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The Role of Synaptic Cell Adhesion Molecules and Associated Scaffolding Proteins in Social Affiliative Behaviors

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Abstract

Social affiliative behaviors -- engagement in positive (i.e. non-aggressive) social approach and reciprocal social interactions with a conspecific -- comprise a construct within the NIMH RDoC Social Processes Domain. Affiliative behaviors are disrupted in multiple human neurodevelopmental and neuropsychiatric disorders, such as autism, schizophrenia, social phobia, and others. Human genetic studies have strongly implicated synaptic cell adhesion molecules (sCAMs) in several such disorders that involve marked reductions, or other dysregulations, of social affiliative behaviors. Here, we review the literature on the role of sCAMs in social affiliative behaviors. We integrate findings pertaining to synapse structure and morphology, neurotransmission, postsynaptic signaling pathways, and neural circuitry to propose a multi-level model that addresses the impact of a diverse group of sCAMs, including neurexins, neuroligins, protocadherins, immunoglobulin (Ig) superfamily proteins, and leucine rich repeat proteins, as well as their associated scaffolding proteins, including Shanks and others, on social affiliative behaviors. This review finds that the disruption of sCAMs often manifests in changes in social affiliative behaviors, likely through alterations in synaptic maturity, pruning, and specificity leading to excitation / inhibition imbalance in several key regions, namely the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), hippocampus, and ventral tegmental area (VTA). Unraveling the complex network of interacting sCAMs in glutamatergic synapses will be an important strategy for elucidating the mechanisms of social affiliative behaviors and the alteration of these behaviors in many neuropsychiatric and neurodevelopmental disorders.

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Keywords

synapse; neurexin; neuroligin; SHANK; cadherin; NMDA; affiliation; behavior

Introduction

Social affiliative behaviors -- engagement in positive (i.e., non-aggressive) social approach and reciprocal social interactions with a conspecific -- comprise a construct within the NIMH Research Domain Criteria (RDoC) Social Processes Domain and are disrupted in multiple human neurodevelopmental and neuropsychiatric disorders, such as autism, schizophrenia and social phobia. Because major disruptions of social affiliative behaviors are common, highly disabling, and refractory to currently-available pharmacological treatments, research into the underlying genetic and molecular basis of social affiliation deficits should be prioritized so that psychiatric treatment can be advanced. In this review, we will examine the neural circuits and molecular mechanisms of social affiliative behaviors, and will focus on the role of synaptic cell adhesion molecules (sCAMs) in these behaviors.

Synapses are highly complex, dynamic structures at the interfaces between neurons and are critical for neuron to neuron communication in the brain. sCAMs are transmembrane or membrane-tethered proteins involved in the maintenance, function, and elimination of synapses. sCAMs can belong to several protein families, including neurexins, neuroligins, cadherins, protocadherins (Pcdhs), immunoglobulin superfamily (IgSF) proteins, and leucine-rich repeat (LRR) proteins. Historically, sCAMs are defined by their combination of repeated adhesion protein domains and their location at the synapse. sCAMs sit on the pre- and/or postsynaptic membrane and bind trans-synaptically to other sCAMs, as well as intracellularly to cytoskeletal elements and scaffolding proteins.

Human genetic studies have strongly implicated sCAMs in several neuropsychiatric and neurodevelopmental disorders involving marked reductions, or other dysregulations, of social affiliative behaviors. Most notably, neurexins and neuroligins have been associated with autism spectrum disorder (ASD), a neurodevelopmental disorder largely defined by reduced or dysregulated social affiliative behaviors (1). Neurexins have been linked to several other disorders associated with social difficulties, including Pitt-Hopkins syndrome, schizophrenia, intellectual disability, attention deficit and hyperactivity disorder (ADHD), and bipolar disorder (2). Additionally, a member of the IgSF, close homologue of L1 (CHL1), has been associated with autism, intellectual disability, and schizophrenia (3-6). A well-studied family of sCAM-associated scaffolding proteins, SHANKs, have been implicated in various neurodevelopmental and psychiatric disorders, including ASD, intellectual disability, schizophrenia, and ADHD (7). Several genes in the cadherin and Pcdh families have also been associated with neuropsychiatric disorders, including epilepsy, intellectual disability, ASD, schizophrenia, and bipolar disorder (8).

