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Authors

Ekstrom, Arne
Viskontas, Indre
Kahana, Michael
et al.

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Review

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5 Memory
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7 ABBREVIATED TITLE: Neurons and Ensemble Activity in Human Memory
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10 AUTHORS: Arne Ekstrom^{1,2}, Indre Viskontas³, Michael Kahana⁴, Josh Jacobs⁵, Kristen
11
12 Upchurch², Susan Bookheimer¹, and Itzhak Fried²
13
14
15

16 1. Center for Cognitive Neurosciences, Semel Institute, Dept. of Psychiatry and Biobehavioral
17
18 Sciences, UCLA School of Medicine
19

20 2. Department of Neurosurgery and Biobehavioral Sciences, University of California, Los
21
22 Angeles, CA.
23

24 3. Department of Psychology, University of California, Los Angeles, CA.
25

26 4. Department of Psychology, University of Pennsylvania, Philadelphia, PA.
27

28 5. Department of Neuroscience, University of Pennsylvania, Philadelphia, PA.
29

30
31 CORRESPONDING AUTHOR:
32

33
34 Dr. Arne Ekstrom
35 UCLA Brainmapping Center
36 660 Charles Young Dr.
37 Los Angeles, CA 90095
38 email: ekstrom@ucla.edu
39

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Abstract

Recording the activity of neurons is a mainstay of animal memory research, while human recordings are generally limited to the activity of large ensembles of cells. The relationship between ensemble activity and neural firing rate during declarative memory processes, however, remains unclear. We recorded neurons and local field potentials (LFPs) simultaneously from the same sites in the human hippocampus and entorhinal cortex in patients with implanted intracranial electrodes during a virtual taxi-driver task that also included a memory retrieval component. Neurons increased their firing rate in response to specific passengers or landmarks both during navigation and retrieval. Although we did not find item-specificity in the broadband LFP, both theta and gamma band LFPs increased power to specific items on a small but significant percent of channels. These responses, however, did not correlate with item-specific neural responses. To contrast item-specific responses with processes-specific responses during memory, we compared neural and LFP responses during encoding (navigation) and retrieval (associative and item-specific recognition). A subset of neurons also altered firing rates non-specifically while subjects viewed items during encoding. Interestingly, LFPs in the hippocampus and ERC increased in power non-specifically while subjects viewed items during retrieval, more often during associative than item-recognition. Furthermore, we found no correlation between neural firing rate and broadband, theta-band, and gamma-band LFPs during process-specific responses. Our findings suggest that neuronal firing and ensemble activity can be dissociated during encoding, item-maintenance, and retrieval in the human hippocampal area, likely relating to functional properties unique to this region.

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8 Differentiating the role of single neurons from ensemble activity is a particularly important issue
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10 in memory studies. Neurons demonstrate stimulus selectivity in the hippocampal area (O'Keefe
11 and Dostrovsky, 1971), a region critical for human memory (Scoville and Milner, 1957; Vargha-
12 Khadem et al., 1997). Furthermore, studies have also shown that neurons in the hippocampus
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14 code stimuli "sparsely," such that relatively few neurons are active at any given time during
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16 behavior (Marr, 1971; McNaughton and Morris, 1987; Waydo et al., 2006). In contrast, local
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18 field potentials (LFPs), a measure of summed neural signal, respond during more gross aspects of
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20 memory performance and exhibit less stimulus specificity in these same brain regions (Fernandez
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22 et al., 1999; Buzsaki, 2005). Although simultaneous single neuron and LFP recordings are
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24 possible in the rodent and primate via invasive electrodes, neurophysiological studies of human
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26 memory generally rely on ensemble recordings using functional magnetic resonance imaging
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28 (fMRI) or EEG at the scalp. The fMRI BOLD signal, however, may have a variable relationship
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30 with neural firing rate and LFPs (Logothetis et al., 2001; Huettel et al., 2004), correlating more
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32 strongly with LFPs than neural firing rate under some conditions (Logothetis et al., 2001;
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34 Logothetis, 2003). To investigate the relationship between ensemble and neuron activity during
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36 memory processes, we chose a paradigm studied in both humans and rodents with fMRI, LFPs,
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38 and single neurons: spatial navigation and the representation of spatial landmarks (Aguirre et al.,
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40 1996; Burgess et al., 2001; Eichenbaum, 2004; Janzen and van Turennout, 2004; Buzsaki, 2005;
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42 McNaughton et al., 2006).

