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Schema-Dependent Gene Activation and Memory Encoding in Neocortex

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When new learning occurs against the background of established prior knowledge, relevant new information can be assimilated into a schema and thereby expand the knowledge base. An animal model of this important component of memory consolidation reveals that systems memory consolidation can be very fast. In experiments with rats, we found that the hippocampal-dependent learning of new paired associates is associated with a striking up-regulation of immediate early genes in the prelimbic region of the medial prefrontal cortex, and that pharmacological interventions targeted at that area can prevent both new learning and the recall of remotely and even recently consolidated information. These findings challenge the concept of distinct fast (hippocampal) and slow (cortical) learning systems, and shed new light on the neural mechanisms of memory assimilation into schemas.

Memory consolidation consists of two processes. Cellular consolidation is mediated by synaptic and signal transduction mechanisms that store newly encoded memory traces on-line (*1*, *2*). Systems consolidation involves a time-limited interaction between the medial temporal lobe and the neocortical areas that eventually store long-term memory traces (*3*–*5*). Studies monitoring cerebral glucose use, immediate early gene (IEG) activation, and dendritic spine formation (*6*–*9*) indicate that rapid on-line encoding of episodic-like memory in the hippocampus can be followed by temporally graded neural changes in the medial prefrontal (mPFC), orbitofrontal (Orb), and retrosplenial (RSC) cortices.

This apparent sequence of events does not preclude the possibility of simultaneous encoding or "tagging" in the hippocampus and cortex (*9*, *10*). Indeed, when systems consolidation occurs in the presence of relevant prior knowledge (*11*, *12*), the "assimilation" of new paired-associate (PA) memories into existing activated cortical schemas proceeds very rapidly (*13*), reflecting an influence of prior knowledge on the rate of consolidation (*14*). The associative encoding of such PAs requires the hippocampus (*13*, *15*, *16*), accompanied by novelty-triggered cellular consolidation (*17*), but may also involve simultaneous cortical encoding. However, if parallel cortical encoding into a schema occurs, it may be driven solely in a bottom-up manner by the hippocampus or may also reflect the influence of activated prior knowledge already stored in cortex.

Study 1 mapped IEG activation in numerous brain areas of rats during both the retrieval of original PAs and the learning of new PAs after extensive prior training of a schema over many weeks (fig. S1). Guided by the retrieval cue of different flavors of food given in the start box of an event arena on each of six daily training trials, the animals learned to recall the location of the appropriate sand well, where they were rewarded by retrieving more of that same flavored food. Once performance reached asymptote over 6 weeks (fig. S2), a critical session of retrieval and new learning was conducted.

The 21 trained animals were then divided into three groups (Fig. 1A), to which a group of seven caged control animals (group CC) was added. One group had six trials with the original set of PAs and thus had only to retrieve (group OPA, i.e., original paired-associates). Another group had four successive trials with the original PAs and was then exposed to two new PAs that we had shown (*13*) could be encoded and successfully assimilated into the existing cortical schema (group NPA, i.e., new paired-associates). The third group was exposed to six new combinations of flavor and location that constituted a set of six new PAs (group NM, i.e., new map). Although this group was subjected to much greater "novelty," it was in a manner that should not allow successful cortical assimilation (timeline in Fig. 1A). The performance during that single session reflected these different conditions (Fig. 1B; latency data in fig. S3). After a further interval of 80 min (optimized for IEG signal detection of the neural correlates of the events of trials 5 and 6), the animals were first given a cued-recall test. This showed effective memory for the new PAs in the NPA group but no learning by the NM group (Fig. 1C). Brain sections were then prepared for histochemical analysis of two plasticity-associated IEGs—*Zif268* (*Egr1*) and *Arc* (activity-regulated cytoskeleton-associated protein) (*18*, *19*). Quantitative blind analysis of entire brain regions revealed a striking learning-associated increase in IEG expression in the prelimbic region (PrL) of the mPFC that was nonmonotonic with respect to the extent of learning-associated novelty (Fig. 1, D and E). IEG expression was highest in the NPA rats for whom activated prior knowledge was relevant to new PA information.

