Neuronal ensemble dynamics in social memory
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Abstract
A large body of evidence suggests that cognitive functions rely on the coordination of ensembles of neurons across brain circuits. One example is social memory, the ability to recognize and remember other conspecifics. A broad range of brain regions have been implicated in social behaviors and memory processes. At the single-cell level, neurons from different brain areas have responded to specific social features. The coordination of these ensembles both within a region and across structures is required to support social memory and decision-making. The synchronous activation of these neuronal ensembles could allow for the integration of different aspects of a social episode into a unified representation of experience. In this review, recent results on the circuit basis and physiological mechanisms of social memory are discussed, from a systems neuroscience perspective. An integrative framework of the neuronal ensemble dynamics supporting this fundamental cognitive ability is proposed.

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Introduction
Social behaviors are a central aspect of many animal taxa, including humans. In order to navigate their social world, animals are required to interact and recognize other conspecifics. They need to encode and remember the identity and previous interactions with other members of their group in order to adapt and make decisions about their behavior. This ability is referred to as "social memory", a specific type of declarative memory [1]. Investigating the neural basis of social memory has been traditionally challenging due to its inherently multi-modal nature and the complexity of social behaviors.

However, in recent years, the development of new technologies to record [2] and manipulate neural circuits [3] in behaving animals (particularly in rodents) and novel computational tools for the analysis of neural activity and behavior [4] have helped to shed light into the brain mechanisms of social memory. Many aspects of social behaviors are being tested in laboratory settings with the use of traditional [5] and non-traditional model organisms [6,7]. While there are fundamental differences between the repertoire of social behaviors across species, there is one key feature that is common to all of them: their ability to recognize and remember other conspecifics. Focusing primarily in the rodent literature, in this review, recent findings are discussed in an effort to put forward an emerging, system neuroscience framework of the neuronal ensemble dynamics that support social memory.

Anatomical basis of social memory
Most of the research in social memory have been focused on brain structures that are well known for their role in declarative memory [1], such as the hippocampus (HP) and the medial prefrontal cortex (mPFC). Social memory has been shown to share a common anatomical and physiological basis with other types of memories but also important differences in terms of circuits, cell types and neurotransmitters.

The hippocampus has been shown to be fundamental for the encoding, consolidation and recall of declarative memories [1,8]. Most of the work about the synaptic and network mechanisms that support these processes have focused on spatial memory paradigms. This emphasis originated after the remarkable discovery that individual hippocampal pyramidal cells increase their firing rate at specific locations ('place fields') [9,10] and form, as a population, a 'cognitive map' of the environment [11]. More recent evidence indicated that these 'place cells' do not encode space in an absolute manner but rather respond to behaviorally salient features in space, time and other arbitrary domains [12–14]. Therefore, hippocampal cognitive maps constitute a neural coding mechanism that organizes relational information about events experienced during behavior [15]. In recent years, several findings have emphasized that the hippocampus is also involved in the processing of social episodes. The CA1 [16,17] and CA2 [18–22] regions of the dHP have been implicated in encoding various features of social representations, including the

position of other conspecifics, as well as in consolidating a social episode [23]. CA1 pyramidal cells in the ventral hippocampus (vHP), which receive projections from dorsal CA2 region of the hippocampus (dHP), have been shown to be necessary for storing the memory of a conspecific [24–26]. On the other hand, parvalbumin interneurons in ventral hippocampus are involved in social memory discrimination [27]. Both dorsal and ventral hippocampus send projections and receive inputs from other regions that have been also implicated in social memory. A projection from ventral CA1 to the nucleus accumbens (NA) has been reported to be necessary for social memory encoding and recall [24,25]. Cell ensembles in the PFC increase or decrease their activity during social explorations in an ON and OFF manner [28]. In addition, adult-born neurons in the dentate gyrus (DG) are required for social memory maintenance [29], and activity-dependent tagging of DG cells during fear learning showed reactivation of these cells during social but not stressful experiences [30]. Furthermore, projections from the lateral entorhinal cortex to DG [31] and CA2 [32] are needed for social memory formation and retrieval, potentially conveying discriminant olfactory cues to the hippocampus [33]. The lateral septum, one of the main target areas of CA2 [20,34], has been linked to various social behaviors, including social recognition before an aggressive encounter [34] and kinship recognition [35].

