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Dendritic structural plasticity and neuropsychiatric disease

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Abstract

The structure of neuronal circuits that subserve cognitive functions in the brain is shaped and refined throughout development and into adulthood. Evidence from human and animal studies suggests that the cellular and synaptic substrates of these circuits are atypical in neuropsychiatric disorders, indicating that altered structural plasticity may be an important part of the disease biology. Advances in genetics have redefined our understanding of neuropsychiatric disorders and have revealed a spectrum of risk factors that impact pathways known to influence structural plasticity. In this Review, we discuss the importance of recent genetic findings on the different mechanisms of structural plasticity and propose that these converge on shared pathways.

TOC blurb

The morphology of dendrites and dendritic spines changes with development and as a result of activity-dependent plasticity mechanisms. Penzes and colleagues describe the altered dendritic structural plasticity that is associated with some neuropsychiatric disorders and consider the underlying molecular mechanisms, based on recent genetic discoveries.

The highly specialized morphology of neurons provides the substrate to build the circuits that underlie human cognition and behaviour. The shaping of neuronal circuits occurs in sequential developmental phases and is refined by activity-dependent mechanisms and environmental cues¹. Many neuronal subcompartments have been shown to change in response to activity; these include dendritic arbors and spines, the axon initial segment and presynaptic boutons². The different sites of structural plasticity that work in concert to ensure precise brain wiring are therefore sensitive to dysregulation at multiple levels and on different timescales. In particular, morphological changes in dendritic spines have been the

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focus of intense investigation owing to their proposed role in several neuropsychiatric disorders³.

Neuropsychiatric disorders are a heterogeneous group of mental disorders that manifest psychiatric symptoms and demonstrable brain pathology and are thought to arise from disruptions of the synaptic circuits that subservise cognitive, social and emotional processing⁴. Since the advent of genomic technologies, genetic risk factors for neuropsychiatric disorders are being identified at an unprecedented rate, providing a window into the molecular basis of disease. Remarkably, the pathways that are being uncovered intersect with mechanisms regulating the growth and structural plasticity of synapses, which may be important for understanding the nature of these disorders. Structural plasticity of circuits involves changes in both excitatory and inhibitory neurons and in both presynaptic and postsynaptic termini (reviewed in REF 2); however, genetic studies indicate that excitatory postsynaptic compartments may be particularly important in the aetiology of a wide range of neuropsychiatric disorders⁵⁻⁸.

In this Review, we focus on the structural plasticity that occurs at postsynaptic sites, the dendrites and spines of excitatory neurons, which are atypical in several neuropsychiatric disorders and in which synaptic plasticity mechanisms have been extensively studied. We emphasize the integration of biological insights from large-scale genomic studies of idiopathic neuropsychiatric disorders of neurodevelopmental origin, including intellectual disability, epilepsy, autism spectrum disorder (ASD), schizophrenia and bipolar disorder. Although epilepsy is typically classified as a neurological condition, we include it in this Review because it shares many genetic risk factors with ASD and intellectual disability⁹. In addition, epilepsy is often comorbid with intellectual disability and ASD, and individuals with epilepsy often present with various neuropsychiatric symptoms¹⁰. Each neuropsychiatric disorder that we discuss is associated with a distinct pattern of dendritic spine pathology, and mounting evidence implicates the altered structural plasticity of spines as a central disease mechanism in these disorders.

Dendritic structural plasticity

Although multiple brain regions are likely to have a role in the development of neuropsychiatric disorders, the human neocortex has an important role in higher-order brain functions (such as cognition) that are dysfunctional in many neuropsychiatric disorders. Thus, we here consider the postsynaptic elements of cortical circuits — the dendrites and spines of pyramidal neurons — and describe their developmental timeline and the mechanisms regulating their activity-dependent remodelling.

Dendritic spines and brain development.

Cortical pyramidal neurons are the main excitatory cells of the neocortex¹¹. During development, pyramidal neurons elaborate complex dendritic arbors, which increase their surface area and connectivity (FIG. 1a). Maturing dendrites become studded with small protrusions called dendritic spines, which host the majority of the excitatory synapses in the brain. The total excitatory input that a neuron can receive is dependent on the complexity of the dendritic arbor and the density and size of spines, which together form the neuron's

synaptic input field. The growth of dendrites and spines is therefore fundamental to the development of neuronal circuits.

Dendrites provide the support on which dendritic spines grow, and during early rodent development, the growth of both structures is intimately linked¹². Later in development, dendritic branches become stabilized and uncoupled from the morphological changes to dendritic spines. Dendrites are therefore much less dynamic than dendritic spines in mature neurons. Dendritic spines compartmentalize the postsynaptic machinery and assist in the independent regulation of synaptic inputs¹³. Spines are typically less than 1 (μm^3) in size and exist on a morphological continuum from long, thin filopodia to large, mature spines with a defined spine head¹⁴. Filopodia are thought of as immature spines because they arise early in development, are highly dynamic and often lack functional synapses. By contrast, mature (or ‘mushroom’) spines are typically more stable and have an enlarged spine head containing neurotransmitter receptors and a postsynaptic density (PSD). Given that certain neuronal subtypes do not have spines, the reason for the existence of such a broad array of spine morphologies in pyramidal neurons remains somewhat enigmatic; however, their precise shape and plasticity are likely to influence the regulation and compartmentalization of biochemical and electrical signalling that are required to form complex and adaptable circuits¹⁵.

In the human neocortex, dendrites can be recognized approximately halfway through gestation (17–25 weeks), whereas spines appear late in the second trimester (26–34 weeks) (FIG. 1a). The appearance of spines coincides with a period of intensive dendritic growth and cortical thickening¹⁶. The number of spines increases rapidly in the perinatal and postnatal periods and reaches its peak early in infancy (1–2 years) before progressively declining in a period known as ‘pruning’, which continues into adolescence and adulthood¹⁷. The elimination of spines indicates the start of a fine structural reorganization of the cortex and is concurrent with the observation of cortical thinning (measured by MRI) in late childhood to adolescence^{1,18}. The developmental changes in this period are consistent with the emergence of higher cognitive functions such as attention, working memory, cognitive control and response inhibition¹. In humans, childhood is a period of massive structural refinement at the level of dendritic arbors and spines that is critically important for attaining properly functioning and adaptable synaptic circuits. Importantly, early life witnesses the intersection of a waning developmental and a growing experience-dependent influence on plasticity, each affecting spines on their own timescales.

Activity-dependent structural plasticity.

Spines are highly dynamic in nature and have a remarkable capacity to undergo structural changes in the young and adult brain^{19,20}. Spines can grow, shrink, form de novo and be maintained or be eliminated, all of which contribute to the formation and experience-dependent optimization of neuronal circuits²⁰. In addition, the morphological modifications of spines are widely regarded as the structural basis for learning and encoding memories^{21,22}. Spine plasticity is affected by multiple factors, including developmental stage, brain region, sensory experience and synaptic activity²⁰. Recent super-resolution

imaging techniques have been instrumental in shaping our knowledge of the type and extent of the structural changes that take place (BOX 1).

Activity-dependent changes in spines are known to occur via at least two distinct cellular mechanisms: Hebbian and homeostatic plasticity. Hebbian synaptic plasticity is a mechanism through which correlated pre-synaptic and postsynaptic activity leads to durable changes in synaptic function²³. Long-term potentiation (LTP) and long-term depression (LTD) are two forms of Hebbian plasticity that can induce long-lasting increases or decreases in spine size, respectively²⁴ (FIG. 2a). LTP is also associated with an increase in the number and stability of spines. LTP involves actin polymerization, an enlargement of the PSD and an increase in AMPA receptor (AMPA) surface trafficking²⁵. Opposing structural rearrangements occur during LTD, including spine shrinkage, a decrease in actin polymerization and a reduction of surface AMPARs.

Homeostatic plasticity is an overarching form of plasticity that restrains cellular and circuit excitability within physiological limits². Synaptic scaling is a form of homeostatic plasticity through which neurons can adjust the strength of their synaptic connections, by regulating the surface expression of AMPARs, in response to global changes in circuit activity²⁶. Morphological correlates of synaptic scaling have been demonstrated²⁷, which is perhaps not surprising given the strong correlation between spine size and AMPAR content²⁸. Activity deprivation, a model for studying homeostatic plasticity, has been shown to increase the density or size of spines *in vitro*²⁹ and *in vivo*^{30–32}, presumably to compensate for the loss of synaptic input (FIG. 2b). By contrast, prolonged activity (such as that experienced during seizures) reduces spine number and size^{33,34}. However, the exact morphological changes in spines that occur when modelling homeostatic plasticity *in vivo* appear to be variable and highly dependent on the experimental model used^{35,36}, highlighting our incomplete knowledge of this process.

Although neuronal activity plays a critical part in shaping the growth and structure of spines, recent studies have also shown that spines can form in the absence of glutamate release³⁷. Thus, activity-dependent and activity-independent forces influence structural plasticity and, together, these dynamically regulate the overall number and morphology of spines (FIG. 2c).

Atypical spine and dendrite development

Spine pathology is a common feature of many neuropsychiatric disorders and refers to any shift in the size, shape or density of dendritic spines from that expected in a given brain region and developmental time point (FIG. 1b,c). Changes in spine morphology are often reported in human and animal models because they are easily observable by light microscopy. Given the tight relationship between spine structure and function, even small alterations in average spine size may reveal a profound dysfunction at the cellular or circuit level. Furthermore, imbalances in the processes governing spine formation and elimination can lead to a net change in spine density that, when summated with changes in dendritic complexity, can dramatically alter a neuron's synaptic input field (FIG. 1d). However, detailed reports of atypical spine development in human neuropsychiatric disorders remain scarce, presumably owing to the limited availability of post-mortem brain tissue. This

limitation also makes individual findings difficult to generalize to wider populations. In addition, such studies are subject to many confounding factors³⁸ that can impede the discovery of robust disease pathophysiology. These factors have led to variations in findings across studies; however, certain trends can be distilled.

Spine pathology in intellectual disability.

Post-mortem studies of unclassified intellectual disability (previously termed mental retardation) were among the first to suggest a connection between dendritic defects and neuropsychiatric disorders. Spines on cortical neurons from individuals with intellectual disability have been described as long and thin, indicative of an immature morphology, and display fewer spines per dendritic branch³⁹. Several studies have noted reduced complexity of both the apical and the basal dendrites of cortical pyramidal neurons in the brain tissue of individuals with intellectual disability compared with controls⁴⁰.

Spine pathology in autism spectrum disorder.

Studies of individuals with ASD have found that they exhibit higher spine densities than control subjects on the apical dendrites of layer II pyramidal neurons in the frontal, parietal and temporal lobes and the layer V projection neurons of the temporal lobe^{41,42}. These observations suggest a disruption of the balance between spine formation and elimination. Coincident with these results, longitudinal MRI studies have demonstrated an enlargement of brain volume and cortical grey matter in ASD that begins before 2 years of age^{43,44}. This period parallels the rapid expansion of spine and dendrite formation in the human brain that peaks in the first 2 years of life^{16,17}, suggesting that spine development during this period leads to an overabundance of spines in ASD.

Spine pathology in epilepsy.

In patients with temporal lobe epilepsy, layer III cortical pyramidal neurons have lower spine densities and fewer dendritic branch points than controls; however, it is thought that these changes may be caused by excitotoxicity⁴⁵. The reductions in grey matter observed by MRI in temporal lobe epilepsy patients appear not to be due to cell loss but rather to reflect the occupation of a smaller volume by neurons with sparser dendritic trees⁴⁶. Nonetheless, it is not yet clear whether the dendritic changes observed in epilepsy are the cause or consequence of epileptic seizures³⁴.

Spine pathology in schizophrenia and bipolar disorder.

