The Hippocampus and Social Impairment in Psychiatric Disorders

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Social deficits, such as poor social skills (i.e., the inability to engage in appropriate and effective social interactions) and social withdrawal, are prevalent across psychiatric disorders and often co-occur with hippocampal structural and functional abnormalities. The centrality of both social and hippocampal dysfunction in psychiatric research prompts the question: Are they linked? The social cognitive map framework provides a clue: The hippocampus tracks social information in the physical environment, maps others along social dimensions, and supports social memory and decision-making. Hippocampal dysfunction might disrupt social map representation and contribute to commonly seen social behavioral symptoms. This review summarizes evidence for the role of the hippocampus in social cognitive mapping, followed by evidence that hippocampal dysfunction and social dysfunction co-occur in psychiatric disorders. We argue that the co-occurrence of hippocampal and social impairment may be related via hippocampal social cognitive mapping.

Functions ascribed to the hippocampal formation, such as spatial representation and episodic memory, can be explained by a more general function: cognitive mapping (i.e., relational modeling; Tolman 1948; O’Keefe and Nadel 1978; Schiller et al. 2015). Map-like information is encoded by a wide variety of cell types in the hippocampal formation (i.e., dentate gyrus, hippocampal CA subfields, subicular complex, entorhinal cortex). In the spatial domain, pyramidal neurons in the hippocampal formation encode current location (“place cells”; O’Keefe and Nadel 1978) periodically fire to “tile” the environment (“grid cells”; Hafting et al. 2005) and give distance and direction information to landmarks (Deshmukh and Knierim 2013), boundaries (Solstad et al. 2008), objects (Høydal et al. 2018), and goals (Sarel et al. 2017)—all functions consistent with spatial mapping. The hippocampal formation also encodes head direction (Sargolini et al. 2006), speed (Kroppf et al. 2015), and routes (Javadi et al. 2017), and individual cells can alter their firing properties on the basis of the current behavioral goal (Wood et al. 2000).

Episodic information is organized in a similar manner as physical space. The hippocampus encodes a “memory space” by binding elements of experience (Eichenbaum 2014). For example, the hippocampus encodes conjunctive information, such as the combination of particular places and items (Komorowski et al. 2009), tracks temporal context (“time cells”; MacDonald et al. 2011), and links events across time (Davachi and DuBrow 2015). This form of mapping extends beyond the spatial and episodic domains and reflects a general relational process: Sensory (Teki et al. 2012; Julian et al. 2018), abstract (reward; Gauthier and Tank 2018), and even conceptual (Quian Quiroga et al. 2009; Constantinescu et al. 2016) information with similar statistical structure (e.g., the same number of dimensions) is encoded similarly by the hippocampal formation and often by the same cells that map the spatial environment.

The literature suggests an emerging view: The hippocampal formation extracts and organizes behaviorally relevant information about the current space (e.g., physical space, task space) into a relational format (Behrens et al. 2018; Bellmund et al. 2018; Schafer and Schiller 2018). In other words, the hippocampal formation models the underlying statistical regularities of experience, binding informational elements into maps of arbitrary scale (e.g., from specific to general) and abstraction (i.e., information not reducible to immediate sensory perception, such as reward).

Cell types in the hippocampal formation could be considered basis functions, whose flexible reweighting allows for a wide range of relational structures to be encoded and stored in a map-like format (Behrens et al. 2018). Map retrieval may occur via pattern completion, whereby partial, noisy inputs are “completed” into stored representations by spreading ensemble activation: The network of neurons activated at encoding reactivates and stabilizes upon partial activation due to intrahippocampal recurrent excitation (Gold and Kesner 2005; Okamoto and Ikegaya 2018). Maps should be encoded and stored in a nonoverlapping fashion, so as to not interfere with each other when retrieved (i.e., pattern separation; Yassa and Stark 2011)—with hippocampal remapping possibly reducing interference between related representations (Colgin et al. 2008).

Generalizing from stored maps could constrain representations of the current space and generate predictions...
of future states (e.g., available trajectories and possible outcome values) through map-based simulations—crucially reducing the computational cost of predicting real-world outcomes where the possibilities are practically unlimited. Cognitive maps may be fundamentally predictive, with map elements representing predictions of future states that can be integrated with other predictions (e.g., reward) to compute values (Stachenfeld et al. 2017). Alternatively, maps may be used as inputs in decision-making processes (Miller et al. 2018) by providing the model for simulations and predictions about relationships between stimuli (Hindy et al. 2016), even stimuli that were never directly experienced together (i.e., inferences). For example, in familiar spaces, place cell sequences can reactivate to simulate spatial trajectories to rewards (Singer and Frank 2009), even for entirely novel trajectories (Ólafsdóttir et al. 2015).

In spaces with unfamiliar statistical structure, relational elements of stored maps are retrieved and reconfigured into novel sequences to represent possible maps and trajectories (Bellmund et al. 2018), perhaps guided by prediction error–related plasticity. Such reconfiguration may even allow the construction of entirely imagined episodes (Schacter et al. 2012). Ultimately, cognitive mapping is about goal pursuit: Relational models are a flexible substrate to predict information about current and future spaces and engage in goal-directed behavior to maximize reward and minimize threat (Behrens et al. 2018; Bellmund et al. 2018; Schafer and Schiller 2018).