Detailed analysis revealed three broad patterns of IEG activation (fig. S4 and tables S1 and S2). First, a group of cortical regions [PrL, anterior cingulate (ACC), and RSC] showed the same nonmonotonic pattern of higher Zif268 and Arc expression in group NPA as in groups OPA and NM, despite the latter group being exposed to greater novelty (Figs. 1E and 2A); analyses of variance (ANOVAs) based on average values from all three regions showed a significant inverted U-shaped effect (Fig. 2A). Non-mnemonic aspects such as motivation were excluded as contributing factors by analysis of latency rather than choice (see fig. S3). Second, and in contrast, area CA1 of the hippocampus (Fig. 2B) showed a large increase in Arc expression in groups NPA and NM, with a monotonic trend favoring the highest expression in group NM; Zif268 levels were unchanged (see also fig. S7). Third, certain cortical regions showed little absolute change in IEG expression across the trained groups or relative to group CC [including the primary somatosensory "barrel" cortex (Ssp); Fig. 2C]. Barrel cortex was therefore chosen as the control region for study 2.

In study 2, we sought to determine whether the significant increase in both Zif268 and Arc

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in PrL reflects parallel encoding of task-related memory traces in cortex. Bilateral drug infusion cannulae were stereotaxically implanted into PrL and, as a within-subjects cortical control, into barrel cortex. New animals were trained on the initial schema over 6 weeks (PAs 1 to 6; see figs. S9 and S10) and then subjected to an extensive series of within-subjects interventions investigating the impact of blocking α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) or *N*-methyl-D-aspartate (NMDA) receptors during both retrieval (Fig. 3) and new learning (see Fig. 4 and table S3 for design).

Performance on PAs 1 to 6 was stable throughout 6 months of training and testing (fig. S10), and we assumed that the original schema was fully consolidated in cortex. We first hypothesized that interrupting excitatory neurotransmission in the PrL region displaying the largest IEG elevation in cortex in association with learning would disrupt the retrieval of original PAs. Indeed, inactivation of PrL by 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) prevented successful retrieval, whereas control infusions of CNQX into barrel cortex had no effect (Fig. 3A). Second, we asked whether the same would be seen for new PAs that had been encoded only 24 hours earlier. If schema-dependent encoding occurs in a network involving PrL, and if consolidation occurs rapidly against the background of an existing schema, then disruption of fast transmission might impair memory—even though a hippocampal index trace (*20*) might still remain. CNQX inactivation of PrL blocked cued recall of such newly stored PAs (Fig. 3B). Third, in common with previous studies of olfactory, spatial, and PA memory showing that NMDA receptor–dependent activity is not required for the retrieval of memory traces in the hippocampus (*15*, *21*), microinfusion of D(–)-2-amino-5-phosphonovaleric acid (D-AP5) into the PrL also had no effect on cued recall of both original and newly stored PAs (Fig. 3, C and D).

Despite the hippocampal-dependent nature of new PA encoding, we observed that blockade of either AMPA receptor–mediated fast transmission or NMDA receptor–dependent mechanisms in the PrL at the time of learning impaired consolidation (Fig. 4, A and B). The functional inactivation caused by CNQX would, as shown electrophysiologically (*15*), have lasted ~1 to 2

