3389/fncir.2020.00009. PMID: 32308573; PMCID: PMC7146027.*
4. *Colón-Ramos DA. Synapse formation in developing neural circuits. Curr Top Dev Biol. 2009; 87:53-79. doi: 10.1016/S0070-2153(09)01202-2. PMID: 19427516; PMCID: PMC7649972.*
5. *Fuchs E, Flügge G. Adult neuroplasticity: more than 40 years of research. Neural Plast. 2014;2014:541870. doi: 10.1155/2014/541870. Epub 2014 May 4. PMID: 24883212; PMCID: PMC4026979.*
6. *Vergara RC, Jaramillo-Riveri S, Luarte A, Moënne-Loccoz C, Fuentes R, Couve A, Maldonado PE. The Energy Homeostasis Principle: Neuronal Energy Regulation Drives Local Network Dynamics Generating Behavior. Front Comput Neurosci. 2019 Jul 23;13:49. doi: 10.3389/fncom.2019.00049. Erratum in: Front Comput Neurosci. 2020 Oct 29;14:599670. doi: 10.3389/fncom.2020.599670. PMID: 31396067; PMCID: PMC6664078.*
7. *Koga K, Descalzi G, Chen T, Ko HG, Lu J, Li S, Son J, Kim T, Kwak C, Huganir RL, Zhao MG, Kaang BK, Collingridge GL, Zhuo M. Coexistence of two forms of LTP in ACC provides a synaptic mechanism for the interactions between anxiety and chronic pain. Neuron. 2015 Jan 21;85(2):377-89. doi: 10.1016/j.neuron.2014.12.021. Epub 2014 Dec 31. Erratum in: Neuron. 2015 May 20;86(4):1109. PMID: 25556835; PMCID: PMC4364605.*

8. *Pereda AE. Electrical synapses and their functional interactions with chemical synapses. Nat Rev Neurosci. 2014 Apr;15(4):250-63. doi: 10.1038/nrn3708. Epub 2014 Mar 12. PMID: 24619342; PMCID: PMC4091911.*
9. *Jabeen S, Thirumalai V. The interplay between electrical and chemical synaptogenesis. J Neurophysiol. 2018 Oct 1;120(4):1914-1922. doi: 10.1152/jn.00398.2018. Epub 2018 Aug 1. PMID: 30067121; PMCID: PMC6230774.*
10. *Cole AA, Reese TS. Transsynaptic Assemblies Link Domains of Presynaptic and Postsynaptic Intracellular Structures across the Synaptic Cleft. J Neurosci. 2023 Aug 16;43(33):5883-5892. doi: 10.1523/JNEUROSCI.2195-22.2023. Epub 2023 Jun 27. PMID: 37369583; PMCID: PMC10436760.*
11. *Qi, Cai & Luo, Li-Da & Feng, Irena & Ma, Shaojie. (2022). Molecular mechanisms of synaptogenesis. Frontiers in Synaptic Neuroscience. 14. 939793. 10.3389/fnsyn.2022.939793.*
12. *Preobraschenski J, Kreutzberger AJB, Ganzella M, Münster-Wandowski A, Kreutzberger MAB, Olsthoorn LHM, Seibert S, Kiessling V, Riedel D, Witkowska A, Ahnert-Hilger G, Tamm LK, Jahn R. Synaptophysin accelerates synaptic vesicle fusion by expanding the membrane upon neurotransmitter loading. Sci Adv. 2025 Apr 25;11(17):eads4661. doi: 10.1126/sciadv.ads4661. Epub 2025 Apr 23. PMID: 40267188; PMCID: PMC12017324.*
13. *Wu Q, Sun M, Bernard LP, Zhang H. Postsynaptic density 95 (PSD-95) serine 561 phosphorylation regulates a conformational switch and bidirectional dendritic spine structural plasticity. J Biol Chem. 2017 Sep 29;292(39):16150-16160. doi: 10.1074/jbc.M117.782490. Epub 2017 Aug 8. PMID: 28790172; PMCID: PMC5625046.*
14. *Qi C, Luo LD, Feng I, Ma S. Molecular mechanisms of synaptogenesis. Front Synaptic Neurosci. 2022 Sep 13;14:939793. doi: 10.3389/fnsyn.2022.939793. PMID: 36176941; PMCID: PMC9513053.*
15. *Reissner C, Runkel F, Missler M. Neurexins. Genome Biol. 2013;14(9):213. doi: 10.1186/gb-2013-14-9-213. PMID: 24083347; PMCID: PMC4056431.*
16. *Boxer EE and Aoto J (2022) Neurexins and their ligands at inhibitory synapses. Front. Synaptic Neurosci. 14:1087238. doi: 10.3389/fnsyn.2022.1087238*
17. *Glasgow SD, McPhedrain R, Madranges JF, Kennedy TE and Ruthazer ES (2019) Approaches and Limitations in the Investigation of Synaptic Transmission and Plasticity. Front. Synaptic Neurosci. 11:20. doi: 10.3389/fnsyn.2019.00020*

