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Involvement of medial prefrontal cortex NMDA and AMPA/kainate glutamate receptors in social recognition memory consolidation

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ABSTRACT

Social recognition memory (SRM) enables the distinction between familiar and strange conspecifics, a fundamental ability for sociable species, such as rodents and humans. There is mounting evidence that the medial prefrontal cortex plays a prominent role both in shaping social behavior and in recognition memory. Glutamate is the major excitatory neurotransmitter in the brain, and activity of its ionotropic receptors is known to mediate both synaptic plasticity and consolidation of various types of memories. However, whether these receptors are required in the medial prefrontal cortex (mPFC) for SRM consolidation remains elusive. To address this issue, we submitted rats to a social discrimination paradigm, administered infusions of NMDA- and AMPA/kainate-receptors antagonists into the prelimbic (PrL) subdivision of the mPFC at different post-encoding time points and evaluated long-term memory retention twenty-four hours later. We found that blocking NMDA receptors immediately after the sample phase, but not 3 h later, impaired SRM consolidation, whereas the blockade of AMPA/kainate receptors immediately and 3 h, but not 6 h after the sample phase, prevented long-term memory consolidation. These results highlight the importance of the mPFC in social cognition and may contribute towards the understanding of the dysfunctional social information processing that underlies multiple neuropsychiatric disorders.

1. Introduction

The ability to recognize individual conspecifics is a crucial feature of social species. It constitutes a basic requirement for social behaviors, such as group formation and organization, which ultimately lead to survival (Insel & Fernald, 2004; Leser & Wagner, 2015; Thor & Holloway, 1982). Social information processing engages a wide and complex circuitry, which includes the dorsal and ventral hippocampus, basolateral and medial amygdala, insular cortex, lateral septum and the medial prefrontal cortex (mPFC) (Cavalcante et al., 2017; Garrido Zinn et al., 2016, 2018; Okuyama, Kitamura, Roy, Itohara, & Tonegawa, 2016).

The mPFC plays a key role in social behaviors, both in rodents and humans (Bicks, Koike, Akbarian, & Morishita, 2015; Ko, 2017). Neurons within this region show increased activation in response to social interaction (Lee et al., 2016; Murugan et al., 2017) and decreased activity during social avoidance (Lee et al., 2015), whereas excitatory/inhibitory imbalance in the mPFC induces social dysfunction (Yizhar et al., 2011). Moreover, malfunctioning of prefrontal cortical areas has been implicated in disorders that impair social behavior such as autism spectrum disorders and schizophrenia (Radeloff et al., 2014; Zhou, Fan, Qiu, & Jiang, 2015).

Social learning can be assessed in rodents through the social discrimination paradigm (Engelmann, Wotjak, & Landgraf, 1995). In this task, adult animals are initially exposed to a previously unencountered juvenile conspecific. Subsequently, the animals are reexposed to the now-familiar juvenile and to a novel one. Due to their innate tendency to investigate novelty, animals exhibit preferential exploration of the novel juvenile, therefore revealing recognition memory for the familiar one (Engelmann et al., 1995; Garrido Zinn et al., 2016; Kogan, Frankland, & Silva, 2000).

As with other forms of learning, recently acquired social information undergoes the process of consolidation, by which a labile trace is stabilized over time to ensure long-term memory (LTM) storage (Kogan et al., 2000; McGaugh, 2000). Glutamate is the major excitatory neurotransmitter in the brain and activation of its receptors elicit the principal forms of synaptic plasticity, which are believed to underlie learning and memory (Diering & Huganir, 2018; Meldrum, 2000).

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Indeed, post-learning activity of ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA) receptors at different time points is necessary for the consolidation of multiple forms of memory (Guzmán-Ramos, Osorio-Gómez, Moreno-Castilla, & Bermúdez-Rattoni, 2012; Izquierdo et al., 1992; Izquierdo & Medina, 1997; Robbins & Murphy, 2006; Shimizu, Tang, Rampon, & Tsien, 2000). In spite of mounting evidence indicating the important contribution of mPFC to social information processing, the role of ionotropic glutamate receptors in this area for SRM consolidation remains unclear.

Thus, in this study, we used a pharmacological approach to verify the involvement and temporal dynamics in the requirement of ionotropic glutamate receptors on SRM consolidation. For this, we administered AMPA/kainate and NMDA receptors antagonists into the prelimbic cortex (PrL) at different time points after the sample phase of the social discrimination task and assessed LTM retention twenty-four hours later.

