HHS Public Access

Author manuscript

Trends Neurosci. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Trends Neurosci. 2021 October ; 44(10): 793–807. doi:10.1016/j.tins.2021.08.005.

Hippocampal contributions to social and cognitive deficits in autism spectrum disorder

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Abstract

Autism spectrum disorder (ASD) is characterized by hallmark impairments in social functioning. Nevertheless, non-social cognition, including hippocampus-dependent spatial reasoning and episodic memory, is also commonly impaired in ASD. ASD symptoms typically emerge between 12–24 months of age, a time window associated with critical developmental events in the hippocampus. Despite this temporal overlap and evidence of hippocampal structural abnormalities in ASD individuals, relatively few human studies have focused on hippocampal function in ASD. Herein, we review the existing evidence for the involvement of the hippocampus in ASD, and highlight the hippocampus as a promising area of interest for future research in ASD.

Keywords

fMRI; Social; Spatial; Memory; Cognitive Mapping; Neurodevelopmental Disorders

The Neuroanatomy of ASD: Knowns and Unknowns

Autism Spectrum Disorder (ASD; see glossary) is primarily characterized by impairments in social communicative functioning and repetitive behaviors/restricted interests. In addition to these core symptoms, individuals with ASD often show associated problems including sensory and cognitive impairments, for instance deficits in executive functioning, **spatial reasoning**, working memory and **episodic memory** [1]. ASD is heterogeneous in both its clinical presentation and developmental trajectory. Though animal research provides crucial mechanistic information, it is limited by difficulties in modeling idiopathic ASD and measuring social and behavioral features in a translationally meaningful way. Human neuroscience studies, including those using functional magnetic resonance imaging (fMRI), fill this gap by investigating the structure and function of various brain regions and networks

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Declaration of interest:
The authors declare no competing interests in relation to this work.

in individuals with ASD and their associations with clinical symptoms. For instance, the default mode [2,3] and salience [4] networks have been frequently implicated, as well as changes in local and long-range connectivity throughout the brain [6,7] (Box 1).

A major focus of human neuroimaging work in ASD is the 'social brain', or the neural substrates involved in processing social information [8,9]. However, the majority of these studies explore only a particular subset of social functions in ASD, such as emotion recognition, theory of mind, face perception, or social reward [8]. Partially due to limitations in existing experimental paradigms, which tend to use static stimuli and not respond dynamically to participants' responses, deficits in social interaction and reciprocal relationships remain underexplored. Recent behavioral work has exhibited the utility of computational modeling and social games for characterizing the cognitive strategies employed by individuals with ASD during social interactions [10,11]. Some fMRI studies have employed, for instance, a cyberball game to probe responses to social rejection in ASD [12–14]. However, the cyberball task is limited in the types of social behavior it can model, and as in social neuroscience research more generally, neuroimaging work in ASD has yet to make efficient use of interactive social decision-making tasks.

Despite a wealth of research on the neural correlates of ADS, a conclusive picture still seems far from reach. The current literature is conflicted, and studies have shown few brain regions with consistent or explanatory functional alterations in ASD (Box 1). The hippocampus, in particular, has been the focus of very few functional neuroimaging studies in ASD, perhaps because historically, evidence of hippocampal involvement in social behavior has been relatively sparse. Additionally, limited attention has been given to hippocampal-driven functions of memory and spatial reasoning in ASD research, as impairments in these functions are not core aspects of the ASD phenotype. However, in light of current discussions surrounding the role of the hippocampus in social cognition [15–17], the hippocampus is poised as a prime brain region of interest for investigation. Recent work has reconceptualized the functions of the hippocampal system, shifting away from frameworks focused primarily on memory and spatial reasoning, to ones that frame the hippocampus as an organizer of information. Among the concepts that have been discussed in this context is **cognitive mapping** [18–21], which supports not only memory and spatial reasoning, but also a multitude of other functions. By providing models of the relationships between concepts, cognitive maps may be used to make predictions and support adaptive decision-making [22,23]. For example, maps of social relationships help us predict the actions of others and respond appropriately ourselves, just as maps of physical locations help us flexibly navigate within a changing environment [24]. These ideas implicate the hippocampus in the tracking of social relationships [17], making it an excellent candidate to study in the context of ASD. While we highlight in this review the relevance of the hippocampus to ASD research, it is not our goal to claim that the hippocampus uniquely underlies the pathophysiology of the disorder, but rather that it may represent a critical component within a system of altered brain regions that work in tandem to contribute to the ASD phenotype.

In this review, we highlight the hippocampus as a brain region of interest for investigating the neural underpinnings of ASD. As discussed in more detail later, several lines of

evidence support this idea. Briefly, (1) The hippocampus contributes to several functions that are disrupted in ASD, most notably social interaction, but also memory and spatial reasoning; (2) There is substantial evidence for abnormal hippocampal structure and some evidence for abnormal hippocampal function in individuals with ASD; (3) The hippocampus reaches major developmental milestones around 2 years of age, just as ASD symptoms typically become increasingly apparent. We further argue that deficits in social behavior, memory, and spatial reasoning may co-occur in ASD due to an underlying impairment in complex hippocampal-driven cognitive mechanisms and policies, including cognitive mapping, affordance perception, and model-based planning.

ASD and Impairments in Memory, Spatial Reasoning, and Social Interaction

Intuitively, prior neuroimaging work in ASD has focused on core symptoms, as well as those that can be easily experimentally prodded. Deficits in memory and spatial reasoning have been typically overlooked due to their non-core status, and impairments in social interaction are often bypassed possibly because it has been historically difficult to simulate and manipulate peer interaction inside of a scanner. However, these symptoms are critical components of the ASD phenotype and offer a unique lens with which to explore neurobiological changes.

Memory

Individuals with ASD show memory impairments that span several domains. Deficits in episodic memory are consistently reported in ASD. There continues to be debate regarding which specific aspects of episodic memory are impaired in ASD, as both encoding and retrieval processes have been implicated [25]. However, recent fMRI studies provide evidence for primary deficits in retrieval, likely as a result of disrupted hippocampal connectivity [26]. Other work has shown that memory in ASD decreases as a function of task complexity [27,28], suggesting a link between memory and other cognitive impairments in ASD. Furthermore, compared to typically developing individuals, those with ASD have difficulties remembering faces as well as scenes that depict people interacting, suggesting that memory is especially impaired for social stimuli [29]. Such deficits have implications for social behavior, and likely contribute to problems with peer interaction.

