Review Article

Dynamic Control of Synaptic Adhesion and Organizing Molecules in Synaptic Plasticity

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Synapses play a critical role in establishing and maintaining neural circuits, permitting targeted information transfer throughout the brain. A large portfolio of synaptic adhesion/organizing molecules (SAMs) exists in the mammalian brain involved in synapse development and maintenance. SAMs bind protein partners, forming trans-complexes spanning the synaptic cleft or cis-complexes attached to the same synaptic membrane. SAMs play key roles in cell adhesion and in organizing protein interaction networks; they can also provide mechanisms of recognition, generate scaffolds onto which partners can dock, and likely take part in signaling processes as well. SAMs are regulated through a portfolio of different mechanisms that affect their protein levels, precise localization, stability, and the availability of their partners at synapses. Interaction of SAMs with their partners can further be strengthened or weakened through alternative splicing, competing protein partners, ectodomain shedding, or astrocytically secreted factors. Given that numerous SAMs appear altered by synaptic activity, in vivo, these molecules may be used to dynamically scale up or scale down synaptic communication. Many SAMs, including neurexins, neuroligins, cadherins, and contactins, are now implicated in neuropsychiatric and neurodevelopmental diseases, such as autism spectrum disorder, schizophrenia, and bipolar disorder and studying their molecular mechanisms holds promise for developing novel therapeutics.

1. Synapses

It is estimated that there are more than one hundred billion neurons in the human brain, connected to one another by hundreds of trillions of contact points called synapses. These synaptic connections wire select neurons into functional neuronal circuits, enabling the brain to process and transfer information. Each synapse consists of a patch of “presynaptic membrane” from one neuron (typically an axon terminus) adhered to a patch of “postsynaptic membrane” from a second connecting neuron (typically a dendrite), and the space between them called the “synaptic cleft.” At chemical synapses, which comprise the vast majority of synapses in the brain, action potentials (i.e., electrical activity) from the presynaptic neuron trigger the release of neurotransmitters into the synaptic cleft, provoking molecular and cellular responses in the postsynaptic neuron in a process referred to as “synaptic activity.” The presynaptic side of the synapse hosts the molecular machinery needed to release and recycle synaptic vesicles containing these neurotransmitters. The postsynaptic side of the synapse responds to the released vesicle contents via receptors and channels and triggers downstream cellular responses. It is still not well understood how neurons wire together into specific circuits and, in particular, how correct synaptic connections are established and maintained over time. Remarkably, synaptic connections are dynamic and can change. In response to synaptic activity, they undergo structural and functional alterations as part of a process called “synaptic plasticity.” Synaptic plasticity can involve changes to the molecular components present at a synapse, the location of these components at a synapse, the efficiency with which a synapse can communicate, and even whether a synapse is maintained or completely disappears; for excellent recent reviews see [1–3]. Mechanisms of synaptic plasticity are widely believed to be involved in long term memory [1–3]. Alterations at synapses have commonly been monitored through two important phenomena: long term potentiation (LTP) and long term depression (LTD), processes...
that cause an increase or decrease in synaptic strength, respectively (as gauged by the electrical output produced by the postsynaptic neuron in response to synaptic stimulation). LTP and LTD are also thought to be involved in memory and learning. Synapses, thus, through their role in mediating connections between neurons and their ability to change through mechanisms of synaptic plasticity play an essential role in proper brain function.

2. Protein Networks at Synapses and Their Relation to Disease

Synapses contain a staggering number of proteins. Extensive proteomics studies and review of the literature estimate that there are ~1,900 to more than ~2,700 proteins localized at synapses [4–6]. The synaptic proteins identified include ones involved in exocytosis and recycling of synaptic vesicles, receptors for different neurotransmitters, ion channels, extracellular matrix proteins, cell adhesion molecules, cytoskeletal proteins, scaffolding proteins, membrane transporters, GTPases, phosphatases, and molecules involved in protein degradation. However, where the exact boundary of a synapse lies is vague (i.e., where it starts and stops), so scientists have typically relied on the ability of a protein to be co-isolated with synaptosomal membrane fractions and/or microscopy to designate a synaptic identity. Also it is not known which of these many different proteins are found at a particular synapse or how their distribution and expression level varies over the different synapse types.

More than a decade ago, it was suggested that defects at synapses would underlie many neurodevelopmental and neuropsychiatric diseases [7]. Hundreds of genes are now implicated in diseases like schizophrenia, autism spectrum disorder, and other behavioral and cognitive disorders, and many of them indeed code synaptic proteins ([8–11]; https://sfari.org/resources/sfari-gene). For this reason, the term “synaptopathies” is increasingly used to refer to neurodevelopmental proteins, scaffolding proteins, membrane transporters, GTPases, phosphatases, and molecules involved in protein degradation. However, where the exact boundary of a synapse lies is vague (i.e., where it starts and stops), so scientists have typically relied on the ability of a protein to be co-isolated with synaptosomal membrane fractions and/or microscopy to designate a synaptic identity. Also it is not known which of these many different proteins are found at a particular synapse or how their distribution and expression level varies over the different synapse types.

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Figure 1: SAMs. Prominent families of SAMs with putative synaptic localization and function are shown. Prototypes used to depict the domain organization are indicated. From top to bottom the following is listed: neurexin 1α and neurexin 1β (NRXN1α and NRXN1β; neurexins); CNTNAP2 (contactin associated protein-like); NLGN1 (neuroligins); CLSTN3 (calsyntenins); NEGR1 (Iglons which include NEGR1, NTM, LSAMP, and OPCML); Sirp α (signal regulatory proteins); NPTN (neuroplastin); IGSF8 (immunoglobulin superfamily); IL1RAPL1 (interleukin 1 receptor accessory protein-like); ICAM5 (intercellular adhesion molecules); MDGA1 (MAM domain containing glycosylphosphatidylinositol anchor); NCAM1 (neural cell adhesion molecules); CNTN2 (contactins); LICAM (L1 cell adhesion molecules); NRCAM (neuronal cell adhesion molecules); Neol (neogenin); SDK1 (sidekick cell adhesion molecules); PTPRD (protein tyrosine phosphatase receptor types D, F, and S); CDH2 (cadherins); PCDH1 (protocadherins); ELFN2 (extracellular leucine rich repeat and fibronectin type III domain containing); LRTM1 (leucine rich repeats and transmembrane domains); LRRTM1 (leucine rich repeat transmembrane neuronal); LINGO1 (leucine rich repeat and Ig domain containing); SLITRK1 (SLIT and NTRK-like family member); LRFN1 (leucine rich repeat and fibronectin type III domain containing); ADGRL1 (adhesion G protein-coupled receptor type L; previously known as latrophilins); ADGRB1 (adhesion G protein-coupled receptor type B, previously known as brain-specific angiogenesis inhibitor). Several large polymorphic families including the ephrin receptors, integrins, and plexins are not shown. The domain abbreviations used in the text are for laminin G/neurexin/sex hormone binding globulin or LNS domains (L); epidermal growth factor repeat (EGF); coagulation factor 5/8 type C (F58C); fibrinogen-like (FBG); extracellular cadherin (EC); alpha/beta (α/β); immunoglobulin (Ig); Toll/Il-1 receptor homology (TIR); meprin, A-5 protein, receptor protein tyrosine phosphatase mu (MAM); fibronectin type 3 (FN); protein tyrosine phosphatase (PTP); leucine rich repeat (LRR), N-terminal leucine rich repeat (LRRNT); C-terminal leucine rich repeat (LRRCT); galactose binding lectin domain (LEC); olfactomedin-like domain (OLF); hormone binding domain (HBD); GPCR-autoproteolysis inducing (GAIN); thrombospondin (TSP). Other abbreviations are signal peptide (SP) and transmembrane segment (TM). Alternative splice insert sites are indicted for the SAMs NRXN1α, NRXN1β, and NLGN1, as they are referred to in the text.
4. Plastic Interactions within the Synaptic Cleft

