

## Brief Communication

# Reactivation-dependent amnesia for object recognition memory is contingent on hippocampal theta–gamma coupling during recall

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Hippocampal dopamine D1/D5 receptor-dependent destabilization is necessary for object recognition memory (ORM) updating through reconsolidation. Dopamine also regulates hippocampal theta and gamma oscillations, which are involved in novelty and memory processing. We found that, in adult male rats, ORM recall in the presence of a novel object, but not in the presence of a familiar one, triggers hippocampal theta–gamma coupling. Hippocampal theta–gamma coupling (hPAC) does not happen when ORM destabilization is prevented by blocking D1/D5 receptors, but artificial hPAC generation during recall in the presence of a familiar object enables the amnesic effect of reconsolidation inhibitors. Therefore, hPAC controls ORM destabilization, and its modulation could increase reconsolidation-based psychotherapy efficacy.

[Supplemental material is available for this article.]

Object recognition memory (ORM) is essential for remembering facts and events because it allows individuals to identify familiar items and discriminate them from novel ones (Cole et al. 2019). However, ORMs are not fixed but dynamic, and can be temporarily destabilized when recalled simultaneously with novelty detection (Rossato et al. 2007; Winters et al. 2011). When induced by the perception of a novel object in a familiar environment, ORM destabilization is controlled by hippocampal dopamine D1/D5 receptors (Rossato et al. 2015; Gonzalez et al. 2021) and enables memory updating through PKM $\zeta$ , Zif268, mTOR, and BDNF-dependent reconsolidation mechanisms (Myskiw et al. 2008; Radiske et al. 2017; Rossato et al. 2019; Gonzalez et al. 2019, 2021). Brain oscillations are repetitive rhythmic fluctuations of local field potentials caused by the synchronized electrical activity of neurons (Buzsáki et al. 2012). Memory encoding, recall, and maintenance have been associated with hippocampal oscillations in the theta and gamma bands (Düzel et al. 2010), which can interact with each other (Lisman and Jensen 2013). These interactions, known as cross-frequency coupling, are believed to coordinate hippocampal neuronal activity during memory processing (Jensen and Colgin 2007; Sauseng et al. 2008; Lisman and Jensen 2013). In particular, hippocampal theta–gamma phase-amplitude coupling (hPAC) is associated with the detection of a mismatch between perception and expectation as well as with memory reorganization (Kragel et al. 2020; López-Madróna et al. 2020), which are likely to accompany recall-induced hippocampus-dependent ORM destabilization. However, the possible interplay between hippocampal theta–gamma oscillations and ORM destabilization has not yet been studied. To do that, we implanted adult male Wistar rats (3 mo old, 300–350 g) with drug injection cannulas and/or electrode arrays in dorsal CA1 and trained them in the novel object recognition

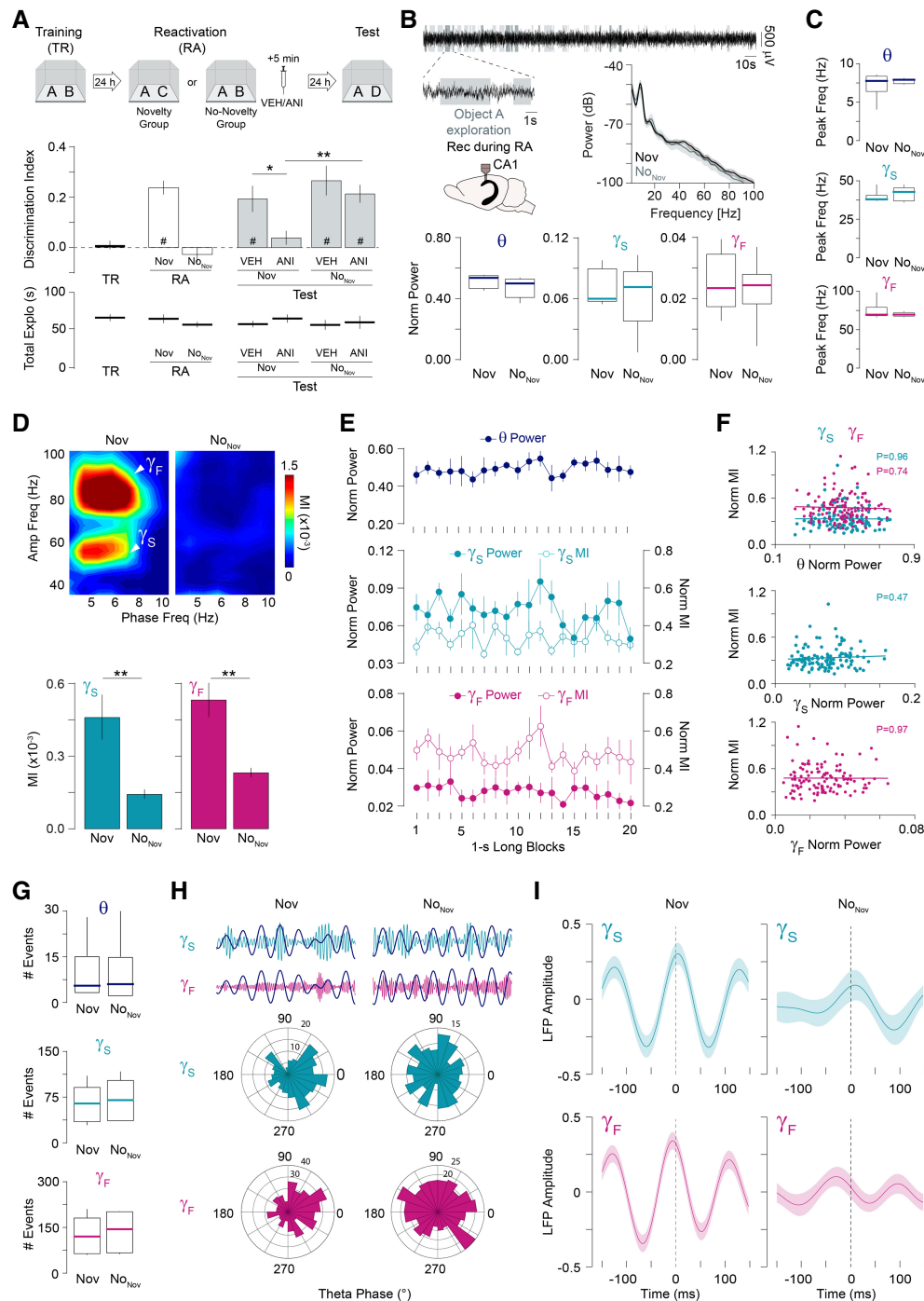
task, an incidental learning paradigm based on the rodents' in-born preference for novelty (Ennaceur and Delacour 1988) involving exposure to two different but behaviorally equivalent novel stimuli objects A and B in a familiar open field arena during 5 min (see the [Supplemental Material](#) for additional details; Lima et al. 2009; Furini et al. 2010; ILL-Raga et al. 2013) that many consider a suitable model for studying episodic-like memory in rodents (Antunes and Biala 2012; but see also Bussey et al. 2013). One day after training, rats were placed again in the training arena and exposed for 5 min to one of the objects presented during the training session (object A) alongside a novel object (object C) in order to reactivate the memory of object A and induce its hippocampus-dependent destabilization (Novelty group). To differentiate ORM destabilization-specific mechanisms from those associated just with ORM recall a different group of trained animals was submitted to a memory reactivation session in the presence of familiar objects A and B (No-Novelly group). As expected, Novelty group animals discriminated familiar object A from novel object C, but No-Novelly group animals spent the same amount of time exploring familiar objects A and B during the reactivation session. Confirming previous results (Rossato et al. 2007), postreactivation intra-CA1 infusion of the protein synthesis inhibitor anisomycin (160  $\mu$ g/ $\mu$ L) impaired memory for object A in Novelty group animals, but not in No-Novelly group animals, during a 5-min-long retention test session in the presence of novel object D carried out 24 h after the reactivation session ( $F_{(1,28)} = 15.26$ ,  $P = 0.0005$  for novelty effect;  $F_{(1,28)} = 6.279$ ,  $P = 0.0183$  for anisomycin effect;  $F_{(1,28)} = 4.258$ ,  $P = 0.0484$  for novelty  $\times$  anisomycin interaction in two-way ANOVA) (Fig. 1A). Total exploration time did not differ