**MAPPING SOCIAL SPACE**

Understanding social relationships, contexts, and dimensions (e.g., hierarchy), and inferring the likely mental states and actions of others, are all important for humans to successfully navigate ambiguous, often changing social environments to maximize social reward and minimize social threat. Social information varies continuously along dimensions, suggesting that, much like the hippocampus does for other domains, the hippocampus may organize social information into maps to guide social decision-making (“social navigation”; Tavares et al. 2015; Montagrin et al. 2018; Schafer and Schiller 2018). For example, social dimensions of power and affiliation impact social relationships in rodents (Insel and Fernald 2004), nonhuman primates (Brent et al. 2013), and humans (Todorov et al. 2008; Fiske 2012). The hippocampus is important in both dimensions, such as in representing and updating social hierarchies (Kumaran et al. 2012, 2016) and in affiliative behaviors (Machado and Bachevalier 2006).

The dimensions of power and affiliation are computed jointly by the hippocampus (along with other regions; e.g., dorsolateral prefrontal cortex, inferior parietal lobule, precuneus/posterior cingulate cortex) as a two-dimensional social coordinate space (Tavares et al. 2015). Specifically, in a role-playing game where participants interact with characters during functional magnetic resonance imaging (fMRI), hippocampal signal correlated with social interaction decisions along power and affiliation dimensions. Characters were plotted in this two-dimensional social space relative to the participants’ point of view. As information from interactions accumulated, hippocampus activity correlated with vector angles from participant to characters in social space, tracking the relative power and affiliation of each character across time. In other words, the hippocampus tracked social trajectories. The magnitude of this hippocampal effect correlated with self-reported social skills, suggesting that social mapping is important to social behavior (Tavares et al. 2015). Indeed, hippocampal-dependent memory predicts social network size in healthy adults (Stiller and Dunbar 2007), whereas hippocampus damage impairs social memory (Sanders and Warrington 1971) and leads to smaller social networks (Davidson et al. 2012).

Maps represent relationships between elements, without explicitly encoding the elements themselves. For example, hippocampus activity relates to faces associated with biographical or behavioral information (Todorov et al. 2007) and faces that are famous or personally known (Trinkler et al. 2009), but not faces unassociated with other social information (Bird et al. 2007; Aly et al. 2010). Additionally, maps represent information abstracted away from sensory details, suggesting social cognitive maps about a specific individual could be activated by different sensory cue types (e.g., a person’s name or a photo of their face). Indeed, hippocampal neurons that preferentially activate to familiar faces relative to other visual stimuli (Kreiman et al. 2000) can also respond invariantly to the same individual across sensory modalities (Quian Quiroga et al. 2009), suggesting they store a conceptual representation of specific individuals. The hippocampus appears therefore crucial to social memory that relates the conceptual representation of an individual to other stored social information (e.g., prior interactions, behavioral tendencies, etc.). For example, the hippocampus may stabilize character judgments by relating current behavior to past behavior (Croft et al. 2010).

As in other forms of mapping, social cognitive maps could allow the simulation and prediction of social information—such as what thoughts and behaviors someone is likely to engage in, and outcomes of social reward and threat. In addition to maps related to others, self-related hippocampal maps (e.g., representing one’s own experiences, behavioral tendencies) could also be generalized to constrain the computational expense of social prediction and decision-making. Indeed, self-related hippocampal memory may inform inferences about others’ mental states (i.e., mentalizing) during events, especially when an individual has perceived the other person as similar and has experienced a similar event (Perry et al. 2011).

Mapping could also extend to relationships in social contexts themselves: The hippocampus encodes information both within and across contexts (Davachi and DuBrow 2015), a function that could extend to the social domain to enable accurate predictions in diverse social situations. Normative social behavior is contextual; accurate action selection depends on organizing a broad range of social information—the current place (e.g., a sporting event vs. work), the persons involved (e.g., family vs.
strangers), and their likely moods (e.g., disappointment after a team’s loss vs. excitement after a win). Social cognitive mapping may provide the substrate to make these predictions and engage in subtle, situation appropriate social behavior.

**NEURAL MECHANISMS OF SOCIAL MAPPING**

Social mapping functions may encode information similarly to more basic forms of mapping (e.g., spatial). Hippocampal subregions dorsal CA2 (dCA2; posterior in humans) and ventral CA1 (vCA1; anterior in humans) are especially important to social recognition (Hitti and Siegelbaum 2014; Smith et al. 2016; Meira et al. 2018), and both subfields contain place cells that encode social information (Alexander et al. 2016; Danjo et al. 2018; Omer et al. 2018), suggesting place cell activity could partially underlie social recognition. CA2 and CA1 also have densely distributed oxytocin and vasopressin receptors, which are neuropeptides important in many social and bonding behaviors and are mediators in CA2’s role in social recognition (Smith et al. 2016; Lin et al. 2017). Oxytocin in particular tunes CA2 to CA1 information processing: Oxytocin receptor binding enhances information transfer from CA2 to CA1 (Tirko et al. 2018) and increases the signal-to-noise ratio in CA1 by modulating CA1 inhibitory interneurons (Owen et al. 2013).

