The chemical synapse

- Synapses are functional connections between neurons, or between neurons and other types of cells.
- A typical neuron gives rise to several thousand synapses, although there are some types that make far fewer.

Action potentials **cannot cross the synaptic cleft**
Nerve impulse is carried by **neurotransmitters**

Classification of synapses by:

- Cytoarchitecture
- Based on method of signal conduction (electrical/chemical)
- Based on conductance of postsynaptic membrane to selective ion species (excitatory/inhibitory)

Cytoarchitectural Classification of Synapses

– Axo-dendritic synapse

– Axo-somatic synapse

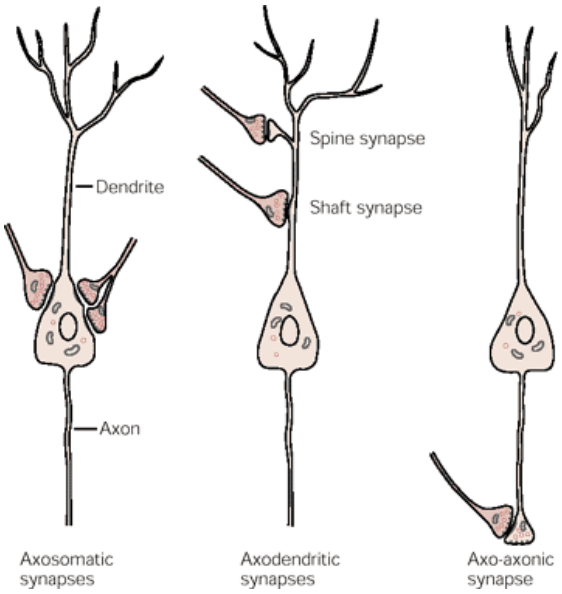
– Axo-axonic synapse

– Dendro-dendritic synapse

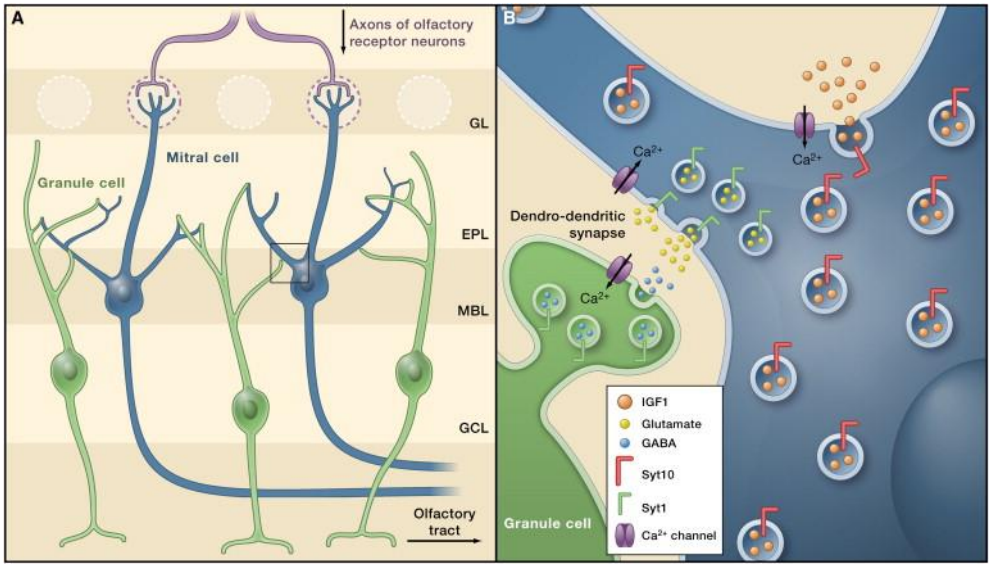
– Soma-somatic synapse

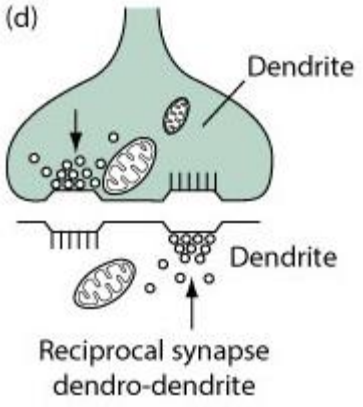
– Neuromuscular synapse (skel m.: NM junction)

