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The Hippocampus, Medial Prefrontal Cortex, and Selective Memory Retrieval: Evidence From a Rodent Model of the Retrieval-Induced Forgetting Effect

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ABSTRACT: Inhibition is an important component of many cognitive functions, including memory. For example, the retrieval-induced forgetting (RIF) effect occurs when extra practice with some items from a study list inhibits the retrieval of the nonpracticed items relative to a baseline condition that does not involve extra practice. Although counterintuitive, the RIF phenomenon may be important for resolving interference by inhibiting potentially competing retrieval targets. Neuroimaging studies suggest that the hippocampus and prefrontal cortex are involved in the RIF effect, but controlled lesion studies have not yet been performed. We developed a rodent model of the RIF training procedure and trained control rats and rats with temporary inactivation of the hippocampus or medial prefrontal cortex (mPFC). Rats were trained on a list of odor cues, presented in cups of digging medium with a buried reward, followed by additional practice trials with a subset of the cues. We then tested the rats' memories for the cues and their association with reward by presenting them with unbaited cups containing the test odorants and measuring how long they persisted in digging. Control rats exhibited a robust RIF effect in which memory for the nonpracticed odors was significantly inhibited. Thus, extra practice with some odor cues inhibited memory for the others, relative to a baseline condition that involved an identical amount of training. Inactivation of either the hippocampus or the mPFC blocked the RIF effect. We also constructed a computational model of a representational learning circuit to simulate the RIF effect. We show in this model that "sideband suppression" of similar memory representations can reproduce the RIF effect and that alteration of the suppression parameters and learning rate can reproduce the lesion effects seen in our rats. Our results suggest that the RIF effect is widespread and that inhibitory processes are an important feature of memory function. © 2014 Wiley Periodicals, Inc.

KEY WORDS: hippocampus; prefrontal cortex; interference; retrieval inhibition

INTRODUCTION

Inhibition is an important component of many cognitive functions, including attention, perception, language, thought, and action (Dagenbach and Carr, 1994). A common pattern in the literature is that the processing of one item is facilitated while the processing of potentially competing items is inhibited. For example, selective attention to one item is accomplished, in part, by inhibiting attention to distractors (Tipper, 1985). Similarly, semantic cueing with one homophone (e.g., bank-money) inhibits cueing with another (bank-river, Simpson and Kang, 1994). These examples of selective inhibition based on feature-similarity may be functionally analogous to the visual system's center-surround receptive field mechanism of contrast enhancement, except that it is not constrained to a clearly defined two-dimensional topology of similarity. A comparable form of inhibition occurs in the domain of memory. The retrieval-induced forgetting (RIF) effect (Anderson et al., 1994) occurs when retrieval practice with some items from a study list inhibits the retrieval of the nonpracticed items relative to a baseline condition that does not involve retrieval practice.

In typical studies of the RIF effect, subjects are trained on a list of category-exemplar word pairs (e.g., FRUIT—apple, FRUIT—orange, etc.). After the initial training trials, subjects are given additional retrieval practice with some of the items from the list (e.g., FRUIT—a___, in response to which the subject is expected to retrieve "apple"). Subjects then undergo retrieval testing in which they are asked to recall as many of the exemplars from the training list as possible. Unsurprisingly, recall of the practiced items generally is improved, relative to a baseline condition in which no retrieval practice was given. However, recall of the nonpracticed items is significantly inhibited relative to baseline. Importantly, this retrieval inhibition occurs even though the nonpracticed items are given the same amount of training as the baseline items, indicating that it is the retrieval practice with some items that causes poorer retrieval of the nonpracticed items (Anderson et al., 1994).

Experimentally, the RIF effect is manifested as a retrieval failure, wherein recall of the nonpracticed items is poorer than baseline. Indeed, the phrase 'retrieval-induced forgetting' implies a memory failure. However, the RIF phenomenon may be a highly adaptive mechanism for resolving interference. Interference is a critical problem for high volume memory systems in which many items have mutual

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associations. In everyday situations, successful memory retrieval depends on the ability to retrieve the correct target item from memory while inhibiting the retrieval of potentially competing, inappropriate memories. For example, remembering where I parked my car this morning requires that I retrieve today's parking spot without retrieving all the other places that I have parked recently.

Inhibiting the retrieval of competing memories is an effective strategy for reducing interference, and experimental evidence suggests that RIF serves this purpose. The RIF effect occurs specifically in response to retrieval competition (for review see Levy and Anderson, 2002). Consistent with this interpretation, words that are strong exemplars of a category (e.g., apple) produce greater retrieval competition and are inhibited more strongly than weak exemplars (e.g., kiwi). Moreover, the inhibition of nonpracticed items is time-limited, persisting for at least 1 h but less than 24 h in Levy and Anderson's (2002) paradigm, suggesting that the RIF effect provides an ongoing mechanism for highlighting recently or frequently used memories for easy retrieval.

The RIF phenomenon has been extensively studied in humans. In addition to the cue-recall task described above, it has been demonstrated with recognition memory (Spitzer and Bauml, 2007), implicit memory (Veling and van Knippenberg, 2004), semantic memory (Johnson and Anderson, 2004), visuospatial object memory (Ciranni and Shimamura, 1999), eyewitness memory (MacLeod, 2002), and even foreign language acquisition (Levy et al., 2007). Previous neuroimaging studies have implicated the hippocampus and the prefrontal cortex (PFC) in the RIF effect (Anderson and Green, 2001; Wimber et al., 2008) and several other kinds of retrieval inhibition (Wagner et al., 2001; Depue et al., 2007; Crescentini et al., 2010). Some authors have argued that retrieval inhibition involves direct interactions between the hippocampus and PFC, with the PFC exerting executive control over hippocampal retrieval processes (Anderson and Green, 2001; Bunge et al., 2004; Munakata et al., 2011). However, to date, there has not been an animal model of the RIF effect, and no controlled lesion studies of retrieval inhibition have been performed. In this study, we adapted the RIF procedure for use in rodents by presenting rats with a list of odor cues, followed by extra practice with some of the odors (or no extra practice in the baseline condition) and then testing of their memory for the odors. We then used temporary neurochemical inactivation to examine the respective roles of the hippocampus and the medial prefrontal cortex (mPFC) in mediating the RIF effect.

