Integrins in synapse regulation

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Abstract | Integrins are a large family of extracellular matrix (ECM) receptors. In the developing and adult brain, many integrins are present at high levels at synapses. The tetrapartite structure of synapses — which comprises presynaptic and postsynaptic neurons, the ECM and glial processes — places synaptic integrins in an excellent position to sense dynamic changes in the synaptic environment and use this information to coordinate further changes in synapse structure and function that will shape neural circuit properties. Recent developments in our understanding of the cellular and physiological roles of integrins, which range from control of neural process outgrowth and synapse formation to regulation of synaptic plasticity and memory, enable us to attempt a synthesis of synaptic integrin function.

Counter receptors
Molecules that bind to cell surface receptors. Counter receptors for integrins include neural cell adhesion molecule L1 (NCAML1) and vascular cell adhesion protein 1 (VCAM1), which themselves are cell surface proteins.

Adaptor proteins
Molecules containing distinct modular domains that typically mediate protein–protein interactions and allow these proteins to form signal transduction complexes.

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Integrins are a family of heterodimeric, transmembrane cell surface adhesion receptors for components of the extracellular matrix (ECM) and for counter receptors on adjacent cells[1,2]. Intracellularly, integrins link to the actin cytoskeleton via adaptor proteins, such as talin and vinculin, and engage second messenger signalling cascades. By connecting the ECM to the intracellular cytoskeleton and signalling pathways, integrins act in a bidirectional manner to transduce mechanical signals between the extracellular milieu and the cell[1–5].

In the developing nervous system, in which cell and tissue architecture undergo extensive reorganization, integrins control cell migration, cortical layer formation and neurite outgrowth. Integrins also affect synapse formation during development and regulate various synaptic functions in the adult brain. Moreover, studies suggest that integrin-mediated regulation of synapses, which is closely associated with ECM remodelling and glial cell activity, is an important component of the function of the tetrapartite synapse (FIG. 1). In rodents, compromising integrin activity impairs synaptic transmission and long-term synaptic plasticity[6–21]. These changes accompany deficits in working memory and behavioural alterations that are often associated with neurological disorders.

Despite the mounting evidence for the various roles of synaptic integrins, many questions remain about the underlying mechanisms. For example, it is not known whether different integrin subtypes differentially control specific neural circuits and, if so, how this is achieved. We also do not yet understand the precise molecular mechanisms by which integrins regulate synaptic transmission or, conversely, how neural activity and the state of ECM organization affect integrin activity. The goal of this Review is to provide mechanistic insights into integrin-dependent synapse regulation and to offer an overview of the mechanisms that might link integrin dysfunction to altered behaviour and brain diseases.

Integrin structure and signalling

Activation

Integrins are heterodimers of α- and β-subunits. In mammals, which express 18 different α-subunits and 8 different β-subunits, 24 distinct integrin αβ-heterodimer combinations have been reported[1]. As mechanical signal transducers, integrins undergo allosteric conformational changes according to their functional state[1–3] (FIG. 2). Inactive αβ heterodimers adopt a closed conformation both in their large extracellular domains and in their short intracellular tails. Binding of an intracellular ligand such as talin (BOX 1) opens the outer membrane clasp to facilitate binding to the ECM (a process known as inside-out signalling). Conversely, binding of an extracellular ligand at the interface between the extracellular domains of α- and β-subunits opens the inner membrane clasp between the cytoplasmic tails of α- and β-subunits to allow the binding of various linker proteins (known as outside-in signalling). Upon activation, the extracellular domains of integrins adopt an open conformation, and clustering of integrin heterodimers promotes strong adhesion. Thus, the density of ECM target proteins can influence the degree of integrin activation and signalling.

Because of the causal link between ligand binding and the shift to the open conformational state of integrins, some molecules that were previously assumed to act as integrin inhibitors (such as extracellular ligand mimetics) can actually activate integrins[4]. Therefore, the outcomes of experiments designed to manipulate integrin activity need to be interpreted with caution. Interestingly, a *Drosophila melanogaster* screen for mutations that alter the ECM-binding affinity of integrins

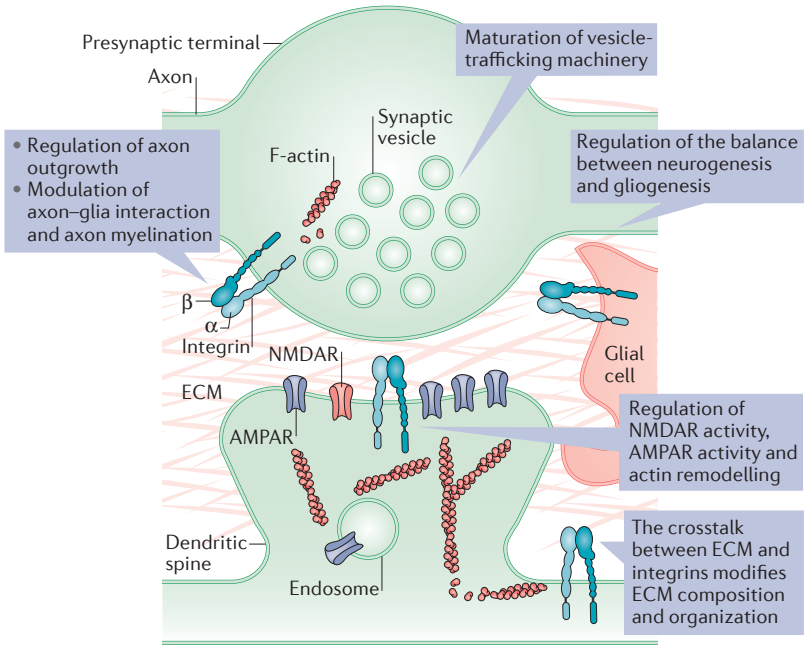


Figure 1 | **Integrin functions are associated with every component of the tetrapartite synapse.** The schematic summarizes the known localization and roles of integrins at the synapse. Integrins have a major role in several events that occur before synapse formation. Integrins control the differentiation of neural stem cells and influence the balance of the number of neurons and glial cells produced[39]. Subsequently, the crosstalk between integrins and growth factors, in concert with extracellular matrix (ECM)–integrin interactions, modulates neuronal migration along radial glial fibres into the cortical marginal zone and axonal outgrowth[39,46–49]. In the cortical marginal zone, the interaction of neuronal integrins with specific ECM components (such as reelin) guides the route of further neuronal migration[43,152]. The interaction between neuronal and glial integrins is thought to regulate the composition of the ECM, which is required for proper laminar structure in the cortex[48,153]. The presynaptic and postsynaptic neurons of a synapse are often found to be in contact with a glial process, and the ECM occupies the extracellular space between these cells to form the fourth component of the tetrapartite synapse. By serving as major receptors for ECM proteins, integrins link dynamic changes in the ECM with changes in synapse structure and function. Integrin-dependent myelination of axons and maturation of the vesicle-trafficking machinery have been suggested to regulate maturation of glutamatergic synapses[7,27,154–156]. At dendritic spines, integrins regulate structural and functional plasticity by controlling actin remodelling and glutamate receptor trafficking. AMPAR, AMPA receptor; NMDAR, NMDA receptor.

identified more mutations that activate integrins than mutations that inactivate integrins; thus, the inactive state of integrins may represent their basal state[22].

