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 PKMζ, 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-Madrona 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' inborn 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-Novelty group). As expected, Novelty group animals discriminated familiar object A from novel object C, but No-Novelty 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 µg/µL) impaired memory for object A in Novelty group animals, but not in No-Novelty 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 × anisomycin interaction in two-way ANOVA) (Fig. 1A). Total exploration time did not differ

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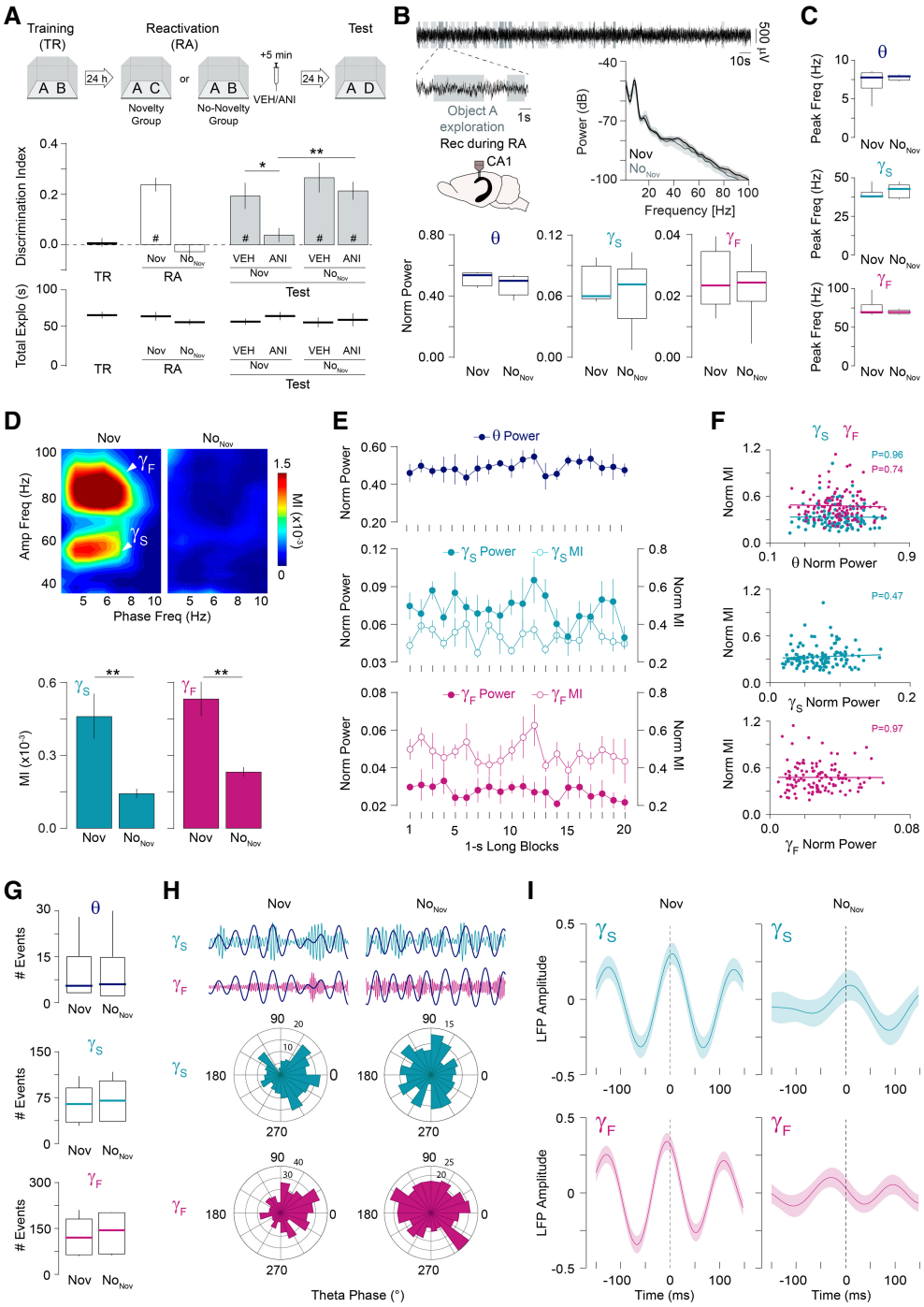

Figure 1. (*A*, *top* panel) Experimental protocol. (*Bottom* panels) Rats were trained (TR) in the novel object-recognition task using two novel stimuli objects A and B. One day later, they were submitted to an ORM reactivation session (RA) in the presence of familiar object A and novel object C (Novelty group; Nov) or in the presence of the familiar objects A and B (No Novelty group; No_{Nov}) 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 (θ, 4–10 Hz), slow gamma (γ_S; 35–55 Hz), and fast gamma power (γ_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.

