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On the novel mechanisms for social memory and the emerging role of neurogenesis

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ABSTRACT

Social memory (SM) is a key element in social cognition and it encompasses the neural representation of conspecifics, an essential information to guide behavior in a social context. Here we evaluate classical and cutting-edge studies on neurobiology of SM, using as a guiding principle behavioral tasks performed in adult rodents. Our review highlights the relevance of the hippocampus, especially the CA2 region, as a neural substrate for SM and suggest that neural ensembles in the olfactory bulb may also encode SM traces. Compared to other hippocampus-dependent memories, much remains to be done to describe the neurobiological foundations of SM. Nonetheless, we argue that special attention should be paid to neurogenesis. Finally, we pinpoint the remaining open question on whether the hippocampal adult neurogenesis acts through pattern separation to permit the discrimination of highly similar stimuli during behavior.

1. Introduction

Without large-scale collective behavior, it is possible that none of the key components of our civilization would have emerged (Goldstone and Gureckis, 2009; Kelly et al., 2017; Nathan Spreng, 2013). Throughout the evolutionary process, we have developed skills that allow us to make inferences on what is happening to other people - their intentions, feelings, emotions and thoughts – as part of a broader concept of social cognition (Ochsner and Lieberman, 2001). Elementary to our social cognition is to acquire, consolidate and eventually retrieve the traits of other individuals; which we named as social memory (SM), for the purpose of this review.

A common feature of several neuropsychiatric disorders is the impaired ability to process social information (Gayer-Anderson and Morgan, 2013; Lord et al., 2000; Thorup et al., 2006), which has been igniting the field of neurobiological basis of SM. Here, we review some of the newest findings, focusing on rodents and two brain areas: the olfactory bulb (OB) and the hippocampus (HIP). We also present evidence supporting the pivotal role of neurogenesis on SM persistence. Finally, we share some thoughts about the future directions in this field.

2. The core concepts of social memory in rodents

The diverse event-related elements that compose episodic memories may be retrieved by answering questions such as "what", "where", "when" and "who" (Tulving, 2001, 1983). Although those elements can be assessed simultaneously in humans (Horner and Burgess, 2014, 2013), in mice they are frequently analyzed separately by using distinct protocols (Engelmann, 2009; Perna et al., 2015). For instance, the object recognition test is commonly used to evaluate most of the aspects of episodic-like memories, while the social recognition test is one alternative to evaluate the “who” component of episodic-like memories.

Different paradigms can be used to test SM in laboratory. For instance, there is the habituation-dishabituation (Ferguson et al., 2002; Perna et al., 2015), the partner preference (Perna et al., 2015; Winslow, 2003), the social transmission of food preference (Bessières et al., 2017; Loureiro et al., 2019; Wrenn, 2004), the volatile cage (Hädicke and Engelmann, 2013; Noack et al., 2010), the social aggression context-associated (Crestani et al., 2018) and many more. In this review we will focus on two specific paradigms: social recognition and social discrimination. The following premises guided our choice: (1) they are feasible to be tested in rats and mice; (2) both paradigms allow testing long-term SM; and (3) in both protocols there are minimal interference of reproductive and aggressive behaviors.

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Behavioral aspects of SM have both recognition and discrimination components (Camats Perna and Engelmann, 2016). The recognition protocols predict the presentation, in sequence, of the same social stimulus (Table 1). On the other hand, the discrimination component involves the simultaneously presentation of two social stimuli, one familiar and one novel (Table 2). Moreover, the discrimination protocols have additional features, since during the test session the experimental subject has to recognize the familiar stimulus at the same time it is acquiring the information about the novel subject. In fact, it should be noted that SM, like any other memory, is a complex and dynamic process, making it practically impossible to completely dissociate the components of sociability, recognition, discrimination and social novelty preference when we are evaluating it in laboratory animals (Okuyama, 2018).

Rodents use mainly olfactory information to sample conspecifics (Brennan and Kendrick, 2006). Accordingly, the time the experimental animal spends smelling the social stimulus is the independent variable in practically all studies on SM, and can be quantified manually or automatically. Therefore, it is paramount to have a slight understanding about the olfactory system physiology.

Social behavior in most vertebrates is mediated by chemosensory cues detected and processed by both the main olfactory and the vomeronasal systems (Kelliher, 2007). Chemoreceptors randomly distributed in the main olfactory epithelium (MOE) detect odors (Chess et al., 1992; Ishii et al., 2001; Serizawa et al., 2004) and generate a combination of unique sensorial responses that are sent to the main olfactory bulb (MOB), which processes and distributes information to areas located in the thalamus, limbic system and cortex (Sánchez-Andrade et al., 2005; Sanchez-Andrade and Kendrick, 2009). From the olfactory cortex there are substantial projections to the dorsomedial thalamus and to the ventral part of the submedial nucleus, which projects to the frontal cortex. In addition, projections from the olfactory lateral tract reach the lateral entorhinal cortex and, through the perforating pathway, to the hippocampus. Thus, the information about odors are able to reach the upper cortical areas involved in awareness, as well as areas involved in motivational and emotional responses (Fujioka et al., 2009; Kogan et al., 2000; Licht and Meredith, 1987; Sanchez-Andrade and Kendrick, 2009).