This review proposes a mechanistic model for the role of sCAMs in social affiliation behaviors using evidence from rodent models. The NIMH RDoC defines social affiliation as social approach (i.e. initiation of interaction with another) and engagement (i.e. maintenance

of interaction beyond initiation) in positive social interactions with other individuals. In this review, we will focus on the role of sCAMs in the three-chamber social approach assay (9, 10) as well as the direct social interaction assay. We do not include studies of social novelty, social memory, aggression, mating, or maternal behaviors, although these are important areas of future focus. By focusing on a key RDoC behavior rather than putative rodent models of complex disorders, our review can approach the mechanistic detail – at the molecular, cellular, circuit, and behavioral levels – necessary to develop new treatment targets for disruptions of this important behavioral domain. This review finds that the disruption of sCAMs often manifests in changes in social affiliative behaviors, along with alterations in dendritic spine morphology and glutamatergic transmission in several key regions, namely the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), ventral tegmental area (VTA), and hippocampus.

Neurexins and neuroligins

Neurexins

The neurexin family of proteins are key organizers of the synapse, with thousands of isoforms and multiple binding partners. Neurexins are present at presynaptic membranes of excitatory and inhibitory synapses (11, 12) (see Figures 2 and 3). They have been shown to be involved in recruitment of synaptic vesicles to the presynaptic membrane for release and in triggering postsynaptic differentiation (11, 13). Neurexins bind GABA-A receptors in addition to other sCAMs, including neuroligins, dystroglycan, LRR transmembrane (LRRTM) neuronal proteins, cerebellins, calstentens, latrophilins, and neurexophilin (14-21). In humans and mice, there are three genes encoding classic neurexins: *Nrxn1*, *Nrxn2*, and *Nrxn3* (22). Neurexin genes in vertebrates have two promoters with the ability to produce either alpha- or beta-neurexin transcripts (22). The *Nrxn* genes differ in alternative splicing and expression patterns (22, 23) (see Supplementary Table 1).

The reported effects of deleting *Nrxn1* on rodent social affiliation are varied, including decrease (24, 25), increase (26), and no change in the behavior (27, 28). These inconsistencies across studies could be due, in part, to variable expressivity of the mutation related to differing genetic backgrounds of the models (26, 28) and to variation across studies in methods, including behavioral testing procedures, age of the mice at testing, and other differences (see Supplementary Table 2).

In contrast to the variability found with *Nrxn1* deletions, knockout of *Nrxn2* has been shown consistently to decrease social affiliation (27, 29, 30). Knockout of *Nrxn2* also impacted excitatory neurotransmission in layer V of the somatosensory cortex, namely by decreasing the frequency of miniature excitatory postsynaptic currents (mEPSCs) and NMDAR transmission (29). Studies examining the impact of *Nrxn3* on social affiliation were not found in our literature search. Overall, while the role of *Nrxn1* is more uncertain, it seems clear that *Nrxn2* plays a role in social affiliation. More work needs to be done to test the region- and cell-specificity of the role of neurexins in social affiliation, in addition to the potential role of spine changes in the mechanistic pathway linking neurexins to social affiliation behavior.

Neuroligins

The most-studied postsynaptic binding partners for neurexins are neuroligins. Neuroligins facilitate presynaptic neurexin clustering and affect synapse maturation (13, 31). Some work (mostly in overexpression or knockdown models) indicates that neuroligins may influence synaptogenesis, along with spine morphology and number (11, 32-34), though those findings are in conflict with other work examining knockout models (31). In mice, there are four neuroligins, which differ in their cell-type specific expression and binding specificity.

Neuroligin-1 (encoded by *Nlgn1*) is found at excitatory synapses throughout the brain and, in addition to extracellular interactions with presynaptic neurexins, binds several postsynaptic scaffolding proteins via its cytoplasmic domain, including PSD-95, S-SCAM, Shank1, and Shank3 (35-38). Knockout of *Nlgn1* led to decreased social affiliation, decreased long-term potentiation in Hip CA1, and decreased NMDA/AMPA ratio in the striatum (39). Knockin of a deleterious *Nlgn1* allele, a P89L substitution originally identified in a proband with ASD, led to decreased social affiliation in a mouse model (40). On the other hand, overexpression of *Nlgn1* failed to affect social affiliation, as did knockdown of *Nlgn1*(41, 42).

Neuroligin-2 (*Nlgn2*) is present at the postsynaptic membrane of inhibitory synapses throughout the brain (43). Knockout and knockdown of *Nlgn2* had no effect on social affiliation behavior (42, 44, 45). Conditional knockout of *Nlgn2* in the medial prefrontal cortex (mPFC), however, did lead to decreased social affiliation, accompanied by a decrease in inhibitory transmission, as indicated by a decrease in amplitude and frequency of miniature inhibitory postsynaptic currents (mIPSCs) in the mPFC (46). Conditional, region-specific overexpression of *Nlgn2* in the hippocampus did not affect social affiliation (47). Transgenic overexpression of *Nlgn2* has led to decreased social affiliation and an increase in frequency of mEPSCs in layer II/III of the prefrontal cortex (48).

