

Review

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Review

Abnormalities in Cytoskeleton and Molecular Motors in Psychiatric Disorders: Focus on Schizophrenia and Autism Spectrum Disorder

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Abstract

Elucidating the pathophysiological mechanisms of mental disorders remains a critical challenge in psychiatric research. Recent studies have highlighted the potential involvement of cytoskeletal and molecular motor abnormalities in the development of mental disorders such as schizophrenia and autism spectrum disorder (ASD). This review synthesizes the latest findings on the relationship between cytoskeletal and molecular motor abnormalities and mental disorders. The cytoskeleton, composed of microtubules, actin filaments, and intermediate filaments, along with molecular motors such as kinesins, dyneins, and myosins, plays crucial roles in neurodevelopment, synapse formation, and neurotransmission. In schizophrenia, decreased expression of the microtubule-associated protein *MAP2* and abnormalities in the *DISC1* gene have been reported, potentially leading to dendritic morphological abnormalities and neurodevelopmental disorders. Additionally, abnormalities in molecular motors such as *KIF17* and *KIF1A* have been implicated in synaptic plasticity disturbances. In ASD, *Myosin Id* has been identified as a risk gene, with its localization in dendritic spines recently elucidated. Furthermore, abnormalities in actin-related proteins such as *SHANK3* and *CYFIP1* have been shown to cause synaptic dysfunction. These findings suggest that mental disorders arise from complex pathologies involving multiple cytoskeletal and molecular motor-related protein abnormalities. Future research should focus on elucidating the functions of individual proteins and adopting a comprehensive approach that includes glial cells. Advances in this field may deepen our understanding of the pathophysiological mechanisms of mental disorders and potentially lead to the development of novel therapeutic strategies.

Keywords: cytoskeleton; molecular motors; schizophrenia; autism spectrum disorder; microglia

1. Introduction

Neurons possess a highly organized cytoskeletal system that enables them to maintain their unique morphology and specialized functions. This cytoskeletal network, composed primarily of microtubules, actin filaments, and intermediate filaments, plays essential roles in numerous cellular

processes, including neuronal development, polarity establishment, axonal and dendritic outgrowth, and synapse formation (1). In addition, molecular motors—particularly members of the kinesin superfamily (KIFs)—travel along these cytoskeletal tracks to transport various intracellular cargos, thereby contributing critically to the maintenance of neuronal function (2,3).

Recent research has revealed that abnormalities in cytoskeletal structures and molecular motor proteins are deeply implicated in the pathophysiology of several psychiatric disorders, most notably schizophrenia and autism spectrum disorder (ASD) (4,5). In this review, we summarize the fundamental functions of the cytoskeleton and molecular motors, and we discuss how disruptions in these systems contribute to psychiatric disease mechanisms, with a particular focus on schizophrenia and ASD.

2. Schizophrenia and ASD: Shared Features and Key Differences

Both schizophrenia and autism spectrum disorder (ASD) are characterized by difficulties in social interaction; however, their developmental trajectories differ markedly. Individuals with ASD typically exhibit delays in the acquisition of social skills from early childhood, whereas those with schizophrenia often show relatively typical social functioning prior to disease onset, with social deficits emerging as symptoms progress. Sensory processing abnormalities are observed in both conditions, but they present differently: ASD is typified by consistent hypersensitivity or hyposensitivity to specific stimuli, while schizophrenia is characterized primarily by perceptual distortions associated with hallucinations and delusions, which can fluctuate depending on symptom severity.

Cognitively, ASD is often associated with a detail-focused processing style and difficulty integrating information into a global context. In contrast, schizophrenia is notable for disorganized thinking, impaired attention, and variability in cognitive performance corresponding to symptom fluctuations. Although genetic factors contribute to both disorders, ASD generally demonstrates a stronger inherited component.

The age of onset and clinical course also differ. ASD symptoms manifest in early childhood and persist throughout life, whereas schizophrenia typically develops in late adolescence or early adulthood and follows a pattern of alternating acute episodes and periods of remission. Behavioral characteristics diverge as well: individuals with ASD frequently show strong adherence to routines or circumscribed interests, whereas repetitive behaviors in schizophrenia often arise from delusional beliefs or hallucinatory experiences.