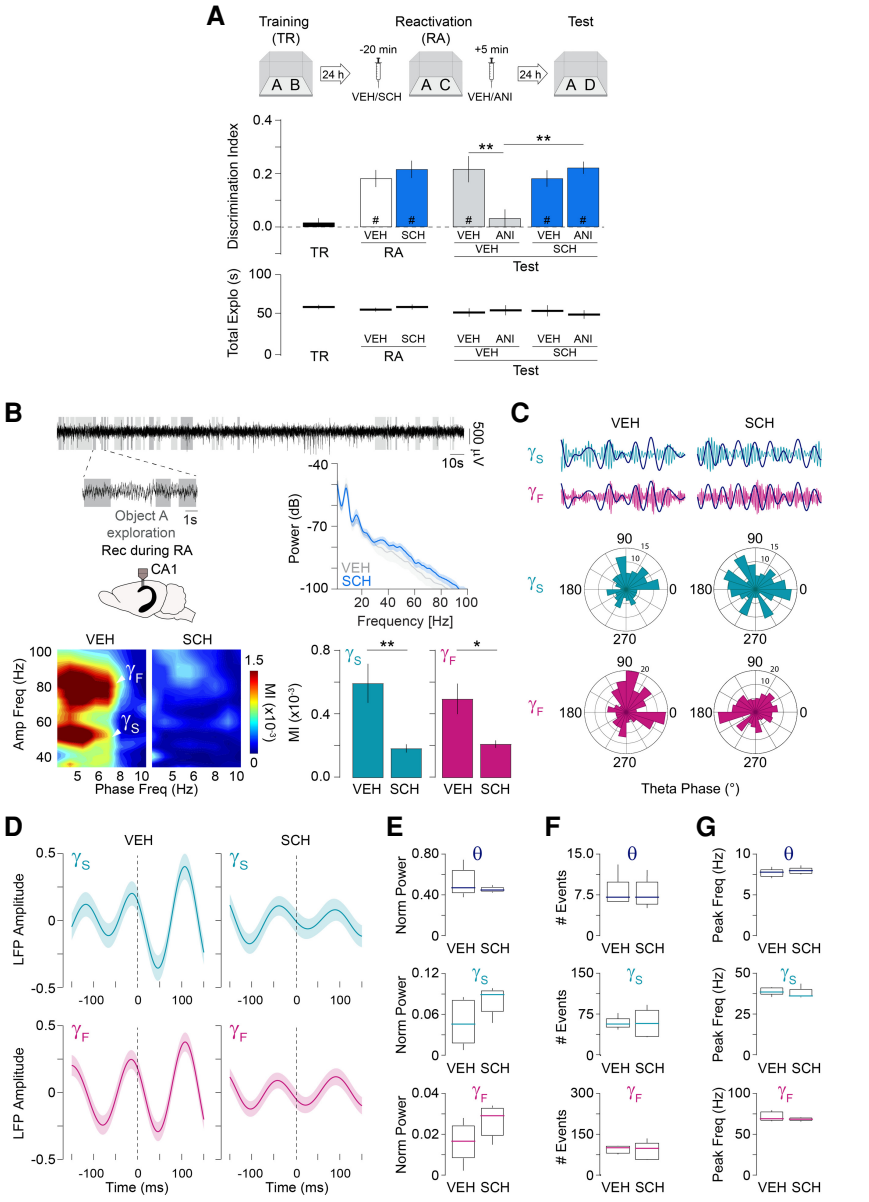

Figure 2. (*A, top* panel) Experimental protocol. (*Bottom* panels) Rats were trained (TR) in the novel object-recognition task using two novel stimuli objects A and B. One day later, they received bilateral intra-CA1 infusions of vehicle (VEH) or SCH23390 (SCH; 1.5 µg/µL) and 20 min thereafter were 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, θ, 4–10 Hz; slow gamma band, γ_S, 35–55 Hz; fast gamma band; γ_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 (θ; 4–10 Hz), slow gamma (γ_S; 35–55 Hz) and fast gamma (γ_F; 65–100 Hz) differed between Novelty and No-Novelty groups (θ power: $t_{(10)}=1.259$, $P=0.2366$; γ_S power: $t_{(10)}=0.3817$, $P=0.7107$; γ_F power: $t_{(10)}=0.3694$, $P=0.7195$. θ peak: $t_{(10)}=0.7125$, $P=0.4925$; γ_S peak: $t_{(10)}=0.9832$, $P=0.3487$; γ_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 (γ_S MI: $t_{(10)}=3.364$, $P=0.0072$; γ_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 (θ power: $F_{(3.799,18.99)}=0.4088$, $P=0.7911$; γ_S power: $F_{(4.248,21.24)}=1.065$, $P=0.4005$; γ_F power: $F_{(3.789,18.94)}=0.6366$, $P=0.6349$; γ_S MI: $F_{(3.638,18.19)}=0.7915$, $P=0.5354$; γ_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 (θ events: $t_{(10)}=0.000$, $P>0.9999$; γ_S events: $t_{(10)}=0.3297$, $P=0.7484$; γ_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 (γ_S: $Z=9.36$, $P<0.0001$; γ_F: $Z=19.02$, $P<0.0001$ for Novelty group; γ_S: $Z=0.47$, $P=0.6250$; γ_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 prereactivation administration of the D1/D5 receptor antagonist SCH23390 (1.5 µg/µL) 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 × 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 (γ_S MI: $t_{(8)} = 3.372$, $P = 0.0098$; γ_F MI: $t_{(8)} = 2.688$, $P = 0.0276$ for VEH vs. SCH in unpaired *t*-test. γ_S: $Z = 5.06$, $P < 0.0001$; γ_F: $Z = 7.30$, $P < 0.0001$ for VEH, γ_S: $Z = 1.54$, $P = 0.215$; γ_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 (θ power: $t_{(8)} = 1.016$, $P = 0.3393$; γ_S power: $t_{(8)} = 1.899$, $P = 0.0940$; γ_F power: $t_{(8)} = 1.888$, $P = 0.0958$. θ peak: $t_{(8)} = 0.8534$, $P = 0.4183$; γ_S peak: $t_{(8)} = 0.7129$, $P = 0.4962$; γ_F peak: $t_{(8)} = 1.074$, $P = 0.3140$. θ events, $t_{(8)} = 0.1118$, $P = 0.9137$; γ_S events: $t_{(8)} = 0.03252$, $P = 0.9749$; γ_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 (γ_S MI: $t_{(10)} = 2.939$, $P = 0.0148$; γ_F MI: $t_{(10)} = 5.998$, $P = 0.0001$ for No_{TBS} 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-µA biphasic pulses given at 500 Hz repeated at intervals of 130 msec, 500-µsec pulse width) and 5 min thereafter were given bilateral intra-CA1 infusions of vehicle or anisomycin (160 µg/µL). 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 × 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 × 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 × 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.