– Neuroglandular synapse



Dendro-dendritic synapses are present only in few regions of the brain

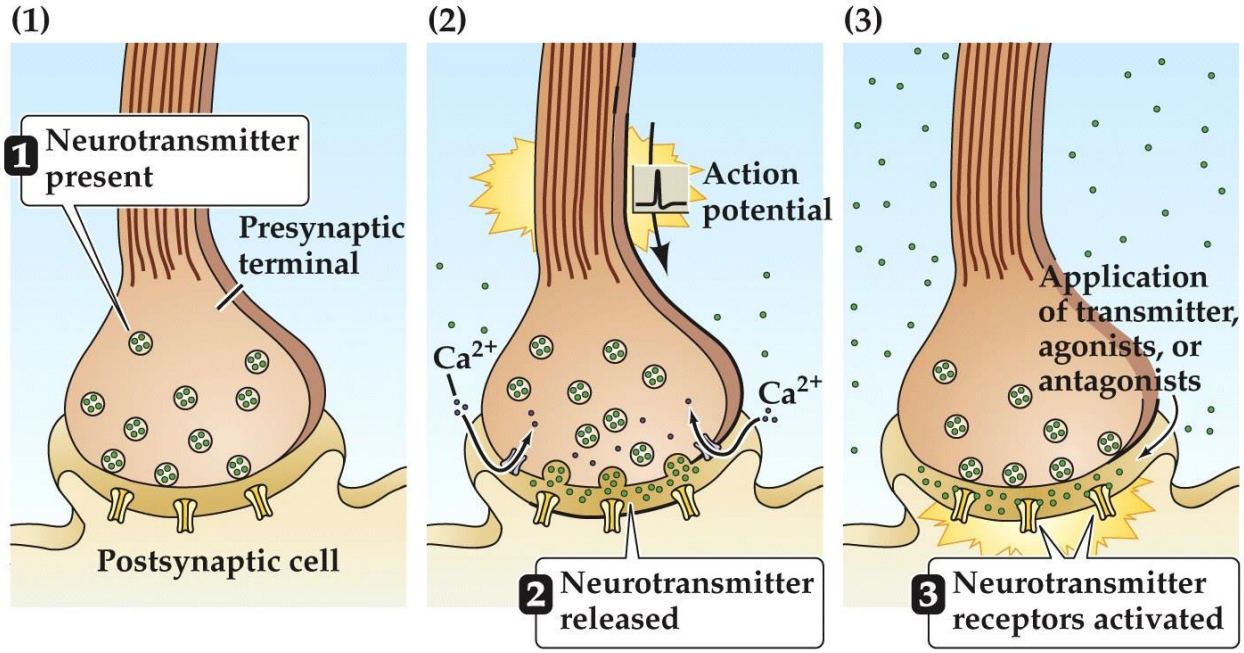




Organization of the **olfactory bulb**. Axons of olfactory receptor neurons project onto glomeruli (GL) in the olfactory bulb. Within the external plexiform layer (EPL) of the bulb, dendrites from large excitatory neurons (mitral cells, MC) form **reciprocal dendrodendritic synapses** with small inhibitory neurons (granule cells [GC]). Mitral cells relay sensory signals to higher regions of the brain via the olfactory tract. GCL, granule cell layer; MBL, mitral cell body layer.

Criteria for chemical transmission

1. Synthesis of the neurotransmitter in the *presynaptic nerve terminals*
2. Storage of the neurotransmitter in *secretory vesicles.*
3. Regulated release of neurotransmitter in the synaptic space between the pre- and post-synaptic neurons.
4. Presence of *receptors on the postsynaptic* membrane; receptor activation mimics the effect of nerve stimulation
5. A means for "*termination" of the action of the* released neurotransmitter.



NEUROSCIENCE 5e, Box 5A

The CNS synapse

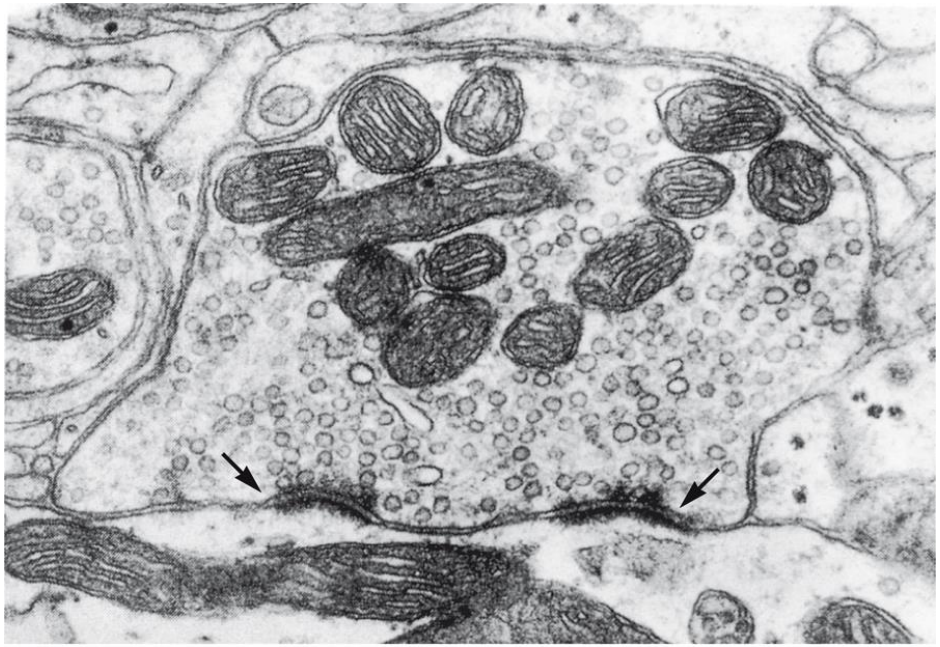
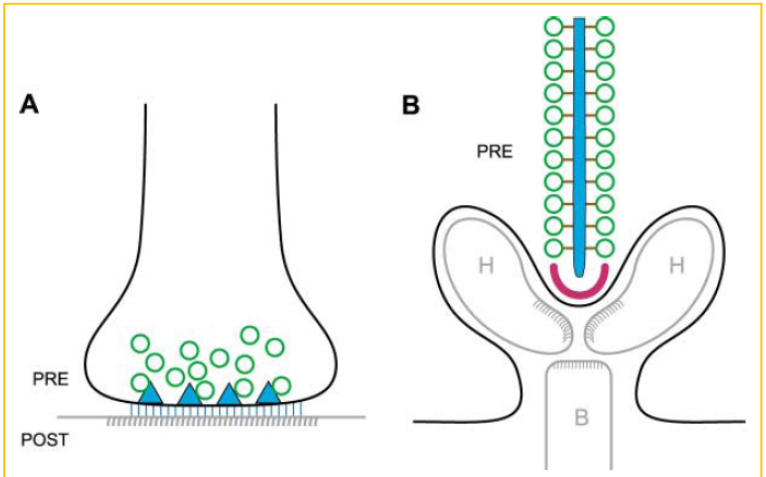


Figure 8–7 The fine structure of a presynaptic terminal. This electron micrograph shows a synapse in the cerebellum. The large dark structures are mitochondria. The many small round bodies are vesicles that contain neurotransmitter. The fuzzy dark thickenings along the presynaptic membrane (**arrows**) are the active zones, specialized areas that are thought to be docking and release sites for synaptic vesicles. The synaptic cleft is the space just outside the presynaptic terminal separating the pre- and postsynaptic cell membranes. (Reproduced, with permission, from J. E. Heuser and T. S. Reese.)