In schizophrenia, aberrant spine density has been reported in multiple brain regions (reviewed in REF. 47). The most reproducible observation is a reduction of spine density on layer III pyramidal neurons of the neocortex compared with controls⁴⁸. More recently, a study found that pyramidal neurons in the same layer of the auditory cortex had a specific reduction in the number of small spines⁴⁹. Post-mortem studies of schizophrenia have also found evidence for reduced complexity of basal dendrites in layer III and layer V pyramidal neurons of the prefrontal cortex (PFC) compared with controls^{50,51}. Atypical dendritic development was again reported in a more recent study that found reduced dendrite length in layer III pyramidal neurons in the PFC of individuals with schizophrenia and, for the first

time, bipolar disorder; however, this study did not replicate the lower spine density reported previously for schizophrenia⁵². A separate study reported lower dendrite length and spine density in the PFC of individuals with bipolar disorder but no changes in spine density in individuals treated with lithium, suggesting that lithium ameliorates spine pathology in bipolar disorder⁵³. Despite these important findings, it is not known when the structural deficits occur in these disorders, as brain samples are typically collected from deceased adults. The favoured hypothesis in schizophrenia is that the lower spine density is the result of accelerated pruning of synapses during adolescence⁵⁴. This view is supported by longitudinal MRI studies reporting higher rates of grey matter reductions in individuals who go on to develop schizophrenia⁵⁵, which may in part be due to spine and dendrite loss. Furthermore, studies show that the onset of cognitive symptoms preceding psychosis coincides with the biological process of spine pruning in late childhood to adolescence⁵⁶.

Spine pathology in syndromic disorders.

In addition to idiopathic disorders, there has been a prominent focus on dendritic structure in Mendelian forms of disease with known genetic aetiology, such as Fragile X syndrome, Rett syndrome and Down syndrome, each of which has a characteristic spine pathology (reviewed in REF. ⁵⁷). In these cases, human post-mortem data have been supported by findings from animal and stem cell models (BOX 2), which together provide a more persuasive assessment of spine pathology. These models also open up avenues to investigate the underlying mechanisms in syndromic disorders⁵⁸. Studies of syndromic intellectual disability demonstrate that stratification of individuals on the basis of genetic aetiology can help to identify distinct spine pathologies and that different spine pathologies can converge on cognitive dysfunction⁴⁰. However, animal models often fail to recapitulate the inherent polygenic nature of many idiopathic neuropsychiatric disorders, which is why the analysis of human brain tissue and stem cells remains essential. Models of syndromic disease also have limited utility in modelling idiopathic neuropsychiatric disorders as intellectual disability, ASD and epilepsy are often comorbid in the same individual (as observed in Fragile X syndrome).

Patterns of spine pathology.

As described above, defective cortical pyramidal neurons have been observed in a range of different neuropsychiatric disorders, mostly in the frontal and temporal lobes. Early-onset developmental disorders such as intellectual disability and ASD are associated with too few or too many dendritic connections, respectively. Epilepsy, which is often comorbid with intellectual disability and ASD, is mainly characterized by fewer dendrites and spines. By contrast, schizophrenia and bipolar disorder, the later-onset psychiatric disorders, are both reported to have fewer dendritic spines and simplified arbors compared with controls. Further studies at different time points of illness are required to know exactly how and when these dendritic changes occur.

Genetic risk and structural plasticity

Neuropsychiatric genetics.

Neuropsychiatric disorders are known to have a strong genetic component, but their genetic architecture is complex⁵⁹. Genetic studies of common variants and rare variants in neuropsychiatric disorders have discovered a range of genes and chromosomal regions involved in disease risk. Genome-wide association studies (GWAS) of common risk variants in schizophrenia and bipolar disorder have been successful in identifying a growing number of synaptic genes that are related to disease^{60,61} (TABLE 1; Supplementary Table S1). In addition, a wide range of rare and highly penetrant copy number variants (CNVs), consisting of large chromosomal deletions or duplications, have been implicated in the aetiology of multiple neuropsychiatric disorders⁶², several of which alter the structural plasticity of neurons (TABLE 1).

The most recent success in revealing the genetic landscape of psychiatric disorders has come from studies using whole-genome sequencing and exome sequencing to identify protein-coding variants^{63–67}. To aid in the interpretation of these genetic risk factors, enrichment analyses have been an invaluable and unbiased way to identify functionally relevant gene sets and biological pathways relevant to neuropsychiatric disorders⁸. Through such analyses, processes including cytoskeletal organization^{68,69}, transcriptional regulation and chromatin modification^{6,70,71} have all been suggested to be altered in different neuropsychiatric disorders; however, postsynaptic signalling at glutamatergic synapses appears to be the most prominent shared biological process across multiple disorders^{5–8,63,68,72}, and many of the genes identified are likely to impact spine plasticity. This observation has prompted the need for a detailed examination of the relationship between neuropsychiatric risk factors and the mechanisms of structural plasticity.

Exome sequencing studies have been particularly helpful for biologists as they implicate specific genes rather than the multigene loci often associated with GWAS and CNV studies. Therefore, exome data provide a rich source of information that can assist in disentangling the biological pathways involved in neuropsychiatric disorders and may be critical in unravelling the disease pathways that could underlie spine deficits in neuropsychiatric disorders (FIG. 3).

The complex polygenic nature of neuropsychiatric disorders suggests that many different mutations of varying severity are expected to hit a range of synaptic pathways that converge on spine plasticity. Each pathway, or functional group of proteins, could represent a different dimension that may contribute to deficits in structural plasticity (FIG. 3). Below, we discuss prominent classes of proteins and pathways that are at the convergence point of dendritic structural plasticity and neuropsychiatric genetics, exemplifying each class with well-characterized representatives. These examples may help the functional interpretation of other potential candidate genes that are identified in genetic studies of neuropsychiatric disorders.

Cell adhesion.

Cell adhesion molecules (CAMs) comprise a diverse set of proteins with large extracellular domains that serve as trans-synaptic anchors, ligands, receptors and mediators of activity-

dependent signalling⁷³. Neurexins and neuroligins are among the best studied CAMs and have been strongly implicated in several neuropsychiatric disorders. Deletions in *NRXN1* were some of the first CNVs to be associated with schizophrenia⁷⁴, whereas a range of loss-of-function and de novo mutations in neuroligin genes (*NLGN1–3* and *NLGN4X*) are detected in individuals with ASD^{64,75}. Alterations in neurexin family members have also been reported in epilepsy and in neuropsychiatric disorders that are comorbid with epilepsy^{76,77}.

The presynaptic neurexins (neurexin 1 (NRXN1)–NRXN3) participate in heterophilic trans-synaptic interactions with the postsynaptic neuroligins, which triggers the recruitment of the scaffolding molecules and receptors necessary for synapse formation in co-culture models⁷⁸. In vitro, disruption of all neurexins in hippocampal neurons reduces synaptic stability and increases synapse elimination, implicating neurexins in the stabilization of nascent synapses⁷⁹. In cultured rat hippocampal neurons, neuroligin 1 (NLGN1) overexpression increases spine density, whereas knockdown of NLGN1, NLGN2 or NLGN3 reduces spine number⁸⁰. NLGN3-R451C mice, which model a human ASD mutation, have a marked increase in spine dynamics due to spine destabilization in the anterior frontal cortex⁸¹. The same mutation increases the number of dendritic branch points in the stratum radiatum region of the hippocampus⁸².

Contactin-associated protein-like 2 (CNTNAP2; also known as CASPR2) is a more distantly related member of the neurexin family, with a role in structural neurodevelopment. Homozygous loss of *CNTNAP2* in humans causes a severe neurodevelopmental syndrome, whereas heterozygous mutations have been found in individuals with schizophrenia, epilepsy and autism^{83–85}. In vitro, mature mouse cortical neurons lacking *Cntnap2* have a reduced number of spines, which exhibit an altered morphology and reduced levels of the AMPAR subunit GluA1 (also known as GRIA1)⁸⁶. Live imaging of layer V pyramidal cells in vivo shows that spine deficits may be caused by increased spine elimination, as spine formation is unaffected in *Cntnap2*-knockout mice⁸⁷. In vitro knockdown of CNTNAP2 in developing mouse neurons causes the collapse of dendritic branches and reduction of spine head size without affecting spine or synapse density⁸⁸. Together, these experiments support a role for CNTNAP2 in the structural integrity of mature dendritic branches and the stability of newly formed spines.

Mutations in a wide variety of other synaptic CAMs, including protocadherins, contactins, Down syndrome cell adhesion molecule (DSCAM) and cadherins, are linked to both early-onset and late-onset neuropsychiatric disorders and have marked effects on structural plasticity (TABLE 1; Supplementary Table S1) These functions at multiple stages of dendritic development may explain why variations in CAMs are associated with a wide range of disorders with varying onset. A prominent role of CAM networks in neuropsychiatric disorder aetiology is consistent with their well-documented roles in multiple steps of circuit formation and remodelling, including synapse formation, specification and stabilization. As these adhesion events are largely activity-independent, CAMs may underlie activity-independent spine pathology processes.

Glutamate receptors.

Excitatory neurotransmission in the brain is mediated primarily by AMPARs and NMDA receptors (NMDARs). Each glutamate receptor consists of four subunits, encoded by multiple genes (*GRIA1–GRIA4* (AMPA) and *GRIN1, GRIN2A–GRIN2D* and *GRIN3* (NMDAR)), which are expressed with distinct spatio-temporal patterns during brain development. Glutamate receptors and their associated auxiliary subunits have been implicated in neuropsychiatric disorders by a variety of different genetic studies (TABLE 1). *GRIA1* and *GRIN2A* were identified as genome-wide significant susceptibility genes in the largest GWAS of schizophrenia to date⁶⁰. Exome sequencing studies have revealed de novo variants affecting *GRIN2A* in individuals with schizophrenia, and recurrent de novo variants in *GRIN2B* have been identified in individuals with ASD, making it one of the strongest candidate ASD susceptibility genes^{63,64}.

AMPARs have a central role in the structure and function of spines. Spine size is robustly correlated with AMPAR content, with large spines containing more AMPARs, enhancing their synaptic strength²⁸. Glutamate signalling through AMPARs is sufficient to induce the formation of new spines and maintain existing spines in hippocampal slice cultures, suggesting that appropriate levels of AMPARs are required for activity-dependent sculpting of neuronal circuits^{89,90}. The GluA1 subunit is particularly important in activity-dependent AMPAR insertion into spines during LTP and experience-dependent plasticity in vivo^{91,92}. The carboxy-terminal tail of GluA1 may be directly required to generate stable increases in spine size in vitro during chemically induced LTP, providing a link between structural and functional plasticity⁹³.

NMDARs are well recognized for their role in the induction of LTP and LTD, which cause long-lasting changes in spine size⁹⁴ (FIG. 2a). However, blockade of NMDAR in postnatal hippocampal slice cultures results in increased dendritic arborization and synapse number, demonstrating that NMDARs can also influence neuronal development⁹⁵. Knockdown of the obligatory NMDAR subunit GluN1 (encoded by *GRIN1*), in hippocampal organotypic slice cultures causes increased spine motility and destabilization of spine structure, which is dependent on the GluN1 intracellular carboxyl terminus, implicating NMDARs in the control of spine dynamics⁹⁶. An ASD-linked rare mutation in the GluN2B (encoded by *GRIN2B*) carboxy-terminal tail results in decreased surface trafficking and a reduction in the spine density of cultured hippocampal neurons⁹⁷. In vivo, loss of *GRIN2B* causes reductions in spine density in CA1 hippocampal neurons, whereas deletion of *GRIN2A* causes decreases in dendritic complexity in the hippocampal dentate gyrus^{98,99}. Interestingly, the predominant subunit used in the assembly of NMDARs changes during development from GluN2B (ASD-associated) to GluN2A (schizophrenia-associated)¹⁰⁰. This developmental switch may reflect the importance of NMDA subunits at different phases of synaptic maturation and may implicate distinct NMDA-dependent mechanisms in governing the neurobiology and onset of ASD and schizophrenia.