The mPFC works intimately in concert with the hippocampus, receives direct projections from the vHP and has been highlighted for its important role in the long-term consolidation of memories and the formation of higher-order 'schemas', potentially contributing to transform episodic memories into semantic concepts [36,37]. In support of this hypothesis in the context of social memory, the mPFC has been implicated in the encoding of higher-order social relationships, such as dominance and social rank [38,39]. In addition, a subpopulation of pyramidal cells in the mPFC were shown to be activated after social interactions and their silencing impaired social memory formation [40]. Moreover, altered synaptic connectivity was found to underlie social memory deficits in a mouse model of autism spectrum disorder and replicating this alteration in wild-type animals resulted in impaired social recognition [41]. Furthermore, a subpopulation of neurons from the prelimbic portion of the mPFC that projects to the NA are active during social investigation [42]. Selective excitation of these neurons via optogenetic stimulation resulted in decreased social preference, with no effect on novel object preference, while inhibition of mPFC neurons that project to the shell of the NA impairs social recognition without affecting social preference.

Several subcortical brain structures have also been involved in social memory. One of them is the medial septum, where serotoninergic modulation bidirectionally controls social memory formation [43]. In addition, inhibition of cholinergic neurons in the medial septum/diagonal band of Broca impaired conspecific discrimination [44]. In another subcortical structure, the supra-mammillary nucleus, a subset of neurons that modulate the output of CA2 hippocampal neurons under a high cholinergic tone [45], was shown to be activated when animals interacted with novel conspecifics [46]. In addition to the cholinergic and serotonergic systems, there are other neurotransmitters that are crucial for social behaviors, such as vasopressin and oxytocin. The vasopressin 1b receptor (Avpr1b), profusely expressed in the paraventricular nucleus of the hypothalamus (PVN) and CA2 [20,34,47], is required for social recognition in various social contexts, including aggression [34], territoriality and pair bonding [48,49]. Oxytocin receptors (Oxtr) are also expressed in the supraoptic and PVN areas of the brain and CA2/CA3a areas of the hippocampus [47,50]. They have been shown to be necessary for conspecific discrimination, presumably by increasing the saliency and rewarding value of the stimulus animal [51]. Importantly, stimulation of axons in the basolateral amygdala (BLA) originated from oxytocin-expressing neurons in the PFC, and abolished the ability of mice to distinguish familiar, but not novel, conspecifics [52].
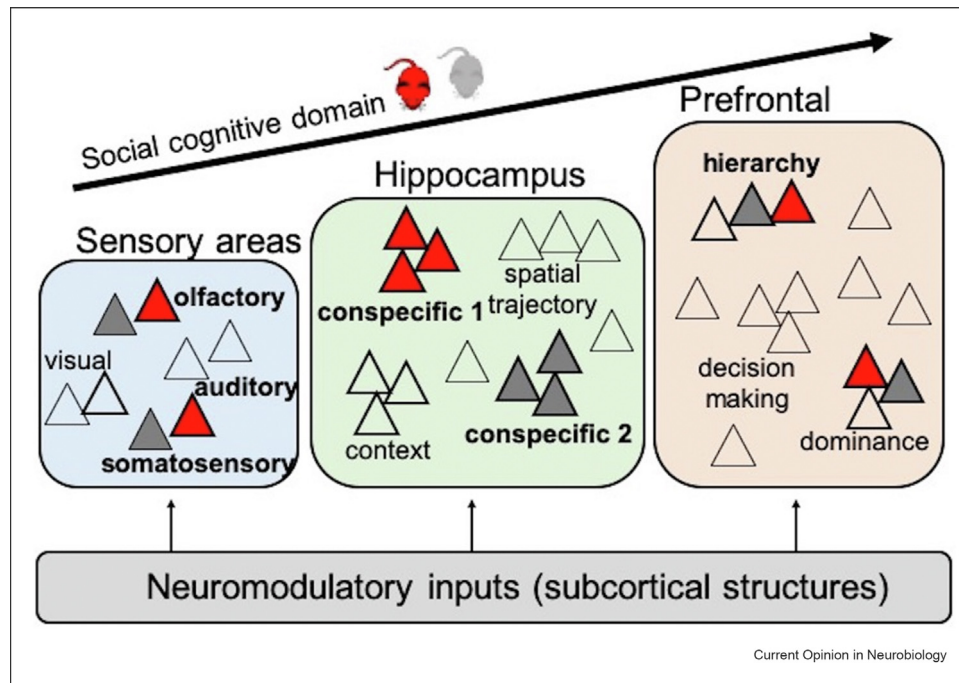
In summary, multiple brain regions are involved in various aspects of social memory, with a large overlap, but also some distinct specializations with the circuits, cell types and neurotransmitters involved in other types of declarative memory. This body of evidence suggests that social memory relies on the coordination of cell ensembles across distributed brain structures (Figure 1), as is the case for other cognitive functions.