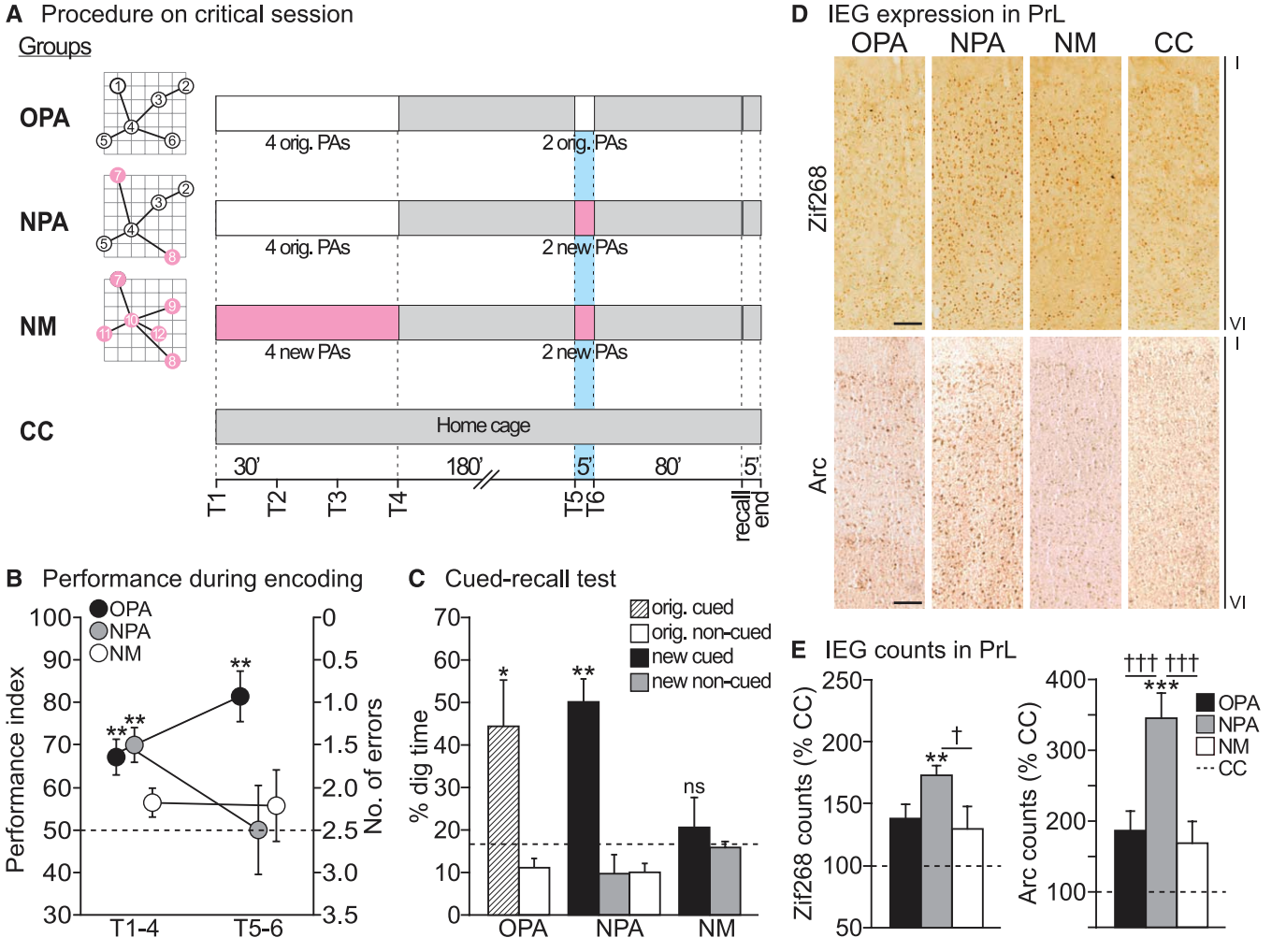

Fig. 1. Immediate early gene (IEG) activation in cortex during paired-associate (PA) learning. (**A**) Design for the critical session shows behavioral procedures across groups over 360 min (white, original PAs; pink, new PAs; blue, trials for which *Zif268/Arc* protein was measured). Immediately after testing, rats were transcardially perfused and their brains taken for IEG analysis. T1 to T6, trials 1 to 6; recall, cued-recall test. (**B**) Choice performance differed across groups and trials (Group × Trial interaction, $F = 4.52$, df = 2/18, $P < 0.05$); for trials 1 to 4, it was above chance at ~70% for groups OPA and NPA (*t* test, *P*s < 0.01 relative to chance) but at chance for group NM [not significant (ns)]. Performance was high for trials 5 and 6 in group OPA ($P < 0.01$) but at chance for the two new PAs of groups NPA and NM (ns). (**C**) The cued-recall test showed that the new PAs of group NPA had been learned effectively in one trial ($P < 0.01$ versus chance). In contrast, group NM failed to learn (ns). (**D**) IEG expression in PrL (layers I to VI) for both Zif268 and Arc. Scale bars, 100 μm. (**E**) The nonmonotonic increase of IEG expression in PrL revealed a significantly different pattern of expression across groups (Zif268: $F = 6.24$, df = 3/20, $P < 0.01$; Arc: $F = 14.13$, df = 3/24, $P < 0.001$), with group NPA differing from group CC (*) and the other trained groups (†) [Ryan-Einot-Gabriel-Welsch Range (REGWR) test]. *,†$P < 0.05$; **$P < 0.01$; ***,†††$P < 0.001$. Data are means ± SEM.

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hours, barely extending into the systems consolidation time domain of hours to days. It is therefore most logical to suppose that it interrupted a necessary parallel encoding of traces within a cortical network involving PrL. CNQX infusion into barrel cortex had no effect (Fig. 4A).