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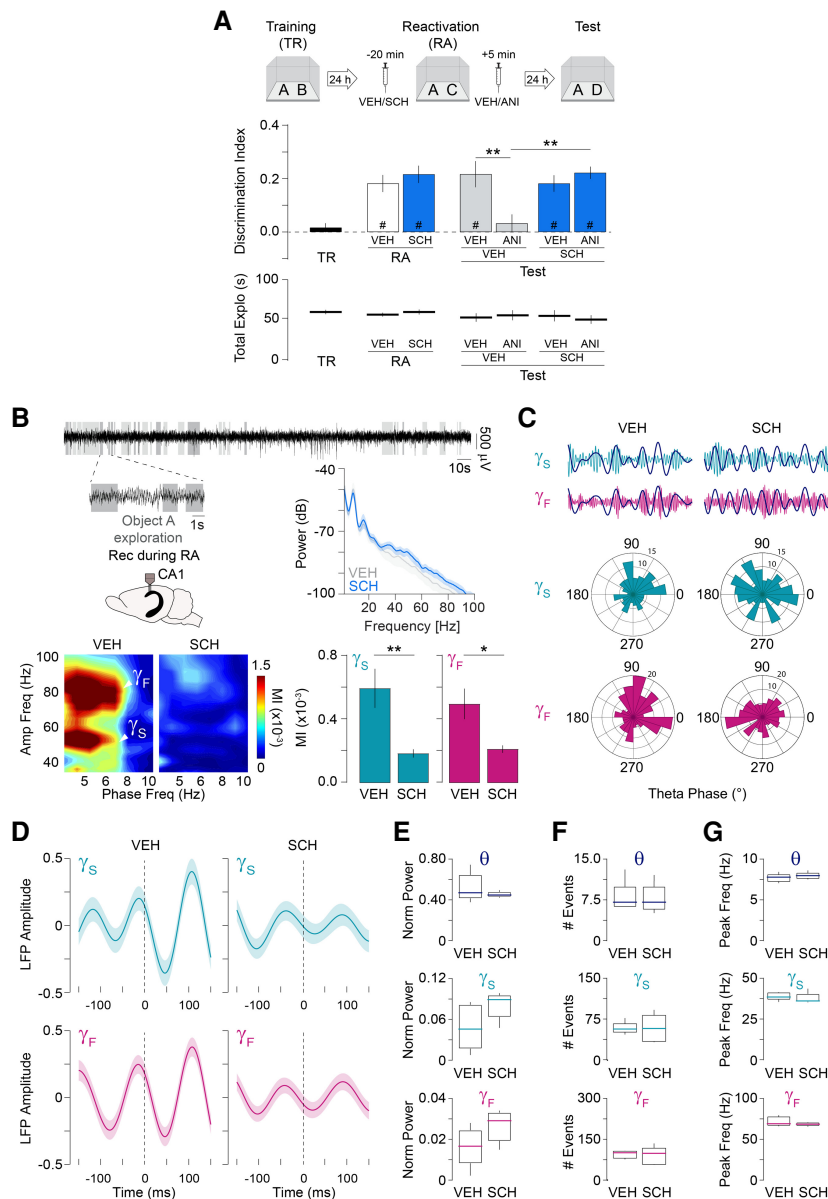
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**Figure 1.** (A, top panel) Experimental protocol. (Bottom panels) Rats were trained (TR) in the novel object-recognition task using two novel stimuli objects A and B. One day later, they were submitted to an ORM reactivation session (RA) in the presence of familiar object A and novel object C (Novelty group; Nov) or in the presence of the familiar objects A and B (No Novelty group; No<sub>Nov</sub>) and 5 min thereafter received bilateral intradorsal CA1 infusions of vehicle (VEH) or anisomycin (ANI). ORM retention was evaluated 1 d after RA by reexposing the animals to familiar object A alongside novel object D (Test). Discrimination Index and Total Exploration time are shown. TR, RA, and Test sessions lasted 5 min ( $n=8$  animals/group). (B) LFPs from dorsal CA1 were recorded during RA. Data corresponding to object A exploration time windows were analyzed. (Top panel) Representative raw data trace and power spectrum density plots. (Bottom panel) Normalized theta ( $\theta$ , 4–10 Hz), slow gamma ( $\gamma_S$ ; 35–55 Hz), and fast gamma power ( $\gamma_F$ ; 65–100 Hz). (C) Peak frequency of theta, slow gamma, and fast gamma oscillations. (D, top panel) Representative phase-amplitude comodulograms. (Bottom panel) Theta–slow gamma and theta–fast gamma modulation index (MI). (E) Normalized theta, slow gamma, and fast gamma power and normalized MI calculated in nonoverlapping 1-sec-long blocks for Novelty group animals. (F) Linear correlations between normalized theta, slow gamma, or fast gamma power and normalized MI calculated in nonoverlapping 1-sec-long blocks for Novelty group animals. (G) Number of theta, slow gamma, and fast gamma events. (H; top panel) Theta filtered LFP traces in blue, slow gamma filtered LFP traces in cyan, and fast gamma filtered LFP traces in purple. (Bottom panel) Rose plots showing slow and fast gamma event distribution within the theta cycle. (I) Averaged LFP signal (z-score) triggered by the peak of gamma events. The plot begins 150 msec before the maximum of the gamma event ( $n=6$  animals/group). (#)  $P < 0.05$  in one-sample Student's  $t$ -test with theoretical mean = 0, (\*)  $P < 0.05$ , (\*\*)  $P < 0.01$ , unpaired  $t$ -test or Bonferroni's multiple-comparisons test after two-way ANOVA.



