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Network biology: A promising approach for drug target identification against neurodevelopmental disorders

Wayez NAQVI; Ananya SINGH; Prekshi GARG; Prachi SRIVASTAVA*

Amity Institute of Biotechnology, Amity University, Lucknow, 226028, India

Abstract: Biological entities are involved in complicated and complex connections; hence, discovering biological information using network biology ideas is critical. In the past few years, network biology has emerged as an integrative and systems-level approach for understanding and interpreting these complex interactions. Biological network analysis is one method for reducing enormous data sets to clinically useful knowledge for disease diagnosis, prognosis, and treatment. The network of biological entities can help us predict drug targets for several diseases. The drug targets identified through the systems biology approach help in targeting the essential biological pathways that contribute to the progression and development of the disease. The novel strategical approach of system biology-assisted pharmacology coupled with computer-aided drug discovery (CADD) can help drugs fight multifactorial diseases efficiently. In the present review, we have summarized the role and application of network biology for not only unfolding the mechanism of complex neurodevelopmental disorders but also identifying important drug targets for diseases like ADHD, Autism, Epilepsy, and Intellectual Disability. Systems biology has emerged as a promising approach to identifying drug targets and aiming for targeted drug discovery for the precise treatment of neurodevelopmental disorders.

Introduction

The study of the molecular and genetic basis of diseases has been revolutionized in the past decade by the application of next-generation sequencing technologies and computational approaches. One of the biggest challenges these days is the identification of clinically relevant data from the plethora of data available. The functionality of biomolecules is widely known to be interdependent, forming a complex biomolecular network including protein-protein interaction (PPI), metabolic, signaling and transcription-regulatory networks. For instance, a disease is rarely an outcome of the dysfunction of a single gene; rather, it is a consequence of the malfunction of complex networks that regulate genes, tissues and organ systems (Liu *et al.*, 2020). Network biology has emerged as an important approach to understand and integrate these complex networks and gain knowledge of clinically actionable data for understanding the molecular mechanism of diseases, which can provide biological insights for the diagnosis and treatment of these diseases. PPI network has turned out to be an asset in this context (Furlong, 2013). Based on the results of experimental methods, the human interactome was estimated to contain ~65000 protein interactions (Stumpf *et al.*, 2008). Biological networks have been used to interpret disease mechanisms to study comorbidities, drug-target interactions and discover network-based biomarkers. Thus, network biology can be used to understand complex genotype-phenotype relations of human diseases (Furlong, 2013). In the present paper, we review the literature on network analysis related to neurodevelopmental disorders (NDDs).

NDDs are a class of disorders that affect brain development and functions characterized by the inability to reach cognitive, emotional, and motor developmental milestones; they pose a serious health problem affecting >3% of children worldwide (Parenti *et al.*, 2020). NDDs include attention-deficit/hyperactivity disorder (ADHD), intellectual disability (ID), autism spectrum disorder (ASD) and epilepsy. Studies provide compelling evidence that many disease genes map to a much smaller number of biological subnetworks (Hormozdiari *et al.*, 2015), suggesting the involved genes share a common molecular
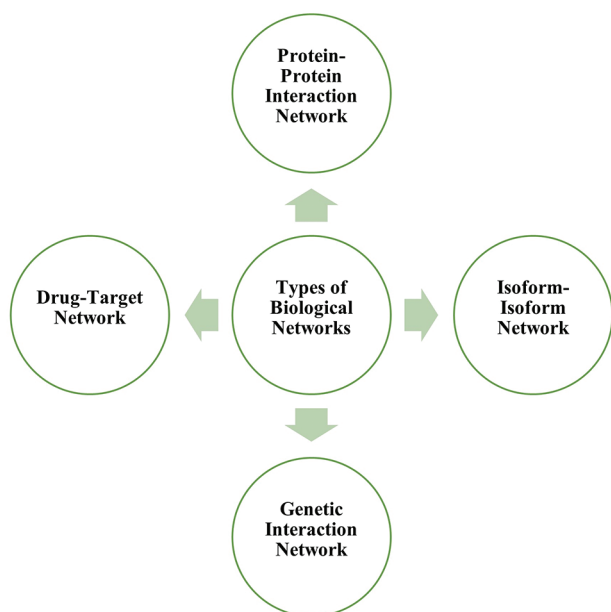
FIGURE 1. Different types of biological networks that can be studied through network biology.

pathway, resulting in comorbidity of two or more of these disorders. For instance, a combination of ID, ASD and epilepsy is frequently reported in individual patients (Parenti *et al.*, 2020). Network modelling approaches have been applied to explain the above-stated comorbidity and identify candidate genes leading to advancements in the effective treatment of NDDs.

By combining information from genomic data of the disease and the PPI network, network-based techniques may also be utilized to comprehensively evaluate and prioritize disease indications for therapeutic targets (Han *et al.*, 2021). Drug target prioritization and identification are being aided by novel network propagation methods that incorporate heterogeneous biological networks (Ji *et al.*, 2019). As one of the key objectives in drug discovery, the network biology technique for drug-target identification provides a quick and systematic evaluation of both individual and combination drug targets (Han *et al.*, 2021). In the present review, we also discuss the application of network biology for the identification of drug-targets against neuro-developmental diseases.