We were concerned about the extent of a brain region functionally affected by the volumes of drug we used (0.5 μl bilaterally). This was chosen, on the basis of pilot data, to affect a high proportion of the volume of PrL, but it may have been too little to affect much of the barrel cortex that served as our control. As a "positive" control, we therefore trained our animals on a separate runway "gap-crossing" task that requires whisker sensation (*22*, *23*). We established that a larger infusion of CNQX into barrel cortex (2.0 μl) is required to severely disrupt this control task, but this still did not affect new PA learning (fig. S12). Thus, the regional dissociation in cortex is meaningful.

These findings indicate that the assimilation of rapidly acquired new PA information into existing cortically based mental schemas is associated with cortical encoding of information during hippocampal-dependent learning, and that this simultaneous encoding is essential for long-term memory. First, when animals learned two new PAs (group NPA), there was an immediate up-regulation of two IEGs (Zif268 and Arc) in connected regions of the neocortex previously implicated in remote memory consolidation—PrL, ACC, and RSC (*5*). We postulate that this likely reflects a top-down influence on IEG activation (*14*) because the lower elevation of IEG expression in cortex of group NM, which was no greater than that associated with memory retrieval (group OPA), was commensurate with that group being unable to incorporate new PAs into a nonexistent cortical schema. In contrast, the relatively higher Arc expression of group NM in hippocampus