**Figure 2.** (A, top panel) Experimental protocol. (Bottom panels) Rats were trained (TR) in the novel object-recognition task using two novel stimuli objects A and B. One day later, they received bilateral intra-CA1 infusions of vehicle (VEH) or SCH23390 (SCH; 1.5  $\mu\text{g}/\mu\text{L}$ ) and 20 min thereafter were submitted to an ORM reactivation session (RA) in the presence of familiar object A and novel object C. Five minutes post-RA, animals received bilateral infusions of VEH or anisomycin (ANI) in dorsal CA1. ORM retention was evaluated 1 d after RA by reexposing animals to familiar object A alongside novel object D (Test). Discrimination Index and Total Exploration time are shown. TR, RA, and Test sessions lasted 5 min ( $n=8$  animals/group). (B) Local field potentials from dorsal CA1 were recorded during RA. Data corresponding to object A exploration time windows were analyzed. (Top panel) Representative raw data trace and power spectrum density plots. (Bottom panel) Representative phase-amplitude comodulograms and modulation index (MI) for theta-slow gamma and theta-fast gamma coupling. Theta band,  $\theta$ , 4–10 Hz; slow gamma band,  $\gamma_S$ , 35–55 Hz; fast gamma band,  $\gamma_F$ , 65–100 Hz. (C, top panel) Theta filtered LFP traces in blue, slow gamma filtered LFP traces in cyan, and fast gamma filtered LFP traces in purple. (Bottom panel) Rose plots showing slow and fast gamma event distribution within the theta cycle. (D) Averaged LFP signal (z-score) triggered by the peak of gamma events. Plot begins 150 msec before the maximum of the gamma event. (E) Normalized theta, slow gamma, and fast gamma power. (F) Number of theta, slow gamma, and fast gamma events. (G) Peak frequency of theta, slow gamma, and fast gamma oscillations ( $n=5$  animals/group). (#)  $P < 0.05$  in one-sample Student's  $t$ -test with theoretical mean = 0, (\*)  $P < 0.05$ , (\*\*)  $P < 0.01$ , unpaired  $t$ -test or Bonferroni's multiple-comparisons test after two-way ANOVA.