Figures

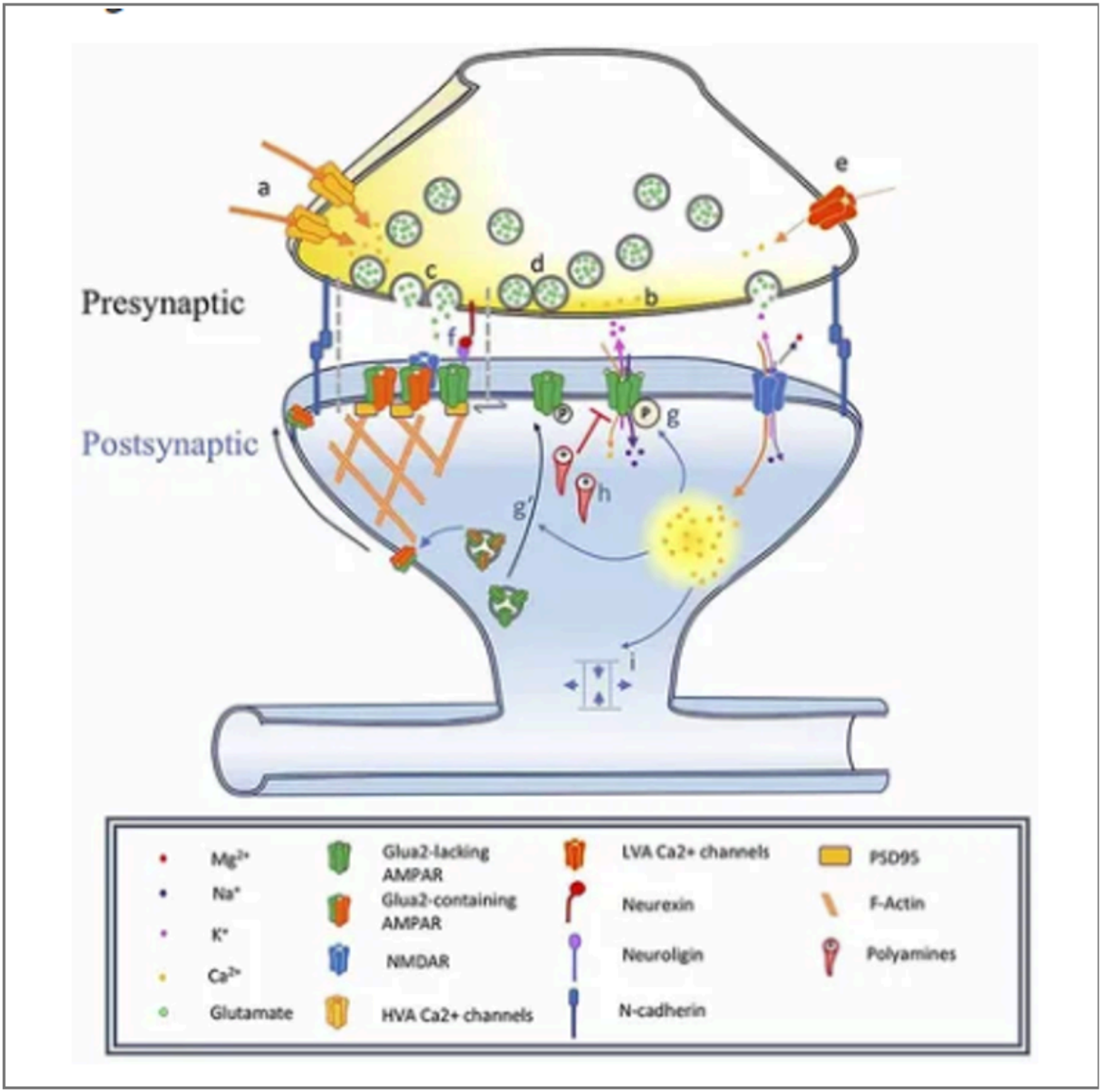


Figure 1

Model of Synapse Formation

Proteins involved in synapse formation process

Protein	Function	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8
Synaptophysin	Marker of synaptic vesicles						
BDNF	Promotes synaptic growth and plasticity						
Neurexin	mediating trans-synaptic signaling, guiding synapse formation, and fine-tuning synaptic function and stability.						
Neuroligin	connecting neurons (via neurexins on the other side) to organize and maintain synaptic structure and function, influencing learning, memory, and network properties.						
Synapsin	Regulate neurotransmitter release by tethering synaptic vesicles to skeleton						
PSD-95	A scaffolding protein in postsynaptic density that organizes synaptic signalling complexes						
SNAP-25	A component of SNARE complex essential for synaptic vesicle fusion						

Figure 2

Proteins that regulate Synapse formation process with their functions

accession ID’s of designated proteins

Protein’s name	Uniprot ID	PDB ID	Column 4	Column 5	Column 6	Column 7	Column 8
Neuroligin	QN2Q7						
Synapsin	P17600	1PK8					
SNAP-25	P60880	6WVW					
Synaptophysin	P08247	9B9Q					
Neurexin	Q9ULB1	3POY					
PSD-95	P78352	3ZRT					
BDNF	P23560	1B8M					

