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# Recognition memory for social and non-social odors: Differential effects of neurotoxic lesions to the hippocampus and perirhinal cortex

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ABSTRACT

The contributions of the hippocampus (HC) and perirhinal cortex (PER) to recognition memory are currently topics of debate in neuroscience. Here we used a rapidly-learned (seconds) spontaneous novel odor recognition paradigm to assess the effects of pre-training *N*-methyl-D-aspartate lesions to the HC or PER on odor recognition memory. We tested memory for both social and non-social odor stimuli. Social odors were acquired from conspecifics, while non-social odors were household spices. Conspecific odor stimuli are ethologically-relevant and have a high degree of overlapping features compared to non-social household spices. Various retention intervals (5 min, 20 min, 1 h, 24 h, or 48 h) were used between study and test phases, each with a unique odor pair, to assess changes in novelty preference over time. Consistent with findings in other paradigms, modalities, and species, we found that HC lesions yielded no significant recognition memory deficits. In contrast, PER lesions caused significant deficits for social odor recognition memory at long retention intervals, demonstrating a critical role for PER in long-term memory for social odors. PER lesions had no effect on memory for non-social odors. The results are consistent with a general role for PER in long-term recognition memory for stimuli that have a high degree of overlapping features, which must be distinguished by conjunctive representations.



## 1. Introduction

Recognition memory is the ability to remember previously encountered items, a faculty essential to declarative memory. It is well established that the medial temporal lobe (MTL), which includes the hippocampus (HC) as well as the adjacent entorhinal cortex, perirhinal cortex (PER) and postrhinal cortex (parahippocampal cortex in primates), is critical to declarative memory (Eichenbaum, 2000; Suzuki & Eichenbaum, 2000; Squire, 2009; Teyler & Rudy, 2007). Damage encompassing these brain areas leads to deficits in declarative memory, including recognition, spatial, temporal order, episodic, and semantic memory (O'Keefe & Nadel, 1978; DeVito & Eichenbaum, 2011; Eichenbaum, Yonelinas, & Ranganath, 2007; Fortin, Agster, & Eichenbaum, 2002; Kesner, Raymond, Gilbert, & Barua, 2002; Squire, Stark, & Clark, 2004). However, the specific function of individual MTL structures, including the nature of their contribution to recognition memory, remains unclear.

One prominent theory proposes that item and context information are processed in segregated parallel streams through PER and postrhinal cortex, respectively, and converge onto the HC to contribute to the formation of episodic memories (Brown & Aggleton, 2001; Diana, Yonelinas, & Ranganath, 2007; Eichenbaum et al., 2007; Teyler & Rudy, 2007). This theory suggests that the HC is critical for episodic memory, but not for item recognition memory, a notion that remains a subject of debate (Albasser, Davies, Futter, & Aggleton, 2009; Broadbent, Gaskin, Squire, & Clark, 2010; Brown & Aggleton, 2001; Fortin, Wright, & Eichenbaum, 2004; Fortin et al., 2002; Winters, Saksida, & Bussey, 2008). The same model proposes that PER is crucial for item memory, in part based on observations that PER plays an important role in object recognition memory (Aggleton, Albasser, Aggleton, Poirier, & Pearce, 2010; Albasser et al., 2009; Brown & Aggleton, 2001; Eichenbaum et al., 2007; Winters et al., 2008). However, recent evidence suggests that the role of PER in item memory is more complex than originally thought. For instance, several studies have shown that PER is particularly necessary when objects contain a high degree of overlapping features (Albasser et al., 2009; Buckley, Booth, Rolls, & Gaffan, 2001; Bussey, Saksida, & Murray, 2002; Eacott, Machin, & Gaffan, 2001; Norman & Eacott, 2005; Wan, Aggelton, & Brown, 1999; for a review see Winters et al., 2008). PER-lesioned animals demonstrate greater levels of impairment as the degree of feature ambiguity increases (Bartko, Winters, Cowell, Saksida, & Bussy,

*Abbreviations:* MTL, medial temporal lobe; HC, hippocampus; vHC, ventral hippocampus; PER, perirhinal cortex; LEC, lateral entorhinal cortex; NMDA, *N*-methyl-D-aspartate; *DI*, unadjusted discrimination index; *DI'*, normalized discrimination index.

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2007; Buffalo, Bellgowan, & Martin, 2006; Bussey et al., 2002). PER lesions also cause impairments in distinguishing simultaneously-presented stimuli, suggesting that PER might mediate the perceptual disambiguation of overlapping stimulus representations, in addition to serving aspects of recognition memory (Baxter, 2009; Bussey, Saksida, & Murray, 2006; but see Suzuki, 2009, 2010). Notably, perceptual and mnemonic theories of the contributions of PER to recognition processes are largely based on studies using visual stimuli. The question of whether PER plays a generalized role in recognition memory and/or perception outside the visuotactile realm is not well understood.

The overall objective of this study was to extend these influential theories by directly comparing the roles of the HC and PER in odor recognition memory. Specifically, we used olfactory stimuli to determine whether these theories extend to another modality, and to directly compare the use of social and non-social stimuli. Rodents are capable of rapidly learning and remembering odors over long periods of time, and have particularly sensitive olfactory discrimination abilities (Linster, Johnson, Morse, Yue, & Leon, 2002; Schellinck, Price, & Wong, 2008). Here, we contrast the use of highly overlapping social odors and relatively distinctive non-social odors.