Neuroligin-3 (*Nlgn3*) is found at both excitatory and inhibitory synapses throughout the brain (49). Knockin of the deleterious *Nlgn3* allele R451C (a mutation identified in autistic probands) has been reported to decrease social affiliation in some cases (50-52) and to result in no change in others (53-56). One study showed variation in results on social affiliation (no change / decrease) based on the assay used, yet consistent increases in excitatory transmission in hippocampal CA1, as measured by fEPSP, NMDA/AMPA ratio, mEPSC frequency, and NMDAR-dependent LTP (57). Among these studies, researchers tested the impact of genetic background, showing that, for *Nlgn3R451C* knockin mice, social preference in a 3-chamber assay was eliminated on a 129S2/SvPasCrl background but maintained on a C57BL/6J background (52, 53). In contrast to the knockin R451C models, knockout of *Nlgn3* does not consistently affect social affiliation (50, 58, 59). However, one study did find that both global knockout of *Nlgn3* and conditional knockout of *Nlgn3* in ventral tegmental area (VTA) dopaminergic neurons led to reduced social affiliation (60). Neuroligin 4 (*Nlgn4*) seems to be limited to glycinergic synapses throughout the brain and central nervous system more generally (61). Thus far, there is one report that knockout of *Nlgn4* led to a decrease in social affiliation (62).

Together, current data generally support a role for neuroligins in social affiliation, with some variation in how they impact related neurotransmission. One way *Nlgn3* impacts social affiliation is through GluA2-lacking AMPA receptors at inputs onto dopaminergic neurons in the VTA (60), while *Nlgn2* and inhibitory transmission are implicated in the mPFC; though, the detailed mechanisms involved still need to be clarified (45, 46, 48).

Cadherins

There are over 100 members of the cadherin superfamily, defined by the presence of one or more approximately 110 amino acid-long cadherin domains in their extracellular portions. Subfamilies of cadherins include the classical cadherins (including type I and type II cadherins), desmosomal cadherins, protocadherins, calsyntenins, and atypical/7-transmembrane cadherins. Cadherins have been implicated in pre- and postsynaptic organization and are likely to play key roles in synapse formation and plasticity as well as in spine maintenance (63, 64). Despite being implicated in neurodevelopmental disorders with social impairments (8), cadherins have received relatively little attention in research related to social behaviors. The present review found research on social affiliation for only two cadherin superfamily genes: calsyntenin-2 (*Clstn2*) and protocadherin-10 (*Pcdh10*).

Calsyntenin-2 resides on the postsynaptic side of both inhibitory and excitatory synapses in most areas throughout the brain (65), and *Clstn2* knockout mice exhibited decreased social affiliation (66). Protocadherin-10 is present in excitatory synapses and engages in homophilic, and limited heterophilic, *trans*- and intracellular interactions (67-69). It is expressed throughout the brain, though with some regional specificity that varied depending on whether mRNA or protein expression was analyzed (67, 70, 71). Haploinsufficiency of *Pcdh10* in mice decreased social affiliation and led to an increased density of morphologically immature dendritic spines in the BLA (72). Importantly, decreased social affiliation in the *Pcdh10* model was rescued by acute, systemic treatment with D-cycloserine, a partial glycine agonist that enhances NMDAR signaling (72).

Thus, though a couple members of the cadherin superfamily have been implicated in social affiliation, there is a vast amount of work still to be done to elucidate the potential roles of the remaining family members. Given the association of many protocadherins with changes in synapse structure and with neuropsychiatric disorders, further study of this diverse subfamily in relation to social affiliation, in particular, should be pursued (73, 74).

Immunoglobulin (Ig) superfamily (IgSF)

Many sCAMs belong to the IgSF, whose members are defined by the presence of extracellular Ig domains similar to those in antibodies, each comprised of a sandwich of two β -sheets. Multiple members of this family have been implicated in synapse formation, maintenance, and plasticity (75). Unfortunately, few IgSF members have been examined in the social affiliation literature as of yet.

Close homologue of L1 (*Ch11*) is involved in synapse maintenance, via influences on presynaptic organization (85, 86). *Ch11* is expressed on the presynaptic membrane of excitatory and inhibitory neurons throughout the brain and is also expressed by some glia

(78, 80, 86). Its intracellular binding partners include heat shock cognate 71 kDa protein (Hsc70), synaptosomal nerve-associated protein 25, vesicle-associated membrane protein (VAMP/synaptobrevin), and cysteine string protein, while extracellular interactions with integrins have also been reported (82, 85, 86). Knockout of *Ch11* led to a decrease in social affiliation (87).