The vomeronasal system in rodents (reviewed by Brennan and Kendrick, 2006; Dulac and Torello, 2003) detects pheromones, but also odors in general (Baxi et al., 2006; D'Aniello et al., 2017). Most of studies on vomeronasal system focus on understanding how female mice form a memory of the pheromonal signal from the male with which they had mated (Thoß et al., 2019; also see the review Martinez-Marcos, 2009).

Apart from its role as sensorial detector, we argue that OB neural ensembles may encode social memory traces. The excitotoxic lesions of the OB cause relevant impairment in SM recognition (Bluthé and Dantzer, 1993; Matochik, 1988). Our research group have previously showed that inhibiting protein synthesis immediately and 6 h after training impaired long-term SM consolidation (Pena et al., 2014). Additionally, changes in OB network activity have been observed during social recognition task, such as: (1) the retrieval of long-term social memory positively correlates with fast gamma power in the OB (Almeida-Santos et al., 2019) and; (2) the activity of the OB's granular cell layer predicts with 100 % accuracy the familiar versus non-familiar animal identification, 24 h after the first encounter (Lüscher Dias et al., 2016). Furthermore, oxytocin, a well-known pro-social peptide released from cortical inputs into the OB specifically modulates SM recognition (Oettl et al., 2016).

Although suggestive, these results do not address whether ensembles in the OB, in fact, are part of the SM engram. Recently, it was demonstrated that odor-related memories are stored in the anterior olfactory nucleus (Aqrabawi and Kim, 2020) and piriform cortex (Meissner-Bernard et al., 2019). However, whether social content shares similar mechanisms to odor memory formation and storage in olfactory-related structures remains largely unknown.

Among the structures with which the OB synapses, we can highlight the hippocampus. Only two synapses separate the MOB from the dentate gyrus of the hippocampus, via lateral entorhinal cortex and perforating lateral pathway (Vanderwolf, 1992). There is also top-down modulation from the hippocampus to the OB, through projections to the granular cell layer of the OB, via the entorhinal cortex and directly through the ventral hippocampus CA1 (vCA1) (Van Groen and Wyss, 1990). To date, several studies have suggested that both identification of olfactory patterns, as well as their interpretation and formation of related memories, depend on bidirectional interaction between the OB and the hippocampal areas (Almeida-Santos et al., 2019; Eichenbaum, 2000; Martin et al., 2007; Nadel and Moscovitch, 1997; Wiltgen et al., 2004). Interestingly, these regions - OB and hippocampus - are the two main areas of the brain where neurogenesis occurs (Aimone et al., 2011; Bond et al., 2015; Kempermann et al., 1996; Sahay et al., 2011). We explore this topic in more detail later (see the section "The emerging role of neurogenesis on social memory").

3. Molecular mechanisms underlying social memory

Memory storage is a dynamic process resulted from multiple levels of brain organization. The molecular and cellular modifications are the

Table 1
Studies investigating the recognition component of social memory.

	Species	Training length	STM	LTM	Social stimulus	Experimental apparatus	Social stimuluspresentation	References
RECOGNITION	Rat	5 min.	≤2h	x	Male juvenile	Usually its homecage	Free	Burman and Mendl, 2000; Everts and Koolhaas, 1997; Hliňák and Krejči, 1995; Kelly and Tran, 1997; Lemaire, 2003; Lemaire et al., 1992; Moura et al., 2010; Shahar-Gold et al., 2013; Terranova et al., 1994; Thor et al., 1982
	Mouse	1–1.5 min.	2h	x	Male juvenile	Standard mouse cagedifferentof it homecage	Free	Fukushima et al., 2008; Ishikawa et al., 2014; Nomoto et al., 2012; Tanimizu et al., 2017
		2 min.	30 min.	24 h;7d	Male juvenile	Standard mouse cagedifferentof it homecage	Free	Kogan et al., 2000; Leroy et al., 2017; Meira et al., 2018
		3 min.	2h	24 h	Male juvenile	Standard mouse cagedifferentof it homecage	Free	Fukushima et al., 2008; Inaba et al., 2016; Ishikawa et al., 2014; Nomoto et al., 2012; Serita et al., 2019; Suzuki et al., 2011
		5 min.	≤1.5h	24 h;7d	Male juvenile	Standard mouse cagedifferentof it homecage	Plasticcylinder	Almeida-Santos et al., 2019; Guarnieri et al., 2020; Gusmão et al., 2012; Jaimes et al., 2020; Lüscher Dias et al., 2016; Monteiro et al., 2014; Pena et al., 2014; Pereira-Caixeta et al., 2018, 2017

Table 2
Studies investigating the discrimination component of social memory.

