

# Perirhinal and postrhinal, but not lateral entorhinal, cortices are essential for acquisition of trace eyeblink conditioning

Eugénie E. Suter,<sup>1</sup> Craig Weiss, and John F. Disterhoft

*Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611, USA*

The acquisition of temporal associative tasks such as trace eyeblink conditioning is hippocampus-dependent, while consolidated performance is not. The parahippocampal region mediates much of the input and output of the hippocampus, and perirhinal (PER) and entorhinal (EC) cortices support persistent spiking, a possible mediator of temporal bridging between stimuli. Here we show that lesions of the perirhinal or postrhinal cortex severely impair the acquisition of trace eyeblink conditioning, while lateral EC lesions do not. Our findings suggest that direct projections from the PER to the hippocampus are functionally important in trace acquisition, and support a role for PER persistent spiking in time-bridging associations.

The behavioral paradigm of trace eyeblink conditioning (tEBC) is hippocampal-dependent in animals (Solomon et al. 1983; Moyer et al. 1990; Kim et al. 1995; Weiss et al. 1999a) and human data implicate awareness in tEBC acquisition (Clark and Squire 1998; Knuttnen et al. 2001), suggesting tEBC as a model for human declarative memory (Weiss and Disterhoft 2011). While tEBC acquisition is severely impaired with hippocampal lesions (Weiss et al. 1999a), consolidated retention is independent of the hippocampus (Kim et al. 1995). The Standard Consolidation Theory holds that hippocampal memories are transferred to extrahippocampal sites for long-term storage (Squire and Zola-Morgan 1991); other theories of consolidation also propose a greater involvement of extra-hippocampal sites in long-term or oft-revisited memories (Nadel and Moscovitch 1997; Winocur et al. 2010).

The rat parahippocampal region (PH), a homolog of the primate and human medial temporal lobe, comprises entorhinal (EC), perirhinal (PER), and postrhinal (POR) cortices and mediates much of the cortical input and output of the hippocampus (Fig. 1A; Scharfman et al. 2000; Furtak et al. 2007). The lateral EC (latEC), but not the medial EC (mEC), is required for the retention of tEBC (Morrissey et al. 2012), while the acquisition of tEBC depends on the mEC (Ryou et al. 2001), suggesting differential roles of PH cortices on this task across learning. Here, we tested the hypothesis that PER, POR, and latEC regions are critically important for the acquisition of tEBC.

The role of the hippocampus in tEBC may involve binding together the conditioned (CS) and unconditioned (US) stimulus across the “trace” period, the temporal gap between stimuli, since delay paradigms, in which CS and US are temporally contiguous, are not forebrain-dependent (Christian and Thompson 2003; Woodruff-Pak and Disterhoft 2008). Early human and animal studies of hippocampal lesions included damage to the PH (Mishkin 1982; Corkin et al. 1997) and later work showed that deficits in primates attributed to the hippocampus were in part due to PH destruction (Zola-Morgan et al. 1989). As input and output regions of the hippocampus, PH cortices have come under increased scrutiny and recent work has established time- and task-related requirements for PH subregions.