2. Materials and methods

2.1. Animals

Adult (3-month-old, 300–330 g) and juvenile (22–30 postnatal days) male *Wistar* rats (CrlCembe:WI) were obtained from the Centro de Modelos Biológicos e Experimentais (CeMBE) of the Pontifical Catholic University of Rio Grande do Sul (PUCRS). Animals were housed four to a cage, maintained under a 12/12-h light/dark cycle (lights on at 7 a.m.) and allowed *ad libitum* access to food and water. All procedures were approved by the Animal Committee on Ethics for the Care and Use of Laboratory Animals of PUCRS, in compliance with National Institutes of Health guidelines for the care and use of laboratory animals.

2.2. Surgery

Adult animals were submitted to stereotaxic surgery under anesthesia (75 mg/kg ketamine plus 10 mg/kg xylazine, intraperitoneally) and implanted bilaterally with stainless steel 22-gauge guide cannulae. The tips of the cannulae were aimed 1.0 mm above the prelimbic cortex (PrL; anterior +3.2, lateral ± 0.8, ventral −3.0 mm, relative to bregma, Paxinos & Watson, 2007). The guide cannulae were fixed to the skull with dental acrylic cement. All animals were allowed seven days for recovery from surgery before behavioral procedures. Animals were handled once daily for three consecutive days before the behavioral experiments.

2.3. Social discrimination paradigm

The experimental apparatus consisted in a black acrylic open-field arena (60 × 40 × 50 cm) placed in a dimly illuminated room. Two identical transparent Plexiglas cylindrical cages (9 cm diameter × 13 cm height) were positioned inside the arena near to the corners. The cage walls were perforated (1 cm diameter spaced by 1 cm) in order to allow the passage of olfactory cues while preventing direct interaction between adults and juveniles. Water-filled bottles were placed above each cylinder to prevent adults from moving or climbing it. The arena and the cylinder cages were cleaned with 70% (vol/vol) ethanol before and after each use.

Adult animals were individually habituated to the open-field arena for 20 min per day for 4 consecutive days. The empty cylinder cages were kept inside the arena during the habituation session. Juveniles were habituated to being placed in the cylinder cages for 20 min, 24 h before the sample phase. The sample phase was conducted 24 h after the last habituation session, when adult animals were individually placed in the center of the arena and allowed to freely explore for 1 h an unfamiliar juvenile placed in one of the cylinder cages (randomly selected and counterbalanced for each group) and an empty cylinder. After the sample phase, animals were randomly divided in control (Veh) or drug groups and microinjections into the PrL were carried out at different time points after the sample phase. On the retention test, which occurred 24 h later, adult animals were placed again in the same arena with the previously presented juvenile (familiar) and a second juvenile (novel) that had no prior contact with the adult, who was placed inside the cylinder that had been empty during the sample phase. Animals were allowed to freely explore the set-up for 5 min, after which they were returned to their home cages. The two juveniles were from different home cages to prevent redundancy of olfactory cues. During the retention test, the time adult animal spent exploring each juvenile (familiar and novel) was measured by a trained experimenter, blinded to the animal's condition (treatment *vs.* control). Social exploratory behavior was defined as sniffing and touching the cylinder cages. A preference for the novel animal over the familiar animal indicates memory consolidation for the familiar conspecific.

2.4. Pharmacological treatments

Drugs were purchased from Sigma-Aldrich®. Doses were chosen based on previous works, in which their effect on memory variables was established (Barros et al., 2000; de Souza Silva, Huston, Wang, Petri, & Chao, 2016; Myskiw, Fiorenza, Izquierdo, & Izquierdo, 2010; Vianna et al., 2000). 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 1 μg/μL) an AMPA/kainate receptor antagonist and D(-)-2-Amino-5-phosphonopentanoic acid (AP5, 5 μg/μL), a NMDA receptor antagonist, were both dissolved in sterile saline (NaCl 0.9%), which was administered to the control groups. All infusions were bilateral and a volume of 1 μL per side was infused in the PrL. At the time of infusion, a 30-gauge infusion needle tightly connected to a Hamilton microsyringe by polyethylene tubing was introduced into the guide cannula. The infusion cannula protruded 1 mm beyond the guide cannula tip. Infusion was carried out at a 1 μL/min rate and the infusion cannula was left in place for additional 60 s to ensure maximal diffusion and prevent backflow, after which it was carefully withdrawn. This procedure was repeated on the other side.