Extracellular ligands

The heterogeneity of integrin subtypes reflects the heterogeneity of the various ECM ligands to which integrins bind. The α-subunit of integrins dictates ligand-binding specificity[1,2]. For example, α5-, α8- and αV-containing integrins recognize the Arg-Gly-Asp (RGD) amino-acid sequence in matrix molecules such as fibronectin and thrombospondin and thus belong to the RGD receptor family of integrins. Others — such as α3- and α6-containing integrins — bind to laminin, whereas α1- and α2-containing integrins bind to collagen. Several integrin subunits are expressed in the brain[23] and are present at synapses. Among the integrins that are expressed in the brain, those containing β1 and β3 subunits are the most well studied: the β1 subunit pairs with various α-subunits, including α3, α5, α8 and αV[23–26], whereas the β3 subunit exclusively pairs with the αV subunit[25,27,28].

Because some integrin subtypes share common extracellular ligands, it will be important for future work to clarify how functions ascribed to different integrin subtypes result from binding to a specific integrin ligand and to determine the extent of functional redundancy among integrin subtypes that are expressed in the same cells. In particular, the extracellular ligands of synaptic integrins remain to be identified. The ECM is substantially remodelled during development, and ECM composition is also likely to differ spatially across the extracellular environment of various neurons and synapses. For instance, perineuronal nets are specialized ECM structures that form later in development[29]: they surround cell bodies and proximal processes of specific neurons and are thought to restrict synaptic plasticity in the mature brain[30,31]. Determining the precise ECM ligand for different integrins is not only complicated by the dynamic changes in the ECM that occur during synapse maturation, the localization and function of integrins themselves might also change with synapse maturation. Therefore, the identification of the native ECM ligands of synaptic integrins remains a challenge.

Intracellular binding partners

Intracellularly, the most crucial ligand of integrins is talin, the binding of which to the cytoplasmic tail of the β-subunit is conserved from invertebrates to mammals[32]. *In vitro*, talin binding alone is sufficient to activate integrins; however, *in vivo*, other binding partners — including activators such as kindlins or integrin-linked protein kinase (ILK) and inactivators such as integrin cytoplasmic domain-associated protein 1 (ICAP1) or filamin — orchestrate integrin-activation states[3–5] (BOX 1). Importantly, to date, the established integrin-binding partners and signalling mechanisms have been mostly characterized in non-neuronal cells. Thus, their impact on synaptic integrin signalling needs to be tested.

Recent studies have revealed the identity of several molecules that directly interact with the intracellular domain of the β-subunit and are important for integrin function at synapses. The cytoplasmic tail of β1-containing integrin directly binds to ARG (a non-receptor tyrosine kinase that is also known as Abelson tyrosine-protein kinase 2 (ABL2)) and activates its kinase activity[33]; ARG-mediated signalling that is triggered by the binding to β1-containing integrin plays a part in shaping dendrite morphology, synapse maintenance and hippocampal-dependent behaviours[34] (see below). The cytoplasmic tail of β3-containing integrin can directly bind to the intracellular domain of the GluA2 AMPA receptor (AMPAR) subunit[35]. Given the requirement for β3-containing integrins in activity-dependent synaptic scaling of AMPARs (see below), it would be of interest to delineate the molecular mechanisms that regulate the binding of β3-containing integrins to GluA2 (REFS 36–38). Whether GluA2 binding to β3-containing integrins is modified by other proteins interacting with the cytoplasmic tail of β3 subunits also requires

Perineuronal nets
Specialized extracellular matrix structures that surround the somata and proximal dendrites of certain neuron types. They are important for synaptic stabilization and have been suggested to be crucial for the closure of critical periods.

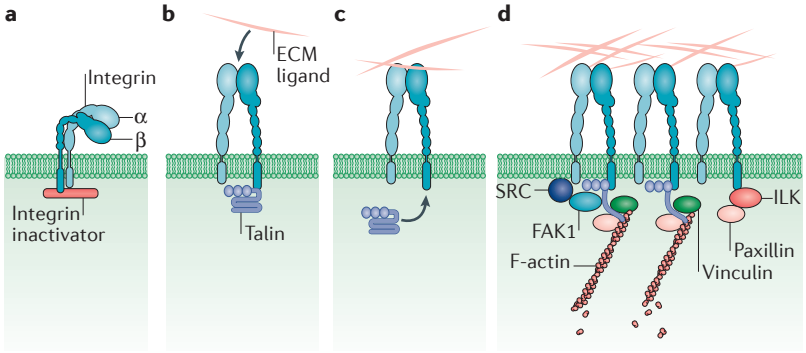


Figure 2 | **Integrin activation and signalling. a** | Inactive integrins exist in a closed conformation, with extracellular domains bent and cytoplasmic tails associated with integrin inactivators such as filamin, integrin cytoplasmic domain-associated protein 1 (ICAP1) and SHANK-associated RH domain-interacting protein (SHARPIN). **b** | During inside-out signalling, binding of talin to the cytoplasmic tail of integrins results in the extension of their extracellular domains, which facilitates binding to the extracellular matrix (ECM) ligand. **c** | During outside-in signalling, binding of the ECM ligand to the integrin extracellular domains opens the clasp formed between the membrane proximal regions of the cytoplasmic tails of the α- and β-subunits of inactive integrins, which helps to recruit talin. **d** | Clustering of integrins promotes the assembly of focal adhesions and engages integrins in active signalling when they are tethered to F-actin. Focal adhesion kinase 1 (FAK1) cooperates with and binds to the protein kinase SRC to promote turnover and signalling of integrin focal adhesions. Dynamic actin remodelling also determines the structural stability of focal adhesions. Integrin-linked protein kinase (ILK), which links to other components of focal adhesions such as paxillin, can be recruited to focal adhesions by interacting with the cytoplasmic tail of β-containing integrins.

consideration. The identification and characterization of additional novel proteins interacting with synaptic integrins will help to provide mechanistic insights into integrin action at synapses.