Types of Biological Network

Several types of biological networks include protein interaction networks, isoform-isoform networks, genetic interaction networks, metabolic networks, brain networks and drug-target networks. Fig. 1 depicts the various types of biological networks.

Protein-protein interaction network
PPI depicts the relationships between two or more proteins characterized by biochemical interactions in cells. The nodes represent the proteins, and the edges explain the interaction between them. The protein interaction network (PIN) are a valuable tool for the study of large-scale interactomes and functional annotations of proteins and serve as an evolutionary analytical tool based on specific subnetworks and the identification of hub proteins (Hao *et al.*, 2016). Table 1 enlists various bioinformatics tools for curating human protein network.

Isoform-isoform network
A protein isoform, also known as a protein variant, is a member of a set of highly similar proteins encoded by a single gene or gene family but differ genetically. While many isoforms serve the same or comparable biological tasks, some have distinct functions. Isoforms are formed via alternative transcription, splicing, 3′-end formation, translation and post-translational modification. A protein, which is a single node in the PPI network, transforms into a sub-network of interaction between the several isoforms encoded by the underlying gene; thus isoform-isoform network can be understood as a network and may offer potential application to identify an isoform-specific mutation that could help in the treatment of diseases (Liu *et al.*, 2020). The IIIDB database can be freely accessed and allows searching for isoform-isoform interaction network modules (Tseng *et al.*, 2015).

Genetic interaction network
The genetic interaction network is the network demonstrating gene interrelations. These networks can forecast more known and unknown disease-gene connections for a certain disease. The genetic interaction network is able to predict disease-gene relationships without using generic protein-protein

TABLE 1

List of bioinformatics resources for curating the human protein interaction network

Databases	Description	Website	References
STRING	STRING is a database of known and predicted protein-protein interactions (PPI).	https://string-db.org	Szklarczyk *et al.* (2011)
HPRD	Human PPI data.	http://www.hprd.org	Prasad (2009)
BioGRID	BioGRID is a protein, genetic and chemical interaction repository.	https://thebiogrid.org	Chatr-Aryamontri *et al.* (2015)
MINT	MINT focuses on PPI that have been experimentally verified and are taken from the scientific literature by expert curators.	https://mint.bio.uniroma2.it	Licata *et al.* (2012)
Interactome3D	Interactome3D is a web service for structurally annotating PPI networks.	https://interactome3d.irbbarcelona.org	Mosca *et al.* (2013)

TABLE 2

Summary of bioinformatics resources for constructing the drug-target network

Databases	Description	Website	References
DrugBank	DrugBank is an online database containing information on drugs and drug targets.	DrugBank Online | Database for Drug and Drug Target Info	Law et al. (2014)
DGIdb	Drug–gene interaction database.	https://dgidb.org	Freshour et al. (2021)
STITCH	Integrates information about interaction from the metabolic pathway, crystal structure, binding energy and drug-target interaction.	http://stitch.embl.de/	Kuhn et al. (2010)
SuperPred	Experimental and predicted compound-protein interactions.	https://prediction.charite.de	Nickel et al. (2014)

networks. More research is being done to tune the effectiveness of genetic interaction networks in identifying potential candidate genes. Genetic interaction networks can be analysed through STRING (Szklarczyk et al., 2021) and GeneMANIA (Warde-Farley et al., 2010).

Drug target network

The drug-target network is a bipartite network where some nodes represent the drug sets, and others represent the target (gene). Drug targets are nodes in the human interactome inextricably linked to treatment indication and side effects. The network-based location of each drug module also defines its pharmacological and biological relationships with other drugs (Liu et al., 2020). Table 2 enlists various bioinformatics tool for construction the drug-target network.

Brief Guide to Network Analysis

Many fundamental and translational neuroscience investigations continue to focus on the principal attributes of a node in a network as mentioned in Fig. 2 and described below:

Degree: The number of connections (edges) between nodes determines the degree of a node in a network. The degree distribution is contrasting in nature, with nodes either having few or many connections.

Shortest path: The shortest path between two nodes is the one that requires the least number of nodes to connect them (Furlong, 2013). The use of shortest pathways to connect node pairs in biological networks is strongly motivated. The shortest route approach is frequently employed to assign orientations to edges in PPI networks to infer regulatory pathways from genes that match and identify genes or essential elements associated with cancer and other diseases (Liu et al., 2020).

Clustering coefficient: The clustering coefficient of a node is a measure of the degree of interconnectivity of its neighbors. It is calculated as the number of edges between neighbors of a node divided by the number of all possible edges between them. The value ranges from 0–1 (Furlong, 2013).

Betweenness centrality: Betweenness measures the global importance of nodes in communicating based on the number of shortest paths that pass through the node (Furlong, 2013). Studies have shown that proteins with a high degree of betweenness are more likely to be pleiotropic and disease-related genes. The betweenness of the brain functional networks has also been a topic of interest in testing brain activity (Liu et al., 2020).

Density: The percentage of actual connections among a network's possible connections is known as "network density." A connection between two "nodes" is referred to as a "possible connection" whether or not it actually exists. A network with higher associations will have higher density and lesser resilience to changes.

Degree distribution: The degree distribution indicates the probability that a network node chosen at random has a degree of k.

