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**Graphical Abstract**

**Highlights**
- Prefrontal α7 nAChRs are critical for encoding of associative recognition memory
- Prefrontal α4β2 nAChRs are required for retrieval of associative recognition memory
- α7 and α4β2 nAChRs gate bidirectional plasticity at hippocampal-prefrontal synapses
- Bidirectional plasticity underlies the role of nAChR in associative recognition

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**In Brief**
Sabec et al. reveal a divergence in function of prefrontal nicotinic receptor subtypes in different stages of long-term associative recognition memory that relates to bidirectional modulation of synaptic plasticity at hippocampal-prefrontal synapses.

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Nicotinic Acetylcholine Receptors Control Encoding and Retrieval of Associative Recognition Memory through Plasticity in the Medial Prefrontal Cortex

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SUMMARY

Nicotinic acetylcholine receptors (nAChRs) expressed in the medial prefrontal cortex have critical roles in cognitive function. However, whether nAChRs are required for associative recognition memory and the mechanisms by which nAChRs may contribute to mnemonic processing are not known. We demonstrate that nAChRs in the prefrontal cortex exhibit subtype-specific roles in associative memory encoding and retrieval. We present evidence that these separate roles of nAChRs may rely on bidirectional modulation of plasticity at synaptic inputs to the prefrontal cortex that are essential for associative recognition memory.

INTRODUCTION

Associative visual recognition is the ability to integrate the identity of an object with the location in which it was encountered (Dickerson and Eichenbaum, 2010). Associative recognition memory consists of initial encoding and subsequent retrieval and depends on the medial prefrontal cortex (mPFC) integrating information received from the hippocampus (HPC) and other brain regions (Barker et al., 2007, 2017). Acetylcholine is essential for a variety of complex behaviors such as the performance of attention and learning tasks (Wallace and Bertrand, 2013; Parikh et al., 2007), and cholinergic deficits are central to the etiology of dementias (Picciotto and Zoli, 2002). To date, there has been a focus on muscarinic acetylcholine receptors in mPFC-dependent memory (Barker and Warburton, 2008). However, it is not known whether nicotinic acetylcholine receptors (nAChRs) in the mPFC play any role in encoding, consolidation, or retrieval of associative recognition memory in rats.

Synaptic plasticity is considered essential for learning and memory (Martin et al., 2000). nAChRs are expressed throughout the mPFC (Poorthuis et al., 2013), and their activation can give rise to synaptic plasticity (Verhoog et al., 2016; Couey et al., 2007; Udakis et al., 2016). HPC input to the mPFC is crucial for associative recognition memory (Barker et al., 2017), but whether activation of nAChRs governs synaptic plasticity at HPC-mPFC synapses and how such nicotinic modulation may be involved in distinct phases of associative recognition memory are not known.

We now test the hypothesis that specific nAChRs induce different forms of synaptic plasticity to bring about encoding and retrieval of associative recognition memory. We report that homomeric α7 nAChRs are essential for both encoding of associative recognition and induction of long-term potentiation (LTP) of HPC-mPFC synapses. In contrast, α4β2-containing (α4β2) nAChRs are essential for both retrieval of associative memory and long-term depression (LTD). Selective inhibition of LTP or LTD expression mechanisms prevented memory encoding and retrieval, respectively. We conclude that different nAChRs in the mPFC promote LTP or LTD of HPC-mPFC synapses to enable encoding or retrieval of associative recognition memory.

RESULTS

α7 nAChRs Are Required for Encoding and α4β2 nAChRs for Retrieval of Associative Recognition Memory

Selective antagonists of α7 and α4β2* receptors were infused into-cortically into mPFC during different phases of the object-in-place (OiP) task (Figure 1A). The α7 nAChR antagonist methyllycaconitine citrate (MLA) (100 nM), when given prior to the sample phase, impaired OiP discrimination (MLA versus vehicle [Veh] t(10) = 2.756, p = 0.021). Thus, following MLA, discrimination was not different from chance, while the vehicle group had a significant discrimination (MLA t(10) = 0.372, p = 0.717; Veh t(10) = 6.368, p < 0.001; Figure 1Bi). In contrast, there were no deficits in OiP when MLA or vehicle was delivered after the sample phase (MLA t(11) = 3.335, p = 0.007; Veh t(11) = 4.382, p = 0.001; MLA versus Veh t(11) = 0.820, p = 0.429; Figure 1Bi) or prior to the test phase (MLA t(9) = 5.559, p < 0.001; Veh t(9) = 4.145, p = 0.003; MLA versus Veh t(9) = 0.190, p = 0.854; Figure 1Bi).

