

## Symposium

# Synaptic Actin Dysregulation, a Convergent Mechanism of Mental Disorders?

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Actin polymerization governs activity-dependent modulation of excitatory synapses, including their morphology and functionality. It is clear from human genetics that neuropsychiatric and neurodevelopmental disturbances are multigenetic in nature, highlighting the need to better understand the critical neural pathways associated with these disorders and how they are altered by genetic risk alleles. One such signaling pathway that is heavily implicated by candidate genes for psychiatric and neurodevelopmental disorders are regulators of signaling to the actin cytoskeleton, suggesting that its disruption and the ensuing abnormalities of spine structures and postsynaptic complexes is a commonly affected pathway in brain disorders. This review will discuss recent experimental findings that strongly support genetic evidence linking the synaptic cytoskeleton to mental disorders, such as schizophrenia and autism spectrum disorders.

**Key words:** actin; Arp2/3; autism; dendritic spine; NMDA receptor; schizophrenia

## Introduction

Dendritic spines are the postsynaptic sites of most excitatory synaptic contacts. They are less than a femtoliter in volume, and yet they are necessary for information coding and memory storage. The underlying cytoskeleton of the spine is almost exclusively composed of a highly branched meshwork of actin filaments (Korobova and Svitkina, 2010), with ~85% of the filaments constantly remodeling with an average turnover time of 44 s in the spine head (Star et al., 2002). Multiple lines of evidence, including imaging, biochemical, and genetic studies, demonstrate that the modulation of this underlying actin cytoskeleton is a critical driver of most of the essential functions of the spine, including their development (Sala and Segal, 2014) trans-synaptic adhesion (Spence and Soderling, 2015), receptor anchoring and trafficking (Allison et al., 1998; Glebov et al., 2015; Loebrich et al., 2016), and structural plasticity during LTP and LTD (Dillon and Goda, 2005).

Consistent with the central role of actin remodeling in governing most spine functions, dysfunction of the signaling pathways that reorganize synaptic actin is associated with a diverse range of developmental brain disorders, including autism spec-

trum disorders (ASDs), schizophrenia, and intellectual disability. Indeed, human risk alleles for these disorders in genes, such as *SHANK3*, *GIT1*, *DISC1*, *SRGAP3*, *OPHN1*, *LIMK1*, *NRG1*, *CYFIP1*, *SYNGAP1*, *KALRN*, *NCKAP1*, and *CNKSR2*, regulate the upstream signaling events that induce actin cytoskeletal dynamics in dendritic spines (Meng et al., 2002; Govek et al., 2004; Gu et al., 2005; Hayashi-Takagi et al., 2010; Carlson et al., 2011; Won et al., 2011; Durand et al., 2012; De Rubeis et al., 2013; Han et al., 2013; Sanders et al., 2015). Moreover, features of neurons regulated by actin, such as spine density and morphology, are often abnormal in subjects with developmental brain disorders (Williams et al., 1980; Hutsler and Zhang, 2010). In this review, we cover recent studies in model organisms, such as mouse, as well as in postmortem human brain samples, that investigated how perturbations in actin intersect with synaptic, circuit, and behavioral phenotypes relevant to these disorders.

## Synaptic cytoskeletal disturbances that drive abnormal wiring and behavior

The architecture of the actin cytoskeleton within the postsynaptic spine is predominately branched actin filaments that are formed by the Actin-related protein-2/3 (Arp2/3) complex (Korobova and Svitkina, 2010). The Arp2/3 activator, WAVE1, is present within spines, and Arp2/3 is specifically enriched within a submembrane region (20–100 nm from the membrane) surrounding the spine head (Soderling et al., 2007; Rác and Weinberg, 2008). Several lines of evidence support a possible role for dysregulation of signaling upstream of Arp2/3 in developmental brain disorders. For instance, one function of *DISC1*, a susceptibility gene for schizophrenia, is to regulate Rac signaling to spine actin via the guanine nucleotide exchange factor Kalirin-7 (Hayashi-Takagi et al., 2010). Additionally, postmortem analysis reveals decreased expression of proteins that

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regulate synaptic actin signaling, including the Rho-family GTPases (Hill et al., 2006; Hayashi-Takagi et al., 2010). Another schizophrenia-linked gene, *DTNBP1*, encodes the protein disbindin-1, which assembles a protein complex with Abi1 and WAVE family members that may be important for maintaining normal spine morphology (Ito et al., 2010). Copy number variants associated with schizophrenia also impact key cytoskeletal signaling molecules, including CYFIP1 and WRP/srGAP3, which regulate Rac-to-WAVE signal transduction (Soderling et al., 2002; Stefansson et al., 2008; Addington and Rapoport, 2009; Zhao et al., 2013). More recently, the gene encoding the WAVE1 regulatory protein, NckAp1, has been identified as a strong risk allele for autism (Sanders et al., 2015). Recent work by the Lewis laboratory (see below) has also shown that the expression of subunits of the Arp2/3 Complex is significantly down-regulated in the prefrontal cortex (PFC) from individuals with schizophrenia (Datta et al., 2016).