Synaptic cell adhesion molecule 1 (SynCAM1; a.k.a. Cell Adhesion Molecule 1 [Cadm1]) is involved in the processes of synapse formation pre- and postsynaptically and maintenance via heterophilic transsynaptic binding, as well as in the recruitment of NMDA receptors to the postsynaptic membrane via binding to intracellular effector molecules (76, 77, 79, 81). SynCAM1 is present on both presynaptic and postsynaptic sides of excitatory and inhibitory synapses throughout the brain (76, 83). It is involved in homophilic as well as heterophilic binding with other members of the SynCAM family (specifically with SynCAM2), and also interacts with CASK and syntenin (76, 77). Knockout of the *Cadm1* gene (which encodes SynCAM1) led to a decrease in social affiliation (84).

Neural growth regulator 1 (NEGR1, a.k.a. Kilon/IGLON4) is a glycosylphosphatidylinositol (GPI)-linked member of the IgLON family, a subfamily of the IgSF, and is involved in the regulation of synapses, largely active in axons, growth cones, and presynaptic terminals early in development and in spines later in development (88). *Negr1* is expressed in multiple regions throughout the brain and binds both homophilically and to heterophilic ligand opioid-binding cell adhesion molecule (OBCAM) (89, 90). It is found on the presynaptic membrane early in development and on the postsynaptic membrane later in development (88). Both knockdown and knockout of *Negr1* have been reported to result in reduced social affiliation (91-93). These behavioral changes have been accompanied by decreases in spine density, number of parvalbumin-positive interneurons, neurogenesis, and axon growth in the hippocampus (91-93).

Given the vast number of IgSF sCAMs, there is much more work to be done in testing their relationship to social affiliation. However, current data on the select genes that have been tested (*Ch11*, *Cadm1*, *Negr1*) suggest important roles for members of this family in the regulation of social affiliative behaviors. Work with *Negr1*, in particular, indicates that spine and synapse formation in the hippocampus is likely involved in behavioral alterations (91-93).

Leucine-rich repeat (LRR) proteins

Leucine-rich repeat (LRR) proteins are defined by LRR domains, comprised of an α - β horseshoe fold, and are known for their role in protein interaction and cell adhesion. Many members of this structurally-defined family have been identified as sCAMs. LRR proteins have been implicated in synapse formation, maturation, maintenance, and plasticity (94, 95). Only a few members of the LRR family have been assessed for effects on social affiliation: netrin-G ligand 2 (NGL-2), synaptic adhesion like molecule (SALM1), and LRR transmembrane neuronal 1 (LRRTM1).

NGL-2 (*Lrrc4*) is implicated in postsynaptic organization and in synapse formation, differentiation, and maintenance, brain-specific, and expressed in several regions including the cerebellum, cerebral cortex, occipital lobe, frontal lobe, temporal lobe, and putamen, with localization specifically to the postsynaptic side of excitatory synapses (96). NGL-2 binds trans-synaptically to netrin-G2 and intracellularly to PSD-95 and is involved in the recruitment of NMDA receptors (97). Knockout of *Lrrc4* led to a decrease in social affiliation, with knockouts demonstrating decreased frequency and amplitude of mEPSCs, AMPAR- and NMDAR-related synaptic activity, and long term potentiation in the hippocampus (98). Treatment of the mice with an NMDAR-agonist, D-cycloserine, recovered social affiliative behavior (98), similar to findings for *Pcdh10* haploinsufficient mice noted above (78).

SALM1 (*Lrfn2*) has been implicated in synapse development and differentiation, along with recruitment of NMDA receptors (99, 100). It is found on the postsynaptic side of excitatory synapses throughout the brain and binds intracellularly to scaffolding proteins PSD95, SAP97, and SAP102 (99, 100). Knockout of *Lrfn2* led to a decrease and to no change in social affiliation in separate studies (101, 102). The decrease in social investigation and interaction in the *Lrfn2* mutant mice was paired with fewer, more irregular dendritic spines, decreased mEPSC frequency, and an increase in silent synapses in the hippocampus (102).

Finally, LRRTM1 (*Lrrtm1*) resides on the postsynaptic side of excitatory synapses throughout the brain, binds trans-synaptically to α - and β -neurexins, and is a neurexin ligand involved in both pre- and postsynaptic differentiation (103-105). However, knockout of *Lrrtm1* reportedly had no effect on social affiliation (106). From this subsample of LRR proteins, NGL-2 and SALM1 have been implicated in social affiliation, perhaps in part through changes in glutamatergic transmission in the hippocampus, although region-specific knockout and rescue will be needed to test the role of specific circuits.

sCAM-associated scaffolding proteins

Due to limitations in space, the sCAM-associated scaffolding proteins, including the Shank family, are discussed in detail in the Supplemental Information.

