Synaptic recognition molecules in development and disease

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Abstract

Synaptic connectivity patterns underlie brain functions. How recognition molecules control where and when neurons form synapses with each other, therefore, is a fundamental question of cellular neuroscience. This chapter delineates adhesion and signaling complexes as well as secreted factors that contribute to synaptic partner recognition in the vertebrate brain. The sections follow a developmental perspective and discuss how recognition molecules (1) guide initial synaptic wiring, (2) provide for the rejection of incorrect partner choices, (3) contribute to synapse specification, and (4) support the removal of inappropriate synapses once formed. These processes involve a rich repertoire of molecular players and key protein families are described, notably the Cadherin and immunoglobulin superfamilies, Semaphorins/Plexins, Leucine-rich repeat containing proteins, and Neurexins and their binding partners. Molecular themes that diversify these recognition systems are defined and highlighted throughout the text, including the neuron-type specific expression and combinatorial action of recognition factors, alternative splicing, and post-translational modifications. Methodological innovations advancing the field such as proteomic approaches and single cell expression studies are additionally described. Further, the chapter highlights the importance of choosing an appropriate brain region to analyze synaptic recognition factors and the advantages offered by laminated structures like the hippocampus or retina. In a concluding section, the profound disease relevance of aberrant synaptic recognition for neurodevelopmental and psychiatric disorders is discussed. Based on the current progress, an outlook is presented on research goals that can further advance insights into how recognition molecules provide for the astounding precision and diversity of synaptic connections.

1. Introduction

The synaptic connectivity patterns in the complex neuropil packed with neurons and glia are being revealed in stunning detail by connectomic reconstruction studies (Kasthuri et al., 2015; Motta et al., 2019). This chapter provides a molecular perspective on how these circuitry patterns are established in the vertebrate brain and reviews adhesion and signaling complexes that contribute to neuronal partner recognition during synapse development and refinement. A series of subcellular events assembles synapses in late prenatal and early postnatal stages, following axon guidance and dendrite differentiation (Biederer, Kaeser, & Blanpied, 2017; Bury & Sabo, 2016; Emperador-Melero & Kaeser, 2020; Südhof, 2018; Yoshihara, De Roo, & Muller, 2009). Filopodia enable axonal contacts with postsynaptic target cells, resulting in the reorganization of the actin cytoskeleton at these sites. In nascent presynaptic terminals, discrete exocytotic areas termed active zones are formed to establish the molecular machinery that couples

calcium influx to synaptic vesicle fusion. The active zone precisely aligns with a specialized postsynaptic membrane domain of the target neuron, which is built through the recruitment of scaffold proteins into the postsynaptic density (PSD) and the sorting and stabilization of neurotransmitter receptors. The assembly of pre- and post-synaptic specializations is coordinated and can even be instructed in time and space by adhesion complexes, some of which include secreted molecules. The components of these trans-synaptic complexes often share similar extracellular domains yet engage in diverse cell–cell interactions and exhibit distinct dynamic properties and subcellular localizations (Apóstolo & de Wit, 2019; Benson & Huntley, 2012; Chamma & Thoumine, 2018; Missler, Südhof, & Biederer, 2012). Partner recognition between neurons during synapse development hence involves a rich repertoire of molecular players.

How molecular recognition specifies neuronal connectivity continues to be a question at the forefront of molecular and cellular neuroscience (Sanes & Zipursky, 2020). The cellular expression patterns of recognition molecules provide intriguing leads to ask how they contribute to this diversity (Favuzzi et al., 2019; Foldy et al., 2016; Paul et al., 2017). Moreover, proteomic analyses of synaptic surface proteins have begun to reveal the molecular complexity of these adhesion complexes (Cijsouw et al., 2018; Loh et al., 2016; Takano et al., 2020). Yet, even if each of these recognition factors would execute a different role to specify synapses, they could not individually account for the vast number of connections. Indeed, multiple molecular themes enhance the power of these factors to generate and diversify synaptic recognition patterns as summarized in Box 1 and Fig. 1. These themes are highlighted throughout this chapter.

This chapter follows a developmental perspective on synaptic recognition molecules in vertebrate systems. In Section 2, we discuss how these molecules guide the establishment of neuronal connectivity. Synaptic recognition not only helps to find the right partners, it also allows for rejection of incorrect partner choices as described in Section 3. Section 4 presents how synapse organizing adhesion molecules can act beyond the formation of synapses and contribute to the diversification of synapse types. Once synapses are formed, removing or pruning those connections recognized as inappropriate is a key developmental process and described in Section 5. The concluding Section 6 outlines the profound disease relevance of aberrant synaptic recognition, with a focus on neurodevelopmental and psychiatric disorders. The role of glial factors in synapse development is the focus of another chapter (reference chapter "Role of astrocytes in synapse formation

BOX 1 Molecular concepts at play to generate and diversify synaptic recognition

Regional expression variation: The families of synaptic recognition molecules have several members. Restricting their expression to select brain regions, or to subtypes of neurons and synapses, can increase their power to establish connectivity patterns. Case in point: The homophilic protein Cadherin-9 is expressed in the developing hippocampal CA3 and dentate gyrus and facilitates synapse formation between their neuronal populations (Williams et al., 2011).

Combinatorial expression: The concerted expression and function of recognition molecules can increase their individual ability to specify synaptic connections. Case in point: LRRTM and Neuroligin family members, which both individually engage Neurexins as presynaptic proteins, act together at postsynaptic sites of developing hippocampal neurons to control excitatory synapse number and glutamatergic transmission (Ko, Soler-Llavina, Fuccillo, Malenka, & Südhof, 2011; Siddiqui, Pancaroglu, Kang, Rooyakkers, & Craig, 2010).

Coincidence detection: Combinatorial assembly of multiple recognition factors into higher order adhesion complexes enables coincidence detection and validate neuronal partner choice. Case in point: Simultaneous binding of Latrophilin 3, FLRT3 and Teneurin-2 in a ternary complex is required for input-specific synapse formation in the hippocampal CA1 area (Sando, Jiang, & Südhof, 2019).

Temporally defined roles: Recognition molecules act during restricted temporal windows to enable proteins to act in different developmental contexts. Case in point: Pre- and post-synaptic Cadherins are required for synapse assembly in young neurons, but dispensable for synapse assembly in maturing neurons (Bozdagi, Valcin, Poskanzer, Tanaka, & Benson, 2004).

Post-transcriptional modifications: Alternative splicing profoundly increases the molecular diversity of synaptic recognition molecules. Case in point: Cell-type select utilization of six alternative splice sites in Neurexins gives rise to ~1300 isoforms that can differentially engage with a variety of ligands (Schreiner, Simicevic, Ahrne, Schmidt, & Scheiffele, 2015; Treutlein, Gokce, Quake, & Südhof, 2014).

Post-translational modifications: The range of recognition interactions can be increased through post-translational modifications that endow molecules with different binding properties. Case in point: Modification of the extracellular domain of presynaptic Neurexin-1 with heparan sulfate glycans promotes binding to postsynaptic LRRTM proteins (Roppongi et al., 2020; Zhang et al., 2018).

Subcellular targeting: Adhesive recognition molecules can interact with receptors/ligands on distinct target domains of neurites to guide inputs. Case in point: Netrin-G1 and Netrin-G2 are expressed in axons originating from different neuronal populations and restrict their cognate Netrin-G ligands NGL-1 and NGL-2 to subdendritic segments of hippocampal CA1 neurons (Matsukawa et al., 2014; Nishimura-Akiyoshi, Niimi, Nakashiba, & Itohara, 2007).

BOX 1 Molecular concepts at play to generate and diversify synaptic recognition—cont'd

Restrictive factors: Along with positive factors enabling synaptic partner recognition, negative factors can lower the rate of synapse formation, restrict inappropriately formed synapses, or tip the balance to remove synapses that only need to be formed transiently in development. Case in point: MDGA Ig superfamily members bind Neuroligins in *cis* to restrict interactions between Neuroligins and Neurexins in *trans* (Lee et al., 2013; Pettem, Yokomaku, Takahashi, Ge, & Craig, 2013).
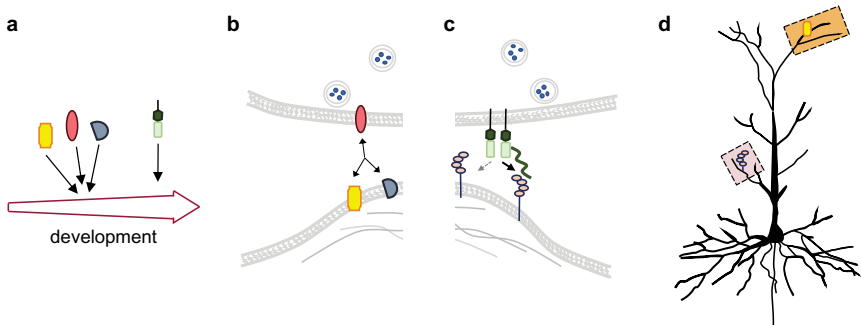

Fig. 1 Molecular themes that increase the coding power of synaptic recognition factors described in Box 1. (A) The diagram depicts recognition factors expressed during distinct developmental windows. These patterns include transient co-expression, providing for temporally defined functional cooperation. (B) The combinatorial expression of synaptic recognition factors that form multimeric complexes enables them to cooperate. (C) Post-translational modifications such as glycans (green line) can modulate and even enable recognition. (D) Recognition factors can exhibit sub-cellular localization to different domains of neurites. This cellular targeting defines their synaptic site of action.

and maturation" by Tan et al.). Throughout, we provide examples that highlight that it is crucial to choose an appropriate brain region to analyze synaptic recognition and how laminated structures like the retina and hippocampus provide an anatomical matrix that facilitates these studies. The scope of this chapter is unusually broad, and we would like to apologize to the colleagues whose work we could not reference here.

2. Wiring neuronal partners through adhesive recognition

The specificity of synaptic recognition is perhaps best illustrated by those regions of the central nervous system (CNS) that exhibit a laminar architecture of neuronal connectivity, providing a structural basis for the integration of inputs. The anatomical stratification of these brain regions facilitates studies of synaptic recognition and examples are depicted in Fig. 2.