To examine possible mechanisms of the RIF effect and inform our interpretation of temporary inactivation data, we also constructed a computational model of a representational learning circuit and trained it on the RIF task. Because RIF functions to suppress retrieval of similar memories that may compete with the target memory, while sparing dissimilar memories that do not threaten interference, we based our model on a high-dimensional metric of similarity. Consequently, suppression of potentially competing memories could be achieved via sideband suppression within this high-dimensional metric space, a technique that we previously have used to model the processing of perceptually similar odorants (Cleland et al., 2009; Cleland and Linster, 2012). Importantly, in this model framework, similarity is conceptualized broadly to include learned associations among odor cues and contexts encountered during the training experience. That is, it includes all of the shared elements that could lead to interference between memories. After modeling the RIF effect, we manipulated appropriate model parameters to simulate the effects of hippocampal or prefrontal cortical inactivation.

METHODS

Overview

We trained rats on a rodent version of the RIF task which involved training on a list of odor cues, followed by extra practice with some of the odors (or no extra practice in the baseline condition) and then testing of the odor memories. We conducted three experiments: (1) to determine whether the RIF effect can be seen in rodent olfactory memory, (2) to determine whether hippocampal inactivation disrupts the RIF effect, and (3) to determine whether mPFC inactivation disrupts the RIF effect. We then assessed our results using a computational model.

Subjects, Surgical Procedures, and Infusions

Subjects were 64 adult male Long-Evans rats (Charles River Laboratories, Wilmington, MA). Rats were assigned to either a hippocampal inactivation group ($n = 16$), an mPFC inactivation group ($n = 16$), an unoperated control group ($n = 16$), or hippocampal ($n = 8$) or mPFC ($n = 8$) saline control groups. Unoperated controls and rats given saline infusions did not differ on any measure of performance, so they were combined into a single control group. For rats assigned to infusion groups, bilateral guide cannulae (one injection site in each hemisphere, Plastics One, Roanoke, VA) were stereotaxically positioned just above the target location so that the infusion cannula, which protruded 1.0 mm beyond the tip of the guide cannula, would be positioned in the target area (Fig. 1, dorsal CA1: 3.6 mm posterior and 2.6 mm lateral to bregma, 2.2 mm ventral to the cortical surface; mPFC: 3.2 mm anterior and 0.5 mm lateral to bregma, 2.7 mm ventral to the cortical surface). The guide cannulae were secured to the skull with bone screws and dental acrylic. The rats were given an antibiotic (5 mg/kg Baytril) and an analgesic (5 mg/kg ketoprofen) before surgery. After at least 1 week of recovery, the rats were placed on a restricted feeding regimen (80–85% of free feeding weight) and began training. Temporary inactivation of the hippocampus or mPFC was induced by infusing the $GABA_A$ agonist muscimol into the corresponding region of the brain. Specifically, 30 min before the relevant training sessions, 0.5 μL of a 1 mg/mL muscimol solution in saline or the same volume of saline vehicle was infused into each hemisphere at a