It is represented as p_k,

$$p_{k=} \frac{N_k}{N}$$

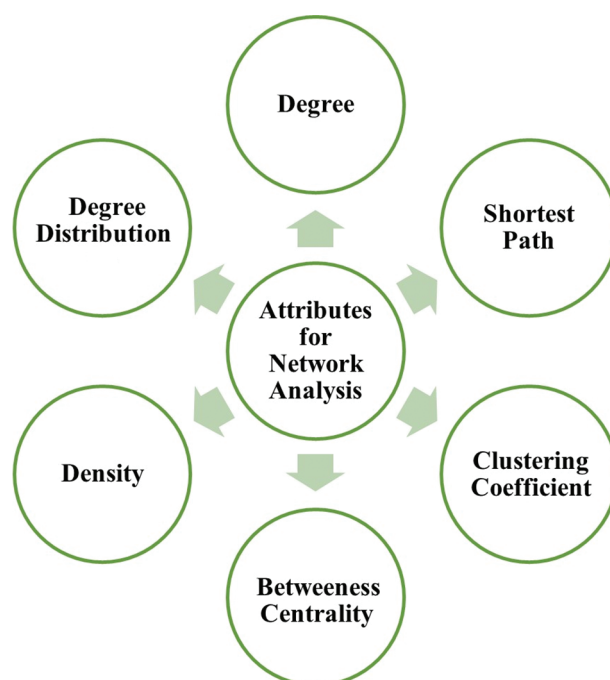where N_k is the number of nodes that have degree k and N is the total number of nodes.

FIGURE 2. Principal attributes for network analysis.

TABLE 3

list of tools used for network analysis

| Name	Description	Link
Arena 3D	3D visualization of multilayer networks.	http://www.arena3d.org
BioMiner	Biochemical network analysis, modelling and visualization.	/
Cytoscape	Network visualization and analysis. With over 200 plugins.	http://www.cytoscape.org/
NeAT	Network topological and clustering analysis.	https://rsat01.biologie.ens.fr/rsa-tools/index_neat.html
PathwayAssist	Navigation and analysis of biological pathways.	/
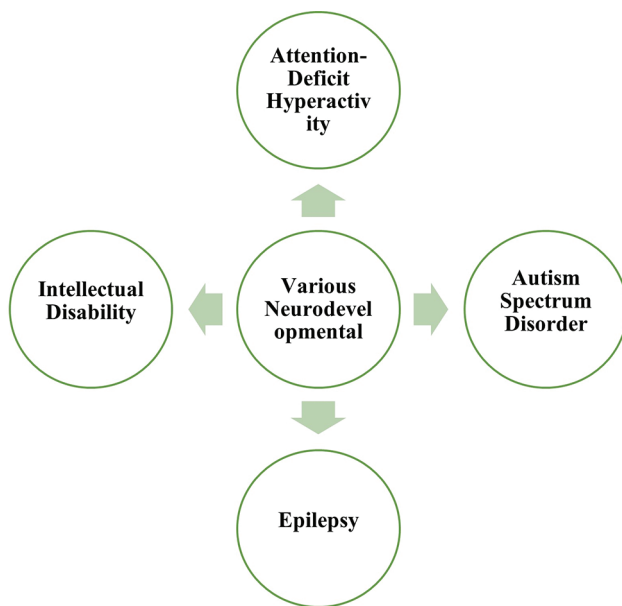
FIGURE 3. Important neurodevelopmental disorders included in the present study.

A list of tools that can be used for network analysis is described in Table 3.

Role of Network Biology in Neurodevelopmental Disorders

Network biology approaches can be utilized in the study of various neurodevelopmental disorders as depicted in Fig. 3.

Attention-deficit hyperactivity disorder
ADHD is a neurodevelopmental condition that first appears in children and is characterized by persistent, inappropriate impulsivity, hyperactivity and inattention (Hayman and Fernandez, 2018). The worldwide prevalence of ADHD ranges from 1.4%–5% (Nickel *et al.*, 2014). In childhood, ADHD is more common in men than women, with a 3:1 ratio between the sexes. There are three sub-categories of ADHD, pertaining to the type of behavioural symptoms: predominantly hyperactive/impulsive, predominantly inattentive, and combined type (Hayman and Fernandez, 2018). ADHD is often associated with other psychiatric and behavioural disorders, developmental disorders (e.g., dyslexia, autism), depression, and anxiety (Nickel *et al.*,

2014). From the literature review, 105 genes associated with ADHD have been identified and genetics play an important role in this disorder. From twin studies, the heritability value of ADHD is found to be 0.76. In addition to biological variables like extremely low birth weight, prenatal nicotine exposure, stress, and alcohol intake, environmental pollutants such as lead and polychloride biphenyls, increased the probability of ADHD in children (Hayman and Fernandez, 2018). The current treatment of ADHD is age specific (Lola *et al.*, 2019). Medications include methylphenidates (e.g., Ritalin, Concerta) and amphetamines (e.g., Adderall, Vyvanse) and behavioural therapy (Hayman and Fernandez, 2018).

Network biology for attention-deficit hyperactivity disorder symptom analysis
Using the network modelling approaches symptoms can be viewed as networks that reveal the complex relationship between the symptoms. The relationship between 18 symptoms in the Diagnostic Statistical Manual (DSM-5) criteria was explored through network biology. The outcomes of the ADHD symptom network were predicted using centrality, node strength and clustering coefficient.