Proposed mechanistic model

We propose that sCAMs affect social affiliation behavior via one or more of the following mechanisms: altered specificity during synaptogenesis, disrupted synaptic maturation, and/or altered synaptic pruning. According to our model, the net effect of these mechanisms is alteration in excitatory / inhibitory balance in circuits relevant to social affiliative behaviors (circuits including mPFC, BLA, VTA, ACC, and hippocampus; see Figure 1).

With a single exception (noted below), the following evidence for disrupted synaptic specificity, maturation, and pruning was accompanied by a decrease in social affiliation. Evidence of altered synaptic specificity includes abnormal axon projections, which is seen in the hippocampus of a *Negr1* model (91), and abnormal dendritic arborization, which is seen in the ACC and in the striatum of *Shank3* models (107, 108). Evidence of disrupted synaptic maturation includes abnormal active zones, vesicle pools, neurotransmitter receptor density,

PSD scaffold, synaptic strength, and spine morphology. Abnormal vesicle pools were seen in a transgenic overexpression model of *Nlgn2* (48). Stabilization of actin was able to rescue social affiliation deficits and accompanying decreased NMDAR transmission in a *Shank3* model, suggesting that compromised actin in PSD scaffolding contributed to the decrease in social affiliation (109). Immature spine morphology was seen with haploinsufficiency of *Pcdh10* in the BLA (72), *Lrfrn2* in the Hip (102), and *Shank3* in the ACC (107). A higher number of mature excitatory synapses was demonstrated in the hippocampus in a *Lrfrn2* model (102).

Evidence of altered synaptic pruning includes altered microglial function, altered arbor maturation, and abnormal density of circuit constructs. Change in density of circuit constructs is seen in *Nlgn2* models. Specifically, overexpression of *Nlgn2* during early development led to a decrease in the ratio of asymmetric to symmetric synapses, and mPFC-specific knockout of *Nlgn2* led to decrease in GAD65-positive synapse density (46, 48). Change in spine density / number, which could indicate either altered synaptic maturation or synaptic pruning, was seen in *Pcdh10* (72), *Negr1* (93), *Lrfrn2* (102), *Shank2* (110), *Shank3* (107, 108, 111), *Magi2* (S-SCAM) (112), and *Dlgap2* (PSD-95) (113) models. The *Pcdh10* model is unique among the other studies in demonstrating an increase in spine density in the BLA (though the spines are also more immature and as such are likely less functional) (72). Models of *Negr1*, *Shank2*, and *Magi2* demonstrated a decrease of spine density / number in the hippocampus (93, 110, 112). There was also a decrease in spine density in the somatosensory and visual cortex in a *Lrfrn2* model and in the OFC/mPFC in a *Dlgap2* model (though in this case, there was an increase, not a decrease, in social affiliation) (102, 113). *Shank 3* models showed a decrease in spine density in the ACC and striatum (107, 108).

Alterations in E/I balance has been a prominent hypothesis for the neurobiology of autism for decades (114, 115), however mechanisms by which alterations in ASD genes might lead to these E/I imbalances in specific circuits, which in turn leads to behavioral phenotypes, remain largely unclear. Moreover, there appears to be heterogeneity of such imbalances (some evidence for excess of excitation, and some for excess of inhibition) and their interpretation (116-118), which may be related to the large number of genes involved in varying pathways in ASD. While there is mixed evidence cited above, the majority of the studies we reviewed point to a decrease in excitation in relation to inhibition, leading to decreased social affiliation. Several studies demonstrate decreased excitatory transmission, including *Nrxn2* in the somatosensory cortex (29), *Lrrc4* in the hippocampus (98), *Shank2* in the hippocampus (110, 119), and *Shank3* in the striatum, ACC, VTA, and striatum (60, 107, 108, 111). In a *Shank3* model, the pattern of E/I depended on region, with decreased excitation and increased inhibition in the hippocampus and decreased inhibition in the mPFC (120). Additionally, two studies demonstrated a decrease in inhibition, specifically in the mPFC in an mPFC-specific knockout of *Nlgn2* (46) and in the hippocampus in a global knockout of *Negr1* (92). More specific than general E/I balance, several studies across models and regions demonstrated impaired glutamatergic transmission. Impaired glutamatergic transmission was seen in *Nrxn2* model in somatosensory cortex (29), in *Lrrc4* in the hippocampus (98), *Shank2* in the Hip (121, 122), and *Shank3* in the striatum, hippocampus, and PFC (123-126). Interestingly, an age-effect was found in *Shank2* mice such that there was an increase in glutamatergic transmission in the hippocampus at P14 and

a decrease at P24 (127). These findings in sum point to a general pattern of decreased excitation and glutamatergic transmission associated with decreased social affiliation, though there is variation related to model, age, and region tested that should be further explored.