Treatment approaches differ substantially between the two disorders. ASD management relies primarily on behavioral interventions and social skills training, while schizophrenia is mainly treated with antipsychotic medications. Language and communication patterns also vary, with ASD often involving delayed or atypical language development, whereas schizophrenia is characterized by disturbances in language driven by thought disorder. It is important to recognize that both ASD and schizophrenia exhibit substantial heterogeneity, and symptom presentation varies widely among individuals.

3. Pathophysiology of Schizophrenia and ASD

Schizophrenia and autism spectrum disorder (ASD) share several neurobiological features, although their clinical presentations differ considerably. Both disorders are increasingly understood as complex neurodevelopmental conditions that impact brain structure and function across multiple levels. Abnormalities in neurotransmitter systems are observed in both schizophrenia and ASD. Dysregulation of the dopaminergic and glutamatergic pathways has been particularly well documented. While the dopamine hypothesis has long been central to schizophrenia research, alterations in dopaminergic function have also been reported in ASD. Similarly, disruptions in glutamatergic signaling have been implicated in both conditions, potentially affecting synapse formation and neuronal plasticity (6).

Structural brain abnormalities are another point of convergence. Changes in gray and white matter volumes have been reported in regions such as the prefrontal cortex, temporal lobe, and amygdala, areas that are critical for social cognition and emotional processing. Functional neuroimaging studies have revealed disorder-specific patterns of functional connectivity during both resting-state and task performance. Notably, abnormalities in the default mode network—which is involved in self-referential processing and aspects of social cognition—have been identified in both schizophrenia and ASD (7).

Genetically, both disorders are highly polygenic, involving numerous susceptibility genes related to neurodevelopment, synaptogenesis, and neurotransmission. Variants in genes such as SHANK3 and NRXN1 have been implicated as risk factors for both ASD and schizophrenia (5). Additionally, growing evidence suggests an important role for immune dysregulation and inflammation. Maternal immune activation has been shown to influence fetal brain development and increase the risk for later neuropsychiatric disorders (8). Markers of neuroinflammation, including microglial activation and altered cytokine levels, have been reported in both ASD and schizophrenia (9).

Despite these shared biological features, the two disorders also exhibit distinct clinical trajectories, symptom profiles, and treatment responses, indicating the presence of disorder-specific pathophysiological mechanisms. Moreover, given the substantial heterogeneity within each disorder, generalization must be made with caution. Continued research is expected to refine our understanding of the commonalities and differences in the neural underpinnings of schizophrenia and ASD.

4. Roles of the Cytoskeleton in the Nervous System

The neuronal cytoskeleton—particularly the microtubule network—plays roles far beyond simple structural support. It also serves as a fundamental “track system” for intracellular transport mediated by molecular motors. Studies by Hirokawa and colleagues have demonstrated that a wide variety of vesicles and organelles are transported along microtubules within neurons (10).

Microtubules are hollow cylindrical polymers composed of α - and β -tubulin heterodimers. In neurons, they play essential roles in axonal and dendritic extension and maintenance, intracellular cargo trafficking, the transport of synaptic vesicles containing neurotransmitters, and chromosome segregation during cell division (11–13). Notably, the dynamic instability of microtubules—the continuous cycles of polymerization and depolymerization—has been shown to be crucial for neuronal plasticity (14).

Actin filaments are double-helical polymers formed by the assembly of globular actin (G-actin). In neurons, they contribute to several key processes, including the formation of growth cones and axon guidance, dendritic spine formation and structural plasticity, maintenance of presynaptic terminals, and regulation of local protein synthesis (15,16). Dynamic remodeling of the actin cytoskeleton is known to play a central role in synaptic plasticity and memory formation (17).