Symptom networks indicated that symptoms are clearly split into two domains: inattentive and hyperactive/impulsive. Visual examination revealed that hyperactive/impulsive symptoms are tightly grouped, whereas inattentive symptoms are scattered. This trend was more distinct at the level of p 0.05.

Centrality was used to calculate the relatedness of individual symptoms, with higher values suggesting greater relative relevance of symptoms in the network. The symptom 'loses things' from the inattentive domain had the highest betweenness centrality, followed by symptoms 'interrupts', 'motor driven' and 'leaves seats' from the hyperactive domain. The study highlighted the importance of hyperactive symptoms in ADHD patients. Further analysis of the ADHD symptom network could reveal symptoms of clinical importance (Silk *et al.*, 2019).

Identification of brain subnetworks related to attention-deficit hyperactivity disorder
The identification of subnetworks related to ADHD was based on the clustering of regions of interest (ROIs) of the brain. The clustering was done using a spectral clustering algorithm. Four

TABLE 4

List of identified drug targets in attention-deficit hyperactivity disorder (ADHD) using the network pharmacology approach

Drug-target	Description	References
DRD2	Dopamine receptor D2, also known as D2R, is a protein that is encoded by the DRD2 gene in humans. G-protein coupled D2R inhibits adenylyl cyclase activity and mediates cognitive flexibility in humans.	Song et al. (2022), Armstrong and Strange (2001)
CHRNA3	It encodes a member of the nicotinic acetylcholine receptor family of proteins. The encoded proteins are ligand-gated ion channels that play a role in neurotransmission that is particularly crucial for normal cognitive function, including functions of the prefrontal cortex that are disrupted in ADHD.	Song et al. (2022), Wilens and Decker (2007)
TNF	Tumor necrosis factor (TNF) is a multifunctional proinflammatory cytokine that belongs to the TNF superfamily. It is used by the immune system for cell signaling. Assay for TNF showed lower levels of TNF in subjects with ADHD, suggesting its role in the etiology of ADHD.	Song et al. (2022), Misiak et al. (2022)
IL6	Interleukin-6 (IL-6) is a proinflammatory cytokine and an anti-inflammatory myokine. Studies report higher unstimulated levels of peripherally measured IL-6 in subjects with ADHD suggesting that peripheral inflammation may be connected to the neurofunctional changes seen in ADHD, which include decreased dopamine levels and compromised noradrenergic neurotransmission.	Song et al. (2022), Misiak et al. (2022), Elsadek et al. (2020)
KCNJ3	KCNJ3 encodes for G protein-activated inward rectifier potassium channel 1 (GIRK-1) that has a predominant function in regulating neuronal excitability and synaptic transmission. Inhibition of GIRK channels may also contribute to the improvement of anxiety symptoms and thus can also be targeted for the treatment of ADHD, as anxiety disorder is the most common comorbidity of ADHD.	Song et al. (2022), Kobayashi et al. (2010)
SLC6A4	The SLC6A4 gene encodes for serotonin transporter, also known as sodium-dependent serotonin transporter. It stops serotonin activity by transporting serotonin back into the brain cells that release it. Various SLC6A4 variants are linked to ADHD.	Srivastava et al. (2019), Sonuga-Barke et al. (2011)
DRD4	DRD4 encodes for the G-protein-coupled D4 subtype of dopamine receptor, which inhibits adenylyl cyclase. Several behavioural abnormalities, including ADHD, are associated with mutations in this gene.	Song et al. (2022), Verma et al. (2020), Tovo-Rodrigues et al. (2013)

clusters were identified, showing that the average functional brain network comprises four sub-networks. The sub-network related to ADHD was identified by calculating betweenness centrality, shortest path, clustering coefficient and the proposed graph entropy for each cluster of the control group and ADHD group. The only statistically significant correlation between children with ADHD and controls was the entropy in cluster 2.

The brain regions included in cluster 2 were composed of the bilateral pre- and post-central cortex, superior temporal gyrus, and inferior frontal gyri. This cluster presents statistically higher entropy for children with ADHD than for control (p-value = 0.002). The data showed significantly higher uncertainty or randomness in the sub-network structure of cluster 2 in children with ADHD than in the control (Lola et al., 2019).

Identification of drug-targets for attention-deficit hyperactivity disorder

Network-based pharmacology (Li, 2021) approaches were used for the identification of novel drug-targets for the prophylactic and therapeutic treatment of ADHD. Table 4 lists some drug-targets that can be targeted for effective prophylactic and therapeutic treatment of ADHD.

Autism spectrum disorder

ASD is a heterogeneous group of disorders caused by abnormal brain development and neural reorganisation at a young age and is characterised by core abnormalities in two areas—social communication and restricted, repetitive sensory–motor behaviours (Lord et al., 2018). One in 100 children across the world is diagnosed with ASD, with the average affected male-to-female ratio being 4.2 (Zeidan et al., 2022). The heritability index of ASD was calculated to be 0.50 and the shared familial environmental influence was 0.04 (Sandin et al., 2017). Linkage and association studies were used to identify various susceptible loci (2q24–2q31, 7q, 17q11–17q21) and candidate genes (NRXN1, NLGN3, NLGN4, SHANK3, and CNTNAP2) that support the heterogeneity of ASD (Kumar and Christian, 2009). The only two FDA-approved drugs for use in children and adolescents with ASD include risperidone and aripiprazole (Goel et al., 2018).