Olfaction is a critical modality for mammals, guiding numerous aspects of their daily lives including food preference, reproductive status, maternal bonding, and identification of conspecific allies and predators (Doty, 1986; Sanchez-Andrade & Kendrick, 2009; Schellinck et al., 2008). Furthermore, olfactory inputs are highly interconnected with numerous mnemonic structures. In particular, the olfactory bulbs have direct projections to a number of putative memory structures in the MTL (Brennan & Kendrick, 2006; Kay, 2008).

Importantly, social odors are processed differently and have a unique composition compared to non-social odors. The rodent olfactory system is comprised of two distinct pathways, the main olfactory pathway and the accessory (vomeronasal) olfactory pathway, which are thought to transmit differential information about volatile and non-volatile olfactory stimuli, respectively (Martinez-Marcos, 2009). Social odors from conspecifics are composed of a complex assortment of various molecules with components shared between individuals, conveying information about the age, sex, health status, and relatedness (Brennan & Kendrick, 2006). These social odors are processed through both olfactory pathways, while non-social odors are processed through the main olfactory pathway.

Here, we use odor-based stimuli in an adaptation of the spontaneous novel object recognition paradigm (Ennaceur & Delacour, 1988; Monaghan et al., 2010; O'Dell, Feinberg, & Marshall, 2011; Spinetta et al., 2008) to elucidate the effects of pre-training lesions to the HC and PER on odor recognition memory. Additionally, we tested five retention intervals (5 min, 20 min, 1 h, 24 h, or 48 h) because of known time-dependent contributions of the HC (Anderson, 2007; Rolls, 1996; Zola-Morgan & Squire, 1990) and PER (Mumby, Piterkin, Lecluse, & Lehmann, 2007; Sacchetti, Sacco, & Strata, 2007) to other memory tasks. In particular, these retention intervals allowed assessment of short- and long-term odor recognition memory.

We also tested the effects of HC and PER lesions on recognition memory for both conspecific social odors and non-social odors (household spices). Conspecific and household odor stimuli represent an ecological and arbitrary approach, respectively, to the study of odor recognition memory (Domjan, Cusato, & Krause, 2004). Considering that HC lesions have been shown to impair various aspects of social memory (Alvarez, Wendelken, & Eichenbaum, 2002; Kogan, Franklandand, & Silva, 2000), it is possible that the HC plays a general role in social odor memory. Also, because PER has been implicated in the learning of social stimuli (Furtak, Allen, & Brown, 2007; Kholodar-Smith, Allen, & Brown, 2008; Petrulis & Eichenbaum, 2003), we sought to investigate whether PER lesions differentially affect recognition memory for social versus non-social odors.

Overall, HC-lesioned rats showed normal recognition memory for social and non-social odors, whereas PER-lesioned rats were selectively impaired in the long-term recognition memory for social odors. These data demonstrate that the HC is not necessary for short- or long-term odor recognition memory, consistent with models of HC memory function (Diana et al., 2007; Eichenbaum et al., 2007). These findings also indicate that the PER is not always critical for "item" memory (Eichenbaum et al., 2007), but rather only necessary when the cues are more complex or have a high degree of overlapping features (Bussey et al., 2006; Suzuki, 2009). Importantly, PER-lesioned rats demonstrated normal recognition of social odors at short intervals (5 and 20 min), providing strong evidence that the impairment was not due to a perceptual deficit. Overall, these findings contribute to a growing body of knowledge about the roles of the HC and PER in recognition memory for both social and non-social stimuli. These data are consistent with the hypothesis that PER contributes to recognition memories that require long-term storage of conjunctive feature representations.

## 2. Methods and materials

### 2.1. Subjects

Seventy-four male Long-Evans rats were used in this study: 39 served as conspecific odor donors, and 35 underwent surgical and behavioral procedures (375–450 g at the time of surgery). Rats were individually housed in clear rectangular polycarbonate cages and maintained on a 12 h light–dark cycle (lights off at 8:00 am). Access to food and water was unrestricted before surgery. Following surgery, rats were mildly food restricted to maintain 85% of their free-feeding body weight with free access to water throughout testing. All surgical and behavioral methods were in compliance with the University of California Irvine Institutional Animal Care and Use Committee guidelines.

### 2.2. Surgeries

Rats were randomly assigned to treatment groups: bilateral HC Lesion ($n = 9$), HC Control ($n = 8$), PER Lesion ($n = 10$), or PER Control ($n = 8$). Lesions were induced by infusions of *N*-methyl-D-aspartate (NMDA; Sigma, St. Louis, MO), in order to produce excitotoxic neural damage. Rats received a pre-operative injection of buprenorphine (0.5 mg/kg, 0.2 mg/ml, i.p.) approximately 10 min prior to induction of anesthesia. During surgery, all rats were administered glycopyrrulate (0.2 mg/ml, 0.5 mg/kg, s.c.) to help prevent respiratory difficulties and 5 ml Ringer's solution with 5% dextrose (s.c.) for hydration. General anesthesia was induced (5%) and maintained by isoflurane (1–2.5%) mixed with oxygen (800 ml/min). Rats were placed into the stereotaxic apparatus (Stoelting Instruments, Wood Dale, IL) and the scalp was locally anesthetized with Marcaine® (7.5 mg/ml, 0.5 ml, s.c.). The skull was exposed following a midline incision and adjustments were made to ensure bregma, lambda, and sites ±0.2 mm lateral to the midline were level.

Following lesion procedures for the HC or PER (details below), skull fragments were replaced and anchored in position over the exposed cortex with bone wax. Incision sites were sutured and dressed with Neosporin®. Rats were returned to their home cages and monitored until they awoke from anesthesia. One day following surgery, rats were given an analgesic (Flunixin, 50 mg/ml, 2.5 mg/kg, s.c.) and Neosporin® was applied to the incision site.