The highly stereotyped laminar architecture of the retina has provided for pioneering studies to identify cell type-specific connectivity (Fig. 2A). It is organized into layers that contain either cell nuclei (the outer and inner nuclear layers and ganglion cell layer) or synaptic connections between projecting axons and dendrites (the outer and inner plexiform layers). In the outer plexiform layer, rod and cone photoreceptor cells form synapses with bipolar and horizontal cells. In the narrow inner plexiform layer of the mouse retina, the dendrites of >40 types of retinal ganglion cells (RGCs) receive inputs from >50 types of bipolar and amacrine cells (Macosko et al., 2015; Yan et al., 2020; Zeng & Sanes, 2017).

Another important brain region organized in a laminated manner is the hippocampus, where granule cells in the dentate gyrus, pyramidal neurons in the CA3 area, and pyramidal neurons in CA1 form three cell layers that are connected into a trisynaptic circuit (Fig. 2B). Additional projections add to these intrinsic connections as illustrated by pyramidal neurons in CA1. While their dendritic segments in the stratum radiatum receive inputs from Schaffer collateral axons of CA3 neurons, the more distal domains of apical dendrites of CA1 neurons in the stratum lacunosum-moleculare are contacted by axons of the temporoammonic branch of the perforant path from the entorhinal cortex. Specific partner recognition is required for all these connections, including subcellular input targeting.

The patterning of synaptic connectivity on a subcellular level is also exemplified by Purkinje cells, the principal output neurons of the cerebellum. The proximal and distal dendritic segments of a Purkinje cell receive glutamatergic innervation originating from the inferior olivary nucleus (one climbing fiber input) and cerebellar granule cells (thousands of parallel fiber inputs), respectively (Hirano, 2018; Kano, Watanabe, Uesaka, & Watanabe, 2018). In addition, Purkinje cells receive GABAergic inputs from local stellate and basket cells that form synapses on the shafts of their dendrites and soma, respectively.
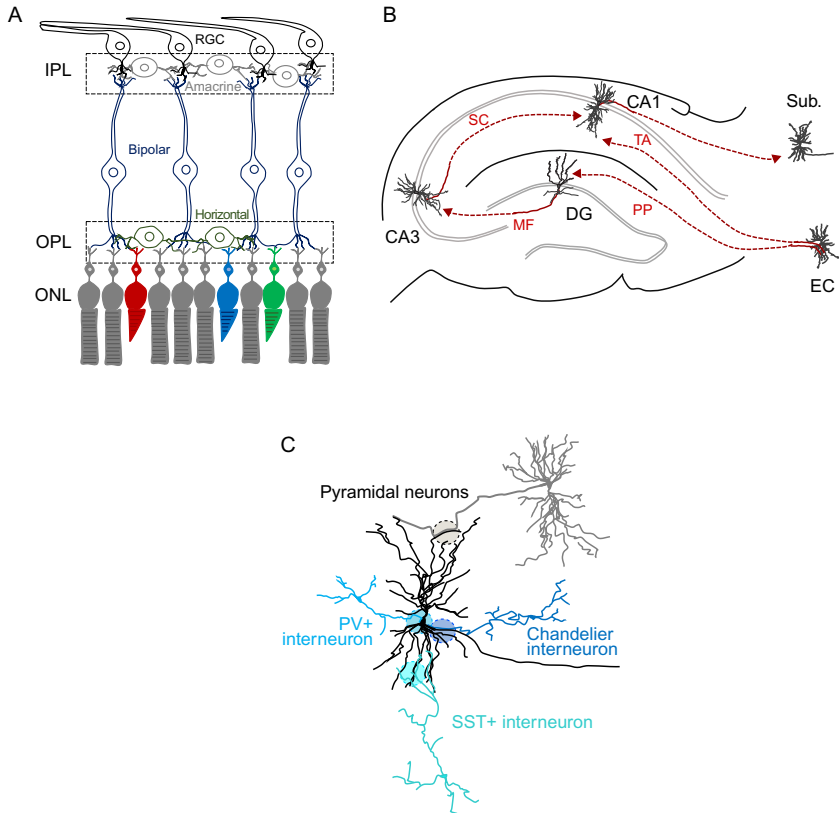
Fig. 2 Simplified illustrations of neuronal connectivity in select brain regions. (A) The retina exhibits exemplary laminar organization of cell types and synaptic connections. Rod (grey) and cone (red, green, blue) photoreceptors are located in the outer nuclear layer (ONL). Photoreceptors form synapses with bipolar cells (dark blue) and horizontal cells (dark green) in the outer plexiform layer (OPL). In the inner plexiform layer (IPL), neurites from retinal ganglion cells (RGCs, black), bipolar cells and amacrine cells (light grey) form synapses. (B) In the classic trisynaptic circuit of the hippocampus, dentate gyrus (DG) granule cells receive via the perforant path (PP) inputs from the entorhinal cortex (EC). DG neurons project via mossy fibers (MF) to CA3 pyramidal neurons, which project via Schaffer collaterals (SC) to CA1 pyramidal cells. In one of the additional projections, CA1 pyramidal neurons receive direct inputs from the EC via the tempo-roammonic (TA) pathway. CA1 pyramidal cells project to the subiculum (Sub) and EC (not shown). (C) Cortical pyramidal neurons (black) receive excitatory inputs from other pyramidal neurons (grey) and in addition subcellularly targeted inhibitory inputs from GABAergic neurons including Parvalbumin-positive (PV) interneurons, Somatostatin (SST)-positive interneurons, and Chandelier cells.

How connectivity patterns arise can not only be understood by analyzing target cells but also by comparing different populations of cells providing inputs to the same target neurons. For example, interneurons in the hippocampus and cortex make their inhibitory inputs to specific subcellular sites of pyramidal neurons, a targeting precision that plays central roles in controlling neuronal activity and network function (Cardin, 2018; Pelkey et al., 2017). Different types of GABAergic neurons synapse onto distinct subcellular compartments like soma and proximal dendrites, distal dendrites, or the axon initial segment, as shown for fast-spiking Parvalbumin (PV)-positive basket cells, Somatostatin-positive interneurons, and Chandelier cells, respectively (Fig. 2C).

In this section, we focus on major classes of recognition factors known to play key roles in establishing connectivity between distinct neuronal populations, including Cadherins, immunoglobulin superfamily molecules and leucine-rich repeat domain containing proteins. Roles of molecules in the recognition events that diversify synapse types, such as Neurexins and their partners, are described in Section 4. Fig. 3 shows proteins discussed below and their domain organization.

2.1 Classical Cadherins

The Cadherin (*Ca*lcium-*d*ependent ad*her*ent prote*in*) superfamily of single-pass transmembrane glycoproteins has more than 100 members in mammals and is characterized by two or more Extracellular Cadherin (EC) domains. Most Cadherins engage in homophilic interactions in *trans* mediated principally by the most membrane-distal EC domain (Brasch, Harrison, Honig, & Shapiro, 2012). While these interactions tend to be weak, Cadherins can be ordered into arrays for strong adhesion (Al-Amoudi, Diez, Betts, & Frangakis, 2007). Binding of Cadherin proteins to partners in *cis* further extends their interaction repertoire. The ∼20 classical Cadherins, comprised of type I and II Cadherins differing in a motif in the most distal EC domain, share a highly similar intracellular sequence with an extended β-catenin-binding motif. Complex intracellular interactions provide means by which the strength of Cadherin-based adhesion can be adjusted (Brigidi & Bamji, 2011).

Classical Cadherins play diverse roles in the development and maintenance of synaptic circuits (Friedman, Benson, & Huntley, 2015). Most type I Cadherins, including the extensively studied N-Cadherin, are broadly expressed in the CNS, whereas type II Cadherins mostly exhibit distinct
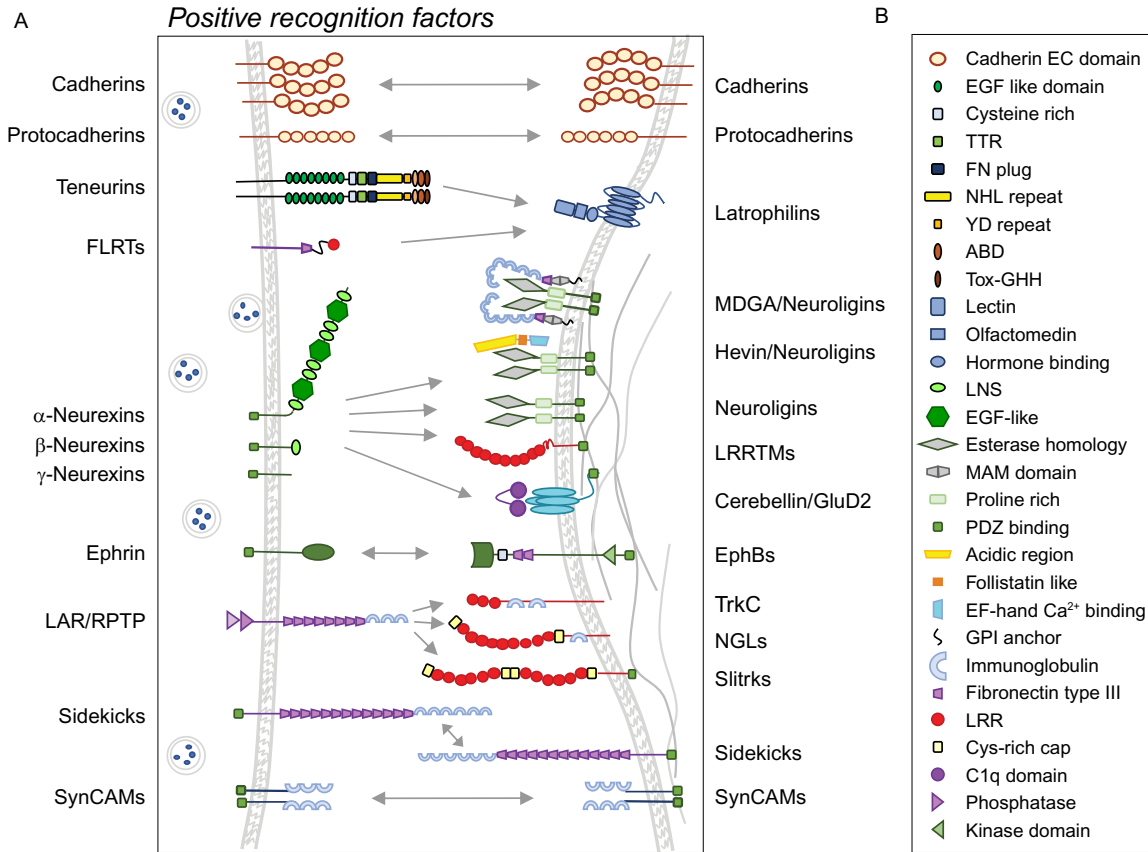
Fig. 3 See figure legend on next page.