Identification of novel genes related to autism spectrum disorder

Autistic-related neurological illnesses were identified, and a gene network for each member of the autism sibling group was created to detect genetic overlap between them.

<div align="center">

TABLE 5

List of identified drug targets in autism spectrum disorder (ASD) using network pharmacology approach

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Drug-target	Description	References
SLC6A4	The *SLC6A4* gene encodes for serotonin transporter, also known as sodium-dependent serotonin transporter associated with serotonin dysregulation, which has been related to ASD at the epigenetic, genetic, and physiological levels. Studies suggest that variation in the SLC6A4 gene is linked to ASD.	Srivastava *et al.* (2019), Wongpaiboonwattana *et al.* (2020)
$5HT_{1D}$	$5HT_{1D}$ encodes for 5-HTR$_{1D}$, i.e., 5-hydroxytryptamine (serotonin) receptor 1D. It also induces vasoconstriction, which is dysregulated (over-represented) in ASD.	Koch and Demontis (2022), Owens (2021)
MAPK3	Copy number variations impacting a variety of chromosomal areas have been associated with the development of schizophrenia and autism. One of these regions is 16p11.2, which has about 25 genes in it, including mitogen-activated protein kinase 3 (*MAPK3*), a critical component of the MAPK/ERK kinase cascade.	Linlin *et al.* (2022), Gai *et al.*, (2022)
IL-6	Interleukin-6 (IL-6) is a pro-inflammatory cytokine and an anti-inflammatory myokine. Studies suggest that abnormal levels of cytokines can potentially be used as a biomarker for the treatment of ASD. Serum levels of IL-6 was elevated in subjects with ASD.	Linlin *et al.* (2022), Chen *et al.* (2022), Zhao *et al.* (2021)
MAPK1	*MAPK1* encodes for a member of the MAP kinase family involved in the MAPK pathway that is involved in synaptogenesis. Alteration in the MAPK pathway may contribute to ASD.	Linlin *et al.* (2022), Chen *et al.* (2022), Rosina *et al.* (2019)
TNF	Tumor necrosis factor (TNF) is a pro-inflammatory cytokine. Results point to a potential role of increased proinflammatory cytokine production in the pathophysiology of autism.	Linlin *et al.* (2022), Kalkan *et al.* (2016)
AKT1	*AKT1* encodes for AKT1 kinase. Signaling involving AKT1 kinase is essential for the normal development and functioning of the brain. Certain experiments suggest that AKT inhibitor rescue social deficits and thus can be used for the treatment of ASD.	Gai *et al.* (2022), Verma *et al.* (2020), Xing *et al.* (2019)
ACTB	*ACTB* encodes for an actin protein. These proteins control dendritic spine shape and density, features often altered in ASD. Recent studies unveiled that ASD-related behavior can be rescued either by manipulating certain actin regulators and thus, these can be targeted for developing new ASD treatments.	Gai *et al.* (2022), Hlushchenko *et al.* (2018)
DRD2	Certain specific SNPs in *DRD2* increase the risk of ASD. These single nucleotide polymorphisms can be therapeutically targeted for alleviating the symptoms and complications of ASD.	Koch and Demontis (2022)
GRIA2	The glutamate receptor produced by this gene serves as a ligand-gated ion channel in the brain and is crucial for excitatory synaptic transmission. ASD proband was found to have de-novo nonsense mutations in the *GRIA2* gene.	Koch and Demontis (2022)
SCN2A	Autism is linked to loss-of-function mutations in the *SCN2A* gene. *SCN2A* mutations linked to ASD damage the encoded protein NaV1.2, a sodium channel crucial for action potential initiation and propagation in growing excitatory cortical neurons.	Koch and Demontis (2022), Kruth *et al.* (2020)

According to the findings, more than half of the known autism genes have also been related to other neurological illnesses. These results indicate the existence of molecular overlap and suggest that these conditions may share molecular mechanisms with autism, which may provide insight into understanding the hereditary basis of this complicated disorder.

A network-based approach was applied for the identification of disease-causing genes. A PPI network was generated that included proteins in the list of sibling autism disorders but not in the autism candidate list. A total of 334 novel genes that interact with autism genes were discovered. Using the same microarray data as the healthy controls, 87% of them were discovered to be significantly differentially expressed in autistic people (Parikshak *et al.*, 2015).

Identification of drug-target for autism spectrum disorder
Network-based pharmacology (Li, 2021) approaches were used for the identification of novel drug-targets for the treatment of ASD. Table 5 below enlists some drugs that can be targeted for effective prophylactic and therapeutic treatment of ASD.

Epilepsy
Epilepsy is a brain illness characterised by an enduring (i.e., persistent) proclivity to have seizures that are not triggered by any immediate central nervous system damage, as well as the neurobiological, cognitive, psychosocial, and social repercussions of seizure recurrences (Beghi, 2020).