SAMs are strategically positioned to contribute to synaptic plasticity, given that they can alter synapse structure and function through their ability to sculpt and regulate synaptic protein interaction networks. Below we highlight several important mechanisms that have come to light that regulate SAMs, their diversity, and their functions in a synaptic activity-dependent way. We further present supporting examples to illustrate the general themes (Figure 3).

4.1. Alteration of SAM Protein Levels in the Synaptic Cleft

It has long been held that synaptic protein abundance is implicated in synaptic plasticity. In particular, altering the abundance of a specific SAM at a synapse could fundamentally impact the development, maintenance, and ultimate elimination of that synapse. A number of studies have used quantitative proteomics of synaptosomal fractions to correlate synaptic protein abundance (including those of SAMs) to events implicated in synaptic plasticity, for example, the long term synaptic adaptions that accompany the administration of drugs of abuse. Repeated morphine administration robustly downregulated CNTN1, L1CAM, neurocan, and OPCML in striatal presynaptic fractions [27], while in a second study neurexin, NCAM, and NTM protein levels decreased more than 40% in rat forebrain synaptosomal fractions, though in this case OPCML protein levels were unaltered [28]. Importantly, these studies showed that the abundance of synaptic proteins was altered in a highly selectively way. Of 175 proteins that could be identified proteomically, only 30 were robustly and consistently altered by morphine treatment.
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Figure 3: SAMs can contribute to synaptic plasticity. SAM function can be regulated by synaptic activity through different processes. Protein levels can change (1) as a result of altered localization targeting a protein to or away from the synaptic membrane surface (1a), protein synthesis (1b), protein degradation (1c), and ectodomain shedding (1d). The availability of members within a broad portfolio of potential partners can be altered (2). SAMs can be diversified through alternative splicing (3). SAMs can be repositioned in the synaptic cleft (4). Protein interactions supported by SAMs can be modulated by astrocytic factors (5). Details are as discussed in the text.

(i.e., 17%), indicating that the SAMs that were altered represented highly significant changes [27]. In other studies, experience dependent plasticity induced in animals by trimming their whiskers to cause sensory deprivation resulted in ~20% to ~30% lower levels for the SAMs Pcdh1, ICAM5, Plexin-A1, and Lphn 3 in juvenile mice (a period where synaptogenesis peaks) [29]. Also in this latter study, the protein abundance was only very selectively altered; only a small number of proteins were affected which included specific SAMs, while 95% of the 7000 tentative synaptic proteins examined showed no significant changes [29]. The above proteomic studies signify that the protein abundance of SAMs can change in response to events triggering synaptic plasticity. However, several caveats exist. These proteomic approaches offer only a global view of protein abundance, profiling changes in protein levels averaged over a large, heterogeneous population of synapses pooled together from many different kinds of neurons and supporting glial cells. In addition, only those proteins that are technically accessible were monitored, that is, only those proteins which were extracted in sufficiently abundant quantities to enable their detection and analysis by mass spectrometric methods [30].

How do protein levels for a specific SAM change in response to synaptic activity at a specific, single synapse or just a small subset of select synapses? Several processes have been identified that modulate SAM protein levels at the level of a single synapse, altering synapse morphology and stabilizing (or destabilizing) synaptic strength on a very local scale in response to synaptic activity (see (1a)–(1d) in Figure 3).

(i) SAMs can accumulate or be depleted from membrane surfaces in the synaptic cleft as a result of altered stability, for example, due to loss of stabilizing partners, recruitment, trafficking, internalization, and/or phosphorylation of cytoplasmic tails. For instance, levels of neurexin 1β at the synaptic membrane rise in response to neural activity, apparently due to an increase in stability (or suppressed dynamics) at the synaptic terminal [31]. NLGN1 and NLGN3 have increased surface membrane levels upon chemically induced LTP and decreased levels after LTD as a result of being dynamically exchanged at the postsynaptic membrane through active cytoskeleton transport [32]. In addition, surface expression of NLGN1 is also increased through CAMKII phosphorylation of its cytoplasmic tail in response to synaptic activity [33]. Other SAMs such as OPCML, CNTN1, and cadherins also display decreasing or increasing protein levels in the synaptic cleft in response to synaptic activity as a result of internalization into the cell or mobilization to the synaptic membrane surface [34–37].

(ii) Protein levels can rise in the synaptic cleft as a result of activity-induced expression via local protein synthesis at the synapse (recently reviewed in [38]). For example, expression of LRRTM1 and LRRTM2 (synaptic organizers that induce presynaptic differentiation) increases as a function of synaptic activity because influx of Ca2+ into the postsynaptic neuron following NMDA-receptor activation induces nuclear Ca2+-dependent transcription [39]. α-Dystroglycan expression is also upregulated by prolonged increased neuronal activity at inhibitory synapses in the CNS elevating its protein levels [40]. In addition, local
translation of DSCAM in dendrites has been shown to be rapidly induced by synaptic activity [41].