Spatial reasoning

Current literature presents a heterogeneous picture of spatial reasoning in ASD [30]. Nevertheless, there is substantial evidence suggesting deficits in this domain. Relative to typically developing individuals, those with ASD have difficulties navigating to previously learned locations of hidden objects in virtual reality spaces, suggesting diminished ability to generate maps of the environment [31]. Similarly, children with ASD spend less time actively exploring novel real-world [32] and virtual [33] environments than their typically developing peers. Individuals with ASD also show spatial navigation deficits when learning routes through virtual mazes, an effect that seems to be related to reduced cognitive flexibility and memory for landmarks [34].

It is possible that these navigation deficits are related to difficulties integrating knowledge about one's physical abilities and opportunities for action with the properties of the environment, a concept known as affordance perception. Indeed, individuals with ASD show impairments in tasks of affordance perception, including judging reachable distances [35]. In contrast to these findings of impaired spatial reasoning and navigation, a number of studies have reported typical abilities or even strengths in similar domains, such as visual search and mental shape rotation [36,37]. Such discrepancies may be explained via the nature of the tasks. Individuals with ASD may show strengths in more perceptual visual-spatial tasks but exhibit impairments with more pragmatic and multidimensional aspects of spatial reasoning, including navigation [30].

Social Interaction

Social interaction deficits are at the crux of ASD. Common deficits include difficulties in holding conversations, interviewing for and maintaining jobs, establishing and sustaining relationships with both friends and romantic partners, and modulating behavior in different social contexts. In addition to core difficulties with reciprocal relationships, individuals with ASD often display a diverse set of deficits with more fundamental social functions, including with face processing, understanding and expressing emotions, theory of mind, and interpreting nonliteral language, such as sarcasm and metaphor [38]. Several umbrella theories attempt to explain such behaviors, including for instance the social motivation hypothesis, which argues that ASD stems from diminished social motivation [39]. However, these models are not fully explanatory. For example, reward deficits in ASD do not appear to be specific to the social domain, and support for the social motivation hypothesis differs depending on the type reward subtype being examined [40,41]. Much of the neuroimaging research, both in ASD and social neuroscience in general, has targeted these more basic social building-blocks without directly probing reciprocal social relationships [42], despite the crucial relevance of the latter as a core aspect of social behavior. Further research is necessary to untangle the unifying elements and neural correlates of the higher-level social interaction deficits that characterize those with ASD.

Hippocampal Function Underlies Memory, Spatial Reasoning, and Social Interaction

Individuals with ASD have impairments in functions that span multiple domains, including, though of course not limited to, memory, spatial reasoning, and social interaction. Notably, these three functions are all supported by the hippocampus. Hippocampal involvement in memory and spatial reasoning is well-established, whereas the link between hippocampal function and social behavior has more recently gained traction. Given such overlap, disruptions in hippocampal function may very well contribute to many of the symptoms seen in ASD.

Memory

The link between the hippocampus and episodic memory was first conceptualized in the 1950's, when a patient referred to as H.M. developed amnesia after bilateral removal of the hippocampus [43]. Since then, our understanding of the role of the hippocampus

in memory has expanded dramatically. Numerous case studies have reported amnesia in patients with hippocampal lesions [44], and we now know that the hippocampus plays a critical role in both the **encoding** and **retrieval** processes of memory [45,46]. Interestingly, the hippocampus has also been shown to support social memory. Hippocampal activation during face recognition tasks increases with the familiarity of faces, suggesting that the role of the hippocampus in memory processes may be linked to the organizing of social information [47]. Findings from animal research suggest that social recognition memory is specifically supported by the CA2 region of the hippocampus [48] (Box 3).

Spatial Reasoning

The idea that the hippocampus is important for spatial reasoning originated from the discovery of "place cells," referring to neurons which fire at specific locations within an environment [49]. Subsequent studies in animals have shown other categories of spatial cells in the hippocampus, including head direction cells, grid cells, and boundary cells [50]. Neuroimaging and recording studies in the human hippocampal system provide evidence for analogous signals [51–54]. Structural MRI findings support the notion of hippocampus supporting spatial reasoning, although the magnitude and the specifics of the effects have been debated. Among healthy individuals, larger hippocampal volume is associated with more flexible navigation [55]. Similarly, among London taxi drivers, more navigation experience is associated with larger hippocampal volume [56]. Hippocampal activity is important for spatial reasoning in real-word scenarios, such as representing distances between real-world locations [57]. Though some have argued that the hippocampus supports navigation primarily through its roles in memory, findings of hippocampal involvement in complex spatial cognition suggest a more complex mechanism. For instance, the hippocampus is activated during oddity judgement of complex scenes regardless of memory accuracy, suggesting it supports spatial reasoning through more general cognitive representations of space rather than memory alone [58].

Social Interaction

Though past research has provided evidence for hippocampal involvement in the perception of the emotions of others [59,60], it is relatively recently that the role of the hippocampus in mediating more complex social behaviors, including reciprocal social interaction, has been clarified [15–17,61,62]. The ability of the hippocampus to support the flexible use and organization of information is crucial for complex behaviors across many domains, including the social domain [19,61]. Performing in social situations requires acquiring information and using it to navigate complex relationships. To succeed, one must be able to infer the emotions and intentions of others, predict their actions, and keep track of a dynamically changing social "environment".

The cognitive map theory suggests that the hippocampus plays a role in the organization of social information by framing it in a spatial-like or relational context [16,17]. During a virtual role-playing game in which participants interacted with characters to find a job and a home, a two-dimensional geometric model of social relationships framed by power and affiliation was predictive of hippocampal activity. Such findings implicate the hippocampus in the organization of social information in a "social map" [15], which provides a sort

of guide for navigating variable and dynamic social relationships. If the hippocampus is necessary for social performance, those with atypical hippocampal functioning should show impairments in this domain. Indeed, amnesic patients with hippocampal damage are reported to have smaller social networks than typically developing individuals, an effect thought to result from impaired social functioning [63]. A possible interpretation for the findings is that the social deficits of these individuals stemmed from a reduced ability to generate cognitive maps [62].