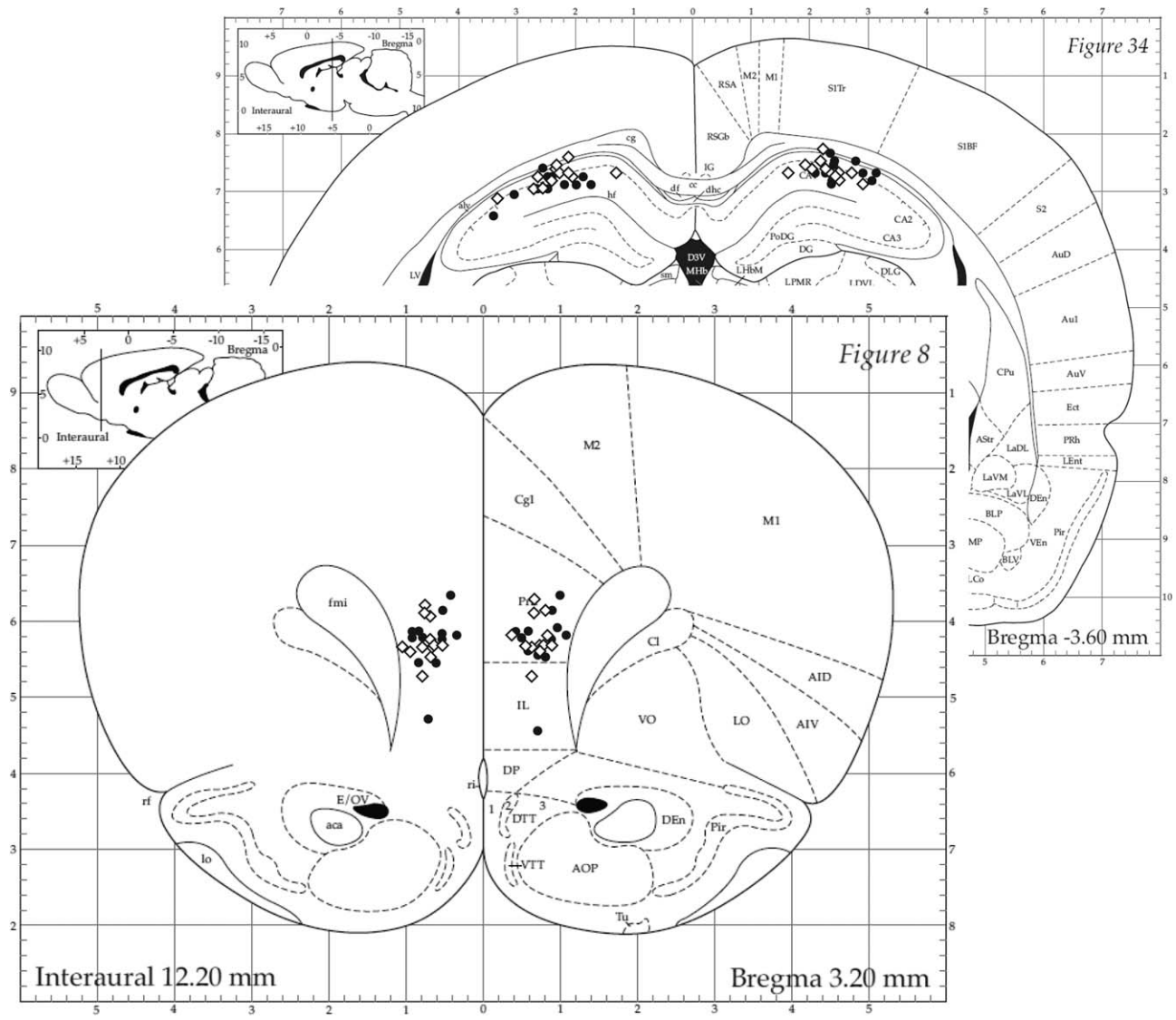

FIGURE 1. Locations of the infusion cannulae in the dorsal hippocampus and medial prefrontal (prelimbic and infralimbic) cortex are shown on images adapted from (Paxinos and Watson, 1998). Cannula placements for rats in the baseline condition are indicated by filled circles, whereas placements for rats in the extra practice condition are indicated by open diamonds.

rate of 0.5 μL/min. The infusion cannulae were left in place for 1 min after the infusions. All procedures complied with guidelines established by the Cornell University Institutional Animal Care and Use Committee.

Apparatus and Behavioral Training Procedures

Details of the apparatus and odor stimuli have been published elsewhere (Butterly et al., 2012). Briefly, the rats were trained in a white Plexiglass chamber (45 cm × 60 cm × 40 cm deep) equipped with a removable divider which separated the chamber into an odor presentation area and an intertrial interval area. Before training, the rats were shaped to dig for buried rewards (45 mg sucrose pellets, Bioserve, Frenchtown, NJ) in ceramic cups (8.25 cm in diameter, 4.5 cm deep) filled with corncob bedding material. A list of six pure odorants served as the odor cues (propyl butyrate, ethyl acetate, anisole, ethyl isovalerate, furfuryl propionate, and *n*-butyl glycidyl ether). A seventh odorant (1-butanol) was used as a distractor stimulus that was never rewarded. In each case, a volume of each odorant calculated to generate an equivalent vapor phase partial pressure after dilution was mixed with 50 mL of mineral oil (10 Pa, Cleland et al., 2002, 2009). A total of 10 mL of each odorant solution was then mixed with 2 L of corncob bedding material and stored in air-tight containers. For all training and testing procedures, the odorants were presented one at a time, alongside an identical cup containing bedding scented with the distractor odor, which was never baited.

Within each of the inactivation conditions described above, half the rats were assigned to the baseline condition and the

other half were assigned to the extra practice condition. Training and testing took place in a single session incorporating all three phases: training, extra practice (or a delay of equivalent duration), and testing. During training, all of the rats were given six trials with each of the six odor cues, presented in an unpredictable sequence. For each trial, the cups containing the odor cue with a buried reward and the distractor odor were placed into the chamber, the divider was raised, and the rat was allowed to approach the cups and dig until he retrieved the reward. For rats in the extra-practice condition, three of the six odors were designated P (practiced), and the other three were designated NP (nonpracticed). Subjects in this group received four additional training trials with each P odor, but did not receive any additional training with the NP odors. Rats in the baseline condition were not given extra practice on any of the odors. The extra practice trials required 5 min, so rats in the baseline condition were given a 5 min delay after training in order to produce an equivalent delay before testing, which occurred immediately thereafter. The test trials were identical to the training trials, except that neither cup was baited. The amount of time the rat spent digging in the unbaited cup containing the target odor served as our measure of how well the rats remembered the odor and its association with reward (Cleland et al., 2009). Digging times were measured with a stopwatch by an experimenter blind to the rat's condition. The rats were given four test trials, two with P odors, and two with NP odors. The selection of the test odors from the training list and the order of presentation of the P and NP odors were counterbalanced across subjects. Each rat in the baseline condition was yoked to a rat in the extra practice condition for the selection of test odors, such that the two groups were tested with identical odors.

Data Analysis

In order to correct for potential differences in perseverative tendencies or overall responsiveness, the amount of time spent digging in the distractor cup was subtracted from the time spent digging in the test odorant for each trial. Thus, our digging time score reflects how much more time the rats spent digging in the target odor than in the distractor odor. Distractor effects were minor: control rats spent 0.59 ± 0.18 sec digging in the distractor cups, mPFC inactivation rats spent 1.28 ± 0.27 sec, and HPC inactivation rats spent 0.18 ± 0.06 sec. In each experiment, our goal was to determine whether extra practice affected memory for the odors (i.e., improved memory for the P odors or impaired memory for the NP odors), relative to the baseline condition which did not involve extra practice. We used Welch's *t*-tests to compare digging times for the practiced and nonpracticed odors separately to the baseline condition, with Bonferroni correction for two comparisons (i.e., $\alpha = 0.025$). For significant outcomes, we report effect size (Cohen's *d*).

Computational Modeling

We constructed a computational model of a representational learning circuit to model the RIF effect. In this class of circuit, neural representations of external stimuli are high-dimensional and can be arbitrarily complex, yet retain quantifiable similarity relationships with one another. The RIF effect in the model is based on sideband suppression generated by each of these representations—that is, representations generate "surround" inhibition of similar (neighboring) representations in their high-dimensional similarity space. Hence, training on some items from a list will suppress memories of other items from that list to the degree that they are similar to the trained items, but will not suppress memories of dissimilar items (e.g., items drawn from dissimilar lists or learned in a different context). Note that we use the term "similarity" broadly to include not only perceptual similarity but also similarities derived from learned associations such as those formed when items are part of the same learning experience, which might lead to retrieval competition and interference. This conforms to experimental observations in which memory for items drawn from different categories was not impaired by the RIF effect (Anderson et al., 1994). Extra training on half of the elements from a list of odors therefore should actively impair memories for other odorants from the same list that do not also receive additional training, whereas parameter changes intended to simulate the effects of hippocampal or mPFC inactivation should reduce or eliminate the RIF effect, reflecting experimental data.