To confirm these effects, the experiment was repeated with α-bungarotoxin (α-BGT; 1 μM). Infusion of α-BGT prior to the sample phase impaired OiP encoding (α-BGT versus Veh...
t(8) = 2.559, p = 0.034), and animals failed to discriminate (α-BGT t(8) = 0.075, p = 0.942; Veh t(8) = 3.419, p = 0.009; Figure 1Bii). There was no deficit in OiP when α-BGT or vehicle was delivered prior to the test phase (α-BGT t(7) = 4.601, p = 0.002; Veh; t(7) = 5.360, p = 0.001; α-BGT versus Veh t(7) = 1.276, p = 0.243; Figure 1Bii). Thus, α7 nAChRs in mPFC are critical for encoding, but not for consolidation or retrieval of long-term associative recognition memory.

Infusion of the α4β2* nAChR antagonist DHβE (1 μM) impaired discrimination when given prior to the test phase (DHβE t(8) = 0.141, p = 0.891; Veh t(8) = 6.954, p < 0.001; Figure 1C); there was a significant difference between DHβE and vehicle (DHβE versus Veh t(8) = 2.467, p = 0.036). Memory was not impaired following administration of DHβE either prior to the sample phase (DHβE t(8) = 7.643, p < 0.001; Veh t(8) = 5.593, p = 0.001; DHβE versus Veh t(8) = -1.085, p = 0.310) or after the sample phase (DHβE t(11) = 6.342, p < 0.001; Veh t(11) = 4.831, p = 0.001; DHβE versus Veh to test phase had no effect on OL memory (Figures 1E and 1F; MLA t(11) = 4.220, p = 0.001; Veh t(11) = 4.263, p = 0.001; MLA versus Veh t(11) = -2.36, p = 0.081; DHβE t(11) = 11.193, p < 0.001; Veh t(11) = 5.366, p < 0.001; DHβE versus Veh t(11) = -1.188, p = 0.260). In addition, neither MLA nor DHβE had any effect on total exploration times (Table S2).

α7 and α4β2 nAChRs Are Required for LTP and LTD, Respectively

To probe how nAChRs may contribute to separate phases of associative recognition we examined, in vitro, synaptic plasticity at the HPC-mPFC pathway (Banks et al., 2015) that is essential for OiP memory (Barker et al., 2017). A spike-timing-dependent plasticity protocol (STDP; Parent et al., 2010) resulted only in a transient increase in HPC-mPFC EPSCs (t(7) = -0.410, p = 0.694; Figures 2A and 2I). To test whether nAChR subtypes can regulate synaptic plasticity, selective agonists were applied with STDP. In the presence...
of the α7 nAChR agonist PNU-282987 (1 μM) LTP was induced by STDP ($t_{(7)} = 4.059$, $p = 0.005$; Figures 2B and 2I). LTP was prevented by co-application of α7 nAChR antagonist MLA (100 nM) ($t_{(8)} = -1.583$, $p = 0.152$; Figures 2B and 2I) or intracellular 1,2-bis(o-aminophenoxy)ethane-N,N,N’,N’-tetraacetic acid (BAPTA) (1 mM) ($t_{(8)} = -0.708$, $p = 0.510$; Figures 2F and 2I).

LTD was induced when STDP was delivered in the presence of the α4β2* agonist RJR-2403 oxalate (3 μM) ($t_{(7)} = -4.518$, $p = 0.003$; Figures 2C and 2I); LTD was prevented by co-application of the α4β2* antagonist DHβE (1 μM) ($t_{(7)} = 1.100$, $p = 0.308$; Figures 2C and 2I). Interestingly, α4β2* nAChR activation coupled with STDP reversed prior α7 nAChR induced LTP ($F_{(2,14)} = 8.963$, $p = 0.003$; Figures 2D and 2J). Moreover, LTD was blocked in the presence of gabazine (250 nM) ($t_{(5)} = 0.651$, $p = 0.544$; Figures 2E and 2I), suggesting GABAergic transmission is required for LTD induction.

Neither α7 nor α4β2* nAChR agonists affected synaptic transmission in the absence of STDP (PNU $t_{(5)} = -0.489$, $p = 0.645$; RJR $t_{(5)} = -1.126$, $p = 0.311$; Figures 2G and 2H). Together, these results demonstrate that paired pre- and postsynaptic activity combined with α7 or α4β2* nAChR activation differentially induces LTP and LTD at the HPC-mPFC pathway. LTP may rely on α7 nAChR-mediated increases in intracellular calcium and LTD on α4β2* nAChR-mediated GABAergic inhibition.