Given the connectivity of dCA2 and vCA1, their relative social specialization, and that CA2 is unnecessary for spatial memory (Hitti and Siegelbaum 2014), dCA2–vCA1 circuitry may be specialized to perform social computations (Bienkowski et al. 2018; Meira et al. 2018). Recent work suggests that dCA2 pyramidal neurons, which are necessary for social recognition encoding, consolidation, and retrieval, send excitatory projections to vCA1 pyramidal neurons that are also necessary for social recognition (Meira et al. 2018). Thus, dCA2 could act as a social information processing hub, regulated by the binding of oxytocin and vasopressin receptors, that modulates excitatory drive onto vCA1 in social information processing.

There may also be specialized ventral CA3 (vCA3) to vCA1 circuitry that contributes to social recognition. Ventral, but not dorsal, CA3 is necessary for encoding social recognition memory (Chiang et al. 2018). Given little evidence for a functional relationship between vCA3 and dCA2, projections from vCA3 and dCA2 may form distinct pathways and integrate in vCA1 (Meira et al. 2018). vCA3 and dCA2 may also provide different types of social information: vCA3 is unnecessary for social memory recall, for example, suggesting dCA2–vCA1 might underpin vCA1’s role in social memory retrieval. Thus, multiple specialized circuits in the hippocampus likely contribute to social relational modeling.

Circuits within the hippocampus do not act alone: The hippocampus is central within a wider network for social mapping and map-based decision-making. For example, inputs from amygdala to vCA1 affect social interaction (Felix-Ortiz and Tye 2014), perhaps by contributing information about the salience or behavioral relevance of incoming social information. Projections from vCA1 pyramidal neurons to nucleus accumbens shell are necessary for social recognition (Okuyama et al. 2016), and plasticity in this pathway modulates social reward and affiliation (Walum and Young 2018). Projections from vCA1 to medial prefrontal cortex (mPFC) are also necessary for social recognition and likely reflect social memory retrieval (Phillips et al. 2018), in agreement with a proposed role for mPFC in retrieving hippocampal representations to guide decision-making (Kaplan et al. 2017). Indeed, mPFC to dorsal periaqueductal gray circuitry directly modulates social behaviors (Franklin et al. 2017). mPFC activity also impacts the activity of the amygdala and nucleus accumbens (Öngür and Price 2000), suggesting it could regulate interactions between these regions and the hippocampus in social mapping. Network-wide distribution of oxytocin receptors is evident as well. In addition to the hippocampus, oxytocin receptors are dense in the amygdala, nucleus accumbens, and mPFC (Huber et al. 2005; Smeltzer et al. 2006; Ross et al. 2009).

**SOCIAL NAVIGATION**

Social behavior may be understood as an act of social navigation based upon social maps. Social information is complex and ambiguous; social maps may allow for the prediction of subsequent social information—constraining the computational complexity of social inferences and decision-making. Relational organization could underpin relational social memory, and enable simulations and predictions about others’ mental states and likely actions, as well as outcomes such as social reward or social threat—in turn supporting decision-making, such as whether to engage in affiliative or social avoidance behaviors. Inaccurate maps would lead to poor or erroneous organization of social information, poor social predictions, and ultimately maladaptive social behavior. The co-occurrence of hippocampal and social dysfunction in psychiatric disorders may reflect the disruption of relational social information processing (e.g., social memory, social context, relative power, and affiliation).

As mentioned above, Tavares et al. (2015) found that hippocampal tracking of a power by affiliation social space correlated with self-reported social anxiety, suggesting that the integrity of social space mapping could relate to psychiatric symptoms. Considering others as “locations” and relationships as “trajectories” in social space offers a powerful framework to explain and make novel predictions about social dysfunction. In the text to follow, insights into the link between social dysfunction and hippocampal structure and function in four disorders (schizophrenia, autism spectrum disorder [ASD], major depressive disorder [MDD], and social anxiety disorder [SAD]) will be discussed. For each disorder, we present evidence for co-occurring social and hippocampal dysfunction, evidence directly connecting the hippocampus to social dysfunction (Table 1), and the potential explanatory power of the social mapping framework.
**Table 1. Summary of evidence for social dysfunction, hippocampal abnormalities, and work connecting social dysfunction with hippocampal abnormalities in psychiatric disorders**