2.5. Histology

Cannulae placements were determined by infusing 4% (vol/vol) methylene blue into the cannulae 2 days after the last behavioral procedure. The spread of the dye was taken as an estimate of the drugs' diffusion. Placements were considered correct when the spread was 1 mm^3 or less from the intended infusion sites. Fig. 1 depicts a schematic drawing of the infusion sites.

From an initial pool of 90 rats, 10 were excluded from the analyses due to cannulae misplacement (blinded to the animal's condition, treatment *vs.* control) and 4 were excluded because the headpiece was missing. In the experiments involving NMDA receptors, the exclusions were: 0 h (2 Veh, 2 AP5); 3 h (2 AP5). In the experiments involving AMPA receptors, exclusions: 0 h (1 Veh, 1 CNQX); 3 h (3 Veh, 3 CNQX).

2.6. Statistical analyses

Experimental data were converted in percentage of total juvenile exploration time and expressed as means and standard error (SE). One-sample Student's *t*-test analysis was performed to assess differences to the theoretical mean of 50%. Two-way repeated measures ANOVA, where the within-subjects factor was juvenile (familiar *vs.* novel) and the between-subjects factor was treatment (Veh *vs*. Drug), followed by Bonferroni's *post hoc* test were performed to assess differences in percentages of exploration time for novel juveniles. Unpaired *t*-test was performed to analyze differences in total exploration time between drug and control groups. GraphPad Prism® software was used to analyze the data and $p < 0.05$ was considered statistically significant.

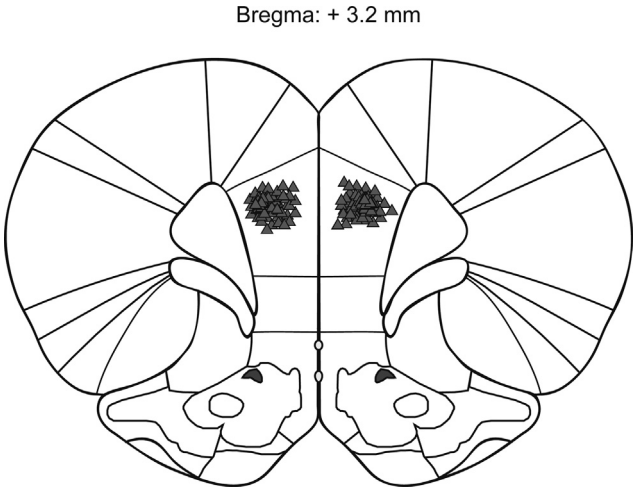

Fig. 1. Bilateral cannulae placements in the prelimbic cortex. Schematic drawing representing the infusion sites (gray triangles) in the prelimbic cortex for each animal included in the final analyses. Adapted from Paxinos and Watson (2007).

3. Results

3.1. The blockade of NMDA receptors in the mPFC immediately but not 3 h after the sample phase impairs SRM consolidation

In order to determine the involvement of NMDA receptors in the mPFC on SRM consolidation, immediately after the sample phase, animals received intra-PrL infusions of vehicle (Veh) or of the NMDA receptor antagonist, AP5 (5 μg/μL). On a 5-min retention test, conducted 24 h later, Veh-treated animals were able to recognize the familiar juvenile, while AP5-treated animals were not (Fig. 2a; One-sample *t*-test; Veh: $t_{(6)} = 4.253, p < 0.01$; AP5: $t_{(6)} = 0.07, p > 0.05$). Two-way ANOVA revealed no effect of treatment ($F_{(1,12)} = 0.00$, $p > 0.05$), but significant effect of juvenile ($F_{(1,12)} = 9.236$; $p < 0.05$) and interaction between factors ($F_{(1,12)} = 9.99$; $p < 0.01$). Bonferroni's post-test revealed significant differences between Veh-N and AP5-N groups on the retention test ($p < 0.05$, n = 7). Total exploration time during the retention test did not differ between groups (Fig. 2b; unpaired *t*-test: $t_{(26)} = 1.27$, $p > 0.05$, n = 7 animals per group).