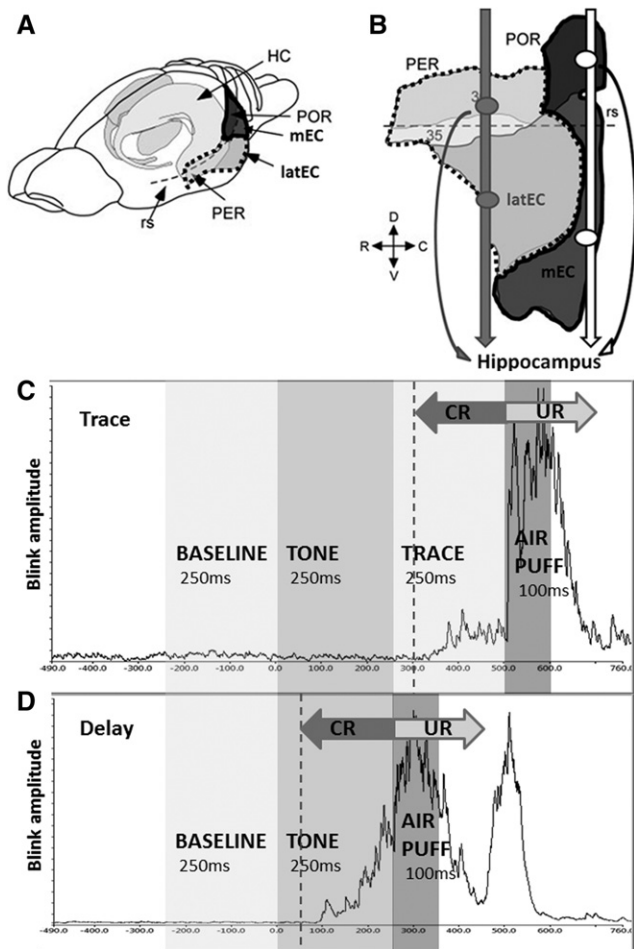
The PER and POR are thought to subservise different pathways into and out of the hippocampus, with the POR and mEC continuing the “where” pathway from higher-order visual and other orienting stimuli, while the PER and latEC process “what” stream information (Eichenbaum et al. 2012). The PER receives multimodal sensory inputs and projects into the hippocampus mainly via the latEC, while the POR receives input mainly from visuospatial centers and projects to the mEC (Furtak et al. 2007). The hippocampal input in the CA1 and subiculum is segregated based on its origin in the PER/latEC or POR/mEC pathways (Naber et al. 1997), and the hippocampal output is similarly organized (Kloosterman et al. 2003b). Of note, in addition to heavy reciprocal projections with the EC, the main source of input to the hippocampus, both the PER and the POR also project directly to the hippocampus (Naber et al. 1999, 2001; Furtak et al. 2007). The functional importance of these (anatomically minor) pathways (Furtak et al. 2007), however, is not established.

The perirhinal and lateral entorhinal cortices both support persistent spiking *in vitro* (Egorov et al. 2002; Tahvildari et al. 2007; Navaroli et al. 2012), suggesting that these areas may support trace-bridging mechanisms independent of hippocampal function. Both the PER and latEC are essential for the acquisition of time-bridging trace fear (Kholodar-Smith et al. 2008; Bang and Brown 2009a; Esclassan et al. 2009). Receiving inputs at the PER from multiple higher-order sensory areas (Furtak et al. 2007), the PER and latEC are excellent candidates for a site that maintains recent inputs for association in the hippocampus proper after a temporal delay. In addition, the PER is essential in fear acquisition to discontinuous tones, which may be a function of auditory “object recognition” or of temporal tracking similar to that in trace tasks (Bang and Brown 2009b). A function for the PER in associative conditioning is supported by *in vitro* work, where the PER responds with universal depression to unpaired, but potentiates to paired cortical stimuli (Unal et al. 2012).

The temporal gradient of the hippocampus dependence in forebrain-dependent tasks (Kim et al. 1995) raises the question of whether the role of PH areas in acquisition and consolidation resembles that of the hippocampus, or parallels the post-consolidation recruitment of cortical areas (Squire and Zola-Morgan 1991; Nadel and Moscovitch 1997; Winocur et al. 2010). Ryou et al. (2001) showed impaired tEBC acquisition and decreased hippocampal task-related activity following entorhinal lesions centered on the mEC. In rats, retention of tEBC is dependent on

<sup>1</sup>Corresponding author  
E-mail [suter@northwestern.edu](mailto:suter@northwestern.edu)