| Disorder | Social dysfunction | Hippocampal abnormalities | Social hippocampus links |
|----------|--------------------|----------------------------|--------------------------|
| SCZ      | Social withdrawal  | Smaller volume             | Negative symptoms (incl. social withdrawal) |
|          | Fewer relationships| Reduced CA3 dendritic spine density | Inversely correlated with hippocampal volume |
|          | Impaired emotion recognition | Fewer GABAergic interneurons (esp. in CA2) | Hippocampus activity related to emotion recognition deficits |
|          | Impaired mentalizing | White matter tract impairments in fornix (major output of hippocampus) | Mouse model: reduced CA2 inhibitory interneurons, hyperactive pyramidal neurons, social memory impairments |
|          | Failure to update social reward expectancies | Hippocampal hyperactivity | Mouse model: vCA1 to mPFC alterations in mouse model correlated with social memory deficits |
|          | Social ambiguity interpreted as social threat | Hippocampal functional network disturbances | Mouse model: CA1–mPFC plasticity is reduced, long-term social recognition is impaired; deficits are improved with oxytocin treatment |
| ASD      | Social isolation   | Larger volume              | Metabolic alterations correlated with social impairment |
|          | Impaired emotion recognition | Reduced hippocampal dendritic branching | White matter alterations between hippocampus and mid-fusiform (face processing tract) |
|          | Impaired mentalizing | Reduced GABA receptor density in CA1, CA2, prosubiculum, and subiculum | Mouse model: vCA1 to mPFC alterations in mouse model correlated with social memory deficits |
|          | Using social context to understand nonliteral language | Increased GABAergic interneuronal cell packing in dentate gyrus, CA1, CA3 | Mouse model: CA1–mPFC plasticity is reduced, long-term social recognition is impaired; deficits are improved with oxytocin treatment |
|          | Impaired social memory | Reduced covariation between hippocampus and PFC in episodic memory | Mouse model: hippocampus to nucleus accumbens projections mediated chronic social stress and social withdrawal |
| MDD      | Poor social decision-making | Smaller volume             | Hippocampal activation during social rejection |
|          | Poor social skills | Decreased soma size         | Treatment normalized hippocampal activation to emotional faces |
|          | Less social interaction | Densely packed cells        | Mouse model: hippocampus to nucleus accumbens projections mediated chronic social stress and social withdrawal |
|          | Sense of not belonging | Hippocampal functional network disturbances | Mouse model: hippocampus to nucleus accumbens projections mediated chronic social stress and social withdrawal |
|          | Perceive hostility in relationships | Hippocampal activity correlates with episodic memory and spatial navigation deficits | Mouse model: hippocampus to nucleus accumbens projections mediated chronic social stress and social withdrawal |
|          | Restricted social networks | | |
|          | Impaired emotion recognition | | |
|          | Impaired mentalizing | | |
| SAD      | Fear of social situations | Volume alterations (inconclusive evidence) | |
|          | Fear of evaluation and embarrassment | Hippocampal hyperactivation related to: |
|          | Difficulty maintaining relationships | negative associations with neutral faces | |
|          | Impaired emotion recognition | harsh facial stimuli | |
|          | Impaired mentalizing | preparation for public speaking | |
|          | | mentalizing | |
|          | | emotion recognition (entorhinal and parahippocampal) | |
|          | | Treatment reduces both social anxiety and hippocampal activity to social anxiety—inducing tasks | |
|          | | Posttreatment changes in hippocampal activity correlate with reductions in social anxiety | |

Citations are in text. This table is not meant to be exhaustive—rather it summarizes some of the evidence for co-occurrence of social and hippocampal alterations in psychiatric disorders and suggests a link between them may be based in social cognitive map-related mechanisms.

(SZC) Schizophrenia; (ASD) autism spectrum disorder; (MDD) major depressive disorder; (SAD) social anxiety disorder.

**SCHIZOPHRENIA**

**Social Dysfunction**

Social impairments are core to schizophrenia. They precede onset, predict disease severity (Green et al. 2015), and lead to social withdrawal, including fewer relationships and a low marriage rate (Thara and Srinivasan 1997; Harley et al. 2012). Although some social impairments in schizophrenia may result from nonsocial sources (e.g., psychotic symptoms), specifically social dysfunctions are likely key to social impairments as well: Social cognitive factors explain a unique amount of variance in social skills (Pinkham and Penn 2006). For example, social inferences such as emotion recognition and mentalizing (i.e., inferring others’ mental states; Bora and Pantelis 2013) are deficient in schizophrenia, occur across sensory modalities (Leitman et al. 2010; Chung et al. 2014), and correlate with real-world social functioning (Brüne 2005; Fett et al. 2011). Additionally, emotion recognition and mentalizing deficits present early and are stable over time, sometimes persisting after treatment, and exist to a lesser extent in unaffected relatives (Bediou et al. 2007; Penn et al. 2008; Bora and Pantelis 2013), suggesting that social dysfunction may be a risk factor for schizophrenia.

**Hippocampal Abnormalities**

Hippocampal abnormalities are also central to schizophrenia (Tamminga et al. 2010; Lodge and Grace 2011). Hippocampal volume is consistently smaller in schizophrenia (Adriano et al. 2012) along with cellular changes, such as reduced CA3 dendritic spine density (Kolomeets et al. 2013). Hippocampal hyperactivity and reduced volume are associated with social impairments, and studies using oxytocin treatment (Bora and Pantelis 2013) have shown that reducing social anxiety reduces hippocampal activity and improves impairments. This suggests that social dysfunction may be a risk factor for schizophrenia.
Evidence Connecting the Hippocampus to Social Dysfunction

Although psychotic symptoms are often effectively reduced with dopamine treatment, social withdrawal is largely unaffected (Remington et al. 2016), suggesting social impairments may be explained by hippocampal abnormalities themselves—such as volume loss that is unaltered by dopamine stabilization (Panenka et al. 2007). Consistent with this view, individuals with more prominent negative symptoms (i.e., a range of deficits that include social withdrawal) have smaller hippocampal and parahippocampal volumes (Sigmundsson et al. 2001; Wible et al. 2001; Anderson et al. 2002). Meta-analysis reveals that less hippocampal activity is related to emotion recognition deficits in schizophrenia (Taylor et al. 2012). Further, plasma oxytocin and anterior hippocampus volume are inversely correlated in schizophrenia, and oxytocin levels predict emotion recognition abilities (Goldman et al. 2008). A mouse model of a genetic risk factor for schizophrenia provides more granular evidence: The genetic microdeletion of 22q11.2 severely impacts social recognition, likely because of reduced CA2 parvalbumin interneuron density and inhibitory signaling and neuronal hyperpolarization that effectively silences CA2 pyramidal neurons even under direct stimulation (Piskorowski et al. 2016).