(iii) SAM levels can also decrease at synapses as a result of degradation, thereby regulating synapse development and survival. Evidence is building that highly targeted protein degradation takes place at synapses locally and that it can be regulated by synaptic activity (for recent review see [38]). Intriguingly, elegant studies have revealed that the C. elegans SAM, SYG-1, can locally inhibit an E3 ubiquitin ligase complex that targets proteins for degradation, protecting adjacent synapses from elimination [42].

(iv) One particular form of proteolysis, ectodomain shedding, is now widely documented to regulate SAM protein levels in the synaptic cleft. During shedding, the extracellular domain of a SAM is proteolytically released from its transmembrane segment or its GPI anchor that tethers it to the synaptic membrane. Liberating the SAM ectodomain permits the protein interactions and extracellular matrix to be remodeled within the synaptic cleft. Ectodomain shedding is involved in structural as well as functional synaptic plasticity and impacts key processes like LTP and LTD (for recent reviews see [43, 44]). Exactly where the released ectodomains end up is unclear. Do they remain in the synaptic cleft, binding and blocking their normal protein partners from forming trans-synaptic interactions? Or are the shed ectodomains lost from the synaptic cleft, diffusing outwards to affect other neighboring synapses? Alternatively, are they perhaps simply degraded locally?

Both presynaptic as well as postsynaptic SAMs have been demonstrated to undergo ectodomain shedding in vitro and in vivo. Activity-dependent proteolytic release has been shown for many well-known SAMs, including neuroligins, neurexins, calsyn-tenins, S1PRs, ICAMs, LRAs, Slitrks, and nectins, and their release is executed by various proteases including matrix metalloproteases, ADAM proteases, and alpha/gamma-secretases [14, 43, 45–53]. The downstream consequence of ectodomain shedding varies. In the case of the postsynaptic adhesion molecule NLGNI, shedding destabilizes the presynaptic partner neurexin 1β at synapses and decreases the presynaptic release probability of synaptic vesicles, thereby depressing synaptic transmission [48, 50]. Ectodomain release of NLGNI has relevance for disease, because it is promoted by epileptic seizures [50]. Release of the Sirp α ectodomain has a completely different consequence, because it promotes synapse maturation [51]. Likewise, ectodomain release of CLSTN1, which is found on the postsynaptic membrane of inhibitory and excitatory synapses, permits the transmembrane stub and Ca2+-binding cytoplasmic domain to be internalized and accumulate in the spine apparatus where it is thought to carry out a role in postsynaptic Ca2+-signaling [54].

Taken together, multiple processes exist that regulate protein levels of specific SAMs in the synaptic cleft of single synapses in response to synaptic activity.

4.2. Availability of a Broad Portfolio of Different SAMs Containing Variable, Synergistic, and Competing Partners. It is estimated that there are more than 470 putative cell adhesion molecules in humans [55], although how many of these are expressed in the brain and are synaptic is not known. Nevertheless, a broad portfolio of SAMs has been validated to date and it provides a powerful mechanism to generate a myriad of different possible interactions, some of which can be affected by synaptic activity, thereby contributing to mechanisms of synaptic plasticity (see (2) in Figure 3). Diversity is achieved in several ways. Most SAMs are modular in nature and use a combinatorial approach to build up their extracellular region by alternating different structural modules, for example, Ig domains, FN3 domains, and cadherin EC domains (Figure 1). In addition, most SAM families contain several members that, while sharing a conserved domain structure, vary in amino acid sequence. In some families, individual members are diversified even further through alternative splicing of their mRNA, inserting, deleting, or exchanging anywhere from one to more than a hundred amino acids in the encoded protein. For instance, more than a thousand splice variants have been demonstrated for neurexins (discussed below).

The portfolio of SAMs can be expanded even further on a functional level in two key ways. First, SAMs can assume evolving functions over time, carrying out one function during the early stages of brain development, while connectivities are being formed, and then switching to another function in the mature adult brain. For example, early during synapse development, neuroligins and LRRTMs appear to compensate for one another; however once synapses have formed, neuroligins and LRRTMs affect excitatory synaptic transmission differently [56]. Likewise, during early development cadherins are important for synapse adhesion, stabilization, and synaptogenesis in young neurons; however once mature synapses have formed, they no longer are needed to keep neuronal and synaptic structures in place but appear to play a role in signaling, structural plasticity, and cognitive function [34]. Second, certain SAMs appear to work together synergistically, generating new functions that do not extend to the individual members alone. Case in point, different combinations of protocadherin family members form dimeric cis-complexes that oligomerize into larger tetrameric trans-complexes; the functional roles of these different species are still being worked out [57, 58]. Members of different families can also interact with each other in a mix-and-match approach. For example, cadherins bind each other to form trans-complexes spanning the synaptic cleft, but they also can bind protocadherins side-by-side forming cis-complexes [34].

Given such a broad portfolio of SAMs, how different are the proteins functionally or are many of them redundant? The extent to which different SAMs carry out substantially different functions or are redundant is controversial. Some SAMs clearly have discrete and different biological functions. For example, NLGNI can induce synapse formation in young
Figure 4: Synaptic protein interaction network coordinated by neurexins. (a) Neurexins (blue ovals) bind many protein partners tethered to the postsynaptic membrane including neuroligins, LRRTMs, α-dystroglycan, calsyntenins (CLSTN), and the GABA_\text{A}-receptor, as well as partners that are secreted such as neurexophilins. (b) NLGN1 and LRRTM2 can both bind neurexins at an overlapping binding site generating two competing \textit{trans}-interactions. (c) Neurexins and MDGA1 can both bind NLGN2 at an overlapping binding site generating competing \textit{cis}- and \textit{trans}-interactions.

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primary hippocampal cultures, but SynCAM1 cannot [59]. Members of the same SAM family can also have dramatically different roles; NLGN2 is found exclusively at inhibitory synapses, while NLGN1 is found predominantly at excitatory synapses [23]. Likewise, Slitrk1 and Slitrk3 promote excitatory versus inhibitory synapse formation, respectively [60, 61]. However, equally so, SAMs can also demonstrate functionally redundant actions. For instance, LRRTM1, LRRTM2, NLGN1, and NLGN3, proteins that increase synapse numbers in vitro, appear functionally redundant because only knockdown of all four proteins together decreases the number of formed synapses significantly [62]. Thus, though many SAMs exist, their exact functional roles and the extent to which these are unique or overlap needs to be further investigated, both alone and in the broader context of the synaptic cleft.