	Species	Training length	STM	LTM	Social stimulus	Experimental apparatus	Social stimulus presentation	References
DISCRIMINATION	Rat	4 min.	≤1 h	x	Male juvenile	Usually homecage	Free	Dluzen et al., 1998; Engelmann et al., 1995; Lukas et al., 2013
		5 min.	5 min.	x	Juvenile	Circular arena	Wire cylinder	Reichelt et al., 2020
		3 × 10 min.	2h	x	Juvenile	Modified radial arm maze	Plastic cylinder	Sawangjit et al., 2017
		1 h	–	24 h	Juvenile	Open field arena	Plastic cylinder	Cavalcante et al., 2017; Zinn et al., 2016
		4 min.	1 h	24 h	Male and Female Juvenile	Standard mouse cage different fromhomecage	Free	Bielsky et al., 2005; Engelmann, 2009; Engelmann et al., 2011; Hädicke and Engelmann, 2013; Lukas et al., 2013; Perna et al., 2015; Richter et al., 2005; Wanisch et al., 2008
	Mouse	5 min.	5 min.	24 h; 7d	Male and Female Juvenile	3 chamber cage	Wire cylinder	Chiang et al., 2018; Jacobs and Tsien, 2017; Leung et al., 2018; Lin et al., 2018; Liu et al., 2018; Macbeth et al., 2009
		5 min.	–	24 h	Littermate (familiar); non-littermate (novel)	3 chamber cage	Separated chambers with perforated walls	DeVito et al., 2009; Hitti and Siegelbaum, 2014; Yang et al., 2020
		10 min.	30 min.	24 h	Juvenile or littermate	3 chamber cage	Wire cylinder	Greish et al., 2019; López-Cruz et al., 2017; Meira et al., 2018; Moy et al., 2004; Tatsukawa et al., 2018

basic steps for that organization expresses as behavior, reason why knowing the molecular basis of a memory is imperative. Unfortunately, compared to other hippocampus-dependent memories, much less is known about the molecular basis of SM. In addition, most studies aimed to name the molecular players of SM consolidation focusing on short-term memory (Leung et al., 2018).

The consolidation of SM seems to rely on protein synthesis, though the exact time-window may vary according to the brain region (Camats Perna and Engelmann, 2016; Engelmann, 2009; Gur et al., 2014; Kogan et al., 2000; Richter et al., 2005). In the hippocampus, for instance, the amnesic effect of anisomycin administered immediately after the acquisition dependents on how long the trial last (Pena et al., 2014; Tanimizu et al., 2017).

Tanimizu and collaborators evaluated the expression of c-Fos and Arc during SM formation in mice and revealed four essential brain areas: hippocampus (CA1 and CA3), medial pre-frontal cortex (mPFC), anterior cingulate cortex (ACC) and basolateral amygdala (BLA). Additionally, the authors performed a network analysis using correlation of c-Fos among these brain regions. The results suggested that there are distinct roles for each brain area in social recognition memory consolidation, but attributed the role of orchestrator to the hippocampus (Tanimizu et al., 2017).

One particularly important protein in the synaptic events surrounding the memory consolidation is the cAMP-responsive element-binding protein, CREB (Kida et al., 2002). For instance, transgenic mice expressing an inducible CREB repressor did not have long-term SM (Tanimizu et al., 2017), while the upregulation of CREB-mediated transcription enhanced long-term SM formation (Suzuki et al., 2011). Accordingly, transgenic mice overexpressing CaMKIV, which positively regulates CREB expression, have presented SM consolidation enhancement (Fukushima et al., 2008).

SM consolidation may also be closely linked to glutamate signaling in the hippocampus. It has been demonstrated that blocking AMPA, but not NMDA receptors, into the hippocampal CA1 region, immediately after training session, impaired long-term SM (Almeida-Santos et al., 2019). Moreover, in another study, genetic manipulation to overexpress the NR2B subunit of the NMDA receptor can either improve (Jacobs and Tsien, 2012) or impaired (Jacobs and Tsien, 2014) SM, depending on whether the social stimulus is a juvenile or an adult mouse, respectively. In addition, SM with 1 h duration is impaired by the knockout of the NR1 subunit of NMDA receptors in CA1 and CA3, but not in the DG. The same study used hM4D(Gi) virus to hinder hippocampal activity and found that ventral, but not dorsal, CA3 inhibition impaired memory (Chiang et al., 2018). Other molecular targets that have been studied in SM are the ones involved in protein traffic. For instance, Lnx1 is a scaffold protein specifically expressed in CA3, which deletion causes NMDA hypo-function and SM deficit (Liu et al., 2019). Synaptic trafficking of the NMDA receptors in CA2 pyramidal neurons depends on SorCS2 protein, which deficiency causes significant SM deficit, with no change in sociability, olfaction, anxiety, or several hippocampal-dependent behaviors (Yang et al., 2020).