Epilepsy is one of the most common neurological illnesses. It affects 50 million individuals globally at any given moment, according to the World Health Organisation,

TABLE 6

List of identified drug targets in epilepsy using network pharmacology approach

Drug-target	Description	References
ADK	Adenosine kinase is an important enzyme produced by the inhibitory neuromodulator adenosine. Adenosine deficiency results in prolonged or recurrent seizures. Initially, adenosine levels increased as a protective mechanism, but low levels of adenosine resulted in the overexpression of adenosine kinase and astrocyte proliferation or astrogliosis, which eventually resulted in seizures.	Boison (2008)
TrKb	Seizures increase the expression of brain-derived neurotrophic factor (BDNF) and activation of tropomyosin receptor kinase B (TrkB) in the mossy fiber pathway of the hippocampus. Binding of BDNF to TrkB results in the dimerisation of receptors, followed by the activation of tyrosine kinase activity and phosphorylation of specific tyrosines. Transgenic BDNF or TrkB overexpression increases the susceptibility or severity of epilepsy.	McNamara and Scharfman (2012)
mTOR	The mammalian target of rapamycin (mTOR) signaling pathway is involved in epileptogenesis; whenever seizures occur in the body, the mTOR pathway is activated, followed by an increase in phospho-S6 expression, which acts as a biomarker in epilepsy.	Zeng et al. (2009)
TNFα	Tumour necrosis factor alpha (TNFα) is a cytokine regulator. TNFα, which is secreted by microglia, has the ability to activate astrocytes. TNFα has the ability to regulate neuron activity and induce epilepsy by increasing glutamate release, decreasing -aminobutyric acid expression, inducing neuroinflammation, and influencing synaptic function in astrocytes.	Chen et al. (2021)
REST	Repressor element 1-silencing transcription (REST) protects against seizures by downregulating BDNF and its receptor, TrkB. In epilepsy patients, however, REST increases to a greater extent, allowing downregulation of the glutamate receptor subunit GluR2. As a result of which, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors lacking GluR2 subunits cause an increase in Ca^{2+} permeability, which eventually leads to excitotoxicity, cell death and seizures.	Butler-Ryan and Wood (2021)
JAK-STAT	Many immune and inflammatory diseases are linked to the Janus kinase-signal transducer and transcriptional activator (JAK-STAT) signaling pathway. Inflammatory cytokines, growth factors, or other chemical messengers frequently activate the receptors, which then recruit and activate JAK to initiate the signal transduction cascade. It can phosphorylate STAT once activated. Increasingly, studies have discovered that the JAK-STAT pathway is involved in the development of epilepsy. Although the JAK/STAT signaling pathway was previously thought to be involved in immune system regulation, it was discovered to be upregulated in the hippocampus, which could result in the development of epilepsy.	Sun et al. (2022)
PGE2	In models of chronic inflammation and neurodegeneration, activation of EP2 receptors can also promote oxidative damage and neurotoxicity, as well as the induction of a slew of proinflammatory mediators, most notably in activated microglia.	Emma and Soldner (2019)

and 2% of the current world population has had epilepsy, has epilepsy currently, or will have epilepsy at some point in the future (Prinz, 2008).

Even though epilepsy refers to a group of disorders with a variety of causes and symptoms, all forms of epilepsy are characterised by recurrent seizures caused by abnormal electrical activity in the brain, most commonly in the form of synchronised discharges of nerve cells (neurons) that are not synchronously active during normal brain activity (Prinz, 2008).

Computer model for the understanding of epilepsy

In an ingenious sequence of experiments, Soltesz and colleagues merged the results of decades of study into a physiologically realistic, cellularly exact computer model of the dentate gyrus, a brain region implicated in temporal lobe epilepsy, the most common kind of epilepsy in adults. They demonstrated that the creation of a few numbers of highly linked "hub" neurons following brain injury is sufficient for the development of hyperexcitability and epilepsy using this computer model, which would be impossible to replicate in the brain (Morgan and Soltesz, 2008).

The neural network computer model developed by Soltesz (2008) is part of a new generation of large-scale, extremely detailed, and complex network models that attempt to rebuild entire brains or portions of brains in the computer. Models like this are starting to reveal new information regarding the significance of cellular and synaptic characteristics, as well as network topology, in influencing network activity in both healthy and diseased or disordered brains. Morgan and Soltesz's network model (2008) is made up of 50,000 individual model neurons from a number of morphological and electrically diverse categories discovered in the dentate gyrus, and it preserves the empirically documented relative abundance ratios of those cell types.

Each model neuron is a complex, geographically extended model with anatomical, cellular, and electrical

TABLE 7

List of intellectual disability (ID)- and autism spectrum disorder (ASD)-associated genes

Biological function	Genes
Presynaptic vesicle cycling and transport	*GDI, CASK, AP-4, AP4BP1, AP4E1, AP4S1, AP4M1, IL1RAPL1, OPHN1, RAB39B.*
Cytoskeleton dynamics	*ARHGEF6, ARHGEF9, FGD1, IQSEC2, LIMK1, OPHN1, OCRL1, MEGAP, PAK3.*
Cell-adhesion and trans-synaptic signalling	*CASK, CDH15, CNTN4, KIRREL3, NLGN3, NLGN4X, NRXN1, PTCHD1, PCDH9, SHANK3.*
Translational regulation, protein degradation and turnover	*CUL4B, FBOX40, MEF2, UBR1, UBE2A, UBE3A, UPF3A, SMG6, EIF4A3, RNPS1.*

qualities tuned to reflect all available information from decades of research on the dentate gyrus and adjacent brain areas (Morgan and Soltesz, 2008).