The power of a broad portfolio of SAMs binding each other and sculpting interactomes within the synaptic cleft is beautifully illustrated by the complex interaction network that has been revealed centered on neurexins. Presynaptically tethered neurexins reach across the synaptic cleft to bind postsynaptic ligands such as the neuroligins, LRRTMs, and α-dystroglycan, forming \textit{trans}-synaptic bridges (Figure 4(a)). Neurexins also recruit calsyntenins, though whether this interaction is direct or indirect is debated [14, 63, 64]. At excitatory synapses, neurexins extend across the synaptic cleft to bind postsynaptic ligands such as the neuroligins, LRRTMs, and α-dystroglycan, forming \textit{trans}-synaptic bridges (Figure 4(b)). Because these postsynaptic partners utilize the same or an overlapping binding surface on neurexin, LRRTM2 and NLGN1, for example, compete with each other for neurexin binding, though the
Neurexins form one of the best studied families of SAMs diversified through alternative splicing. Neurexins are encoded by three genes (1, 2, and 3) that each produce a short beta form and a long alpha form, by virtue of two different promoters [23]; see also Figure 1. Single molecule mRNA sequencing of tens of thousands of neurexin mRNAs has demonstrated that there are at least ~1,400 variants by one report and more than 2,000 variants by another in the adult mouse brain [73, 74], though the transcripts are not all equally abundant [74]. Alternative splice inserts can be incorporated at six places in the extracellular region of neurexin 1α (SS#1 through SS#6), adding polypeptide inserts of up to 30 amino acids at five of these insertion sites; see Figure 1 and [23, 74]. Incorporation of splice inserts has functional consequences because several inserts have been shown to regulate the interaction of neurexins with different postsynaptic partners. For example, incorporation of SS#2 in the L2 domain of neurexin 1α decreases its binding to α-dystroglycan, while SS#4 regulates the affinity of neurexins to postsynaptic partners such as neureligins, LRRTMs, α-dystroglycan, cerebellin precursor protein, and latrophilin/ADGRL (recently reviewed by [23, 68, 75]). Proteomic quantitation has confirmed that distinct neurexin splice variants bind different amounts of protein partners, corroborating a mechanism whereby alternative splicing regulates the binding affinity of neurexins for different ligands in vivo [76]. From a biochemical and protein structural perspective, SS#2 and SS#4 change the affinity of Ca$^{2+}$-binding sites central to protein interaction sites on the L2 and L6 domains, while SS#4 also induces structural plasticity because it can adopt multiple conformations [77–79]. From a functional perspective, mice engineered to constitutively include SS#4 in neurexin 3α show a decrease in synaptic strength and impaired LTP in vivo because postsynaptic AMPA-receptor levels are decreased at the synapse (as a result of increased AMPA-receptor endocytosis), although the underlying mechanism is not clear [80]. For most neurexin splice inserts, however, their effects on protein structure and function are not well delineated. Likewise, the function of rare neurexin splice variants, in which multiple domains are deleted, is also not known, nor if these yield functional proteins in the first place [74].

The very large portfolio of neurexin alternative splice forms is strategically positioned to play an important role in synaptic plasticity. In the mammalian brain, specific neurexin splice forms demonstrate cell type specific distributions and brain region specific expression both at the mRNA as well as the protein levels [73, 76, 81]. Importantly, incorporation of certain splice inserts is neuronal activity dependent, and an altered splicing profile can be reversed [82–84]. For example, analysis of mRNAs in single medium spiny neuron cells (MSN) demonstrated that neurexin 1α and neurexin 1β are prevalent in D1-R-MSNs, but much less so in D3-R-MSNs, and mostly contain the SS#4 insert [81]. However, exposure to repeated cocaine administration, a circumstance triggering synaptic plasticity, reduces neurexin 1 mRNA levels in D3-R-MSNs even further and alters the profile of splice forms [81]. Therefore, alternative splicing of neurexins generates diversity of protein structure and function, and it can be regulated by events linked to synaptic plasticity.
Other SAM families are regulated by alternative splicing in their extracellular domain as well, altering the affinity with which they bind protein partners in the synaptic cleft. These include the neuroligins where splice inserts regulate interactions with neurexins (refer back to Figure 1, [85–88]); PTPr and PTPrσ where splicing regulates binding to Slitrks, interleukin-1 receptor accessory protein (ILIRAP), and SALM3 [89–94]; and the family of adhesion GPCRs where alternative splicing alters the domain composition of the extracellular region and consequently the profile of interacting protein partners [95].

4.4. Altered Location of SAMs within the Synaptic Cleft. The advent of powerful high resolution microscopy techniques has revealed that SAMs can be redistributed within the synaptic cleft in response to synaptic activity (see (4) in Figure 3). Recent studies show that the synaptic cleft is made up of structurally distinct subcompartments and SAMs can segregate to different regions of the cleft. Upon synaptic activity, however, certain molecules can move within or to the periphery of the synaptic cleft. The impact of these redistributions on synaptic function, however, is not clear. For instance, SynCAM1 and EphB2 receptor tyrosine kinase (EphB2) are two postsynaptic SAMs with different roles. SynCAM1 induces synapse formation and subsequently also maintains excitatory synapses, while EphB2 promotes excitatory synaptogenesis in the rapid early phase of synaptogenesis before neurons mature. By tracking SynCAM1 and EphB2 in the synaptic cleft at excitatory synapses, Perez de Arce and coworkers demonstrated that SynCAM1 is located around the cleft’s edge while EphB2 is embedded deeper within the central PSD region [96]. Strikingly, upon application of an LTD paradigm, SynCAM1 underwent redistribution on the surface of the synaptic membrane forming puncta of increasing size, an intriguing finding given that SynCAM1 regulates LTD in vivo and suggesting this redistribution has functional significance [96]. Another SAM, N-cadherin, forms trans-synaptic bridges with N-cadherin molecules tethered to the opposing synaptic membrane. N-cadherin plays an important role presynaptically by regulating synaptic vesicle recruitment and recycling, and postsynaptically in spine remodeling and trafficking of AMPA-Rs, which is important for hippocampal LTP [97]. Superresolution microscopy has shown that N-cadherin localizes predominantly as puncta at the periphery of synapses and to a much lesser extent along the synaptic cleft in unstimulated cultured hippocampal neurons [97]. However, upon synaptic stimulation followed by a rest period, N-cadherin distributes broadly throughout the synaptic cleft [97]. Thus an increasing body of work shows that SAMs can be redistributed as a result of synaptic activity, likely altering protein interactomes in the synaptic cleft. How different SAMs are redistributed and the impact of such redistribution on synaptic function remain to be further elucidated.