The hypothesis that disrupted regulation of Arp2/3 activity can underlie the synaptic and behavioral phenotypes associated with these developmental brain disorders has recently been tested (IH Kim et al., 2013). Loss of Arp2/3 activity in cortical pyramidal neurons resulted in an immediate impairment of LTP-induced spine structural plasticity and induced a progressive loss of spines *in vivo*. The time course of these synaptic deficits overlapped with the development of multiple positive, negative, and cognitive-type behavioral symptoms that were consistent with a schizophrenia-like model. In a follow-up study (IH Kim et al., 2015), it was found the positive-like symptoms responded to antipsychotics (haloperidol) and were demonstrated to be due to the loss of Arp2/3 activity in the PFC. Interestingly, pyramidal neurons of the PFC that had lost Arp2/3 became more excitable as spines were lost, and they projected to the dopamine-producing neurons of the ventral tegmental area/substantia nigra pars compacta. The resulting circuit abnormality resulted in elevated striatal dopamine levels, which may explain the efficacy of haloperidol in this model.

Although these studies have examined the role of Arp2/3 in maintaining dendritic spines of mature neurons, it is also likely to be important during the early development of excitatory synapses. This developmental wiring of neuronal networks involves the initiation of spine formation (dendritic filopodial emergence) and spine maturation (spine head enlargement and subsequent AMPA-type glutamate receptor recruitment or synapse “unsilencing”). The role of dendritic filopodia in spinogenesis is supported by several lines of evidence. Specifically, filopodia initiate contacts with synaptic partners (Jontes and Smith, 2000; Yuste and Bonhoeffer, 2004) to create a synapse (Fiala et al., 1998; Harris, 1999) and that dendritic filopodia select appropriate axons with which to form connections (Lohmann and Bonhoeffer, 2008).

Most filopodial structures are composed of bundled linear parallel actin filaments (Svitkina et al., 2003); however, recent electron microscopy imaging suggests that dendritic filopodia are composed of branched filaments of mixed polarity, implying that the actin structure of dendritic filopodia is unique and requires Arp2/3 activity to form (Korobova and Svitkina, 2010). In contrast to this, mDia2, an actin nucleator that promotes linear actin filaments, facilitates dendritic filopodial formation, suggesting that linear actin filaments promote nascent filopodial emergence (Hotulainen et al., 2009). Recently, the roles of Arp2/3 activity in this initial stage of excitatory synapse formation were tested (Spence et al., 2016). It was found that loss of either Rac or Arp2/3 activity promoted dendritic filopodial emergence, rather than impairing their formation. This is in line with prior data showing that dendritic filopodia exhibit unique actin regulatory proteins,

such as SrGAP3/WRP, which turns off Rac activity and facilitates filopodial emergence (Soderling et al., 2002; Carlson et al., 2011). Perhaps more interestingly, dendritic protrusions that form in the absence of Arp2/3 fail to recruit AMPA-type glutamate receptors and do not undergo the developmental process of synapse unsilencing (Spence et al., 2016).

Abnormalities in synapse development and AMPAR-dependent unsilencing are likely to be relevant to neurodevelopmental disorders. For example, in mouse models of Fragile-X syndrome, there is a delay in the unsilencing of synapses in the barrel cortex (Harlow et al., 2010). In contrast, other models of ASD, such as *Syngap1* mutant mice, appear to unsilence their synapses prematurely in the hippocampus (Rumbaugh et al., 2006; Clement et al., 2013). Evidence suggests that both mouse models exhibit altered regulation of the synaptic cytoskeleton (see also below) (Carlisle et al., 2008; Chen et al., 2010; Dolan et al., 2013). Thus, dysfunctional regulation of Arp2/3-dependent actin remodeling may impact not only the density of synapse formation, but also severely impact the functional connectivity of these synapses.