From single cells to ensemble dynamics across species

Electrophysiological recordings in humans and other primates have shown that single neurons respond to social features or even to the identity of specific individuals. Single cells in the human medial temporal lobe (MTL) increase their firing rates in response to faces [53] and other features related to specific individuals [54]. It was suggested that a subpopulation of neurons in the MTL encode the semantic knowledge of individual identity [54]. These 'grandmother cells' respond to the face, name or voice of a particular individual and are invariant to the context or sensory features of the stimuli [53,54]. In macaques, cells that respond to faces were also described in the inferotemporal cortex (IT) [55]. Later, Tsao and colleagues showed that neurons that respond to different facial features (such as orientation or shape) are anatomically segregated into 'patches' along the IT anatomical axis [56].

In other species, single cells in the CA1 hippocampal region of rats [16] and bats [17] have been shown to fire in response to the position of other conspecifics. In

Figure 1

Schematic of how several brain structures can contribute to the formation of a social memory. Single neurons (triangles) that respond to specific features (sensory features, behavioral features …) can coordinate into an ensemble of neurons that represent the various elements of social episodes (such as the identity of various conspecifics -in red and grey- or complex aspects of behavior, such as hierarchy). While the different ensembles in more primary sensory areas can code single sensory modalities, they could combine into an episode through hippocampal neuronal ensembles, with an abstract social meaning (i.e., hierarchy) encoded in cortical ensembles.

mice, cells from the hippocampus, predominantly from the dorsal CA2 [23] and ventral CA1 [24–26] respond to social interactions and distinguish between novel and familiar conspecifics [22]. Interestingly, neurons in the hippocampus [33] and lateral septum [35] can differentiate between odors of different conspecifics. On the other hand, responses of a subset of mPFC neurons that projects to the NA show mix selectivity for social and spatial information [42]. Single neuron's responses in other areas, such as glutamatergic neurons in the medial preoptic area, respond to social stimuli, but not to other rewarding stimuli [57]. Importantly, it has also been shown that subsets of neurons from the mPFC increase or decrease their firing rates during specific social behaviors (approach, retreat …) in mice [58] and bats [59] as well as during social interactions with either male or female conspecifics [60].

In recent years, a paradigm shift in systems neuroscience facilitated by the possibility to record simultaneously from large numbers of neurons put forward the idea that neuronal ensembles, rather than single neurons, are the *functional units* for information processing in the brain [61,62]. This ensemble of neurons can provide both robustness and flexibility to support complex functions, such as encoding, consolidation and retrieval of memories, including social
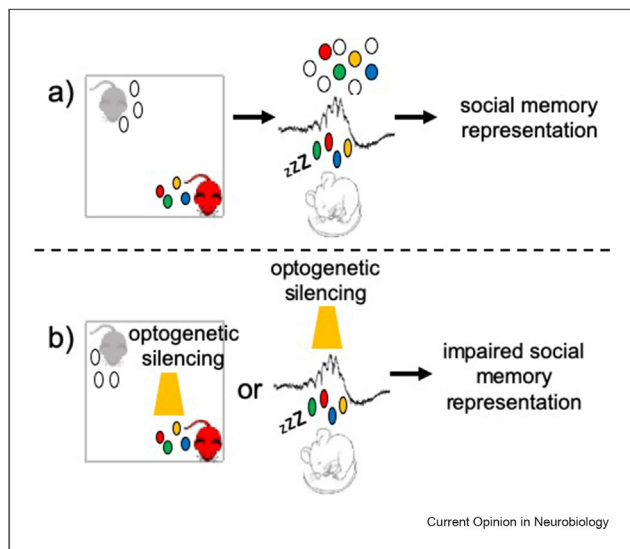
information. In order to encode a social episode, different types of information need to be combined into an integrated representation. On one hand, an animal has to identify the other conspecific(s) using whichever available (or more salient) sensory modalities (olfactory, visual, somatosensorial etc.). On the other hand, the interaction will take place in a particular spatiotemporal context. In addition, social interactions can also have different valence, ranging from negative (such as aggression) to positive (e.g., mating). A flexible and efficient way to generate a unified representation of such an episode would be to combine the representation of individual features (e.g., conspecific odor, location, valence, etc.) via synchronous activation of cell ensembles (Figure 2b).

In summary, while single neurons can respond to specific sensory features, behavioral categories or even social identity, the coordination of distributed neuronal ensembles is needed for the formation of complex representations, such as that of a social episode.