Kandel, Principles of Neural Sciences, 2013

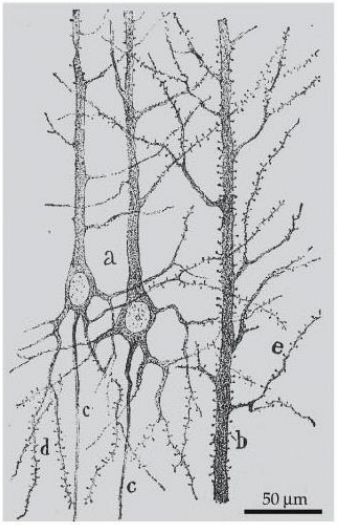


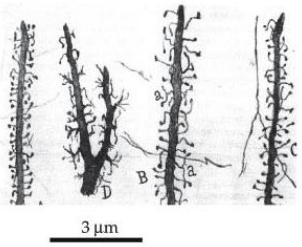
Presynaptic Structures at a Conventional and a Photoreceptor Ribbon Synapse

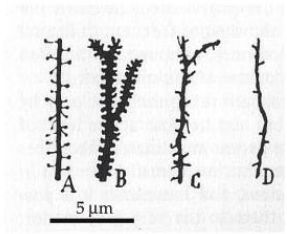
At conventional synapses (A) the right staining conditions can reveal a two-dimensional web of pyramidal particles apposed to the presynaptic membrane. These particles are thought to be linked by filaments and connected to the postsynaptic membrane by another set of filaments or pegs. Ribbon synapses (B) have a more complex structure. The presynaptic terminal of a rod or cone cell surrounds the dendrites of the postsynaptic cells, typically two horizontal cell processes and one bipolar cell process arranged in the characteristic pattern shown here. Aligned with this on the presynaptic side is a "ribbon," in fact, a plate seen here in cross-section, to which rows of vesicles are tethered by thin filaments. Between the bottom of the ribbon and the presynaptic membrane lies a structure sometimes called the arciform density.

Wilson, 2003

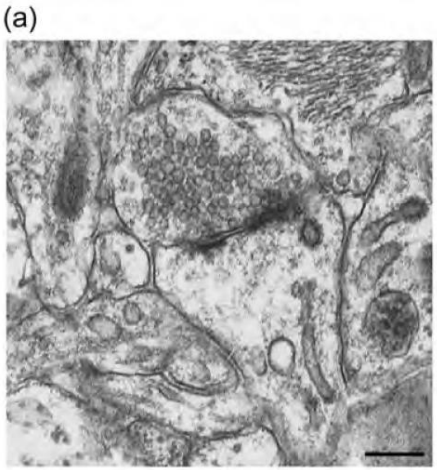
The structure of a CNS excitatory synapse