To verify whether NMDA receptors are required beyond the immediate post-encoding period for SRM consolidation, another group of animals received bilateral intra-PrL infusions of Veh or AP5 3 h after the sample phase. On the retention test, 24 h later, both Veh- and AP5-treated animals demonstrated intact SRM (Fig. 2c; One-sample *t*-test; Veh: $t_{(8)} = 2.43$, $p < 0.05$; AP5: $t_{(6)} = 3.53$, $p < 0.05$). Two-way ANOVA showed significant effect of juvenile ($F_{(1,14)} = 15.01$, $p < 0.01$) but no significant effect of treatment ($F_{(1,14)} = 0, p > 0.05$) or interaction between the variables ($F_{(1,14)} = 0.03771$, $p > 0.05$). *Post hoc* Bonferroni's test revealed no statistically significant differences between Veh-N and AP5-N groups ($p > 0.05$, n = 7–9). Total exploration time during the retention test did not differ between groups (Fig. 2d; unpaired *t*-test: $t_{(30)} = 1.21$, $p > 0.05$, n = 7–9 animals per group). These results demonstrate that the blockade of NMDA receptors in the mPFC immediately but not 3 h after the sample phase impaired SRM consolidation.

3.2. The blockade of AMPA/kainate receptors in the mPFC immediately and 3 h but not 6 h after the sample phase impairs SRM consolidation

In order to determine the involvement of AMPA/kainate receptors in the mPFC on SRM consolidation, different groups of animals received bilateral intra-PrL infusions of Veh or of the AMPA/kainate receptor antagonist, CNQX (1 μg/μL) immediately after the sample phase. On the retention test, carried out 24 h later, Veh-treated animals were able to recognize the familiar juvenile while CNQX-treated animals were not (Fig. 3a; One-sample *t*-test; Veh: $t_{(7)} = 3.35$, $p < 0.05$; CNQX: $t_{(7)} = 0.37, p > 0.05$). Two-way ANOVA showed no effect of treatment ($F_{(1,14)} = 0$; $p > 0.05$), but significant effects of juvenile ($F_{(1,14)} = 10.54$; $p < 0.01$) and interaction between factors treatment and juvenile ($F_{(1,14)} = 8.791$; $p < 0.05$). Bonferroni's post-test revealed significant differences between Veh-N and CNQX-N groups on the retention test ($p < 0.05$, n = 8). Total exploration time during the retention test did not differ between groups (Fig. 3b; unpaired *t*-test: $t_{(30)} = 0.80$, $p > 0.05$, n = 8 animals per group).

When infusions occurred 3 h after the sample phase, Veh-treated animals were able to recognize the familiar juvenile, while CNQX-infused animals exhibited SRM consolidation impairment (Fig. 3c; One-sample *t* test; Veh: $t_{(5)} = 7.07$, $p < 0.001$; CNQX: $t_{(5)} = 0.36$, $p > 0.05$). Two-way ANOVA showed no effect of treatment ($F_{(1,10)} = 0.3083$; $p > 0.05$), but significant effect of juvenile ($F_{(1,10)} = 16.01$; $p < 0.01$) and interaction between factors treatment and juvenile ($F_{(1,10)} = 20.97$; $p < 0.01$). Bonferroni's post-test revealed significant differences between Veh-N and CNQX-N groups on the retention test ($p < 0.001$, n = 6). Total exploration time during the retention test did not differ between groups (Fig. 3d; unpaired *t*-test: $t_{(22)} = 0.67$, $p > 0.05$, n = 6 animals per group).

Since the blockade of AMPA/kainate receptors impaired SRM consolidation immediately and 3 h after the sample phase, we decided to test at a later time point. For this, another group of animals received bilateral intra-PrL infusions of Veh or CNQX 6 h after the sample phase. As shown on Fig. 3e, both Veh- and CNQX-treated animals were able to recognize the familiar juvenile (Veh: $t_{(8)} = 2.83$, $p < 0.05$; CNQX: $t_{(8)} = 3.15, p < 0.05$). Two-way ANOVA showed significant effects for juvenile ($F_{(1,16)} = 17.92$; $p < 0.001$), but no effect of treatment ($F_{(1,16)} = 0$; $p > 0.05$) or interaction between factors ($F_{(1,16)} = 0.04735$; $p > 0.05$). Bonferroni's post-test revealed no statistically significant differences between Veh-N and CNQX-N groups ($p > 0.05$, n = 9). Total exploration time during the retention test did not differ between groups (Fig. 3f; unpaired *t*-test: $t_{(34)} = 0.2196$, $p > 0.05$, n = 9 animals per group).