AMPARs and NMDARs are the centrepiece of the activity-dependent mechanisms shaping dendritic spines. Hence, alterations in glutamate receptor expression, trafficking or function, caused by genetic variation, are likely to have important structural implications, especially in postnatal structural plasticity and activity-dependent development.

Scaffold proteins.

One of the most recognizable features of dendritic spines is the presence of a PSD, constructed from a complex network of scaffold proteins. Scaffold proteins have a highly modular domain structure and contain protein interaction sites enabling them to tether receptors, ion channels and cytoskeletal elements together to regulate synaptic structure¹⁰¹. SH3 and multiple ankyrin repeat domains (SHANK) and ankyrin (ANK) proteins are two types of scaffold proteins from the ankyrin repeat domain-containing protein (ANKRD) family. *SHANK2* and *SHANK3* mutations are two of the most prominent risk factors for ASD¹⁰². In addition, exonic mutations in *SHANK1–SHANK3* have been identified in a wide range of neurodevelopmental disorders^{63,64,67}. Large GWAS have implicated *ANK3* as one of the very few genome-wide significant susceptibility genes for bipolar disorder⁶¹. These studies and others strongly implicate postsynaptic scaffolds in the pathogenesis of neuropsychiatric disorders (TABLE 1).

In *Shank3*-knockout mice, hippocampal neurons have decreased dendritic complexity and synapse density in vitro¹⁰³. In addition to hippocampal dysfunction, SHANK3-deficient mice have reduced total spine density in medium spiny neurons expressing the dopamine D₂ receptor but not the D₁ receptor in vivo¹⁰⁴. These observations implicate SHANK3 in the structural development of specific striatal circuits important for social behaviour. Interestingly, re-expression of SHANK3 in adulthood can rescue dendritic spine deficits and behavioural abnormalities¹⁰⁵, indicating that neuronal circuits can be readjusted even after the major neurodevelopmental events shaping brain architecture have passed. The schizophrenia-linked R117X mutation in *SHANK3* reduces spine density in cortical neurons in vivo, consistent with post-mortem studies in schizophrenia¹⁰⁶. The ASD-linked InsG3680 mutation also causes a significant decrease in spine density in homozygous mice. Another set of *SHANK3* mutations identified in individuals with ASD causes deficits in hippocampal spine morphology and actin polymerization in vitro¹⁰⁷.

The scaffold protein ANK3 (also known as ankyrin-G) is another ANKRD protein with important functions in spine plasticity¹⁰⁸. The 190 kDa ANK3 isoform regulates spine head size and neck diameter. ANK3 accumulates in spine heads after chemical LTP, and knockdown of ANK3 disrupts LTP-induced increases in spine head size and density in cortical cultures. Notably, ANK3–190 is driven into spines upon lithium treatment in rats¹⁰⁹, suggesting that this treatment induces similar mechanisms to LTP. Lithium has pleiotropic effects on cellular signalling; however, part of its effect on ANK3 transport may result from its role as a regulator of microtubule-related trafficking¹¹⁰. Thus, reduced ANK3 expression in spines may compromise the structure of mature spines and their ability to undergo activity-dependent structural changes.

Scaffold proteins are central hubs of the synapse, bringing upstream CAMs and receptors together with downstream signalling proteins and cytoskeletal elements. These are all classes of proteins that are individually relevant for neuropsychiatric disorders. Genetic insults to these structures would be expected to have diverse effects on both activity-dependent and activity-independent pathways regulating spine structure, possibly contributing to the wide spectrum of disorders with genetic variants in protein scaffolds (TABLE 1).

Calcium signalling.

The regulation of calcium influx into spines is crucial for activity-dependent signalling in neurons. Calcium channels are also important for activity-dependent postsynaptic structural refinement^{111,112}. Calcium entry into spines is primarily controlled by synaptic activity and the gating properties of NMDARs and voltage-gated calcium channels (VGCCs), which trigger calcium-dependent signalling cascades¹¹³. Calcium channel genes *CACNA1C* and *CACNB2* were found to be genome-wide significant in a GWAS combining data from five major psychiatric disorders¹¹⁴. In addition, rare coding variants in calcium-channel-related genes have been discovered in a number of different neuropsychiatric disorders and are enriched in individuals with schizophrenia^{115,116}.

CACNA1C encodes the pore-forming α -subunit of the L-type VGCC $\text{Ca}_v1.2$ and is a consistently replicated genome-wide-significant risk factor for bipolar disorder and schizophrenia^{60,61}. Heterozygous mutations in *CACNA1C* cause Timothy syndrome, a rare developmental disorder associated with cognitive dysfunction and autism¹¹⁷. $\text{Ca}_v1.2$ channels are widely expressed in dendrites and spines, where they regulate calcium entry¹¹⁸. Brain imaging studies have found that the *CACNA1C* risk allele is associated with an age-related prefrontal cortical thinning in individuals with bipolar disorder¹¹⁹. Activity-dependent pruning of the excitatory synapses of medium spiny neurons is dependent on Ca^{2+} entry through $\text{Ca}_v1.2$ in co-culture models, indicating that pruning may play a part in this age-related thinning¹²⁰. Transgenic mice engineered with a Timothy-syndrome-related mutation in *CACNA1C* have decreased basal dendrite complexity in layer II/III, reminiscent of post-mortem analyses in bipolar disorder¹²¹. Disruption of downstream calcium-dependent signalling can also impair neuronal structure. A de novo ASD mutation in the catalytic domain of calcium/calmodulin-dependent kinase type II (CAMKII) decreases binding to other ASD-related proteins including SHANK3, the NMDAR subunit GluN2B, and the VGCC $\beta 2a$ subunit, causing reduced targeting to spines and reduced spine density in hippocampal cultures¹²².

Thus, elements of the calcium signalling pathway are directly involved in the structural rearrangement of neurons and may be particularly important for circuit remodelling after synaptic activity. Calcium triggers multiple downstream signalling pathways and may therefore affect an array of different cellular events linked to structural plasticity. Disruption to calcium signalling caused by genetic mutation would conceivably contribute to pathogenesis in early and late neuro-developmental events (TABLE 1).

Small GTPases.

Small GTPases are a large superfamily of regulatory proteins that induce activation of downstream signalling upon binding of GTP, which they then hydrolyse to GDP. RAS-related C3 botulinum toxin substrate 1 (RAC1) and RAS activation have been extensively characterized in vitro as causative factors in spine formation, enlargement, maturation and stabilization as well as synapse strengthening^{123,124}, whereas transforming protein RhoA (RHOA)¹²⁵ and RAP¹²⁶ activation causes spine shrinkage and elimination as well as synapse weakening. GTPase activation is provided by the action of guanine nucleotide exchange factors (GEFs) and inactivation by GTPase-activating proteins (GAPs).

RAS has a well-documented role in regulating synaptic plasticity¹²⁷ and has been implicated in intellectual disability¹²⁸. RAS is classically activated in response to stimulation of receptor tyrosine kinases by neuro-trophins, inducing phosphoinositide 3-kinase (PI3K) and extracellular-signal-regulated kinase (ERK) signalling that promotes AMPAR membrane insertion and spine enlargement¹²⁹ (FIG. 4). RAS/RAP GTPase-activating protein SynGAP (SYNGAP1) is a brain-specific RAS-GAP that is highly abundant in the PSD. Mutations within *SYNGAP1* cause intellectual disability, epilepsy and ASD¹³⁰. Defects in spine and synapse formation were observed in cultured *Syngap1*-knockout mouse neurons^{131,132}, whereas *Syngap1*^{-/+} mice accumulated glutamate receptors in spines earlier than wild-type mice, resulting in significantly higher spine density and impaired synaptic plasticity¹³³. Although heterozygous *Syngap1* mutants display few synaptic defects in adulthood, conditional knockout during an early developmental stage was sufficient to induce learning deficits in adult mice, suggesting that SYNGAP1 and RAS regulation are critical during early neuronal development¹³⁴.

Mutations within *NFI*, which encodes neuro-fibromin (another RAS-GAP present within spines), cause neurofibromatosis and intellectual disability¹³⁵. Neurofibromin is required for normal spine density¹³⁶. In addition, conditional knockout of *Tsc1* and *Tsc2*, two genes encoding GAPs for the RAS-like GTP-binding protein Rheb (RHEB), in mice revealed the central importance of these molecules in maintaining normal spine size and density¹³⁷. In humans, mutations in *TSC1* and *TSC2* cause tuberous sclerosis complex, a disorder associated with intellectual disability, ASD and epilepsy¹³⁸. Therefore, RAS and/or RHEB regulation by GAPs is integral to the formation and development of spines, and its dysregulation is intimately linked to neuropsychiatric disorders.

RHOA and RAC1 are the archetypal RHO family members and control separate and opposing rearrangements of the actin cytoskeleton^{124,125} (FIG. 4). Several RHO-GEFs and RHO-GAPs have been associated with neuropsychiatric disorders and regulate spines. Kalirin and triple functional domain protein (TRIO) are highly homologous, multifunctional proteins that contain both RAC-GEF and RHO-GEF domains. Both proteins are abundant in spines and regulate spine maintenance¹³⁹. A dual *Trio* and *Kalrn* knockout in mice resulted in an 80% loss of spines within CA1 hippocampal neurons and profound effects on LTP induction¹⁴⁰. A rare mutation in the RAC-GEF domain of *KALRN*, detected in individuals with schizophrenia and major depressive disorder (MDD), induces spine loss in vitro and is associated with reduced cortical thickness in individuals with schizophrenia carrying the mutation¹⁴¹. Another mutation in *KALRN*, P2255T, is the only exonic mutation with an association with schizophrenia¹⁴² and recent studies suggest that it causes dendrite simplification¹⁴³. Furthermore, a homozygous missense variant in *KALRN* causes intellectual disability¹⁴⁴. Mutations in *TRIO* and/or *KALRN* have been detected in intellectual disability^{145,146} and in whole-exome sequencing studies in ASD⁷⁰ and developmental disorders¹⁴⁴. Notably, alterations in the kalirin–RAC–serine/threonine protein kinase PAK (PAK1) pathway have been reported in post-mortem studies in schizophrenia. These changes include reduced expression of kalirin 7 (REFS 147,148), increased expression of kalirin 9 (REF 149), reduced PAK1 phosphorylation and increased myosin light chain phosphorylation¹⁴⁸. [Au:OK?] Similarly, levels of the closely related RAC1

homologue, CDC42, were reduced in human schizophrenia cortex^{148,150}. Interestingly, despite their overlapping function within spines, mutations within *TRIO* and altered *KALRN* expression are linked to different disease states — *KALRN* with schizophrenia^{128,129} and *TRIO* with ASD and/or intellectual disability^{70,151}. This difference may be a direct result of disrupted GTPase activity at key stages of spine formation and maturation, given that *TRIO* is expressed during early development¹⁵² and the main neuronal kalirin isoform, kalirin 7, is expressed at later stages¹⁵³.

Several other RAC1 and/or RHO regulators and targets have been linked to intellectual disability. Of these, *OPHNI* (encoding oligophrenin 1)^{154,155}, *ARHGEF6* (REF. 156) and *PAK3* regulate spine plasticity^{157,158}. Interestingly, mutations in *GITI1*, encoding a protein that regulates synapse formation¹⁵⁹ and spine density¹⁶⁰ and alters RAC and/or PAK3 signalling, has been linked to schizophrenia¹⁶¹. The related family members, *PAK2* and *PAK7*, have also been found to play a key role in regulating neuroplasticity and psychoses, suggesting a functional link to schizophrenia^{162,163}. In addition, the intellectual-disability-linked gene *ARHGEF2*, encoding the GEF H1, has been implicated in regulating spine density and length as well as AMPAR mediated structural plasticity¹⁶⁴. The gene encoding WAVE-associated RAC GTPase-activating protein (WRP), *SRGAP3*, may be associated with intellectual disability¹⁶⁵ and has been functionally linked to impaired spine precursor formation on dendrites, resulting in reduced spine density and mushroom spine number. Indeed, loss of WRP impairs learning and memory in heterozygous and null mouse models, highlighting the importance of this GAP in spine development and neuropsychiatric disorders¹⁶⁶.