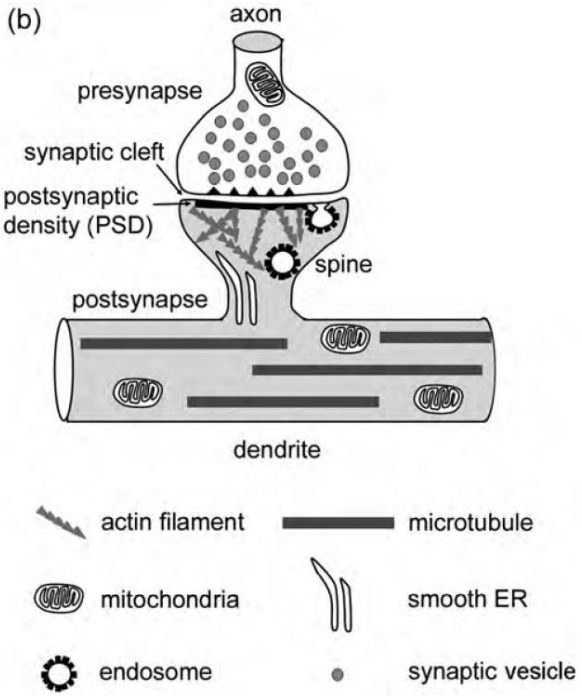






Cajal's classic drawings of dendritic spines

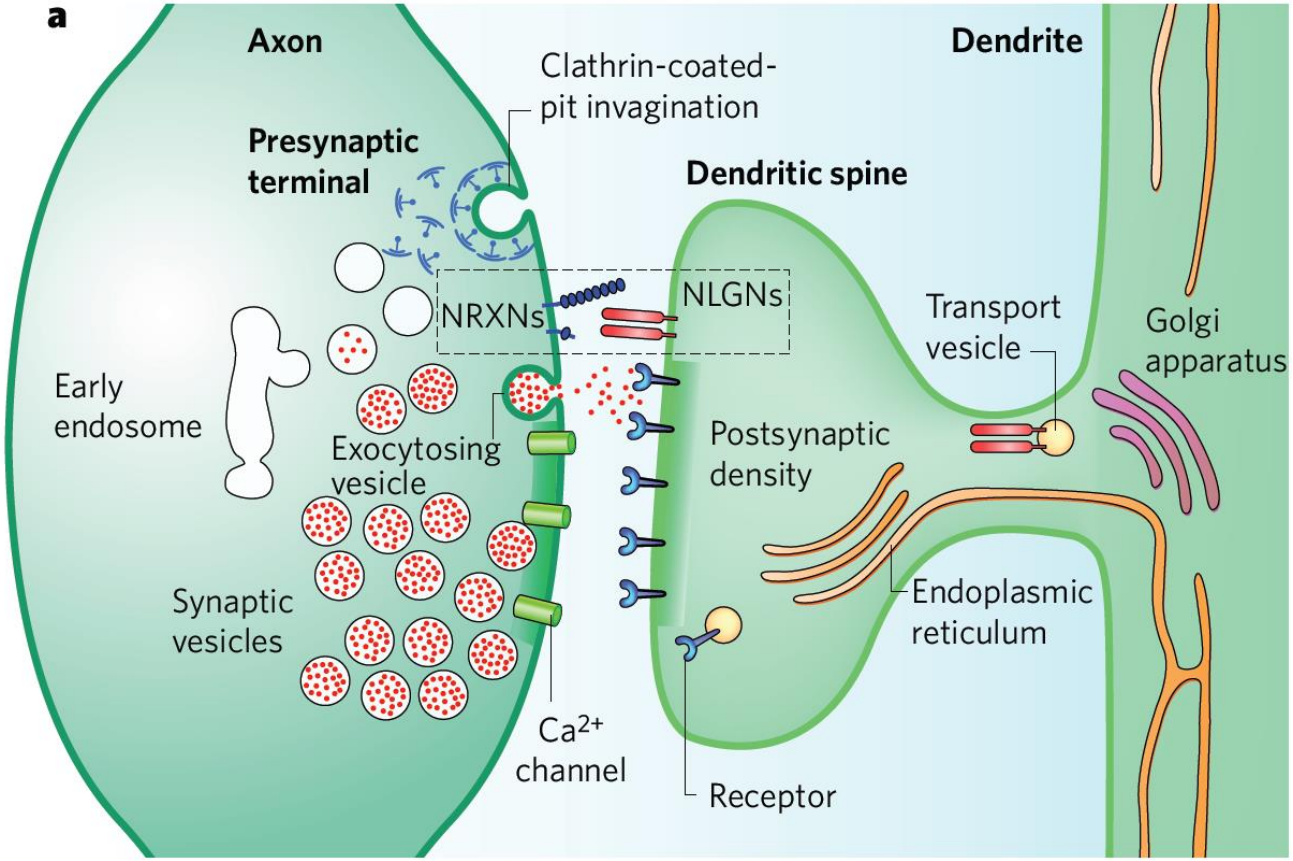




S. Okabe
Microscopy **62(1)**: 51–62 (2013)

Fig. 1. Ultrastructure of the excitatory synapse. (a) Transmission electron micrograph of an excitatory synapse in the mouse hippocampus. Scale bar, 200 nm. (b) Major cytoplasmic components of the presynaptic and postsynaptic cytoplasm of the excitatory synapses.

The structure of a CNS excitatory synapse



Schematic diagram of a typical synapse formed by an axonal presynaptic terminal onto a postsynaptic spine, and of the role of the trans-synaptic cell-adhesion molecules neurexins and neuroligins in synapse alignment and specification. See Südhof, T.C. 2008. *Nature*455:903-911 for details.

Adhesion molecules in neuronal synaptic junctions

Synapses between neurons represent a subtype of intercellular junctions (adhesive junctions) highly specialized for cellular communication.

Differently from other junctions, synapses are ASYMMETRICAL:

- presynaptic specialization (usually axonal, contains the “active zone” for NT release)

- postsynaptic specialization (usually dendritic, contains the postsynaptic density translating the NT signal)

CNS synapses do not display a basal membrane (as the neuromuscular junction) in the synaptic cleft. Pre- and post- synaptic terminal adhesion is assured by transmembrane **ADHESION MOLECULES**

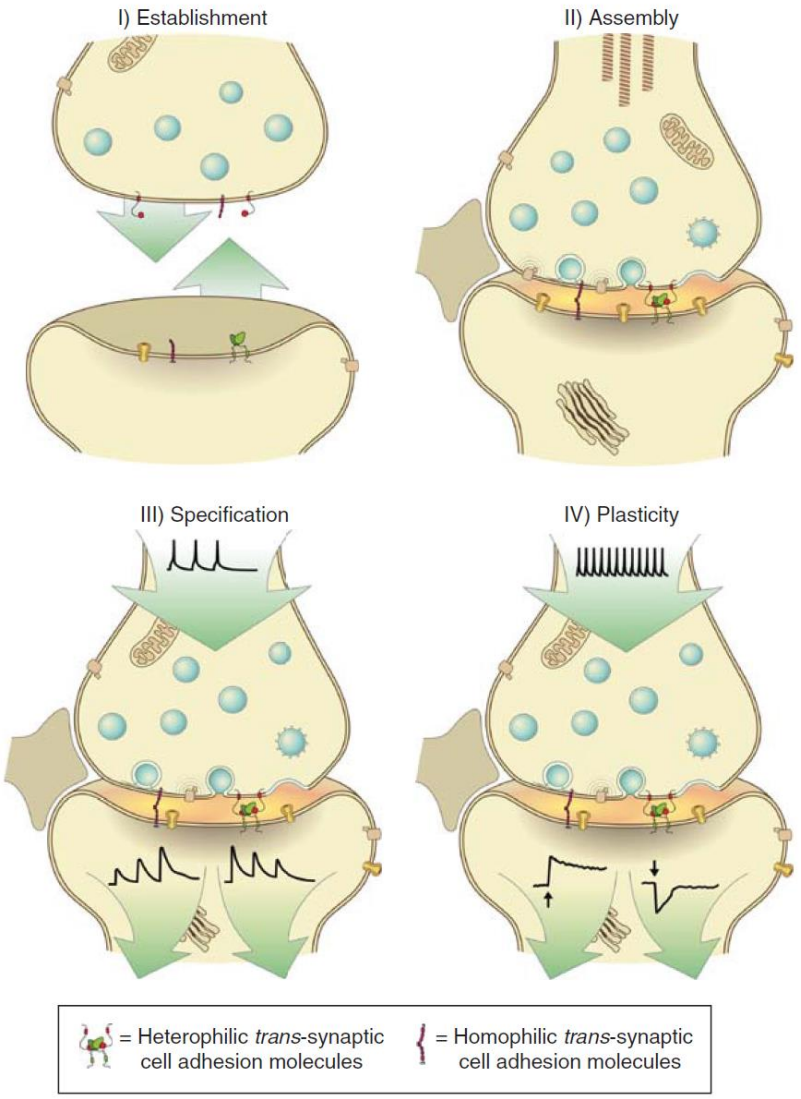
Roles of synaptic adhesion molecules

Synaptic cell adhesion involves multiple, partially overlapping processes.

(I) Initial establishment of axo-dendritic contacts may require heterophilic and homophilic cell adhesion molecules to recognize appropriate pre- and postsynaptic partners.

(II-II) During the molecular assembly (II) and functional specification (III) of synapses, synaptic cell adhesion molecules mediate recognition, physical cell–cell adhesion, and serve as anchor proteins to cluster or recruit receptors and components of the pre- and postsynaptic signaling machinery. Their action eventually leads to synapses with distinct physiological properties as exemplified by distinct responses to the same stimuli.

(IV) In adaptive events, for example during memory formation, synaptic cell adhesion molecules also may contribute to structural changes and functional synaptic plasticity such as long-term potentiation or depression.



Adhesion molecules in synaptogenesis

No single pair of synaptic adhesion molecules seems to be sufficient to organize all aspects of synapse development. They might have overlapping functions or act together at synaptic sites. One intriguing possibility is that the presence of particular sets of these molecules at synaptic sites might serve to specify certain classes or types of synapses.