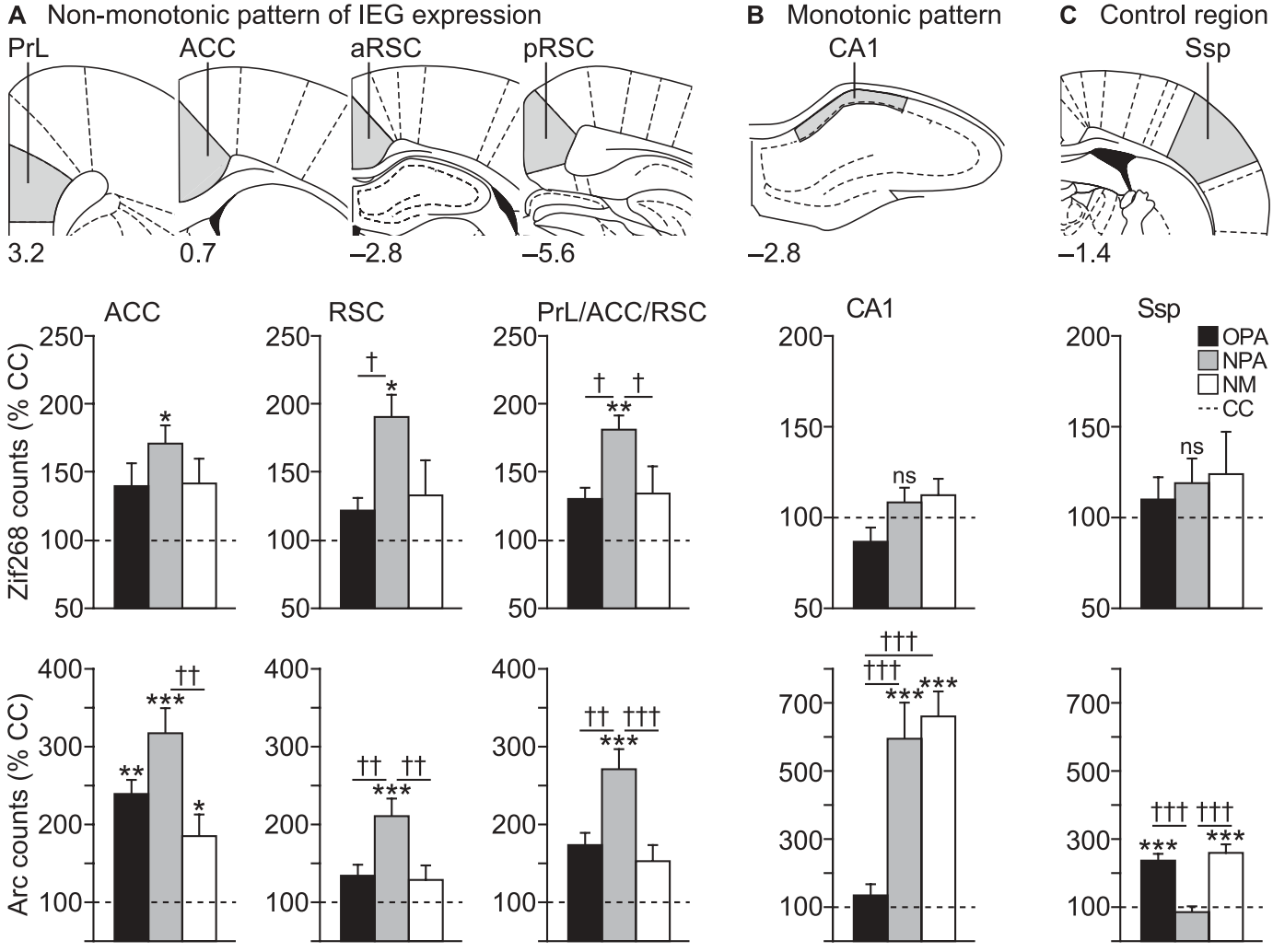

Fig. 2. IEG activation in cortex and hippocampus. (**A**) We found a similar pattern across a group of connected structures (PrL, ACC, and RSC) that, considered together, showed an overall inverted U-shaped function across groups for both Zif268 ($F = 6.16$, df = 3/20, $P < 0.01$) and Arc ($F = 13.95$, df = 3/24, $P < 0.001$). The individual region analyses were also significant (Zif268: PrL data in Fig. 1E; ACC, $F = 3.83$, $P < 0.05$; RSC, $F = 4.44$, $P < 0.05$; Arc: ACC, $F = 14.00$, $P < 0.001$; RSC, $F = 7.70$, $P < 0.01$). In each of these regions considered in isolation, group NPA showed significantly higher IEG expression than group CC and, particularly for Arc, higher levels than groups OPA and NM (REGWR tests, *P* values displayed). (**B**) In the hippocampus, the trend across groups with respect to area CA1 was, in contrast, a monotonic increase as a function of novelty (i.e., highest in group NM). For Arc, this was highly significant ($F = 19.51$, df = 3/24, $P < 0.001$); no significant group differences were seen for Zif268 ($F < 1$, ns). Across the PrL, ACC, and RSC considered together, the nonmonotonic pattern differed from the monotonic pattern shown in CA1 (Region × Group interaction for Arc: $F = 20.58$, df = 3/24, $P < 0.001$). (**C**) In barrel cortex (Ssp), no significant differences were seen across groups in Zif268 ($F < 1$, ns), but the data for Arc showed a paradoxical groups difference ($F = 22.34$, df = 3/24, $P < 0.001$), with groups OPA and NM being above groups NPA and CC (*P*s < 0.001). The numbers below each picture represent the distance (in mm) from bregma. *$P < 0.05$ versus group CC; †$P < 0.05$ versus trained group; **,††$P < 0.01$; ***,†††$P < 0.001$. Data are means ± SEM.