Expression of α7 nAChR LTP Is Dependent on Atypical PKCs, while α4β2 nAChR LTD Requires GluA2 Internalization

To test whether bidirectional plasticity may provide a mechanism by which different nAChR subtypes contribute to associative recognition, we first determined whether α7 and α4β2*
nAChR-gated plasticity could be blocked by selective manipulation of intracellular mechanisms that mediate LTP or LTD expression. Zeta inhibitory peptide (ZIP) blocks LTP through inhibition of atypical PKC isoforms PKC<sub>i</sub> and PKM<sub>z</sub> (Serrano et al., 2005; Ren et al., 2013). Loading mPFC pyramidal cells with ZIP (3 μM) via the recording electrode blocked α7 nAChR-dependent LTP (t(6) = −0.975, p = 0.367; Figures 3A and 3D). In contrast, α7 nAChR-LTP was not blocked by postsynaptic loading of scrambled ZIP (t(6) = 4.047, p = 0.007; Figures 3A and 3D).

To test expression mechanisms of α4β2 nAChR-induced LTD, we used the peptide GluR2<sub>3g</sub> (30 μM) to inhibit activity-driven endocytosis without affecting basal transmission or LTD (Ahmadian et al., 2004; Brebner et al., 2005). Postsynaptic loading of GluR2<sub>3g</sub> blocked α4β2 nAChR-dependent LTD (t(6) = 0.470, p = 0.655; Figures 3B and 3D). LTD was not blocked by the inactive peptide, GluR2<sub>3A</sub> (t(7) = −3.215, p = 0.015; Figures 3B and 3D).

α7 nAChR-induced LTP was not affected by GluR2<sub>3g</sub> (30 μM) (t(4) = 3.290, p = 0.030; Figures 3C and 3D), and α4β2 nAChR-dependent LTD was not affected by ZIP (3 μM) (t(3) = −4.504, p = 0.020; Figures 3C and 3D), thus confirming the selectivity of the GluR2<sub>3g</sub> for LTD and ZIP for LTP.

### Blocking Expression Mechanisms of LTP and LTD Prevents Encoding and Retrieval of Associative Recognition Memory, Respectively

We next tested the hypothesis that if the different forms of nAChR-induced plasticity are essential for the separate phases of associative recognition memory, then selective blockade of LTP and LTD expression mechanisms in vivo should result in selective deficits in encoding and retrieval, respectively.

Infusion of ZIP (10 mM) prior to the sample phase impaired OiP performance compared to scrambled ZIP (Scr-ZIP; 10 mM) (ZIP versus Scr-ZIP t(11) = 3.293, p = 0.004); discrimination following ZIP was not different from chance (ZIP t(11) = −1.189, p = 0.260; Scr-ZIP t(11) = 3.622, p = 0.004; Figure 3E). In contrast, memory was not impaired when ZIP was infused prior to the test phase (ZIP t(11) = 6.491, p < 0.001; Scr-ZIP t(11) = 4.095, p = 0.002; ZIP versus Scr-ZIP t(11) = 1.553, p = 0.149; Figure 3E). Therefore, selective blockade of LTP in the mPFC causes a deficit in associative recognition memory encoding but is without effect on memory retrieval.

Delivery of TAT-GluR2<sub>3g</sub> (30 μM) (Cazakoff and Howland, 2011) or control peptide (Scr TAT-GluR2<sub>3g</sub>; 30 μM) had no effect on OiP discrimination when delivered prior to the sample phase (TAT-GluR2<sub>3g</sub> t(11) = 5.204, p < 0.001; Scr TAT-GluR2<sub>3g</sub> t(11) = 8.670, p < 0.001; TAT-GluR2<sub>3g</sub> versus Scr TAT-GluR2<sub>3g</sub> t(11) = 0.716, p = 0.489; Figure 3F). In contrast, infusions given
before the test phase produced a significant difference in memory performance between conditions (TAT-GluR23, versus Scr TAT-GluR23, t(11) = 2.251, p = 0.046). Thus performance under TAT-GluR23 did not differ from chance (TAT-GluR23, t(11) = 1.527, p = 0.115) in contrast to control performance (Scr TAT-GluR23, t(11) = 6.423, p < 0.001: Figure 3F). Selective blockade of LTD in the mPFC therefore causes a deficit in long-term associative recognition memory retrieval but is without effect on memory encoding.