expression patterns across areas of brain and spinal cord and are concentrated at nascent synaptic sites early in postnatal development. Cadherins provide for synaptic targeting across many brain regions. For example, blocking N–Cadherin function with antibodies in the developing chick optic tectum causes incoming retinal ganglion cell axons to overshoot their targets in a culture system (Inoue & Sanes, 1997). Similarly, an N–Cadherin zebrafish mutant shows defects in retinal lamination among several other neurite projection deficits of retinal cells (Masai et al., 2003). Moreover, N–Cadherin shapes connectivity by acting together with other family members like Cadherin–8, illustrating the importance of temporally correlated expression. This is exemplified by the topographic mapping of converging thalamic input streams to the barrels of the somatosensory cortex in the early postnatal period. While N–Cadherin becomes concentrated at thalamocortical synapses of the stream arising from ventral posterior medial nucleus (Huntley & Benson, 1999), Cadherin–8 is enriched at synapses of the other stream from the medial division of the posterior nucleus (Gil, Needleman, & Huntley, 2002) when these projections develop. Akin to the abovementioned findings from the chick tectum, the application of N–Cadherin function–blocking antibodies to organotypic co–cultures of thalamus and somatosensory cortex results in thalamic axons overshooting their targets in layer IV (Poskanzer, Needleman, Bozdagi, & Huntley, 2003). Another example for the role of classical Cadherins in target recognition is provided by Cadherin-6. Its deletion in mice impairs axon–target matching for a subset of RGCs whose axons fail to stop at their normal targets in the subcortical visual nuclei, and instead innervate inappropriate visual nuclei (Osterhout et al., 2011). In the cerebellum, Cadherin–7 is expressed in mossy fiber neurons of the pontine nucleus and their targets, the cerebellar granule neurons, but not in climbing fiber neurons, during the synaptogenic stage of development (Kuwako, Nishimoto,

Fig. 3 Recognition molecules that promote synaptic connectivity. (A) Factors promoting recognition and synaptic connections. Pre- and postsynaptic membranes are shown on the left and right, respectively. EphB, EphB receptors; FLRTs, fibronectin LRR transmembrane proteins; GluD2, glutamate receptor delta 2; LAR/RPTPs, LAR-type receptor protein tyrosine phosphatases; LRRTMs, leucine-rich repeat transmembrane proteins; MDGA, MAM domain-containing GPI-anchor proteins; NGLs, Netrin-G ligands; Slitrk, Slit- and Trk-like protein; SynCAMs, Synaptic Cell Adhesion Molecules; Trk, neurotrophin receptor-tyrosine kinase. (B) Domains utilized by the recognition molecules shown in (A). ABD, antibiotic-binding domain-like; C1q, complement component 1q domain; EC, extracellular cadherin domain; EGF, epidermal growth factor; FN, fibronectin; LNS, laminin-neurexin-sex hormone binding globulin domains; LRR, leucine-rich repeat; NHL, ncl-1, HT2A and lin-41 domain; TTR, transthyretin-related domain; YD, tyrosine aspartate repeat.

Kawase, Okano, & Okano, 2014). In agreement with a role in synaptic recognition, homophilic Cadherin-7 signaling induces presynaptic differentiation of pontine nucleus axons in co-culture assays and knockdown of Cadherin-7 in pontine nucleus neurons *in vivo* severely impairs their connectivity with granule cells in the developing cerebellum.

Apart from guiding long-range connectivity between brain regions, Cadherins also specify synaptic targeting of distinct neuronal populations within the same region. In the hippocampus, Cadherin-9 is specifically expressed in CA3 pyramidal neurons and dentate gyrus (DG) granule neurons (Bekirov, Needleman, Zhang, & Benson, 2002). Cadherin-9 knockdown from either CA3 or DG neurons exclusively reduces DG–CA3 mossy fiber synapse formation without affecting non-DG synapses (Williams et al., 2011). This is reminiscent of the role of Cadherin-8 in the development of synaptic laminae of the direction-selective retinal circuit within the inner plexiform layer, where different subtypes of bipolar cells specifically connect with their respective targets of starburst amacrine cells and retinal ganglion cells in appropriate sublaminae. Cadherin-8 and 9 are selectively expressed in bipolar cells and control the targeting of their axons to sublaminae in the inner plexiform layer by a heterophilic mechanism (Duan, Krishnaswamy, De la Huerta, & Sanes, 2014). Moreover, combinatorial interactions between six Cadherins (Cadherins 6, 7, 8, 9, 10 and 18) generate the appropriate connectivity between distinct bipolar cells, starburst amacrine cells and retinal ganglion cells to establish the complex direction-selective circuit of the mouse retina (Duan et al., 2018). Together, a wealth of data has established Cadherins as synaptic recognition factors throughout the brain and underlines the importance of their regional and temporal expression patterns, including their combinatorial expression, for circuit development.

2.2 Protocadherins

The largest subfamily within the Cadherin superfamily consists of Protocadherins, each containing six extracellular EC domains that are diverse among the isoforms and a short, constant cytoplasmic domain. Based on the genomic organization of the respective genes, Protocadherins are subdivided into gene clusters with 58 large variable exons in mice encoding α-, β-, and γ-Protocadherins, with multiple members within each cluster (Mountoufaris, Canzio, Nwakeze, Chen, & Maniatis, 2018; Wu & Maniatis, 1999). In addition, there are ∼10 nonclustered δ-Protocadherins (Hulpiau & van Roy, 2009). Clustered Protocadherins are expressed in a combinatorial and stochastic fashion (Schreiner & Weiner, 2010;

Thu et al., 2014). Protocadherin proteins from the same and different clusters promiscuously form isoform-independent *cis* dimers through membrane proximal repeats with efficient *trans* binding between the dimers. Further, Protocadherins show *cis* interactions with classical Cadherins (Weiner & Jontes, 2013). Apart from multifaceted functions in nervous system development including neuronal survival and dendritic and axonal arborization (Lefebvre, 2017), clustered Protocadherins can generate cell-specific recognition codes. One example is in the mouse barrel cortex, where clustered Protocadherins are required for lineage-dependent postnatal reciprocal synaptic connections between excitatory layer IV neurons (Tarusawa et al., 2016). In hippocampal pyramidal neurons, conditional deletion of the atypical Protocadherin Celsr3 after the first postnatal week results in a ~50% decrease in the number of excitatory but not inhibitory synapses (Thakar et al., 2017). Similar to Dscams (see below), Protocadherins can also mediate self-/non-self-discrimination for self-avoidance and restriction of synapse formation as shown for γ-Protocadherins in starburst amacrine cells in the retina (Ing-Esteves et al., 2018). These studies show intriguing roles of this diverse protein family in synaptic recognition.

2.3 Immunoglobulin superfamily members

The first discovered calcium-independent adhesion molecules are the proteins of the immunoglobulin (Ig) superfamily (IgSF). They were identified in parallel to the Cadherin superfamily and are now known to have at least 500 members, with roughly half expressed in neurons. Many members of the IgSF have been implicated in cell-type-specific recognition throughout brain development. Their extracellular domains are comprised of multiple Ig domains that engage in homophilic as well as heterophilic binding (Verschueren et al., 2020; Wojtowicz et al., 2020), often in combination with fibronectin III domains. A prominent group within the Ig superfamily is the L1 family, consisting of L1 (also known as Neuron-glia Cell Adhesion Molecule NgCAM), Close Homolog of L1 (CHL1), Neuron-glia-related Cell Adhesion Molecule (NrCAM), and Neurofascins. The L1 family plays roles in subcellular-specific targeting in several circuits. In the mouse brain, Neurofascin-186 (NF186) is enriched at the axon initial segment (AIS) of several cell types, such as cerebellar Purkinje neurons, hippocampal granule cells and neocortical pyramidal cells. NF186 in Purkinje neurons binds Neuropilin-1 expressed on axons of GABAergic basket neurons to restrict formation of the complex pinceau synapses at the Purkinje AIS, named for their brush-like appearance (Ango et al., 2004; Telley et al., 2016). In

the neocortex, instead of AIS-enriched NF186, pan-axonally expressed L1 is required for selective innervation of pyramidal neuron AIS by GABAergic Chandelier cells (Tai, Gallo, Wang, Yu, & Van Aelst, 2019). In both cases, anchoring the L1 family member by the cytoskeletal ankyrin G/spectrin complex is necessary for this localized innervation. The cooperation and coincidence detection by Ig recognition factors is illustrated by NrCAM and CHL1 in the sensory-motor circuit of the mouse spinal cord. They interact on GABApre interneurons with the Ig complex of Contactin 5 and Cntn-associated protein 4 (Caspr4) on proprioceptive sensory neurons to guide inhibitory synapse formation precisely at the axonal termini of sensory afferents (Ashrafi et al., 2014). Synaptic recognition includes inter-actions with astrocytic processes and a proximity-labeling approach per-formed in a partner-specific manner has recently mapped the proteome of astrocyte-neuron contacts in the cortex (Takano et al., 2020). NrCAM was one of the astrocyte-expressed proteins identified at these perisynaptic sites. Intriguingly, extracellular Ig interactions of astrocytic NrCAM are required for normal inhibitory synapse number and strength, while intra-cortical excitatory synapses are unaffected by NrCAM loss in astrocytes. This work advances our understanding of the roles that perisynaptic astro-cyte contacts and NrCAM in particular play in synapse organization. It addi-tionally highlights the power of targeted proteomic approaches to define synaptic recognition.

Studies in the retina have implicated other IgSF families in synaptic rec-ognition, including the Down syndrome cell adhesion molecules (Dscams, comprised of Dscam and Dscam-like1), Sidekicks (Sdk1 and 2) and GPI-anchored Contactins (Cntns 1-6), which mostly bind homophilically. In the chick retina, isoforms of these proteins are expressed by largely non-overlapping subsets of bipolar cells, amacrine cells and retinal ganglion cells, with cells expressing the same molecule projecting to the same inner plexiform layer lamina (Yamagata & Sanes, 2008, 2012; Yamagata, Weiner, & Sanes, 2002). The isoform-specific adhesion between these proteins mediates lamina-specific connectivity in the retina, although inter-esting differences have been observed across molecules and species. One example are Dscams, which are required for synaptic lamination in the chick retina (Yamagata & Sanes, 2008). Their function in synapse specification does not appear to be conserved in the mammalian retina, and Dscam in the mouse retina facilitates neurite self-avoidance by counteracting cell type-specific adhesion by Cadherins and Protocadherins (Fuerst, Koizumi, Masland, & Burgess, 2008; Garrett, Khalil, Walton, & Burgess, 2018). Sidekicks are expressed in subsets of retinal neurons in chick and mice and

are critical for laminar restriction of their neurites (Krishnaswamy, Yamagata, Duan, Hong, & Sanes, 2015; Yamagata & Sanes, 2018). Further, dendrites of mouse amacrine cells and retinal ganglion cells expressing Sdk1 but not Sdk2 arborize in the same stratum in the inner plexiform layer and this sublaminar restriction is disrupted in absence of Sdk1 (Yamagata & Sanes, 2018).