In addition to CA2 and CA1 hippocampal regions, the entorhinal cortex-dentate gyrus (EC-DG) circuit seems necessary and sufficient for SM recall. For instance, disrupting the PAK (p21-activated kinase) signaling, a key pathway important for cytoskeletal reorganization, leads to impairments in synaptic function and social recognition memory (Leung et al., 2018).

4. From no hippocampus to the all in the CA2

The effect of protein inhibitors, as well as lesion studies had disagreed about whether the hippocampus is a neural substrate for SM (Bannerman et al., 2001; Engelmann, 2009; Ferguson et al., 2001; Kogan et al., 2000; Richter et al., 2005; Samuelsen and Meredith, 2011; Squires et al., 2006). Additionally, c-Fos expression in the hippocampus after a single social encounter, which matches up with the acquisition phase of SM, is not consistent either (Lüscher Dias et al., 2016; von Heimendahl et al., 2012). Therefore, for a long time the dependency of the hippocampus in SM was questioned.

The skepticism about the role of hippocampus on SM has been overcome by modern molecular tools such as, optogenetics and chemogenetics, that allow a much more precise manipulation of hippocampal neurons. In this scenario, the dorsal CA2 region of the hippocampus (dCA2) (Kohara et al., 2014; Lein et al., 2005; Pang et al., 2019; Piskorowski and Chevaleyre, 2018; Sekino et al., 1997) has been standing out as the SM neural substrate. Hitti and Siegelbaum (2014) generated a transgenic mouse line (Amigo2-Cre) that expresses Cre recombinase predominantly in CA2 pyramidal neurons (PNs) in adult mice. Surprisingly, the irreversible inactivation of CA2 impaired SM, but not other hippocampus-dependent memory or olfaction. Using the lesion approach, others reinforce the importance of CA2 region to SM (Stevenson and Caldwell, 2014). Although both studies did not address long-term SM, they ignited an avalanche of papers focusing on the physiological role of dCA2 (Alexander et al., 2019, 2018, 2016; Brown

et al., 2020; Dudek et al., 2016; Leroy et al., 2017; Meira et al., 2018; Smith et al., 2016; Srinivas et al., 2017). For instance, the reversible and dynamic inhibition of dCA2 showed its importance in all SM phases: acquisition, consolidation and retrieval (Meira et al., 2018). Interestingly, the same authors showed that inhibiting dCA2 does not disrupt a well-consolidated SM trace, though impaired its retrieval. Furthermore, Smith and collaborators (2016) found that activating vasopressinergic terminals in dCA2 during the acquisition phase improved SM tested 24 h and 7 days later. And most recently, it has been demonstrated that dCA2 ensembles activation, during the social exploration of previously unknown conspecifics, are reactivated during sharp-wave ripples (SWRs) (Oliva et al., 2020).

In the previous section, we presented evidence that SM acquisition and retrieval alter c-Fos expression in the hippocampus (Lüscher Dias et al., 2016; Tanimizu et al., 2017). In view of the recent knowledge about the role of CA2 in SM, an unavoidable question is whether c-Fos expression changes following SM acquisition or retrieval in the CA2, specifically. Surprisingly, we could not find any study addressing this question. Thus, we would like to share some thoughts to attempt understanding the scarceness of data in this particular subject. First, the intrinsic electrophysiological proprieties of the CA2 neurons may limit the c-Fos expression at levels that the current tools are able to detect. For instance, CA2 neurons have high synaptic stability and are resistant to conventional plasticity-inducing paradigms (Chevaleyre and Siegelbaum, 2010; Talley et al., 2001; Zhao et al., 2007). Second, c-Fos may not be a suitable marker to estimate the CA2 neurons activity. In this case, the most likely candidate would be Arc, since its expression is detected in CA2 neurons (Alexander et al., 2016; Wintzer et al., 2014). Therefore, these data bring up an additional challenge for researchers interested in unveil the mechanisms involved in CA2 role on SM, which is to expand their methods beyond the classic measurement of IEGs expression.

Adding to the solid evidence associating dCA2 and SM, some authors claim that ventral CA1 neurons (vCA1) store social memory. Optogenetic inhibition of vCA1, but not dCA1, increased the olfactory exploration of a familiar mouse and decreased the discrimination score (Okuyama et al., 2016). Similarly, in rats, vCA1 neurons, but not dCA1, respond specifically to the presence of conspecifics in a gap paradigm, and this response was dependent on the sex and the individual presented (Rao et al., 2019). Moreover, the optogenetic activation of parvalbumin interneurons (PVIs) in the vCA1 impaired SM retrieval, but not acquisition (Deng et al., 2019). In addition to vCA1 and dCA2, CA3 is also involved in SM recognition. The deletion of NMDA receptor subunit 1 gene (NR1), which abolishes NMDA receptor synaptic plasticity, in CA3 pyramidal cells, but not in DG granule cells, impaired SM (Chiang et al., 2018). Furthermore, they also inhibited CA3 activity and found that ventral, rather than dorsal CA3 is necessary for the encoding of SM.