Intermediate filaments comprise various filamentous proteins that provide structural integrity. In neurons, major intermediate filament proteins include nestin, vimentin, and neurofilaments (18). They are involved in maintaining cellular structural stability, regulating axonal diameter, and controlling neuronal differentiation and maturation (18,19).

Together, these cytoskeletal systems establish the structural foundation of neurons and orchestrate essential processes underlying neurodevelopment, connectivity, and plasticity. Consequently, disturbances in cytoskeletal organization can profoundly affect neuronal function and contribute to neuropsychiatric disease mechanisms.

5. Roles of Molecular Motors in Neurons

Molecular motors are protein complexes that utilize the energy derived from ATP hydrolysis to transport cargos along cytoskeletal filaments. In neurons, three major classes of molecular motors—

kinesins, dyneins, and myosins—play indispensable roles in maintaining cellular function and supporting neurodevelopment.

The kinesin superfamily proteins (KIFs) mediate predominantly anterograde transport toward the plus-end of microtubules, delivering cargos from the soma to distal axons and dendrites (20). Comprehensive studies by Hirokawa and colleagues have identified 45 KIF genes in humans and mice, each responsible for transporting distinct sets of cargos (11). Key functions of neuronal KIFs include the anterograde transport of synaptic vesicles, neurotransmitter receptors, mitochondria, and mRNA-containing granules, as well as the delivery of neurotrophic factors (21–23). Among them, KIF1A, KIF5, and KIF17 have been shown to be particularly important for neuronal function (10).

Dynein, in contrast, mediates retrograde transport toward the minus-end of microtubules, moving cargos from axonal terminals back toward the cell body (24). Its major roles include the retrograde trafficking of synaptic vesicles, neurotransmitter receptors, and various organelles; the transport of neurotrophic factor signaling endosomes; and the redistribution of cellular components during axon regeneration (25–28).

Myosins function primarily along actin filaments (29). Numerous myosin family members are expressed in neurons, where they regulate the transport of diverse cargos and modulate actin architecture to influence synaptic activity. Myosins contribute to dendritic spine morphogenesis, local mobility of synaptic vesicles, growth cone motility, and the regulation of synaptic plasticity (30–33). Myosin II, V, and VI in particular have been demonstrated to play essential roles in neuronal physiology.

Together, these molecular motor systems coordinate the highly dynamic intracellular transport processes required for neuronal development, synaptic function, and circuit maintenance. Dysfunction in any of these motor proteins can profoundly disrupt neuronal connectivity and is increasingly recognized as a key contributor to neurodevelopmental and psychiatric disorders.

6. Cytoskeletal and Molecular Motor Abnormalities in Schizophrenia

Schizophrenia is a psychiatric disorder characterized by hallucinations, delusions, cognitive impairments, and disturbances in emotion and behavior. Accumulating evidence indicates that abnormalities in cytoskeletal components and molecular motor proteins are present in the brains of individuals with schizophrenia and are closely linked to disease pathophysiology.

Among microtubule-related abnormalities, reduced expression of the microtubule-associated protein MAP2 has been reported in the prefrontal cortex and hippocampus of patients with schizophrenia (34,35). Because MAP2 plays a critical role in the formation and maintenance of dendrites, decreased expression is thought to contribute to dendritic morphological abnormalities and impaired dendritic function. In addition, DISC1 (Disrupted in Schizophrenia 1), a susceptibility gene for schizophrenia, regulates microtubule stabilization and intracellular transport. Dysfunction of DISC1 is believed to impair neurodevelopment and synaptic plasticity (36,37).

Abnormalities in actin-related proteins have also been identified in schizophrenia. Postmortem studies have reported altered expression of components of the WAVE complex—such as CYFIP1, NCKAP1, and WASF1 (38)—which regulates actin polymerization and contributes to dendritic spine formation. Disruption of this complex is expected to lead to synaptic dysfunction (39). Increased expression of calponin-3, an actin-binding protein, has also been observed in the prefrontal cortex of patients (40). Elevated levels of calponin-3 may contribute to aberrant stabilization of the actin cytoskeleton (41).