We used the NEST simulator (Diesmann and Gewaltig, 2001; Gewaltig and Diesmann, 2007, http://www.nest-initiative.org) and the PyNN model specification package (Davison et al., 2008, http://neuralensemble.org/PyNN) to implement a network of 100 leaky integrate-and-fire (LIF) pyramidal neurons (Fig. 2A; Pyr) that received analogue excitatory input (specific to a given odor cue) as well as global periodic inhibition in the gamma band (40 Hz) generated by an oscillator process. Cue representations comprised spatial patterns of excitatory input to these pyramidal neurons (temporal profiles of input were not manipulated). This input generated action potentials in pyramidal neurons that were phase-constrained to periods of disinhibition. Higher levels of input generated correspondingly phase-leading action potentials within phases of declining inhibition (phase or precedence code, Linster and Cleland, 2010; Panzeri et al., 2010). Pyramidal cells delivered this spiking output onto a layer of 100 output layer neurons (OLNs). Connectivity between the pyramidal cell layer and the OLN layer was pseudorandom and uniformly distributed with a 50% probability of connection.

Pyr-to-OLN synapses were sensitive to pyramidal cell spike timing according to a spike timing-dependent plasticity (STDP) rule implemented as described in Linster and Cleland (2010) (Fig. 2B, Table 1). Briefly, earlier pyramidal cell spikes (preceding the evoked postsynaptic spike, if any) yielded increased Pyr-to-OLN weights after conditioning, whereas later Pyr spikes (following the OLN spike) progressively produced lower, eventually negligible weights, thereby sparsening the OLN-level representation.

To generate a metric in which greater neuronal activity levels and sparser spatial representations in the OLN layer both reflect greater learning, we measured learning as follows. A cue-evoked barrage of phase-constrained Pyr spikes produced either

zero or one spike per cycle in any given OLN. The mean spike phase (in ms) of the activated OLN population was calculated for each oscillation period, and the reciprocal of this mean phase was used as the learning metric. Specifically, the strengthening of Pyr-to-OLN synapses produced an increased phase lead in follower OLNs. Sparsening the OLN representation by reducing the number of activated OLNs via learning also generated an increased phase lead, as the most lagging OLNs were the ones eliminated. Increased phase leads, corresponding to increased values in the reciprocal mean spike phase in ms^{-1}, indicate greater learning. The ordinates in Figures 3D–F denote a reasonable range for values of this metric after substantial learning, corresponding to a difference in mean spike times of roughly 1 ms.

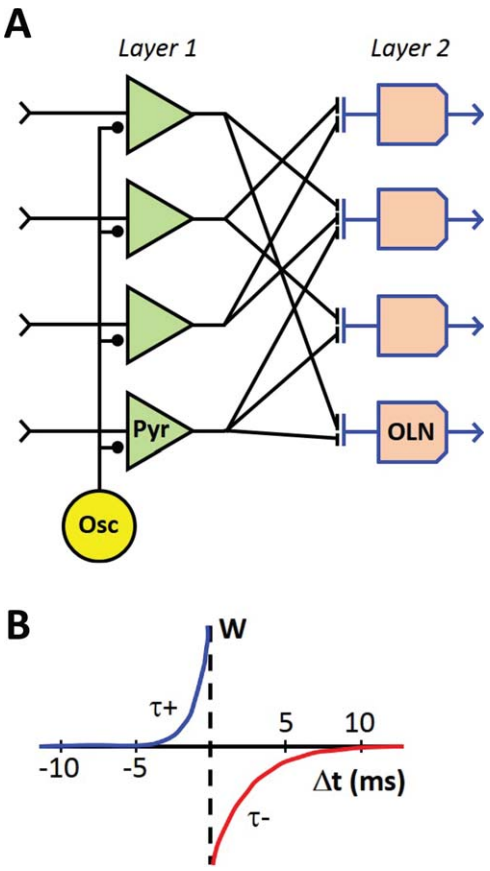

FIGURE 2. Computational model features. A: Schematic of the model. Input representations (cues, HDRs; see text) excite the 100-neuron population of spiking pyramidal neurons (Pyr; four depicted) comprising layer 1 of the network. Oscillatory inhibitory input (Osc; 40 Hz gamma) also is delivered to these same neurons, shaping the timing of action potentials such that each Pyr neuron fires either one or zero spikes per gamma oscillation, with greater input excitation producing a corresponding phase lead within the low-inhibition window. Pyr spikes excite output layer neurons (OLNs; Layer 2) via plastic synapses that follow the STDP learning rule (Song et al., 2000, see text). The pattern of OLN activation comprises the output representation that is shaped by learning. B: The spike timing-dependent plasticity rule. The abscissa denotes the time difference between a presynaptic Pyr spike and a postsynaptic OLN spike across a given synapse; if the Pyr spike precedes the OLN spike, the time difference is negative and the synapse is strengthened, whereas if the OLN spike precedes the Pyr spike, the time difference is positive and the synapse is weakened. The amount of strengthening or weakening per cycle depends on this spike time difference as well as on the absolute vertical scale values $W+$ (for the positive wing of the rule) and $W-$ (for the negative wing) and on the characteristic time constants for each curve ($\tau+$, $\tau-$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 1.

Model Parameters

	Control	HPC lesion	mPFC lesion
σ	1	5	2.5
$W+$	0.5	0.5	0.1
$W-$	0.6	0.6	0.06
$\tau+$	5	5	5
$\tau-$	5	5	5

The σ parameter denotes the relative similarity of cues on a list (i.e., the radius of the hypersphere containing a family of HDRs) and hence their degree of competitive overlap and sideband suppression. Values are scaled to control; lower values represent higher similarity and stronger competition. The STDP scale variables $W+$ and $W-$ determine the scale of weight increases and reductions (respectively) produced via spike timing-dependent plasticity (STDP); together, they instantiate learning rate within the model. The STDP time constants $\tau+$ and $\tau-$ are in ms; σ and W are unitless. Other model parameters (not shown) were unchanged across conditions.