Integrins in neural development

Neural migration and circuit formation

In line with the actions of integrins in mechanical signal transduction, many studies indicate that integrins are involved in cell migration, neuronal process outgrowth and branching. In embryonic and adult neurogenic regions such as the ventricular and the subventricular zones[39], integrins — together with the ECM, growth factor receptors, and other adhesion proteins such as reelin, cadherins, nectin and neural cell adhesion molecule L1 — support the differentiation and maintenance of neural stem cells[40–46]. Integrins also guide cells departing from the stem cell niche. In newly differentiated neurons, β1-containing integrins promote axon growth by binding to semaphorin 7A, an axon guidance cue that activates focal adhesion kinase (FAK) and mitogen-activated protein kinase (MAPK) signalling[47].

The modulatory roles of integrins in neuronal migration depend on the specific integrin subtypes that are present; for example, the differential substrate specificity of αV and α3 subunits biases the adhesive preference (for glia versus other neurons) of the neurons in which they are expressed[48]. Notably, the β3 subunit, which, in the brain, partners only with αV-containing integrins, does not have an appreciable role in neuronal migration[48]; it is therefore likely that the αV subunit regulates neuronal migration and axon pathfinding by pairing with other β-subunits, such as β5 and β8 subunits. These subunit-specific integrin functions are finely tuned by signalling that involves adhesion receptors that are myelin associated and/or linked to actin, ECM proteins and growth factors[49]. Further *in vivo* characterization of the mechanisms of differential regulation of integrin subtype expression and function will be important to clarify how the diversity of integrin subtypes facilitates the complex changes in cellular orchestration that take place during brain development.

Synapse formation and maturation

Concurrent to neuronal process outgrowth, integrins regulate synapse formation and maturation. In hippocampal neuron cultures, β1-containing integrins promote astrocyte-dependent excitatory synaptogenesis[50]. Furthermore, deleting β1-containing integrin at an embryonic stage in mice compromises the synaptic vesicle pool that is required for sustained neurotransmitter release in acute slices from adult mice[7]. β3-containing integrins and integrin-regulated ARG aid synapse maturation by promoting the developmental reduction in presynaptic neurotransmitter-release efficacy and a switch in postsynaptic NMDA receptor (NMDAR) subunit composition from GluN2B-containing to GluN2A-containing receptors, which are properties associated with mature synapses[27,51]. More recently, β1-containing integrins have been shown to subtly regulate both dendrite arbor size and synapse density. Upon conditional deletion of β1 subunits in mice from embryonic day 11.5, hippocampal CA1 pyramidal neurons showed reduced dendritic arbor size and synapse density at postnatal day 42 (P42), but not at P21, compared with controls[34]. However, conditional loss of β1 subunits at a later stage, starting from about P14, did not produce apparent structural defects in adult mice (although a functional deficit in synaptic plasticity was observed (see below))[7]. Therefore, a requirement for β1-containing integrins in some aspect of dendrite outgrowth and synapse formation at an earlier stage of development could influence the subsequent maintenance of dendritic arbor and synaptic contacts. Interestingly, a similar late-appearing phenotype of reduced dendrite arbor size and synapse density is present in mice lacking ARG[52] and in mice in which the α3 subunit is conditionally ablated[53]. This suggests that ARG acts downstream of α3β1 integrin heterodimers. Moreover, ARG seems to signal via its substrate $p190^{GAP}$ to inactivate RHOA GTPase[33,34,53,54]. The molecular and cellular basis for the late-appearing phenotypes resulting from the loss of β1 and α3 subtypes could be a differential degree of compensation by other integrin subtypes that are more effective during earlier stages of development.

Integrins in mature neural circuits

Basal synaptic transmission

Integrins continue to be expressed at mature synapses, where they regulate basal synaptic transmission. For example, in cultured spinal cord neurons, β1- and β3-containing integrins control the trapping of glycine receptors at inhibitory synapses, thus affecting synaptic strength and

Box 1 | **Intracellular regulators of integrin activation**

The activity and conformational states of integrins are tightly regulated by molecular interactions, particularly those that are mediated by the intracellular domain (FIG. 2). The three main integrin activators that have been highly studied are talin, kindlins and integrin-linked protein kinase (ILK).

Talin

The amino-terminal head domain of talin binds with high affinity to an NPxY motif in the membrane distal part of the cytoplasmic tail of integrin β-subunits, whereas its rod domain contains multiple binding sites for actin and vinculin. The binding of talin to the β-subunit is crucial for integrin activation[145]. Although talin binding alone is sufficient to activate integrins *in vitro*, many other molecular interactions influence integrin activation *in vivo*. These include integrin inactivators[5], some of which compete with talin to bind to the integrin cytoplasmic domains (FIG. 2a,b).

Kindlins

Three kindlin homologues — kindlin 1, kindlin 2 and kindlin 3 — are expressed in mammalian cells. Kindlins bind to the cytoplasmic domain of β-subunits at a site that is distinct from the talin-binding site and are functionally required for integrin activation: loss of expression of the ubiquitously expressed kindlin 2 results in embryonic lethality, similarly to loss of the β1 subunit. However, the exact mechanism by which kindlins regulate integrin function remains to be clarified.

ILK

ILK functions as an adaptor protein to link integrins to other components of focal adhesions such as paxillin, PINCH and parvin. The kinase activity of ILK does not seem to be required for it to function as an integrin adaptor protein.

neuronal excitability[55]. Interfering with integrins changes the synaptic dwell time of glycine receptors by altering the oligomerization state of the gephyrin scaffold[55]. Curiously, β1-containing integrins increase synaptic glycine receptor abundance, whereas β3-containing integrins decrease it. These effects are mimicked by thrombospondin and fibrinogen, which are ligands for β1- and β3-containing integrins, respectively. Given that thrombospondin and fibrinogen are released upon injury, integrins may have a crucial role in adjusting neuronal excitability under pathological conditions[55].

A unique role for β3-containing integrins in regulating AMPARs at excitatory synapses has been shown by studies in cultured hippocampal neurons. Interfering with the ligation of β3-containing integrins to the ECM either by using RGD peptides or by exogenously overexpressing a dominant-negative form of the β3 subunit reduces synaptic strength by decreasing the number of postsynaptic AMPARs[8]. The constitutive stabilizing effect of β3-containing integrins on AMPARs is cell autonomous and specific to GluA2-containing AMPARs. It seems to be independent of the activation state of β3-containing integrins[35] or actin filaments but requires basal NMDAR activity, Ca^{2+} influx and activation of the small GTPase RAS-related protein RAP1A[8]. β1-containing integrins are also present in hippocampal pyramidal neurons, in which they regulate dendritic spine morphology by driving actin remodelling via a NMDAR-dependent mechanism[14], which is likely to involve ARG[51,56]. Moreover, β1-containing integrins are enriched within the postsynaptic density, where AMPARs are also concentrated[57].