The Ig family of Synaptic Cell Adhesion Molecules (SynCAMs) is comprised of four members also known as Cadms (Cell adhesion molecules) or Nectin-like molecules (Biederer & Shrestha, 2015; Frei & Stoeckli, 2014). These vertebrate-specific proteins engage in homo- and heterophilic binding, with select pairwise interaction patterns between distinct members (Fogel et al., 2007; Kakunaga et al., 2005; Shingai et al., 2003; Thomas, Akins, & Biederer, 2008). SynCAM 1 is required and sufficient for excitatory synapse formation as shown in the hippocampal CA1 area (Robbins et al., 2010). SynCAM 1 also contributes to synaptic recognition in the CA3 area, where it organizes mossy fiber inputs to pyramidal neurons and is additionally required for mossy fibers to form synapses onto fast-spiking, PV-positive interneurons (Park et al., 2016). In the visual cortex, SynCAM 1 acts postsynaptically in PV-positive interneurons to promote their innervation by long-range thalamocortical inputs (Ribic, Crair, & Biederer, 2019) with implications for inhibitory network maturation and cortical plasticity (Ribic & Biederer, 2019). SynCAM 1 organizes synapses in the retina as well and contributes to cell–cell recognition in the outer plexiform layer. Here, it is expressed on mouse rod photoreceptor terminals and is required for their interactions with processes of horizontal cells and bipolar cell dendrites and the assembly of triadic rod ribbon synapses (Ribic, Liu, Crair, & Biederer, 2014).

The homophilic protein Kirrel3/Neph2 has provided insight into roles of Ig interactions in target recognition in the hippocampus. It is expressed by DG granule neurons and calbindin-positive GABAergic neurons in CA3 and regulates the development of mossy fiber synapses between these two cell types (Martin et al., 2015). With respect to hippocampal mossy fiber synapses, a proteomic approach that combined biochemical fractionation and FACS sorting has recently identified the Ig protein IgSF8 as a novel component of these large synaptic specializations (Apóstolo et al., 2020). IgSf8 is not only strongly enriched at mossy fiber synapses, it also acts as presynaptic organizer of their ultrastructure and connectivity. Methodologies that map the proteomes of different synapse types as in this study will advance our understanding of how recognition factors contribute to the staggering diversity of synapses across brain regions.

2.4 Leucine-rich repeat family proteins

The leucine-rich repeat (LRR) family of synaptic adhesion molecules is characterized by the presence of multiple consecutive LRR motifs in the extracellular domain which engage in diverse trans-synaptic interactions. LRR proteins have been implicated in all steps of circuit formation from neuronal migration and neurite outgrowth, to the formation and functional assembly of synaptic contacts (Schroeder & de Wit, 2018). The major subfamilies are Netrin-G ligands (NGLs, also called laminets), LRR Transmembrane proteins (LRRTMs), Slit and NTRK-like proteins (Slitrks), Fibronectin LRR Transmembrane proteins (FLRTs) and Synaptic Adhesion-Like Molecules (SALMs, also called LRFNs). LRR proteins provide examples for differential roles of family members in synaptic recognition and the specification of connectivity. Here, NGL-1 and -2 localize to the postsynaptic membrane and form trans-synaptic complexes selectively with GPI-anchored Netrin-G1 and -G2, respectively. In the neocortex and hippocampus of mice, Netrin-G1 and -G2 are distributed on different populations of developing axons (Nishimura-Akiyoshi et al., 2007). Their partners NGL-1 and -2 are concentrated in distinct segments within dendrites of these target areas that correspond to the termination zones of axons expressing Netrin-G1 or -G2 (Matsukawa et al., 2014). In Netrin-G1 and -G2 deficient mice, axonal pathfinding is normal, but the differential distribution of NGL-1 and -2 across dendritic segments is selectively disrupted. Consistent with a role of this subcellular targeting in synaptic recognition, NGL-2 loss selectively reduces the density of spines in the dendritic segment where CA1 pyramidal neurons receive Schaffer collateral inputs, while spine density on their distal dendrites is unaffected (DeNardo, de Wit, Otto-Hitt, & Ghosh, 2012). These studies provide an example for how differential subcellular targeting and adhesive interactions properties can be utilized to generate recognition codes.

The members of the FLRT family, FLRT1-3, were identified as high-affinity postsynaptic ligands of the Latrophilin family of adhesion-type G-protein coupled receptors (O'Sullivan et al., 2012). FLRT2 and FLRT3 show cell-type-specific expression patterns, with complementary and non-overlapping expression in the hippocampus. FLRT3 is highly expressed during the first 2 postnatal weeks in the principal cells of DG and CA3, and its conditional knockdown in the hippocampus of rat pups reduces spine density in DG granule cells and lowers the strength of perforant path inputs onto these cells (O'Sullivan et al., 2012). The FLRT ligands Latrophilin 2 and 3 localize to different dendritic domains

of CA1 pyramidal neurons and are essential for synapse formation by entorhinal cortex afferents and Schaffer collateral axons in these strata, respectively (Anderson et al., 2017; Sando et al., 2019). Both pre- vs post-synaptic localizations of Latrophilins have been reported in different regions of the hippocampus, suggesting they may localize to both sides of synapses, perhaps in a synapse-type specific manner (Anderson et al., 2017; O'Sullivan et al., 2012; Sando et al., 2019).

2.5 Teneurins

Teneurins are large transmembrane proteins that play roles in dendrite morphogenesis, axon pathfinding, partner selection and synapse differentiation (Arac & Li, 2019). They form a family of four proteins comprised of a large C-terminal extracellular domain including eight epidermal growth factor (EGF) motifs, a single transmembrane region, and an N-terminal cytoplasmic domain. Teneurins form constitutive *cis* dimers through the membrane proximal EGF repeats and are involved in homophilic and heterophilic *trans* interactions that mediate target recognition. Here, trans-synaptic homophilic interactions of Teneurin-3 control targeting of axons from proximal CA1 neurons to their targets in the distal subiculum (Berns, DeNardo, Pederick, & Luo, 2018). Teneurins can also bind Latrophilins, and these heterophilic high-affinity *trans* interactions provide for synapse-specifying functions of Teneurins and are regulated by alternative splicing (Li et al., 2018; Silva et al., 2011). Intriguingly, simultaneous binding of Teneurin-2 and FLRT3 to Latrophilin 3 promotes Schaffer collateral-CA1 synapse formation (Sando et al., 2019). This coincidence detection via a ternary interaction, akin to a two-factor authentication protocol, highlights the coding power for target-dependent synapse specification provided by multimeric recognition complexes.

3. Restrictive recognition cues shape neuronal connectivity

In concert with the positive, synapse-promoting cell surface interactions described above, cell-surface interactions and molecules secreted from target and non-target cells can also prevent the inappropriate formation of synapses. Such restrictive recognition cues can act locally to refine connection specificity. Alternatively, soluble restrictive factors can act at a distance to the extent they are diffusible within the neuropil. Select restrictive factors discussed below are depicted in Fig. 4A.
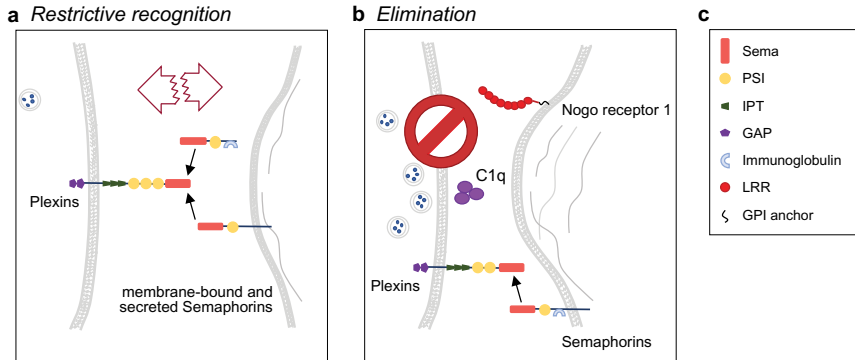
Fig. 4 Recognition molecules that restrict synaptic connectivity or participate in synapse elimination. (A) Factors restricting synaptic connections. (B) Factors that eliminate synapses once formed. Pre- and post-synaptic membranes are shown on the left and right, respectively. C1q, complement component 1q. (C) Domains utilized by the molecules in (A, B). GAP, GTPase activating domain; GPI, glycosylphosphatidylinositol; IPT, Immunoglobulin-like fold shared by Plexin and transcription factors, LRR, leucine-rich repeat; PSI, Plexin, Semaphorins and Integrin domain; Sema, Semaphorin domain.

3.1 Semaphorin–Plexin interactions

Some of the best understood restrictive recognition mechanisms are mediated by Semaphorin–Plexin signaling, which prevents mismatches in synaptic connections by inhibiting inappropriate target selection. This has been demonstrated in the hippocampus, retina, olfactory bulb, striatum and spinal cord (Pasterkamp, 2012; Yoshida, 2012). In the mouse hippocampal CA3 area, the transmembrane Semaphorins Sema6A and 6B, expressed on CA3 pyramidal neurons, interact with Plexin A4 on mossy fibers to control their lamina–restricted projection to the stratum lucidum of CA3 (Suto et al., 2007; Tawarayama, Yoshida, Suto, Mitchell, & Fujisawa, 2010). Sema6A and 6B are required for the repulsion of Plexin A4–expressing mossy fibers, preventing them from forming aberrant projections into stratum radiatum and stratum oriens. Semaphorin–Plexin signaling can also restrict connectivity by acting in the same cells as shown in hippocampal DG granule cells. Here, the transmembrane Semaphorin Sema5A is highly expressed in developing granule cells and signals through its receptor Plexin A2 co-expressed by these cells to suppress spinogenesis (Duan et al., 2014).