Dalva et al., 2007
NATURE REVIEWS
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8:206-220

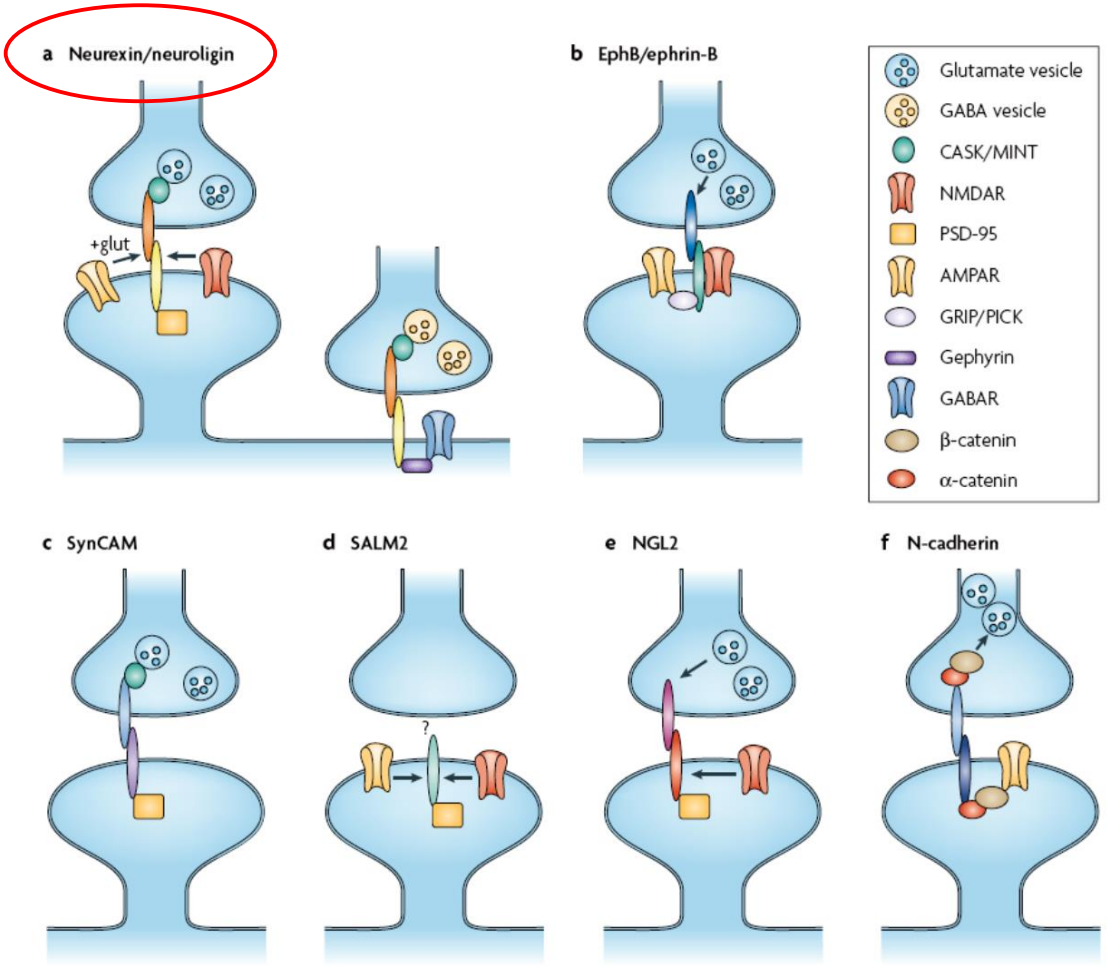


Figure 3 | **Trans-synaptic signalling during synaptogenesis: *in vitro* evidence.** A number of trans-synaptic adhesion molecules are able to control different aspects of synapse development in neuronal cultures and heterologous cell co-cultures. **a** | Neurexins and neuroligins can induce the formation of both excitatory and inhibitory synapses. **b** | EphBs can organize both pre- and postsynaptic glutamatergic terminals through mechanisms requiring defined EphB2 protein domains, and signal to induce dendritic spine formation. **c** | Synaptic cell adhesion molecule (SynCAM) triggers presynaptic maturation but does not yet have a defined role in postsynaptic differentiation. **d** | Synaptic adhesion-like molecule 2 (SALM2) can regulate the organization of the postsynaptic terminal but not the presynaptic terminal (its presynaptic ligand is unknown). AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors), and to a lesser degree NMDARs (*N*-methyl-D-aspartate receptors), can be found at SALM2-induced synapses. **e** | Netrin G2 ligand (NGL2) can organize pre- and postsynaptic terminals of excitatory synapses. NMDARs are recruited to these sites, but not AMPARs. **f** | Finally, N-cadherin and catenins are required for the formation of normal presynaptic vesicle reserve pools and have a well-described role in the formation, development and stability of dendritic spines by signalling through Rho GTPases. Cadherins also associate with AMPARs through β-catenins. Arrows indicate that recruitment/clustering occurs, but the mechanism is unclear. '?' indicates that the presynaptic ligand is unknown. CASK, calcium/calmodulin-dependent serine protein kinase; GABAR, γ-aminobutyric acid receptor; GRIP, glutamate receptor interacting protein; MINT, (Munc 18 interacting protein; lin-10/X11); PICK, protein interacting with C kinase; PSD-95, postsynaptic density protein-95.