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49 The parahippocampal cortex shows greater activation in human fMRI studies when
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51 subjects view spatial scenes compared to faces and objects (Epstein and Kanwisher, 1998;
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53 Epstein et al., 2003). To investigate the navigational relevance of parahippocampal activation,
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55 Janzen and van Turrenout (2004) had subjects explore a virtual environment in which they
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57 experienced landmarks (located at decision points) and non-landmarks. The parahippocampal
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3 cortex showed greater activation when subjects viewed landmarks during a recognition task
4 compared to non-landmarks, even though both types of objects were experienced during
5 navigation (Janzen and van Turenout, 2004). We have previously shown that neurons in the
6 entorhinal cortex (ERC) and posterior parahippocampal gyrus increase firing when patients
7 implanted with intracranial depth electrodes viewed specific landmarks during spatial navigation
8 (Ekstrom et al., 2003). We could not determine, however, whether the same neurons that
9 responded to landmarks during navigation continued to fire selectively for landmarks during
10 retrieval. Further, because we did not simultaneously record ensemble activity with neurons, we
11 could not compare the activity of groups of neurons in the parahippocampal region (ERC and
12 parahippocampal gyrus) with that of individual neurons. A second objective of our study,
13 therefore, was to analyze LFP and neuron responses during viewing of spatial landmarks and
14 following navigation during retrieval.
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29 A final objective of our study was to simultaneously compare neural firing rate and LFPs
30 to determine the extent to which they perform overlapping or independent computations in
31 memory. Neural firing rate represents the activity of action potentials from individual neurons
32 and small groups of neurons (Harris et al., 2000). LFPs, in contrast, largely represent the
33 summation of synaptic activity – primarily excitatory post-synaptic potentials (EPSPs) – due to
34 sinks and sources induced by movements of these currents (Nicholson, 1973; Mitzdorf, 1985).
35 The LFP is primarily composed of low frequency activity (<100Hz) because the extracellular
36 media acts as a low-pass filter, largely dampening the activity of action potentials, which are
37 typically above 100Hz (Bedard et al., 2004). The degree to which neural firing rate and LFPs
38 overlap in a brain region therefore may relate to the degree to which synaptic input and action
39 potentials are coordinated. Estimates of the relation between cellular firing rate and LFPs suggest
40 some regional variability, to be expected based on cellular morphology, arrangement of inputs,
41 and anatomical layout of neurons that differ between regions (Mitzdorf, 1985). For example,
42 gamma band activity and neural firing rate appear to be strongly coupled in mouse visual cortex
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3 (Nase et al., 2003) and human auditory cortex (Mukamel et al., 2005) during behavior, although
4 the correlation between LFPs and neural firing rate in primate infero-temporal cortex is
5 significantly lower (Kreiman et al., 2006). While previous studies demonstrated phase locking
6 between single neurons and gamma band activity in the rodent hippocampus (Bragin et al., 1995),
7 it is not known whether behaviorally-induced increases in neural firing rate are accompanied by
8 increases in LFP power – particularly during memory encoding and retrieval. By recording under
9 two different behavioral conditions: self-paced navigation and timed stimulus recognition, we
10 explored different conditions that could dissociate LFPs and neural firing rate.
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23 MATERIALS AND METHODS