In the developing mouse retina, Sema6A acts as a repulsive cue to direct laminar termination away from inappropriate sublaminae. Sema6A and its receptor Plexin A4 are expressed in a complementary fashion in a subset

of amacrine cells and of retinal ganglion cells in the inner plexiform layer that differ in their response to a luminance change (Matsuoka et al., 2011). Mice lacking Plexin A4 or Sema6A exhibit severe mistargeting of these cell projections to sublaminae of the inner plexiform layer. Similarly, Sema5A and Sema5B, acting through their receptors Plexin A1 and A3, constrain the neurites from multiple retinal neuron subtypes to the inner plexiform layer (Matsuoka et al., 2011). In the absence of these molecules, retinal neurons fail to correctly stratify in the inner plexiform layer and neurites become mistargeted to the outer portions of the developing retina. These results support that Semaphorins specify laminar stratification through restrictive recognition.

Semaphorins also restrict synaptic recognition in other neural circuits. In the mouse spinal cord, repulsive interactions between secreted Sema3E, expressed on the cutaneous maximus motor neurons, and PlexinD1, expressed on sensory afferents, prevents the formation of direct sensory-motor neuron synapses (Pecho-Vrieseling, Sigrist, Yoshida, Jessell, & Arber, 2009). Sema3E-Plexin D1 signaling also negatively regulates thalamo-striatal synapse formation selectively on direct pathway medium spiny neurons (Ding, Oh, Sabatini, & Gu, 2011). While these examples highlight the restrictive activities of Semaphorin–Plexin interactions during circuit assembly, it should be noted that depending on the context, these ligand-receptor systems can promote connectivity as shown, e.g., for Sema4D that enhances inhibitory synapse formation in the hippocampus (Acker, Wong, Kang, & Paradis, 2018). Semaphorins and their receptors additionally play important roles during later stages of circuit refinement that are discussed in Section 5.

3.2 Other restrictive recognition factors

The FLRT family member FLRT2 and Unc-5C, a receptor for Netrin axon guidance cues, are expressed in a strikingly complementary fashion within specific retinal sublaminae of the developing inner plexiform layer. Heterophilic repulsion between FLRT2 and Unc-5c has been proposed to mediate the laminar restriction of presynaptic starburst amacrine cells and a subset of ON-OFF direction-selective ganglion cells (Visser et al., 2015). Synapse-restricting recognition is provided in the hippocampus during early postnatal development by the GPI-anchored Nogo Receptor 1 (NgR1), which acts through its co-receptor TROY to limit excitatory synapse formation and maturation (Lee et al., 2008; Wills et al., 2012).

4. Beyond making connections: Creating synapse diversity

Synapses are structurally and functionally highly diverse. During their assembly, cell-surface adhesion molecules and secreted factors modulate and even instruct pre- and post-synaptic differentiation at nascent contact sites. Many synapse organizing membrane proteins have been identified based on their synaptogenic ability in a mixed co-culture assay of neurons and non-neuronal cells (Biederer & Scheiffele, 2007). The co-culture assay serves to identify the sufficiency of candidate molecules to induce synaptic specializations, however it is unable to differentiate between their activities across the steps of synapse formation, stabilization and maturation. Additional tests are required to dissociate these roles of synapse organizing proteins, including loss-of-function analyses and acute interference with their interactions. Since the structural and functional diversity of synapses is best studied in the complex environment of the brain, we prioritize in this Section *in vivo* over *in vitro* studies evaluating roles of these proteins.

As a prerequisite to understand the molecular basis of synapse diversity, much progress has been made to parse out the transcriptional diversity of neurons in the mouse brain (see for examples, Paul et al., 2017; Tasic et al., 2016). Recently, Rico and colleagues made significant progress by demonstrating that cell type-specific expression patterns of recognition factors not only create molecular fingerprints to assign neuronal identities but also underly their connectivity patterns (Favuzzi et al., 2019). Using cell sorting, RNA sequencing and mouse genetics, they identified recognition factors that are differentially expressed between interneuron types in the developing mouse cerebral cortex and that allow these neurons to target distinct subcellular compartments of pyramidal cells. This study revealed presynaptic molecular programs that specify the sites where synaptic inputs are formed (see also Section 4.5). Such innovative analyses of cellular expression patterns promise to advance new insights into the organizing principles of input-specific connectivity and microcircuit wiring. Below, we describe select recognition factors to highlight how they can diversify synapse types.

4.1 Synapse-type specific functions of Neurexin–Neuroligin complexes

Much of our current understanding of the creation of synapse diversity derives from the trans-synaptic interactions of presynaptic Neurexins

(Südhof, 2017). Mammalian Neurexins are encoded by three genes giving rise to Neurexin 1-3, each with three promoters that can drive transcription of a longer α-Neurexin and shorter β-Neurexin isoform, and a γ isoform that lacks most of the extracellular domain (Roppongi et al., 2020; Tabuchi & Südhof, 2002; Ushkaryov, Petrenko, Geppert, & Südhof, 1992; Yan et al., 2015). Mice lacking all isoforms of α-Neurexins have ultrastructurally normal synapses and unaltered numbers of excitatory synapses, but Ca^{2+}-triggered neurotransmitter release is severely impaired (Missler et al., 2003; Varoqueaux et al., 2006). Inhibitory synapse number is significantly reduced in Neurexin triple KO mice (Dudanova, Tabuchi, Rohlmann, Südhof, & Missler, 2007). Neuroligins were the first of the post-synaptic ligands identified for Neurexins and form a family of four members. Intriguingly, Neuroligin-1 and Neuroligin-2 localize to excitatory and inhibitory synapses, respectively, pointing to synapse-type specific roles of their complexes with Neurexins (Song, Ichtchenko, Südhof, & Brose, 1999; Varoqueaux, Jamain, & Brose, 2004). Mice lacking the three Neuroligins have impaired synaptic transmission but unaltered synapse number (Varoqueaux et al., 2006). Neurexins engage in multiple extracellular interactions in addition to binding Neuroligins, establishing Neurexins as presynaptic hub proteins (Südhof, 2017).

Neurexin/Neuroligin complexes are involved in the functional specification of synapses. In agreement with their selective localization to excitatory and inhibitory synapses, deletion of Neuroligin-1 or -2 impairs evoked excitatory or inhibitory synaptic transmission, respectively (Chanda, Hale, Zhang, Wernig, & Südhof, 2017; Chubykin et al., 2007). Studies of Neurexins in interneurons reveal an even more diverse picture. Conditional deletion of α and β isoforms of Neurexin 1, 2 and 3 from fast-spiking PV-positive interneurons in the prefrontal cortex results in a loss of the inhibitory synapses they form and a decrease in synaptic strength but no impairment in action potential-triggered Ca^{2+} influx. In contrast, pan-Neurexin deletion in Somatostatin-positive interneurons causes no synapse loss but a large decrease in action potential-triggered Ca^{2+} influx that also suppresses synaptic strength (Chen, Jiang, Zhang, Gokce, & Südhof, 2017). Neurexins hence perform distinct roles in specifying synaptic properties that depend on pre- and postsynaptic partner combinations.

4.2 SynCAM cell adhesion molecules

SynCAMs are synaptogenic Ig proteins and induce functional presynaptic specializations (Biederer et al., 2002; Czondor et al., 2013; Fogel et al., 2007). SynCAM 1 is primarily postsynaptic at excitatory hippocampal

CA1 synapses, with a smaller fraction present in the presynaptic membrane (Perez de Arce et al., 2015). Loss of SynCAM 1 in mice reduces excitatory synapse number and temporal control of its forebrain expression in mice has demonstrated that it is first sufficient to promote excitatory synapse number in the hippocampal CA1 area and then required to maintain them (Robbins et al., 2010). A postsynaptic role of SynCAM 1 in the specification of synaptic inputs was shown in the visual cortex of mice. Cell–type specific knockdown of SynCAM 1 in PV-positive interneurons revealed that it is required in these cells to receive long-range thalamocortical excitatory inputs while its loss in the same cells does not impact short-range intracortical excitatory synapses (Ribic et al., 2019). SynCAMs hence engage in postsynaptic recognition to promote and specify synaptic connectivity.

4.3 Protein tyrosine phosphatases

The Leukocyte common antigen–receptor protein tyrosine phosphatases (LAR–RPTPs) comprise of the PTPσ, PTPδ and LAR proteins that organize excitatory and inhibitory synapse assembly (Han, Jeon, Um, & Ko, 2016). LAR–RPTPs contribute to the specification of synapses in a target–dependent manner by binding to multiple distinct postsynaptic ligands, such as NGL-3, TrkC, Slitrks, Synaptic Adhesion-Like Molecules (SALMs) and Interleukin 1 receptor accessory protein-like 1 (IL1RAPL1) (Han et al., 2016; Lie, Li, Kim, & Kim, 2018). This target-dependent role in synapse specification is shown by results that PTPσ is required for excitatory synapse induction by Slitrk1 (Han et al., 2018), while PTPδ is required for IL1RAPL1-mediated excitatory presynaptic differentiation (Yoshida et al., 2011) as well as Slitrk3-mediated inhibitory presynaptic differentiation (Yim et al., 2013). Conditional deletion of individual or all LAR–RPTPs either globally or selectively in excitatory cortical and hippocampal neurons does not affect spontaneous or evoked AMPAR–mediated synaptic transmission but does impair NMDA–receptor–mediated responses (Kim et al., 2020; Sclip & Südhof, 2020). This indicates that LAR–RPTPs specify functional postsynaptic properties.

4.4 Ephrin-EphB receptors

An additional class of trans-synaptic organizers with a direct signaling capability are the EphB receptor tyrosine kinases and their ephrinB ligands, which mediate excitatory synapse development in the hippocampus and cortex (Henderson & Dalva, 2018). Here, EphB-ephrinB signaling regulates

spinogenesis as well as the clustering of glutamate receptors (Dalva et al., 2000; Henkemeyer, Itkis, Ngo, Hickmott, & Ethell, 2003; Kayser, McClelland, Hughes, & Dalva, 2006; Segura, Essmann, Weinges, & Acker-Palmer, 2007). Postsynaptic EphB2 can simultaneously bind to its ephrinB ligands and NMDA receptors, controlling the mobility of these receptors (Dalva et al., 2000; Washburn, Xia, Zhou, Mao, & Dalva, 2020). Another role in specifying synaptic properties is provided by postsynaptic ephrinB3, which balances the extent to which glutamatergic synapses are formed on dendritic shafts vs spines (Aoto et al., 2007).