A prominent role for small GTPase regulatory pathways in neuropsychiatric disorders (TABLE 1) is consistent with their regulation of multiple spine and/or dendrite remodelling processes. Most severe mutations in these genes seem to be associated with early-onset neuropsychiatric disorders, such as intellectual disability and ASD, suggesting an important role in the early formation of synaptic circuits.

Novel therapeutic avenues

Traditional pharmacological treatments for neuropsychiatric disorders have typically targeted serotonin reuptake (tricyclic or selective serotonin reuptake inhibitor antidepressants¹⁶⁷) and dopamine receptors (antipsychotics for schizophrenia and bipolar disorder¹⁶⁸), whereas epilepsy treatments employ a range of sodium, calcium and GABAergic channel regulators depending on seizure type¹⁶⁹. Although efficacious for many patients, these treatments suffer from various serious drawbacks. For example, antidepressants and anti-psychotics can cause serious side effects that result in high rates of noncompliance. Furthermore, antipsychotic use ameliorates the positive symptoms of schizophrenia and bipolar disorder with limited efficacy in treating negative and cognitive defects, whereas many sufferers of depression are resistant to treatment¹⁷⁰. These limitations have prompted the search for novel drug targets, informed by molecular and genetic studies, which can circumvent the negative side effects of traditional therapeutics while improving patient outcomes (FIG. 4). A greater understanding of the molecular substrates of dendritic and spine alterations in neuropsychiatric disorders may facilitate the development of novel

therapeutic approaches to reverse or delay neuronal defects and, therefore, the course of disease.

Despite the prevalence of adhesion and scaffold molecules identified in genetic studies of neuropsychiatric disorders, difficulty in targeting such classes has precluded the development of any clinically relevant drugs. Of the risk genes associated with neuropsychiatric disorders, membrane receptors have received the greatest attention in drug development, although recent clinical studies suggest that GTPase signalling pathways represent a novel therapeutic avenue. Below, we review recent developments in drug development targeting glutamatergic, calcium and GTPase signalling pathways within the synapse.

Targeting glutamate receptors.

Owing to their central importance in synaptic transmission and plasticity and their extensive genetic links to neuropsychiatric disorders, NMDARs¹⁷¹ and AMPARs¹⁷² have been the focus of many drug development attempts. Emerging data suggest that structural modulation of neurons through pharmacological intervention underlies some of the beneficial effects of NMDAR and AMPAR regulators in disease^{173,174}. Indeed, as described above, it is hypothesized that reducing excessive glutamatergic activity and/or spine formation in ASD may be beneficial, whereas enhancing spine formation, stabilization and plasticity may be the goal in schizophrenia and bipolar disorder.

Interest in the NMDARs as a pharmacological target was spurred by the striking effect of the pore blocker ketamine on individuals with depression¹⁷⁵. In contrast to typical antidepressants, a single intravenous injection of ketamine can produce a rapid, long-lasting reduction in the symptoms of depression (reviewed in REF. 176). Atypical spiny synapse connectivity has been reported in MDD¹⁷⁷ and bipolar disorder⁵², and stress, a risk factor in MDD and bipolar disorder, causes spine alterations in animal models^{178,179}. Accordingly, evidence shows that ketamine acts, at least in part, by modulating spine plasticity¹⁸⁰. For example, ketamine rapidly increased the number and function of new spiny synapses in the PFC of rats through mechanisms involving mammalian target of rapamycin (mTOR) signalling, reversing stress-induced synaptic deficits¹⁸¹. In another study, ketamine enhanced spine formation and induced a larger-scale remodelling of the dendritic arbor at different rates¹⁷³.

Despite its remarkable antidepressant effects, ketamine can induce psychotic behaviour and cognitive defects in healthy individuals and exacerbate schizophrenia psychoses^{182–184}. Furthermore, controversy exists over its mechanism of action. Indeed, mechanisms involving AMPAR regulation¹⁸⁵, reduction of presynaptic inhibitory GABAergic input¹⁸⁶, alterations in NMDA-mediated miniature excitatory postsynaptic currents¹⁸⁷ and metabolism of ketamine to (2*R*,6*R*)-hydroxynorketamine¹⁸⁸ have been proposed (reviewed in REFS 189,190). The underlying effects have been extensively linked to the altered translation of brain-derived neurotrophic factor (BDNF), which has been shown to have a crucial role in mediating the sustained antidepressant effects of ketamine^{191,192}. Therefore, a greater understanding of ketamine's modulation of spine plasticity is crucial to engineer drugs

developed for maximal efficacy in neuropsychiatric disorders with minimal psychomimetic and cognitive side effects.

NMDAR partial agonists, such as glycine/D-serine and D-cycloserine, have been shown to be efficacious in reducing depression in schizophrenia^{193–195} and ASD¹⁹⁶ and lack the psychomimetic side effects of ketamine. The success of NMDAR partial agonism is exemplified by rapastinel, a tetrapeptide derivative of the B6-B21 monoclonal antibody, which targets the glycine-binding site¹⁹⁷. This brain-permeable compound has shown promise in both preclinical and clinical trials, including fast-acting antidepressant effects similar to ketamine in the absence of psychomimetic side effects¹⁹⁸, which has warranted ‘fast-tracking’ to phase III clinical trials (NCT02951988 (REF. 199) and NCT02943564 (REF. 200)). Of particular interest is the ability of rapastinel to reverse social phenotypes in preclinical animal models, suggesting that NMDAR regulation is a potential treatment for ASD^{201,202}. Several studies show that rapastinel acts, at least in part, by modulating spine plasticity; treatment rapidly increased the number and function of spine synapses in the apical dendritic tuft of layer V pyramidal neurons in the medial PFC¹⁸⁰, enhanced the recovery of spines after insults²⁰³ and increased sensitivity to LTP and metaplasticity²⁰⁴. Apimostinel, a rapastinel derivative that is suitable for oral dosage, has recently been developed, and early clinical trials for depression have recently been completed, although results are pending (NCT02067793 (REF. 205)).

Increased AMPAR ligand binding has been observed in the striatum of individuals with schizophrenia and suicide victims²⁰⁶, suggesting deregulation of AMPAR activity in MDD and schizophrenia. Indeed, preclinical study of the role of positive allosteric modulators (PAMs; including ampakines) revealed a striking antidepressant effect in a variety of mouse models (reviewed in REF. 207). Furthermore, PAMs increased synaptic plasticity and showed promise in cognitive enhancement²⁰⁸. Thus, AMPARs may represent a promising therapeutic target in regulating cognitive impairment and mood disorders, such as bipolar disorder, schizophrenia and MDD. Ampakines have been shown to modulate spine plasticity, which may underlie part of their action. They facilitate dendritic recovery and improve synaptic plasticity and memory in middle-aged rats²⁰⁹ and promote spine actin polymerization in a model of Angelman syndrome²¹⁰. The ampakines CX546 and aniracetam reduced prepulse inhibition in a mouse model of schizophrenia²¹¹. This effect may be linked to the ability of CX546 to prime spines for structural plasticity, promote spine head enlargement and (in presynaptic terminals) increase the probability of neurotransmitter release²¹².

Clinical trials assessing the efficacy of ampakines in disease yielded mixed results. Phase I clinical trials assessing the suitable dosage of the AMPAR–PAM, Org 26576, revealed the drug was well tolerated, and a second study suggested both an improvement in depressive symptomatology and signs of cognitive enhancement^{213,214}. However, the PAM CX516 showed varying efficacy, failing to produce significant improvement in cognitive function in individuals with fragile X syndrome or schizophrenia²¹⁵. Despite the potential identified in preclinical studies, these results suggest that clinical efficacy is dependent on the drug mechanism or molecular and genetic context of disease. Further studies are required to confirm the potential of ampakines in AMPAR-related neuropsychiatric disorders.

Inhibition of AMPAR may be beneficial in neuropsychiatric disorders associated with an increased excitatory-to-inhibitory ratio²¹⁶, such as epilepsy, ASD and some forms of intellectual disability. Indeed, the clinically approved AMPAR inhibitor perampanel has efficacy in reducing tonic-clonic seizures²¹⁷. However, general AMPAR inhibition leads to an array of side effects and, to date, no selective subunit inhibitors have been isolated²¹⁸. To address this lack of specificity and avoid unwanted side effects, novel brain-region-specific protein modulators of AMPAR activity have been developed that inhibit the interaction of AMPARs with transmembrane AMPAR regulatory proteins (TARPs; encoded by genes *CACNG1–CACNG8* (REF. 191)). Of particular interest is TARP λ 8, which is expressed within the forebrain where it regulates AMPAR protein levels, surface expression and function²¹⁵. As a result, disrupting the TARP λ 8–AMPA interaction yields brain-region-selective AMPAR regulation. Recently, compounds that selectively inhibit the AMPAR–TARP λ 8 interaction have been shown to prevent seizures in animal models without the motor side effects associated with general AMPAR inhibition^{219,220}. As TARP λ 8 is underexpressed in schizophrenia²²¹ and *CACNG2* and *CACNG8* have been implicated as risk factors in schizophrenia and bipolar disorder (TABLE 1), compounds able to stabilize AMPAR–TARP complexes may provide a therapeutic strategy. TARPs target AMPAR to the PSD²²² and are required for LTP²²², suggesting that TARP regulators may be of substantial benefit to disorders stemming from abnormal structural plasticity.

Targeting calcium signalling.

Calcium signalling is central to dendritic development and spine plasticity, with the L-type VGCC mediating synaptic calcium influx in response to membrane depolarization²²³. Within the brain, Ca_v1.2 and Ca_v1.3 (encoded by *CACNA1C* and *CACNA1D*, respectively) are the predominant forms of the pore-forming calcium channel subunits and are major risk genes in a range of neuropsychiatric disorders (TABLE 1). They have been the target of effective VGCC channel blockers (CCBs; including nifedipine, verapamil and diltiazem²²³) developed for hypertension and arrhythmia. The ability to repurpose VGCC–CBCs for neuropsychiatric disorders prompted studies in the 1980s and 1990s, with several positive outcomes as adjunctive therapies to antipsychotics²²⁴. However, critical evaluation of multiple studies found that these drugs were as effective as placebo or produced inconsistent results^{225,226}. Identification of *CACNA1C* in GWAS as a risk factor in schizophrenia²²⁷ and bipolar disorder⁶¹ has prompted assessment of isradipine in schizophrenia (currently recruiting, NCT01658150 (REF 228)), and early trials suggest potential in bipolar disorder²²⁹. The observation that Ca_v1.2 is the major target of cardiac-protective and pulmonary-protective drugs prompted attempts to target Ca_v1.3 (REF 230). Such a strategy may avoid non-neural activation of Ca_v1.2 and thus facilitate Ca_v1.3-selective brain targeting and a higher tolerable dosage. A recent screen identified Cp8 as a compound exhibiting 600-fold selectivity for Ca_v1.3 over Ca_v1.2 (REF 230). Such Ca_v1.3 selective compounds could provide a novel route to regulate *CACNA1D*-dependent neuropsychiatric disorders. Future work aimed at revealing the modulation of dendritic and spine plasticity by such compounds may support VGCCs as a valuable therapeutic target in neurodevelopmental disorders.

Targeting small GTPases.

Small GTPases have been the target of extensive drug discovery efforts, largely owing to their role in cancers, providing a bounty of therapeutic agents with already well-characterized tolerability. Thus, reversing the RAS dysregulation caused by *NFI* and *SYNGAP1* mutations (see above) may be a valuable target for repurposing efforts in neuropsychiatric disorders.