Effective social interaction also depends on knowledge of the location of social others within the physical environment. Recent animal work suggests the presence of “social place-cells” within the hippocampus that represent both one’s own location and the positions of others [64]. Additionally, the human hippocampus is known to perform grid-like mapping for one’s own simulated movements [24] as well as planned navigation in the absence of imagined movement [65]. Though it has yet to be investigated, the human hippocampus may track others’ spatial movements through similar mechanisms. As such, the hippocampus is likely involved in encoding locations of individuals in the physical space as well. Perhaps related to alterations in this function, individuals with ASD often show difficulties in maintaining appropriate physical distance from other people [66] as well as deficits in **joint attention** and social orienting [67], suggesting impaired conceptualizations of interpersonal space. Given its seemingly critical role in social interaction, the hippocampus is an excellent candidate to study in the context of disorders characterized by social impairment (Box 2).

Hippocampal Involvement in ASD – What Do We Know?

Altered hippocampal structure in ASD

Alterations in hippocampal structure in ASD have been widely reported. Most studies have observed enlarged hippocampal volume in children [68,69] and adolescents [69,70] with ASD. However, reduced volume [71] or no significant differences when compared to typically developing children [72] have also been found. Perhaps explaining this inconsistency, a recent longitudinal study examining 200 young children with ASD noted an atypical coupling between hippocampal volume and total brain size. Among children with ASD, the hippocampus was found to be relatively larger in a subset of children with enlarged brain volume, but relatively smaller in a subset of children with reduced brain volume, compared to typically developing children with comparable brain sizes [73]. Such findings fit well with the heterogeneity of the disorder – hippocampal volume appears to be atypical in multiple ways within ASD. In addition to atypical volume, individuals with ASD appear to have alterations in hippocampal shape [74] as well as abnormal hippocampal texture features extracted using radiomic analysis, an automated technique that converts medical imaging data into measures of shape, size, density, and texture as a means for characterizing image heterogeneity [75]. Further, white matter tracts between the hippocampus and mid-fusiform gyrus as well as between the amygdala and the mid-fusiform gyrus appear to be altered [76]. While the amygdalo-fusiform and left hippocampo-fusiform tracts showed alterations consistent with whole brain effects, only the right hippocampo-fusiform tract showed the opposite pattern of reduced across-fiber diffusivity in ASD compared to typically developing individuals. The hippocampo-fusiform

pathway is important for face processing [76]; as such, one may speculate that reduced axon diameter and subsequent neurotransmission speed between the hippocampus and the fusiform contribute to some of the social deficits in ASD.

Altered hippocampal function in ASD

So far, few studies have directly investigated hippocampal function in individuals with ASD. Nevertheless, the existing literature suggests significant alterations in hippocampal activity. Task-based **fMRI** research has implicated the hippocampus in impaired learning and memory, perception of social emotion, and sensory hypersensitivity in ASD. For example, studies have investigated **transitive inference**, a form of relational learning that allows for inference of relationships between representations that have not yet been explicitly compared. Transitive inference is heavily implicated in the formation of cognitive maps and is supported by the hippocampus [20]. Although typically developing and ASD individuals recruit the hippocampus and the caudate nucleus comparably during training on a transitive inference task, functional connectivity between these regions during training is only associated with subsequent performance among those with ASD [77]. Within individuals with ASD, transitive inference performance declines with more severe symptoms [77]. Such results suggest that individuals that show impairments in forming relational representations have more severe ASD symptoms and reduced connectivity between the hippocampus and the caudate nucleus, perhaps reflective of deficits in cognitive mapping. Furthermore, compared to typically developing individuals, those with ASD have widespread reduced **functional connectivity** of the hippocampus within a whole-brain network during episodic memory retrieval [26]. Stronger functional connectivity between the hippocampus and other regions of the DMN during rest [78] and increased hippocampal activation during executive functioning tasks [79] have also been identified. Finally, compared to typically developing individuals, those with ASD have also displayed increased hippocampal activation in response to vicarious social [80,81] but not physical pain [80], suggesting an effect unique to complex emotions. In addition to cognitive and socioemotional impairments, evidence supports hippocampal involvement in sensory hypersensitivity in ASD: relative to typically developing individuals, individuals with ASD showed increased activation of the hippocampus during presentations of mildly aversive auditory and visual stimuli [82]. Though these studies span multiple behavioral domains, they suggest that atypical hippocampal activity and functional connectivity may underlie a diverse set of symptoms in ASD.

Developmental timeline

In infants who eventually develop ASD, core features of the disorder typically become apparent over the first two years of life [83,84]. Common early signs include difficulties in joint attention, eye-contact, orienting to name, and speech development [83]. The developmental timeline of the hippocampus suggests some alignments with these behavioral developmental milestones. For instance, the hippocampus increases in volume over the first months of life, and begins to plateau around age two years [85]. In particular, the period around 18–24 months of age is a major milestone in hippocampal development. During this time, neurons in the dentate gyrus and CA3 acquire sufficient maturity to form connections to the cerebral cortex and achieve adult-like morphology [86] (Box 3). In

contrast, other subcortical structures such as the amygdala are relatively well-developed by birth [87], whereas some cortical structures, particularly the prefrontal cortex, continue to mature throughout adolescence [88] and even young adulthood. Postnatal neurogenesis in the dentate gyrus has been discussed as a possible contributor to the encoding of temporal relationships [89], and the CA3 region is known to support the acquisition of spatial associations [90,91]. Based on these observations, it seems plausible that if any alterations in hippocampus development were to occur, concurrent problems in these functions would likely arise. Somewhat relatedly, prior to 18–24 months of age, most children are unable to form lasting memories of commonplace events, leading to inability in recalling this period later in life [86]. Additionally, the use of spatial context to guide search for objects emerges around 24 months, suggesting the development of allocentric representations of space [86], also supported by the hippocampus. Thus, the coinciding developmental time course of ASD symptom onset and hippocampal growth and connectivity calls for further research into the possible links between aberrant hippocampal development and the behavioral manifestations of ASD.