between Novelty and No-Novelty groups or between training and reactivation sessions. Local field potentials from dorsal CA1 were recorded during the reactivation session. Data from time windows corresponding to object A exploration events were extracted, merged, and analyzed (see the [Supplemental Material](#) for additional details). Neither the power nor the frequency peak of theta ( $\theta$ ; 4–10 Hz), slow gamma ( $\gamma_S$ ; 35–55 Hz) and fast gamma ( $\gamma_F$ ; 65–100 Hz) differed between Novelty and No-Novelty groups ( $\theta$  power:  $t_{(10)} = 1.259$ ,  $P = 0.2366$ ;  $\gamma_S$  power:  $t_{(10)} = 0.3817$ ,  $P = 0.7107$ ;  $\gamma_F$  power:  $t_{(10)} = 0.3694$ ,  $P = 0.7195$ .  $\theta$  peak:  $t_{(10)} = 0.7125$ ,  $P = 0.4925$ ;  $\gamma_S$  peak:  $t_{(10)} = 0.9832$ ,  $P = 0.3487$ ;  $\gamma_F$  peak:  $t_{(10)} = 0.8611$ ,  $P = 0.4094$  for Novelty vs. No-Novelty in unpaired  $t$ -test) (Fig. 1B,C). However, hPAC was stronger in Novelty group animals than in No-Novelty group animals ( $\gamma_S$  MI:  $t_{(10)} = 3.364$ ,  $P = 0.0072$ ;  $\gamma_F$  MI:  $t_{(10)} = 4.063$ ,  $P = 0.0023$  for Novelty vs. No Novelty in unpaired  $t$ -test) (Fig. 1D) and independent of theta and gamma fluctuations ( $\theta$  power:  $F_{(3.799, 18.99)} = 0.4088$ ,  $P = 0.7911$ ;  $\gamma_S$  power:  $F_{(4.248, 21.24)} = 1.065$ ,  $P = 0.4005$ ;  $\gamma_F$  power:  $F_{(3.789, 18.94)} = 0.6366$ ,  $P = 0.6349$ ;  $\gamma_S$  MI:  $F_{(3.638, 18.19)} = 0.7915$ ,  $P = 0.5354$ ;  $\gamma_F$  MI:  $F_{(2.775, 13.88)} = 0.6842$ ,  $P = 0.5659$  in one-way ANOVA with Geisser-Greenhouse correction) (Fig. 1E,F). In fact, the number of theta and gamma events, defined as periods during which the power of the corresponding frequency band exceeded 2.5 SD, did not differ between Novelty and No-Novelty groups ( $\theta$  events:  $t_{(10)} = 0.000$ ,  $P > 0.9999$ ;  $\gamma_S$  events:  $t_{(10)} = 0.3297$ ,  $P = 0.7484$ ;  $\gamma_F$  events:  $t_{(10)} = 0.3339$ ,  $P = 0.7454$  for Novelty vs. No-Novelty in unpaired  $t$ -test) (Fig. 1G), but while in No-Novelty animals gamma events were uniformly distributed over the theta phase, in Novelty animals they occurred preferentially at the peak of the theta cycle ( $\gamma_S$ :  $Z = 9.36$ ,  $P < 0.0001$ ;  $\gamma_F$ :  $Z = 19.02$ ,  $P < 0.0001$  for Novelty group;  $\gamma_S$ :  $Z = 0.47$ ,  $P = 0.6250$ ;  $\gamma_F$ :  $Z = 2.68$ ,  $P = 0.0688$  for No-Novelty group in Rayleigh test) (Fig. 1H,I).

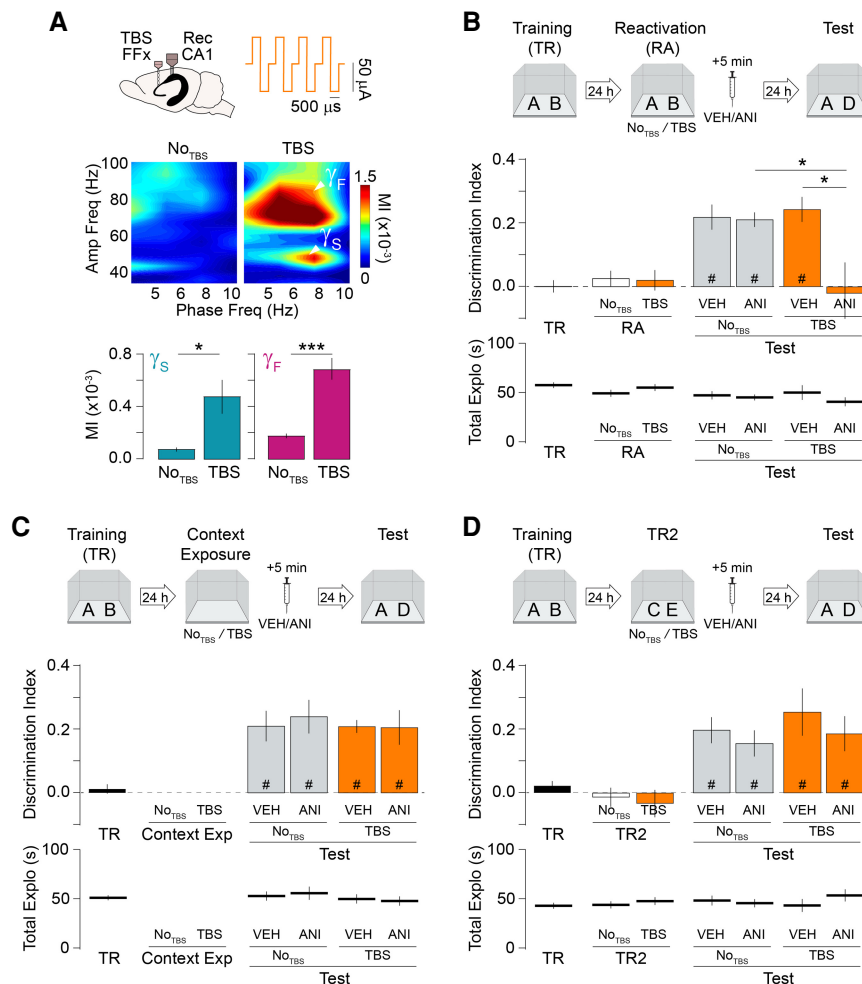
Hippocampal dopamine D1/D5 receptors are essential for ORM destabilization (Gonzalez et al. 2021) and hence, intra-CA1 preactivation administration of the D1/D5 receptor antagonist SCH23390 (1.5  $\mu\text{g}/\mu\text{L}$ ) impedes the amnesia induced by the postreactivation administration of the protein synthesis inhibitor anisomycin without affecting ORM recall ( $F_{(1,28)} = 4.090$ ,  $P = 0.0528$  for anisomycin;  $F_{(1,28)} = 4.674$ ,  $P = 0.0393$  for SCH23390;  $F_{(1,28)} = 9.849$ ,  $P = 0.004$  for SCH23390  $\times$  anisomycin interaction in two-way ANOVA) (Fig. 2A). In line with the hypothesis that hPAC is