Finally, the apparent ambiguity between dorsal and ventral, as if it were one or the other substrate of SM, reconciles when we look at the connections between these two hippocampal portions (Fig. 1). dCA2 targets a vCA1 site containing pyramidal neurons that project to the NAc shell (Meira et al., 2018). One suggestion is that social information may flow from main olfactory/vomeronasal to dCA2-vCA1-NAc (Okuyama, 2018).

Overall, with these body of newest evidence, the misgivings about the role of the hippocampus in SM faded away.

5. Why social isolation dramatically affect SM persistence?

Social species, such as rodents and humans, rely on interacting with conspecifics to maintain their survival and mental health (Arthur, 2006; Cacioppo et al., 2011; Hawkley and Cacioppo, 2010; Pressman and Cohen, 2005). Thus, it is expected that depriving rodents from socialization, named here as social isolation (SI), would have profound physiological impacts (Guarnieri et al., 2020; also see review by Mumtaz et al., 2018).

The magnitude and reversibility of the effects of SI depend on when it is applied (post-weaning or adulthood) and how long it last (hours, days or months). Post-weaning or long-term SI comprehend a stress-induced model with wider and unspecific effects on memory (Domeney and Feldon, 1998; Fone and Porkess, 2008; Gentsch et al., 1988; Makinodan et al., 2012; Wilkinson et al., 1994; Wongwitdecha and Marsden, 1996). For the purpose of this review, we will direct our attention to short periods of SI during the adulthood, and its effect on SM.

The first paradigm to study SM used SI animals (Thor et al., 1982) and found that both rats and mice socially isolated for 24 h or a few days do not expressed SM 24 h after training (Bluthé and Dantzer, 1993; Kogan et al., 2000; Sekiguchi et al., 1991; Thor et al., 1982). From the

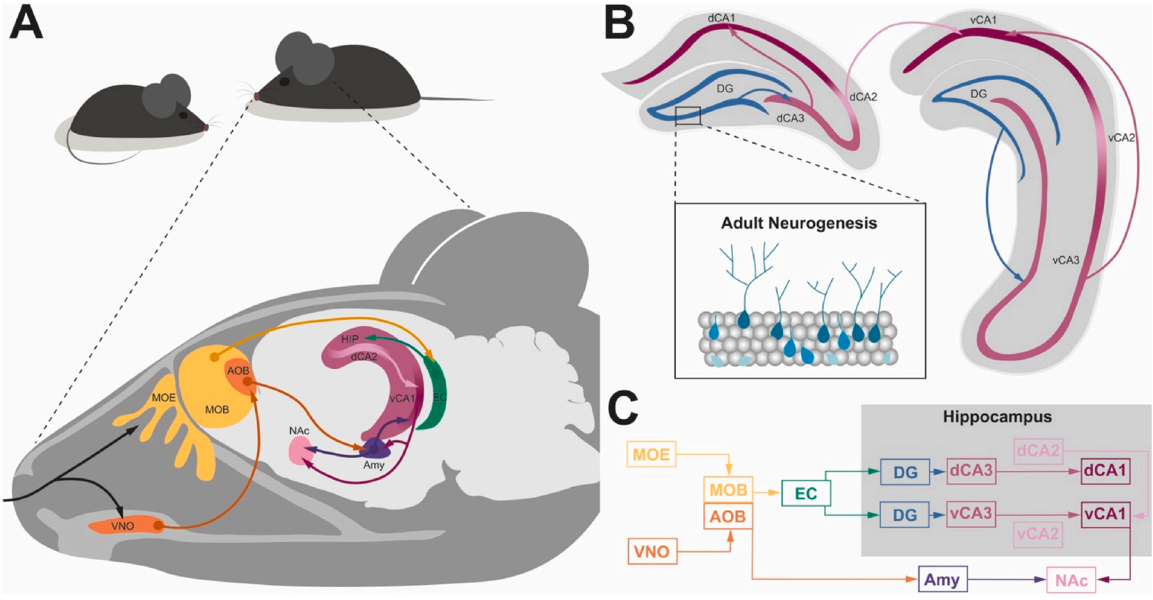

Fig. 1. State of art of social memory neural underpinnings on mouse (2-column fitting image). A. An illustration of social memory neural circuit on mouse brain. B. A close look into the intrahippocampal circuit involved in social memory. C. Diagram of the social memory neural circuit. Amy: Amygdala; AOB: accessory olfactory bulb; dCA1: dorsal CA1; dCA2: dorsal CA2; dCA3: dorsal CA3; DG: dentate gyrus; EC: Entorhinal cortex; HIP: Hippocampus; MOB: main olfactory bulb; MOE: main olfactory epithelium; NAc: nucleo accumbens; vCA1: ventral CA1; vCA2: ventral CA2; vCA3: ventral CA3; VNO: vomeronasal organ.