4.5 Synapse diversification involves secreted factors

Neurons locally secrete factors that contribute to synapse-type specific recognition. Wingless and Int-1 proteins (Wnts) induce presynaptic assembly (Sahores, Gibb, & Salinas, 2010; Umemori, Linhoff, Ornitz, & Sanes, 2004) and neuronal Pentraxins cluster ionotropic glutamate receptors at excitatory postsynaptic sites (Pelkey et al., 2015). Other secreted neuronal factors are Fibroblast growth factors (FGFs), and FGF-22 and FGF-7 differentially control synapse formation (Dabrowski, Terauchi, Strong, & Umemori, 2015; Terauchi et al., 2015; Umemori et al., 2004). In the hippocampus, they are highly expressed in CA3 pyramidal neurons during synaptogenesis and serve as retrograde presynaptic organizers of excitatory and inhibitory synapses, respectively, on CA3 pyramidal neurons. Another neuronally secreted factor that controls synaptic connectivity is the protein Complement Component 1q Subcomponent-like 3 (C1ql3). C1ql3 contains two globular domains originally identified in the protein C1q that assembles the initiating complex of the complement cascade in the immune system. C1ql family members bind the adhesion G protein-coupled receptor BAI3 (Bolliger, Martinelli, & Südhof, 2011; Sigoillot et al., 2015). Presynaptic deletion of C1ql3 in basolateral amygdala neurons causes a strong loss of their excitatory outputs to the prefrontal cortex (Martinelli et al., 2016).

Cerebellins (Cblns), another class of secreted C1q family members, are critical adaptors for multiple pre- and post-synaptic molecules. Cbln1 is secreted from cerebellar granule neurons and binds simultaneously to its postsynaptic receptor, the Glutamate Receptor Delta-2 (GluD2) on dendritic spines of Purkinje cells and a splice form of presynaptic Neurexin on cerebellar granule cell axons. Neurexin-Cbln1-GluD2 signaling leads to presynaptic vesicle accumulation as well as the postsynaptic accumulation of GluD2, illustrating coordinated pre- and postsynaptic differentiation by trans-synaptic interactions (Ito-Ishida et al., 2012; Matsuda et al., 2010).

Other examples for synapse-specifying secreted factors include Cbln4 that is secreted by Somatostatin-positive interneurons to bridge presynaptic Neurexin and GluD1 in layer 2/3 pyramidal neurons in the somatosensory cortex (Fossati et al., 2019). In addition, Cbln4 expressed by cortical Somatostatin-positive interneurons is required for their ability to innervate dendrites of pyramidal neurons, and exogenous expression of Cbln4 in PV-positive interneurons is sufficient to re-direct their inhibitory inputs to pyramidal neuron dendrites (Favuzzi et al., 2019). Cerebellins thereby serve as secreted 'match-makers' to spatially specify synapse formation.

Among astrocyte-secreted factors, Hevin/SPARCL1 was reported to bridge interaction-incompatible Neurexin 1α and a splice isoform of Neuroligin-1 at thalamocortical synapses (Singh et al., 2016). While validating the synaptogenic role of Hevin/SPARCL1, another study has used conditional knock-out of Neuroligins and Neurexins to show that Hevin acts independent of them in cultured neurons (Gan & Südhof, 2020). Synapse-type specific roles of Hevin for bridging Neurexin/Neuroligin complexes could resolve this discrepancy but remain to be tested.

4.6 Diversification of synaptic recognition proteins by alternative splicing

Alternative splicing of synaptic recognition molecules enhances their molecular diversity far beyond the limited number of genes, controlling their ectodomain interactions with synaptic ligands. Alternative splicing of cell adhesion molecules regulates synapse development as exemplified by Neurexins. Their alternative splicing at six canonical splice sites (SS1–SS6) in their ectodomains can generate over 1300 detectable isoforms (Schreiner et al., 2014; Treutlein et al., 2014). Single-cell profiling of mRNAs as well as ribosome-associated transcripts complemented by mass-spectrometric profiling of isoforms in the adult mouse brain have revealed hundreds of alternatively spliced Neurexin mRNAs with remarkable cell type-specificity and brain region-select regulation (Fuccillo et al., 2015; Furlanis, Traunmüller, Fucile, & Scheiffele, 2019; Schreiner et al., 2015). For example, in the mouse hippocampus, the SS4^{+} Neurexin isoform is selectively expressed in GABAergic PV-positive interneurons while the SS4^{−} isoform is the major isoform in glutamatergic pyramidal cells in the CA1 region (Nguyen et al., 2016). This posttranscriptional processing is extensively used to control synaptic recognition by Neurexins. One example is provided by LRRTMs and Latrophilins that bind Neurexins only when they lack an insert in splice site 4 (SS4^{−}) (Boucard, Ko, & Südhof, 2012; Etherton, Blaiss, Powell, & Südhof, 2009; Siddiqui et al., 2010), while

Cerebellin 1 only binds to SS4$^+$ Neurexins (Uemura et al., 2010). Alternative Neurexin splicing impacts synaptic composition and transmission as shown by studies in which the SS4 insert in Neurexin-3 was constitutively retained *in vivo*. This decreased postsynaptic levels of AMPARs in hippocampal neurons, a non-cell-autonomous phenotype shared by Neurexin-3 knock-out neurons (Aoto, Martinelli, Malenka, Tabuchi, & Südhof, 2013). These results highlight the need for profiling the cell-type-specific splicing patterns of other recognition molecules.

4.7 Post-translational modifications modulate and mediate synaptic recognition

Modifications such as phosphorylation, glycosylation, and palmitoylation are abundant in synaptic proteins and regulate their subcellular localization and protein–protein interactions. One example for the regulation of synaptic adhesion molecules with synaptogenic activity by posttranslational modification is provided by SynCAM 1. Site-specific N-glycosylation of its most membrane-distal Ig domain promotes trans-synaptic SynCAM interactions and is required for synapse induction (Fogel et al., 2010). Further, polysialic acid is attached to N-glycosylation sites of a subset of SynCAM 1 proteins in the developing mouse brain and this modification blocks homophilic SynCAM 1 binding (Galuska et al., 2010). Diverse cell-surface recognition codes can be created by glycan modifications as shown for the covalent attachment of long, heterogeneous chains of the glycosaminoglycan heparan sulfate to ectodomains of synapse organizers (Condomitti & de Wit, 2018). These heparan sulfate glycans are bound by heparan sulfate-binding proteins, thereby expanding interactions beyond adhesion of protein domains alone. Here, the glial-derived GPI-anchored Glypican 4 is modified by heparan sulfate and forms a glycan-dependent complex with postsynaptic LRRTM4 to promote excitatory synapse development (de Wit et al., 2013; Siddiqui et al., 2013). The Neurexin-1 extracellular domain is also modified by heparan sulfate and this modification is required for presynaptic differentiation induced by its postsynaptic Neuroligin and LRRTM ligands (Roppongi et al., 2020; Zhang et al., 2018).

4.8 Cooperation of co-expressed recognition molecules

A growing body of evidence demonstrates that multiple synapse organizing proteins are often present at the same synapse, with several of them known to share trans-synaptic partners. This sets the stage for coincidence detection of

the presence of recognition factors. At hippocampal DG excitatory synapses, presynaptic Neurexin 1 forms a complex with presynaptic PTPσ that also involves the modification of Neurexin with heparan sulfate, and both proteins cooperate in synaptogenesis mediated by postsynaptic LRRTM4 (Roppongi et al., 2020). This shows that the themes of post-translational diversification and concerted function can be combined to control recognition systems. Combinatorial roles were additionally shown for LRRTMs and Neuroligins in early postnatal development. Whereas individual or combined knockdown of LRRTM1 and LRRTM2 in cultured hippocampal neurons does not affect number of excitatory synapses, the additional loss of Neuroligin-1 and Neuroligin-3 leads to an extensive reduction of synapse number in an activity-dependent manner (Ko et al., 2011). Moreover, N-Cadherin is required for the postsynaptic adhesion molecules Neuroligin-1, SynCAM 1 and LRRTM2 to promote presynaptic differentiation as well as to enable postsynaptic differentiation by Neurexin-1β (Stan et al., 2010; Yamagata, Duan, & Sanes, 2018). Further, development of inhibitory synapses is jointly controlled by the postsynaptic organizers Slitrk3 and Neuroligin-2 (Li et al., 2017). These examples provide intriguing evidence that cooperative action of recognition molecules specifies synapses in a manner that depends on the molecular makeup of their synaptic clefts.

5. Refining neuronal connectivity through eliminating synapses

Once neuronal connections are established, synapses that were inappropriately formed or only need to be present during a select developmental period are removed. This refinement is critical for experience-dependent neuronal network maturation and involves microglial, astrocytic, and neuronal recognition factors. Several molecules involved in synapse elimination are depicted in Fig. 4B.

Tailoring synaptic connectivity includes microglia that migrate to 'tagged' synapses and engulf presynaptic terminals (Ji, Akgul, Wollmuth, & Tsirka, 2013; Paolicelli et al., 2011; Schafer et al., 2012; Weinhard et al., 2018). Multiple immune system effector molecules have been implicated in synaptic elimination by microglia in the CNS. The roles of these pruning molecules are best understood in the mouse retinogeniculate system, which is well suited to investigate synaptic pruning due to the anatomical precision with which eye-specific RGC inputs are refined and the fact that pruning in this brain region occurs during a narrow postnatal window. Here, the complement

cascade that serves in the innate immune system to tag debris for phagocytosis has been found to mark synapses for removal by microglia (Stevens et al., 2007). The abovementioned complement factor C1q is expressed in developing but not mature RGCs and localizes to the synapses between RGCs and their target neurons in the dorsolateral geniculate nucleus (dLGN). C1q knock-out mice have defects in synaptic refinement in the dLGN by P30, supporting that inappropriate retinal inputs were not properly pruned. Loss of synaptically localized C3, another complement protein, or astrocyte-secreted transforming growth factor-β (TGF-β) also results in decreased synaptic pruning in the retinogeniculate system (Bialas & Stevens, 2013; Schafer et al., 2012; Stevens et al., 2007). Other mechanisms that involve microglia are also in play in the dLGN. Following visual stimulation, microglia upregulate the cytokine TNF-associated weak inducer of apoptosis (TWEAK) and relay neurons increase expression of the TWEAK receptor, the Fibroblast growth factor-inducible protein, 14 kDa (Fn14). Neuronal Fn14 is required for the vision-dependent strengthening of bulbous spines contacted by RGCs when not bound by TWEAK. If Fn14 is bound by TWEAK at synapses proximal to microglia, their signaling decreases the number of bulbous spines via a mechanism distinct from phagocytic engulfment. Microglial TWEAK hence locally balances the refinement of dLGN inputs in a sensory experience-dependent manner (Cheadle, Rivera, Phelps, & Ennis, 2020).