RAS requires post-translation prenylation for its membrane insertion and full activity. The observation that limiting the addition of a farnesyl group to oncogenic RAS abrogated its transforming activity spurred the development of compounds to inhibit this process (reviewed in REF 231). Most of these agents inhibit farnesyltransferase (FT), but others (including statins) target farnesyl diphosphate synthesis to limit RAS activity. The potential of FT inhibitors and statins to treat neurological disease has been shown preclinically in mouse models of neurofibromatosis type 1 (REFS 232,233), prompting clinical trials in neurofibromatosis type 1 patients. The FT inhibitor tipifarnib produced significant increases in emotional health and suggestive evidence of improved cognitive function²³⁴. Similarly, lovastatin improved synaptic plasticity²³⁵ and learning and memory in neurofibromatosis type 1 patients during early-phase clinical trials^{236,237}. However, a recent, larger trial of lovastatin failed to show benefit in cognition to children with neurofibromatosis type 1 (REF 238). Thus, these studies suggest that RAS inhibitors are useful in neuropsychiatric disorders stemming from overactive RAS. Despite preclinical promise, conclusive evidence of the effects of RAS regulation in human neurodevelopmental disease is lacking.

Conclusions and future directions

Spine pathology is a convergence point of many neuropsychiatric disorders, as supported by mounting evidence from human post-mortem, cellular, animal and genetic studies. The most important advance in the past decade has come from translating human genetic information into bona fide risk factors and meaningful disease pathways in order to successfully model structural deficits under experimental conditions. Although this Review has covered many of the critical pathways involved in spine plasticity and disease, there are clearly other important pathways and genes that we have not been able to cover, including those affecting Wnt signalling, the actin cytoskeleton and chromatin remodelling^{71,239,240}. As the genetic studies of neuropsychiatric disorders progress, we can expect more disease-relevant biological processes to be revealed as well as a more complete understanding of the role of structural plasticity in other psychiatric conditions where genetic and experimental data are still emerging, such as attention-deficit hyperactivity disorder (ADHD), anxiety and depression. Functional analysis of these newly discovered genetic risk factors will be paramount to uncover novel mechanisms and pathways leading to atypical spine and dendrite development. In this endeavour, omic technologies and systems biology-level investigations will be essential to deconstruct the global alterations taking place in model systems. Drug discovery efforts may then be designed with genetic and pathway disruptions as a guide to better target underlying disease mechanisms.

In addition to genetics, new technological advancements in stem cell reprogramming and imaging (BOXES 1,2) have substantially improved our understanding of the mechanisms

regulating spine plasticity in health and disease. To further our understanding of structural deficits in human brain, future neuropathological studies should aim to stratify individuals on the basis of genetics and disease severity to address the considerable heterogeneity in neuropsychiatric disorders. The challenge for the future will be to integrate our expanding knowledge of human disorders into more comprehensive models of disease. Human neurons derived from genetically defined individuals will likely play a critical role (BOX 2), overcoming the limited genetic complexity and species differences inherent in animal models. Stem cell models provide a unique opportunity to examine the effects of new drugs that target structural plasticity pathways directly in dysmorphic patient neurons and in a high-throughput manner. The fact that structural pathology can be observed before cognitive symptoms in certain disorders suggests that there are critical time windows for treatment strategies to prevent disease onset²⁴¹. Furthermore, several mouse models have also shown that certain structural and behavioural deficits can be reversed in adult animals^{105,242–244}, offering hope for treating human conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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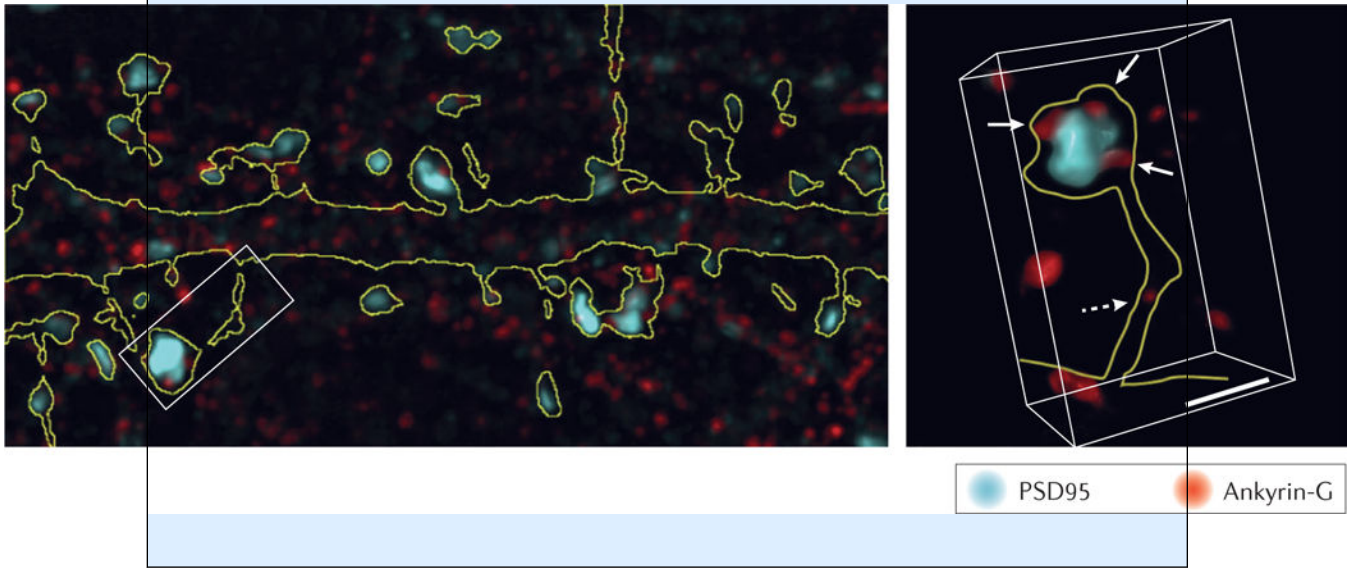
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Box 1 |**Super-resolution imaging of dendritic spines**

In recent years, super-resolution techniques that are able to break the diffraction limit of light microscopy (~200 nm) have routinely allowed fluorescent imaging with resolutions down to 50 nm (reviewed in REF 245). This ability has led to characterization of the dendritic spine in unprecedented detail and revealed novel mechanisms of structural regulation. Structured illumination microscopy¹⁰⁸ and novel image deconvolution protocols²⁴⁶ allow resolving power down to ~100–200 nm. This increased resolution allowed for the characterization of ankyrin-G nanodomains within spine necks and their regulatory role in dendritic spine morphology (see the figure)¹⁰⁸. However, techniques that rely on single-molecule localization (stochastic optical reconstruction microscopy (STORM) and photoactivated localization microscopy) or stimulated excitation emission depletion (STED) have garnered great interest owing to their ability to observe filament formation and protein complex distributions within spines. For example, STORM imaging was pivotal in the observation of previously uncharacterized presynaptic mitochondria that contribute to long-term plasticity²⁴⁷ and endogenous brain-derived neurotrophic factor (BDNF) granules that were enriched in the presynaptic but not postsynaptic areas²⁴⁸. In addition, the resolution afforded by STED microscopy revealed that the spine neck is vital in compartmentalizing synaptic signals²⁴⁹ and undergoes actin-dependent changes in size²⁵⁰ in response to long-term potentiation²⁵¹.

A major advantage of super-resolution techniques over electron microscopy is the ability to observe changes within live cells. For example, dynamic imaging of dendritic spine extension and retraction was achieved at nanoscale resolution using membrane-selective photo-switchable probes²⁵². In addition, super-resolution imaging has been applied to actin dynamics within the spine over extended periods of structural change with lateral resolutions exceeding 50 nm (REFS 250,253,254). Such studies revealed the role of actin in driving vesicle–membrane fusion²⁵⁵, a distinct AMPA receptor (AMPA) trafficking mechanism within subsets of spines²⁵⁶ and the formation of postsynaptic density–AMPA scaffolds that contribute to receptor clustering and responsiveness^{257,258}.

Thus, the rapid development of fluorescent imaging techniques has provided previously unachievable insight into dendritic spine structure and regulation. Increasing access to these imaging techniques will undoubtedly result in an even greater understanding of the structural mechanisms underlying neuronal function. PSD95, postsynaptic density protein 95 (also known as DLG4). Figure adapted with permission from REF. 108, Elsevier.



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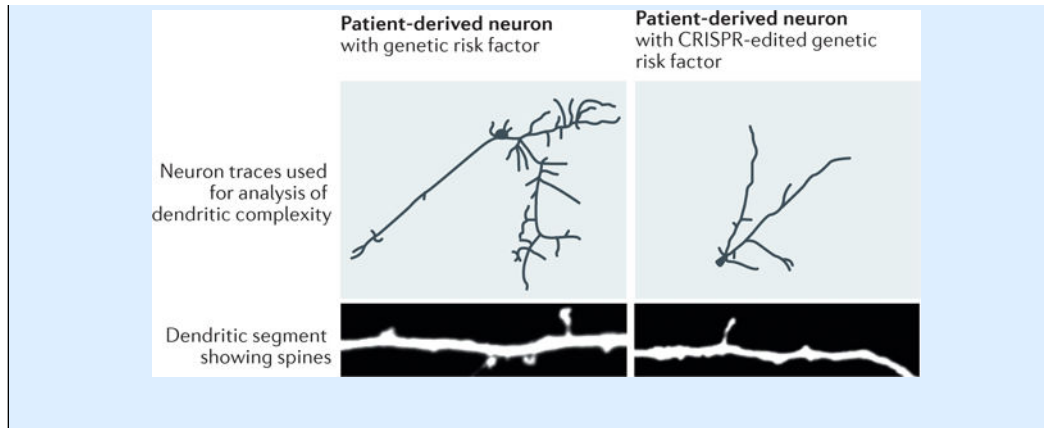
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Box 2 |**Stem cell models of atypical dendrite and spine development**

Progress in stem cell reprogramming technologies has revolutionized the way we can study neuropsychiatric conditions. Analysis of the structural and activity-dependent development of human induced pluripotent stem cell (iPSC)-derived neurons is still nascent and promises to complement human post-mortem and MRI studies, enabling research into the early molecular and cellular events that lead to neuropsychiatric disorders. To date, there have been several key insights from studies looking at dendritic and spine dysmorphogenesis in genetically defined human stem cells:

- iPSC-derived human neurons in which *SHANK3* is conditionally deleted display neurodevelopmental deficits with decreased dendritic complexity and synapse density¹⁰³.
- iPSC-derived human neurons generated from individuals with Timothy syndrome (in which there are mutations in *CACNA1C*) display defects in activity-dependent dendritic retraction¹²¹.
- A single-nucleotide polymorphism near microRNA locus *MIR137* that was identified in a genome-wide association study of schizophrenia is associated with increased dendritic complexity (see the figure) and an increased proportion of spines containing the AMPAR subunit GluA1 in patient iPSC-derived neurons²⁵⁹.
- Deletion of chromosome band 7q11.23 causes Williams–Beuren syndrome, and the same copy number variant is also associated with autism spectrum disorder (ASD). Neurons derived from iPSCs from individuals with the typical 7q11.23 deletion have a larger number of dendrites and dendritic spines and increased total dendrite length compared with controls²⁶⁰.
- Deletion of *MECP2* causes Rett syndrome, whereas duplication of *MECP2* causes a severe neurodevelopmental disorder with similar phenotypes. iPSC-derived neurons from individuals with Rett syndrome have a decreased spine density. Conversely, iPSC-derived neurons from individuals with *MECP2* duplications have increased dendritic complexity concomitant with an increased number of immature spines and a reduction of mature spines but no change in total spine number^{261,262}.
- iPSC-derived neurons from individuals with atypical Rett syndrome, caused by mutations in *CDKL5*, have an increased number of dendritic protrusions²⁶³.
- A heterozygous *NRXN1* deletion akin to those found in individuals with schizophrenia and ASD does not impair synapse number or dendrite development in iPSC-derived human neurons²⁶⁴.