24 Behavioral Methods

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32 Subjects first navigated a virtual-reality environment (VR) as if they were a taxi-driver by
33 picking up passengers and delivering them to specific stores using our previously reported VR
34 paradigm “yellowcab” (Ekstrom et al., 2003; Ekstrom et al., 2005; see Figure 1a). Subjects
35 navigated a 3x3 block city composed of 3 stores and 6 non-task relevant buildings. Subjects
36 searched for passengers and delivered passengers to stores they were explicitly instructed to find
37 within the city. Passengers were placed randomly throughout the city after each successful
38 delivery. When a subject picked up a passenger, the passenger’s picture appeared on the screen
39 for 2 seconds with instructions of which store to find. When subjects dropped off a passenger,
40 the passenger’s picture appeared again for 2 seconds. Subjects delivered 9 different passengers to
41 the three different stores. The methods described here for navigation in VR are similar to those
42 previously described in Ekstrom et al. (Ekstrom et al., 2003) except a) unique passenger identities
43 were employed so that responses to specific passengers could be compared with responses to
44 specific stores b) subjects were explicitly instructed to remember which stores and passengers
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3 they met, what passengers were delivered to which stores, and the order that passengers appeared
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5 in the game.
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8 Subjects then performed two different retrieval tasks: in the item recognition condition
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10 (Figure 1b), subjects were presented with previously-seen and novel (lure) pictures of passengers
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12 and stores and indicated with a keypress whether or not a stimulus was seen during navigation.
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14 During the associative recognition condition (Figure 1c) subjects viewed pairs of stimuli; either a)
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16 a passenger and a store or b) two passengers side-by-side. Subjects indicated a) whether they
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18 delivered the passenger to that store or b) which of the passengers was encountered first during
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20 navigation. The associative recognition conditions provided additional experimental conditions
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22 under which subjects viewed the same stimuli. Because the primary focus of this paper was on
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24 item vs. encoding/retrieval processes, we do not discuss or present the details of these two
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26 conditions further, referring to the three retrieval conditions as the memory condition. Some of
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28 the conditions employed in the navigation and memory conditions are similar to those used
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30 previously in an fMRI study by Burgess et al (Burgess et al., 2001).
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34 During the memory condition, a total of 19 items (13 passengers and 6 stores) were
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36 shown to subjects. Three novel stores and four novel passengers were presented during the
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38 recognition block so that not all items presented during the recognition condition would be
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40 familiar. Each stimulus or pair of stimuli was presented three times during each condition; each
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42 stimulus appeared on the screen for 3 seconds followed by a jittered inter-stimulus interval period
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44 of 1 sec +/- 500 msec. When patients performed a second session, they were tested in a novel
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46 spatial environment with a novel arrangement of stores and passengers. All patients who
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48 participated provided informed consent. All studies conformed with the guidelines of the
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50 Medical Institutional Review Board at UCLA.
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56 Electrophysiological Methods
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3 Patients were implanted with depth electrodes for seizure monitoring and subsequent
4 resection planning; all surgeries were performed by I.F. At the tip of each depth electrode a set of
5 eight 40- μ m platinum-iridium microwires provided possible cellular and LFP signals (with a
6 ninth wire distal to the recording site serving as reference). Anatomical locations of electrodes
7 were verified by fusing CT scans taken while electrodes were implanted with high resolution
8 MRI scans taken immediately before implantation (Figure 1d). Signals from each microwire
9 were amplified (gain = 10,000), digitally sampled at 27.8 kHz, and bandpass filtered between 1
10 Hz and 6 kHz (Neuralynx, Tucson, AZ). Action potentials were isolated using *waveclus*.
11
12 Neural events were first thresholded using the raw filtered data and then clustered based on
13 separation of wavelet coefficients (Quiroga et al., 2004; Quiroga et al., 2005). All clusters were
14 re-sorted manually to ensure maximum separation of different waveforms; clusters that showed
15 contamination from 60Hz activity were discarded. LFP signals were resampled at 256 Hz and
16 bandpass filtered between 1 and 100 Hz. We used the 1-100 Hz band for our assessment of
17 selectivity of hippocampal area LFPs because computational estimates suggest this frequency
18 band contains primarily synaptic activity and is largely free of action potentials (Mitzdorf, 1985;
19 Bedard et al., 2004). We also investigated responses to the same behavioral variables in the theta
20 (4-8 Hz in human) and gamma (30-100 Hz) ranges. A 60Hz notch filter (59.9 to 60.9 Hz stop
21 filter constructed in Matlab) was applied to remove noise contamination from power lines.
22 Responses that were identical on neighboring channels were not considered in the analysis.
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47 Analysis