It would be of interest to examine the extent of co-localization of β1 and β3 subtypes at individual synapses, their endogenous ECM ligands and how the differential regulation of the two integrin subtypes is achieved. In non-neuronal cells, actin remodelling controls the structural stability of integrin-containing focal adhesion sites[58–62]. Similarly, spine actin remodelling triggered by β1-containing integrins could alter the properties of the postsynaptic scaffold to affect the β3-containing integrin-dependent regulation of synaptic AMPARs.

Homeostatic synaptic scaling

Chronic alteration of network activity induces compensatory changes in synaptic strength, called homeostatic synaptic plasticity, that help to prevent excessive changes in the overall excitability of the neuron (BOX 2). β3-containing integrins are required for one form of homeostatic synaptic plasticity (FIG. 3). In hippocampal cultures, prolonged block of action potentials with tetrodotoxin results in a 'scaling up' of the number of synaptic AMPARs that are present at the synapse. In parallel, surface β3-subunit expression also increases. However, in hippocampal cultures from β3-subunit-null mice, such tetrodotoxin-dependent scaling up of AMPARs is absent[8,63]. Notably, tumour necrosis factor (TNF; also known as TNFα), a pro-inflammatory cytokine that is released from glia, rapidly increases surface expression of β3-containing integrins in hippocampal neurons[8] and is required for tetrodotoxin-induced synaptic scaling up of AMPARs[64]. Therefore, TNF and β3-containing integrins may be part of the signalling cascade that mediates homeostatic AMPAR scaling. The involvement of β3-containing integrins in homeostatic synaptic scaling in other brain regions and other types of neurons remains to be tested.

In contrast to β3-containing integrins, the surface levels of β1-containing integrins are not modified by chronic changes in network activity and do not seem to play a part in homeostatic synaptic plasticity[8]. It will be of interest to examine the possible roles for other integrin subtypes in homeostatic synaptic plasticity.

Hebbian synaptic plasticity

Long-term potentiation (LTP) is a cellular model for memory that has been extensively studied in the hippocampus (BOX 2). The role of integrins in LTP was initially investigated using RGD peptides and inhibitory antibodies against integrins. In acute hippocampal slices, high concentrations of RGD peptides consistently impair LTP maintenance in area CA1. Although LTP induction is intact, in the presence of RGD peptides, potentiation gradually declines over tens of minutes[9–13]. Likewise, function-blocking antibodies against α5- and β1-containing integrins, but not antibodies against αV- or α2-containing integrins, impair LTP stabilization in CA1 neurons[14,15,28]. Subsequent studies using mutant mice with altered levels of specific integrin subtypes have confirmed the involvement of α3-, α5-, α8- and β1-containing integrins in LTP maintenance[7,16–19,25] (TABLE 1). Although β1-containing integrins have a role in synapse maintenance and basal synaptic transmission in hippocampal CA1 neurons[7,16,34], these functions are separable from the requirement for β1-containing integrins in LTP. The deletion of β1 subunits from postnatal

Synaptic dwell time
The amount of time during which a diffusible molecule remains inside the synapse.

Focal adhesion sites
Specialized sites of adhesive contact where integrins link the extracellular matrix to intracellular signalling complexes and to the actin cytoskeleton.

Long-term potentiation
(LTP). A long-lasting (hours or days) increase in the response of neurons to stimulation of their afferents following a brief patterned stimulus (for example, a 100 Hz stimulus train).

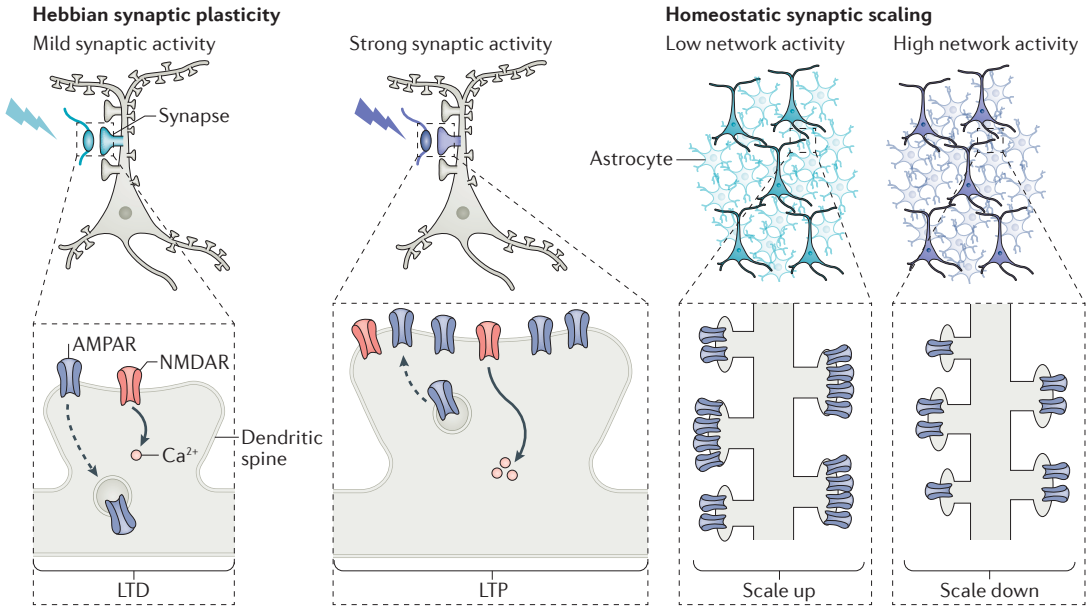
week 2 produces no appreciable effects on synaptic properties under basal conditions but impairs LTP[7,16]. This contrasts with the synaptic functions of β3-containing integrins. Acute hippocampal slices from β3-subunit-deficient mice show normal LTP in CA1 neurons[19]: thus, β3-containing integrins are dispensable for LTP but are required for homeostatic synaptic scaling. Interestingly, neither β1- nor β3-containing integrins seem to participate in long-term depression (LTD)[19]. Similarly, α3 and α8 subunits, which pair with β1 subunits, are dispensable for LTD[17,18]. Thus, different integrin subtypes have specific roles in different forms of synaptic plasticity.