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**Figure 1.** Parahippocampal cortices and eyeblink conditioning paradigm. (A) Anterolateral view of the rat brain showing subregions of the parahippocampal gyrus (adapted from Furtak et al. 2007 with permission from John Wiley and Sons © 2007). (B) Parahippocampal area unfurled with major projections indicated by arrows (adapted from Furtak et al. 2007 with permission from John Wiley and Sons © 2007). (C,D) EBC trial sequence with an example of a well-learned eyeblink conditioned response (CR); (C) trace = 250 msec, (D) delay (trace = 0 msec). Dotted line (200 msec prior to airpuff) indicates the onset of the CR period for data analysis. (HC) hippocampus, (rs) rhinal sulcus.

latEC function, but not on the mEC (Morrissey et al. 2012). We used selective electrolytic lesions to test the individual contributions of the PER, POR, and latEC to the acquisition of time-bridging trace as well as to delay eyeblink conditioning.

Rats were trained on trace and delay EBC after at least a 5-d recovery from bilateral electrolytic or sham lesion surgery at the PER or latEC or POR. Male Fischer 344xBrown Norway rats of at least 3 mo in age received bilateral lesions (200  $\mu$ A  $\times$  20 sec or sham: no current  $\times$  20 sec) under isoflurane anesthesia, followed by attachment of a tethering apparatus to the skull, with two electromyogram leads implanted in the orbicularis oculi muscle as described previously (Weiss et al. 1999b), to allow recording in the freely moving rat. Controls included shams as well as rats with tether-only surgery, as no differences were seen in behavior among these groups. The tether-only controls ensured an adequate statistical power to detect a difference between groups on the delay paradigm.

The tasks consisted of eyeblink conditioning in a light- and sound-attenuating chamber, using a tone CS and airpuff US (Fig.

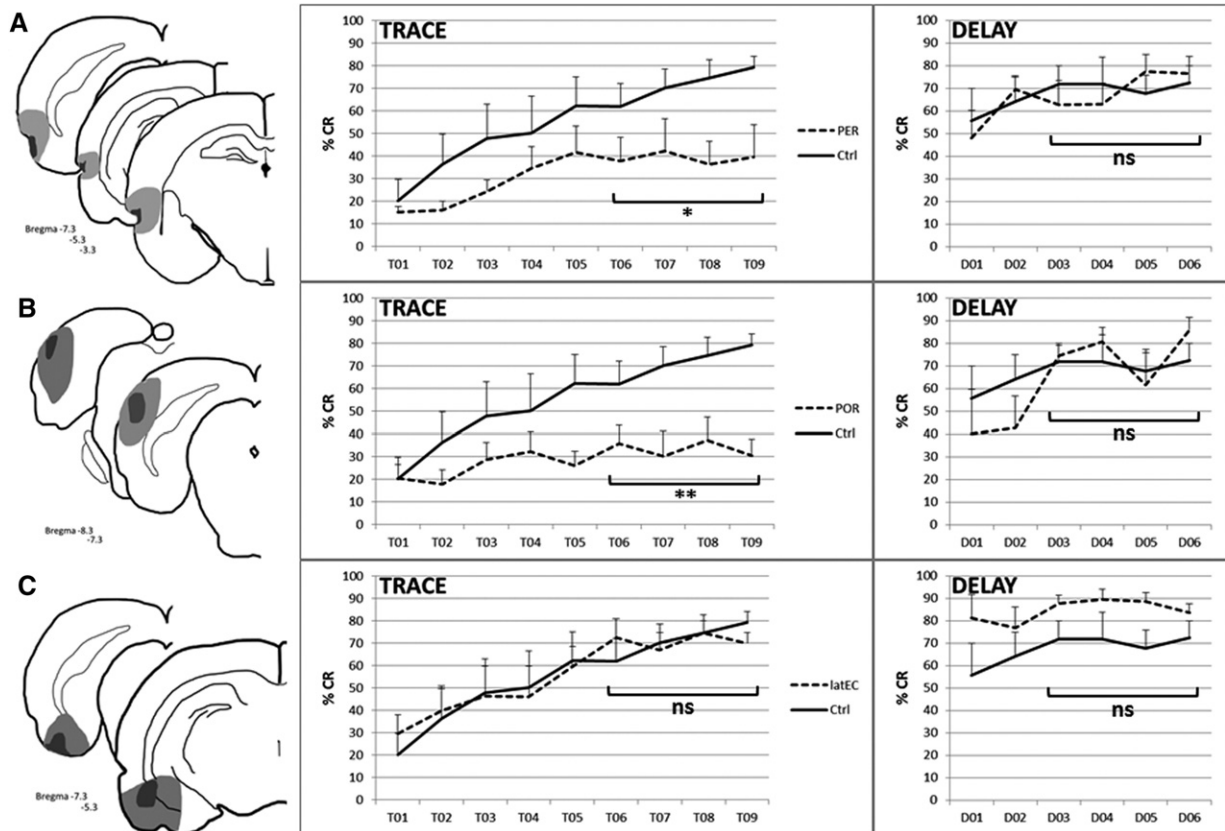
1C,D). One habituation session was given, followed by training twice daily with 30 trials per session. The experimenter was blind to the lesion status. Eyeblink responses were evaluated as follows: a conditioned response (CR) was defined as an increase in EMG activity for at least 15 msec within the 200 msec preceding US onset, with an amplitude at least four standard deviations above the mean of the baseline (250 msec preceding CS onset). Trials with excessive activity during the baseline were excluded by removing any trial whose mean baseline was more than two standard deviations above the session mean. Percentages of CRs for the final four sessions (after animals had reached a behavioral plateau) were analyzed with repeated measures ANOVA and Fisher's PLSD post-hoc test in StatView. Rats received nine or ten sessions (5 d) of trace EBC, followed by six sessions (3 d) of delay EBC. Of the POR lesioned rats, three did not complete delay training due to technical difficulties. Following perfusion with 10% formalin, brains were cryoprotected in 30% sucrose, sliced, and stained for histological classification with Prussian Blue and Cresyl Violet.