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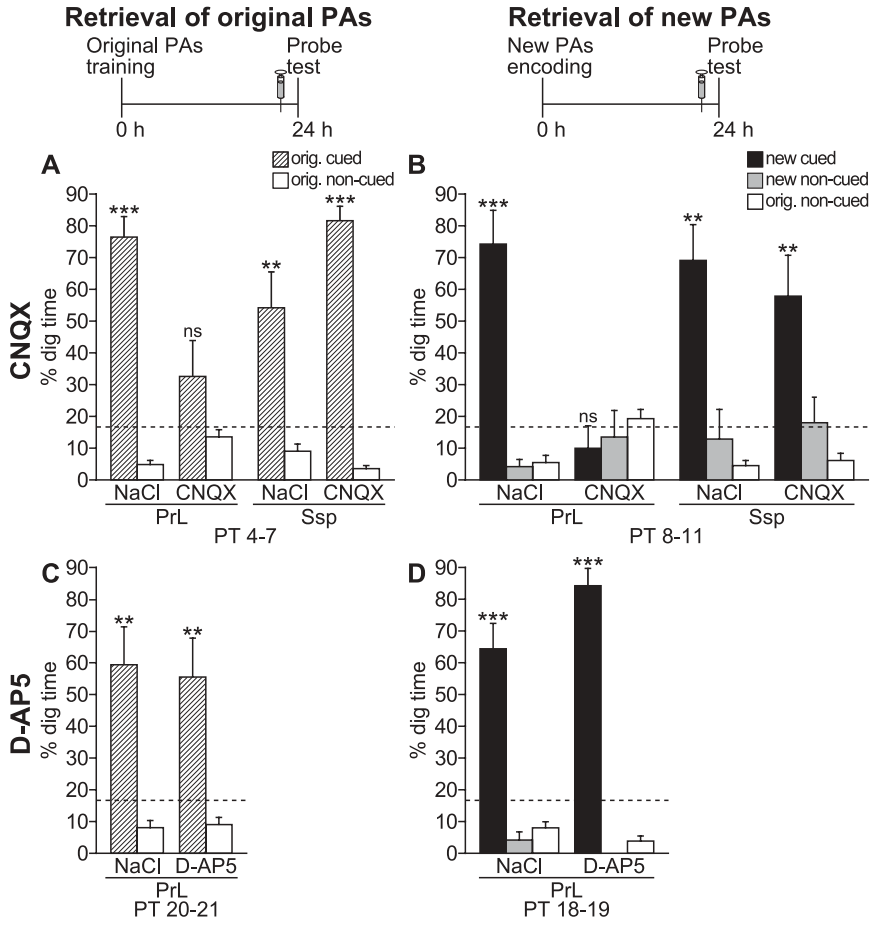