### Targeting actin regulators for mental disorders

Upstream of Arp2/3 is the Rho GTPase family, the best studied of which are Rac1, RhoA, and Cdc42. Rac1 stimulates spine formation, dendrite initiation, elongation, and branching complexity (Threadgill et al., 1997). The major downstream effectors of Rac1 are p21-activated kinase (PAK) and LIM-domain containing protein kinase (LIMK), which facilitate actin filament assembly through the phosphorylation and inactivation of cofilin (Sells et al., 1997; Arber et al., 1998), a major actin-severing protein (Bamburg, 1999; dos Remedios et al., 2003). Abnormalities in Rho GTPase signaling have been identified as a prominent cause of intellectual disability (Allen et al., 1998; Ramakers, 2002). Regulation of the RhoA pathway in the inner cortical plate is crucial for controlling brain size and connectivity, and its dysregulation by *de novo* mutations is considered to confer a high risk for autism and schizophrenia (Lin et al., 2015). Emerging evidence suggests that aberrant Rac1/PAK signaling could lead to abnormal neuronal connectivity and synaptic function, as well as deficient cognitive and emotional functioning. Forebrain-specific dominant-negative PAK transgenic mice display fewer dendritic spines in cortical neurons, impaired synaptic plasticity, and specific deficits in the consolidation of long-term memory (Hayashi et al., 2004). Rac/PAK signaling is also defective in Fragile-X syndrome, the most common form of inherited intellectual disability (Chen et al., 2010). Administration of a PAK inhibitor rescues Fragile-X syndrome phenotypes, such as seizures, hyperactivity, and repetitive movements (Dolan et al., 2013). In the NAc of mice after chronic social defeat stress and human subjects with depression, Rac1 transcription is found to be reduced, which is associated with a repressive chromatin state surrounding Rac1 promoter (Golden et al., 2013).

ASDs are characterized by social deficits and repetitive behaviors, and are accompanied by several comorbidities, including intellectual disability, anxiety, hyperactivity, and epilepsy. Genetic analysis of autistic patients suggests that autism-associated *de novo* variants converge on the genes involved in the regulation of actin filaments and the formation and function of synapses (Gilman et al., 2011). Haploinsufficiency of *Shank3* gene, which encodes a synaptic scaffolding protein at glutamatergic synapses (Naisbitt et al., 1999; Sheng and Kim, 2000; Hayashi et al., 2009), is one of the most prevalent and highly penetrant monogenic causes of autism (Bonaglia et al., 2001; Durand et al., 2007; Sebat

et al., 2007; Betancur and Buxbaum, 2013). Mice with Shank3 deletions or mutations exhibit ASD-like behaviors and synaptic deficits (Jiang and Ehlers, 2013; Duffney et al., 2015; Bidinosti et al., 2016; Zhou et al., 2016). Shank forms a complex with  $\beta$ PIX, the guanine nucleotide exchange factor involved in Rac1 activation (Manser et al., 1998), and overexpression of Shank in cultured neurons promotes synaptic accumulation of  $\beta$ PIX (Park et al., 2003). A recent study (Duffney et al., 2015) has found that the expression of  $\beta$ PIX is strongly reduced in the PFC of *Shank3*-deficient mice, which leads to the decreased Rac1 activity. The Rac1 downstream effectors, active PAK and LIMK, are also significantly reduced in *Shank3*-deficient mice, which results in the disinhibition of cofilin. Consequently, the level of F-actin is substantially decreased in PFC of *Shank3*-deficient mice. In corroboration with these results, overexpression of Shank3 has been found to enhance actin polymerization by interacting with the Arp2/3 complex (Durand et al., 2012) and increase F-actin levels (Han et al., 2013).