4.5. Astrocytic Control of SAMs. A fascinating development has been the demonstration that astrocytes (a type of glial cell found interspersed between neurons which can ensheathe synapses) secrete factors that modulate the action of SAMs (see (5) in Figure 3). During the development of the nervous system, astrocytes regulate synapse formation and remodeling, impacting synapse number through their ability to promote the formation and elimination of synapses [98]. A single mouse astrocyte can ensheathe more than 100,000 synapses [99]. In the mature brain, astrocytes also can modulate synaptic plasticity [98]. Immature astrocytes secrete thrombospondin 1 and thrombospondin 2 (TSP-1 and TSP-2), large, trimeric extracellular matrix proteins that promote the formation of silent synapses in vitro and in vivo (i.e., synapses that are presynaptically active, but postsynaptically silent because they lack functional AMPA-Rs) [100]. TSP1 can bind postsynaptic neuroligins, increasing the speed of excitatory synapse formation at early stages in cultured rat hippocampal neurons, although not the final density of the synapses formed in mature neurons [101]. Hevin, another protein secreted by astrocytes, can modify the interaction between two SAMs in the synaptic cleft by working as an adaptor protein [102]. Hevin binds directly to neurexin α and NLGN1(+B), a pair of SAMs that normally do not interact, and engages them in a trans-synaptic bridge promoting excitatory synapse formation [102]. It is thought that the nine-amino-acid splice insert at site B in NLGN1(+B) sterically blocks the interaction between NLGN1 and the sixth LNS domain of neurexin α (L6) (refer back to Figure 1) thereby forming a key component of the “neurexin-neuroligin splice code,” reviewed in [23]. The bridging of neurexin α and NLGN1(+B) by hevin, overriding the splice code, was shown to be critical to form thalamocortical connections in the developing visual cortex in vivo [102]. Therefore, astrocytes by secreting proteins that interact with bona fide SAMs can modify their interactions and regulate protein interactomes in the synaptic cleft.

4.6. Novel Mechanisms to Regulate SAMs. It is likely that additional novel mechanisms exist that regulate SAMs, impacting their function in synaptic activity-dependent ways. One tantalizing mechanism is that SAMs undergo protein structural changes in response to synaptic activity. Perhaps mechanisms will be validated confirming that SAMs can sense synaptic activity in the synaptic cleft and adjust their protein interactions in response via (allo)steric mechanisms. Certainly, incorporation of an alternative splice insert in a SAM in response to synaptic activity (as discussed above) would be one way to induce a protein conformational change. Such a splice insert driven conformational change would have the potential to alter protein interactions within the synaptic cleft. The splice inserts SS#1 and SS#6 in neurexin α are of interest in this respect because they integrate into molecular hinges within the neurexin ectodomains and are poised to alter the conformation of domains with respect to one another. However, it is not known yet if these splice inserts are subject to activity-dependent incorporation [74, 103]. A novel protein conformation or interaction site in a SAM might also be induced upon binding of a protein partner and controlled though synaptic activity-induced expression of that partner (refer back to Figures 2(b) and 2(c)). Neuronal activity-induced expression of α-dystroglycan [40], which binds the L2 domain of neurexin α and appears to sterically block the interaction of neurexin α with neuroligins via the L6
domain, is a prime example [68] (refer back to Figure 1). Synaptic stimulation also appears to induce homodimerization of N-cadherin, an event altering the overall protein architecture [104]. Lastly, the protein conformation of a SAM containing Ca$^{2+}$-binding sites might also be altered by changes in Ca$^{2+}$ levels in the synaptic cleft as a result of synaptic activity, affecting its interactions with protein partners. Experimental evidence is accumulating that Ca$^{2+}$ levels decrease in the synapse cleft in response to (prolonged) synaptic activity, a result of Ca$^{2+}$ flooding into the presynaptic terminal during synaptic vesicle release and/or into the postsynaptic terminal upon NMDA-receptor activation [105, 106]. It has been suggested that the extracellular Ca$^{2+}$-level in the synaptic cleft is ~1 mM and can drop significantly, maybe as much as 30–60% as presynaptic and postsynaptic channels open [107]. Studies on trans-complexes of cadherins have shown that their interactions depend in part on extracellular Ca$^{2+}$ levels and are rapidly decreased when extracellular Ca$^{2+}$ is depleted [108]. Thus, additional and novel mechanisms to regulate SAMs in response to synaptic activity may be validated in the near future.

5. SAMs Are Implicated in Neuropsychiatric and Neurodevelopmental Diseases

Many SAMs, including neurexins, neuroligins, LRRTMs, and other leucine rich repeat containing proteins, contactins, CNTNAPs, and cadherins are now implicated in neuropsychiatric and neurodevelopmental diseases, such as autism spectrum disorder, schizophrenia, bipolar disorder, epilepsy, and mental retardation [8, 20, 22, 24, 26, 109]. Initially, it was speculated that these molecules played crucial roles in the formation of synapses, and their lesion would lead to large scale disruption of synapse formation. Nevertheless, it was puzzling why deficits in such molecules, if indeed so essential for synapse formation, were selectively linked to cognitive and behavioral disorders, leaving other brain functions such as the coordination of movement or the processing of auditory and visual information apparently undisturbed. It is now recognized that there is a very large portfolio of SAMs in the mammalian brain, and there is not one single SAM, which when deleted, is sufficient to prevent synapse formation on a large scale given their partially redundant and overlapping functions. Furthermore, we now realize that the function of SAMs is much more complex and nuanced than purely synaptic activity modifying their protein interactions and function.

6. Conclusion

SAMs play a key role in establishing and maintaining synapses; they are involved in synapse formation, development, maturation, and elimination. Through their roles at synapses, SAMs are in position to impact the flow of information throughout the brain and beyond. Exciting work is being done to investigate the extent to which SAMs respond to synaptic activity modifying their protein interactions and function. Because SAMs are implicated in neuropsychiatric and neurodevelopmental disorders, studying their precise molecular mechanisms and interaction modes with their partners holds promise that this information can eventually be leveraged to design completely novel therapeutic strategies that regulate aberrant synaptic communication.

Competing Interests

The author declares that they have no competing interests.

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References

[1] C. H. Bailey, E. R. Kandel, and K. M. Harris, “Structural components of synaptic plasticity and memory consolidation,” Cold Spring Harbor Perspectives in Biology, vol. 7, no. 7, Article ID a021758, 2015.

[2] J. D. Sweatt, “Neural plasticity and behavior—sixty years of conceptual advances,” Journal of Neurochemistry, vol. 139, no. 2, pp. 179–199, 2016.