associated with recall-induced ORM destabilization, we found that SCH23390 infusion before ORM reactivation in the presence of familiar object A and novel object C reduced hPAC during object A exploration ( $\gamma_S$  MI:  $t_{(8)} = 3.372$ ,  $P = 0.0098$ ;  $\gamma_F$  MI:  $t_{(8)} = 2.688$ ,  $P = 0.0276$  for VEH vs. SCH in unpaired  $t$ -test.  $\gamma_S$ :  $Z = 5.06$ ,  $P < 0.0001$ ;  $\gamma_F$ :  $Z = 7.30$ ,  $P < 0.0001$  for VEH,  $\gamma_S$ :  $Z = 1.54$ ,  $P = 0.215$ ;  $\gamma_F$ :  $Z = 1.97$ ,  $P = 0.140$  for SCH23390 in Rayleigh test) (Fig. 2B–D) without affecting the power, number of events or peak frequency of hippocampal theta, slow gamma, and fast gamma oscillations ( $\theta$  power:  $t_{(8)} = 1.016$ ,  $P = 0.3393$ ;  $\gamma_S$  power:  $t_{(8)} = 1.899$ ,  $P = 0.0940$ ;  $\gamma_F$  power:  $t_{(8)} = 1.888$ ,  $P = 0.0958$ .  $\theta$  peak:  $t_{(8)} = 0.8534$ ,  $P = 0.4183$ ;  $\gamma_S$  peak:  $t_{(8)} = 0.7129$ ,  $P = 0.4962$ ;  $\gamma_F$  peak:  $t_{(8)} = 1.074$ ,  $P = 0.3140$ .  $\theta$  events,  $t_{(8)} = 0.1118$ ,  $P = 0.9137$ ;  $\gamma_S$  events:  $t_{(8)} = 0.03252$ ,  $P = 0.9749$ ;  $\gamma_F$  events:

$t_{(8)} = 0.3239$ ,  $P = 0.7543$  for vehicle vs. SCH23390 in unpaired  $t$ -test) (Fig. 2E–G).

Theta-burst stimulation of the fimbria-fornix induces artificial hPAC in awake behaving rats ( $\gamma_S$  MI:  $t_{(10)} = 2.939$ ,  $P = 0.0148$ ;  $\gamma_F$  MI:  $t_{(10)} = 5.998$ ,  $P = 0.0001$  for NoTBS vs. TBS in unpaired  $t$ -test) (Fig. 3A; Shirvalkar et al. 2010), and it has been shown that this manipulation can destabilize memories that are not easily triggered into undergoing reconsolidation (Radiske et al. 2020). Therefore, we evaluated whether fimbria-fornix theta-burst stimulation can turn the memory of object A susceptible to reconsolidation blockers when recalled under conditions unable to induce its destabilization. To do that, rats implanted with stimulation electrodes in the fimbria-fornix and infusion cannulas in dorsal CA1 were trained in

the novel object recognition task using objects A and B and 24 h posttraining subjected to an ORM reactivation session in the presence of the same two objects. During that session, the animals were left unstimulated or received fimbria-fornix theta-burst stimulation (four 50- $\mu$ A biphasic pulses given at 500 Hz repeated at intervals of 130 msec, 500- $\mu$ sec pulse width) and 5 min thereafter were given bilateral intra-CA1 infusions of vehicle or anisomycin (160  $\mu$ g/ $\mu$ L). Object A memory retention was evaluated 1 d later in the presence of novel object C. As can be seen in Figure 3B, unstimulated animals discriminated object A from object C regardless of whether they had received vehicle or anisomycin after the reactivation session. Animals that received theta-burst stimulation during the reactivation session and were given intra-CA1 vehicle after that session also discriminated object A from object C, but those that received anisomycin showed no object discrimination at test ( $F_{(1,34)} = 3.544$ ,  $P = 0.0683$  for stimulation effect;  $F_{(1,34)} = 6.057$ ,  $P = 0.0191$  for anisomycin effect;  $F_{(1,34)} = 5.385$ ,  $P = 0.0264$  for stimulation  $\times$  anisomycin interaction; in two-way ANOVA). Theta-burst stimulation applied during exploration of the training arena devoid of stimuli objects ( $F_{(1,35)} = 0.1502$ ,  $P = 0.7007$  for stimulation effect;  $F_{(1,35)} = 0.08561$ ,  $P = 0.7716$  for anisomycin effect;  $F_{(1,35)} = 0.1304$ ,  $P = 0.7202$  for stimulation  $\times$  anisomycin interaction in two-way ANOVA) (Fig. 3C) or containing two behaviorally equivalent novel objects different from objects A and B ( $F_{(1,31)} = 0.6765$ ,  $P = 0.4171$  for stimulation effect;  $F_{(1,31)} = 1.079$ ,  $P = 0.3070$  for anisomycin effect;  $F_{(1,31)} = 0.06130$ ,  $P = 0.8061$  for stimulation  $\times$  anisomycin interaction in two-way ANOVA) (Fig. 3D) had no effect on object A memory retention and did not make it susceptible to anisomycin administration. Fimbria-fornix theta-burst stimulation did not affect object exploration or locomotor activity during the reactivation session. Total exploration time during the test session did not differ among groups.