Figure 3

accession ID’S of designated proteins

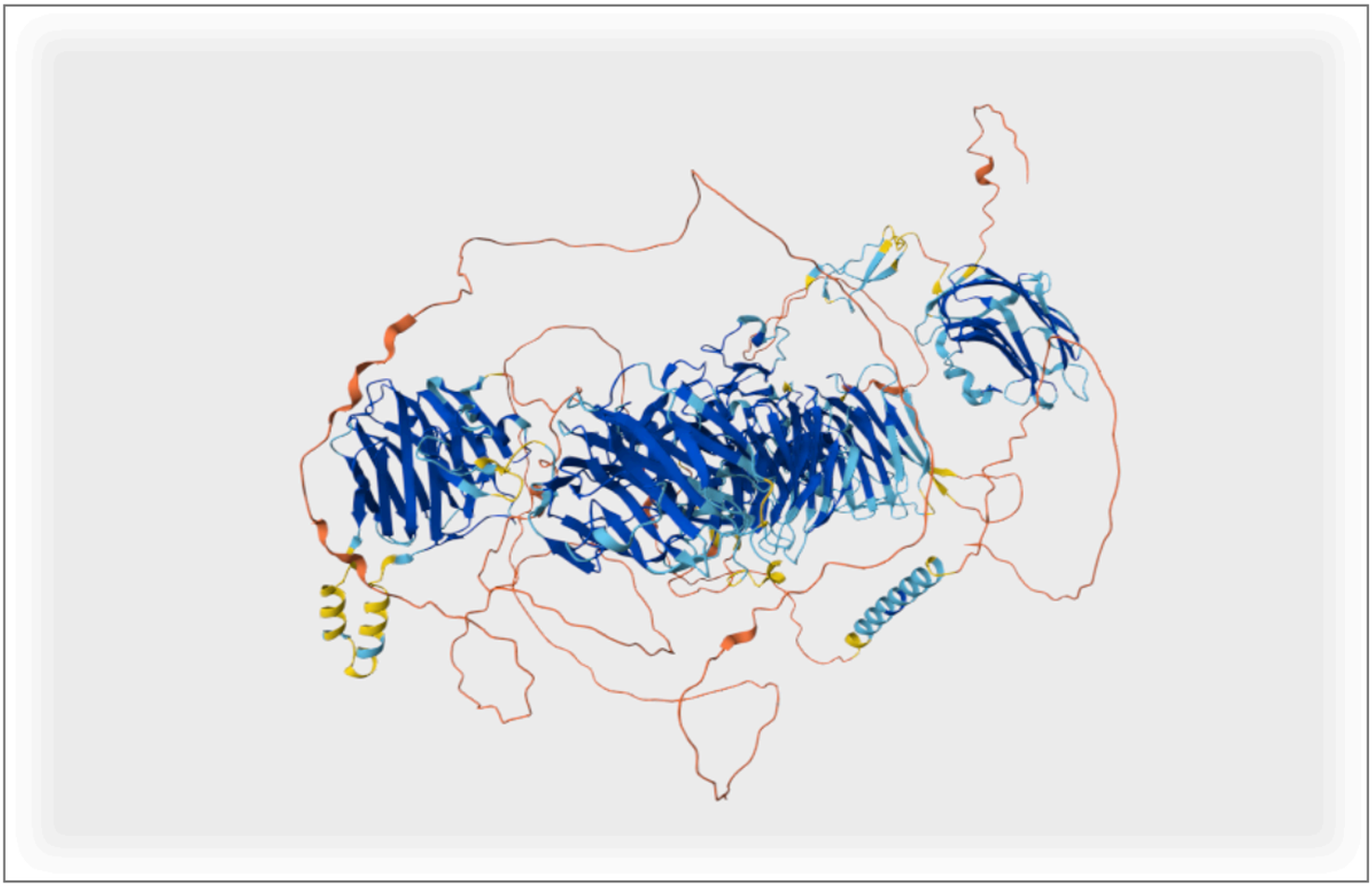


Figure 4

experimentally determined