Dentate gyrus simulations BY Morgan and Soltesz's (2008) stand out as an example of well-executed modelling work. First, they made a clear observation: head injury causes two distinct alterations in the dentate gyrus, which are known to raise the risk of temporal lobe epilepsy. Two examples include the loss of mossy cells and the formation of new excitatory connections (mossy fibres) between granule cells. The healthy dentate gyrus does not have such excitatory recurrent connections between granule cells. Both of these effects of head trauma have been seen in the brains of epilepsy patients, making them potential candidates for a relationship between brain injury and epilepsy development. Second, the authors used their dentate gyrus model to test the effects of mossy cell loss and other topologically distinct types of mossy fibre sprouting on network excitability. Third, they arrived at the realistic and physiologically relevant conclusion that the formation of a few highly connected granule cell hubs is necessary and sufficient for the seizure-causing network hyperexcitability found in epileptic brains.

Identification of drug-targets for epilepsy
Network-based pharmacology (Li, 2021) approaches were used for the identification of novel drug-targets for treatment of epilepsy. Table 6 enlists some drug-targets that can be targeted for effective prophylactic and therapeutic treatment of epilepsy.

Intellectual disability
Neurodevelopmental abnormalities in individuals with intellectual disabilities are characterized by limitations in intellectual functioning and adaptive behaviour. These difficulties are frequently connected to mental health concerns (such as depression and anxiety), as well as neurodevelopmental diseases (such as autism spectrum disorders and attention deficit hyperactivity disorders).

Relationship between intellectual disability and autism spectrum disorder
Munson (Munson et al., 2008) found that there were various IQ-based subgroups of children with autism, each with different cognitive strengths and weaknesses, as well as the

severity of autistic symptoms, after studying 456 children with autism. Finally, Deb and Prasad (1994) discovered that in people with autism and ID, impaired verbal and nonverbal communication, as well as the incidence of repetitive and restricted activities, were more common than people with only autism. When people with autism, whether they have ID or not, are compared to people without ID, the disparities are considerably more obvious.

Jackson et al. (2003) discovered that children with autism responded to verbal solicitations with less positive responses and more no responses in social interactions. Mandelbaum (2006) compared 242 children aged 7–9 years who were classified into one of four groups, including high IQ and autism; developmental language disorder produced similar patterns of performance, while low IQ and autism or low IQ produced similar patterns of performance but differed from the two previous groups. Sensory motor skills, oromotor skills, praxis, and ability/willingness to do activities were all improved in the two previous groups.

Genes linked to intellectual disability and autism spectrum disorder
Understanding the cellular and molecular mechanisms underlying the pathophysiology of ID and ASD-associated genes, as well as assessing the potential pathogenicity of new candidate genes for ID and ASD, functional categorization of proteins encoded by a majority of these genes and elucidation of common pathways, has become critical for understanding the cellular and molecular mechanisms underlying pathophysiology of these genes, and also for assessing the potential pathogenicity of new candidate genes for ID and ASD. As a result of this functional categorization, a variety of cellular functions regulating neuronal structure and function have emerged, which are influenced by abnormalities in the ID and ASD genes as described in Table 7 (Anand and Srivastava, 2014).

Identification of drug-targets for intellectual disability
Network-based pharmacology approaches (Li, 2021) were used for the identification of novel drug-targets for the treatment of ID. Table 8 below enlists some drug-targets that can be targeted for the effective prophylactic and therapeutic treatment of ID.

TABLE 8

List of identified drug targets in intellectual disability (ID) using network pharmacology approach

Drug-target	Description	References
IL1RAPL1	Partial deletions in the *IL1RAPL1* gene cause fragile X syndrome, an X-linked intellectual disability. The *IL1RAPL1* gene is expressed in the hippocampus, implying that it is involved in memory and learning abilities.	Montani *et al.* (2017)
ATRX	The Alpha-thalassemia x-linked intellectual disability (*ATRX*) gene contributes to normal developmental processes. Mutations in these genes cause the α-thalassemia mental retardation syndrome. This syndrome is characterized by intellectual disability, microcephaly (smaller head size due to abnormal brain development) and seizures. Hippocampal-dependent spatial learning and memory are impaired by *ATRX* mutations. Studies can be conducted on *ATRX* gene mutations to develop new therapeutics.	Iwase *et al.* (2017)
IL-6	Interleukin-6 (IL-6) has been shown to affect synaptic plasticity by decreasing LTP, followed by a decline in memory tasks. An increased level of IL-6 is often observed in the brains of autistic people. According to recent research, mice with elevated IL-6 levels demonstrated decreased social interaction and impaired cognition. The mice had decreased inhibitory synaptic formation, which resulted in abnormal changes in the shape, length, and distribution pattern of dendritic spines, indicating a role for this cytokine in the mechanisms underlying autistic-like behaviors.	di Marco *et al.*, (2016)

Use of Deep Learning in Network Biology and Target Identification

As all biological networks can efficiently maintain and quantify the interaction between components of cell systems underlying human diseases, artificial intelligence is a cutting-edge tool to identify novel disease targets and discover novel therapeutics. A number of alternative network techniques are offered to find disease targets, by network-based deep learning network biology analysis algorithms. More crucially, a variety of network-based biology analysis algorithms may investigate the network data from diverse perspectives and, as a result, can offer precise biological explanations (You *et al.*, 2022). Biological networks may encapsulate the characteristics of biological entities and their relationships, making them effective at integrating complex biological data. A network can be conceptualised mathematically as a graph using the formula G = (V, E), where V and E are sets of nodes (vertices) and edges, respectively. Proteins, genes, illnesses, and medications are instances of nodes in biological networks. The edges of the network indicate various biochemical, physical or functional relationships between nodes. To identify therapeutic targets and find new medications, network-based biology analytic algorithms focus on studying molecular networks such as PPI networks, gene regulatory networks, metabolic networks, and drug-drug interaction networks (You *et al.*, 2022).