α- and β-neurexins

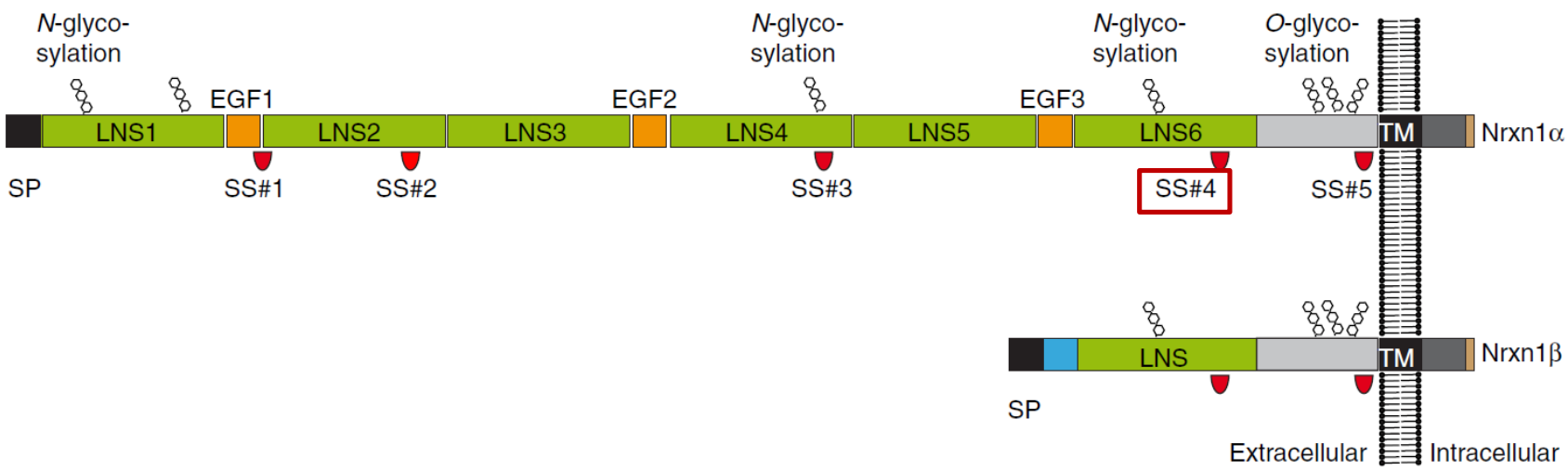


Figure 1 Domain organization of α-neurexins and β-neurexins. Neurexins are type I transmembrane proteins with a single path transmembrane helix (TM) that separates amino-terminal extracellular from cytosolic intracellular domains. The hallmark of neurexins is a cassette of LNS(green)-EGF(orange)-LNS(green) that is repeated three times in α-neurexin (Nrxn1α), albeit with low sequence conservation (16% identity and 27% homology). β-Neurexin (Nrxn1β) starts with its own exon that encodes a signal peptide (SP) and unique 37 histidine-rich residues (blue). The remainder is identical to the corresponding α-neurexin starting from the last LNS domain. Red symbols indicate positions of up to five canonically conserved splice sites (SS#1 to SS#5), and hexamers point to *N*-glycosylation sites and *O*-glycosylation sites. EGF, epidermal growth factor-like domain; LNS, laminin-neurexin-sex hormone binding globulin.

Reissner *et al. Genome Biology* 2013, **14**:213

Trans-synaptic neurexin-neuroligin complexes shape excitatory and inhibitory synapses

Presynaptic **α-neurexins** or **β-neurexins** (red) can interact with dimeric **neuroligins** (green) across the synaptic cleft to regulate important aspects of establishment, differentiation and maturation of synapses. Isoforms and splice variants of both molecules have been proposed to be differentially distributed at excitatory or inhibitory synapses to establish specificity. Note that presence of β-neurexins (β-Nrxn) at inhibitory terminals is unclear, while for neuroligins (Nlgn), Nlgn2 and Nlgn4 show quite specific localization and roles at inhibitory synapses. Intracellularly, the cytosolic domains of Nrxn and Nlgn are able to cluster components of the presynaptic release machinery and of postsynaptic signaling pathways and transmitter receptors (R). The clustering ability of Nrxn and Nlgn variants at excitatory or inhibitory synapses is mostly derived from cell culture assays. PSD95, postsynaptic density protein-95; VGat, vesicular GABA transporter; VGlu, vesicular glutamate transporter.