These results demonstrate that the blockade of AMPA receptors in the mPFC immediately and 3 h, but not 6 h after the sample phase impaired SRM consolidation.

4. Discussion

Here we have demonstrated that post-encoding glutamatergic neurotransmission in the mPFC is necessary for SRM consolidation. We have found that AMPA/kainate receptors in the PrL are involved on SRM consolidation both immediately and 3 h, but not 6 h after the sample phase. We have also demonstrated that NMDA receptors are required immediately after encoding, but this requirement is short-lived, since their blockade 3 h after the sample phase had no effect on SRM consolidation.

Thus, our results are in agreement with previous studies that have implicated prefrontal cortical areas in the circuitry responsible for the consolidation of social recognition memories (Garrido Zinn et al., 2018; Harony-Nicolas et al., 2017; Tanimizu et al., 2017).

Post-learning receptor activity is a general physiological mechanism for memory consolidation (Izquierdo & Medina, 1997; McGaugh, 2000; McGaugh & Izquierdo, 2000). In fact, glutamate release, activation or modification in the number of its receptors are mechanisms that have been demonstrated to participate on the consolidation of several forms of memories in different brain structures (Cammarota, Bernabeu, Izquierdo, & Medina, 1996; Guzmán-Ramos et al., 2012; Izquierdo et al., 1992; Izquierdo & Medina, 1997). Indeed, inhibition of glutamate receptors in different brain regions affects the consolidation of several memories, such as conditioned taste aversion (Guzmán-Ramos et al.,