Pruning in the hippocampal CA1 area involves the Triggering Receptor Expressed on Myeloid cells 2 (TREM2), an innate immune receptor that is required by microglia to refine excitatory inputs in CA1 (Filipello et al., 2018). In addition, the fractalkine receptor Cx3cr1, a chemokine receptor expressed by microglia, contributes to pruning in CA1. Mice lacking Cx3cr1 exhibit increased postsynaptic puncta density, CA1 dendritic spine density and mEPSC frequency, in agreement with an excess of excitatory synaptic sites due to a decrease in pruning (Paolicelli et al., 2011). The effect of Cx3cr1 on microglial-mediated pruning appears to be brain region-dependent, as its deletion in the visual cortex results in no change to synapse turnover (Lowery, Tremblay, Hopkins, & Majewska, 2017).

Microglia-dependent synapse elimination accounts for only part of retinogeniculate circuit refinement. Astrocytes and the factors they secrete add to the complexity of synapse removal (Chung et al., 2013; Vainchtein & Molofsky, 2020). Here, astrocyte-expressed phagocytic receptors (MEGF10 and MERTK) and recognition molecules (ephrinB1) contribute to synapse elimination in dLGN and hippocampal CA1, respectively (Chung et al., 2013; Koeppen et al., 2018).

Additionally, neuronally expressed molecules originally identified in the immune system, including the class I major histocompatibility complex (MHC I) and the secreted Pentraxins, homologs of a class of immune proteins recognizing antigens, participate in synapse removal (Bjartmar et al., 2006; Huh et al., 2000). Neuronal Semaphorins that restrict synaptic recognition in earlier development can also act to eliminate synapses once formed in order to refine connectivity (Riccomagno & Kolodkin, 2015). Semaphorin 3F signaling through the Neuropilin-2/Plexin A3 holoreceptor promotes the progressive elimination of synapses transiently formed by infrapyramidal mossy fiber axon collaterals on the basal dendrites of CA3 pyramidal cells in the maturing hippocampus (P25) (Bagri, Cheng, Yaron, Pleasure, & Tessier-Lavigne, 2003; Liu, Low, Jones, & Cheng, 2005). Similar to the elimination of excess synapses in other regions like the retinorecipient superior colliculus (Cheng et al., 2010) or the Plexin A3/A4-dependent stereotypic pruning of inputs by corticospinal tract axons (Low, Liu, Faulkner, Coble, & Cheng, 2008), this synaptic refinement process in the hippocampus precedes retraction of axons. Further, mice lacking the secreted Semaphorin 3F and its receptor Neuropilin-2 have normal spine density in DG granule cells and cortical layer V pyramidal neurons at P14 but higher density at P21 (Tran et al., 2009). This suggests a role for these recognition molecules in restricting synapse number in the maturing hippocampus, in agreement with the increase in the number of dendritic spines after acute deletion of Neuropilin-2 in adult cortical layer V neurons (Assous et al., 2019). Additional support for roles of Semaphorins in the negative control of synapse density comes from studies of the L1 Ig family member NrCAM, an obligate component of the Semaphorin 3F receptor complex Neuropilin-2/Plexin A3. Deletion of NrCAM results in increased spine number on apical dendrites of star pyramidal neurons in layer 4 of the mouse primary visual cortex at both P21 and P60 (Demyanenko et al., 2014). A classical process of synapse elimination occurs in the cerebellum and is also controlled by Semaphorin/Plexin recognition. Here, climbing fibers project from the contralateral inferior olive and synapse onto Purkinje cells (Hashimoto & Kano, 2005; Kano et al., 2018; Sassoe-Pognetto & Patrizi, 2017). During the first week of postnatal development in rodents, Purkinje cells in the cerebellum are innervated by multiple climbing fibers (Crepel, Mariani, & Delhaye-Bouchaud, 1976). However, by postnatal week three, only one of these original climbing fibers innervates a single Purkinje cell and all other climbing fiber inputs are removed (Chedotal & Sotelo, 1993; Crepel, Delhaye-Bouchaud, & Dupont, 1981;

Mariani & Changeux, 1981). In this process, Semaphorin 3A acts as a retro-grade signal from Purkinje cells to Plexin A4 in climbing fibers to protect one synapse from elimination, whereas Semaphorin 7A facilitates elimination of climbing fiber synapses on Purkinje cells through Plexin C1 and the base-ment membrane–related protein Integrin β1 (Uesaka et al., 2014).

While it is important for circuit refinement to tag specific subsets of syn-apses for removal, it is conceivable that molecules present at the retained synapses serve to prevent pruning. Evidence exists that CD47, another immune system molecule, and its receptor SIRPα are among such factors. CD47 is detected at dLGN synapses during the peak period of their pruning and loss of CD47 or its receptor SIRPα results in a decrease in dLGN excit-atory synapse number and increased microglial engulfment of presynaptic inputs. This in turn significantly impairs retinal innervation (Lehrman et al., 2018).

6. Aberrant synaptic recognition and brain disorders

Genome wide association studies (GWAS) and the characterization of *de novo* mutations in neuropsychiatric disorders strongly support that aber-rations in synaptic adhesion molecules are associated with increased risk for neurodevelopmental and psychiatric disorders. While functional compensa-tion can occur among synaptic adhesion molecules from the same or differ-ent gene families, *de novo* mutations in neuropsychiatric patients provide evidence that a change as small as a single amino acid substitution in a rec-ognition molecule can impact social behaviors and cognitive functions. The notion that even minor disruptions in synaptic recognition perturb synapses and alter circuits is supported by studies in which disorder-linked mutations were introduced into synaptic adhesion molecules. Among the consequences are synapse-type specific alterations, changes in synaptic transmission, and improper connectivity, all of which can impair brain functions.

We focus here on autism spectrum disorders and schizophrenia that present during early and late brain development, respectively. They were selected because altered synapse number and connectivity patterns are part of the etiology of these disorders. Further, a wealth of human genetic data and results from animal models with disease-linked mutations or deletions in synaptic adhesion molecules are available. While the focus of this chapter lies on developmental aspects, it needs to be considered that phenotypes corre-lated with mutations in synaptic recognition factors could in part reflect their functions in the maturing and adult brain.

6.1 Autism spectrum disorders

Autism Spectrum Disorders (ASDs) are a group of developmental disorders characterized by deficits in social–emotional reciprocity, impairments in verbal and nonverbal communication, and repetitive patterns of behaviors and interests that start to manifest early in life. Specifically, ASD symptoms can often be diagnosed around the age of 2. These impairments are distinct from intellectual disability or a general developmental delay.

How do synapses come into play? ASD has a high comorbidity with epilepsy and has long been thought to involve altered synaptic connectivity. This agrees with the onset of its symptoms during the period of most intense synaptogenesis, as well as postmortem data showing increased dendritic spine density in prefrontal cortex (PFC) pyramidal neurons of ASD patients (Hutsler & Zhang, 2010). Patients with ASD also present improper excitatory and inhibitory (E/I) synaptic balance resulting in abnormal transmission and oscillatory anomalies on a brain–wide scale (Cornew, Roberts, Blaskey, & Edgar, 2012; Orekhova et al., 2007). A large body of evidence from GWAS and *de novo* mutation analyses points to malfunctions of synaptic molecules including recognition factors in the etiology of ASD (Geschwind & State, 2015; Sestan & State, 2018). Animal models where synaptic adhesion molecules associated with ASD either carry human disease-linked mutations or are deleted exhibit E/I synaptic imbalance phenotypes as reviewed below. Whether these E/I alterations are cause or consequence of ASD-linked aberrations is being discussed (Antoine, Langberg, Schnepel, & Feldman, 2019), but it can be considered that synaptic adhesion molecules have a role in the homeostatic stabilization of circuits and that disease-linked mutations impair this. Together, the altered expression of ASD-linked synaptic adhesion molecules can impact neuronal transmission and partner recognition as described in this Section. Susceptibility to these mutation effects appears to differ across brain regions and for candidate molecules listed here, the brain area or synapse type that has been characterized is stated.

6.1.1 Neurexins (NRXN genes)

Neurexins have been strongly implicated in ASD, and deletions and rare variants of Neurexin-1α are found in ASD patients (Gauthier et al., 2011; Schaaf et al., 2012; Südhof, 2017; Yan et al., 2008). Neurexin-1α knock-out mice have reduced spontaneous and evoked excitatory synaptic strength in the hippocampus (Etherton et al., 2009). Along with these

synaptic changes, Neurexin-1α knock-outs display increased repetitive grooming behaviors, impaired nest-building, and impaired pre-pulse inhibition, behavioral phenotypes that are linked to neurodevelopmental disorders. Non-social cognitive defects were also observed in rats lacking Neurexin-1α (Esclassan, Francois, Phillips, Loomis, & Gilmour, 2015).

6.1.2 Neuroligins (NLGN genes)

Neuroligin family members are genetically associated with ASD, with mutations found in syndromic and non-syndromic ASD patients (Marro et al., 2019; Nakanishi et al., 2017; Südhof, 2017; Xu et al., 2014). One mutation in Neuroligin-3, R451C, is a highly penetrant missense mutation (Jamain et al., 2003). This mutation resides within the extracellular, cholinesterase-like domain and causes altered intracellular protein trafficking, resulting in lower surface expression (De Jaco et al., 2005). While no loss of excitatory or inhibitory synapse density has been found in Neuroligin-3 knock-out or R415C knock-in mouse lines, Neuroligin-3 R415C knock-in mice display increased inhibitory synaptic transmission in cell layer II/III of the somatosensory cortex that is not seen in the Neuroligin-3 knock-out mice, suggesting a pathological dominant negative effect (Tabuchi et al., 2007). In the somatosensory barrel cortex, *in vivo* spine imaging revealed an increased spine turnover rate in three-week-old Neuroligin-3 R451C knock-in mice (Isshiki et al., 2014). Neuroligin-3 R451C knock-in mice also display social novelty defects with decreased activity in the medial prefrontal cortex (mPFC), an area implicated in ASD. Local field potential recordings in the mPFC of Neuroligin-3 R451C knock-in mice revealed reduced gamma band activity as well as reduced gamma-to-theta amplitude coupling, indicative of inappropriate synaptic connectivity (Cao et al., 2018). *In vitro* patch-clamp recordings in the mPFC found reduced excitability of PV-positive interneurons, but not pyramidal neurons. Interestingly, oscillation-coupled excitation of mPFC PV-positive interneurons via optogenetics was able to rescue gamma-to-theta coupling in Neuroligin-3 R451C knock-in mice, as well as social novelty defects (Cao et al., 2018). Targeting the connectivity of interneurons could therefore be an entry point for the treatment of ASD. ASD-relevant effects of Neuroligin-3 mutations also manifest in the striatal subregion of the nucleus accumbens, where Neuroligin-3 deletion decreases inhibitory transmission and results in repetitive behaviors (Rothwell et al., 2014).