The goal of graph embedding techniques is to develop a low-dimensional vector representation of a graph or of its constituent parts, such as its nodes. Often, this embedding is subsequently repurposed for tasks like link prediction or node classification. A graph domain equivalent to the image convolution in a convolutional neural network is provided by GCN approaches, which specify and employ a spectral- or spatial-based convolution over the graph.

It is crucial to correctly identify interactions of a target with different compounds to describe their binding affinity, or drug-target interactions (DTIs), after the discovery of a therapeutically useful target, such as a protein. This testing procedure produces a list of prospective drug candidates with strong binding affinities to the target, which is commonly known as a screening. Conducting manual screening on thousands of compounds in order to locate a single medicine is costly and time-consuming, as was already explained. Using DDI networks frequently, deep learning techniques attempt to get over this limitation. As a result, the graph deep learning framework often summarises the prediction of drug-target interactions as a link prediction problem. The drug-target prediction problem has been successfully handled by graph-based deep learning methods.

The molecular structure of drugs and targets is considered and examined in a different group of methodologies that define the DTI. In the GCN approach to the DTI prediction problem, the input consists of two graphs: a protein pocket graph and a 2-dimensional (2D) drug molecular graph.

This approach consists of two steps: (i) an initial unsupervised phase that includes an auto-encoder for learning common pocket features and (ii) a supervised graph convolutional binding classifier. The latter is made up of two GCN models that operate simultaneously in a drug GCN and a pocket GCN, which each extract characteristics from a protein pocket graph and a 2D molecule graph. A layer is in charge of combining protein interactions to create a joint drug-target imprint, which is subsequently divided into "binding" and "non-binding" groups (Muzio *et al.*, 2021).

Conclusion

Target-based drug discovery has proven to be extremely effective. The method is not restricted to small-molecule drug discovery. Target-based approaches are commonly used to discover antibody drugs and other protein biologics.

Target-based approaches have the advantage of being easier to execute because they are utilized based on the molecular mechanisms of a drug from an earlier stage, and they are generally faster, easier, and less expensive to develop and run (Croston, 2017).

Optimizing compounds in the absence of a known molecular target, as with a phenotypic strategy, can be difficult. Human genetics is one of the most powerful tools for identifying drug targets. When a human gene is linked to a disease, it is clear that a drug targeting that gene or gene product has a good chance of success.

Although network biology has advanced to new heights, a few limitations still remain. Real-world biological systems are far more complex, with interactions occurring at multiple scales, including gene, RNA, protein, and metabolic levels. The majority of studies tend to focus only on specific levels of interactions among the same type of biomolecules. With the advancement of high-throughput technologies and the accumulation of various omics data, performing network biology analysis by integrating multi-omics data would be intriguing. Most biological networks are static, whereas Real-world biological networks change their structures dynamically over time. Furthermore, some genes may only be expressed in certain tissues and at certain times; biological networks have temporal, dynamic and modular properties. In fact, multilayer biological networks have received a lot of attention in recent years. Multilayer biological network datasets, on the other hand, are not made public. It is possible to develop efficient data-driven frameworks to construct multilayer biological networks with the accumulation of various omics data and the development of network inference techniques Network biology applications require the collaboration of scientists from different fields. Network biology provides effective tools for investigating bioinformatics, and both biologists and medical workers are required to apply the theoretical results (Wang, 2022).

Many fundamental and translational neuroscience investigations continue to focus on candidate genes and candidate theories; thus, skeptics may question the relevance of monitoring whole systems. Biological complexity, on the other hand, must not be overlooked; genome-wide measures, in conjunction with specific gene and pathway research, are essential to uncover the underlying causes of neurodevelopmental and neurodegenerative diseases. Biologists can use well-designed, repeatable molecular profiling studies to test theories and concurrently generate new ones. Gene networks provide an organising structure that facilitates the process of hypothesis creation and testing, despite their vastness and seeming complexity. The overarching concept of using correlational and physical interaction molecular networks in neurobiology to explain molecular system changes may be expanded to a number of methodologies, allowing for examining connections at different levels of inquiry.

The findings of high-quality genome-wide studies will be critical in developing and testing theories that go beyond our current understanding to generate a more comprehensive picture of the issues faced by neurodevelopmental and neurodegenerative illnesses, and potential solutions (Neelroop and Parikshak, 2015).

At this point, network neuroscience has the potential to provide inspiration and resources to the area of child and adolescent psychology, allowing it to make significant progress in understanding the neurobiology of mental disorders that impact children and adolescents. Collaborations among cognitive neuroscientists, clinical psychologists, engineers, and computer scientists will provide the skills needed to harness the power of big data sets to advance our understanding of typical and atypical brain network development (Uddin and Karlsgodt, 2018).

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