**Figure 3.** (A, left panel) Experimental protocol. The fimbria-fornix (FFx) was stimulated using a theta-burst protocol (TBS) and local field potentials from dorsal CA1 were recorded. (Middle panel) Representative phase-amplitude comodulograms. (Right panel) Theta-slow gamma and theta-fast gamma modulation index (MI;  $n = 6$  animals/group). (B, top panel) Experimental protocol. (Bottom panels) Rats were trained (TR) in the novel object-recognition task using novel objects A and B and 1 d later submitted to an ORM reactivation session (RA) in the presence of familiar objects A and B during which they received FFx TBS. Five minutes post-RA, the animals were given bilateral intradorsal CA1 infusions of vehicle (VEH) or anisomycin (ANI). ORM retention was evaluated 1 d after RA by re-exposing the animals to familiar object A alongside novel object D (Test). Discrimination Index and Total Exploration time are shown. TR, RA, and Test sessions lasted 5 min ( $n = 9$ –10 animals/group). (C) Animals were treated as in B, except that they explored the training arena in the absence of stimuli objects (Context Exposure) 24 h after TR ( $n = 9$ –10 animals/group). (D) Animals were treated as in B, except that they explored two novel behaviorally equivalent objects C and E 24 h after TR (TR2;  $n = 8$ –9 animals/group). (#)  $P < 0.05$  in one-sample Student's  $t$ -test with theoretical mean = 0, (\*)  $P < 0.05$ , (\*\*\*)  $P < 0.001$ , unpaired  $t$ -test or Bonferroni's multiple-comparisons test after two-way ANOVA.

Our results indicate that hPAC increases when ORM is reactivated in the presence of a novel object and suggest that this theta–gamma interaction is linked to memory destabilization. Our experiments also reveal that artificial induction of hPAC at the time of reactivation transforms ORMs resistant to recall-dependent amnesia into ORMs susceptible to reconsolidation inhibitors. Indeed, extending earlier findings demonstrating that hippocampal dopamine signaling controls ORM destabilization and enables its updating (Rossato et al. 2015; Gonzalez et al. 2021), our data show that dopamine D1/D5 receptors blockage during ORM recall hinders hPAC as well as the amnesia caused by the postrecall administration of reconsolidation inhibitors, suggesting that the strong hPAC associated with ORM reactivation in the presence of a novel object results from dopamine-mediated match–mismatch computations and triggers the novelty-induced synaptic plasticity processes required for memory updating. In accordance with this hypothesis, theoretical and experimental evidence indicate that the hippocampus functions as a comparator in situations where familiar items are presented in novel configurations (Vinogradova 2001; Lisman and Grace 2005; Kumaran and Maguire 2007; Duncan et al. 2012). Mismatch/novelty signals activate VTA dopaminergic neurons that in turn release dopamine in the hippocampus enhancing LTP and learning (Lisman and Grace 2005), and it has been reported that novelty detection increases hippocampal theta–gamma phase-amplitude coupling (Dzirasa et al. 2009; Kragel et al. 2020). Indeed, cross-frequency coupling and mismatch novelty can induce neuroplasticity in the hippocampus (Aidil-Carvalho et al. 2017; Bergmann and Born 2018) and hippocampal D1/D5 receptor activity gates learning-related long-term changes in synaptic weight of CA1 synapses lowering the threshold for LTD and LTP induction (Li et al. 2003; Lemon and Manahan-Vaughan 2006). In this regard, we previously reported that recall-induced ORM updating is accompanied by an initial depotentiation period followed by a late stage of synaptic efficacy enhancement (Clarke et al. 2010). Indeed, recall-induced ORM destabilization depends on mechanisms responsible for hippocampal LTD induction such as AMPA receptor endocytosis (Lüthi et al. 1999; Rossato et al. 2019), and both ORM restabilization and LTP require protein synthesis as well as BDNF and PKMz activation in CA1 (Yao et al. 2008; Mei et al. 2011; Radiske et al. 2017; Rossato et al. 2019), suggesting that depotentiation and repotentialization of strengthened synapses may underlie ORM updating through reconsolidation. Importantly, we found that the induction of artificial hPAC via fimbria-fornix theta-burst stimulation during recall can make ORMs recalled in the absence of novelty susceptible to reconsolidation blockers, indicating that this manipulation destabilizes the reactivated trace. In hippocampal slices, theta-burst stimulation can induce LTP or depress recently potentiated responses (Kang-Park et al. 2003). This bidirectional change in transmission efficacy depends on the stimulus intensity and the past experience of the synapse, which determine the activation state of signal-transduction pathways that regulate AMPAR phosphorylation and synaptic trafficking essential for LTD and LTP (Lee et al. 2000; Kang-Park et al. 2003). Then, it is possible that fimbria-fornix theta-burst stimulation during ORM recall triggers some of the molecular mechanisms responsible for memory destabilization, which in turn activate those responsible for memory restabilization.

In conclusion, our data show that hPAC during recall enables the association of new and old ORMs through reconsolidation and that dopamine neurotransmission in the hippocampus plays a fundamental role in this process. It has been proposed that hippocampal theta phases coordinate memory encoding and recall in order to avoid information interference (Hasselmo et al. 2002). In this respect, Colgin et al. (2009; Colgin 2015) demonstrated that theta-nested slow gamma oscillations synchronize memory reactivation

while theta-nested fast gamma regulates the acquisition of novel information. So, it is possible that the theta–slow gamma and theta–fast gamma interactions we observed during ORM reactivation reflect a mechanism that facilitates the integration of old and new information, minimizing interference between overlapping representations.