These observations lead to the hypothesis that dysregulation of the synaptic actin cytoskeleton is an important component of the pathology that drives autistic phenotypes in *Shank3*-deficient mice. Interestingly, inhibition of cofilin activity produces a robust rescue of the social preference deficits and repetitive behavior in *Shank3*-deficient mice, which correlates well with the restoration of NMDAR trafficking and function, suggesting a promising therapeutic strategy for autism treatment (Duffney et al., 2015). Inhibiting PAK or Rac1 function in wild-type animals produces ASD-like social deficits and NMDAR hypofunction, whereas elevating Rac1 activity in PFC of *Shank3*-deficient mice leads to the rescue of behavioral and NMDAR abnormality, confirming the importance of Rac1/PAK signaling in autism (Duffney et al., 2015). These lines of evidence have revealed actin dysregulation and ensuing NMDAR hypofunction in PFC pyramidal neurons as a pathophysiological basis for the ASD-like behaviors in a Shank3 model of autism. It also suggests that perturbing the signaling molecules in Rac1/PAK/cofilin pathway to normalize cortical actin dynamics offers a potential therapeutic strategy to ameliorate cognitive and synaptic defects in autism. Nonspecific effects generated by actin-manipulating agents are potentially a concern; however, many actin regulators are largely brain-specific and more likely to represent appropriate future targets. For example, high-throughput gene expression profiling has found that different actin interacting proteins have distinct transcriptional activity in different brain regions and non-CNS areas, thus targeting the actin regulators highly restricted to frontal cortex, such as human PAK3, whose mutation causes X-linked mental retardation (Allen et al., 1998), could enable the specific normalization of actin dynamics at PFC glutamatergic synapses. Moreover, different postsynaptic proteins are differentially affected by altered actin dynamics. As discussed below, Shank3 directly links NMDARs to actin cytoskeleton, making NMDARs particularly sensitive to Shank3-induced changes in actin dynamics.

### Actin abnormalities, NMDA receptor dysfunction, and autism spectrum disorders

Dysfunction of NMDARs has recently been proposed as a candidate mechanism for ASDs, based on the results from animal models of this disorder. Interestingly, animal models of ASD-related phenotypes can display altered (reduced or enhanced) NMDAR function and these autistic-like behaviors are often normalized by pharmacological modulation of NMDARs (Lee et al., 2015a). Although it is clear that multiple mechanisms could lead to altered NMDAR levels, the synaptic actin cytoskeleton is

known to be important for the synaptic retention of NMDARs under basal conditions and during synaptic activity (Rosenmund and Westbrook, 1993; Allison et al., 1998; Morishita et al., 2005), and its dysregulation is likely involved in NMDAR dysfunction.

Multiple examples of reduced NMDAR function associated with ASD-like behaviors have recently been described. For instance, mice lacking the postsynaptic adhesion molecule neuroligin-1 show repetitive self-grooming associated with reduced NMDAR function, which is rescued by treatment of the mice with the NMDAR agonist D-cycloserine to enhance NMDAR function (Blundell et al., 2010). In addition, mice lacking the excitatory postsynaptic scaffolding protein Shank2 have been shown to display autistic-like social deficits that are responsive to D-cycloserine (Won et al., 2012).

Shank family proteins associate with diverse synaptic proteins, including the actin-binding/regulatory proteins cortactin (Du et al., 1998), Arp2/3 (Han et al., 2013), Abp1 (Qualmann et al., 2004; Haeckel et al., 2008),  $\beta$ PIX, and IRSp53 (Bockmann et al., 2002; Soltau et al., 2002; Soltau et al., 2004). These results suggest the strong possibility that deletion of *Shank* genes in mice may decrease synaptic actin filaments, leading to a suppression of the synaptic localization of NMDARs. Recently, four different mouse lines lacking Shank3 have been shown to exhibit reduced NMDAR function and autistic-like behaviors, strongly suggesting that this is a core pathology of these models (Kouser et al., 2013; Duffney et al., 2015; Jaramillo et al., 2015; Speed et al., 2015). Importantly, cofilin inhibition or Rac1 activation, which could enhance synaptic F-actin levels, has been shown to normalize both the reduced NMDAR function and autistic-like behaviors in a line of *Shank3*-mutant mice (Duffney et al., 2015).

Interestingly, excessive NMDAR function may also lead to autistic-like phenotypes. For example, mice and rats prenatally exposed to valproic acid, an antiepileptic agent, display enhanced NMDAR function and autistic-like behaviors (in the case of rats) (Rinaldi et al., 2007), which are rescued by the NMDAR antagonist memantine (KC Kim et al., 2014; Kang and Kim, 2015). Most recently, memantine also rescued repetitive behaviors of mice lacking astroglial glutamate transporter, supporting the notion that excessive NMDAR activity is also associated with autistic-like behaviors (Aida et al., 2015). In some cases, this enhanced NMDAR activity may be linked to altered regulation of the actin cytoskeleton. For example, autistic-like social deficits are observed in mice lacking the excitatory postsynaptic scaffolding protein IRSp53, and an unusually stable synaptic actin cytoskeleton may underlie these phenotypes (MH Kim et al., 2009). *IRSp53*-mutant mice have abnormally stabilized actin filaments in the hippocampus that are resistant to cofilin activation (Chung et al., 2015). This is thought to increase synaptic content of NMDARs under basal conditions and suppress activity-dependent removal of synaptic NMDARs during long-term depression of NMDAR-mediated currents, a process known to require actin depolymerization (Morishita et al., 2005). Memantine, which rescues the social deficits in *IRSp53*-mutant mice, also normalizes the reduced long-term depression of NMDAR-mediated currents (Chung et al., 2015). These results, together with the D-cycloserine results and studies of *Shank3* mutant mice, suggest that NMDAR dysfunction in either direction can cause autistic-like behaviors in animals.