Putative Social Mapping Impairment: Impoverished Maps

Given the evidence for a specific CA2 circuit deficit in schizophrenia, it may be that social relational modeling within the hippocampus itself is impaired: Schizophrenia-related reductions in CA2 inhibitory interneurons hyperpolarize CA2 pyramidal neurons (Piskorowski et al. 2016) and could impair the integration of relational social information into larger relational frameworks. Social information is often ambiguous and continuous, and its efficient use necessitates both extensive relational organization and flexible updating. Individuals with schizophrenia may be impaired in both forming and updating social relational representations—especially as information becomes more abstract (i.e., not reducible to immediate sensory experience), and relational inferences become more complex. Schizophrenia impairments in inferring what others are thinking (i.e., mentalizing) are more pronounced than impairments in inferring what others are doing (Penn et al. 2008) and are related to impairments in using relational information (Uhlhaas et al. 2006). Additionally, schizophrenia impairments in learning and relating information within and across social tasks increase with the complexity of relationships (Penn et al. 2008).

CA2 hyperpolarization combined with aberrant and illusory relational binding in CA3 due to “runaway” pattern completion (Tamminga et al. 2010) could lead to social relational representations and predictions that are both inaccurate and resistant to updating—maps that are impoverished and inflexible. Such relational structures could explain imprecise inferences in schizophrenia: Individuals with schizophrenia report inaccurate interpretations of both social scenes and social faces and tend to view even ambiguous social stimuli as threatening (Phillips et al. 2000).

Social prediction errors also fail to update social expectations: Despite having rewarding social experiences, individuals with schizophrenia do not update expectations for future social reward (Kring and Caponigro 2010), perhaps reflecting an inability to induce plasticity in posterior CA2 to anterior CA1 to nucleus accumbens circuitry (dCA2–vCA1–nucleus accumbens in rodents) and link social maps with reward. Indeed, individuals with schizophrenia show progressively smaller hippocampal and nucleus accumbens volumes over time, relative to controls (Wang et al. 2008). Such impoverished social mapping mechanisms may lead to social rigidity in schizophrenia and help to explain social dysfunction, such as social withdrawal.

AUTISM SPECTRUM DISORDER

Social Dysfunction

ASD prominently features social interaction deficits. Individuals with ASD ineffectively regulate social interactions, show a lack of social reciprocity, and experience social isolation (Baron-Cohen et al. 1985; Dawson et al. 2005; Leekam 2016). Frequently identified social cognitive impairments in ASD are diverse: They include emotion recognition (Harms et al. 2010), mentalizing (Chung et al. 2014), using social context to understand nonliteral language (Krasny et al. 2003), and impairments in social memory for faces and social scenes (Williams et al. 2005).

Hippocampal Abnormalities

Larger hippocampal volumes are often observed in ASD (Schumann et al. 2004; Groen et al. 2010), with hippocampal malformations potentially associated with increased...
seizure risk (Dager et al. 2007), suggesting functional disturbances directly result from ASD hippocampal structural abnormalities. Consistent with increased seizure risk, ASD excitatory–inhibitory balance in the hippocampus may be abnormal. Research shows reduced hippocampal neuronal cell body size and dendritic branching (Raymond et al. 1996) along with subfield specific GABAergic alterations, such as reduced GABA receptor density (Guptill et al. 2007), especially in CA1, CA2, prosubiculum, and subiculum (Blatt et al. 2001), and increased GABAergic interneuronal cell packing in hippocampal subregions dentate gyrus, CA1, and CA3 (Lawrence et al. 2010). Hippocampal abnormalities may have direct cognitive consequences in ASD, such as reduced covariation between the hippocampus and prefrontal regions that relates to memory retrieval failure (Cooper et al. 2017).

Evidence Connecting the Hippocampus to Social Dysfunction

Although relatively little research has directly related the hippocampus to social function in ASD, several indications suggest more work is needed. Individuals with ASD have metabolic abnormalities in the hippocampus that correlate with social impairment (Endo et al. 2007), and white matter tracts are altered between the hippocampus and mid-fusiform gyrus, a pathway important to face processing (Conturo et al. 2008). In a mouse model of ASD, hyperactivity of vCA1 (anterior in humans) to prelimbic mPFC projections relate to impaired social memory (Phillips et al. 2018), suggesting posterior CA2 to anterior CA1 (dCA2–vCA1 in rodents) to mPFC circuitry may be relevant to ASD etiology. Indeed, in another animal model, a synaptic gene (SHANK3) mutation that commonly results in ASD diagnosis reduced synaptic plasticity in a CA1–prelimbic mPFC pathway and selectively impaired long-term social memory—deficits that were reduced with oxytocin administration (Harony-Nicolas et al. 2017).