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## References

- Aidil-Carvalho MF, Carmo AJS, Ribeiro JA, Cunha-Reis D. 2017. Mismatch novelty exploration training enhances hippocampal synaptic plasticity: a tool for cognitive stimulation? *Neurobiol Learn Mem* **145**: 240–250. doi:10.1016/j.nlm.2017.09.004
- Antunes M, Biala G. 2012. The novel object recognition memory: neurobiology, test procedure, and its modifications. *Cogn Process* **13**: 93–110. doi:10.1007/s10339-011-0430-z
- Bergmann TO, Born J. 2018. Phase-amplitude coupling: a general mechanism for memory processing and synaptic plasticity? *Neuron* **97**: 10–13. doi:10.1016/j.neuron.2017.12.023
- Bussey TJ, Barch DM, Baxter MG. 2013. Testing long-term memory in animal models of schizophrenia: suggestions from CNTRICS. *Neurosci Biobehav Rev* **37**: 2141–2148.
- Buzsáki G, Anastassiou CA, Koch C. 2012. The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nat Rev Neurosci* **13**: 407–420. doi:10.1038/nrn3241
- Clarke JR, Cammarota M, Gruart A, Izquierdo I, Delgado-García JM. 2010. Plastic modifications induced by object recognition memory processing. *Proc Natl Acad Sci* **107**: 2652–2657. doi:10.1073/pnas.0915059107
- Cole E, Simundic A, Mossa FP, Mumby DG. 2019. Assessing object-recognition memory in rats: pitfalls of the existent tasks and the advantages of a new test. *Learn Behav* **47**: 141–155. doi:10.3758/s13420-018-0347-9
- Colgin LL. 2015. Theta–gamma coupling in the entorhinal-hippocampal system. *Curr Opin Neurobiol* **31**: 45–50. doi:10.1016/j.conb.2014.08.001
- Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, Moser MB, Moser EI. 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* **462**: 353–357. doi:10.1038/nature08573
- Duncan K, Ketz N, Inati SJ, Davachi L. 2012. Evidence for area CA1 as a match/mismatch detector: a high-resolution fMRI study of the human hippocampus. *Hippocampus* **22**: 389–398. doi:10.1002/hipo.20933
- Düzel E, Penny WD, Burgess N. 2010. Brain oscillations and memory. *Curr Opin Neurobiol* **20**: 143–149. doi:10.1016/j.conb.2010.01.004
- Dzirasa G, Ramsey AJ, Takahashi DY, Stapleton J, Potes JM, Williams JK, Gainetdinov RR, Sameshima K, Caron MG, Nicolelis MA. 2009. Hyperdopaminergia and NMDA receptor hypofunction disrupt neural phase signaling. *J Neurosci* **29**: 8215–8224. doi:10.1523/JNEUROSCI.1773-09.2009
- Ennaceur A, Delacour J. 1988. A new one-trial test for neurobiological studies of memory in rats. 1: behavioral data. *Behav Brain Res* **31**: 47–59. doi:10.1016/0166-4328(88)90157-x
- Furini CR, Rossato JI, Bitencourt LL, Medina JH, Izquierdo I, Cammarota M. 2010.  $\beta$ -Adrenergic receptors link NO/sGC/PKG signaling to BDNF expression during the consolidation of object recognition long-term memory. *Hippocampus* **20**: 672–683. doi:10.1002/hipo.20656
- Hasselmo ME, Bodelón C, Wyble BP. 2002. A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Comput* **14**: 793–817. doi:10.1162/089976602317318965
- Gonzalez MC, Rossato JI, Radiske A, Pádua Reis M, Cammarota M. 2019. Recognition memory reconsolidation requires hippocampal Zif268. *Sci Rep* **9**: 16620. doi:10.1038/s41598-019-53005-8
- Gonzalez MC, Rossato JI, Radiske A, Bevilacqua LRM, Cammarota M. 2021. Dopamine controls whether new declarative information updates reactivated memories through reconsolidation. *Proc Natl Acad Sci* **118**: e2025275118. doi:10.1073/pnas.2025275118
- ILL-Raga G, Köhler C, Radiske A, Lima RH, Rosen MD, Muñoz FJ, Cammarota M. 2013. Consolidation of object recognition memory requires HRI kinase-dependent phosphorylation of eIF2 $\alpha$  in the hippocampus. *Hippocampus* **23**: 431–436. doi:10.1002/hipo.22113