What are the mechanisms by which integrins mediate activity-dependent increases in excitatory synaptic strength? LTP-induction mechanisms require synaptic NMDAR activation and Ca^{2+} influx to engage downstream signalling cascades (BOX 2). Are integrins activated during the triggering of LTP, and do they participate in LTP induction? Alternatively, are integrins engaged in downstream signalling steps? To date, β1-containing integrins are the most actively studied integrin subtype in LTP. The fact that interfering with β1-containing integrin expression or activity compromises LTP maintenance suggests that this integrin subtype has a key function in signalling pathways downstream of NMDAR-dependent LTP induction. Nevertheless, several studies indicate that β1-containing integrins regulate NMDARs. For example, applying RGD peptides or fibronectin (an endogenous β1-subunit ligand) rapidly phosphorylates FAKs and SRC family kinases (SFKs). SFK activation increases tyrosine phosphorylation of GluN2A and GluN2B NMDAR subunits, which enhances NMDAR activity[20,65]. However, it is important to note that RGD peptides can also directly

Box 2 | **Hebbian synaptic plasticity versus homeostatic synaptic plasticity**

The efficacy of information transfer between neurons can change over time, as neurons experience several forms of plasticity. The most extensively studied form of plasticity is Hebbian synaptic plasticity, which is thought to represent a cellular model for particular types of learning and memory[146]. The hallmark feature of Hebbian synaptic plasticity is the idea that correlated activation of presynaptic and postsynaptic neurons can rapidly modify synaptic efficacy in a long-lasting manner via a mechanism that requires NMDA receptors (NMDARs). This change is limited to activated synapses. Correlated high levels of activity result in a strengthening of synaptic efficacy called long-term potentiation (LTP), which is associated with an increase in the number of synaptic surface AMPA receptors (AMPARs). However, correlated moderate levels of activity produce a form of synaptic weakening called long-term depression (LTD), which is associated with an endocytosis-mediated decrease in the number of synaptic AMPARs[147,148]. In general, changes in the level of synaptic surface AMPARs correlate with changes in dendritic spine size: synaptic strengthening is accompanied by an enlargement of dendritic spine size, whereas synaptic weakening is associated with a shrinkage of dendritic spine size (see the figure; left panel).

Neurons also use homeostatic plasticity mechanisms to maintain their intrinsic excitability and help to secure stable network activity[149,150]. Synaptic scaling, a form of homeostatic plasticity that targets postsynaptic receptors, was first identified in cultured neurons, in which global activity perturbation generated compensatory changes at individual synapses in a manner that retained the relative differences in synaptic strengths across synapses[151] (see the figure; right panel). By restoring the average firing rates of a neuron while preserving the relative synaptic strengths, homeostatic synaptic plasticity helps to make possible the various types of information transfer across synapses. Activity perturbation also influences glial cells, which in turn modulate synaptic plasticity. For example, the synaptic scaling that is induced by chronic activity suppression increases the number of synaptic AMPARs through a mechanism that requires tumour necrosis factor (TNF) release from glia[64]. The bottom panels represent a magnified view of the dendritic spines in the dashed areas in the upper panels. The dashed arrows indicate the movement of AMPARs.



Long-term depression (LTD). A long-lasting decrease in the response of neurons to stimulation of their afferents following a brief patterned stimulus (for example, a 1 Hz stimulus train).

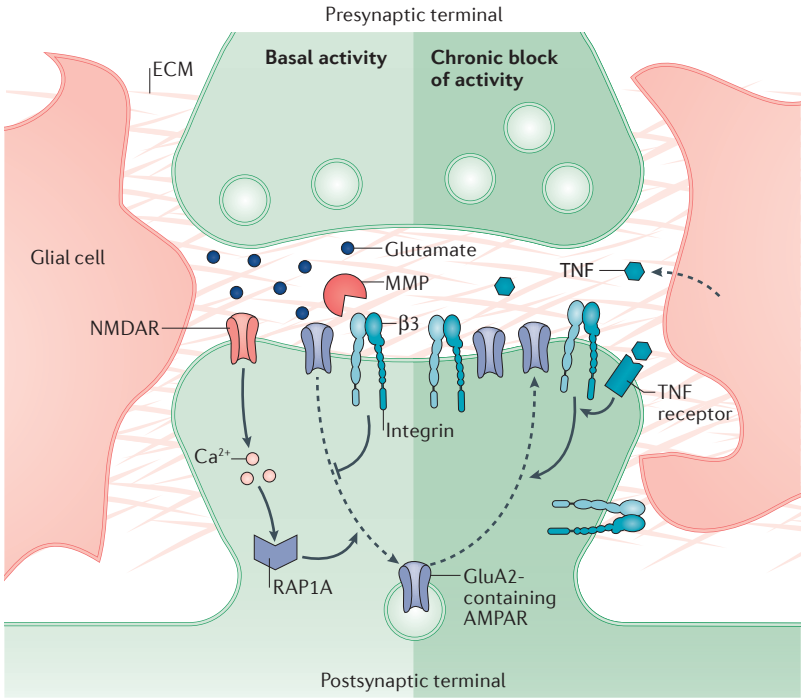


Figure 3 | **AMPA receptor regulation by β3-containing integrins.** Under basal-activity conditions (left panel; pale green shade), β3-containing integrins help to maintain the number and composition of synaptic AMPA receptors (AMPARs). Disengaging β3-containing integrins from their extracellular matrix (ECM) ligand (for example, by applying Arg-Gly-Asp (RGD) peptides) promotes GluA2-containing AMPAR internalization through a mechanism requiring basal NMDA receptor (NMDAR) activity, Ca^{2+} influx and activation of the small GTPase RAS-related protein RAP1A. How the interaction between β3-containing integrins and their ECM ligand is modulated under physiological conditions remains to be determined, although (as is the case for the regulation of β1-containing integrin activity), matrix metalloproteinase (MMP)-dependent cleavage of the ECM could potentially play a part. Following chronic activity deprivation (right panel; dark green shade), β3-containing integrins are required for the homeostatic synaptic scaling of AMPARs. When activity is absent, fewer synaptic vesicles undergo exocytosis at the presynaptic terminal. The drop in extracellular glutamate is detected by surrounding glial cells, which release tumour necrosis factor (TNF). TNF signalling in postsynaptic neurons recruits more β3-containing integrins to the cell surface, which in turn increases the number of synaptic GluA2-containing AMPARs. The precise location of β3-containing integrins at the postsynaptic terminal and the mode by which β3-containing integrins are recruited to the dendritic spine need to be clarified. The dashed arrows indicate the movement of proteins: AMPARs at the postsynaptic terminal are endocytosed from the cell surface (left panel; pale green shade) or inserted to the cell surface (right panel; dark green shade); TNF is released from the glial cell.

act at the glycine-binding site of NMDARs[8]. It would be of interest to confirm the specificity of the effects of modulating β1-containing integrin activity and how such effects are related to the β1-containing integrin-dependent mechanism that sustains LTP expression.