The deficits in memory resulting from blocking expression of plasticity were not a result of motor or attentional impairment, as total object exploration was equivalent between active and inactive peptide conditions for both ZIP and GluR23 (Table S3). Therefore, blockade of LTP (dependent on z7 nAChR) and LTD (dependent on z4/z2 nAChR) resulted in selective deficits in the encoding and retrieval, respectively, of OiP memory.

**DISCUSSION**

Our study takes advantage of the temporal specificity of pharmacological interventions to enable transient receptor inactivation and demonstrates that homomeric z7 and heteromeric z4/z2 nAChR subtypes make differential contributions to cognitive functions and to underlying synaptic plasticity at the HPC-mPFC pathway. These results suggest that different nAChRs promote LTP or LTD to enable encoding or retrieval of associative recognition memory.

Within the mPFC, z7 and z4/z2 subtypes of nAChRs display differential expression across distinct cells and layers (Couey et al., 2007; Poorthuis et al., 2013; Verhoog et al., 2016; Wallace and Bertrand., 2013). In the current work, we focus on HPC input to pyramidal cells in layer V of the mPFC, since this input is crucial for associative recognition memory (Barker et al., 2017). Several factors could contribute to the preferential activation of nAChR subtypes during initial encoding and subsequent memory retrieval (Figure 4). High cholinergic tone promotes encoding of new information by enhancing afferent signals, while lower concentrations may favor recurrent activity and thus consolidation and retrieval (Hasselmo, 2006). Thus, during encoding, synaptic z7 nAChRs, having rapid desensitization and a high-micromolar half-activation dose for acetylcholine (ACh), can be activated by transiently high ACh concentrations released under these conditions (Hasselmo, 2006; Arroyo et al., 2014; Parikh et al., 2007; Bennett et al., 2012; Dani and Bertrand, 2007). Postsynaptic z7 nAChRs on layer V pyramidal neurons can increase calcium influx and drive pyramidal cell depolarization, while astrocytic z7 nAChRs can promote glial D-serine release (Poorthuis et al., 2013; Dani and Bertrand, 2007; Papouin et al., 2017); all of these actions promote LTP (Ya-kel, 2014). Furthermore, z7 nAChR depolarizing currents can inactivate transient K⁺ currents and promote back propagating action potentials to enhance STDP-LTP (Sjöström and Nelson, 2002). Our postsynaptic BAPTA data demonstrate that increases in postsynaptic calcium are critical for z7 nAChR LTD at the HPC-mPFC input. In addition, it has also been shown in some areas, activation of presynaptic z7 nAChRs on glutamatergic terminals can promote LTD (Mansvelder and McGehhe, 2000). Therefore, high ACh release during encoding most likely favors LTP of HPC-mPFC synapses through actions primarily at z7 nAChRs (Figure 4).

Lower concentrations of ACh occur during associative recognition retrieval (Hasselmo, 2006). Diffuse, tonic release of low ACh concentrations likely favors heteromeric z4/z2 nAChR activation (Figure 4), which have low-micromolar effective half-activation doses and are expressed extra-synaptically (Dani and Bertrand, 2007; Arroyo et al., 2014; Bennett et al., 2012). z4/z2 nAChRs in mPFC layers II/III and V are largely restricted to interneurons (Poorthuis et al., 2013; Couey et al., 2007); their activation increases GABAergic drive in LTD. Therefore, low ACh release during retrieval most likely favors LTD of HPC-mPFC synapses through actions primarily at z4/z2 nAChRs on GABAergic interneurons (Figure 4).
Learning is associated with both LTP and LTD (Griffiths et al., 2008; Kemp and Manahan-Vaughan, 2007; Whitlock et al., 2006). Therefore, we employed the widely used peptides ZIP and the GluR2<sub>3</sub>, which prevent surface expression and endocytosis of GluA2-containing AMPA receptors, respectively (Serrano et al., 2005; Ren et al., 2013; Euvander et al., 2014; Ahmadian et al., 2004; Brebner et al., 2005). While there is some debate concerning the precise molecular mechanisms by which ZIP blocks LTP (Wu-Zhang et al., 2012), our data showing that ZIP blocked LTD, but not LTD, while GluR2<sub>3</sub> blocked LTD, but not LTP, demonstrate that each is selective for one form of plasticity. Our data therefore demonstrate that LTD is required for encoding, while LTD contributes to retrieval of associative recognition memory. While we demonstrate a role for nAChRs in both learning and in plasticity, it is nevertheless possible that encoding and retrieval may rely on some additional non-nicotinic forms of LTD and LTD. We speculate that α7 nAChR-dependent enhancement of HPC-mPFC synaptocircuit patterns and strengthens the association between items and their context during learning. α4β2<sup>+</sup> nAChR LTD at HPC-mPFC synapses may promote retrieval by reducing encoding interference from the afferent HPC input and/or increasing the signal to noise ratio of other inputs to the mPFC that are required for retrieval.