- Jensen O, Colgin LL. 2007. Cross-frequency coupling between neuronal oscillations. *Trends Cogn Sci* **11**: 267–269. doi:10.1016/j.tics.2007.05.003
- Kang-Park MH, Sarda MA, Jones KH, Moore SD, Shenolikar S, Clark S, Wilson WA. 2003. Protein phosphatases mediate depotentiation induced by high-intensity theta-burst stimulation. *J Neurophysiol* **89**: 684–690. doi:10.1152/jn.01041.2001
- Kragel JE, VanHaerents S, Templer JW, Schuele S, Rosenow JM, Nilakantan AS, Bridge DJ. 2020. Hippocampal theta coordinates memory processing during visual exploration. *Elife* **9**: e52108. doi:10.7554/eLife.52108
- Kumaran D, Maguire EA. 2007. Match mismatch processes underlie human hippocampal responses to associative novelty. *J Neurosci* **27**: 8517–8524. doi:10.1523/JNEUROSCI.1677-07.2007
- Lee HK, Barbarosie M, Kameyama K, Bear MF, Huganir RL. 2000. Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. *Nature* **405**: 955–959. doi:10.1038/35016089
- Lemon N, Manahan-Vaughan D. 2006. Dopamine D1/D5 receptors gate the acquisition of novel information through hippocampal long-term potentiation and long-term depression. *J Neurosci* **26**: 7723–7729. doi:10.1523/JNEUROSCI.1454-06.2006
- Li S, Cullen WK, Anwyl R, Rowan MJ. 2003. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nat Neurosci* **6**: 526–531. doi:10.1038/nn1049
- Lima RH, Rossato JI, Furini CR, Bevilacqua LR, Izquierdo I, Cammarota M. 2009. Infusion of protein synthesis inhibitors in the entorhinal cortex blocks consolidation but not reconsolidation of object recognition memory. *Neurobiol Learn Mem* **91**: 466–472. doi:10.1016/j.nlm.2008.12.009
- Lisman JE, Grace AA. 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* **46**: 703–713. doi:10.1016/j.neuron.2005.05.002
- Lisman JE, Jensen O. 2013. The  $\theta$ - $\gamma$  neural code. *Neuron* **77**: 1002–1016. doi:10.1016/j.neuron.2013.03.007
- López-Madróna VJ, Pérez-Montoyo E, Álvarez-Salvado E, Moratal D, Herreras O, Pereda E, Mirasso CR, Canals S. 2020. Different theta frameworks coexist in the rat hippocampus and are coordinated during memory-guided and novelty tasks. *Elife* **9**: e57313. doi:10.7554/eLife.57313
- Lüthi A, Chittajallu R, Duprat F, Palmer MJ, Benke TA, Kidd FL, Henley JM, Isaac JT, Collingridge GL. 1999. Hippocampal LTD expression involves a pool of AMPARs regulated by the NSF–GluR2 interaction. *Neuron* **24**: 389–399. doi:10.1016/s0896-6273(00)80852-1
- Mei F, Nagappan G, Ke Y, Sacktor TC, Lu B. 2011. BDNF facilitates L-LTP maintenance in the absence of protein synthesis through PKM $\zeta$ . *PLoS One* **6**: e21568. doi:10.1371/journal.pone.0021568
- Myskiw JC, Rossato JI, Bevilacqua LRM, Medina JH, Izquierdo I, Cammarota M. 2008. On the participation of mTOR in recognition memory. *Neurobiol Learn Mem* **89**: 338–351. doi:10.1016/j.nlm.2007.10.002
- Radiske A, Rossato JI, Gonzalez MC, Köhler CA, Bevilacqua LR, Cammarota M. 2017. BDNF controls object recognition memory reconsolidation. *Neurobiol Learn Mem* **142**: 79–84. doi:10.1016/j.nlm.2017.02.018
- Radiske A, Gonzalez MC, Conde-Ocazone S, Rossato JI, Köhler CA, Cammarota M. 2020. Cross-frequency phase-amplitude coupling between hippocampal theta and gamma oscillations during recall destabilizes memory and renders it susceptible to reconsolidation disruption. *J Neurosci* **40**: 6398–6408. doi:10.1523/JNEUROSCI.0259-20.2020
- Rossato JI, Bevilacqua LR, Myskiw JC, Medina JH, Izquierdo I, Cammarota M. 2007. On the role of hippocampal protein synthesis in the consolidation and reconsolidation of object recognition memory. *Learn Mem* **14**: 36–46. doi:10.1101/lm.422607
- Rossato JI, Köhler CA, Radiske A, Lima RH, Bevilacqua LR, Cammarota M. 2015. State-dependent effect of dopamine D<sup>1</sup>/D<sub>5</sub> receptors inactivation on memory destabilization and reconsolidation. *Behav Brain Res* **285**: 194–199. doi:10.1016/j.bbr.2014.09.009
- Rossato JI, Gonzalez MC, Radiske A, Apolinário G, Conde-Ocazone S, Bevilacqua LR, Cammarota M. 2019. PKM $\zeta$  inhibition disrupts reconsolidation and erases object recognition memory. *J Neurosci* **39**: 1828–1841. doi:10.1523/JNEUROSCI.2270-18.2018
- Sauseng P, Klimesch W, Gruber WR, Birbaumer N. 2008. Cross-frequency phase synchronization: a brain mechanism of memory matching and attention. *Neuroimage* **40**: 308–317. doi:10.1016/j.neuroimage.2007.11.032
- Shirvaskar PR, Rapp PR, Shapiro ML. 2010. Bidirectional changes to hippocampal theta-gamma comodulation predict memory for recent spatial episodes. *Proc Natl Acad Sci* **107**: 7054–7059. doi:10.1073/pnas.0911184107
- Vinogradova OS. 2001. Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. *Hippocampus* **11**: 578–598. doi:10.1002/hipo.1073
- Winters BD, Tucci MC, Jacklin DL, Reid JM, Newsome J. 2011. On the dynamic nature of the engram: evidence for circuit-level reorganization of object memory traces following reactivation. *J Neurosci* **31**: 17719–17728. doi:10.1523/JNEUROSCI.2968-11.2011
- Yao Y, Kelly MT, Sajikumar S, Serrano P, Tian D, Bergold PJ, Frey JU, Sacktor TC. 2008. PKM $\zeta$  maintains late long-term potentiation by N-ethylmaleimide-sensitive factor/GluR2-dependent trafficking of postsynaptic AMPA receptors. *J Neurosci* **28**: 7820–7827. doi:10.1523/JNEUROSCI.0223-08.2008

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