[3] J. Yin and Q. Yuan, "Structural homeostasis in the nervous system: a balancing act for wiring plasticity and stability," Frontiers in Cellular Neuroscience, vol. 8, article 439, 2015.
Neural Plasticity

[4] M. D. R. Croning, M. C. Marshall, P. McLaren, J. D. Armstrong, and S. G. N. Grant, "G2Cdb: the genes to cognition database," *Nucleic Acids Research*, vol. 37, no. 1, pp. D846–D851, 2009.

[5] R. Piechot, K.-H. Smalla, A. Müller et al., "Synprot: a database for proteins of detergent-resistant synaptic protein preparations," *Frontiers in synaptic Neuroscience*, vol. 4, article no. 1, Article ID 1, 2012.

[6] M. Pirroznia, T. Wang, D. Avramidopoulos et al., "SynaptomeDB: an ontology-based knowledgebase for synaptic genes," *Bioinformatics*, vol. 28, no. 6, pp. 897–899, 2012.

[7] H. Y. Zoghbi, "Postnatal neurodevelopmental disorders: meeting at the synapse?" *Science*, vol. 302, no. 5646, pp. 826–830, 2003.

[8] T. Bourgeron, "Current knowledge on the genetics of autism and propositions for future research," *Comptes Rendus Biologies*, vol. 339, no. 7-8, pp. 300–307, 2016.

[9] M. Fromer, A. J. Pocklington, D. H. Kavanagh et al., "De novo mutations in schizophrenia implicate synaptic networks," *Nature*, vol. 506, no. 7487, pp. 179–184, 2014.

[10] J. Hall, S. Trent, K. L. Thomas, M. C. O’Donovan, and M. J. Owen, "Genetic risk for schizophrenia: convergence on synaptic pathways involved in plasticity," *Biological Psychiatry*, vol. 77, no. 1, pp. 52–58, 2015.

[11] Schizophrenia Working Group of the Psychiatric Genomics Consortium, "Biological insights from 108 schizophrenia-associated genetic loci," *Nature*, vol. 511, no. 7510, pp. 421–427, 2014.

[12] M. Y. Zoghbi, "Postnatal neurodevelopmental disorders: meeting at the synapse?" *Science*, vol. 302, no. 5646, pp. 826–830, 2003.

[13] J. L. Pettem, D. Yokomaku, L. Luo et al., "The specific α-neurexin interactor calsyntenin-3 promotes excitatory and inhibitory synapse development," *Neuron*, vol. 80, no. 1, pp. 113–128, 2013.

[14] M. Yamagata, J. A. Weiner, and J. R. Sanes, "Sidekicks: synaptic adhesion molecules that promote lamina-specific connectivity in the retina," *Cell*, vol. 110, no. 5, pp. 649–660, 2002.

[15] K. Lee, Y. Kima, S.-J. Lee et al., "MDGAs interact selectively with neurexin-2: the specific α-neurexin interactor calsyntenin-3 promotes excitatory and inhibitory synapse development," *Journal of Cell Biology*, vol. 200, no. 3, pp. 321–336, 2013.

[16] C. Faivre-Sarrailh and J. J. Devaux, "Neuro-glial interactions at the nodes of Ranvier: implication in health and diseases," *Frontiers in Cellular Neuroscience*, vol. 7, article 196, 2013.

[17] E. Lie, J. S. Ko, S.-Y. Choi et al., "SALM4 suppresses excitatory synapse development by cis-inhibiting trans-synaptic SALM3-LAR adhesion," *Nature Communications*, vol. 7, Article ID 12328, 2016.

[18] J. de Wit and A. Ghosh, "Control of neural circuit formation by leucine-rich repeat proteins," *Trends in Neurosciences*, vol. 37, no. 10, pp. 539–550, 2014.

[19] A. B. Keeler, M. J. Molumbly, and J. A. Weiner, "Protocadherins branch out: multiple roles in dendrite development," *Cell Adhesion and Migration*, vol. 9, no. 3, pp. 214–226, 2015.

[20] C. Redies, N. Hertel, and C. A. Hübner, "Cadherins and neuropsychiatric disorders," *Brain Research*, vol. 1470, pp. 130–144, 2012.

[21] C. Reissner, F. Runkel, and M. Missler, "Neurexins," *Genome Biology*, vol. 14, no. 9, article no. 213, 2013.

[22] P. Rodenas-Cuadrado, J. Ho, and S. C. Vernes, "Shining a light on CNTNAP2: complex functions to complex disorders," *European Journal of Human Genetics*, vol. 22, no. 2, pp. 171–178, 2014.

[23] T. C. Südhof, "Neurelins and neurexins link synaptic function to cognitive disease," *Nature*, vol. 455, no. 7215, pp. 903–911, 2008.

[24] A. Zuko, K. T. E. Kleijer, A. Oguro-Ando et al., "Contactins in the neurobiology of autism," *European Journal of Pharmacology*, vol. 719, no. 1-3, pp. 63–74, 2013.

[25] N. S. Abul-Husn, S. P. Annangudi, A. M. Steward et al., "Chronic morphine alters the presynaptic protein profile: identification of novel molecular targets using proteomics and network analysis," *PLoS ONE*, vol. 6, no. 10, Article ID e25535, 2011.

[26] L. Prokai, A. D. Zharikova, and S. M. Stevens Jr., "Effect of chronic morphine exposure on the synaptic plasma-membrane subproteome of rats: A quantitative protein profiling study based on isotope-coded affinity tags and liquid chromatography/mass spectrometry," *Journal of Mass Spectrometry*, vol. 40, no. 2, pp. 169–175, 2005.

[27] M. T. Butko, J. N. Savas, B. Friedman et al., "In vivo quantitative proteomics of somatosensory cortical synapses shows which protein levels are modulated by sensory deprivation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 8, pp. E726–E735, 2013.

[28] D. C. Dieterich and M. R. Kreutz, "Proteomics of the synapse—a quantitative approach to neuronal plasticity," *Molecular and Cellular Proteomics*, vol. 15, no. 2, pp. 368–381, 2016.

[29] Y. Fu and Z. J. Huang, "Differential dynamics and activity-dependent regulation of α- and β-neurexins at developing GABAergic synapses," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 52, pp. 22699–22704, 2010.

[30] I. U. Schapitz, B. Behrend, Y. Pechmann et al., "Neurelin I is dynamically exchanged at postsynaptic sites," *Journal of Neuroscience*, vol. 30, no. 38, pp. 12733–12744, 2010.