A lack of temporal resolution means that learning impairments in α7 and β2 knockout mice (Picciotto et al., 2001) cannot be attributed to deficits in encoding or retrieval. Our findings now raise the possibility that selective disruption of LTD or LTD may underlie the cognitive deficits previously observed in α7 and β2 knockout mice and that deficits may be specific to encoding and retrieval, respectively (Picciotto et al., 2001).

Activation of nAChRs contributes to a wide range of cognitive functions (Dani and Bertrand, 2007; Levin et al., 2006). Our data showing that α7 and α4β2<sup>+</sup> nAChRs are required for different phases of memory, most likely through differential regulation of HPC-mPFC synaptic plasticity, highlights the complex roles that ACh plays in learning and memory. These data suggest that knowing whether memory deficits are due to deficiencies in encoding or retrieval may enable more targeted pharmacological interventions.

**EXPERIMENTAL PROCEDURES**

Behavioral Procedures
All procedures were conducted in accordance with the UK Animals Scientific Procedures Act (1986) and local University of Bristol ethics regulations. A full description of methods can be found in Supplemental Experimental Procedures. In brief, mPFCs of adult male Lister Hooded rats were bilaterally cannulated (anteroposterior [AP] +3.20; medial-lateral [ML] ± 0.75; dorsoventral [DV] −3.5). Olf and OL tasks were conducted in an open field arena (Figures 1A and 1D). Rats were habituated across 5 days. In Olf, 4 distinct Duplo constructions are presented (5 min), and after 24 hr, the objects are re-presented (3 min) in a novel configuration. In OL, 2 identical Duplo objects are presented (3 min) and then re-presented (3 min) with 1 object in a novel position. Intra-mPFC infusions (1 μL/hemi, 0.5 μL/min) were timed to affect encoding, consolidation, or retrieval. Infusions and objects were counterbalanced within the experiment. Exploration was scored blind to drug condition and discrimination ratio (DR = [moved (s) − unmove (s)]/total (s)) calculated. After experiments, rats were perfused and coronal PFC sections (40 μm) stained with cresyl violet to map cannula tip position against standard sections of rat brain (Paxinos and Watson, 1999).

Electrophysiology
Coronal prefrontal sections (300 μm) were prepared from juvenile (30-day-old) male rats (Parent et al., 2010; Banks et al., 2015) and whole-cell recordings (K-glutamate-based internal) made from layer V pyramidal neurons. Data were collected using an Axopatch 200B amplifier (Axon Instruments) and WinLTP v1.0 software (Anderson and Collingridge, 2007). Cells were held at −70 mV (not adjusted for junction potential). Cells with series resistance >25 MΩ or variation >30% from baseline were discarded from analysis. Basal responses were evoked by extracellular stimulation of HPC input (0.1 Hz), and plasticity was induced by a spike-timing-dependent plasticity protocol (80 trains of pairings delivered at 5 Hz in current clamp), with each train at 5 excitatory postsynaptic potentials (EPSPs) (100 Hz) from the third EPSP to 3 postsynaptic action potentials (APs) evoked by current injection (Parent et al., 2010). Drugs were bath applied or loaded through the recording electrode, as indicated.

Statistical Analysis
Mean DRs were compared using one-sample t tests against zero (chance). Paired two-tailed t tests compared DRs and total exploration times between vehicle and drug conditions. Mean EPSC amplitudes (5 min baseline) were compared against the final 5 min of plasticity by paired two-tailed t tests or repeated-measures ANOVA (Bonferroni corrected post hoc comparisons). Statistical analysis was conducted using raw data, and graphs are presented as means (±SEM) normalized to baseline. Significance was assumed at p < 0.05.

**SUPPLEMENTAL INFORMATION**

Supplemental Information includes Supplemental Experimental Procedures and three tables and can be found with this article online at https://doi.org/10.1016/j.celrep.2018.03.016.

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**AUTHOR CONTRIBUTIONS**

Z.I.B., M.H.S., E.C.W., and S.W. designed experiments. M.H.S. performed and analyzed experiments. Z.I.B. and M.H.S. wrote the manuscript, with feedback from all authors.

**DECLARATION OF INTERESTS**

The authors declare no competing interests.

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