Recent reports provide new insights into the connection between integrin activation and LTP. One clue comes from single-molecule imaging of glutamate receptor subunits in cultured hippocampal neurons using quantum dots. Matrix metalloproteinase 9 (MMP9), which cleaves the ECM and some cell surface proteins, co-localizes with glutamate receptors and is involved in NMDAR-dependent synaptic plasticity[66–68]. Activation of MMP9 increases the lateral diffusion of the obligatory NMDAR subunit GluN1 along the plasma membrane at both synaptic and extrasynaptic sites, and this increase in GluN1 diffusion requires the activation of β1-containing integrins[69]. The increased mobility is not associated with a global change in ECM structure or with cleavage of NMDAR subunits. Therefore, limited remodelling of synaptic ECM by MMP9 might be sensed by β1-containing integrins to adjust the abundance of synaptic NMDARs. Interestingly, reelin (an ECM-like protein) also modulates surface trafficking of GluN1 in a β1-containing integrin-dependent manner[70]. Reelin dysfunction is strongly implicated in several neurological diseases[71–76], some of which might involve impaired integrin signalling (see below).

MMP9-dependent integrin signalling in LTP has been suggested to involve focal activation of MMP9 by the LTP-induction signal and the subsequent cleavage of ECM proteins to generate a ligand for integrin activation[77–82]. Accordingly, the use of high-frequency stimulation to induce LTP in the hippocampus dynamically changes synaptic integrin activity[83]. When a fluorescent probe was used to selectively label activated β1-containing integrins, the number of synapses in hippocampal area CA1 containing the active integrin signal rapidly increased within 2 minutes of eliciting LTP and then gradually returned to the basal level over a period of several minutes. Integrin activation resulted in phosphorylation of downstream tyrosine kinases FAK1 and PYK2β. The subsequent ability to reactivate integrin signalling was associated with a refractory period (~45 minutes) that depended on the replenishment of cell surface β1-containing integrins from an internal pool[83]. Thus, the temporal dynamics of synaptic β1-containing integrin seem to separate the two distinct phases of LTP in which this integrin has a role: early expression and maintenance. The latter phase is impaired by a β1-subunit function-blocking antibody only when the antibody is applied during the refractory period. Consequently, an integrin-dependent mechanism during a defined time window after LTP induction may help to set in motion the subsequent LTP-consolidation process requiring additional actin polymerization and new protein synthesis[9,11,12,15,84,85]. Thus, β1-containing integrins seem to be involved in an intricate regulation of LTP expression that goes beyond MMP9-dependent ECM remodelling and control of the surface diffusion of NMDARs.

Hippocampal-dependent long-term memory

Do integrins contribute to the formation or maintenance of long-term memory? Mice with reduced levels of α3-, α5- and α8-containing integrin subtypes displayed impaired acquisition and long-term storage of spatial memory when tested in the Morris water maze[25]. However, in another study, conditional loss of β1-subunit expression in pyramidal neurons of the hippocampus and forebrain compromised working memory but not spatial memory[16]. Given that conditional loss of α3 subunits also impairs both hippocampal LTP and performance in a working-memory task (but not hippocampal spatial memory), α3β1, α5β1 and α8β1 integrins could be differentially involved in particular types

Table 1 | **The role of integrin subunits in synaptic plasticity and behaviour**

Integrin subunit	Type of synaptic plasticity	Behaviour affected by subunit loss in mice	Behaviour unaffected by subunit loss in mice
α3	LTP[14,17]	• Working memory[17] • Novel-object recognition[53]	• Spatial memory[17] • Innate anxiety[17]
α3, α5 and α8*	LTP[25]	Spatial memory[25]	Cued and contextual fear conditioning[25]
α8	LTP[18]	NA	• Spatial memory[18] • Working memory[18] • Innate anxiety[18]
β1	LTP[7,15,16,19,83]	• Working memory[16] • Spatial memory[83]	• Cued and contextual fear conditioning[16] • Spatial memory[16] • Innate anxiety[19]
β3	Homeostatic synaptic scaling[8,63‡]	• Social interaction[88] • Innate anxiety[19]	Cued and contextual fear conditioning[19]

LTP, long-term potentiation; NA, not applicable. *Tested using triple-heterozygous mice. ‡Tested in culture.

of hippocampal memory[17]. Interestingly, to date, none of the mice in which integrin function has been impaired has been reported to show altered behaviour in amygdala-dependent cued and contextual fear conditioning, the latter also being dependent on hippocampal function[7,16,25]. Therefore, a subset of hippocampal-dependent memory systems seems to be impaired in mutant mice lacking specific integrin subunits, which could reflect, in part, the differential cellular and subcellular localization of various integrin subtypes[23,86].

A recent study has found that infusing neutralizing antisera against β1-containing integrins into the mouse rostral hippocampus blocks the formation of long-term object-location memory[83]. However, memory impairment was observed only when the infusion was matched to the critical time window during which β1-containing integrin is required for the intermediate phase of hippocampal LTP *in vitro*[83] (see above). Thus, these observations suggest that β1-containing integrins are required in the process of consolidation of LTP and hippocampus-dependent long-term memory. Whether and how the β1 subunit paired to different α-subunits mediates distinct aspects of hippocampal-dependent memory remain to be clarified.

Roles for integrins in brain disorders

Anxiety, stress and autism spectrum disorder

In addition to the involvement of synaptic integrins in learning and memory, recent behavioural analyses of mice carrying mutations in β1- and β3-containing integrins have revealed links to several neurological syndromes. Investigating synaptic integrin functions in circuits that are implicated in neurological disorders may help to provide novel insights for tackling these diseases.