In terms of defining the social affiliation circuit that may be affected by sCAMs, this review finds strong evidence implicating several brain regions, including the mPFC, BLA, striatum, ACC, and hippocampus. Accompanying decreased social affiliation, in the hippocampus there has been evidence of altered synaptic specificity in *Negr1* models (91), altered synaptic maturation in *Lrhn2* models (102), and finally changes in spine density / number that could indicate either altered synaptic maturation or pruning in *Lrhn2*, *Shank2*, *Shank3*, and *Magi2* models (102, 110, 112, 128). There is altered synaptic specificity, synaptic maturation, and decreased spine density in *Shank3* models in the ACC (107, 108). Also in *Shank3* mice, altered synaptic specificity and change in spine density were found in the striatum (108, 111). There is evidence of altered synapse maturation based on a increase in spine density and in immature spines in the BLA of *Pcdh10* haploinsufficient mice (72). Additionally, conditional regional knockdowns and knockouts of sCAMs decreased social affiliation, including conditional knockdowns / knockouts of *Shank3*, *Nlgn2*, and *Nlgn3* in the VTA, ACC, and mPFC (46, 60, 107, 129).

Discussion

The overall patterns that we observe in the literature suggest that mutation / dysfunction of sCAM genes alters synaptic maturation, specificity, and pruning and leads to E / I imbalance in several relevant brain regions, including mPFC, BLA, VTA, and hippocampus. Moving forward, study of sCAM gene knockouts on additional genetic backgrounds, more comprehensive studies of mutations in the various sCAMs, and the use of larger sample sizes will help to advance the knowledge base further. Additionally, many of the experiments currently being conducted use global knockouts; while this is a useful starting point, region- and cell-type specific knockouts as well as conditional knockouts at specific developmental time points are needed to provide meaningful information on the role of sCAMs in specific parts of social motivation / approach circuitry across development. Proteomic studies focused on sCAMs of different regions during social affiliation behavior could also provide insight into the circuitry underlying the behavior. Other important areas of future investigation include mechanisms of rescue and whether restoration of function at certain developmental time points or in specific parts of neural circuitry are sufficient to rescue social affiliation overall.

There are also still fundamental gaps in our knowledge base on sCAMs. For some sCAMs, key pieces of basic information (i.e. binding partners, localization within the brain, or localization within the synapse) are still lacking. Advancing our understanding of how each sCAM interacts with glutamatergic receptors and affects spine density, number, and morphology promises to provide greater insight into the mechanisms underlying social affiliation. An additional challenge is studying the role in social affiliation of the many sCAM protein isoforms, with differing binding strengths and specificities, as well as the role of specific binding domains in each protein. By addressing these gaps in future studies, we,

as a field, can gain greater insight into synaptic and circuit mechanisms of social affiliation, its disruption in neurodevelopmental and neuropsychiatric disorders, and potential targets for rescue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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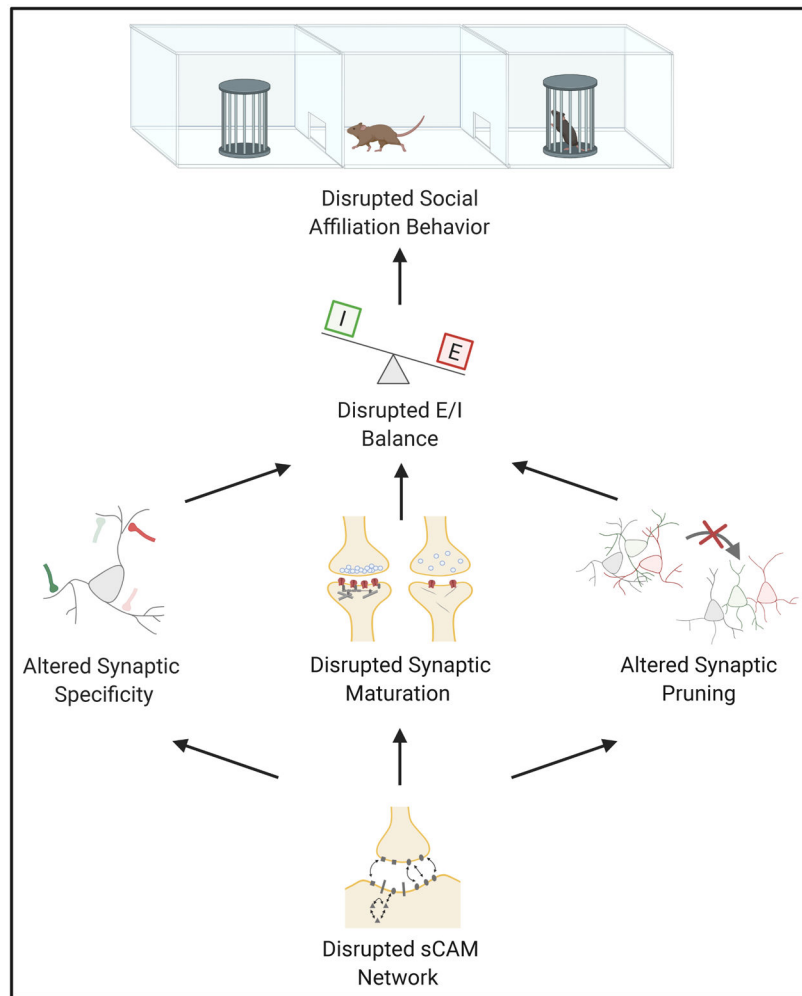