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Key points

- The development of dendritic branches and spines, which host the excitatory postsynaptic machinery, is atypical in neuropsychiatric disorders.
- Genetic risk factors for neuropsychiatric disease converge on genes that encode proteins present in excitatory postsynaptic termini with known roles in dendritic structural plasticity.
- Risk variants in genes regulating structural plasticity may explain the atypical dendrite and spine development observed in individuals with neuropsychiatric disorders.
- Drug discovery efforts targeting the genetic risk factors affecting the structural plasticity of dendritic spines have been successful in improving patient outcomes. Genetics may facilitate the prioritization, or elucidation, of drug targets within neuropsychiatric disorders.
- Stem cell models can be used to model the structural deficits in individuals with neuropsychiatric disease, offering an avenue for screening personalized treatments.

Subject categories

Biological sciences / Neuroscience / Spine regulation and structure / Spine plasticity
[URI /631/378/2597/2599]

Biological sciences / Neuroscience / Diseases of the nervous system / Autism spectrum disorders [URI /631/378/1689/1373]

Biological sciences / Neuroscience / Diseases of the nervous system / Schizophrenia
[URI /631/378/1689/1799]

Biological sciences / Neuroscience / Diseases of the nervous system / Bipolar disorder
[URI /631/378/1689/1333]

Techniques terms

Life sciences techniques, Genomic analysis [Genome-wide association studies]

Life sciences techniques, Genomic analysis [DNA sequencing]

Life sciences techniques [Cellular imaging]

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NIH Research Domain Criteria (RDoC): <https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>

denovo-db (collection of human de novo variants): <http://denovo-db.gs.washington.edu/denovo-db/>

DAVID (Database for annotation, visualization and integrated discovery): <https://david.ncifcrf.gov/>

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Dendritic spines

Micrometre protrusions on dendritic branches of neurons that host the majority of excitatory synapses in the brain.

Genetic risk factors

DNA sequence variants that are associated with increased disease susceptibility.

Synaptic input field

The total number and spatial arrangement of a neuron's postsynaptic receptors. This postsynaptic field is determined by the architecture of the dendritic tree and the number and size of receptor domains contained within dendritic spines.

Postsynaptic density(PSD).

A specialization on excitatory dendritic spines, originally identified by electron microscopy, which contains glutamate receptors and many associated scaffolding and trafficking proteins that are crucial for excitatory synaptic transmission.

Long-term potentiation(LTP).

Long-lasting increase in synaptic strength between neurons, usually resulting from synchronous or temporally coordinated presynaptic and postsynaptic activity,

Long-term depression(LTD).

Long-lasting weakening of synaptic strength between neurons, often resulting from asynchronous presynaptic and postsynaptic activity.

Cell reprogramming technologies

Techniques in biotechnology used to convert one cell type into another using defined biological factors; for example transcription factors can be introduced into adult somatic cells to reprogramme them into induced pluripotent stem cells or induced neurons.

Common variants

Alterations in a DNA sequence, often with small effect on disease risk, which are present in large proportion of the general population (>1%). These are typically single-nucleotide polymorphisms that are identified in genome-wide association study (GWAS).

Rare variants

Mutations in a DNA sequence, often with a large effect on disease risk, which occur only in a small fraction of the general population (<1%). These types of variants are usually identified in family, exome sequencing or copy number variant (CNV) studies.

Genome-wide association studies(GWAS).

Genetic study designed to identify variants in the genome that associate with a disease or trait. Large-scale GWAS have been especially successful in identifying many common risk variants in schizophrenia and bipolar disorder.

Exome sequencing

Genomic sequencing technique used to sequence all of the protein-coding regions (exons) of the genome.

Enrichment analyses

Bioinformatic technique used to identify over-represented gene sets or biological processes from large omic data sets. This method is typically used to understand the concerted function of hundreds of genes and/or proteins from genomic and proteomic data.

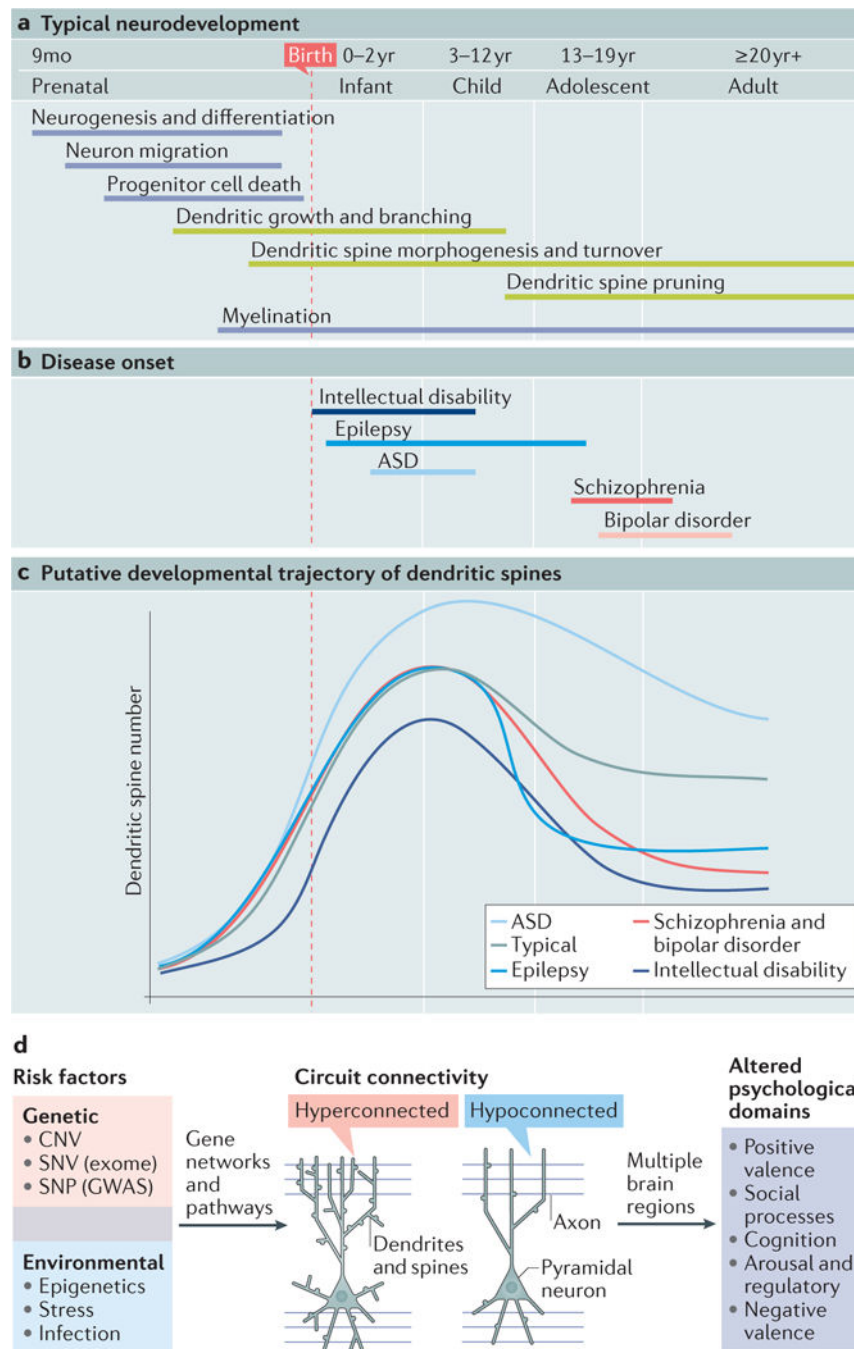


Figure 1]. Spine and dendrite development in health and disease.

a,b) Timeline of the principal cellular events occurring during human brain development^{1,265} and their coincidence with neuropsychiatric diseases of varying onset. Morphological events regulating dendritic structure that are discussed in this Review are highlighted in green. Intellectual disability usually presents in early infancy or early childhood, although in some cases, it cannot be formally diagnosed until later (when standardized tests can be implemented)²⁶⁶. Epilepsy encompasses a broad range of seizure disorders, each with their own typical age of onset. Here, we focus on genetic forms of epilepsy that have their onset

largely in the age range depicted (see REF. 267 for review). The symptoms of autism spectrum disorder (ASD) are recognized early in development and are noticeable in the first few years of life²⁶⁸. These early-onset disorders overlap with the developmental processes of dendritic growth and spine morphogenesis. Bipolar disorder²⁶⁹ and schizophrenia²⁷⁰ are late-onset neurodevelopmental disorders that appear in late adolescence or adulthood, coinciding with the biological process of spine pruning. **c** | Putative developmental trajectories of spine development during typical development or in neuropsychiatric disorders, predicted from post-mortem studies. Studies have found that spine density is reduced in intellectual disability³⁹ and increased in ASD⁴¹, which may suggest a developmental alteration in spine morphogenesis. Spine and dendrite loss in epilepsy is thought to be caused by the onset of seizures⁴⁵ and is depicted as a sharp decline in spine density (however, a primary defect in spine density before seizure onset cannot be excluded). Schizophrenia and bipolar disorder are associated with fewer dendritic spines post-mortem^{48,53}, possibly caused by excessive spine pruning. **d** | Genetic and environmental risk factors for neuropsychiatric disorders are hypothesized to converge on a subset of genetic networks and pathways that regulate dendritic structure and alter the synaptic input field. Both hypoconnected and hyperconnected cells disrupt local and distal connectivity in the brain. Depending on the brain regions affected, this will impact different psychological domains (here, we use the National Institutes of Health Research Domain Criteria (RDoC) relevant to neuropsychiatric disorders; see 'Related links'). CNV, copy number variant; GWAS, genome-wide association study; mo, month; SNP, single-nucleotide polymorphism; SNV, single-nucleotide variation.