Lesions were verified histologically for the inclusion of rats in the PER, POR, latEC, or sham lesion groups (Fig. 2, left column). Behavior was analyzed by comparing percent CR (mean  $\pm$  SEM) for each training session. Repeated measures ANOVA of the final four sessions of conditioning (trace, 6–9; delay, 3–6), showed a significant impairment of a lesion group on trace conditioning ( $F_{(3,18)} = 5.10$ ,  $P < 0.01$ ; Fig. 2, center column), but not on delay conditioning ( $F_{(3,15)} = 1.28$ ,  $P > 0.05$ ; Fig. 2, right column). All groups acquired delay EBC to control levels. Fisher's PLSD showed a significant impairment of both the PER and the POR groups on trace EBC as compared to controls (PER:  $P < 0.05$ , POR:  $P < 0.01$ ; Fig. 2A,B). No statistical difference was seen between the PER and POR groups. The group with lesions of the latEC acquired trace EBC to control levels, with no statistical difference between groups ( $P > 0.05$ ; Fig. 2C).

We found that destruction of the PER or of the POR selectively prevents the acquisition of trace EBC, a forebrain- and hippocampus-dependent task, with no effect on delay EBC. Although the latEC carries PER impulses to the hippocampus, bilateral destruction of the latEC did not impair tEBC. Ryou et al. (2001) showed impaired tEBC acquisition following entorhinal lesions centered on the mEC. While the largest lesions in that study extended into the latEC, the smallest lesions were selective for the mEC, suggesting the mEC damage was responsible for the observed deficit found by Ryou et al. (2001). This conclusion is confirmed by our current finding that latEC-only lesions do not duplicate the deficit found by Ryou et al. (2001) with (medial) EC lesions. These findings are summarized in Figure 3: in acquisition (panel A), the latEC is not essential, whereas the PER, POR, mEC, and hippocampus are required; while in retention (panel B), the hippocampus and mEC are not essential, whereas the latEC is required. The PER and POR have not been tested post-acquisition.