Regarding intermediate filaments, increased expression of GFAP (glial fibrillary acidic protein) has been detected in the prefrontal cortex and hippocampus of individuals with schizophrenia (42). As a major intermediate filament protein in astrocytes, elevated GFAP expression likely reflects neuroinflammatory or neuroprotective responses (43).

Several abnormalities in molecular motor proteins have also been implicated in schizophrenia. Reduced levels of KIF17 have been reported in postmortem brain tissue (44). KIF17 is responsible for transporting the NMDA receptor subunit NR2B, and its dysfunction is believed to impair synaptic

plasticity (45). Specific single nucleotide polymorphisms (SNPs) in the KIF1A gene have been identified as risk factors for schizophrenia (46). Because KIF1A mediates the transport of synaptic vesicle precursors, its dysfunction may reduce synaptic transmission efficiency (47). Recently, mutations in KIF3B have been shown to induce schizophrenia-like phenotypes in mice by impairing NR2A trafficking and disrupting NMDA receptor signaling (48). These findings support the hypothesis that NMDA receptor hypofunction contributes to schizophrenia pathophysiology.

Dynein-related abnormalities include rare variants in the DYNC1H1 (Dynein Cytoplasmic 1 Heavy Chain 1) gene identified in individuals with schizophrenia (49). Because DYNC1H1 is a major component of the dynein complex, its dysfunction is expected to impair retrograde axonal transport (50). Variants in MYO16 (Myosin XVI), a myosin family protein involved in neuronal migration and dendrite formation, have also been reported in schizophrenia (51). Disruption of MYO16 function may impair neural circuit formation.

Collectively, these cytoskeletal and molecular motor abnormalities contribute to a range of pathological processes observed in schizophrenia, including impaired synapse formation and plasticity, abnormal receptor trafficking, disrupted neurodevelopment, dysfunctional neural circuits, and cognitive deficits. These findings underscore the crucial role of intracellular transport and cytoskeletal regulation in the neurobiology of schizophrenia.

7. Cytoskeletal and Molecular Motor Abnormalities in Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impairments in social communication and interaction, together with restricted, repetitive patterns of behavior and interests. In recent years, multiple abnormalities in cytoskeletal components and molecular motor proteins have been reported in the brains of individuals with ASD.

Myosin ID (MYO1D) has been identified as a risk gene for ASD (52). We previously showed that EGFP-tagged Myosin Id, when expressed in cultured neurons, accumulates in dendritic spines (53). Furthermore, this localization critically depends on the TH1 (tail homology 1) domain: deletion of the TH1 domain disrupts the targeting of MYO1D to dendrites and markedly reduces its accumulation in dendritic spines. These findings strongly suggest that MYO1D interacts with actin filaments within dendritic spines and contributes to the regulation of excitatory synaptic transmission, and that disruption of this function may underlie aspects of ASD pathophysiology. The TH1 domain of MYO1D has also been reported to interact with the C-terminus of aspartoacylase, an N-acetylaspartate (NAA)-acylating enzyme (54). NAA is present at high concentrations in the mammalian brain, and reduced NAA levels have been observed in children with ASD compared with typically developing controls (55). These observations further support a functional link between MYO1D and ASD.

Myosin IXb (MYO9B) is known to regulate RhoA activity and to control dendritic morphology in cortical neurons (56). Variants in MYO9B have been suggested to influence ASD risk (5). In addition, cohort studies have reported an association between Myosin XVI and ASD (57). Myosin XVI contributes to neuronal migration and dendritic development, and its dysfunction is thought to lead to defects in neural circuit formation.

Mutations in SHANK3 (SH3 and multiple ankyrin repeat domains 3) are recognized as one of the major genetic causes of ASD (58). SHANK3 plays a key role in organizing the actin cytoskeleton in the postsynaptic density; its disruption leads to defective dendritic spine formation and synaptic dysfunction (59). Duplications and deletions of CYFIP1 (Cytoplasmic FMR1-interacting protein 1) have also been identified as ASD risk factors (60). CYFIP1 is a component of the WAVE complex and regulates actin polymerization; its dysregulation is believed to cause dendritic spine abnormalities (61).