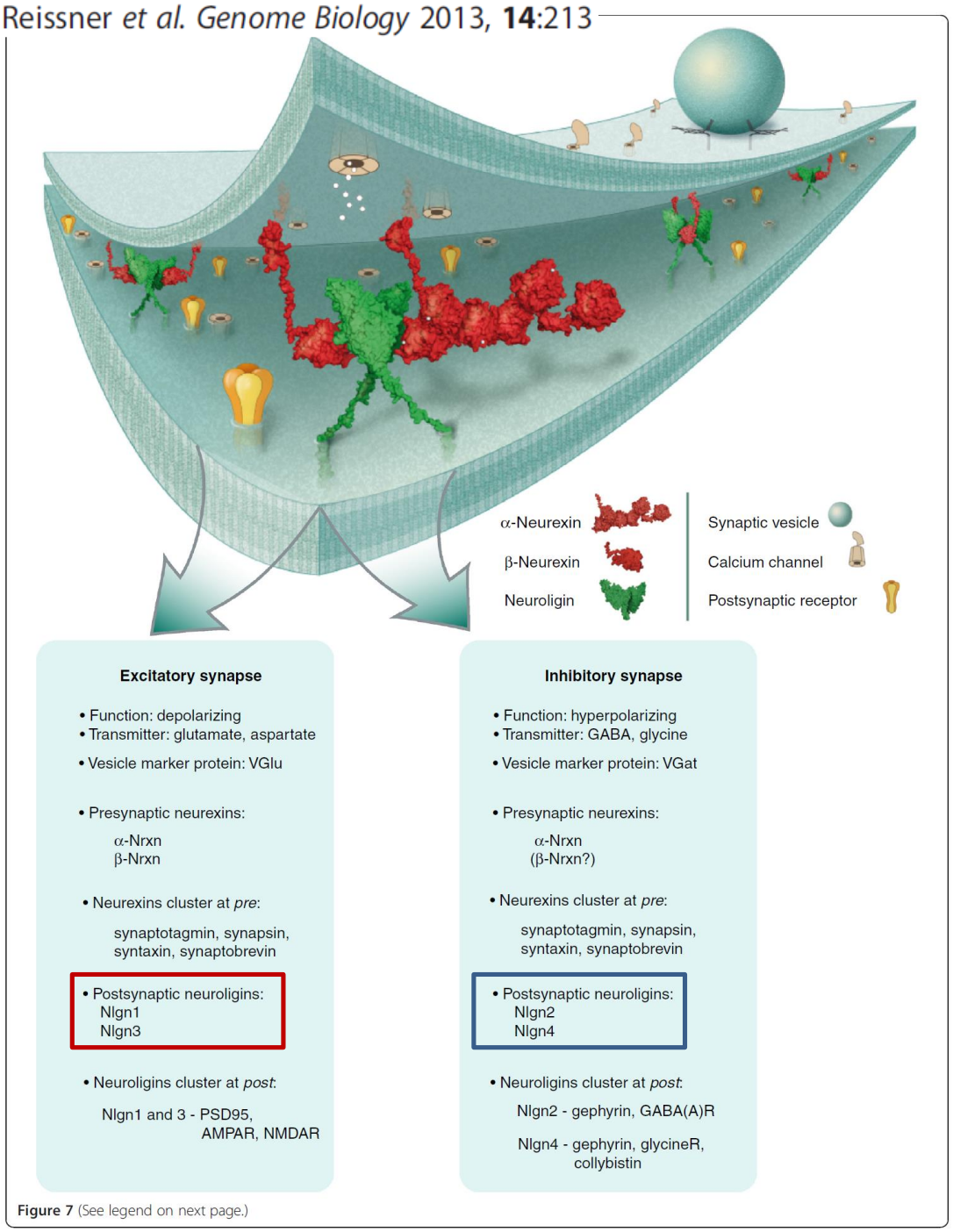


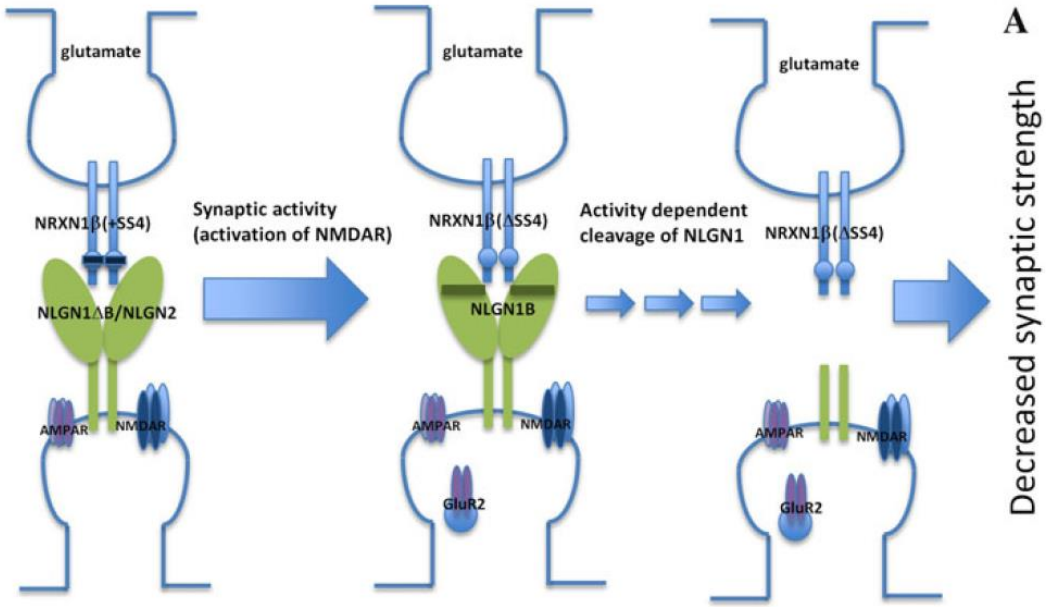
Figure 7 (See legend on next page.)

Table 1 Alternative splicing of NRXNs underlies adhesive code and determines the binding to the different proteins

	α-NRXN + SS4	α-NRXN ΔSS4	β-NRXN + SS4	β-NRXN ΔSS4
NLGN1A	−	+	+	+
NLGN1B	−	−	−	+
NLGN1AB	−	−	−	+
NLGN1(−)	−	+	+	+
NLGN2	+	+	+	+
NLGN3	−	+	+	+
NLGN4	−	+	+	+
Cbln	+	−	+	−
LRRTM	−	+	−	+

The alternative splicing of NRXN is regulated by synaptic activity

Under depolarizing conditions, the expression of NRXN1 without SS#4 increases, whereas the expression of NRXN1 + SS#4 decreases [52]. The depolarization-dependent alternative splicing of NRXN1 may mediate a trans-synaptic ligand switch from e.g. NLGN1DB/NLGN2 toward NLGN1B [52]. The cleavage of NLGN1 is also activity-dependent. Consequently, presynaptic release and thereby synaptic strength are decreased. The proteolytic cleavage is most probably partial



Synaptic adhesion molecules interact with different proteins in the pre- and post-synaptic terminal