Cognitive mapping, affordance perception, and model-based planning in ASD

As discussed above, the hippocampus has been shown to underlie memory, spatial reasoning, and, most recently, social interaction, all three of which are disrupted in ASD. Given this overlap, as well as reported alterations in structure and function of the hippocampus in ASD, it seems plausible that hippocampal alterations may play a role in the development of such symptoms. How is it possible for the hippocampus to be involved in such seemingly disparate roles? One theory posits that the hippocampus supports a variety of functions through cognitive mapping, which represents the capacity to organize conceptual relationships [19,92–94]. Studies using magnetoencephalography (MEG) and electroencephalography (EEG) have shown that the human hippocampal formation performs grid-like mapping of visual space [24] and engages in spontaneous replay to facilitate the generalization of previously learned structures to novel elements [95], supporting a role for the hippocampus in the formation and adaptation of cognitive maps. Complex functions such as memory, spatial reasoning, and socialization all require advanced representational organization systems, which in turn allow for flexible planning and decision-making [20,23] (Box 4). A disruption in core cognitive mapping capacities would affect the ability to perform across numerous domains of behavior, including memory, spatial reasoning, and social behavior, plausibly contributing to the ASD phenotype.

In support of this proposition, individuals with ASD appear to use maladaptive, inflexible spatial navigation strategies, suggestive of difficulties generating cognitive maps of the environment [96]. Without proper models of the environment, the relationships between elements such as individuals, places, and events remain opaque, making predictions about future states exceedingly difficult. Indeed, prior work has shown that individuals with ASD typically engage in **model-free** rather than **model-based** strategies in social situations [97]. That is, they rely heavily on trial-and-error (model-free) rather than forward planning and mental simulation (model-based). Additionally, cognitive mapping requires

an understanding of how one's own position relates to external features. This is closely linked to the concept of **affordance perception**, or the ability to integrate yourself in the environment such that you can intuit what actions you can perform by assessing the relationship between the current environment and your physical capabilities. Interestingly, individuals with ASD show impairments in affordance perception that are associated with heightened social deficits [35].

Given these findings, we hypothesize that deficits in social interaction, memory, and spatial reasoning may co-occur in ASD due to an underlying impairment in complex, hippocampal-driven cognitive mechanisms and policies, including cognitive mapping, model-based planning, and affordance perception. A lack of proper cognitive maps would impair our understanding of the relationships between ourselves and external elements, leading to difficulties in predicting future state in changing situations as well as with assessing the ways we can act within a given environment. For instance, social interaction deficits in ASD may arise from an inability to form internal representations of social relationships, flexibly evaluate and update these relationships, make predictions about the actions of social others, and perceive the affordances provided by other peoples' behavior. We use social representations to store fundamental information about relative intimacy and authority in order to understand how people relate to one another and to ourselves, allowing us to interact appropriately. Without a proper organizational system, it would be incredibly challenging to update our relationships in the face of new information, predict how specific people will behave, or understand how to act appropriately across different social contexts. For example, someone without a well-formed map of social relationships may not know when or with whom it is appropriate to share personal information. Such difficulties are commonly reported in ASD and have significant deleterious impact on individuals with ASD's abilities to form, maintain, and adapt within meaningful, reciprocal relationships. Thus, these ideas implicate hippocampal dysfunction in some of the most debilitating aspects of ASD.

Of course, a disruption in cognitive mapping would likely affect more than the three functions considered in this review. The social, memory, and spatial domains were chosen for their established link to the hippocampus. It is possible that the hippocampus contributes more subtly to other behaviors through cognitive mapping, including behaviors known to be affected in ASD. For example, one could argue that the insistence on sameness (i.e., repetitive behaviors and circumscribed interests) observed in ASD results from an inability to organize complex conceptual information in various domains (Figure 2). Such an integration problem may lead to reduced flexibility and more singular areas of focus. If hippocampal alterations are identified in ASD in association with primary functions in the social, memory, and spatial domains, insistence on sameness will be a promising secondary area to probe in order to explore the full reach of hippocampal contribution to the ASD phenotype.

Concluding Remarks

This review summarizes the evidence that supports a role for the hippocampus in the pathophysiology of ASD. Though limited in number, the few studies highlighting

hippocampal function in ASD provide concrete evidence of disrupted activity. In addition to these direct assessments, there are numerous indications that hippocampal dysfunction may contribute to the ASD phenotype. The hippocampus reaches a milestone of functional maturity at the same age ASD symptoms begin to manifest, suggesting a developmental link. Indeed, structural alterations of the hippocampus are widely observed in children and adolescents with ASD, suggesting atypical formation of the structure and its connections with the rest of the brain. Furthermore, the hippocampus is known to play critical roles in social interaction, memory, and spatial reasoning, all disrupted in ASD, with social interaction deficits being among the most central, but poorly understood, aspects of the disorder. We hypothesize that hippocampal contributions to these seemingly distinct behaviors occur through cognitive mapping, which represents the organization of concepts and binding of relational elements. A disruption in cognitive mapping would likely lead to deficits in model-based planning and affordance perception, both of which are impaired in ASD, thus resulting in maladaptive decision-making and impaired integration of oneself with one's surroundings. Through such mechanisms, atypical hippocampal development may cause significant impairment in social, memory, and spatial domains, thus contributing to ASD phenotypes.

Future neuroimaging studies in ASD should implement experimental paradigms that probe cognitive mapping abilities across various domains, including memory, spatial reasoning, and dynamic social processes. The field of social neuroscience has produced numerous tasks that mimic decisions made during real-life social interactions [15,98,99]. Utilization of such tasks in combination with model-based fMRI in ASD will be critical to explore deficits in planning and navigation in the context of social behavior. To explore the developmental aspect of these effects, tasks appropriate for younger populations should be developed and evaluated in longitudinal studies, both behaviorally and in parallel with fMRI. Such work would allow us to track how cognitive mapping abilities develop in association with hippocampal function, and how the trajectory of this relationship may differ in ASD compared to typical development individuals. While it will be important to investigate the hippocampus directly as a region of interest, whole-brain analyses will be crucial for determining which other brain regions may be working in tandem with the hippocampus to contribute to the ASD phenotype. Furthermore, to assess the specificity of hippocampal contribution to ASD, similar studies should be performed in individuals with other psychiatric disorders, especially those characterized by social impairment. Lastly, although dynamic social interactions are difficult to probe in rodents, animal studies offer a unique opportunity to gain mechanistic insight into cognitive map formation, at least in the spatial domain. Future work should explore the formation of cognitive maps of physical and abstract environments in animal models of ASD.