Rare variants in TUBG1 (γ -tubulin) have been reported in individuals with ASD (62). γ -Tubulin functions as a nucleation factor for microtubule assembly, and its disruption is expected to affect neuronal polarity and migration (63). Mutations in ASPM (abnormal spindle-like microcephaly-

associated protein) have likewise been implicated as risk factors for ASD (64). ASPM plays an important role in the division and differentiation of neural stem cells, and its dysfunction is thought to lead to abnormal cortical development (65).

Rare variants in KIF1A have been identified in patients with ASD (66). KIF1A is essential for the anterograde transport of synaptic vesicle precursors, and its dysfunction is predicted to reduce the efficiency of synaptic transmission (67). Mutations in KIF5C have also been associated with ASD. KIF5C contributes to neuronal polarity and axonal elongation, and its disruption likely impairs neural circuit formation (68).

Taken together, these cytoskeletal and molecular motor abnormalities appear to contribute to ASD pathophysiology through several interrelated mechanisms. First, disturbances in actin-regulating proteins such as SHANK3 and CYFIP1 result in defective dendritic spine formation and synaptic dysfunction, thereby disrupting the normal development and function of neural circuits. Second, abnormalities in kinesins such as KIF5C and dynein-related proteins like DYNC1H1 are expected to impair axonal transport and neuronal migration, leading to structural and functional abnormalities in neural networks. Third, defects in proteins such as MYO9B that regulate neuronal migration and axon guidance may interfere with the precise positioning of neurons and the accurate extension of axons, thereby contributing to macroscopic brain abnormalities. Fourth, dysfunction of ASPM is predicted to alter the division and differentiation of neural stem cells and to disrupt the proper formation of cortical lamination. Fifth, impaired synaptic vesicle transport caused by abnormalities in KIF1A and KIF5C may decrease the efficiency of neurotransmission and compromise information processing capacity.

These findings together suggest that ASD is not caused by a single molecular defect but rather arises from a complex interplay among multiple abnormalities in cytoskeletal and molecular motor-related proteins, which collectively perturb neurodevelopment, synaptic function, and network-level information processing.

8. Microglial Cytoskeleton, Molecular Motors, and Psychiatric Disorders

Recent studies suggest that abnormalities in cytoskeletal organization and molecular motor function in glial cells, in addition to neurons, may also contribute to the pathophysiology of psychiatric disorders. In particular, cytoskeletal remodeling during the activation of microglia—the resident immune cells of the central nervous system—has emerged as a critical factor in disease mechanisms.

Microglia become activated in response to inflammation or injury in the brain and undergo marked morphological changes. The studies by Rosito et al. (2023) and Adrian et al. (2023) provided a detailed description of the dramatic reorganization of the microtubule cytoskeleton that accompanies microglial activation (69,70). In the resting state, microglia exhibit an acentrosomal microtubule array that is distributed throughout the cell. Upon activation, however, microtubules are reorganized into a radial array emanating from the centrosome. This reorganization is associated with a morphological transition from a ramified shape to a more rounded, amoeboid (activated) morphology.

In activated microglia, microtubule polymerization is enhanced and microtubule stability is increased. These changes are regulated by activation of the microtubule-associated protein MAP4 and downregulation of Stathmin 1 (STMN1), a key microtubule-destabilizing protein. During activation, the centrosome also matures and accumulates microtubule-nucleating factors such as γ -tubulin, thereby establishing the centrosome as the principal microtubule-organizing center. At the same time, Golgi-derived, acentrosomal microtubule nucleation is reduced, a process controlled in part by decreased expression of Golgi-associated proteins such as AKAP9.

Cyclin-dependent kinase 1 (Cdk1) has been identified as an upstream regulator of this cytoskeletal remodeling during microglial activation. Activation of Cdk1 promotes microtubule stabilization through phosphorylation-dependent regulation of MAP4, enhances microtubule polymerization via phosphorylation and subsequent degradation of STMN1, and drives centrosome

maturation and its function as a microtubule-organizing center. Collectively, these changes are thought to facilitate efficient secretion of proinflammatory cytokines by activated microglia.