Fig. 3. Memory retrieval with and without cortical interference. (**A**) Retrieval of original PAs during bilateral CNQX-induced inactivation of the PrL region of mPFC and barrel cortex. Control infusions of NaCl. Inactivation of PrL selectively impaired retrieval of original PAs (Dig location × Drug × Brain Region interaction: $F = 11.42$, df = 1/10, $P < 0.01$, Greenhouse-Geisser). Performance was at chance for CNQX into PrL, and above chance for saline into PrL ($P < 0.001$) and CNQX/saline into barrel cortex ($Ps < 0.01$). (**B**) A similar pattern was apparent for retrieval of new PAs ($F = 5.33$, df = 1.22/10.97, $P < 0.05$). (**C** and **D**) Infusion of D-AP5 had no impact on retrieval of original PAs (C) or new PAs (D), with the ANOVAs showing no significant interactions between D-AP5 and saline conditions in either case. PT, probe test. $^{**}P < 0.01$, $^{***}P < 0.001$ versus chance. Data are means ± SEM.

reflects greater novelty and new map learning (*24*, *25*). The lack of correlation between spatial learning and *Zif268* RNA expression has been observed previously (*18*). Second, temporary interruption of AMPA and NMDA receptors in PrL during new PA learning resulted in a failure of memory tested 24 hours later. This is consistent with the idea that Arc activation is necessary for memory consolidation (*26*), but we now argue that hippocampal and cortical gene activation events are equally required for schema assimilation. Third, the cued recall of original and new PA information required AMPA, but not NMDA, receptor transmission in PrL at the time of memory trace reactivation. These findings complement similar data from human brain-imaging studies concerning interactions among the hippocampus, mPFC, and other cortex regions (*27*–*29*). However, they differ in detail from recent observations on "cortical tagging" (*9*). That study showed an increase of c-Fos expression in Orb 90 min after the encoding of a socially transmitted food preference. Local tetrodotoxin-induced interference of Orb impaired recall 30 days after training but had no effect either 1 or 7 days after training. Thus, a slower temporal gradient of consolidation was seen in these experimentally naïve animals.

One theory of systems consolidation contrasts hippocampal fast learning with a slow-learning neocortical system. These differential learning rates were shown in computational modeling to help prevent catastrophic interference of new learning by old information (*30*). This view does not predict IEG activation in cortex at the time of behavioral learning; it is more in keeping with the delayed up-regulation seen at remote time points in previous studies (*5*). Nor does it predict that AMPA receptor– and NMDA receptor–dependent encoding in PrL would be required at the time of behavioral learning for memory 24 hours later, or that AMPA receptor activity in PrL would be required for retrieval within

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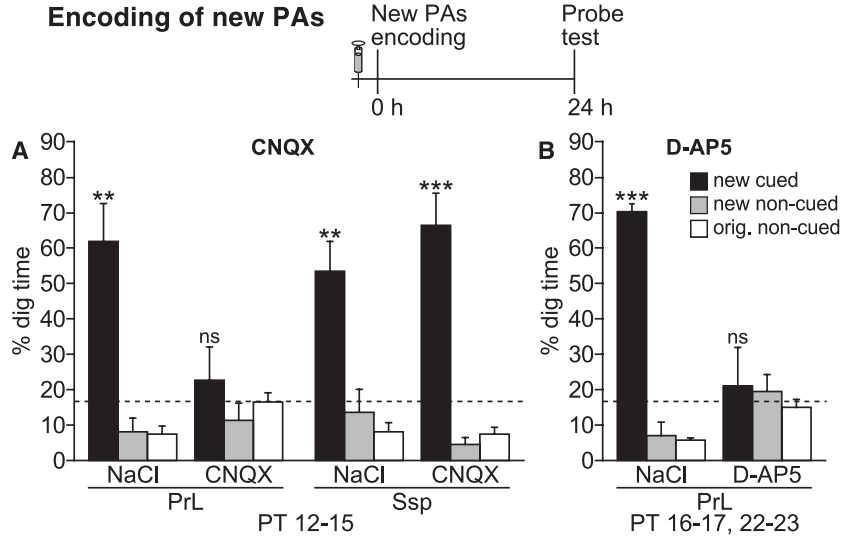