A pilot behavioural analysis found that β3-subunit-null mice exhibited altered anxiety-like behaviour. Compared with control animals, these mice showed less avoidance of the centre area in the open-field test and increased entries to the open arms of the elevated plus maze[19]. By contrast, context- or cue-dependent fear memory was normal in these mice. Notably, mice with conditional loss of β1 subunits show normal behaviour in the elevated-plus-maze test[19]. Thus, β3-containing integrins might have specific roles in circuit functions underlying innate behaviours. Nevertheless, another group has reported normal behaviour of β3-subunit-null mice in the open-field test[87] but has shown that exposing these mice to unpredictable chronic mild stress results in behaviours that are consistent with increased anxiety[87]. Thus, β3-containing integrins seem to bidirectionally modulate the level of anxiety, which is affected by prior exposure to chronic stress. A third behavioural study of β3-subunit-null mice reported increased repetitive self-grooming behaviour when the animals were placed in a novel cage and diminished preference for exploring a novel peer versus a familiar peer[88]. These behaviour patterns are similar to the phenotypes that are observed in autism spectrum disorder (ASD) mouse models[89–93]. Despite the differences in the behavioural phenotypes reported for β3-subunit-null mice, key observations point to a link between β3-containing integrin and neurological symptoms associated with adaptive stress response and social dysfunction, with some phenotypes involving anxiety-like behaviours.

What are the possible mechanisms underlying a role for β3-containing integrins in anxiety-like behaviours, stress responses and phenotypes associated with ASD mouse models? Previous gene-interaction studies in patients with ASD have identified an association between *ITGB3*, which encodes the β3 subunit, and solute carrier family 6 member 4 (*SLC6A4*), which encodes a serotonin transporter[94–97]. Furthermore, hyperserotonaemia is associated with anxiety and stress, and is observed in some patients with ASD[98–100]. Therefore, β3-containing integrins may play a part in the regulation of the serotonergic system. However, it is important to note that alterations in serotonin metabolism have been suggested in a broad range of mental illnesses, including schizophrenia, Alzheimer disease (AD), mental retardation and obsessive–compulsive disorder[101–103]. Therefore, altered serotonin regulation might be a secondary consequence of disease-associated changes in circuit function or organization[104–106].

From a cell physiological perspective, a requirement for β3-containing integrins in homeostatic synaptic scaling might contribute to activity-dependent neural circuit adaptation, and in turn its dysfunctions might promote neurological disorders. Curiously, the anxiolytic phenotype of β3-subunit-null mice is reversed by re-expressing the β3 subunit in the ventral hippocampus of adult mutant mice[19]. This raises questions about the requirement for β3-containing integrin in the ventral hippocampal circuit and about whether this circuit also plays a part in chronic stress-induced anxiety. Interestingly, the stress-induced anxiety that is observed in β3-subunit-null mice is accompanied by changes in synaptic protein levels and dopamine turnover in the midbrain[87]. Thus, exploring the potential role for β3-containing integrins in dopaminergic neurons in the midbrain ventral tegmental area might yield new insights into mechanisms of chronic adaptive responses.

Drug addiction

Integrins are also implicated in drug addiction. Integrin involvement in addictive behaviour was first suggested by a study in which cocaine sensitization in rats was found to alter integrin signalling in the nucleus accumbens (NAc) core[107], an area crucially involved in addictive behaviours[108–111]. In this study, conditional ablation of ILK inhibited chronic cocaine-induced psychomotor sensitization[107]. Another series of studies, in mice, showed that acute or repetitive injection of cocaine caused dynamic changes in the amount of synaptic β1- and β3-containing integrins in the NAc[112]. Changes in synaptic β3-subunit levels correlated more specifically with cocaine-craving behaviour than changes in β1-subunit levels[113]: synaptic β3-subunit expression progressively increased with repeated cocaine self-administration, an effect that was reversed during the first day of extinction training but returned after 3 weeks of extinction training. These temporal dynamics of synaptic β3-containing integrins in the NAc parallel the changes in AMPARs and brain-derived neurotrophic factor (BDNF) levels in the NAc that are observed during extinction training and reinstatement of cocaine craving[114–121]. Importantly, interfering with integrin–ECM interaction in the NAc by microinjecting RGD peptides during self-administration of cocaine prevents the delayed increase in β3-containing integrins during extinction training and the cocaine-induced, but not the cue-induced, reinstatement of craving behaviour. Therefore, the signal from the extracellular ligands of integrins seems to be a key factor in cocaine-seeking behaviour and may underlie distinct phases of addictive behaviour. Establishing the extracellular integrin ligands and their regulation will be important in further clarifying the cellular mechanism that is involved.

How might the ECM signal via β3-containing integrins regulate cocaine-mediated addictive behaviours? It has been suggested that MMP-dependent ECM remodelling is involved, because cocaine-seeking behaviour in rats can be inhibited by a broad-spectrum MMP inhibitor[122]. Furthermore, MMP2 activity in the NAc is stably upregulated upon cocaine withdrawal and rapidly suppressed by cocaine re-administration[123], and inhibiting MMP2 blocks the persistent synaptic potentiation that is induced by periods of cocaine self-administration and extinction. Intriguingly, MMP9 also seems to play a part in this process: MMP9 activity is unaffected during the extinction period but is transiently increased after reinstatement of cocaine-seeking behaviour[123]. Moreover, MMP9 seems to be preferentially involved in cue-induced craving behaviours[123,124]. The differential properties of MMP2 and MMP9 may represent subtle differences in the cellular and synaptic mechanisms that underlie the distinct cocaine-seeking behaviour. Whereas MMP2 is reported to be highly associated with actin-rich motile structures in astrocytes[125], MMP9 is involved in LTP via an interaction with β1-containing integrin and the regulation of dendritic spine morphology[77,78,80]. Therefore, the cellular mode by which MMPs regulate integrin signalling is likely to be distinct. Nevertheless, these observations highlight a general role for MMPs in drug addiction via ECM remodelling involving downstream integrin signalling in a subtype-specific manner.

Another possible role for β1-containing integrins in drug abuse has been reported in experiments using young mice[34]. In response to a single low dose of cocaine, conditional β1-subunit-null mice display significantly heightened locomotor activity, no discriminative exploration for familiar objects and more-erroneous spatial reversal learning compared with wild-type controls[34]. These behavioural deficits are accompanied by structural changes in hippocampal pyramidal neurons (which involve the ARG–$p190^{GAP}$–RHOA signalling pathway) and by decreased apical dendritic arbor size and synapse loss[34,126]. Thus, β1-containing integrin signalling might have a protective role in maturing hippocampal and cortical circuitries that can mitigate the impact of the initial exposure to drugs and could provide a potential target for modulating susceptibility to substance abuse.

It will be of great interest to investigate the underlying cellular mechanisms by which β1- and β3-containing integrins contribute to drug addiction. Understanding the precise mode of activation and inactivation of β1- and β3-containing integrins by ECM remodelling would be informative. Moreover, the differential requirement for β1- and β3-containing integrins in LTP and in homeostatic plasticity suggests that the circuits involved in addiction might depend on a coordination of different forms of synaptic plasticity.