Acknowledgements:

This work was supported by the National Institute of Mental Health, R01MH122611 (SMB, JFF, XG, DS), R01MH123069 (XG, DS), R21MH120789 (XG, DS), R01MH124115 (XG), R01MH119172 (JFF); the National Institute on Drug Abuse, R01DA043695 (XG), R21DA049243 (XG); the National Institute of Neurological Disorders and Stroke, R01NS105845 (JFF); The Ream Foundation (XG, DS, JFF); Seaver Foundation Fellowship (SMB); and Seaver Foundation Rare Disease Program (JFF).

Glossary:

7-tesla MRI scanning
A high resolution MRI device allowing for better signal-to-noise ratio and better visualization of small structures compared to scanners with weaker magnetic fields (such as the commonly used 3-Tesla scanners).

Affordance Perception
the ability to integrate knowledge about one's physical abilities and opportunities for action with the properties of the environment.

Autism spectrum disorder (ASD)
A heterogeneous group of neurodevelopmental disorders primarily characterized by impairments in social communicative and interactive functioning as well as repetitive behaviors and restricted interests.

Cognitive mapping
Cognitive mapping refers to the capacity to organize abstract concepts within a "spatial" framework, thus generating a mental representation that allows for informed behavior.

Default Mode Network (DMN)
a functional brain network primarily composed of the medial prefrontal cortex, posterior cingulate cortex, and angular gyrus. It is typically most active when individuals are not focused on the outside environment.

Episodic memory
memories for specific personal experiences or events.

Functional connectivity
the statistical relationship between the timing of neurophysiological events in spatially distinct brain regions.

Functional Magnetic Resonance Imaging (fMRI)
a neuroimaging technique that measures changes in cerebral blood flow and oxygenation that occur as a result of neural activity.

Insistence on Sameness
part of the diagnostic criteria for ASD. It refers to patterns of rigid and ritualistic behaviors, restricted interests, and difficulties with changes in routine.

Joint attention
the shared focus of two individuals on the same item or scene. Impaired joint attention between a child and caregiver can be an early indicator of ASD.

Memory encoding
the act of automatic or effortful processing of information for later memory storage.

Memory retrieval

the act of accessing stored memories for recall.

Model-based behavior
the process of simulating probable outcomes based on cognitive models or representations in order to make goal-directed decisions in novel situations.

Model-free behavior
The process of relying on previous experiences to inform future decision making without generating a model to inform probable outcomes.

Oxytocin
a neuropeptide involved in social bonding.

Resting state fMRI
a passive type of fMRI scan in which participants do not perform a task. Resting state fMRI is used to determine **functional connectivity** between brain regions at baseline rather than during externally-imposed task.

Salience Network
a functional brain network primarily composed of the anterior insula and anterior cingulate cortex. It is involved in detecting and selecting salient stimuli.

Spatial reasoning
the cognitive capacity to interpret and apply visuo-spatial information.

Transitive inference
a form of relational reasoning in which training on one set of items allows for generalization and the ability to understand the relations between items that have not yet been explicitly compared.

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Box 1:

Neural mechanisms of ASD.

Pre-clinical Research:

Various techniques for modeling ASD have provided important insight into potential mechanisms of action. Much work has centered on mouse models of monogenic ASD syndromes (CNTNAP2, FMR1, MECP2, NLGN3, NLGN4, NRXN1, SHANK3, TSC1/2) and ASD-associated copy number variants (15q11-q13 deletion and duplication, 15q13.3 microdeletion, 16p11.2 deletion and duplication, 22q11.2 deletion) [100]. Models of environmental risk factors, such as the valproic acid (VPA) animal model, are also widely used in ASD research [101].These genetic and environmental animal models have led to the identification of numerous altered cellular mechanisms, including alterations in neural progenitor cells and abnormal neurotransmitter receptor expression [102]. Various behavioral assays have been developed for measuring ASD-like behaviors in these models, including measures of social interaction, social memory, and repetitive behaviors [103]. Though much has been learnt from animal model studies, and despite their utility for translational work around drug discovery for ASD, in terms of addressing mechanistic questions, this research is limited by the inherent inability to replicated the uniquely human clinical hallmarks of ASD in animal models.

Clinical Neuroimaging Research:

Previous neuroimaging studies have investigated numerous brain regions in ASD, many of which were selected for links to social processes ranging from face recognition to theory of mind. Such regions include the amygdala, fusiform gyrus, inferior frontal gyrus, and superior temporal sulcus [104–108]. The cerebellum has also been extensively studied due to its role in movement, language, and social processing, all of which are disrupted in ASD [109]. Additionally, much work has explored non-social aspects of the ASD phenotype, including perceptual differences, executive functioning, and repetitive behaviors. Individuals with ASD show atypical responses in primary sensory cortices across numerous modalities, suggesting a low-level sensory component to perceptual symptoms [110]. Among individuals with ASD, executive functioning deficits are associated with hypoactivity of prefrontal regions [111], and repetitive behaviors are correlated with imbalances in corticostriatal connectivity [112]. Less attention has been given to other cognitive symptoms, including memory and spatial reasoning. Though these functions have been explored behaviorally in ASD [27–29,31–34], investigation of their neural underpinnings are limited.

More recent work has increasingly focused on networks of functionally connected regions, including the Default Mode Network (DMN) and the salience network, as well as general patterns of under- and over-connectivity. Children with ASD appear to have increased within-network connectivity in the DMN, whereas adults and adolescents with ASD show decreased within-network connectivity in the DMN [2]. Children with ASD also display decreased connectivity within the salience network, as well as between the salience network and the DMN [4,113]. More generally, studies point to a pattern of increased local but decreased long-range connectivity across the brain in

ASD [6,7]. However, a recent large-scale study reported an opposite effect, wherein the thalamus showed decreased local connectivity and increased long-range connectivity among individuals with ASD [114]. Despite years of research in this area, effects remain inconsistent across studies and there is still no consensus on which neural alterations are primary rather than secondary or compensatory.