6.1.3 Contactins (CNTNAP genes)

Contactin Associated Protein-like 2 (CNTNAP2) shares extracellular domains with Neurexins and **s**trong genetic data implicate it in ASD, with

genetic variants and microdeletions in the *CNTNAP2* gene associated with ASD (Alarcon et al., 2008; Al-Murrani, Ashton, Aftimos, George, & Love, 2012; Arking et al., 2008; Poot et al., 2010). There is also evidence that a common genetic variant affects inter-region connectivity in the human PFC, with carriers of the risk variant having impaired functional connectivity and significant reductions in grey and white matter volume (Scott-Van Zeeland et al., 2010; Tan, Doke, Ashburner, Wood, & Frackowiak, 2010).

Loss of CNTNAP2 reduces dendritic spine density and *in vivo* imaging in the somatosensory cortex of mice shows that it contributes to an accelerated loss of spines, suggesting CNTNAP2 plays a role in the stabilization of excitatory synaptic connections (Gdalyahu et al., 2015; Varea et al., 2015). In the mPFC, a decrease in both excitatory and inhibitory synaptic inputs was found in cell layer II/III in CNTNAP2 knock-out mice (Lazaro et al., 2019). Further, analyses of local field potentials and unit spiking in awake CNTNAP2 knock-out mice found impairments in oscillations, in agreement with a reduction in coordinated neuronal population activity (Lazaro et al., 2019).

6.1.4 SynCAMs (CADM genes)

Two different missense mutations (H246N and Y251S) in the gene encoding SynCAM 1 have been identified in ASD patients (Zhiling et al., 2008). Both mutations occur in the immunoglobulin domain that is proximal to the cell membrane, which is required for its lateral *cis* interactions (Fogel, Stagi, Perez de Arce, & Biederer, 2011). These mutations render SynCAM 1 more susceptible to protease cleavage, alter its intracellular trafficking, and shorten dendrite length (Fujita et al., 2010; Zhiling et al., 2008). A biological concept-based analysis of ASD-linked SNPs that was cross-validated with patient gene expression data identified several disease-linked clusters, with a prominent cluster for adhesion that includes the gene encoding SynCAM 1 (Esteban, Tonellato, & Wall, 2020). SynCAM 2, a heterophilic binding partner of SynCAM 1, has also been implicated through GWAS in ASD, and is additionally linked to attention-deficit hyperactive disorder, cognitive processing speed and educational attainment (Albayrak et al., 2013; Casey et al., 2012; Davies et al., 2016; Ibrahim-Verbaas et al., 2016; Okbay et al., 2016). Mice in which SynCAM 1 is deleted exhibit lower dendritic spine density and a reduction in excitatory transmission in the hippocampal CA1 area (Robbins et al., 2010) as well as impaired connectivity and E/I balance in the CA3 region (Park et al., 2016). Loss of SynCAM 1 impacts the cortex, too, and reduces thalamocortical inputs to PV-positive interneurons and impedes inhibitory maturation (Ribic et al., 2019).

6.1.5 Cadherins and protocadherins (CDH and PCDH genes)

Single nucleotide polymorphisms (SNPs) close to the genes encoding Cadherin 8, 9 and 10 (*CDH8-10*) are strongly associated with ASD, as well as large deletions in Cadherin 13 (*CDH13*) (Lin, Frei, Kilander, Shen, & Blatt, 2016; Sanders et al., 2011; Wang et al., 2009). The Protocadherin family is also implicated in ASD. Multiple SNPs within the Protocadherin-α gene cluster show significant associations with autism (Anitha et al., 2013). CNVs in Protocadherin 9 (encoded by *PCDH9*) and homozygous deletions in Protocadherin 10 (*PCH10*) have been reported in ASD cases, as well as numerous Protocadherin 19 mutations in families with members diagnosed with epilepsy and mental retardation. Five of these mutations result in early stop codons and two are missense mutations that are predicted to affect calcium binding (Dibbens et al., 2008; Marshall et al., 2008; Morrow et al., 2008). Correspondingly, loss of Protocadherins in mice results in autism-relevant phenotypes. Protocadherin 19 knock-out male mice show abnormal sociability as well as increased grooming, while Protocadherin 10 knock-out male mice exhibit social novelty defects and abnormal gamma oscillations in the basolateral amygdala (Lim, Ryu, Kang, Noh, & Kim, 2019; Schoch et al., 2017).

6.2 Schizophrenia

Schizophrenia, a neurodevelopmental disorder also considered to be synaptic in pathology, presents later in adolescence in a time period that corresponds with the final maturation of the PFC. Postmortem studies of schizophrenia patients show decreased dendritic spine density in layer II/III in the PFC, pointing to a significant loss in synapse number (Garey et al., 1998; Glantz & Lewis, 2000) Schizophrenia patients also display altered PFC gamma band oscillations which are driven through PV-positive interneurons and are presumed to synchronize local cortical networks (McNally & McCarley, 2016). These lower gamma band oscillations in schizophrenia patients suggest chronically dysfunctional long-range synaptic transmission in the cortex (Chen et al., 2014; Grent-t-Jong et al., 2018; Grutzner et al., 2013).

While there has been significantly less success in identifying *de novo* mutations in proteins in schizophrenia patients as compared to ASD due to the challenging genetic heterogeneity of schizophrenia, GWAS studies have provided substantial progress. Genetic risk loci include synapse organizing proteins, suggesting that schizophrenia is a disorder that involves, at least in part, improper synaptic connectivity during development

(Schizophrenia Working Group of the Psychiatric Genomics, 2014). We highlight below representative schizophrenia-relevant synapse organizing proteins for which animal studies have been performed.

6.2.1 Neurexins

Neurexin-1α has been implicated in schizophrenia through copy number variant deletions and duplications (Gauthier et al., 2011; Kirov et al., 2009; Rujescu et al., 2009). As outlined for ASD, Neurexin-1α mice have reduced excitatory synapse strength in the hippocampus, as well as altered behaviors. Specifically, Neurexin-1α knock-out mice display impaired pre-pulse inhibition (PPI), a behavioral assay that measures sensory gating and attentive processing, which is also impaired in human schizophrenia patients (Etherton et al., 2009).

6.2.2 Neuroligins

Damaging missense mutations have been found in the *NLGN2* gene in a cohort of schizophrenia patients. One disease-linked mutant (R215H), fails to bind presynaptic Neurexin and disrupts GABA transmission in a reconstituted system (Sun et al., 2011). Introducing the R215H mutation into Neuroligin-2 in mice results in reduced miniature and evoked inhibitory post-synaptic currents and abnormal gamma oscillations in the PFC (Chen et al., 2020). Neuroligin-2 R215H knock-in mice also exhibit reduced inhibitory synaptic transmission in the hippocampus, with lower inhibitory synaptic marker density and impaired memory processes (Jiang et al., 2018). In the PPI test, Neuroligin-2 R215H mice have performed differently given the study; in one they display impaired PPI, in another enhanced, but this effect may be due to differences in the genetic makeup of the mice analyzed (Chen, Lee, Liao, & Chang, 2017; Jiang et al., 2018).

6.2.3 Leucine-rich repeat transmembrane proteins (LRRTM genes)

The postsynaptic adhesion molecule and Neurexin partner LRRTM1 is encoded by an imprinted gene (disease risk associated with paternal inheritance) and hypomethylation of the promoter significantly increases the risk of developing schizophrenia (Brucato, DeLisi, Fisher, & Francks, 2014; Francks et al., 2007; Ludwig et al., 2009). LRRTM1 is also linked to schizotypy in a non-clinical population (Leach, Prefontaine, Hurd, & Crespi, 2014). Altered excitatory presynaptic protein distribution in the CA1 but not the CA3 region of the hippocampus and a significant decrease in excitatory synapses in the CA1 stratum radiatum have been observed in LRRTM1 knock-out mice, indicating that LRRTM1 supports hippocampal connectivity (Linhoff et al., 2009;

Schroeder & de Wit, 2018; Takashima et al., 2011). To what extent these phenotypes involve interactions with Neurexins is currently unknown.

7. Outlook

As reviewed in this chapter, recognition molecules are now known to play critical roles in neuronal partner identification and the formation and specification of synapses. What are the next key questions? On a functional level, the roles of recognition during the sequential steps of partner contact and synapse assembly remain to be elucidated. As reviewed here, multiple examples exist for proteins that are required and sufficient for neuronal partner recognition. This is not the case for synapse formation, where several proteins are sufficient to drive this process, but none is required. Future studies can test whether select factors that control neuronal partner recognition switch roles after contact and work with synapse-organizing proteins to initiate synapse development. These recognition processes may include positive cooperation as well as competition between recognition factors, mechanisms that we are only beginning to grasp. From a molecular perspective, it will be important to delineate the stoichiometry, subsynaptic distribution and dynamic properties of recognition factors at different synapse types, aiming to reach single synapse resolution. These measurements will determine to what extent the relative abundance and dynamics of recognition factors guide the trajectories along which different synapse types emerge.

The design of future studies will benefit from comparing brain regions and neuron types as this provides opportunities to determine contextual functions of synaptic recognition factors. Region- and neuron-specific roles can be of high relevance for understanding disease processes, including why certain brain areas are more vulnerable to synaptic aberrations than others. An additional health-relevant goal will be to analyze the roles of synaptic recognition once development has been completed. Many of the molecules discussed here persist at mature synapses, indicating functions beyond development that may include synapse maintenance, synaptic plasticity, synapse-type specific control of network maturation, or circuit remodeling. A better understanding of how synaptic recognition shapes the mature CNS can generate leads for therapeutic intervention in disorders of the adult and aging brain and for healthy aging.

These new directions are bound to advance our knowledge of how recognition molecules provide for the precise connectivity of the CNS and the astounding structural and functional diversity of synapses.

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