Neural representations of odor cues consisted of 100-dimensional vectors corresponding to the levels of input to the 100 pyramidal neurons. To generate a list of random high-dimensional odor cue representations (HDRs) with consistent statistical relationships (probability distributions of similarity), we sampled 100 points from a sigmoidal distribution of unit amplitude to generate a "source HDR." To produce each of the odorant stimulus HDRs used for training, we added Gaussian noise to each point of the source HDR, set all resulting negative values to zero, and scaled the distribution linearly so that the maximum value was unity. Hence, each cue HDR was similarly related to the source HDR and also consistently related to one another. The source HDR itself was not used as a cue. The average similarity among the HDRs in a given list can be estimated as the mean radius of a hypersphere containing all of the HDRs in that list. The interrelatedness of the HDRs can be manipulated by increasing or decreasing this radius, making the group of HDRs less or more similar to one another, respectively. The HDRs used for additional practice (P) in each simulation were randomly selected, and 18 separate simulations were performed and averaged together to comprise each figure.

RESULTS

RIF in Controls

Intact control rats showed robust evidence of the RIF effect in the form of inhibited memory for the NP odors compared

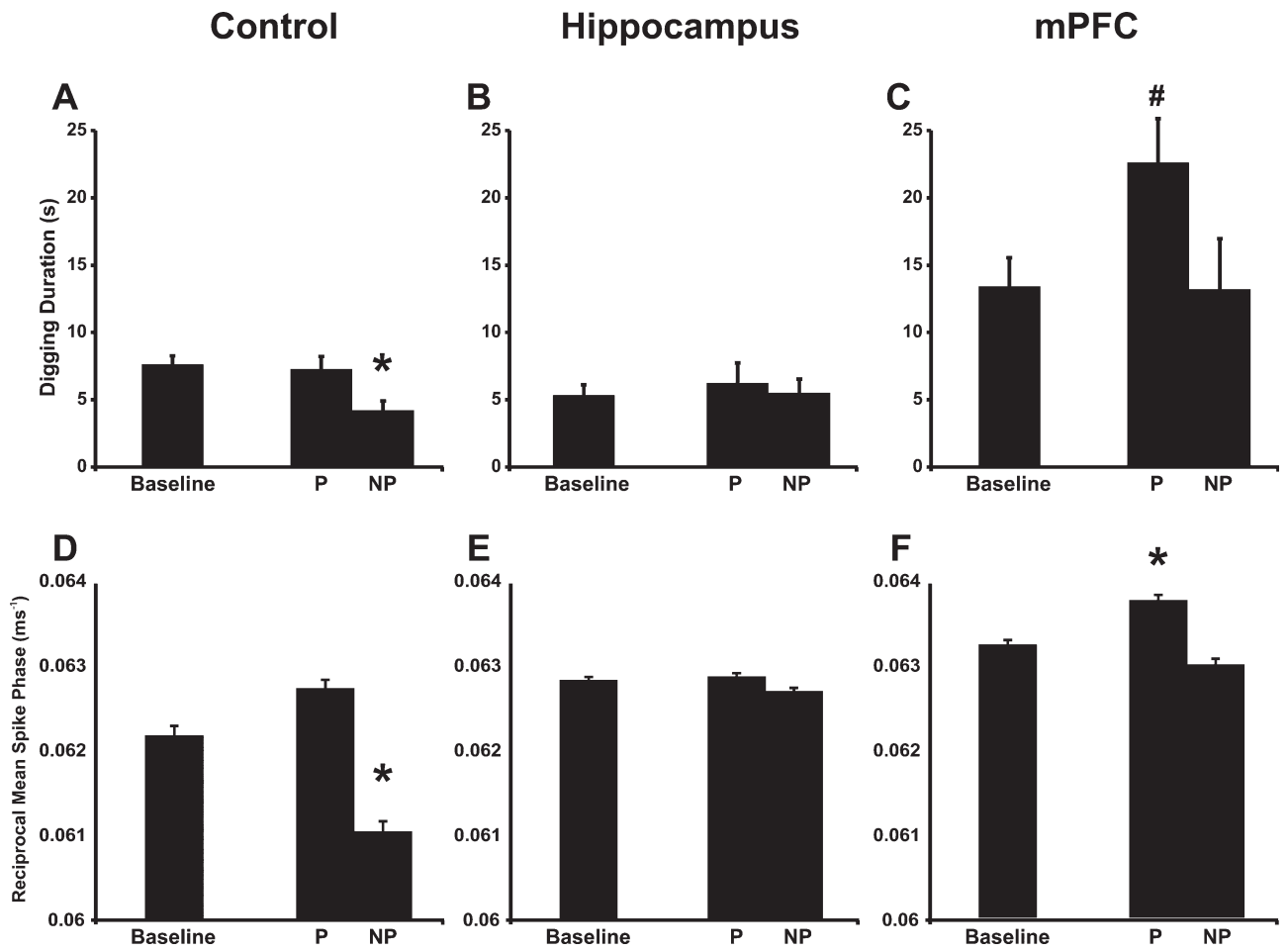

FIGURE 3. Average digging duration in response to the test odors is shown for control (A), hippocampal inactivation (B), and mPFC inactivation groups (C). Digging durations (time spent digging in the test odor cup minus the time spent digging in the distractor cup, see Methods) are shown for rats in the baseline condition and rats that were given extra practice trials, with responses to the practiced (P) and nonpracticed (NP) odors shown separately. Results from our computational model are shown for the simulated controls (D), hippocampal inactivation (E), and mPFC inactivation conditions (F). Parameter changes associated with each inactivation condition are listed in Table 1. Ordinate values are reciprocal mean spike phases (in ms^{-1}) measured in output layer neurons (see Methods). For each plot, the practiced and nonpracticed odors were compared with the baseline condition. Digging times for the nonpracticed odors were significantly reduced only for the control experiment (A and D, $^{*}P < 0.025$, see Methods). Values were significantly increased for the practiced odors only in the model of the mPFC inactivation (F). Digging times for the practiced odors were numerically increased in the rats with mPFC inactivation, relative to baseline, although this difference did not reach our corrected alpha level of 0.025 (C, $^{\#}P = 0.033$). All other comparisons were not significant.

with the baseline condition ($t_{(30)} = 3.63$, $P < 0.001$, $d = 1.09$, Fig. 3A). Importantly, the extra-practice rats were given the same number of trials with the NP odors as were the rats in the baseline condition with their odors; the only difference was that rats in the extra-practice condition were given four additional training trials with the P odors. Thus, consistent with previous studies in human subjects, extra practice with some items from a study list of odors inhibited the retrieval of the nonpracticed items on that list. Contrary to expectations, control rats did not show significantly stronger memories for the P odors, relative to the baseline condition ($t_{(30)} = 0.31$, $P = 0.76$), suggesting that the initial six training trials were sufficient to form asymptotically strong memories that were not measurably strengthened by the four extra practice trials.