Fig. 4. Memory encoding of new PAs with or without glutamate receptor blockade. (**A**) Inactivation of PrL with CNQX at encoding impaired memory retrieval 24 hours later; no effect of infusions into barrel cortex was observed [Dig location × Drug × Brain region interaction: $F = 13.16$, df = 1.13/9.03, $P < 0.01$, Greenhouse-Geisser; *t* tests showed above-chance digging in the probe test 24 hours after encoding for the control conditions ($Ps < 0.01$) but not for CNQX into PrL ($P > 0.05$)]. (**B**) The same bilateral infusions of D-AP5 that had no impact on retrieval of new PAs (Fig. 3D) did impair acquisition when given at the time of memory encoding (Dig location × Drug interaction: $F = 9.86$, df = 1.25/9.98, $P < 0.01$; *t* tests showed a similar pattern for CNQX, $Ps < 0.001$ and ns, respectively). PT, probe test. $^{**}P < 0.01$, $^{***}P < 0.001$ versus chance. Data are means ± SEM.

24 hours of hippocampal-dependent learning. It also predicts that the rapid rate of consolidation that we observed might have caused at least a mild disruption of memory retrieval for original PAs, but original PAs continued to be recalled well.

A second idea, multiple trace theory (*31*), supposes that multiple traces of single-trial episodic events are encoded in both cortex and hippocampus. Our observation of parallel encoding of new PAs in a cortical network involving PrL, ACC, and RSC fits with this idea; however, multiple trace theory predicts that cortical traces may be sufficient for later retrieval but should not be necessary, given that hippocampal traces would be available. Multiple trace theory might accommodate assimilation into a schema as a form of "semanticization"; in that case, assimilation would exclusively involve cortical learning (*32*). However, this account would have to accommodate our previous observations from lesion and pharmacological studies (*13*, *16*) that the hippocampus remains essential for future learning of new PAs. Once a schema is acquired, assimilation of new information in our protocol may indeed represent an instance of hippocampal-dependent "semantic" rather than "episodic-like" learning within a single trial; our cued-recall test does not involve a temporal component (*33*).

Both the standard hypothesis and our schema hypothesis of systems consolidation (*3*, *4*, *34*) require simultaneous cortical encoding or "cortical tagging" (*9*). Models of reconsolidation involving memory updating are also relevant (*29*, *35*, *36*). Disconnected items of detailed information can be encoded in parallel in the neocortex at the same time as an index trace of paired association is encoded in the hippocampus (*20*), but with immediate IEG activation in cortex regulated in part by the relevance of the new information being processed in the hippocampus to an existing cortical schema. According to this version of parallel encoding, systems consolidation may be partly regulated in a top-down manner (*14*, *29*), enabling relevant new PAs to be assimilated into a schema. Recent data on effective connectivity between cortical regions in humans are in keeping with this view (*28*). The necessity for NMDA receptor–dependent mechanisms in specific areas of cortex (e.g., PrL) is also consistent with neural plasticity in cortex being vital at the time of learning. Our hypothesis also correctly predicts that after rapid consolidation, blockade of neural activity between these connected cortical structures would disrupt memory retrieval, as the hippocampal index trace would, on its own, be insufficient for effective retrieval.

Connections from the hippocampus to mPFC display long-term potentiation (*37*), and mPFC interacts with the hippocampus in the acquisition of object-place associations (*10*, *38*). Coherence in the theta-frequency band between mPFC and the hippocampus is observed during working-memory tasks (*39*, *40*), which our PA task also entails as the animals move about the arena to find locations in space that have been recalled by the flavor cue. Intrinsic dynamical oscillations may also be important for integration of cortical circuit performance (*41*), for episodic-like memory (*42*), and during the learning of schemas or their later reactivation (*43*, *44*). Thus, the opportunity to learn about the neural basis of cortical schemas of knowledge is opening up and, as it does so, the use of experienced animals possessing activated cortical networks of prior knowledge points to new ways of thinking about systems consolidation and reconsolidation.

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Supporting Online Material

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