Microglial activation and the accompanying cytoskeletal remodeling are implicated in the pathophysiology of a range of neuropsychiatric and neurodegenerative disorders. In Alzheimer's disease, microglial activation in response to amyloid- β and pathological tau accumulation contributes to disease progression, and cytoskeletal remodeling may regulate phagocytosis of these abnormal proteins as well as the release of inflammatory mediators. In postmortem brains from individuals with schizophrenia and ASD, microglial activation has also been reported, raising the possibility that aberrant cytoskeletal reorganization in microglia influences synaptic pruning and the development and maintenance of neural circuits, thereby contributing to symptom expression.

Targeting microglial cytoskeletal remodeling represents a promising strategy for the development of novel treatments for psychiatric disorders. Adrian et al. (2023) demonstrated that pharmacological inhibition of Cdk1 suppresses microglial activation and reduces the secretion of inflammatory cytokines, suggesting potential therapeutic applications in conditions characterized by excessive neuroinflammation. In addition, drugs that modulate microtubule polymerization and stability may help regulate microglial activation and attenuate pathological neuroinflammation. Manipulating the balance between centrosomal and Golgi-derived microtubule organization could provide further means of controlling microglial morphology and function, thereby slowing or preventing disease progression.

9. Conclusions and Future Directions

Accumulating evidence indicates that abnormalities in cytoskeletal organization and molecular motor function—particularly within the kinesin (KIF) and myosin families—are deeply involved in the pathophysiology of psychiatric disorders such as schizophrenia and ASD. These abnormalities affect multiple aspects of brain function, including neurodevelopment, synapse formation, neurotransmission, and neuronal plasticity, and are thought to form part of the biological basis for the characteristic symptoms and cognitive impairments observed in these conditions.

Recent findings on the localization and function of Myosin Id in dendritic spines provide important clues for understanding the disease mechanisms of ASD. In our laboratory, we plan to further dissect the roles of Myosin Id and to clarify in greater detail how its dysfunction contributes to ASD onset and progression. In parallel, elucidating the mechanisms by which KIFs transport neurotransmitter receptors and synaptic vesicles has provided new perspectives on the pathogenesis of psychiatric disorders (71). A more precise understanding of the functions of individual KIFs and their links to specific psychiatric phenotypes is expected to facilitate the development of novel, mechanism-based therapeutic strategies.

In addition, growing evidence suggests that abnormalities in the cytoskeleton and molecular motors of glial cells—particularly microglia—also play a crucial role in psychiatric disease. Cytoskeletal remodeling accompanying microglial activation is closely associated with a range of functional changes, including the production and release of inflammatory mediators and alterations in phagocytic capacity. These insights are highly informative for identifying new therapeutic targets and deepening our understanding of disease mechanisms. Going forward, more comprehensive research approaches that explicitly consider neuron–glia interactions will be essential.

Key future directions include:

1. Clarifying the relationships between glia-specific cytoskeletal and molecular motor gene variants and psychiatric disorders;
2. Developing novel therapeutic strategies that directly target glial cytoskeletal and molecular motor pathways;
3. Elucidating the roles of cytoskeletal and motor systems in neuron–glia interactions; and
4. Defining how morphological changes in glial cells relate to functional alterations in the context of psychiatric illnesses.

Through these lines of investigation, we anticipate further advances in our understanding of the pathophysiological mechanisms underlying psychiatric disorders, which in turn should contribute to the development of new therapeutic and preventive strategies. Approaches that specifically target microglial cytoskeletal and molecular motor dynamics may exert their effects via mechanisms distinct from conventional neurotransmitter-based treatments and thus hold promise as alternative options for patients with treatment-resistant conditions. Research on cytoskeletal and molecular motor systems lies at the interface of neuroscience and psychiatry and is expected to become increasingly important in the coming years. Ultimately, progress in this field may help improve the quality of life of individuals suffering from psychiatric disorders.

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