We simulated these results using a computational model of a representational learning circuit (see Methods). In order to match the rat training procedures, baseline learning was achieved after training the simulated circuit with six presentations of each of six HDR stimuli in a pseudorandomized order. Subsequently, the circuit was given four additional training presentations with a randomly selected set of three of the HDRs (the "P" HDRs), whereas the other three HDRs (the "NP" HDRs) were not presented again. Under control conditions, the P-type HDRs were not learned significantly better than baseline, because learning was nearly asymptotic after the six baseline training trials (Fig. 3D, P vs. baseline, $t_{(34)} = 2.00$, $P = 0.054$). However, the additional training significantly suppressed memory for the NP-type

HDRs relative to the baseline HDRs (NP vs. baseline, $t_{(34)} = 3.79$, $P < 0.001$, $d = 2.22$).

Effects of Hippocampal Inactivation on the RIF Effect

Temporary inactivation of the dorsal hippocampus completely blocked the RIF effect. Specifically, digging times for the NP odors were not reduced relative to the baseline condition ($t_{(14)} = -0.14$, $P = 0.89$) and digging responses to the P odors were not elevated relative to the baseline condition ($t_{(14)} = -0.55$, $P = 0.59$, Fig. 3B). That is, the performance of rats with hippocampal inactivation was unaffected by the extra practice trials.

Items are strongly associated with the context in which they occur, and the hippocampus is involved in this associative process (e.g., Butterly et al., 2012). Accordingly, we treated contextual associations as shared features of the HDRs in our model and simulated hippocampal inactivation by reducing context-based feature similarity (i.e., by decreasing the average similarity of the HDRs). Specifically, the radius of the hypersphere enclosing the six randomly generated HDRs was increased by a factor of five (Table 1, see Methods), such that the overlap and interactions among HDRs were substantially reduced. As a result, the NP representations were not significantly suppressed by the additional training of the P items relative to the baseline (Fig. 3E, P vs. baseline, $t_{(34)} = 0.49$, $P = 0.63$). As in the control group, asymptotic learning of the baseline items prevented significant additional learning and memory for the P items was not improved by additional training relative to the baseline HDRs (NP vs. baseline, $t_{(34)} = 1.39$, $P = 0.17$).

Effects of mPFC Inactivation on the RIF Effect

Temporary inactivation of the mPFC also blocked the inhibitory component of the RIF effect (Fig. 3C). Rats with mPFC inactivation did not exhibit reduced memory for the NP odors relative to baseline ($t_{(14)} = 0.05$, $P = 0.96$). Interestingly, the rats showed some evidence of improved memory for the P odors compared with the baseline condition, but this effect did not achieve significance with our Bonferroni-corrected alpha level of 0.025 ($t_{(14)} = 2.36$, $P = 0.033$, $d = 0.28$). Thus, mPFC inactivation may have produced a more selective impairment in the inhibition of the NP items than hippocampal inactivation. The apparent increase in overall digging time is discussed below.

Although the PFC is thought to influence memory in a variety of tasks (e.g., Smith et al., 1995; Lee and Solivan, 2010), the specific mechanism by which the PFC participates in the RIF effect is not known. One possibility is that the PFC responds to retrieval conflict by sending feedback to the memory network in order to dynamically enhance sideband suppression and thereby achieve optimal inhibition of potential competitors. Additionally, recent evidence indicates that overall learning is delayed by mPFC inactivation (Peters et al., 2013). Therefore, we simulated mPFC inactivation by reducing the STDP-mediated learning rate (i.e., reducing the values of $W+$ and $W-$), and by modestly decreasing the sideband overlap (increasing σ, Table 1). These manipulations produced a pattern of results very similar to rat behavioral data (Fig. 3F). Specifically, they enabled additional practice to improve cue memory above baseline (P vs. baseline, $t_{(34)} = 3.70$, $P < 0.001$, $d = 2.19$; increasing $W+$ to 0.2 rendered this difference nonsignificant), whereas also eliminating the inhibitory component of the RIF effect (NP vs. baseline, $t_{(34)} = 1.55$, $P = 0.124$).

Group Differences in Digging Response Rates

The key question tested in these experiments was whether additional practice with some odors from the list impaired memory for the nonpracticed odors in control rats and in rats with hippocampal or mPFC inactivation. We used odor-cued digging responses to assess memory and showed inactivation-induced changes in responding to the NP odors in control animals. However, hippocampal and PFC lesions have also been shown to produce a nonspecific increase in behavioral responses (i.e., perseverative responding, Mishkin, 1964; Whishaw and Tomie, 1997). To examine this, we submitted the baseline response rates for control rats and rats in the hippocampal and mPFC inactivation conditions to a one-way ANOVA ($F[2,29] = 9.69$, $P < 0.001$). Post hoc comparisons using Tukey's honestly significant difference showed that inactivation of the mPFC was associated with elevated digging times compared with controls ($P < 0.005$). The digging times of rats given hippocampal inactivation were not significantly different from controls ($P = 0.31$). Thus, in addition to blocking the inhibitory component of the RIF effect, mPFC inactivation caused perseverative responding. We did not include perseveration in our simulation, so Figure 3F does not show the globally elevated response levels observed in rats with mPFC inactivation (Fig. 3C).

DISCUSSION

Like human subjects (Anderson et al., 1994), rats exhibited a robust RIF effect in which practice with some items from a study list inhibited the retrieval of the nonpracticed items. These results suggest that RIF is a widespread phenomenon, occurring in many learning situations and in different species, and they join a growing body of research indicating that inhibitory processes are an important aspect of memory function. We suggest that these inhibitory processes play a critical role in resolving interference. Interference is a critical problem for high volume memory systems, and one mechanism for resolving interference is to inhibit the retrieval of potentially competing memory targets. Previous neuroimaging studies of human subjects have suggested an involvement of the PFC and the hippocampus in these processes (Anderson and Green, 2001; Wimber et al., 2008). The current results confirm this involvement via targeted temporary inactivation of each of these areas,

demonstrating that the RIF effect depends on the integrity of both the mPFC and the hippocampus.