structure of Neurexin

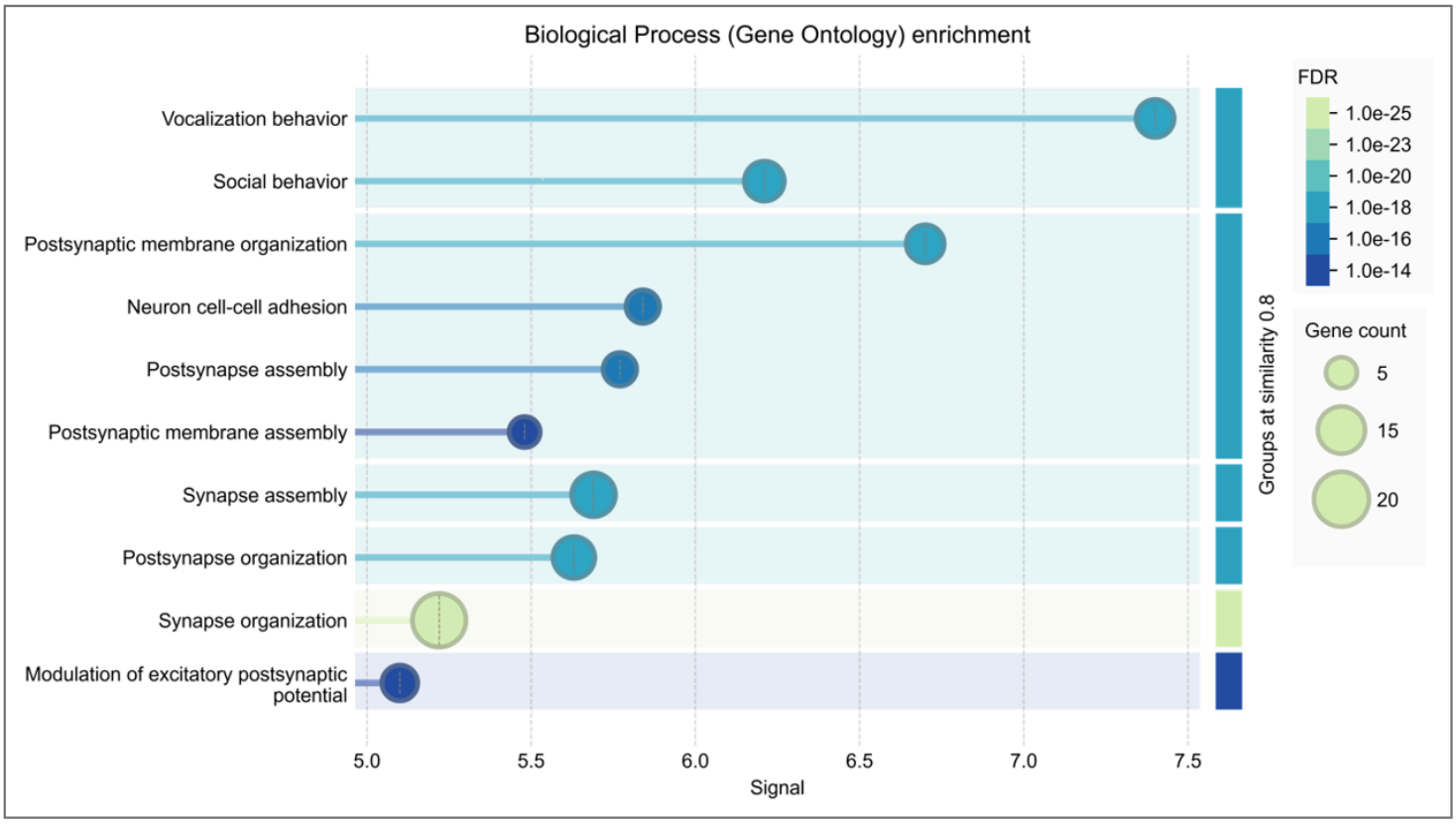


Figure 5

Figure 4- Neurexin's interactome