Putative Social Mapping Impairment: Restricted Mapping

Oxytocin deficiency in ASD could increase neuronal noise in the hippocampus, impair hippocampal processing, and restrict the range of information encoded into maps. Deficient oxytocin binding in the hippocampus could be relevant to ASD, given associations between ASD and the oxytocin receptor gene (LoParo and Waldman 2015), reduced hippocampal oxytocin receptor expression in animal models of ASD (Peñaagarikano 2017), and the efficacy of intranasal oxytocin in improving ASD’s social impairments (Anagnostou et al. 2014). Oxytocinergic impairments in the CA2–CA1 circuit could manifest as impairments in social relational modeling, as well as general impairments in hippocampal mapping, via reduced signal and increased noise in CA1 (Owen et al. 2013).

Modeling is computationally expensive; as the relationships between task elements become more complex, the demands on hippocampal processing might increase (e.g., greater need for spatial and temporal integration of many weak signals): In the case of noisy information processing, background noise may overwhelm signal and statistical mapping processes may break down. Only very robust and regular signals would be reliably encoded, restricting the range of relational structures that can be mapped, stored, and retrieved successfully (e.g., by mPFC) without interference from other maps. Indeed, individuals with ASD have impaired recollection for social stimuli, as well as for other complex stimuli (Williams et al. 2005), and other work shows memory in ASD decreases as a function of task complexity (Minshew and Goldstein 2001).

A restricted mapping range may restrict social cognition and the range of available behaviors, as well as contribute to other restricted behavioral patterns in ASD. Oxytocin treatment, then, would have the potential to improve hippocampal signal-to-noise ratio and social mapping, and lead to better hippocampal map decoding by downstream regions. Such improvements would be reflected in enhanced hippocampal network covariation during hippocampal-dependent behaviors and correlate with improvements in social functions (e.g., social memory), especially when organizing complex information. Consistent with this possibility, oxytocin administration increased mPFC fMRI signal in a double-blinded, placebo-controlled ASD trial, which in turn led to improvements in the individual’s ability to make accurate social inferences under situations of conflicting social information (Aoki et al. 2015). Thus, constrained mapping in the hippocampus has the potential to explain some social impairments in ASD: Restricted mapping may produce restricted social behaviors.

MAJOR DEPRESSIVE DISORDER

Social Dysfunction

MDD has a large impact on social functioning: Common dysfunction includes poor social decision-making (Goddard et al. 1997), poor social skills (Segrin 2000), a sense of not belonging (Hagerty et al. 1996), fewer social interactions (De Choudhury et al. 2013), and relationship difficulty, leading to eventual social isolation (Segrin 2000). Social dysfunction can precede and exacerbate other depressive symptoms (Joiner and Timmons 2002) and even predict suicidal behavior in MDD: Suicide attempts think of social problems as intractable, perceive hostility and a lack of social support in their relationships, and have restricted social networks (Szanto et al. 2012). A mechanistic understanding of social cognitive deficits in MDD is needed: Basic cognitive processes (e.g., attention) do not sufficiently explain social dysfunction in MDD (Ladegaard et al. 2014; Bora and Berk 2016), and social deficits persist even after other depressive symptoms recover (Rhebergen et al. 2010). Individuals with MDD are impaired in mentalizing (Wolkenstein et al. 2011) and have a negativity bias in emotion recognition, whereby faces are perceived as more negative (e.g., sad) than healthy controls perceive them (Fu et al. 2008).
Hippocampal Abnormalities

One of the most replicated neurobiological findings in MDD is the altered shape and smaller volume of the hippocampus (Cole et al. 2011). Smaller volumes may be explained by cellular abnormalities, such as decreased pyramidal soma size and more densely packed pyramidal, granule, and glia cells relative to controls (Stockmeier et al. 2004). Further, networks that include the hippocampus are often dysregulated in MDD (MacQueen and Frodl 2011), including altered covariation with the amygdala and prefrontal cortex (PFC) (Drevets et al. 2008), as well as greater covariation with the default mode network, a set of regions implicated in self- and other-referential thinking that includes the mPFC (Kaiser et al. 2015). Hippocampal abnormalities in MDD have cognitive consequences: Individuals with MDD show hippocampus-related deficits in both episodic memory (Lee et al. 2012) and spatial navigation (Cornwell et al. 2010). The clinical significance of hippocampal changes is clear: Smaller volume is correlated with clinical variables such as childhood abuse, younger age of illness onset, longer time untreated, greater symptom severity, illness burden, and worse treatment outcome (MacQueen and Frodl 2011).

Evidence Connecting the Hippocampus to Social Dysfunction

Hippocampal alterations in MDD have been linked to social dysfunction and withdrawal. Specifically, increased sensitivity to negative social information in MDD relates to hippocampal processing, and social rejection relates to abnormally increased amygdala and parahippocampal gyrus activity (Silk et al. 2017). Additionally, chronic social stress induces social withdrawal via hippocampal projections to nucleus accumbens, as shown by a mouse model of depression (Bagot et al. 2015). Impaired hippocampal representations may be crucial in these social deficits: A lack of episodic memory specificity mediates the relationship between depressive rumination and social decision-making deficits (Raes et al. 2005). Supporting this view, effective treatment of MDD often normalizes hippocampus signal during social functions. For example, after treatment with selective serotonin reuptake inhibitors (SSRIs), which often leads to hippocampal changes (Dale et al. 2016), or cognitive behavioral therapy (Fu et al. 2007, 2008), symptom improvements correlate with the normalization of hippocampal response to emotional faces. Further, experimentally increasing hippocampal acetylcholine activity decreases social interaction in mice, which is reversed by SSRI administration (Mineur et al. 2013), suggesting that hippocampal activity associated with MDD are directly related to social behavior.