The behavioral tasks used to evoke the RIF effect in this new animal model have potentially important procedural differences as well as similarities when compared to the classic human studies of RIF. In typical human studies (e.g., Anderson et al., 1994), subjects are trained on category-exemplar pairs (e.g., FRUIT-apple) and there is no explicit reinforcement. In our studies, rats were trained to associate odor cues with a buried reward. Because the baseline and NP odors had identical reinforcement histories, differential reinforcement of these cues cannot account for the current results. However, we cannot be certain that the reduced responses to the NP items observed in the animal and human tasks are supported by the same underlying mechanism. Nevertheless, the same adaptive outcome is achieved in each case: the less-frequently encountered items are inhibited in a manner that facilitates retrieval of the more frequently encountered items. Moreover, observation of practice-induced inhibition across many different kinds of memory (see Introduction, Ciranni and Shimamura, 1999; MacLeod, 2002; Johnson and Anderson, 2004; Veling and van Knippenberg, 2004; Spitzer and Bauml, 2007) supports the idea that the RIF effect is a general function relevant to many kinds of memory.

In human subjects, the RIF effect seems to depend on the subject actively engaging in a retrieval search. For example, a robust RIF effect is seen when subjects are given partial cuing of the retrieval target (e.g., FRUIT-a_____) during the practice trials, but not when additional training trials are presented with the target item provided (e.g., FRUIT-apple; Anderson et al., 2000). Indeed, such additional training trials are sometimes used as a control condition that is not expected to produce RIF (e.g., Johansson et al., 2007). In contrast, additional training trials produced significant retrieval inhibition with our procedure. This apparent discrepancy may be explained by the sequence of events in our trials. During each trial, the rats approach the cup, investigate the odor and then dig for the reward, which often takes several seconds. Presumably, the rat retrieves the odor-reward association during this time and this supports the digging response, because the rats generally do not dig in the unrewarded distractor cup. Thus, each trial likely involves a significant retrieval component as well as constituting an additional reinforced training trial. In contrast, additional training trials in humans involve the simultaneous presentation of the cue and the target (e.g., FRUIT-apple) and there is little opportunity for the subject to engage in retrieval. Thus, the extra practice trials in our procedure likely involve a retrieval component that is not present in additional training trials used with human subjects.

Although our control subjects showed significant inhibition of the memory for the nonpracticed odors, they did not show the commonly observed improvement in memory for the practiced items, relative to the baseline condition (Fig. 3A). This result suggests that in control rats, the initial six training trials may have been sufficient to form relatively strong memories which were not measurably strengthened by the additional four practice trials. Consistent with this interpretation, previous experience in our laboratory suggests that rats can reliably remember a rewarded odor after only three or four training trials.

Rats given temporary inactivation of the hippocampus did not show enhanced memory for the practiced items nor did they show inhibition of memory for the nonpracticed items. The fact that the muscimol rats responded to the test odors as much as control rats, and much more strongly than they responded to the distractor odor, suggests that they did not simply forget the odors. Rather, the rats given hippocampal inactivation were insensitive to the inhibitory effects of the extra practice trials. Widely accepted theoretical accounts suggest that hippocampal encoding processes are rapid and automatic, whereas learning in extra-hippocampal systems proceeds through the slow accumulation of information across trials (e.g., McClelland et al., 1995). However, our results suggest that hippocampal processing may also be sensitive to the subtle effects of additional training trials on memory retrieval.

So why does the hippocampus play a role in the RIF effect? The answer may lie in the well-known hippocampal role in processing contextual information (for review see Smith, 2008). As discussed above, the RIF effect is thought to be triggered by retrieval competition. Although the odor cues used were not chemically or perceptually similar (i.e., they do not cross-generalize), they were related by virtue of being presented within the same distinctive training context and rats are known to spontaneously associate odors that are presented together (Devito and Eichenbaum, 2011) or within the same environment (Butterly et al., 2012). Within this interpretation, hippocampal processing likely resulted in the association of each odor with the training context, such that any cue that evoked the memory of one odor also would have activated memory representations of the other odors, resulting in retrieval competition. The loss of contextual associations in rats with hippocampal inactivation would result in reduced retrieval competition and, consequently, weaker suppression of the nonpracticed odors (see also Norman et al., 2007). This interpretation was supported by the results of our computational model. Hippocampal inactivation was modeled as a reduction in the average contextual similarity among cues, mediated by an increased hypersphere radius during cue (HDR) generation (see Methods). This reduction in cue competition resulted in a failure to suppress the nonpracticed items, just as hippocampal inactivation did in our rats.

Inactivation of the mPFC completely blocked the inhibitory effect of the extra practice trials and memory for the practiced odors was not significantly better than for the baseline odors. Inactivation of the mPFC also caused an overall increase in responding during the memory test. This overall increase may simply have been due to behavioral perseveration, which is known to result from PFC lesions (Mishkin, 1964). However, perseveration alone cannot explain the selective loss of inhibition, relative to baseline, seen in rats with mPFC inactivation, and we have shown that this inactivation procedure produces severe memory deficits that cannot be attributed to perseveration (Peters et al., 2013). Aside from perseveration, the effects

of hippocampal and mPFC inactivation were essentially equivalent. However, theoretical considerations suggest that the underlying causes of the impairment may have been different in the two regions. Whereas the hippocampal impairment may have been due to altered contextual memory processes, the PFC is known to exert inhibitory control over memory retrieval (Anderson and Green, 2001; Depue et al., 2007; Wimber et al., 2008).