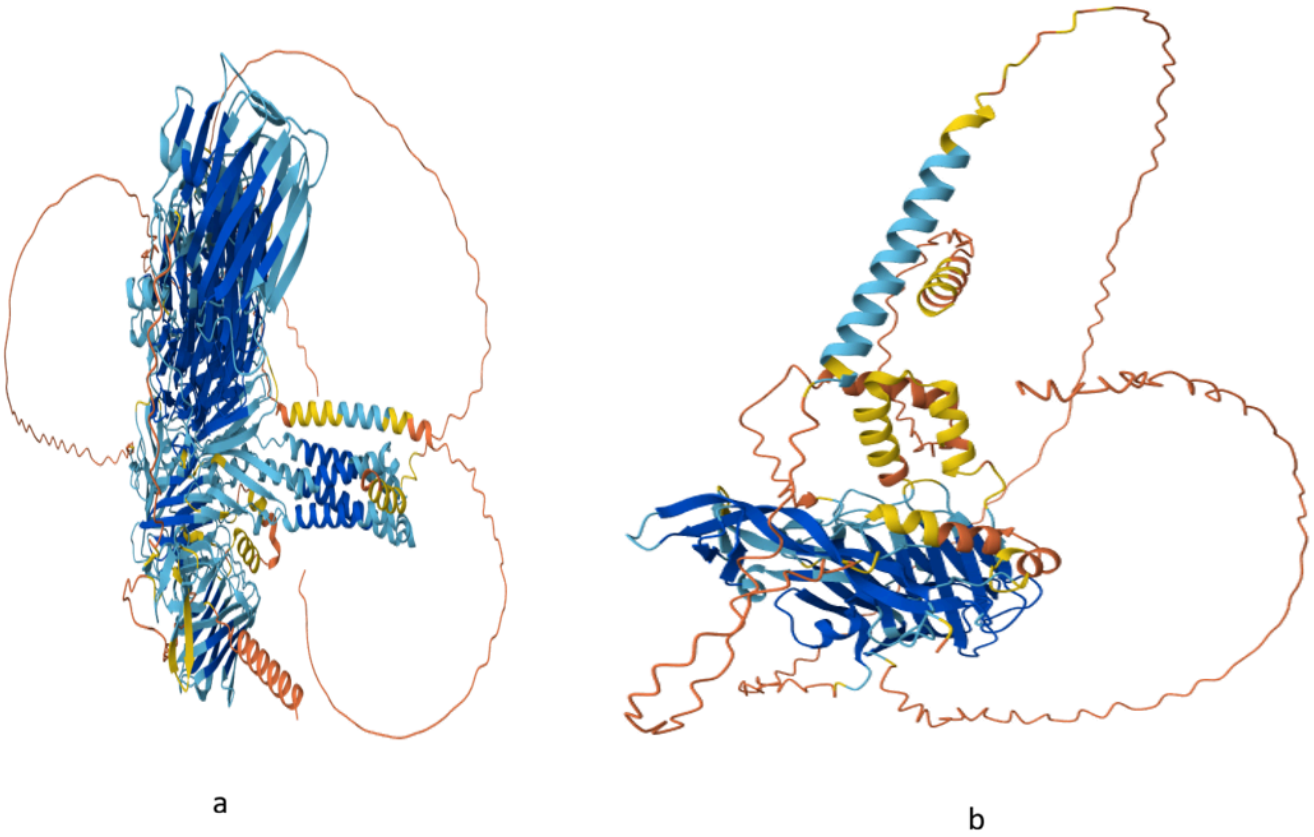


Figure 6

Figure 5-Nature of Neurexin’s interactions

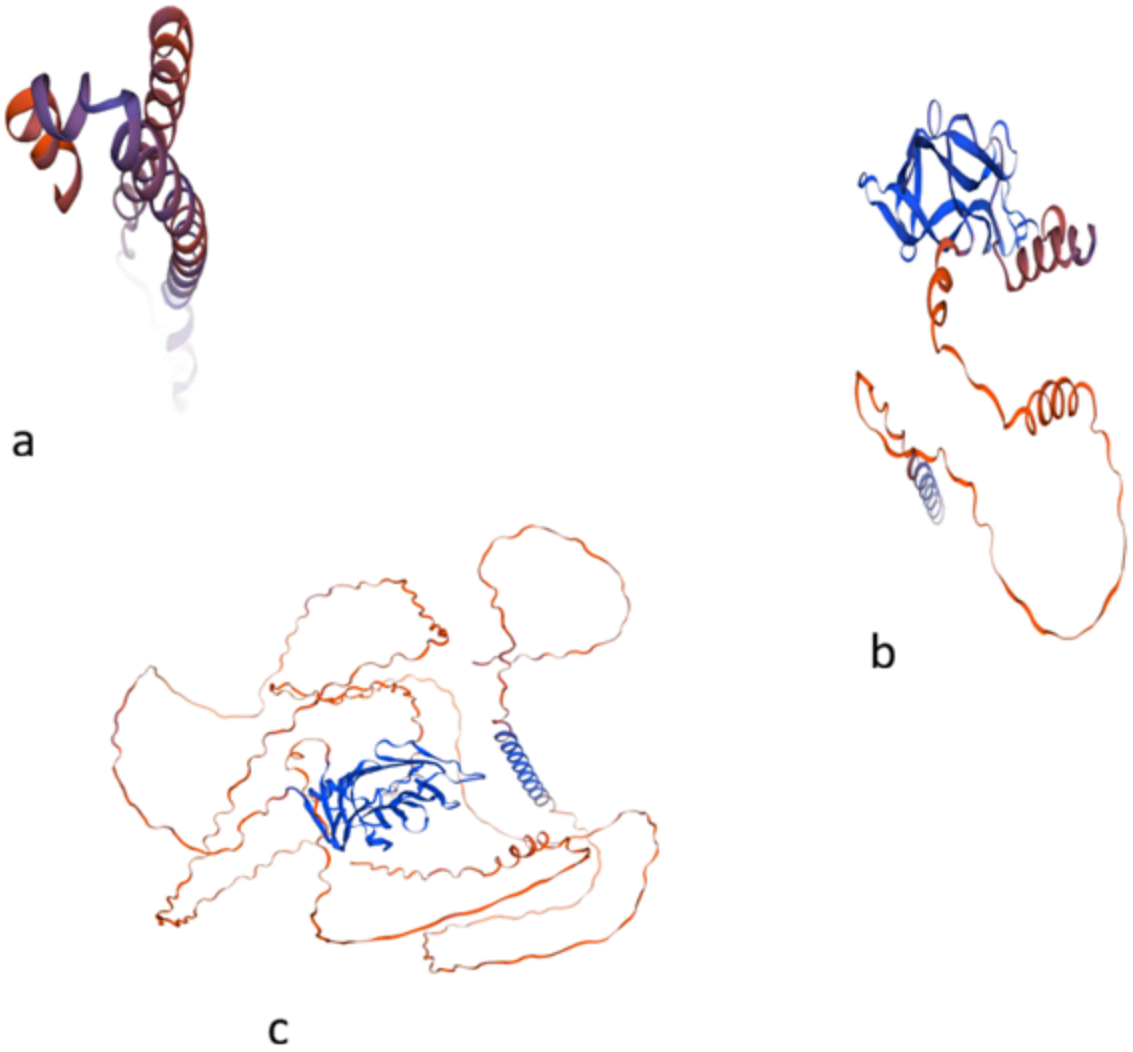


Figure 7