Box 2:

Hippocampal Contribution to Social Impairment in Disorders Other than ASD

Given the strong evidence presented in this review, including the large overlap between ASD symptoms and hippocampal function, it is possible that there is a unique link between hippocampal alterations and the ASD phenotype. However, social behavior is also impaired in a number of disorders other than ASD, including various psychiatric disorders, though often to a lesser extent. It is possible that alterations in hippocampal function actually result in broad disruptions in social processing that affect multiple disorders, including, for example, major depressive disorder and social anxiety disorder [62,115]. Given its developmental time frame, a detriment in hippocampal function may be especially relevant to neuro-developmental disorders, including schizophrenia, attention deficit hyperactivity disorder (ADHD), and nonverbal learning disability, all of which are associated with social impairment. Indeed, recent work has reported structural and functional alterations of the hippocampus in individuals with schizophrenia [116–118], ADHD [119–121], and nonverbal learning disability [122]. In addition to social behavior, deficits in cognitive mapping and model-based planning could explain a range of symptoms common to these psychiatric conditions.

Box 3:

Hippocampal Connectivity

The hippocampus is part of a closely connected system in the medial temporal lobe (MTL), consisting of the perirhinal, parahippocampal, and entorhinal cortices in addition to the hippocampal formation. Information converges on the hippocampal formation through the parahippocampal and perirhinal cortices via the entorhinal cortex [86]. The monosynaptic circuit between entorhinal cortex and CA1 subfield of the hippocampus develops early in infancy, while the more complex trisynaptic circuit, which includes the CA3 and dentate gyrus subregions of the hippocampus, does not form mature connections until 18–24 months of age.

This protracted development is thought to be linked to the emergence of certain forms of memory and spatial reasoning around a similar time point [86]. Though previously thought to be an extension of the CA3, CA2 is now known to possess a unique set of cortical inputs and outputs and a distinct contribution to social memory [48]. Despite its critical role in social memory, a cognitive ability that does not fully develop until childhood, the CA2 develops in fact fairly early, even before the CA1 [123]. As the CA2 primarily projects to other regions of the hippocampal formation and not to the neocortex, it is likely that maturation and subsequent integration of all hippocampal circuits is necessary before social memory functions can be supported [124].

Additionally, functional connectivity analyses have shown that the hippocampus has robust communications with both subcortical and cortical brain regions and networks previously implicated in ASD [125]. The hippocampus is considered a node of the DMN, and is highly connected to regions of the salience network, including the amygdala [126]. Thus, the region-specific effects discussed in this review likely act in conjunction with other circuits. In addition to exploring the unique contribution of the hippocampus itself, future work should investigate how altered connectivity between the hippocampus and other brain regions may contribute to ASD (see Outstanding Questions)

Box 4:

The Hippocampus Supports Complex Cognitive Mechanisms and Behavioral Policies

In recent years, the putative role of the hippocampus has expanded beyond episodic memory and spatial navigation. The hippocampus is now thought to have a broader purpose, supporting complex behaviors through multi-dimensional cognitive mapping [18–21]. In forming mental "maps" of associations between places, events, and concepts, the hippocampus is thought to represent relationships across various dimensions, including spatial, temporal, and social [19,20] (Figure 3). For example, the hippocampus is thought to track the spatial relationships between physical locations, allowing for instance a person to know where their office is located in relation to their home. It may also keep track of the temporal relationships between events, allowing an individual to distinguish between things that occurred in the distant or recent past. Socially, the hippocampus is thought to track one's relationships with other people, allowing the evaluation of elements like closeness and power in order to distinguish between a friend and a boss. Finally, the hippocampus likely similarly tracks relationships between features in any abstract space, including shapes and symbols. The creation and maintenance of such representations may be crucial for successful behavior, including model-based inference, or the process of simulating probable outcomes in order to make decisions about novel situations [23]. In contrast to trial-and-error based (model-free) behavior, model-based behavior relies on an explicit internal model of the environment [127]. Utilization of model-based strategies relies on the acquisition of cognitive maps to understand how elements are connected, thus allowing evaluation of choices based on relative reward [128]. For example, a mental map of the environment may allow us to properly navigate around unexpected road closures by evaluating various routes, whereas knowledge of temporal relationships allows us to make predictions about the future based on the outcomes of past events. Similarly, knowledge about our social relationships with others may allow us to evaluate how a given person is likely to react to a specific action and to modulate our behavior accordingly.

Recent work has shown that the hippocampus and orbitofrontal cortex (OFC) work in tandem to support model-based behavior [22]. Both brain regions work to acquire information about external events. However, while both regions seem to acquire initial, value-neutral relational information, the OFC appears to acquire relationships with motivational significance. Hippocampal cognitive mapping, therefore, may support adaptive behavioral policies in particular. By acquiring relationships between external events, the hippocampus collects and organizes information that then can be used by other brain regions such as the OFC to make informed decisions [22].

Outstanding Questions

- Does the hippocampus display differential activation and functional connectivity profiles in ASD? Task and **resting state fMRI** studies will be critical for investigating how hippocampal functioning may be altered, and how this may affect the actions of wide-scale brain networks.
- How might alterations in hippocampal activity and functional connectivity contribute to specific symptoms in ASD? Given the heterogeneous nature of the disorder, a wide range of clinical measures should be collected and evaluated in relation to hippocampal activity in order to untangle the effects of hippocampal dysfunction on particular aspects of the ASD phenotype.
- Is cognitive mapping disrupted in ASD? If so, how might hippocampal dysfunction contribute to such an impairment? Novel relational learning tasks that require the binding of abstract concepts should be developed for fMRI use in order to further the investigate the neural and behavioral correlates of cognitive mapping in ASD.
- Do individuals with ASD show deficits in forming internal representations of social relationships? How might this affect decision-making in social situations, and what role does the hippocampus play in these deficits? Future neuroimaging work should employ experimental paradigms probing evolving social relationships to investigate the neural drivers of these specific social deficits.
- How does hippocampal function change over the course of development in ASD? Longitudinal studies will be necessary to characterize the precise timing of any hippocampal alterations and the extent to which they coincide with ASD symptom onset.

Highlights:

- Social interaction, spatial reasoning, and memory are supported by the hippocampus and impaired in ASD, but these functions remain understudied in neuroimaging research in ASD.
- There is evidence of altered hippocampal structure and function in ASD.
- The hippocampus and ASD symptom onset display parallel developmental timelines.
- Impaired hippocampal-mediated cognitive mechanisms and policies such as cognitive mapping, affordance perception, and model-based planning may contribute to ASD phenotypes.
- Future neuroimaging research should explore hippocampal functioning in ASD, particularly as a potential neural basis for impairments in reciprocal social relationships in ASD.