perspective of those interested in unraveling the neurobiological bases of SM, these results are intriguing. Why would the absence of social stimulus, even if brief, affect the persistence of SM? As mentioned before, the basic premise of SM paradigms is the assurance that a mouse will prefer to explore/sniff another mouse if it remembers that it has not met it before. Based on that, similar social investigation time in two subsequent encounters with the same juvenile indicate SM deficit. Therefore, one might think that the behavior observed in SI mice is a by-product of something ecologically more relevant, which is the need to re-establish social homeostasis (Matthews and Tye, 2019) rather than a SM deficit *per se*. However, we intend to present evidence supporting the idea the short periods of SI, such as 7 days, impaired the formation of long-term SM, without necessarily interfering in sociability (Leser and Wagner, 2015).

Our research group has been dedicated to understand the effects of SI in the persistence of SM. In our first study we showed that 7 days of SI impaired both social recognition and discrimination, tested 24 h, but not 1−2 hours after training (Gusmão et al., 2012). As we do not see difference in social exploration time during the first session, we infer that SI does not impair sociability. Furthermore, it seems unlikely that SI simply increased sociability, otherwise we should expect deficits in short-term SM as well (Kogan et al., 2000). In the same study we also evaluated other hippocampus-dependent memories, but SI mice behaved like group-housed mice, suggesting a very specific effect of SI on SM.

In an attempt to better characterize the SI effects on SM we focus on two brain areas: OB and HIP. The glutamatergic signaling homeostasis in the OB guarantees the retransmission of an odor's code (Isaacson, 1999; Wagner et al., 2006) and part of the top-down modulation from olfactory cortex and limbic system (Rojas-Líbano and Kay, 2008). We found that SI increases the glutamate release from OB synaptosomes and the blockade of AMPA and NMDA receptors in the early stages of consolidation rescued SM in SI mice. Furthermore, during retrieval of long-term memory, we observed a higher fast Gamma Power in the OB of SI mice (Almeida-Santos et al., 2019). In the same study, we found in SI mice a decreased Theta phase/Fast Gamma amplitude coupling between the OB and the dorsal HIP, during long-term SM retrieval.

In addition to the interpretation that the effect of SI on SM is an outcome of its effect on sociability, which we show evidence here of being unlikely, there is a possibility that by depriving animals from social contact we are affecting their emotional state as well. Frequently long periods of SI induce depression, anxiety and aggressive behaviors in rodents (Krupina et al., 2020; Rodriguez-Romaguera and Stuber, 2018; Wongwitdecha and Marsden, 1996). However, the results are less conclusive when the SI begins in the adulthood and for short periods (Leser and Wagner, 2015; Shahar-Gold et al., 2013).

In a recent study we found that our SI model causes depressive-like behavior estimated in the forced-swimming test, in both male and female Swiss mice. However, SM deficit was observed only in males (Guarnieri et al., 2020). In the same study, we identified that SI reduces de OB volume and altered monoamines in the hippocampus and the OB. Interestingly, antidepressants completely rescued the deleterious effect of SI, only if administered chronically. In conclusion, our study suggested that the effects of SI on depressive-like behavior and SM do not have a cause-effect relationship, but rather are concomitant. When verifying whether depression and SM impairment, caused by SI, shared the same mechanisms we highlighted the central role of neurogenesis (Guarnieri et al., 2020). In fact, increasing neurogenesis with EE rescue the SM deficit of SI mice (Monteiro et al., 2014).

The trait of being excited and pleased by novelty, named neophilia, is a basic premise of several memory paradigms, including SM. Therefore, in addition to the interpretation that the effect of SI on SM may be an outcome of its effect on sociability, one may think that SI mice have SM deficits because they have less interest in social novelty. In fact, there are some studies suggesting that SI impaired the ability of mice to discriminate familiar and novel social stimulus (Gusmão et al., 2012; Liu et al., 2018). However, future studies are necessary to better explore the social novelty preference in SI mice.

6. The emerging role of neurogenesis on social memory

Adult neurogenesis involves the continuous generation of new neurons in two regions of the adult mammalian brain: the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus (DG) (Aguilar-Arredondo and Zepeda, 2018; Drew et al., 2013; Yau et al., 2015; Ziegler et al., 2015). The progenitor cells are originated in these two regions, but the one that multiply in the subventricular zone can migrate, through the rostral migratory pathway, and reach the OB (Deng et al., 2010; Zhao et al., 2008; Ziegler et al., 2015). In mammals, the OB is an evolutionary well-preserved neurogenic zone, while DG is newest (Garthe et al., 2016; Lim and Alvarez-Buylla, 2016; Lledo and Valley, 2016) and has the higher levels of neurogenesis (Gage, 2002; Van Praag et al., 2002). Furthermore, the molecular and morphological steps to progenitor cells become adult neurons differ between OB and DG (Pallotto and Deprez, 2014).