The current investigation shows no difference between PER and POR involvement in trace EBC. Despite a clear separation of connectivity (Furtak et al. 2007) and function on a number of tasks that rely on spatial (POR) or temporal (PER) processing (Norman and Eacott 2005) or visual complexity (PER) (Murray et al. 2007), the POR and PER share strong anatomical interconnectivity (Furtak et al. 2007), and both the POR and PER are required for contextual fear acquisition (Bucci et al. 2000). This suggests that in non-spatial tasks such as tEBC, both the POR and PER may subserve task acquisition.

It has been suggested that time may be tracked in a manner analogous to space within the PH–hippocampus system (Martina et al. 2001; Gorchetnikov and Grossberg 2007). Persistent spiking behavior and requirement in time-bridging tasks suggest a role



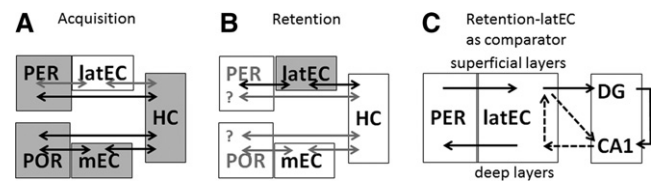
**Figure 2.** Histology (left column) and behavior are shown for each lesion group. (A) PER (N = 6), (B) POR (N = 6, delay N = 3), (C) latEC (N = 4). Controls (N = 6). Light gray shading indicates the maximal and dark gray the minimal extent of the lesions. All the lesions were bilateral. Rats underwent training on trace EBC, followed by delay EBC. Data represent mean %CR ± SEM for each training session for trace (center column) and delay (right column) EBC. Results of repeated measures ANOVA comparing the lesion groups across the last four training sessions are indicated: (\*\*) P < 0.01, (\*) P < 0.05, ns > 0.05 by Fisher's PLSD.

for PER–latEC in temporal navigation, but POR–mEC also shows potential as a timing circuit, due to the periodicity and oscillations demonstrated in spatial navigation (Hasselmo and Brandon 2008). We had hypothesized that a difference in tEBC lesion effects could elucidate which PH pathway functions in bridging time, but we find that tEBC relies on both PER and POR functions.

Interestingly, latEC lesions show a different pattern: we see no effect on trace EBC, even though trace fear acquisition is impaired by M1 antagonist pirenzepine at the latEC (Esclassan et al. 2009). Key differences to the current study include both the fear element of the task and the type of lesion, and render the data easily reconcilable. The latEC is heavily interconnected with lateral amygdala (Furtak et al. 2007), suggesting that fear circuitry is likely to affect latEC function. Additionally, the use of an M1 antagonist suggests a *disruption* of function, which can be more deleterious to hippocampal learning than *destructive* lesions in the hippocampal circuit (Solomon et al. 1983).

Much of the literature emphasizes PER projections to the hippocampus via the latEC. There has been extensive discussion as to signal propagation via direct PER-to-hippocampus projections (Canning and Leung 1997; Liu and Bilkey 1997). Careful follow-up studies, using current sink analysis, conclude that the PER and POR project directly to CA1/subiculum, but do not join the perforant path targeting dentate gyrus (Naber et al. 1999, 2001). In addition, minimal propagation of neocortical stimulation from the PER to the latEC in vitro supports an EC-independent associative role of

the PER (Pelletier et al. 2004). Here we show that, while PER function is essential to tEBC acquisition, the destruction of the latEC has no apparent effect on this task. In the absence of the latEC, essential PER input must reach the hippocampus via a different path, demonstrating that the anatomically minor PER-to-hippocampus direct projection (Furtak et al. 2007) is functionally important, as indicated in Figure 3, A, by the black arrow connecting the PER and the hippocampus. Because we used electrolytic lesions, damage to fibers of passage must be considered in