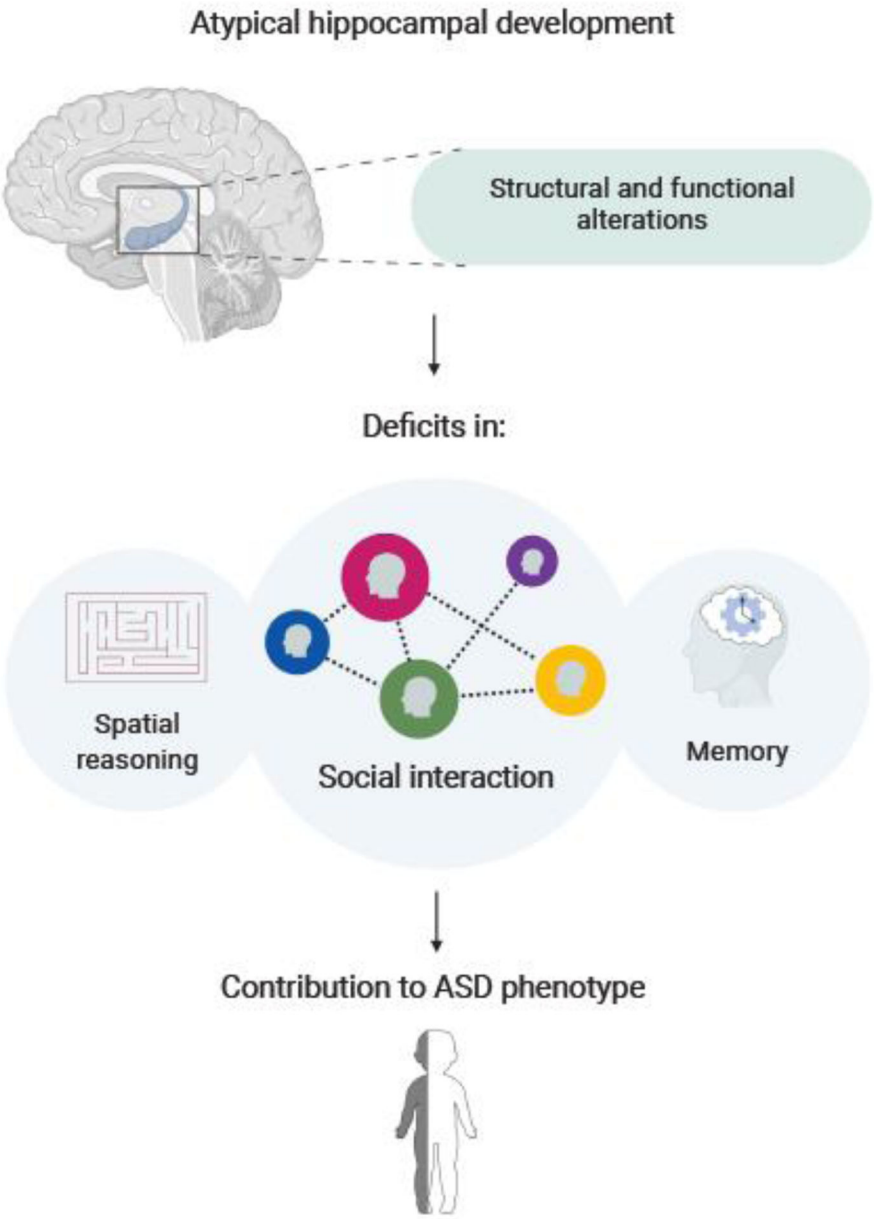

Figure 1 (Key Figure).

Hippocampal abnormalities may contribute to aspects of the ASD phenotype. Structural and functional alterations of the hippocampus may lead to disruptions in the abilities it subserves, including memory, spatial reasoning, and social interaction. Subsequent deficits in these functions may contribute to an ASD phenotype. Figure created with BioRender.com.