A challenge going forward will be to determine whether a significant portion of the NMDAR dysfunctions observed in animal models of ASDs involves actin dysfunction, as it is clear other mechanisms also lead to NMDAR disturbances. For instance, the transcription factor Tbr1 regulates the expression of the gene encoding the GluN2B subunits of NMDARs (Wang et al., 2004a, b). Therefore, the reduced NMDAR function observed

in the amygdala of *Tbr1*-mutant mice (Chuang et al., 2014; Huang et al., 2014; Lee et al., 2015b) is likely to be caused by insufficient levels of GluN2B-containing NMDARs. However, in principle, any proteins that can impact synaptic actin filaments have the potential to be associated with NMDAR dysfunction and autistic-like behaviors in animals. Given that synaptic retention of AMPA receptors also requires intact actin filaments (Allison et al., 1998), defects in actin-binding/regulator proteins may also affect AMPAR-mediated synaptic transmission at excitatory synapses through direct mechanisms or indirectly through modulation of NMDARs. These changes at excitatory synapses may lead to the alteration of the balance between excitatory and inhibitory synapses in a neuron and disruption of neural circuits in the brains of animal models of ASD.

### Altered regulation of actin dynamics and cortical dendritic spine deficits in schizophrenia

In schizophrenia, deficits in cognitive functions are core and clinically critical features of the illness (Elvevåg and Goldberg, 2000). These deficits include working memory impairments, which appear to reflect alterations in specific elements of dorsolateral prefrontal cortex (DLPFC) circuitry that are known to be critical for working memory in primates (Arnsten et al., 2012). For example, reciprocal excitatory connections among DLPFC layer 3 pyramidal cells are thought to mediate sustained neuronal activity during the maintenance phase of working memory tasks in monkeys (Goldman-Rakic, 1995). These connections terminate on dendritic spines; thus, dendritic spine density can serve as a proxy for the number of excitatory inputs that a pyramidal neuron receives (Glausier and Lewis, 2013).

Basilar dendritic spine density has been consistently found to be lower on layer 3 pyramidal cells of the DLPFC (Garey et al., 1998; Glantz and Lewis, 2000; Konopaske et al., 2014) and at least some other cortical regions (Sweet et al., 2009) in subjects with schizophrenia. In contrast, spine density does not appear to be altered on pyramidal neurons in layers 5 or 6 of the DLPFC (Kolluri et al., 2005). These findings have raised the following questions: (1) What pathogenic process might account for lower dendritic spine density in the illness? (2) What molecular mechanisms could explain the presence of spine deficits preferentially on layer 3 pyramidal neurons? (3) Could these mechanisms, and the resulting spine deficits, give rise not only to working memory impairments but also to the psychotic features that are characteristic of schizophrenia?

Convergent lines of evidence suggest that the pathogenic process underlying cortical dendritic spine deficits in schizophrenia involves altered regulation of the actin cytoskeleton required for the formation and maintenance of spines. First, *de novo* mutations in schizophrenia are over-represented among loci encoding cytoskeleton-associated proteins that regulate actin (Fromer et al., 2014). Second, key molecules that regulate actin dynamics exhibit altered expression in the DLPFC of subjects with schizophrenia. For example, Rho GTPase cell division cycle 42 (*Cdc42*) regulates the actin polymerization required for spine maturation (Scott et al., 2003; Saneyoshi et al., 2010); *Cdc42* mRNA levels are lower in the DLPFC of subjects with schizophrenia (Hill et al., 2006), including in layer 3 pyramidal neurons (Datta et al., 2015). Similarly, transcript levels of kalirin, a Rho-family guanine exchange factor that is highly concentrated in spines and regulates spine integrity through Rac signaling pathways (Cahill et al., 2009), are lower in the DLPFC of subjects with schizophrenia (Hill et al., 2006). Finally, expression levels of multiple subunits of the Arp2/3 complex are altered in pyramidal neurons, but

not in other cell types, in DLPFC layer 3 from subjects with schizophrenia (Datta et al., 2016). These findings suggest that the synaptic actin cytoskeleton is impaired in schizophrenia, potentially contributing to decreased spine stability and ultimately spine loss.