**Figure 3.** The direct projection from the PER to the hippocampus (HC) is functionally important for tEBC acquisition. (A) In acquisition, the latEC is not essential (white) whereas the PER, POR, mEC, and HC are required. (B) For retention, the HC and mEC (white) are not essential, whereas the latEC is required; the PER and POR have not been tested post-acquisition. (C) Suggested function of the latEC in tEBC retention: at input in the (superficial) layers of the latEC, incoming information from the PER converges with hippocampal output from the deep latEC, forming a loop that may be used to compare current stimulus associations (HC) with established associative memories (latEC). (DG) dentate gyrus.



interpreting the results. If the deleterious effects of PER lesions were due to deafferentation of the latEC by damaging the fibers of passage, then latEC lesion results should mimic PER lesions, which is not the case.

In contradistinction to our acquisition results, previous studies showed that post-training inactivation of the latEC (using the GABA agonist muscimol) impaired the retention of tEBC (Morrissey et al. 2012). Of note, due to differences in the training schedules, the end of “acquisition” in the current study (day 5: latEC-induced deficit) precedes the onset of “retention” testing in Morrissey et al. (2012) (day 13: no deficit with a latEC lesion) by a week, leaving ample intervening time for memory consolidation processes that apparently account for the observed change in function between these studies. This temporal involvement pattern of the latEC is inverted as compared to that of the hippocampus, which is required for the acquisition, but not for the consolidated retention of tEBC (Kim et al. 1995). The double dissociation between the hippocampus and latEC lesions in the acquisition and retention of trace conditioning suggests that the latEC performs a consolidation-dependent associative role for previously learned time-bridging tasks. Long-term tEBC recall also shows a decreased functional connectivity between the hippocampus and EC, and increased functional connectivity between the EC and the putative storage node prefrontal cortex (Takehara-Nishiuchi et al. 2012), lending indirect evidence for a role for the EC in maintaining post-hippocampal associations. The PER and POR have not been examined in tEBC retention, but related tasks show PER or POR lesion-induced impairment on contextual fear conditioning acquisition with no decrease in impairment for as long as 100-d post-acquisition (Burwell et al. 2004).

The essential nature of the PER in tEBC suggests that persistent spiking mechanisms in this area (Navaroli et al. 2012), but not in the latEC, subserve trace-bridging during acquisition; the post-acquisition involvement of the latEC may reflect later recruitment of time-bridging machinery (Egorov et al. 2002) at a time when the hippocampus is no longer essential.

The latEC furthermore shows a striking pattern of segregation between input and output pathways, with input to the hippocampus arising from the superficial layers of the latEC, but output from the hippocampus projecting to the deep layers of the latEC. The additional flow of hippocampal output from the deep to the superficial EC suggests that the latEC may function as a comparator for hippocampal input and output (Kloosterman et al. 2003a). As such, the latEC's differential role in trace EBC acquisition vs. retention may reflect an increased importance either as a consolidated storage node for hippocampal associative memories, or as a moderator of acquired task performance. This circuit is illustrated in Figure 3, C, by dotted arrows.

In this study we show that tEBC acquisition depends on an intact PER and an intact POR, but not on the latEC, the main mediator of the PER input to the hippocampus. No difference was seen between the effects of the PER and POR lesions, despite functional segregation on other tasks. This suggests that direct projections from the PER to the hippocampal CA1/subiculum are functionally important in trace acquisition, and support a role for PER persistent spiking in time-bridging associations. In addition, our data suggest a role for the latEC specifically in consolidated, but not in the formation of, time-bridging associations. The latEC's increased role after acquisition, in combination with projections that combine hippocampal feedback with hippocampal input from the PER in the latEC's superficial layers, support the concept of the latEC as a monitor for associations formed by the hippocampus. In sum, these findings suggest that further investigation of the communication among the PER, latEC, and hippocampus during different stages of trace EBC is warranted.

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