[31] M. A. Bemben, S. L. Shipman, T. Hirai et al., "CaMKII phosphorylation of neurelin-1 regulates excitatory synapses," *Nature Neuroscience*, vol. 17, no. 1, pp. 56–64, 2014.

[32] L. G. Friedman, D. L. Benson, and G. W. Huntley, "Cadherin-based transsynaptic networks in establishing and modifying neural connectivity," *Current Topics in Developmental Biology*, vol. 112, pp. 415–465, 2015.

[33] K. Pierre, B. Dupouy, M. Allard, D. A. Poulain, and D. T. Theodosis, "Mobilization of the cell adhesion glycoprotein F3/contactin to axonal surfaces is activity dependent," *The European Journal of Neuroscience*, vol. 14, no. 4, pp. 645–656, 2001.

[34] C.-Y. Tai, S. P. Mysore, C. Chiu, and E. M. Schuman, "Activity-Regulated N-Cadherin Endocytosis," *Neuron*, vol. 54, no. 5, pp. 771–785, 2007.

[35] M. Yamada, T. Hashimoto, N. Hayashi et al., "Synaptic adhesion molecule OBCAM; synaptogenesis and dynamic internalization," *Brain Research*, vol. 1165, no. 1, pp. 5–14, 2007.

[36] B. Alvarez-Castelao and E. M. Schuman, "The regulation of synaptic protein turnover," *The Journal of Biological Chemistry*, vol. 290, no. 48, pp. 28623–28630, 2015.
[39] S. N. Hayer and H. Bading, "Nuclear calcium signaling induces expression of the synaptic organizers Lrttm1 and Lrttm2," The Journal of Biological Chemistry, vol. 290, no. 9, pp. 5523–5532, 2015.

[40] H. Pribiag, H. Peng, W. A. Shah, D. Stellwagen, and S. Carbonetto, "Dystroglycan mediates homoeostatic synaptic plasticity at GABAergic synapses," Proceedings of the National Academy of Sciences of the United States of America, vol. 111, no. 18, pp. 6810–6815, 2014.

[41] A. Alves-Sampaio, J. A. Troca-Marín, and M. L. Montesinos, "NMDA-Mediated regulation of DSCAM dendritic local translation is lost in a mouse model of Down’s syndrome," Journal of Neuroscience, vol. 30, no. 40, pp. 13537–13548, 2010.

[42] M. Ding, D. Chao, G. Wang, and K. Shen, "Spatial regulation of an E3 ubiquitin ligase directs selective synapse elimination," Science, vol. 317, no. 5840, pp. 947–951, 2007.

[43] M. Bajor and L. Kaczmarek, "Proteolytic remodeling of the synaptic cell adhesion molecule neurexin-3β by Alzheimer disease α- and γ-secretases," The Journal of Biological Chemistry, vol. 286, no. 4, pp. 2762–2773, 2011.

[44] J. Kim, C. Lilliehook, A. Dudak et al., "Activity-dependent α-cleavage of nectin-1 is mediated by a disintegrin and metalloprotease 10 (ADAM10)," Journal of Biological Chemistry, vol. 285, no. 30, pp. 22919–22926, 2010.

[45] I. Lonskaya, J. Partridge, R. R. Lalchandani et al., "Soluble ICAM-5, a product of activity dependent proteolysis, increases mEPSC frequency and dendritic expression of GluA1," PLoS ONE, vol. 8, no. 7, Article ID e69136, 2013.

[46] R. T. Peixoto, P. A. Kunz, H. Kwon et al., "Transsynaptic signaling by activity-dependent cleavage of neureolin-1," Neuron, vol. 76, no. 2, pp. 396–409, 2012.

[47] C. A. Saura, E. Servián-Morilla, and F. G. Scholl, "Presenilin/y-secretase regulates neurexin processing at synapses," PLOS ONE, vol. 6, no. 4, Article ID e19430, 2011.

[48] K. Suzuki, Y. Hayashi, S. Nakahara et al., "Activity-dependent proteolytic cleavage of neureolin-1," Neuron, vol. 76, no. 2, pp. 410–422, 2012.

[49] A. B. Toth, A. Terauchi, L. Y. Zhang et al., "Synapse maturation by activity-dependent ectodomain shedding of SIRPsα, Nature Neuroscience, vol. 16, no. 10, pp. 1417–1425, 2013.

[50] H. S. Venkatesh, T. B. Johung, V. Caretti et al., "Neuronal activity promotes glioma growth through neurexin-3 secretion," Cell, vol. 161, no. 4, pp. 803–816, 2015.

[51] P.-H. Kuhn, A. V. Colombo, B. Schusser et al., "Systemic substrate identification indicates a central role for the metalloprotease ADAM10 in axon targeting and synapse function," eLife, vol. 5, Article ID e21748, 2016.

[52] L. Vogt, S. P. Schrimpf, V. Meskenaite et al., "Calsyntenin-1, a proteolytically processed postsynaptic membrane protein with a cytoplasmic calcium-binding domain," Molecular and Cellular Neuroscience, vol. 17, no. 1, pp. 151–166, 2001.

[53] X. Zhong, J. Drgonova, C. - Y. Li, and G. R. Uhl, "Human cell adhesion molecules: annotated functional subtypes and overrepresentation of addiction-associated genes," Annals of the New York Academy of Sciences, vol. 1349, no. 1, pp. 83–95, 2015.

[54] G. J. Soler-Llavina, M. V. Fuccillo, J. Ko, T. C. Südhof, and R. C. Malenka, "The neurexin ligands, neurelixins and leucine-rich repeat transmembrane proteins, perform convergent and divergent synaptic functions in vivo," Proceedings of the National Academy of Sciences of the United States of America, vol. 108, no. 40, pp. 16502–16509, 2011.

[55] S. D. Burton, J. W. Johnson, H. C. Zeringue, and S. D. Meriney, "Distinct roles of neurexin-1 and SynCAM1 in synapse formation and function in primary hippocampal neuronal cultures," Neuroscience, vol. 215, pp. 1–16, 2012.

[56] Y. S. Yim, Y. Kwon, J. Nam et al., "Slitrks control excitatory and inhibitory synapse formation with LAR receptor protein tyrosine phosphatases," Proceedings of the National Academy of Sciences of the United States of America, vol. 110, no. 10, pp. 4057–4062, 2013.

[57] J. Ko, G. J. Soler-Llavina, M. V. Fuccillo, R. C. Malenka, and T. C. Südhof, "Neurelixins/LRRTMs prevent activity- and Ca 2+-calmodulin-dependent synapse elimination in cultured neurons," Journal of Cell Biology, vol. 194, no. 2, pp. 323–334, 2011.