It is important to note that at least some of these gene expression alterations are present in layer 5 pyramidal neurons that do not exhibit spine deficits in schizophrenia, and that the levels of these transcripts predict spine density only in pyramidal cells in layer 3 (Hill et al., 2006) (Ide and Lewis, 2010). However, the presence of these alterations in pyramidal cells in both layers suggests that these deficits (1) are not a secondary consequence of a lower number of dendritic spines, and (2) might be a necessary but not a sufficient cause of reduced spine density.

The apparent specificity of the spine deficits to layer 3 pyramidal neurons might reflect disturbances in molecules that are expressed selectively in these neurons. For example, several members of the *Cdc42* effector protein family (*Cdc42ep3* and *Cdc42ep4*), which are inhibited by *Cdc42* activity, are preferentially expressed in layers 2 and 3 of the DLPFC (Arion et al., 2007). In schizophrenia, expression levels of *CDC42EP3* and *CDC42EP4* are upregulated in layer 3 pyramidal cells (Ide and Lewis, 2010; Datta et al., 2015). Signaling via the *Cdc42*-*CDC42EP* complex regulates septin organization, which can act as a barrier in the spine neck that controls the flow of molecules into spines required for F-actin-mediated growth of spines and synaptic potentiation (Joberty et al., 2001; Ewers et al., 2014). The combination of lower levels of *Cdc42* and higher levels of *CDC42EPs* in schizophrenia might alter the septin filament barrier, impair spine plasticity, and result in spine loss (Ide and Lewis, 2010). In addition, recent gene expression studies specifically in DLPFC layer 3 pyramidal cells suggest that dysfunction in the *Cdc42*-PAK-LIMK signaling pathway could also alter actin dynamics (Datta et al., 2015). Thus, the prominence of spine deficits in layer 3 pyramidal cells in schizophrenia might reflect the convergent effects of alterations in different actin pathways, each of which could destabilize the synaptic actin cytoskeleton.

Altered network activity in DLPFC layer 3 could contribute to the working memory impairments present in schizophrenia (Gonzalez-Burgos et al., 2015) and was also hypothesized (Weinberger, 1987) to cause the excessive dopamine release in the associative striatum associated with the psychotic symptoms of the illness (Howes et al., 2012). Evidence for causality in this association was recently provided by findings that deletion of the Arp2/3 complex in mice resulted in cortical spine deficits and a subcortical hyperdopaminergia that improved with antipsychotic medications (IH Kim et al., 2015). Thus, the pathogenic processes and molecular mechanisms producing cell type-specific alterations in actin dynamics could produce cortical dendritic spine deficits as an upstream pathology that subsequently gives rise to excessive striatal dopamine function and the appearance of psychosis in schizophrenia (Lewis and Gonzalez-Burgos, 2006).

### Conclusion and future directions

It is becoming clear from human genetic and brain tissue studies, and from mouse models, that dysfunction of the actin cytoskeleton at excitatory spine synapses is likely a shared molecular pathology across different neurodevelopmental and psychiatric disorders. This realization, however, opens many new avenues for future work that will be required to address critical and complicated questions raised by these findings. First, a better understanding of specific actin-dependent spine functions that are disrupted at different developmental stages and in different brain

regions is clearly needed to better define the molecular mechanisms of these disorders. As human genetic analyses continue to identify new risk alleles, there will also be an increasing need for new animal models to define these mechanisms. Where possible, it will be essential to corroborate findings from animal models with the analysis of clinical samples. Second, a better understanding of how specific mutations of the synaptic actin pathway may result in clinically diverse disorders is needed. The recent focus on Research Domains of Criteria may be beneficial in terms of focusing on behavioral and circuit phenotypes that cross current diagnostic boundaries (Insel et al., 2010). Finally, it is clear that neuronal actin remodeling is critical at other synaptic sites within neurons, including presynaptic terminals and inhibitory synapses. How these may be impacted in the context of disorders whose basis is dysfunctional actin remodeling will be an important future direction.

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