Although the discussion about the existence of adult neurogenesis in humans spans decades (Altman, 1962; Altman and Das, 1965; Boldrini et al., 2018; Drew et al., 2013; Eriksson et al., 1998; Inokuchi, 2011; Lee and Thuret, 2018; Lucassen et al., 2020; Parolisi et al., 2018; Sorrells et al., 2018), the amount of evidence supporting that this process occurs in rodents is solid (Altman and Das, 1965; Gonçalves et al., 2016; Imayoshi et al., 2009; Zhao et al., 2008). However, the newborn neurons functional significance is still under scrutinization.

Studies have examined the neurogenesis role on memory in at least two ways. The first type of experiment asks whether altering neurogenesis before learning affect memory. In general, both approaches to gain (Christian et al., 2014; Creer et al., 2010; Kee et al., 2007; McAvoy et al., 2016; Sahay et al., 2011; Toda and Gage, 2018; Wang et al., 2014) and loss (Arruda-Carvalho et al., 2014; Glover et al., 2017; Jessberger et al., 2009; Ko et al., 2009; Saxe et al., 2006; Vukovic et al., 2013) of function support the principle that neurogenesis has positive effects on memory. Using a loss of function approach, it was showed that the degree of neurogenesis inhibition depends on the method used to inhibit it. Irradiation was more effective (~80 %) in the dorsal dentate gyrus (dDG), while in the OB, the cystosine-β-D-arabinofuranoside (AraC) inhibited around 70 % of the neurogenesis. Interestingly, in the ventral DG (vDG), both methods mentioned above and the temozolomide (TMZ) had similar percentages of neurogenesis inhibition (~45 %). Equally different was the extent of the treatment effects on memory. Contextual fear memory was slightly affected by TMZ, while object recognition and long-term SM were ubiquitously affected by irradiation, AraC and TMZ (Pereira-Caixeta et al., 2018). Accordingly, conditional transgenic mouse strain (TK mice) that selectively reduces adult neurogenesis by treatment with the antiviral drug valganciclovir have deficits in long-term SM (Cope et al., 2020), but not in spatial memory measured in the water maze (Epp et al., 2016).

Increasing neurogenesis rescued the SM impairment observed in socially isolated mice (Guarnieri et al., 2020; Monteiro et al., 2014) and double-transgenic APP/PS1 mice (Hsiao et al., 2014). Furthermore, it seems that SM can be strengthen and prolonged by neurogenesis. Enriched environment (EE), which is well known to improve the birth rate of new neurons (Brown et al., 2003; Clemenson et al., 2015; Garthe et al., 2016), allows SM to persist for a longer duration and to resist to interferences (Pereira-Caixeta et al., 2017). Similarly, the antagonism of NMDA receptors by memantine (MEM) has been showing to be effective on increasing neurogenesis in the DG (Jin et al., 2006; Maekawa et al., 2009) and to improve SM (Fukushima et al., 2014; Jaimes et al., 2020). Altogether, these results suggest that the social aspect of episodic-like memories is particularly sensitive to neurogenesis.

An issue that still remains open concerns the mechanism by which new neurons prolong SM. We had suggested that the maturation of newborn neurons rather than their number predicts the persistence of SM (Jaimes et al., 2020). For instance, as higher is the percentage of

post-mitotic cells, better is the SM performance, and the inhibition of actin polymerization blocked the EE effect on enhancing SM persistence.

The second type of experiment enquiries whether changing the neurogenesis levels after learning alter memory. Akers et al. (2014) were pioneers by describing in a very elegant study that increasing neurogenesis after learning induces forgetting in adult mice. In the same study the authors showed that in infant mice, where the hippocampal neurogenesis levels are high, reducing neurogenesis after memory formation alleviated forgetting. Even though the studies are incipient and not unanimous (Kodali et al., 2016), the propose of the neurogenesis-induced forgetting as a mechanism for newborn neurons on memory is promising (Epp et al., 2016; Gao et al., 2018; Ishikawa et al., 2019).

The two types of studies focused on when the neurogenesis is tune down or up (Frankland et al., 2013). Thus, two theories may be raised about the role of neurogenesis: clearance of old memories and the formation of new ones (Goodwin, 2018). The tendency is to assume one side or the other, since the experimental designs are different: while one modulates neurogenesis before the training session, the other modulates after the already established memory. However, we urge that the real challenge is to design behavioral protocols that combine, at the same time, oscillations in the neurogenesis levels in distinct memory phases. In fact, the homeostatic balance between weakening and strengthen memory traces is the foundation of cognitive flexibility. For instance, one of the hypotheses is that the newborn neurons are key components in the neural circuits underlying the cognitive flexibility (Cuneo et al., 2012; Frankland et al., 2013).

It is unlikely that one unified mechanism will explain the function of newborn neurons on memory transience. Thus, in designing experiments to gain mechanistic insights on neurogenesis effect, it has to be considered the memory's content.