[58] Z. Lu, Y. Wang, F. Chen et al., "Calsyntenin-3 molecular architecture and interaction with neurexin Iα," Journal of Biological Chemistry, vol. 289, no. 50, pp. 34530–34542, 2014.

[59] J. W. Um, G. Pramanik, J. S. Ko et al., "Calsyntenins function as synaptogenic adhesion molecules in concert with neurexins," Cell Reports, vol. 6, no. 6, pp. 1096–1109, 2014.

[60] J. Ko, M. V. Fuccillo, R. C. Malenka, and T. C. Südhof, "LRRTM2 functions as a neurexin ligand in promoting excitatory synapse formation," Neuron, vol. 64, no. 6, pp. 791–798, 2009.

[61] T. Siddiqui, R. Pancaroglu, Y. Kang, A. Rooyakkers, and A. M. Craig, "LRRTMs and neurelixins bind neurexins with a differential code to cooperate in glutamate synapse development," Journal of Neuroscience, vol. 30, no. 22, pp. 7495–7506, 2010.

[62] J. W. Um, T.-Y. Choi, H. Kang et al., "LRRTM3 regulates excitatory synapse development through alternative splicing and neurexin binding," Cell Reports, vol. 14, no. 4, pp. 808–822, 2016.

[63] C. Reissner, J. Stahn, D. Breuer et al., "Dystroglycan binding to α-Neurexin competes with neurexophilin-1 and neurexin in the brain," Journal of Biological Chemistry, vol. 289, no. 40, pp. 27585–27603, 2014.

[64] J. De Wit and A. Ghosh, "Specification of synaptic connectivity by cell surface interactions," Nature Reviews Neuroscience, vol. 17, no. 1, pp. 22–35, 2016.

[65] M. Missier, W. Zhang, A. Rohmann et al., "α-neurexins couple Ca2+ channels to synaptic vesicle exocytosis," Nature, vol. 423, no. 6943, pp. 939–948, 2003.
Neural Plasticity

[1] G. R. Anderson, J. Aoto, K. Tabuchi et al., “β-neurexins control neural circuits by regulating synaptic endocannabinoid signaling,” Cell, vol. 162, no. 3, pp. 593–606, 2015.

[2] A. Gdalyahu, M. Lazaro, O. Penagarikano, P. Golshani, J. T. Trachtenberg, and D. H. Gescwind, “The autism related protein contactin-associated protein-like 2 (CNTNAP2) stabilizes new spines: an in vivo mouse study,” PLoS ONE, vol. 10, no. 5, Article ID e0125633, 2015.

[3] D. Schreiner, T.-M. Nguyen, G. Russo et al., “Targeted combinatorial alternative splicing generates brain region-specific repertoires of neurexins,” Neuron, vol. 84, no. 2, pp. 386–398, 2014.

[4] B. Treutlein, O. Gokce, S. R. Quake, and T. C. Südhof, “Cartography of neurexin alternative splicing mapped by single-molecule long-read mRNA sequencing,” Proceedings of the National Academy of Sciences of the United States of America, vol. 111, no. 13, pp. E1291–E1299, 2014.

[5] A. A. Boucard, A. A. Chubykin, D. Comoletti, P. Taylor, and T. C. Südhof, “A splice code for trans-synaptic cell adhesion mediated by binding of neoRl1in α and β-neurexins,” Neuron, vol. 48, no. 2, pp. 229–236, 2005.

[6] B. Chih, L. Gollan, and P. Scheiffele, “Alternative splicing controls selective trans-synaptic interactions of the neuroligin-neurexin complex,” Neuron, vol. 51, no. 2, pp. 171–178, 2006.

[7] E. R. Graf, Y. Kang, A. M. Hauner, and A. M. Craig, “Structure function and splice site analysis of the synaptogenic activity of the neurexin-Iβ LNS domain,” Journal of Neuroscience, vol. 26, no. 16, pp. 4256–4263, 2006.

[8] A. Yamagata, Y. Sato, S. Goto-Ito et al., “Structure of Slitrk2-PTPβ complex reveals mechanisms for splicing-dependent trans-synaptic adhesion,” Scientific Reports, vol. 5, article no. 9686, 2015.
[104] H. Tanaka, W. Shan, G. R. Phillips et al., “Molecular modification of N-cadherin response to synaptic activity,” Neuron, vol. 25, no. 1, pp. 93–107, 2000.

[105] J. G. G. Borst and B. Sakmann, “Depletion of calcium in the synaptic cleft of a calyx-type synapse in the rat brainstem,” The Journal of Physiology, vol. 521, no. 1, pp. 123–133, 1999.

[106] D. A. Rusakov and A. Fine, “Extracellular Ca\(^{2+}\) depletion contributes to fast activity-dependent modulation of synaptic transmission in the brain,” Neuron, vol. 37, no. 2, pp. 287–297, 2003.

[107] S. M. Smith, J. B. Bergsman, N. C. Harata, R. H. Scheller, and R. W. Tsien, "Recordings from single neocortical nerve terminals reveal a nonselective cation channel activated by decreases in extracellular calcium," Neuron, vol. 41, no. 2, pp. 243–256, 2004.

[108] S. A. Kim, C.-Y. Tai, L.-P. Mok, E. A. Mosser, and E. M. Schuman, “Calcium-dependent dynamics of cadherin interactions at cell–cell junctions,” Proceedings of the National Academy of Sciences of the United States of America, vol. 108, no. 24, pp. 9857–9862, 2011.

[109] C. Reissner, F. Runkel, and M. Missler, “Neurexins,” Genome Biology, vol. 14, no. 9, article 213, 2013.

[110] B. Zhang, L. Y. Chen, X. Liu et al., “Neuroligins sculpt cerebellar Purkinje–cell circuits by differential control of distinct classes of synapses,” Neuron, vol. 87, no. 4, pp. 781–796, 2015.

[111] E. Lee, J. Lee, and E. Kim, "Excitation/inhibition imbalance in animal models of autism spectrum disorders," Biological Psychiatry, 2016.

[112] J. Ko, G. Choi, and J. W. Um, “The balancing act of GABAergic synapse organizers,” Trends in Molecular Medicine, vol. 21, no. 4, pp. 256–268, 2015.

[113] A. M. S. Durieux, J. Horder, and M. M. Petrinovic, “Neuroligin-2 and the tightrope of excitation/inhibition balance in the prefrontal cortex,” Journal of Neurophysiology, vol. 115, no. 1, pp. 5–7, 2016.