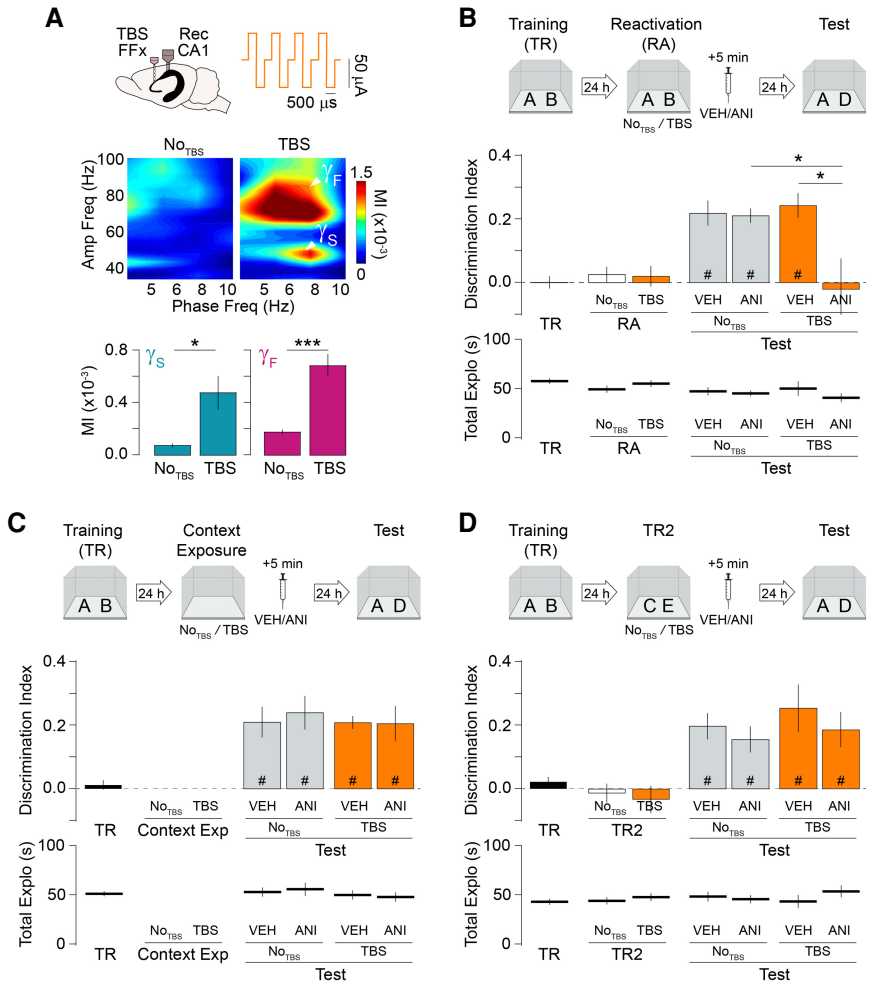

Figure 3. (*A*, *left* panel) Experimental protocol. The fimbria-fornix (FFx) was stimulated using a theta-burst protocol (TBS) and local field potentials from dorsal CA1 were recorded. (*Middle* panel) Representative phase-amplitude comodulograms. (*Right* panel) Theta–slow gamma and theta–fast gamma 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 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 ($n = 9$–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 repotentiation 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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