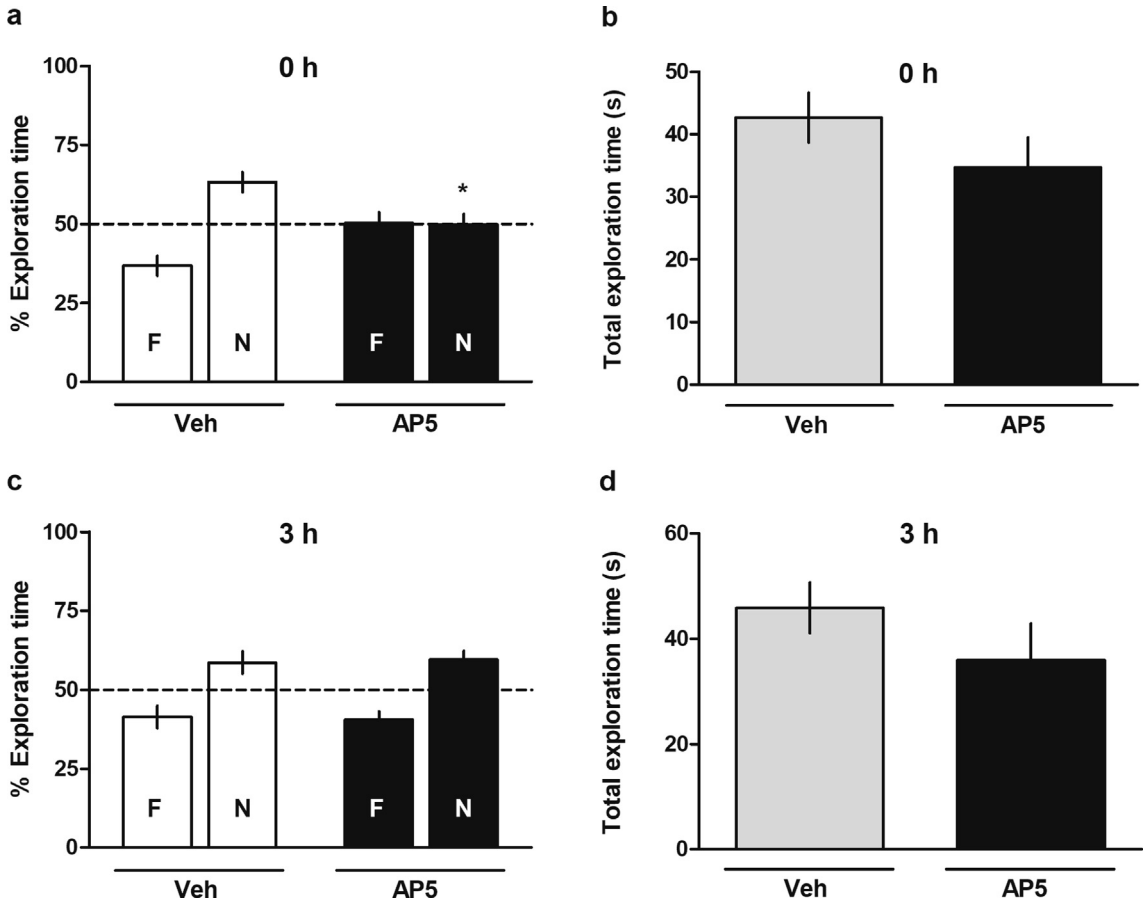

Fig. 2. Intra-PrL infusions of the NMDA receptor antagonist, AP5, immediately but not 3 h after the sample phase impair SRM consolidation. Animals were subjected to a social discrimination task and immediately (a) or 3 h (c) after the sample phase received bilateral intra-PrL infusions of vehicle (NaCl 0.9%, 1 μL per side) or of the NMDA receptor antagonist AP5 (5 μg/μL, 1 μL per side). Twenty-four hours later, animals were subjected to a 5-min retention test in the presence of the familiar juvenile (F) or a novel juvenile (N). Total exploration time during the retention test for the groups treated immediately (b) and 3 h (d) after the sample phase. Dashed line indicates the theoretical means of 50%. Data are expressed as means ± SEM (n = 7–9 animals per group) and presented as percentages of total exploration times. *$p < 0.05$ Veh-N *vs.* AP5-N, Bonferroni's Multiple Comparison Test after two-way repeated measures ANOVA.

2012), conditioned odor aversion (González-Sánchez, Tovar-Díaz, Morin, & Roldán-Roldán, 2019), inhibitory avoidance (Bonini et al., 2003; Izquierdo et al., 2007; Riedel, Platt, & Micheau, 2003), object location (Yamada, Arai, Suenaga, & Ichitani, 2017) and object recognition (Akirav & Maroun, 2006; (Goulart et al., 2010); Winters & Bussey, 2005), among others. In contrast, post-encoding NMDA receptor antagonist infusion in the insular cortex does not affect social recognition memory consolidation (Cavalcante et al., 2017), which suggests that their requirement is not ubiquitous.

The time-limited sensitivity of NMDA receptors blockade on SRM consolidation is consistent with their role in initiating synaptic plasticity (e.g. long-term potentiation and long-term depression) and their early requirement in several forms of learning (Izquierdo & Medina, 1997; Izquierdo et al., 2006; Riedel et al., 2003). On the other hand, AMPA receptors mediate most of the fast excitatory transmission in the brain (Diering & Huganir, 2018; Riedel et al., 2003), and the memory deficits observed following their inactivation in our experiments reflect that ongoing mPFC AMPA/kainate receptors activity is required up to 3 h after learning to ensure long-term SRM consolidation.

Prefrontal cortical areas have also been implicated in other forms of recognition memory, such as the rodents' infalimbic cortex in object recognition (Akirav & Maroun, 2006), the primate's pregenual anterior cingulate cortex in visual recognition (Bachevalier & Mishkin, 1986) and the prelimbic and infralimbic cortices in social odor recognition in rodents (Robinson, Granata, Hienz, & Davis, 2019). Indeed, immediate post-encoding NMDA receptors blockade in the infralimbic cortex impairs the consolidation of object recognition memory (Akirav & Maroun, 2006), while their blockade in the PrL immediately, but not 2 h after training, also impairs memory consolidation in an odor-reward associative learning task (Tronel & Sara, 2003).

Previous works have evaluated the role of the glutamatergic system in social memory. It has been demonstrated that systemic NMDA injections (Hlinák & Krejcí, 2002) or positive allosteric modulation at the receptor's glycine site (Shimazaki, Kaku, & Chaki, 2010) improve short-term SRM, whereas systemic administration of the non-competitive NMDA antagonist, MK-801, produces short-term social memory impairment (Deiana et al., 2015). Moreover, both pre- and post-encoding systemic NMDA receptors blockade have been shown to impair SRM consolidation (Gao, Elmer, Adams-Huet, & Tamminga, 2009). In a genetic study, forebrain-specific inducible knockout of the NMDA receptors NR1 subunit resulted in SRM deficits (Jacobs & Tsien, 2017). However, these systemic approaches do not allow the discrimination of a specific region responsible for the observed outcomes. In this regard, evidence provided by our work could support a role for the mPFC in mediating these effects.