Putative Social Mapping Impairment: Fuzzy Maps

Hippocampal pattern separation may explain commonly observed deficits in episodic memory specificity in MDD (i.e., increased vagueness in memory recall; Eisch and Petrik 2012) and may also be relevant in MDD social mapping—ultimately by increasing feelings of social distance. What differentiates close loved ones from distant strangers is a shared history of reciprocity, common interests, knowledge of the other’s idiosyncrasies, and so on. Impaired social map pattern separation would impair retrieval of that shared history: Maps that relate to specific individuals would be more difficult to disambiguate and retrieve. Impairments in social map differentiation could cause even family members and romantic partners to seem socially distant. Social distance seems implicated in a variety of social deficits in MDD, including perceptions of hostility in interactions, inadequate social support in current relationships (Szanto et al. 2012), and not belonging socially (Hagerty et al. 1996).

Feelings of social distance in MDD may result in part from poor mPFC retrieval of hippocampal social maps. mPFC, a key region in self- and other judgments (Denny et al. 2012) and in using hippocampal representations to guide decision-making (Kaplan et al. 2017), could compute social proximity from hippocampal social map readouts. When mPFC fails to retrieve specific social maps that relate individuals to relevant social information, it may default to representing others as unaffiliated.

Such difficulties in map separation and retrieval might also explain MDD deficits in mentalizing (Wolkenstein et al. 2011): The generalization of hippocampal maps in mentalizing is guided by the perceived similarity between self and others (Perry et al. 2011)—and poor map separation could impair the specificity of social simulations (Williams et al. 1996). In support of this hypothesis, reduced memory specificity in MDD correlated with reduced covariation of posterior cingulate cortex with nearby regions (Zhu et al. 2012)—posterior cingulate cortex being an area implicated (along with mPFC) in default mode self- and other processing (Schilbach et al. 2008) and in mapping social distance (Tavares et al. 2015).

Impaired map pattern separation would also impair the ability to link relational representations of specific individuals with social reward: Decreases in social bonding (i.e., affiliation) could relate to reduced connectivity between maps in anterior CA1 (vCA1 in rodents) and nucleus accumbens (Walum and Young 2018). Individuals undergoing MDD experience a loss of reward from positive social interactions along with hypoactive nucleus accumbens (Hsu et al. 2015), and they tend to develop a less intimate social network (Szanto et al. 2012) and maintain fewer relationships (Segrin 2000). The social relational view might further suggest an explanation for self-related rumination in MDD, via altered hippocampal and mPFC interactions (Cooney et al. 2010): When others are perceived as distant and feelings of social isolation increase, thoughts may increasingly turn inward.

SOCIAL ANXIETY DISORDER

Social Dysfunction

Social phobia is the central clinical feature of SAD (Liebowitz et al. 1985). During social situations, individuals
with SAD feel fear of social evaluation and embarrassment and experience co-occurring physical symptoms, such as increased heart rate and sweating (Stein and Stein 2008). As a result, individuals struggle to maintain relationships, have difficulties advancing their education or careers, and at times avoid social interaction altogether (Liebowitz et al. 1985; Stein and Stein 2008).

Evidence Connecting the Hippocampus to Social Dysfunction

Evidence of altered hippocampal function during social anxiety in SAD is relatively strong: Research has consistently implicated increased hippocampus signal in social phobia—an abnormality that is normalized by effective treatment. For example, individuals with SAD report greater social anxiety and show greater parahippocampus/hippocampus and amygdala activation to negative associations with neutral faces (Schneider et al. 1999) and harsh facial stimuli (Stein et al. 2002; Goldin et al. 2009) but show no differences from controls when viewing physical threat (Goldin et al. 2009). Social behaviors increase social anxiety and parahippocampus/hippocampus activity, such as public speaking (Tillfors et al. 2002), as do expectation of social behaviors, such as preparing for public speaking (Lorberbaum et al. 2004).

Interpreting the mental states of others also causes hyperactivity in the hippocampal formation in SAD. For example, SAD is associated with abnormal activity increases in the hippocampus during mentalizing (Sripada et al. 2009) and in the parahippocampus and entorhinal cortex during emotion recognition (Hattingh et al. 2013). Effective treatment of SAD often normalizes hippocampal function, consistent with a prominent role for the hippocampus in SAD. Serotonin manipulations (Furmark et al. 2002, 2005; Kilts et al. 2006) and cognitive behavioral therapy (Furmark et al. 2002) both reduce social anxiety and normalize hippocampus, parahippocampus, and amygdala fMRI signal in individuals with SAD during social anxiety inducing tasks. Posttreatment changes in the hippocampus persist and correlate with posttreatment reductions in clinical measures of social anxiety for several weeks (Furmark et al. 2005), up to one year (Furmark et al. 2002) or longer—evidence that long-term improvement in clinical symptoms in SAD depends partially upon normalizing hippocampal function.