Figure 6a-Synaptophysin-Neurexin complex

Figure 6b-Neurexin-BDNF complex

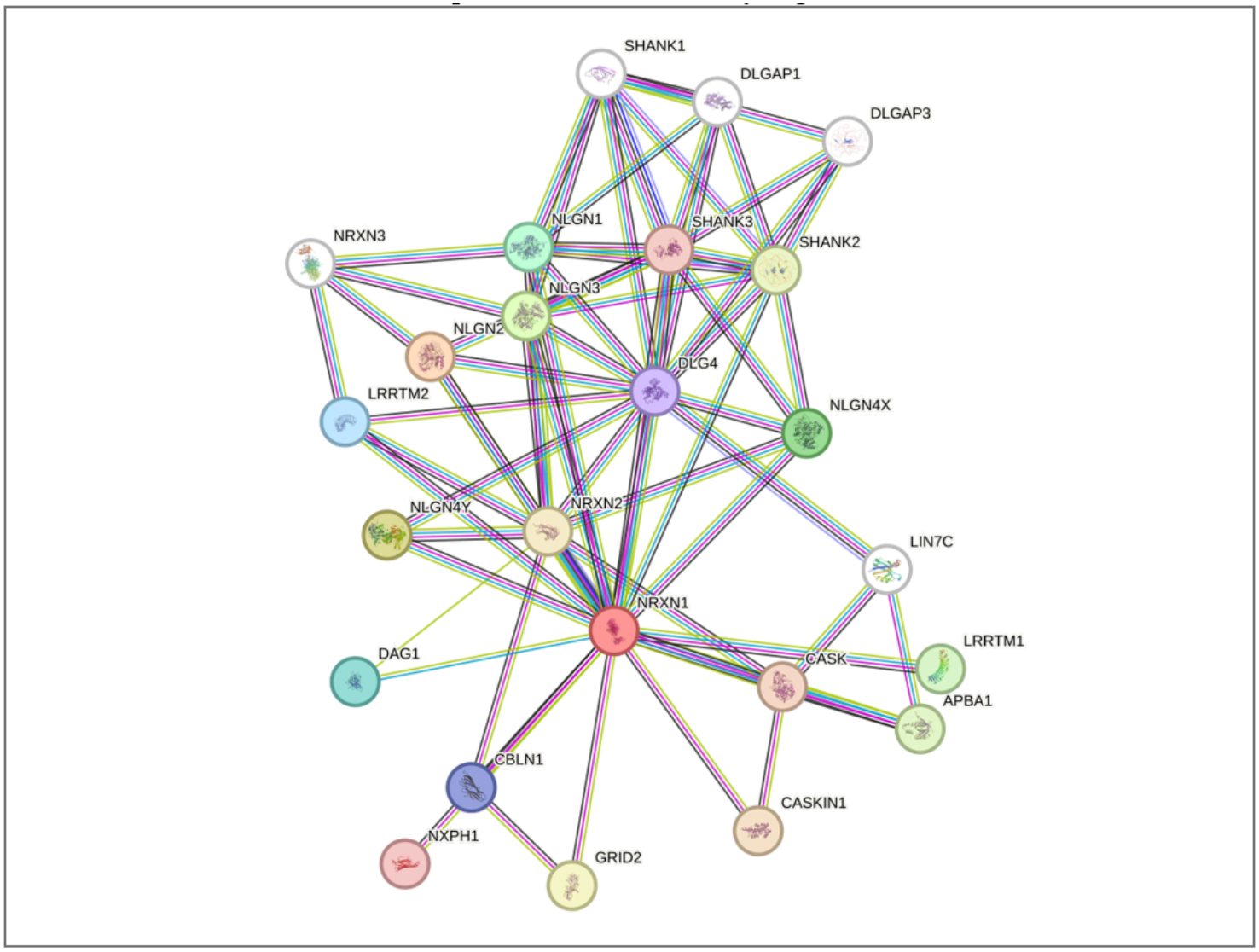


Figure 8

Figure 7a-Predicted structure of Synaptophysin

Figure 7b-Predicted structure of BDNF

Figure 7c-Predicted Structure of Neurexin