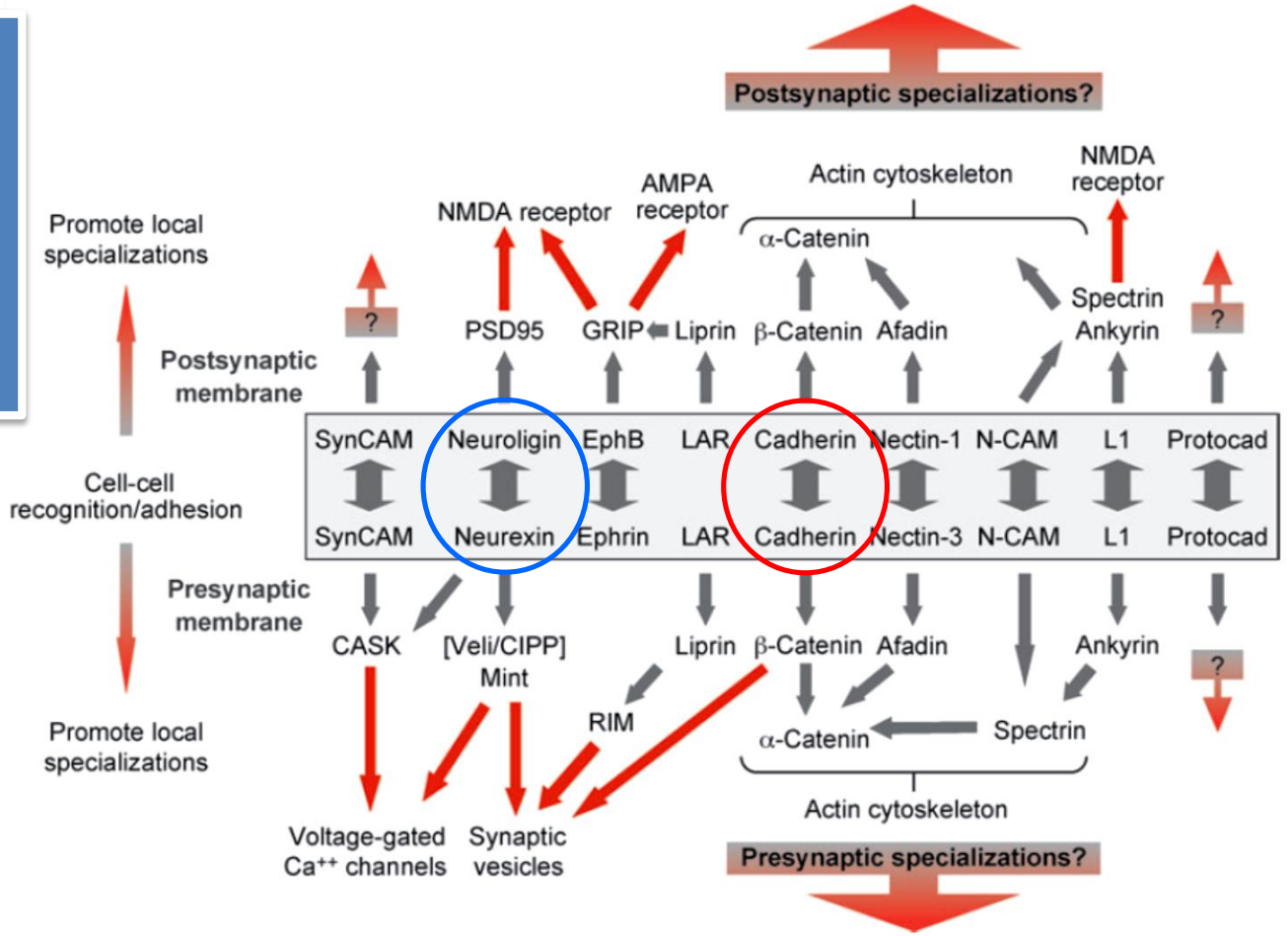


Figure 2

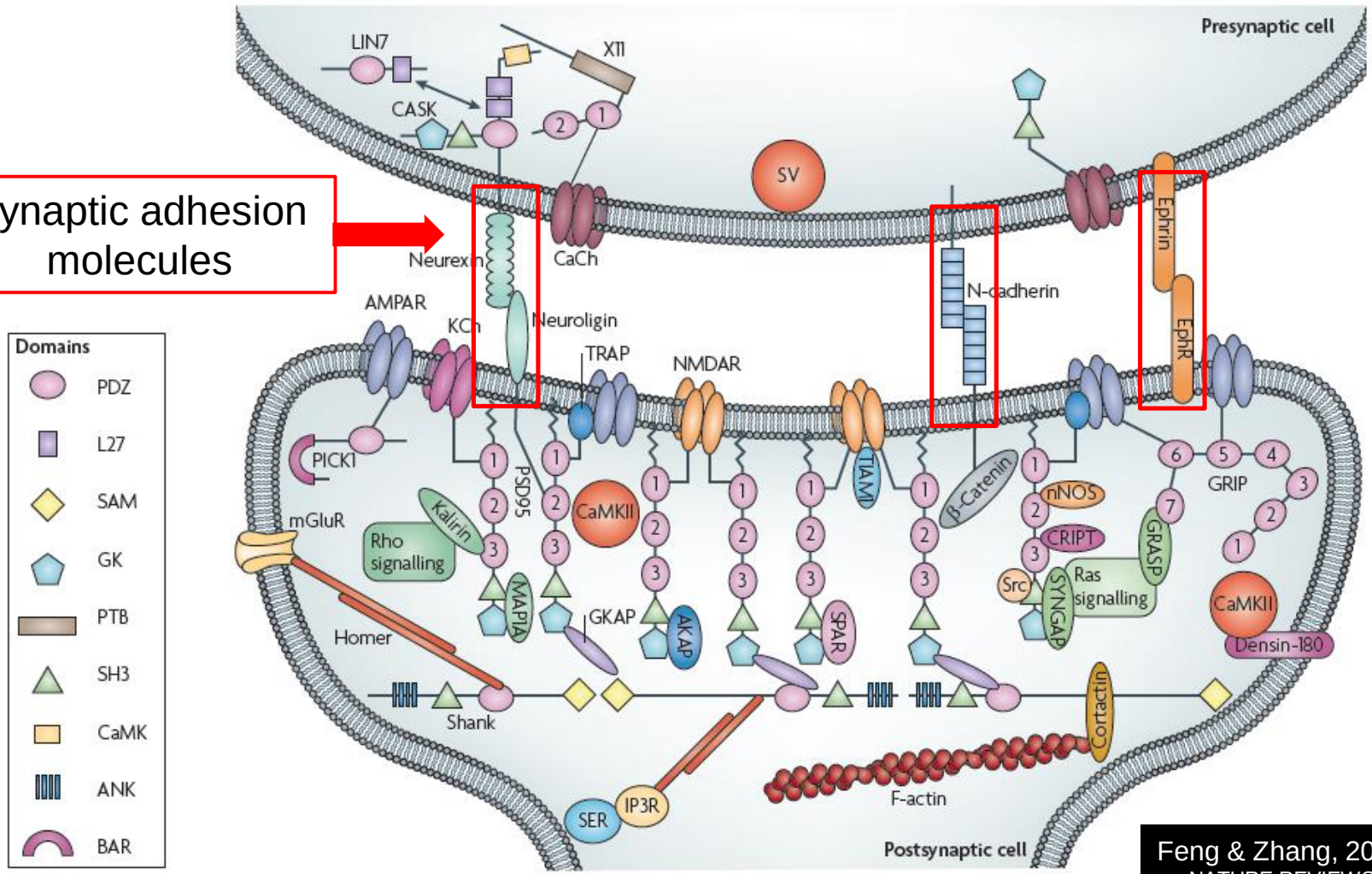
Schematic representations of the neuronal synapse (inset) and protein interactions at the pre- and postsynaptic membranes. Different cell adhesion proteins form homophilic or heterophilic adhesions (*boxed*) and interact with downstream protein networks that describe functional specification of the presynaptic (recruit Ca^{2+} channels, synaptic vesicles) and postsynaptic membranes (recruit neurotransmitter receptors). Abbreviations: AMPA, α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid; CASK, calcium/calmodulin-dependent serine protein kinase; CIPP, channel-interacting PDZ domain protein; GRIP, glutamate receptor-interacting protein; LAR, leukocyte common antigen-related protein; Mint, Munc-18-interacting protein; N-CAM, neural cell adhesion molecule; NMDA, N-methyl-D-aspartic acid; PSD95, postsynaptic density 95; RIM, Rab3-interacting molecule; Veli, vertebrate LIN-7.

Yamada & Nelson, 2007

Annu. Rev. Biochem. 76:267–94

The molecular organization of excitatory synapses

Synaptic adhesion molecules



Feng & Zhang, 2009
NATURE REVIEWS
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