Evidence concerning the role of metabotropic glutamate receptors (mGluRs) in social memory is more limited, though studies suggest that they may interact with ionotropic glutamate receptors in the regulation of social memory (Zoicas & Kornhuber, 2019). Systemic blockade of mGluR2/3 receptors immediately after sample phase enhances short-term social memory in an AMPA receptor-dependent manner (Shimazaki, Kaku, & Chaki, 2007). On the other hand, infusion of a

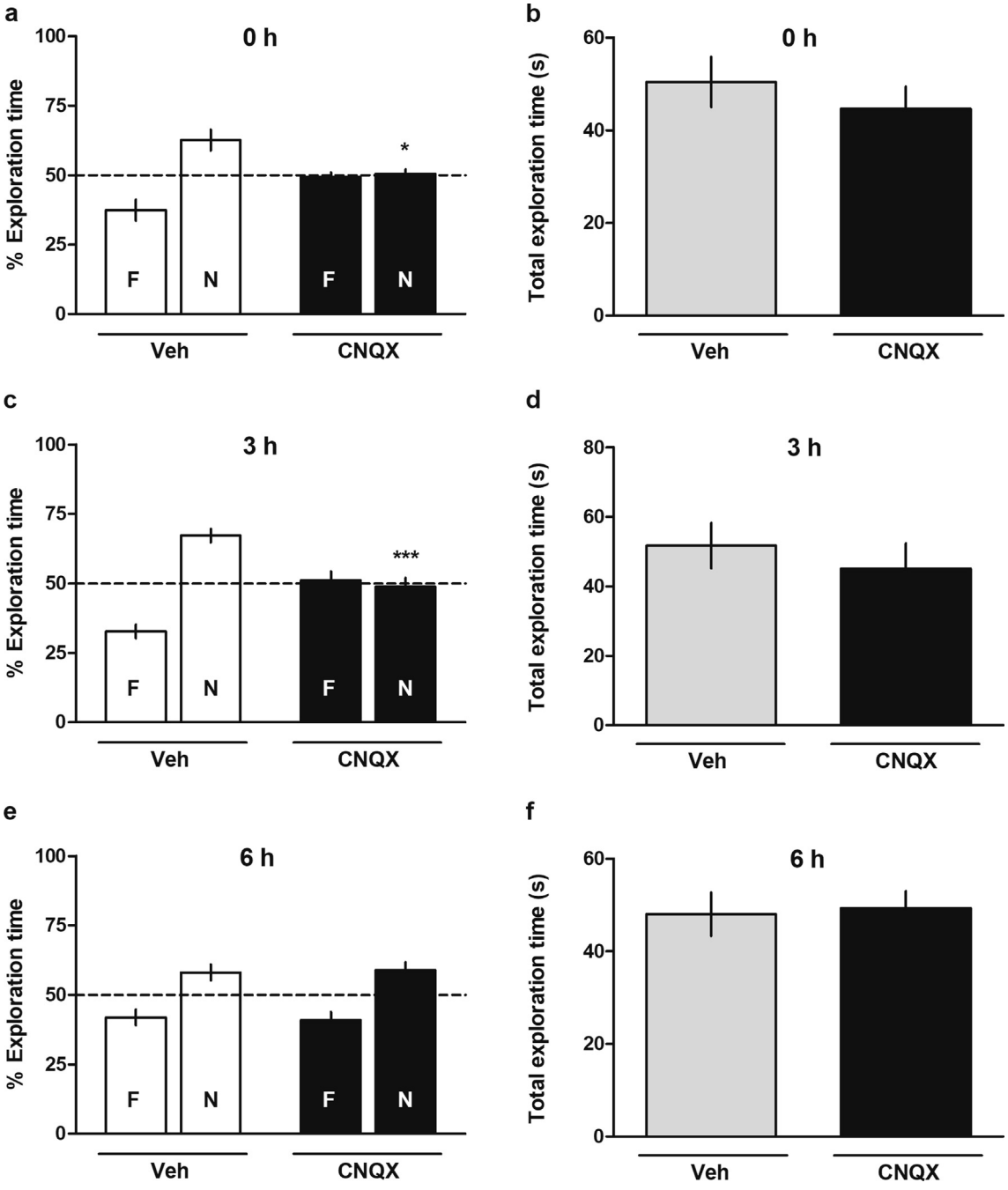

Fig. 3. Intra-PrL infusions of the AMPA/kainate receptor antagonist, CNQX, immediately and 3 h, but not 6 h after the sample phase impair SRM consolidation. Animals were subjected to a social discrimination task and immediately (a), 3 h (c) or 6 h (e) after the sample phase received bilateral intra-PrL infusions of the AMPA/kainate receptor antagonist, CNQX (1 μg/μL, 1 μL per side) or vehicle (NaCl 0.9%, 1 μL per side). Twenty-four hours later, animals were subjected to a 5-min retention test in the presence of the familiar juvenile (F) or a novel juvenile (N). Total exploration time during the retention test for the groups treated immediately (b), 3 h (d) and 6 h (f) after the sample phase. Dashed line indicates the theoretical means of 50%. Data are expressed as means ± SEM (n = 6–9 animals per group) and presented as percentage of total exploration times. $^{*}p < 0.05$ and $^{***}p < 0.001$ Veh-N *vs.* AP5-N, Bonferroni's Multiple Comparison Test after two-way repeated measures ANOVA.

mGluR2/3 agonist, before the sample phase, reverses the memory deficit induced by neonatal NMDA antagonist treatment (Harich, Gross, & Bespalov, 2007).

SRM consolidation induces expression of the immediate early genes c-fos and Arc in the mPFC (Tanimizu et al., 2017) and augments functional connectivity between this area and the hippocampus, both in mice (Tanimizu et al., 2017) and in humans (Meyer, Davachi, Ochsner, & Lieberman, 2019). On the other hand, genetic modifications that inhibit synaptic plasticity between these two regions impair SRM (Harony-Nicolas et al., 2017). In fact, ventral hippocampal (vHip) projections to mPFC have been shown to regulate social memory formation and retrieval, and stimulation of these projections elicits long-term potentiation at vHip-mPFC synapses, which persists for at least 45 min (Phillips, Robinson, & Pozzo-Miller, 2019). Furthermore, bi-directional connections between the BLA and the mPFC (infralimbic and PrL) have been shown to regulate social behaviors (Felix-Ortiz, Burgos-Robles, Bhagat, Leppla, & Tye, 2016) and SRM also enhances functional connectivity between the mPFC and the BLA (Tanimizu