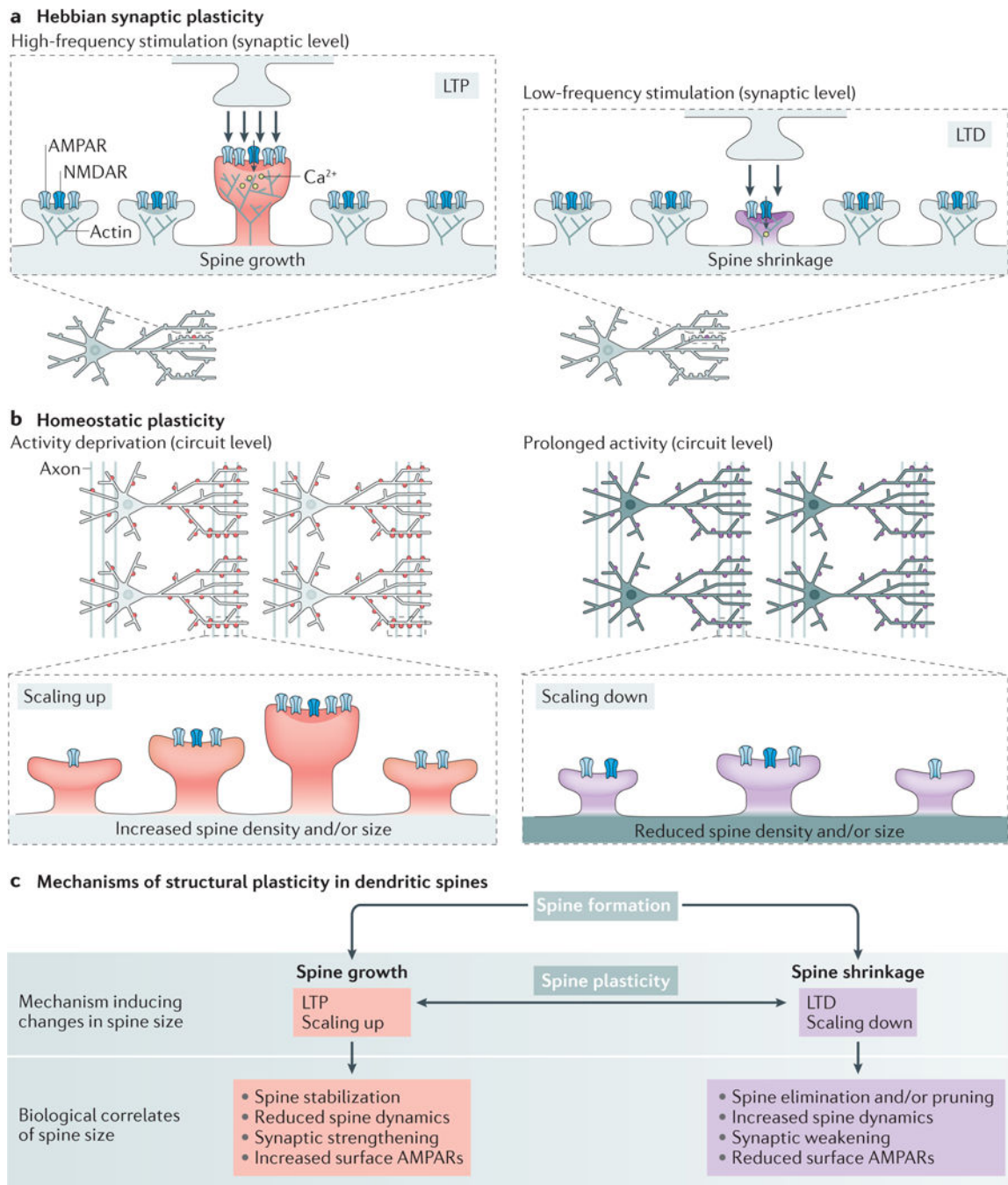


Figure 2|. Mechanisms of structural plasticity.

a | Hebbian synaptic plasticity mechanisms^{25,94}. High-frequency synaptic activity associated with high calcium entry causes long-term potentiation (LTP), which induces spine growth, an enlargement of the postsynaptic density (PSD) and actin polymerization and promotes the surface expression of AMPA receptors (AMPA). Low-frequency synaptic activity associated with modest calcium entry through NMDA receptors (NMDARs) causes long-term depression (LTD), which induces shrinking of the spine and PSD, actin depolymerization and a reduction of surface AMPAR expression. **b** | Proposed mechanisms

of homeostatic synaptic plasticity². Synaptic scaling is a form of homeostatic plasticity that allows neurons to modify their overall synaptic input (excitability) in response to changes in circuit activity²⁶. Activity deprivation causes neurons to scale up, proportionally strengthening synapses by increasing surface AMPAR expression to increase overall synaptic input. Studies have shown that activity blockade in vitro and activity deprivation in vivo can also cause an increase in spine size (or density)^{29,31,32}. Prolonged circuit activity causes neurons to scale down, proportionally reducing synaptic strength by removal of surface AMPARs. Prolonged activity during seizures also reduces the size and number of spines^{33,34}, opposing the morphological effects of activity deprivation. **c** | Summary of mechanisms that can regulate spine development and plasticity. Spine growth can be induced by LTP or scaling up and is associated with spine stability, reduced spine dynamics, increased synaptic strength and increased surface AMPAR expression¹⁴. Spine shrinkage can be induced by LTD or scaling down and is associated with spine destabilization, possibly leading to elimination or pruning of spines, synaptic weakening and a reduction of surface AMPAR expression¹⁴.

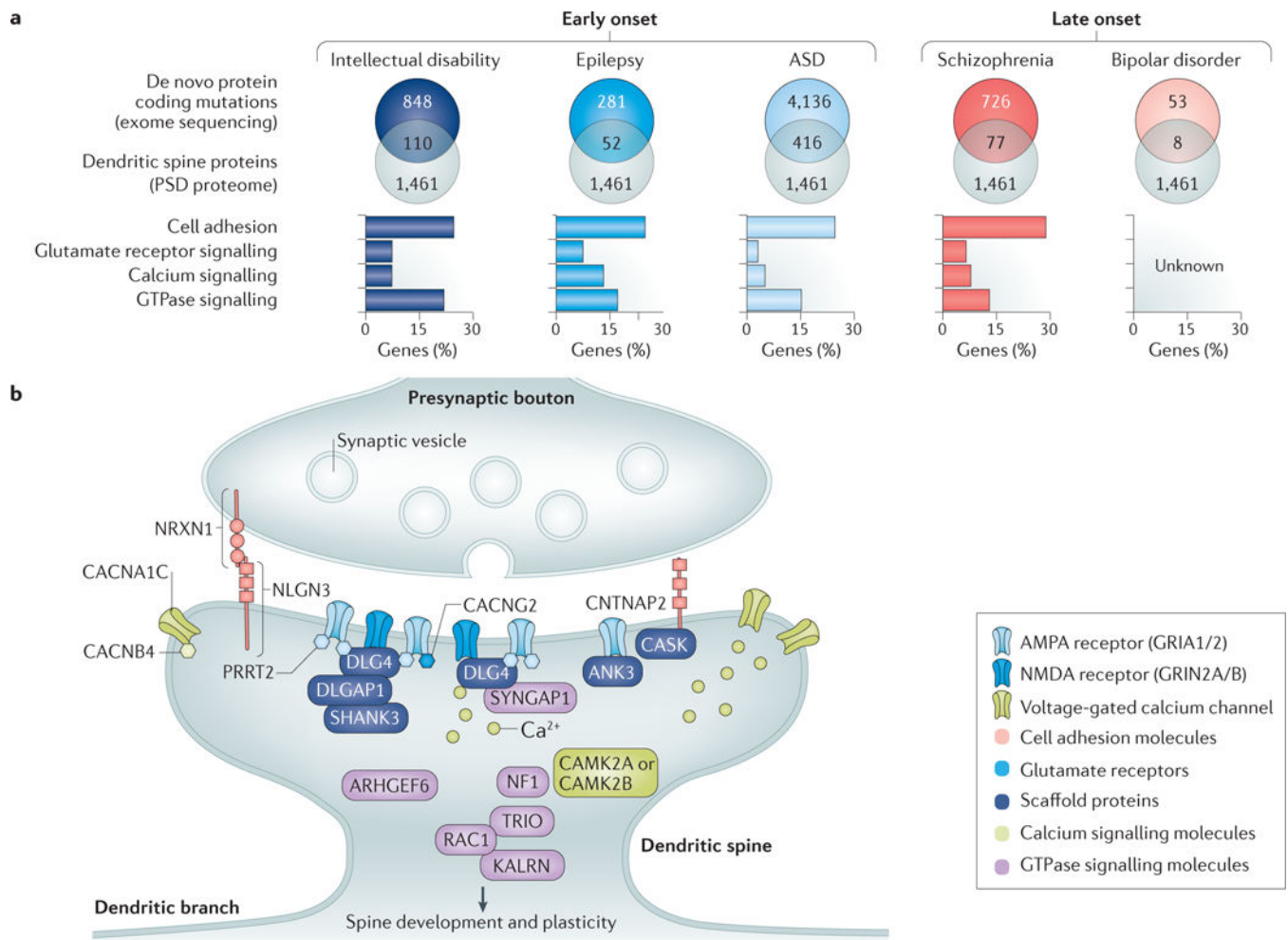


Figure 3]. Neuropsychiatric risk factors and biological pathways regulating structural plasticity.
a |Schematic illustration of a systems biology approach for identifying novel genes likely to affect spine plasticity in neuropsychiatric disorders. Exome sequencing studies of de novo variants are particularly useful for uncovering genetic risk networks involved in different disorders. Although many genes discovered in exome sequencing studies are individually nonsignificant, as a whole, they can reveal a mutational spectrum for each disorder and provide clues for the underlying pathways and networks involved in pathogenesis. In particular, genes with de novo mutations for which the protein products localize to the postsynaptic density (PSD) are excellent candidates for future studies on the dysfunctional pathways altering structural plasticity in neuropsychiatric disorders. To highlight such genes, de novo mutations affecting protein coding for each disorder were intersected with proteins present in the human PSD proteome²⁷¹ (a proxy for the dendritic spine). The number of genes in each overlap is indicated (top panels). All of the de novo data were obtained from denovo-db (see ‘Related links’)²⁷² accessed on 21 September 2017. Additional studies for schizophrenia^{273–275} that were not in the denovo-db were obtained from supplementary data compiled in REF²⁷⁶. Only de novo variants affecting protein-coding regions or splice sites were included (that is, missense, frameshift and splice site mutations, altered stop codons, altered start codons, insertions and deletions). Human PSD proteome data were obtained

from REF. 271. Gene ontologies (GOs) were then used to classify PSD-associated mutations into biological processes relevant to spine structure and function. To do so, GO categories from each data set were defined in DAVID (see 'Related links') v6.8, accessed on 11 November 2017, using the functional annotation chart. Homo sapiens was used as a background, and the 'biological process' ontology (GOTERM_BP_FAT) was used to annotate gene lists. The following ontologies were used to cluster genes into functional pathways: cell adhesion (GO:0007155-cell adhesion), GluR signalling (GO:0007215-glutamate signalling pathway), calcium (GO:0006816-calcium ion transport) and GTPase (G00043087-regulation of GTPase activity). This analysis shows that the de novo mutations affecting PSD proteins cluster into distinct biological pathways to varying degrees, providing an overview of the contribution of each pathway to each disorder (bottom panels). The percentage of genes in each GO category is depicted on the y-axis. Exome sequencing data for bipolar disorder are currently insufficient to classify mutations into categories. **b** | Illustration of a dendritic spine containing different functional groups of neuropsychiatric-disorder-associated risk factors (TABLE 1) that regulate spine structure. Functional groups are colour coded. ANK3, ankyrin 3; ARHGEF9, Rho guanine nucleotide exchange factor 9; ASD, autism spectrum disorder; CACNA1C, voltage-gated calcium channel subunit- α 1Cav1.2; CACNG2, voltage-dependent calcium channel- γ 2 subunit; CACNB4, calcium channel voltage-dependent subunit- β 4; CAMK2A/B, calcium/calmodulin-dependent protein kinase type II subunit- α/β ; CASK, calcium/calmodulin-dependent serine protein kinase; CNTNAP2, contactin-associated protein-like 2; DLG4, disks large homologue 4; DLGAP1, disks large-associated protein 1; GRIA1/2, glutamate receptor ionotropic, AMPA1/2; GRIN2A/B, glutamate receptor ionotropic NMDA2A/B; KALRN, kalirin; NF1, neurofibromin 1; NLGN3, neuroligin 3; NRXN1, neurexin 1; PRRT2, proline-rich transmembrane protein 2; RAC1, RAS-related C3 botulinum toxin substrate 1; SHANK3, SH3 and multiple ankyrin repeat domains protein 3; SYNGAP1, RAS/RAP GTPase-activating protein SynGAP 1; TRIO, triple functional domain protein.