Alzheimer disease

AD is associated with neuronal loss in the hippocampus and cortex. Before the appearance of major pathological features[127–129], there are mild cognitive deficits that are thought to involve synaptic dysfunction[130,131]. Given the roles of integrins in synaptic structure, plasticity and hippocampal memory, several studies have investigated the possible link between integrin activity and AD-related synaptic deficits.

The causal relationship between synaptic impairments and hippocampal memory deficits in AD is supported by the observation that LTP induction is blocked by the extracellular application of amyloid-β (Aβ), a key disease-related protein[132–134]. The possibility that integrin activity plays a part in this LTP block was tested in adult rats using RGD peptides and function-blocking antibodies against integrins[135]. Inhibiting αV-, β1- and/or β3-containing integrins rescued Aβ-induced impairment of hippocampal LTP in the dentate gyrus *in vitro* and in CA1 *in vivo*. In the absence of Aβ, none of the treatments affected basal synaptic transmission and LTP, a finding that is in apparent conflict with the prior studies that have been described above. The difference in findings between this and previous work has been attributed to the low concentrations of RGD peptides used, which are insufficient to interfere with LTP under normal conditions but can counteract the LTP destabilization that is observed in the presence of $A\beta^{135}$. Thus, the mechanism of integrin signalling that restores LTP in the presence of Aβ is different from that

involved in regulating LTP, perhaps requiring different ligand-binding states of integrins. Alternatively, extracellular Aβ could alter the synaptic ECM environment by an unknown mechanism. Notably, the restorative activity of integrin inhibitors involves TNF signalling but not actin modulation[135–137]: phalloidin (a toxin that stabilizes F-actin) does not affect the integrin-dependent, Aβ-mediated block of LTP. This is surprising given the well-described functions of β1-containing integrins in memory consolidation that requires actin polymerization[15,83]. The state of actin in the presence of Aβ and the possible disruption of integrin signalling, perhaps involving its interaction with reelin (see above), remain to be determined. Thus, the basis of the apparently paradoxical role of integrins in LTP under normal conditions and in the presence of Aβ is not clear, although it could involve a shift in the relative contributions of signalling that is media ted by distinct integrin subtypes[138]. It is possible that β3-containing integrins that regulate synaptic transmission in a manner independent of F-actin[8] could have a role in Aβ-mediated block of LTP. It will be of interest to test whether conditional loss of integrins can ameliorate the disease-related phenotypes of AD mouse models *in vivo*.

Concluding remarks

Here, we have reviewed the multifaceted roles of integrins in regulating synaptic functions and modulating the activity of neural circuits. Although we have highlighted the dynamic influence of the extracellular milieu on synaptic signalling, our incomplete understanding of the roles of synaptic integrins underscores our limited knowledge of the functions of the tetrapartite synapse. A deeper understanding of the coordination of ECM remodelling and glial signalling with synaptic functions, which have been traditionally studied with the focus on neuronal components, will help us to better understand the roles of integrin activity in controlling synaptic networks. Moreover, some of the basic properties of integrins, from the level of the macroscopic network down to single molecules, require closer attention to further advance the field of integrin research in the brain.

Although several integrin subtypes are expressed in different brain areas[23], to date, much of our knowledge of the synaptic functions of brain integrins comes from studies of β1-containing integrins and, to some degree, β3-containing integrins. A careful characterization of the cell type-specific expression pattern of the many integrin subtypes in different brain regions is warranted and will enable us to fully interpret their physiological roles in brain functions associated with particular circuits. Protein-localization studies are often hampered by a lack of high-affinity antibodies, and those antibodies available to detect rodent integrin subtypes are no exception. Novel tools that permit epitope tagging of endogenous proteins[139] might resolve this issue. This is important because the differential expression pattern of the integrin subtypes may explain the subtle differences in the behavioural phenotypes that have been associated with integrin mouse mutants (TABLE 1). In the hippocampus, for example, β1-containing integrins are required for working memory, whereas β3-containing integrins seem to be involved in emotional behaviours. Therefore, comparing the localization pattern and the activities of β1- and β3-containing integrins in specific synaptic circuits may help to provide insights into integrin-dependent cellular mechanisms underlying the behaviours that are associated with those circuits. Dynamic changes in synaptic integrins under different conditions (that is, in different brain states, during ageing or in disease) may occur in concert with alterations in the extracellular synaptic environment, and thus the mechanisms regulating ECM composition and dynamics should be considered in parallel to those regulating neuronal and glial integrins.

On a finer scale, several cellular and molecular properties of synaptic integrins remain to be clarified. First, the native ECM ligands of synaptic integrins are largely not known. The identification of integrin ligands will help us to determine the extent to which different integrins share ECM-remodelling cues and to understand how the specificity of an integrin subtype for a given ECM signal is controlled during synapse formation and maturation and synaptic plasticity. Second, the subcellular localization of integrin subtypes in neurons and glial cells and the regulation of their intracellular trafficking are also not well understood. Third, the biophysical properties of synaptic integrin-mediated adhesion are not known. Despite the lack of information about integrins in the brain, prior studies of β1- and β3-containing integrins in fibroblast cells provided some clues as to how the differences in the spatiotemporal dynamics of these two integrin subtypes are set by the threshold for ligand activation and the specific outside-in signalling pathways engaged[58,140–143]. Activation of β1-containing integrins rapidly triggers a strong feedforward adhesion force with increased rigidity to facilitate, for example, cell migration at the leading edge[58,60]. By contrast, β3-containing integrins continuously sense and respond to changes in ECM force and mediate a more labile adhesive interaction[142]. It will be interesting to determine whether neuronal or glial β1- and β3-containing integrins operate under similar principles and the way by which such mechanisms are implemented to regulate synaptic signalling in concert with ECM remodelling. Super-resolution imaging and the application of novel nanoprobes that permit mechanochemical control[144] may help to reveal the details of integrin trafficking and their interactions with other binding partners and signalling components within synaptic nanodomains.

Altogether, much remains to be learned about synaptic integrin mechanisms and functions at all levels. The burgeoning interest in glia and the ECM as key components of the tetrapartite synapse will undoubtedly help to catalyse further advances in the integrin research in the brain. Moreover, recent studies implicating integrins in circuits underlying anxiety, stress and addiction may lead to fresh approaches for tackling the neurological diseases that characterize modern society.

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Competing interests statement
The authors declare no competing interests.