Putative Social Mapping Impairment: Biased Simulations

Individuals with SAD selectively attend to, fear and avoid sources of potential social threat, a process that could include hippocampal map-based simulations of social threat and avoidance. Hippocampal mapping is sensitive to the current behavioral goal of the animal. Similar to how reward location is represented and guides reward-motivated animals’ place cell simulations and decision-making, social threat (e.g., threat of evaluation) may be overrepresented in SAD social mapping (e.g., via overgeneralization from past social experience), and bias simulations of social situations toward negative social outcome predictions (e.g., embarrassment). The bias toward simulating negative social outcomes could help explain SAD inaccuracy in emotion recognition (Hattingh et al. 2013) and mentalizing (Sripada et al. 2009). Thus, hippocampal mapping may ultimately inform social avoidance behaviors in SAD: The hippocampus may chart out “safe” trajectories by which an individual can avoid the threat of social evaluation. Increased hippocampal activity in SAD could reflect hyperactive social simulations, negative outcome predictions, and planning of social avoidance trajectories. As research on hippocampal structure in SAD is mixed, with studies showing greater gray matter volume (Machado-de-Sousa et al. 2014), less gray matter volume (Irle et al. 2010), and no difference (Syal et al. 2012), it is possible such biased simulations reflect impairments within the hippocampus and/or impairments within a larger network—for example, between the hippocampus, amygdala, and mPFC (Tovote et al. 2015). Mapping itself may be biased, or mapping may be largely preserved, and how maps are used in social simulations, predictions, and decision-making may be the source of the bias.

DISCUSSION AND FUTURE DIRECTIONS

Evidence is consistent with links between hippocampal and social dysfunction across psychiatric disorders, including schizophrenia, MDD, SAD, and ASD. Although we believe social mapping deficits may explain these links, we are not claiming that hippocampal dysfunction necessarily leads to social dysfunction, that all social dysfunction reflects hippocampal dysfunction, or that the same impairments must exist in all cases of social hippocampus problems (Fig. 1). Instead, the evidence suggests that specific social symptoms may be explained by hippocampus dysfunction or hippocampal interactions with other regions (e.g., amygdala, mPFC), and a variety of map-related impairments could be implicated. For example, relational modeling itself may be impaired; poor map separation and aberrant map completion could lead to inaccurate social inferences and maladaptive social decision-making; social map-based simulations may be biased toward particular behavioral goals; and so on.

A transdiagnostic social mapping perspective may clarify the mechanisms underlying social symptom overlap in different disorders. For example, social anxiety occurs across disorders, including ASD (Bellini 2006), MDD, and schizophrenia (Schneier et al. 1992), and may have a common cause in social map-based simulations of negative social outcomes. Microdeletion of 22q11.2 causes CA2 and social memory impairments and is associated with both schizophrenia and ASD diagnosis (Piskorowski et al. 2016); however, schizophrenia is associated with reduced hippocampal volume, whereas ASD is associated with increased hippocampal volume. Thus, although their symptoms may be similar, the mechanisms that underlie those symptoms might differ. Oxytocin and vasopressin binding in the hippocampus could additionally hold spe-
cial relevance and explain social information processing deficits across disorders.

A cumulative research program could help resolve the mechanisms of hippocampal social mapping and dysfunction. Ecologically valid experiments are needed to provide further evidence for a link between the hippocampus, social mapping, and social behavior. For example, dynamic tasks are needed to manipulate and measure the interplay between social memory, social predictions, prediction errors, and decision-making; relating and using social information across social contexts; the detection of context-specific social emotions that cannot be decoded from facial expression alone (e.g., shame); and social interactions/relationships that unfold over time.

To characterize hippocampal functions, several considerations should be held in view. Improved spatial resolution may help resolve the contributions of hippocampal subregions to social functions. Patterns of activation may provide more information than mean activation alone, and spatially and temporally distributed signals (e.g., oscillatory activity in magnetoencephalography, dynamic causal modeling in fMRI) may clarify the role of hippocampal representations within larger networks: Problems in social cognitive mapping could occur anywhere within input, central processing, or output structures. As several regions (e.g., posterior cingulate cortex/precuneus, dorsolateral PFC, and inferior parietal lobule) track components of social vectors to others in social space (Tavares et al. 2015), social mapping dysfunction likely results from impairments within a broader network.

Longitudinal research with repeated measures is necessary to account for compensatory processes and plasticity, to track hippocampal structural and functional changes in relation to social cognition and behavior, and to discover predictors for risk and treatment efficacy. Behavioral indices sensitive to hippocampus-mediated social mapping may allow accurate diagnosis of real-world social dysfunction in a cost-effective manner. Interventions additionally may be informed by a social mapping point of view. This includes interventions during development designed to reduce the potential for social stress to sculpt the social mind: Positive social interactions after social stress may mitigate social stress-related changes, including social behavioral changes (Iovovich et al. 2001). Thus, for adolescents undergoing severe social stress, careful attention should be paid to social dynamics (e.g., power and affiliation), given the possibility of a social sensitive period in social mapping.

The social mapping perspective offers the potential for great explanatory power in psychiatry and neuroscience: It is transdiagnostic and dimensional, with specific hypotheses about computational and neurobiological substrates. It suggests ways to improve diagnosis and interventions, informed by a precise view of how relational social cognition may operate. Indeed, social mapping offers the chance for a mechanistic account of social cognition and dysfunction—and to answer core questions about the importance of social relations.

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