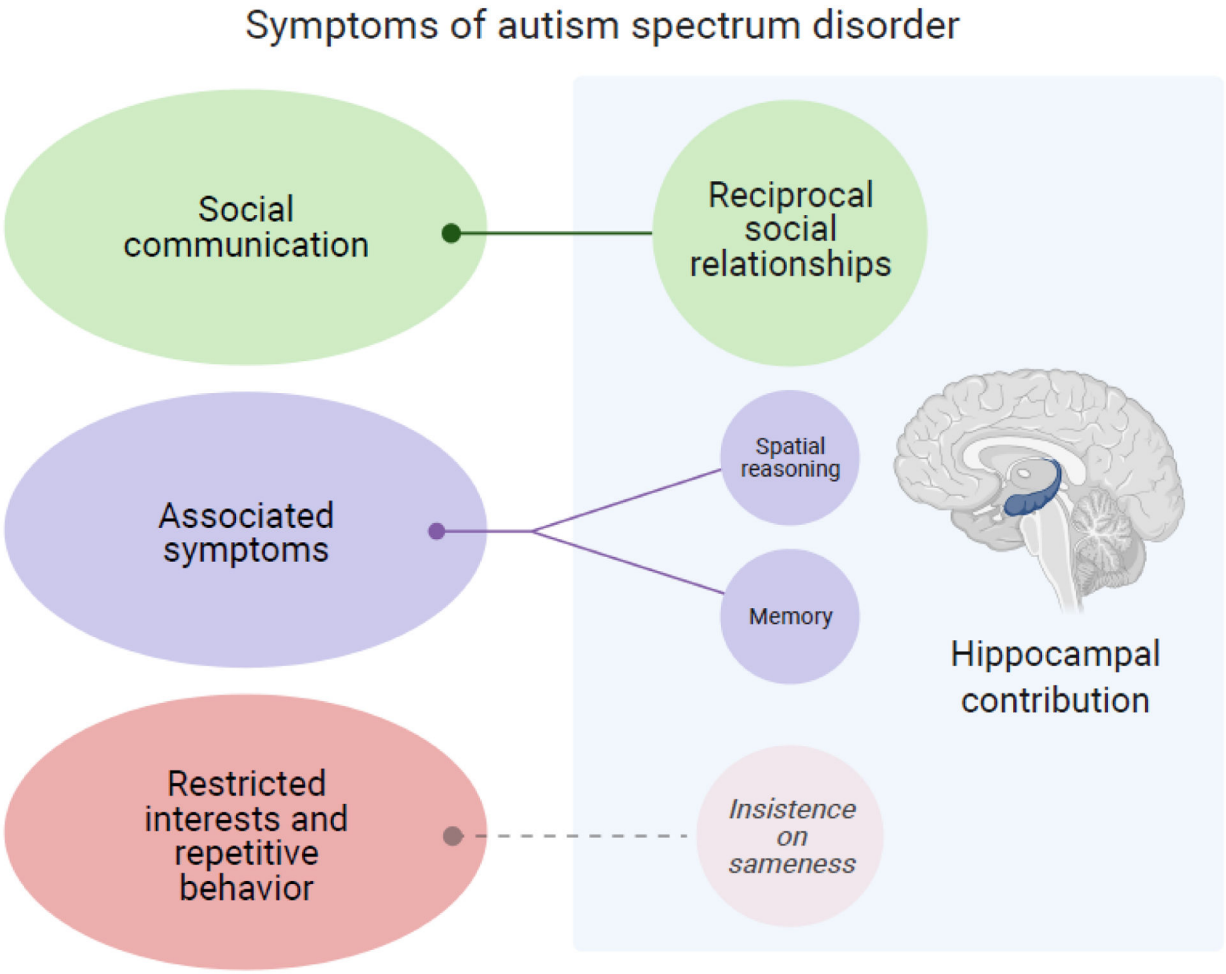

Figure 2:

Impairments in reciprocal social relationships, spatial reasoning, and memory are components of the three main symptom clusters that comprise the ASD phenotype. The hippocampus is known to support these behaviors; hippocampal abnormalities may thus lead to some of the symptoms commonly observed in ASD. Though there is a lack of direct evidence for hippocampal involvement in **insistence on sameness**, a prevalent symptom in ASD characterized by ritualistic behaviors and circumscribed interests, altered functioning of the hippocampus may lead to such behaviors through impairments in cognitive mapping. The size of the circles represents the prominence of each symptom in the ASD phenotype, with larger circles indicating aspects that are more at the core of the disorder. Figure created with BioRender.com.

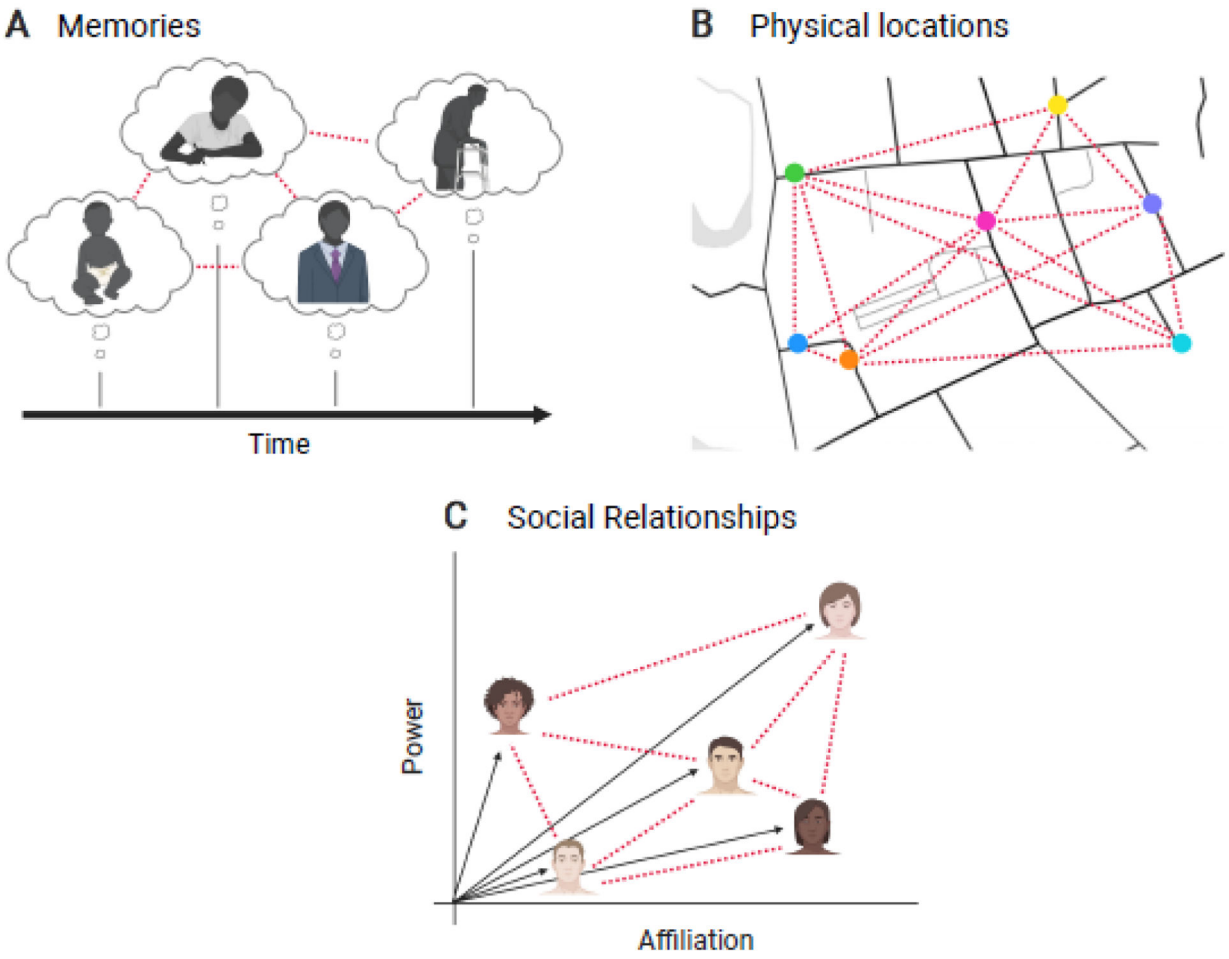

Figure 3.

Cognitive mapping across domains. Cognitive maps store representations of the relationships between elements, including A) memories, B) physical locations, and C) social relationships. In some experimental paradigms, social relationships are conceptualized within a two-dimensional map, as illustrated in the schematic, of varying degrees of affiliation and power. Figure created with BioRender.com.