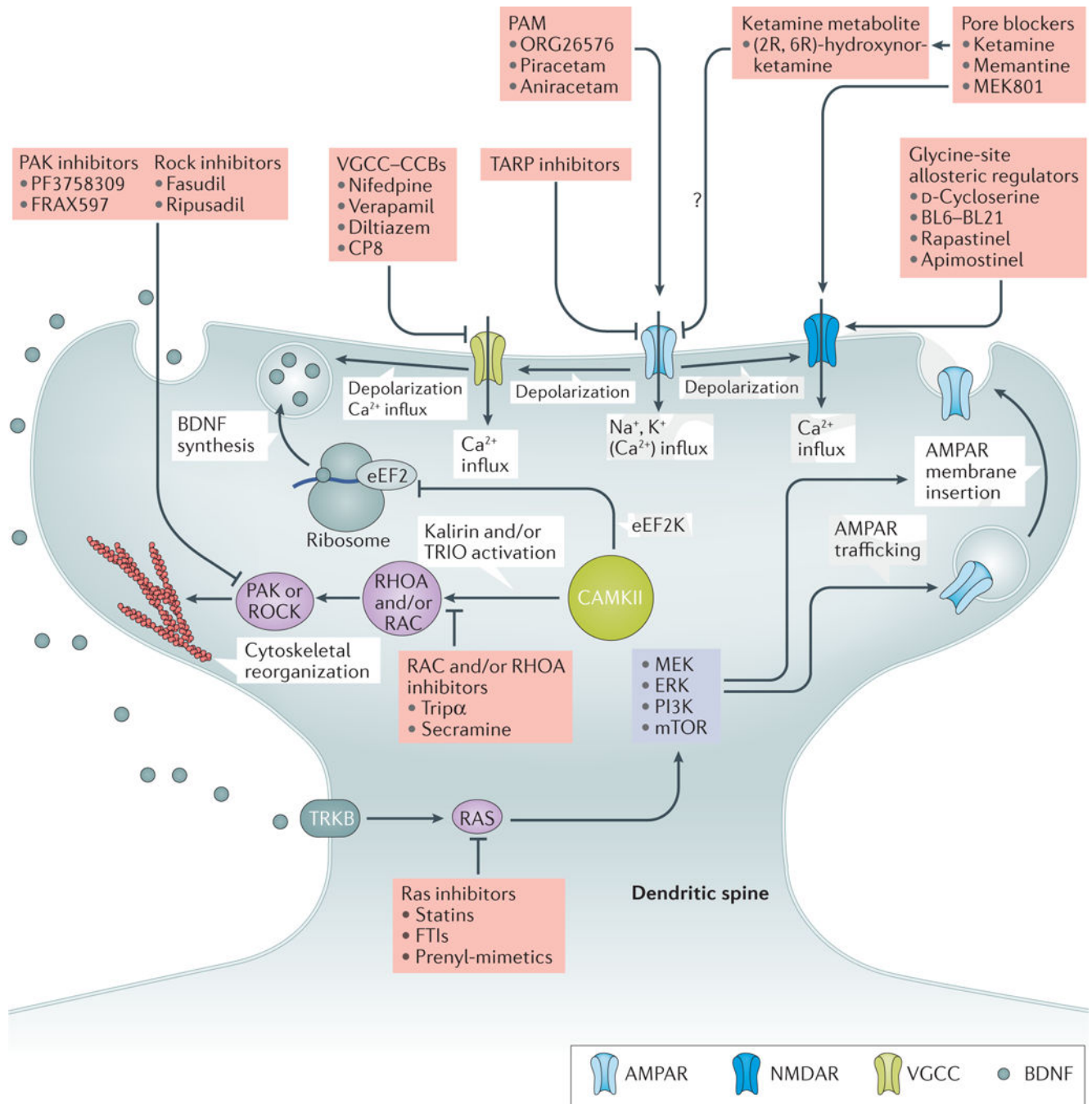


Figure 4. Pharmacological targets and associated structural pathways within the dendritic spine. Within the dendritic spine, AMPA receptors (AMPARs) govern fast synaptic transmission in response to glutamatergic signalling. Glutamate binds to, and activates, AMPARs in response to synaptic activity. The resulting influx of sodium and potassium ions through the open channel results in depolarization²⁷⁷. NMDA receptor (NMDAR) activation occurs in response to glycine and glutamate binding concurrently with depolarization. In addition, depolarization results in the opening of voltage-gated calcium channels (VGCCs; including L-type, $\text{Ca}_v1.2/1.3$ -containing channels). Depolarization and VGCC activation result in

brain-derived neurotrophic factor (BDNF) exocytosis²⁷⁸. Calcium influx activates calcium/calmodulin-dependent kinase type II (CAMKII)²⁷⁹, resulting in activation of GTPase signalling by phosphorylation of kalirin¹³⁹ and/or triple functional domain protein (TRIO)¹⁴⁰. These guanine nucleotide exchange factors regulate RAS-related C3 botulinum toxin substrate 1 (RAC)/transforming protein RhoA (RHOA) to alter cytoskeletal dynamics. GTPase activation can either increase (RAC pathway) or decrease (RHOA pathway) actin polymerization through serine/threonine protein kinase PAK (PAK) or Rho-associated protein kinase (ROCK) pathways to promote spine growth or retraction, respectively^{124,125}. In addition, calcium results in the activation of eukaryotic elongation factor 2 kinase (eEF2K), phosphorylation of elongation factor 2 (EF2) at Thr56 (REF. 192) and inhibition of BDNF translation at ribosomes. BDNF release results in the activation of the BDNF/NT3 growth factor receptor (TRKB; also known as NTRK2) and induction of the RAS pathway through growth factor receptor-bound protein 2 (GRB2) and son of sevenless homologue 1 (SOS1; not shown), which in turn activates the phosphatidylinositol 3-kinase (PI3K) and MEK (MAPK/ERK kinase) and/or extracellular-signal-regulated kinase (ERK) pathways, contributing to long-term potentiation via AMPAR trafficking and membrane insertion within the spine²⁸⁰. Many regulatory compounds targeting key synaptic signalling proteins have been isolated (indicated in the pink boxes). These, or other related small molecules, may have utility in neuropsychiatric disorders by regulating synaptic function and spine dynamics. CCBs, calcium channel blockers; FTIs, farnesyl transferase inhibitors; mTOR, mammalian target of rapamycin; PAM, positive allosteric modulator; TARP, transmembrane AMPAR regulator protein. TRIP α , TRIO inhibitory aptamer; Question mark indicates unknown mechanism.

Table 1 |

Neuropsychiatric risk loci with a reported effect on structural plasticity

| Gene or copy number variant | Gene name or description | Type of effect on spines and/or dendrites | Disease associations |
|-----------------------------|--|---|---|
| Cell adhesion | | | |
| <i>NRXN1</i> | Neurexin 1 | Spine stability ⁷⁹ | SZ ⁸¹ and ASD ⁶ |
| <i>NLGN3</i> | Neurologin 3 | Spine density ⁸⁰ | ASD ⁶⁴ |
| <i>CNTNAP2</i> | Contactin-associated protein-like 2 (also known as CASPR2) | Spine and dendrite stability ⁸⁶⁻⁸⁸ | ID and ASD ⁸³ |
| <i>DSCAM</i> | DS cell adhesion molecule | Dendrite and spine development ²⁸² | ASD ⁶⁴ |
| <i>PCDH10</i> | Protocadherin 10 | Spine density ²⁸³ | ASD ²⁸³ and SZ ⁶³ |
| Glutamate receptors | | | |
| <i>GRIA1</i> | Glutamate ionotropic receptor AMPA type subunit 1 | Spine size ⁹³ | SZ ⁶⁰ , ID ⁶⁵ and ASD ⁶⁴ |
| <i>PRRT2</i> | Proline-rich transmembrane protein 2 | Spine density ²⁸⁴ | Epilepsy ²⁸⁵ |
| <i>CACNG2</i> | Calcium voltage-gated channel auxiliary subunit- γ 2 (also known as TARP- γ 2) | Dendritic arborization ²⁴⁶ | ID ⁷ |
| <i>GRIN2A</i> | Glutamate ionotropic receptor NMDA type subunit 2A | Dendritic arborization ⁹⁹ | SZ ⁶⁰ and epilepsy ²⁸⁶ |
| <i>GRIN2B</i> | Glutamate ionotropic receptor NMDA type subunit 2B | Spine density ⁹⁷ | ASD ⁶⁴ |
| Scaffold proteins | | | |
| <i>SHANK3</i> | SH3 and multiple ankyrin repeat domains 3 | Dendrite and spine development ^{103,106,107} | ASD ^{64,287} |
| <i>ANK3</i> | Ankyrin 3 (also known as ankyrin-G) | Spine size and density and activity-dependent spine enlargement ¹⁰⁸ | BD ⁶¹ |
| <i>DLG4</i> | Discs large MAGUK scaffold protein 4 (also known as PSD95) | Spine density and size; activity-dependent structural plasticity ^{288,289} | ASD and/or ID ²⁹⁰ |
| <i>DLGAP1</i> | DLG associated protein 1 (also known as GKAP and SAPAP1) | Spine size ²⁹¹ | ASD and/or ID ²⁹⁰ |
| <i>CASK</i> | Calcium/calmodulin-dependent serine protein kinase | Spine density and size ²⁹² | ASD and/or ID ²⁹⁰ and DD ⁶⁷ |
| Calcium signalling | | | |
| <i>CACNA1C</i> | Calcium voltage-gated channel subunit- α 1C | Spine density ²⁰ | BD ⁶¹ and SZ ⁶⁰ |
| <i>CACNB4</i> | Calcium voltage-gated channel auxiliary subunit- β 4 | Spine density | SZ ^{115,116} |
| <i>CAMK2B</i> | Calcium/calmodulin-dependent protein kinase II β | Activity-dependent spine formation ²⁹³ and dendritic arborization ²⁹⁴ | ID ²⁹⁵ |
| <i>CAMK2A</i> | Calcium/calmodulin-dependent protein kinase II α | Activity-dependent spine formation ²⁹³ | ASD ⁶⁴ and ID ²⁹⁵ |
| GTPase signalling | | | |

| Gene or copy number variant | Gene name or description | Type of effect on spines and/or dendrites | Disease associations |
|--|---|--|---|
| <i>Cell adhesion</i> <i>SYNGAP1</i> | Synaptic RAS GTPase-activating protein 1 | Spine formation, development and activity-dependent structural plasticity ^{131,132,296} | ID ²⁹⁷ , DD ⁶⁷ and ASD ⁶ |
| <i>TRIO</i> | Trio Rho guanine nucleotide exchange factor | Dendrite development and activity-dependent structural plasticity ¹⁴⁶ | ASD and/or ID ²⁹⁰ |
| <i>KALRN</i> | Kalirin Rho-GEF kinase | Spine morphogenesis and activity-dependent structural plasticity ¹³⁹ | DD ⁶⁷ |
| <i>NFI</i> | Neurofibromin 1 | Spine development and activity-dependent structural plasticity ¹³⁶ | ID ²⁹⁷ |
| <i>ARHGEF6</i> | Rho guanine nucleotide exchange factor 6 | Dendrite development and spine density ¹⁵⁶ | ID ²⁹⁷ |
| <i>OPHN1</i> | Oligophrenin 1 | Dendrite and spine development ¹⁵⁵ | ID ²⁹⁷ and DD ⁶⁷ |
| <i>Copy number variant models</i> | | | |
| 7q11.23 deletion | Williams–Beuren syndrome | Increased dendrite length and spine number ²⁶⁰ | ASD ⁶ |
| 15q11–13 duplication | Dup15q syndrome | Increased spine turnover and decreased spine density ^{81,298} | ASD ⁶ and SZ ²⁸¹ |
| 16p11.2 duplication | None | Dendrite arborization ²⁹⁹ | ASD ⁶ and SZ ²⁸¹ |
| 22q11.2 deletion | DiGeorge/velocardiofacial syndrome | Decreased spine density and stability and increased spine turnover ^{248,300} | SZ ²⁸¹ |

As different neuropsychiatric disorders often share the same risk factors, other disease associations exist that are not referenced herein. ASD, autism spectrum disorder; BD, bipolar disorder; DD, developmental disorder; GEF, guanine nucleotide exchange factor; GWAS, genome-wide association study; ID, intellectual disability; SZ, schizophrenia.