The loss of inhibition in the rats with mPFC inactivation is consistent with studies showing that PFC activity is correlated with stronger retrieval inhibition (Kuhl et al., 2007; Wimber et al., 2008), suggesting that the PFC monitors ongoing retrieval processes and resolves conflict by suppressing the retrieval of inappropriate memories. Retrieval conflict arises when several representations are activated without a single clearly differentiated retrieval target emerging. We suggest that the PFC responds to such conflict by sending feedback to the memory network to boost sideband suppression such that the strongest retrieval target is maintained and its chief competitors are more strongly inhibited. This includes competitors that are perceptually similar and those with similarity due to shared context or other contributing factors. Further supporting this interpretation is a recent study showing that mPFC input to the hippocampus via the nucleus reuniens increases the specificity of memories, while inactivation of the same pathway causes broader generalization (Xu and Sudhof, 2013), the latter of which has been associated with reduced learning (Cleland et al., 2009). Simulations performed with our computational model are consistent with these interpretations. We modeled mPFC inactivation as a reduction in sideband suppression (increased value of σ) along with a reduction in the STDP learning rate (reduced values of $W+$ and $W-$, Table 1). Note that the reduced sideband suppression could also arise from a reduction of mPFC effects on hippocampal function.

Our simulations modeled the mechanisms underlying the RIF effect as sideband suppression—essentially similar to those underlying contrast enhancement in sensory systems. Specifically, both mechanisms regulate the deployment of competitive inhibition according to the similarity between representations, with the important caveat that cue similarity in the present model is not constrained by sensory metrics: quantitative similarity relationships between cues in the model are arbitrary (and of arbitrarily high dimensionality) and incorporate feature-similarity, cue familiarity, contextual relationships, and any other features of cue presentation or history that contribute to perceived similarity relationships among cues. Our simulations of lesion effects on rat behavior suggest that the hippocampus and mPFC may modulate retrieval processes by regulating these sideband suppression mechanisms and their associated learning processes. The underlying algorithm hence may reflect a common neural mechanism in the brain for the management of representations, whether arising from basic sensory processes or from complex cognitive functions.

The RIF phenomenon and related problems in the control of cortical inhibition have been modeled by others, emphasizing data from human subjects. One recent model of inhibitory control presents the PFC as delivering sophisticated, competitive inhibition of other neocortical regions by identifying favored representations and delivering inhibition so as to bias the computational outcome toward these favored representations (Munakata et al., 2011). In the model, this was achieved by a specific activation of favored representations coupled with a diffuse inhibition of nonactivated representations. This model is consistent with research suggesting that PFC biases competition by selectively activating the contextually appropriate response (e.g., Miller and Cohen, 2001; Egner and Hirsch, 2005), and also with our recent findings that the mPFC is not limited to delivering inhibition, but is also involved in promoting memory retrieval (Peters et al., 2013). However, it is not clear that this model can produce the specific inhibition of strong retrieval competitors that is a hallmark of the RIF effect (Anderson et al., 1994).

A second computational model, specifically designed to replicate the complex characteristics of the RIF effect as reported in human subjects, has been presented by Norman et al. (2007). It shares several features with our present model, including an overall strategy of selectively suppressing the strongest competitors, a learning framework in which learning results in memory representations becoming progressively more distinct from one another in order to reduce retrieval competition, and a mechanistic dependence on a global, oscillating inhibitory input to all principal neurons (albeit in the theta frequency band rather than the gamma band). However, other features of the two models are quite different. The Norman et al. (2007) model is a rule-based artificial neural network that incorporates certain relevant priors into its design, such as a global awareness of whether the oscillating level of inhibition is above or below a baseline level, which qualitatively changes the operative learning rule. In contrast, our model is a LIF network with fully localized synaptic plasticity rules and no global state-dependent singularities. The Norman et al. (2007) model is a four-part associative memory network in which representations are in danger of triggering one another via shared excitatory links among neurons commonly activated by both representations; RIF acts to solve this problem by weakening the problematic links, damaging the integrity of the competitor representation in the process. Our present model is a two-layer feed-forward representational learning network, in which repeated representational activation of Layer 1 (Pyr) neurons entrains a representation-specific pattern of Layer 2 (OLN) neurons via a STDP rule (it is the Layer 2 representation that is durably affected by learning in this model). All cue representations are strengthened by repeated presentation of their cues during initial training, and weaken one another during this phase because weakly activated Pyr neurons will have their output synapses weakened owing to STDP. During subsequent "extra practice" with the P cues, the weakly activated elements of competitor (NP) representations will continue to be weakened, but without the opportunity to reassert themselves via presentation of their primary cues. Notably, the P cues are in competition with one another as well, but gain more weight via direct learning than they lose via competition. Ultimately,

in this model, cues that remain important (i.e., continue to be presented) while competing strongly with one another will become progressively more distinct from one another in Layer 2 (cf. Weinberger, 2007; Cleland et al., 2009; Linster and Cleland, 2010), eventually minimizing or eliminating this retrieval competition. Our model demonstrates that a relatively simple algorithm based on the principles of competitor suppression can reproduce the RIF effect—irrespective of whether it is implemented in semantic or episodic memory networks—and can replicate the observed effects of PFC and hippocampal inactivation.

Our results join a growing body of research showing that the hippocampus and PFC are involved in resolving mnemonic interference. Neuroimaging studies with human subjects have shown that the PFC and hippocampus both contribute to the RIF effect (Anderson and Green, 2001; Wimber et al., 2008), and many rodent studies have shown that these structures work cooperatively in various learning and memory tasks (Lee and Solivan, 2008; Navawongse and Eichenbaum, 2013; Xu and Sudhof, 2013). In previous studies, we have shown that inactivation of either the mPFC or hippocampus impairs the ability of rats to resolve proactive interference (Butterly et al., 2012; Peters et al., 2013). High levels of interference are characteristic of many tasks known to be sensitive to hippocampal damage. For example, the hippocampus is required for transitive inference (Dusek and Eichenbaum, 1997), transverse patterning (Dusek and Eichenbaum, 1998), and cue sequence learning (Agster et al., 2002; Fortin et al., 2002), all of which require subjects to select a cue that previously has been rewarded on some trials but not on others, resulting in substantial interference. The PFC has also been directly implicated in resolving interference in humans and rodents (Incisa della Rocchetta and Milner, 1993; Peters et al., 2013). The PFC role in resolving interference is consistent with a number of accounts of PFC function that emphasize its role in the top-down control of memory retrieval processes (Anderson and Green, 2001; Bunge et al., 2004; Munakata et al., 2011). Additional research will be needed to investigate the specific interactions of the hippocampus and PFC in resolving interference.

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