7. Conclusion remarks and future directions

Nowadays, probably more than any other time, we have experiencing the physiological and mental impact that social restrictions have in our lives (Holt-Lunstad, 2018; Holt-Lunstad et al., 2015). Although, in humans, social cognition is strongly impacted by culture, the building blocks of the social brain are highly conserved from an evolutionary point of view (Dunbar, 2009; Dunbar and Shultz, 2007; Insel and Fernald, 2004). Therefore, this review set out to highlight the main neurobiological aspects of SM, which is a key component of social cognition.

The neurobiological study of SM is nowhere near as wide-ranging as those of fear memory, for example. We have been noticing that some factors may be contributing to such disparity. For instance, the protocols to access SM differ in trial's duration, type of stimuli (juvenile, adult, male, female), context (home-cage, three-chamber), pre-training manipulations (social isolation, paired-housed) and some studies restrict the interaction between animals by exposing the social stimulus inside a cup or cage. We assume that as long as each group perform different paradigms and protocols to behaviorally analyze SM, while manipulating neuronal activity, it will be very difficult to reconcile those results in a unique model about the neuronal circuit of SM. In fact, it is possible that the consensus about the elementary neural circuits of fear memory exists because in the majority of studies, the subtle differences between protocols do not eliminate the basic principles of the paradigm: (1) the shock is the unconditioned stimulus and (2) the context and the sound are the conditioned stimuli.

On the top of those difficulties on standardizing the behavioral paradigms to study SM, several studies fail to provide the reader with the details of their experimental protocol. For example, many studies describe the molecular pathways in short-term SM tests and sell these results as if in long-term SM would be the same. For the benefit of the field, we encourage studies that treat short and long-term SM as different entities.

Regarding the mechanisms underlying SM, the pattern separation emerges as a candidate not yet explored. For instance, pattern separation refers to a type of neural coding, whereby overlapping input patterns are coded as less overlapping output codes (McClelland and Goddard, 1996; Rolls, 2016). Empirical data and theoretical models have been suggesting that neurogenesis promotes pattern separation in the DG (Piatti et al., 2013). There are also indications that OB engages on pattern separation with help of the newborn neurons (Gschwend et al., 2015; Li et al., 2018). However, despite the solid evidence linking neurogenesis and SM, further studies are needed to test whether pattern separation is a type of neural coding used to recognize and discriminate conspecifics.

Recent findings based on single-neuron recordings have shown that recognition of faces in humans does not involve pattern separation, but rather partial overlapping assemblies (Quian Quiroga, 2020). Estimating that social recognition in mice would be equivalent to the recognition of faces in humans, we might think that pattern separation is also not evident in rodents. Based on the neuronal activity in vCA1 after exploring a familiar *versus* a novel subject, it was also suggested a partial overlapping assemblies in mice (Okuyama et al., 2016). By contrast, social exploration of familiar, but not novel animal, increases c-Fos expression in DG (Lüscher Dias et al., 2016), which suggests pattern separation. In the same sense, if individuals are encoded by partially overlapping neuronal assemblies only, we should not expect interference of novel social stimulus during the SM formation. However, at least at the behavioral level, the presentation of a juvenile cause retroactive interference on SM (Engelmann, 2009). In his review, Okuyama (2018) suggests that finding the social concept cells is the next step to understand SM in rodents. But the individual mouse-specific firing pattern, similar to concept cells, have not been observed in rodents so far (Alexander et al., 2016; von Heimendahl et al., 2012).

We reviewed several studies that situate CA2 at the center of the neural circuits underlying SM at the same time we proposed neurogenesis as one of the key mechanisms involved in the formation of SM. One may think whether these two elements interact? Even though there are no studies in the literature addressing directly this matter, we can speculate whether the SM-dependency of adult neurogenesis and CA2 activity are simultaneous or independent events. One study found that the immature granule neurons from DG synapse with CA2 pyramidal neurons (Llorens-Martín et al., 2015). It would be very interesting, in the future, to verify whether the promnesic effect of neurogenesis on SM (Jaimes et al., 2020; Monteiro et al., 2014) depends on CA2 activity and/or plasticity, for example.

Overall, the field of SM has been blooming in the past decade. However, much remains to be understood. Does the pattern separation encoding a mechanism involved in the promnesic effect of neurogenesis on SM? Considering the solid evidence for the CA2 role on SM, it would be interesting to address whether CA2 is a target for SI deleterious effect. Equally interesting would be to investigate whether the OB neurons are part of the SM engram, which is certainly a gap that needs to be fulfilled. Finally, we hope to have piqued readers' interest to join us in expanding the neuroscientific research into the mechanisms underlying the social memory engram.

Author statement

All authors wrote the review and discussed critically the content of the papers revised.

Grace S. Pereira and Paula Lunardi: concepted and designed the organization of the MS.

Lara M. Z. Mansk and Laura F. Jaimes: designed the figures.

Declaration of Competing Interest

The authors report no declarations of interest.

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