et al., 2017). From this point of view, one hypothesis is that the late AMPA/kainate receptor-dependent process we have found in the mPFC could be mediating the strengthening between this region's connections and other areas involved in the social memory circuitry, such as the hippocampus and basolateral amygdala.

The fact that we have only used male subjects constitutes a limitation of our study. Sex differences in learning and memory have been reported across a range of tasks (Andreano & Cahill, 2009; Jonasson, 2005). In the social discrimination paradigm, female rats tend to investigate juveniles less intensely than males (Ferguson, Young, & Insel, 2002; Karlsson, Haziri, Hansson, Kettunen, & Westberg, 2015; Markham & Juraska, 2007), a difference attributable to lower testosterone levels in females (Thor, 1980). Yet, female rodents present superior short-term SRM (Markham & Juraska, 2007) and retain recognition responses longer (Ferguson et al., 2002). In females, SRM has been shown to be dependent on estrogens and their receptors, both in the amygdala and in the hippocampus (Lymer, Robinson, Winters, & Choleris, 2017; 2018). Social recognition is highly influenced by the neuropeptides oxytocin and vasopressin, and the sexually dimorphic results possibly arise from the interaction of these transmitters and circulating gonadal hormones (Ferguson et al., 2002). For instance, contrary to males, vasopressinergic signaling is dispensable for SRM in females (Bluthé & Dantzer, 1990). On the other hand, oxytocin is required for social memory both in males and females (Choleris et al., 2007; Engelmann, Ebner, Wotjak, & Landgraf, 1998; Raam, McAvoy, Besnard, Veenema, & Sahay, 2017). Further studies are required to evaluate if the consolidation of SRM in females similarly involves AMPA/kainate and NMDA receptors in the medial prefrontal cortex as we verified in males.

In summary, our work reinforces the importance of mPFC in social cognition and behavior, particularly in SRM consolidation. We show that social memory consolidation requires both NMDA and AMPA/kainate receptors in the immediate post-encoding period, and that the information is further processed by the prelimbic cortex for up to 3 h, in an AMPA/kainate receptor-dependent manner. These results help to elucidate the underpinnings of social memory processing, which is paramount not only for the comprehension of its physiology but also to identify therapeutic targets for the treatment of psychiatric disorders associated with social deficits.

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