Figure 1. Proposed mechanistic model for the role of sCAMs in social affiliative behaviors. This figure shows our proposed model for how disruption of sCAMs could lead to disrupted social affiliation, namely through altered synaptic specificity, synaptic pruning, and/or synaptic maturation that disrupts the E/I balance of the circuit.

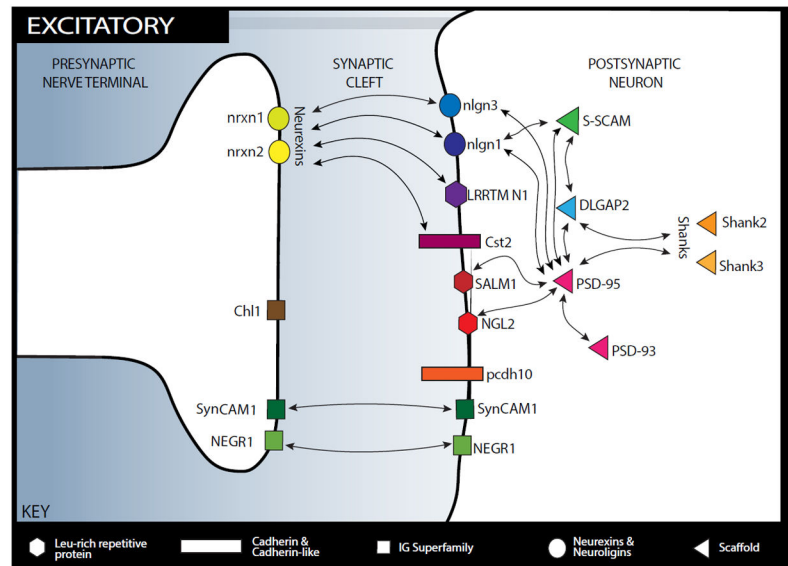


Figure 2. sCAM interaction network in the excitatory synapse.

This figure shows the location of sCAMs discussed in the review within the excitatory synapse as well as their binding partners.

Calsyntenin-2 (Cst2) is a member of the cadherin superfamily and resides on the postsynaptic side of both inhibitory and excitatory synapses.

Cell adhesion molecule L-1 like (Chl1), a member of the immunoglobulin superfamily, resides on the presynaptic membrane and is involved in heterophilic binding, though its specific binding partners are unknown.

Disk large associated protein 2 (DLGAP2) is primarily expressed in the postsynaptic side of excitatory synapses, binds DLG and Shank proteins, and may have a role in enrichment of PSD-95 at the plasma membrane.

Leucine rich repeat transmembrane neuronal 1 (LRRTM N1) resides on the postsynaptic side of excitatory synapses and binds trans-synaptically to neurexins.

Netrin-G ligand 2 (nlg-2) is a member of the leucine rich repeat protein, exists on the postsynaptic side of excitatory synapses, and binds to both netrin-G 2 and PSD-95.

Neural growth regulator 1 (NEGR1) is a member of the immunoglobulin superfamily and its location on pre- and postsynaptic membranes is dependent on development.

The **neurexin** family (shown here are **nrxn1** and **nrxn2**) are predominantly presynaptic organizers of the synapse with thousands of isoforms and multiple binding partners.

Neuroigin 1 (nlg1) resides on the postsynaptic side of excitatory synapses and binds with neurexins and the scaffolding proteins PSD-95 and S-SCAM.

Neuroigin 3 (nlg3) is on the postsynaptic side of both excitatory and inhibitory synapses and binds trans-synaptically to neurexins.