Population dynamics of memory ensembles
The activation of neuronal ensembles encoding aspects of experience follows a precise temporal coordination both during behavior and 'offline' periods (such as rest or sleep). In the hippocampus, the activation of

Figure 2

a) Schematic of how ensembles of neurons that are active during interactions with various conspecifics are later reactivated during offline (sleep) periods. Different colored circles represent different neurons. A neuronal ensemble composed of various neurons can represent a conspecific. b) Optogenetic silencing of these ensembles during behavior (left) or subsequent sleep (right) impair social memory [23].

neuronal ensembles that represent a particular spatial trajectory is recapitulated in a compressed temporal manner during highly synchronous network events, such as theta oscillations and sharp-wave ripples [63,64]. Disruption of sharp-wave ripples during behavior [65,66] or subsequent sleep [67] or silencing specific assembly activity during behavior [68], impairs learning and memory. In an analogous way, it was recently shown that the neuronal ensembles that are active during interactions with particular conspecifics are later reactivated during sleep sharp-wave ripples, and disruption of these ensembles during behavior or post-experience sleep-impaired social memory [23] (Figure 2). In addition, vCA1 neurons that preferentially respond to conspecifics reactivate during sharp-wave ripples, and this phenomenon is abolished in a mouse model of autism [69]. Whether dCA2 and vCA1 reactivation of socially responsive ensembles during sharp-wave ripples serve the same or alternative functions, it remains to be investigated. At the single-cell level, dCA2 cells have been implicated in the encoding of a novel conspecific [19,22,23], whereas vCA1 cells respond to familiar conspecifics [24–26]. One possibility is that the reactivation of ensembles of cells in dCA2 and vCA1 subregions during sharp-wave ripples helps consolidate a novel versus a familiar conspecific respectively in a segregated way. Alternatively, both regions could coordinate together the consolidation of the entire social episode. In this case, complementary aspects of a given social episode could be encoded by dCA2 or vCA1

selectively and their simultaneous reactivation during SWRs could support the integration of these features into a single memory representation. This integrative scenario seems more plausible given the complexity of social memory representations (i.e., more features need to be encoded and reactivated) and the connectivity between dorsal and ventral sides of the hippocampus [19,22,23]. The sequential order of activity of hippocampal cells that encode successive positions along a trajectory and events in time has been proposed as a mechanism for episodic memory [70]. These same mechanisms that generate a 'cognitive map' for space and memories have been proposed to also encode social relationships [71,72]. However, it is not yet clear how the stereotypic temporal organization of ensembles arises based on the diversity and variability of social interactions. While the experience of interacting with a particular conspecific does not impose a temporal order at the behavioral level, an intrinsic sequential structure could arise due to anatomical wiring, cell excitability or input-timing properties of afferent regions.

Social behaviors – an ethological note
The increased interest in understanding the neural basis of behavior promoted the development of a broad variety of social behavioral paradigms that can be used in the laboratory. Even highly simplified social behavioral assays have proven very useful, particularly when combined with cell-type or circuit-specific manipulations. However, the variety and complexity of social interactions that animals exhibit in their natural habitats are far larger than what has been reproduced in laboratory assays (for a recent review see [74]). Importantly, the brain circuits and physiological mechanisms investigated in reduced laboratory preparations have evolved to support more complex demands in environments that are richer than the ones provided by laboratory settings. Interoceptive processes such as the internal state of an animal (motivational, metabolic, endocrine, etc.), can affect the way a subject perceives and interacts with other conspecifics. Even interactions with the same conspecific (or in the same context) can have very different impacts due to these factors and affect both, the innate and cognitive components of social behaviors [73]. On the other hand, social interactions often involve groups of individuals [75], while most laboratory assays only consider a few interacting animals. Animal groups are often organized in a hierarchical manner, and the respective rank of two interacting conspecifics greatly affects their behavior [39]. Environmental conditions (seasons, climate) or variability in the ecosystem of subject animals (predators, resource availability) are key for the social behavior of any individual. As the techniques for animal tracking, analyzing behavior, recording and manipulating brain activity via wireless technology continue to evolve, adopting more naturalistic behavioral paradigms is a pressing need for understanding the neural circuit dynamics of social memory.

Conclusions and future directions

In the last decade, new experimental and theoretical evidences suggest that the coordination of neuronal ensembles across distributed brain structures underlies the generation of complex cognitive functions, including social memory. However, more research is needed in order to understand how individual cell responses, often encoding single sensory modalities, can efficiently generate a unified representation of experience, such as the identity of a conspecific. In addition, it remains to be understood how the episodic and semantic aspects of social memory are integrated in the brain during a social episode. Furthermore, it is still unclear how the temporal coordination of neuronal responses at a behavioral scale during social interactions is generated and later reactivated for memory consolidation. The use of more naturalistic assays could help shed light on how well mechanistic models generated in reduced laboratory paradigms can be extended to explain more complex social behaviors exhibited by multiple animal species in their natural habitats.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

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*   of special interest
** of outstanding interest

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In this study, the authors investigated the dynamics of the spatial and social structure of rewilded laboratory mice in natural environments.