Postsynaptic density protein 93 (PSD-93) is expressed in postsynaptic neurons in excitatory and inhibitory synapses synapse and serves as a scaffolding protein, binding PSD-95, K⁺ channels, and NMDA receptors.

Postsynaptic density protein 95 (PSD-95) is expressed in postsynaptic neurons in excitatory synapse and serves as a scaffolding protein, binding many other SCAMs in addition to NMDAR.

Protocadherin 10 (pcdh10), a cadherin-like protein, is a postsynaptic protein that engages in both homophilic and heterophilic binding.

The **Shank** family (shown here, **Shank2** and **Shank3**) are scaffolding proteins in postsynaptic neurons of excitatory synapses and bind to many synapse proteins as well as glutamatergic receptors directly and indirectly.

Synaptic adhesion like molecule (SALM1) is a postsynaptic molecule in the leucine rich repeat protein family that exists both in excitatory and inhibitory synapses and binds PSD-95.

Synaptic cell adhesion molecule 1 (SynCAM1), a member of the immunoglobulin superfamily, is present on both the pre- and postsynaptic sides and is involved in homophilic as well as heterophilic binding.

Synaptic scaffolding molecule (S-SCAM) resides in the postsynaptic neuron in excitatory and inhibitory synapses and connects to glutamatergic receptors (NMDAR and AMPAR) as well as other synaptic proteins.

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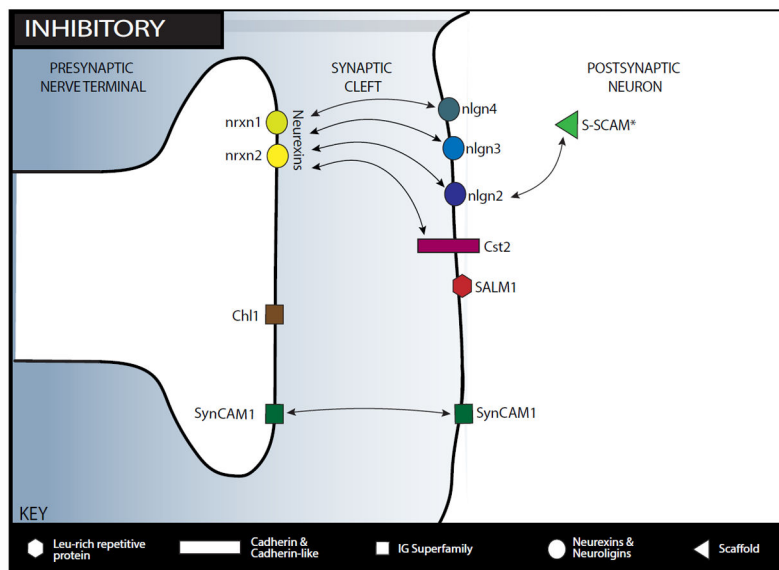


Figure 3. sCAM interaction network in the inhibitory synapse.

This figure shows the location of sCAMs discussed in the review within the inhibitory synapse as well as their binding partners. The following sCAMs are shown:

Calsyntenin-2 (Cst2) is a member of the cadherin superfamily and resides on the postsynaptic side of both inhibitory and excitatory synapses.

Cell adhesion molecule L-1 like (Chl1), a member of the immunoglobulin superfamily, resides on the presynaptic membrane and is involved in heterophilic binding, though its specific binding partners are unknown.

The **neurexin** family (shown here are **nrxn1** and **nrxn2**) are predominantly presynaptic organizers of the synapse with thousands of isoforms and multiple binding partners.

Neuroigin 2 (nlgn2) is on the postsynaptic side of inhibitory synapses and binds with neurexins as well as the scaffolding protein, S-SCAM.

Neuroigin 3 (nlgn3) is on the postsynaptic side of both excitatory and inhibitory synapses and binds trans-synaptically to neurexins.

Neuroigin 4 (nlgn4) is on the postsynaptic side of inhibitory synapses and binds trans-synaptically to neurexins.

Synaptic adhesion like molecule (SALM1) is a postsynaptic molecule in the leucine rich repeat protein family that is present in both excitatory and inhibitory synapses.

Synaptic cell adhesion molecule 1 (SynCAM1), a member of the immunoglobulin superfamily, is present on both the pre- and postsynaptic sides and is involved in homophilic as well as heterophilic binding.

Synaptic scaffolding molecule (S-SCAM) is a scaffolding protein in the postsynaptic neuron in excitatory and inhibitory synapses and interacts with select glutamatergic receptors (NMDAR and AMPAR) as well as other synaptic proteins.