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51 We identified significant responses using 19x2 item x experimental context ANOVAs on
52 the mean log transformed neural firing rate and mean log transformed LFP power, where “items”
53 represented specific stimuli (e.g., a specific passenger or store) and “experimental context”
54 represented the behavioral task the subject performed (e.g., encoding or retrieval). We thus
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3 employed similar methods to those used previously by Ekstrom et al. to detect differences in
4 neural firing rate for landmarks during navigation (Ekstrom et al., 2003). We deemed “item”
5 responses those that showed main effects of item and no interaction effect with experimental
6 context because these responses would be constant across the different retrieval conditions. We
7 deemed “experimental context” responses those that showed main effects of task but no main
8 effect of items because we wished to study responses that were specific to navigation or retrieval
9 and not influenced by specific items. All navigation sequences were replayed using software
10 written in Matlab such that the passenger or store the subject was viewing during navigation was
11 reconstructed during the subject’s entire navigational trajectory. To attempt to equate the number
12 of passenger and store viewings during retrieval, the store or passenger on the right side of the
13 screen was considered the item being viewed during associative recognition. When we compared
14 with viewing the objects on the left side of the screen during the associative recognition,
15 however, our results did not change in terms of the total number of neurons or LFPs responding
16 during item or experimental context conditions.
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42 RESULTS

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46 A total of 10 patients with implanted depth electrodes were tested in our paradigm. Three
47 of these patients were unable to complete the task satisfactorily, e.g. did not complete the three
48 retrieval conditions or did not perform above 50% averaged across conditions. Thus, we report
49 data from seven patients and 9 recording sessions total; patients performed above chance during
50 item recognition (85% hit rate: $t(8)=15$, $p < .000001$; degrees of freedom based on 9 recording
51 sessions) and associative recognition (61% hit rate: $t(8)=3.1$, $p < .01$). We recorded and isolated
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3 a total of 119 neurons in the MTL; 36 were in the hippocampus, 57 in ERC, and 26 in the
4 amygdala. We selected LFP channels based on sites from which we recorded neurons; we thus
5 report from 28 hippocampal, 42 ERC, and 17 amygdala LFP recording sites.
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10 11 12 Landmark-responsive neurons in ERC during navigation and retrieval 13 14 15

16 Previous data have shown that human MTL neurons respond to specific stimuli such as
17 pictures of famous people or unfamiliar faces and places (Heit et al., 1988; Cameron et al., 2001;
18 Quiroga et al., 2005). Given that our task required subjects to encode and maintain
19 representations of stimuli across navigation and different retrieval tasks, we first determined
20 whether neurons and LFPs responded in an item-specific manner during different experimental
21 contexts. We did this by first binning neural firing rate and LFP wavelet-transformed power
22 (Kreiman et al., 2006) while subjects viewed an item (passenger or store) during navigation and
23 retrieval during a 300-1500 millisecond time window post-stimulus, based on our previous
24 findings of MTL neural responses during memory tasks (Viskontas et al., 2006). We considered
25 neurons or LFPs to be item-responsive when we observed significant differences to viewing
26 different passengers or stores (“items”) in an ANOVA ($p < .05$; see methods) across navigation
27 and the memory condition (see Methods).
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42 Neurons in the MTL responded with item-specific changes during navigation and also
43 during the memory condition. In representative examples (Figure 2 a,c,e; raw traces in
44 Supplementary Figure 1), neurons showed increased firing rates when subjects viewed passengers
45 and stores during both the navigation and retrieval. Over the population of MTL neurons from
46 which we recorded, 37% (44/119) of neurons showed significant item-related changes in firing
47 rate throughout navigation and the memory condition. We then subjected each item-responsive
48 neuron to a conservative post-hoc test ($p < .05$, corrected) in which we compared the firing rate to
49 a specific item against the firing rate for all other items for that item-responsive neuron. Seventy-
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3 seven percent (34/44) of item-responsive neurons passed this stricter criterion (Figure 3a); we
4 deemed these responses “item-specific.” The majority (33/34) of these neurons increased or
5 decreased firing to only one or two items (for a breakdown of increasing and decreasing item-
6 specific responses, see Table 1). Thus, the majority of our item-responsive neurons during
7 navigation and retrieval were selective, such that a given item-specific neuron fired to few of the
8 stimuli presented. Although item-specific neurons were evenly distributed across the MTL, we
9 found a greater number item-specific neurons changing firing rate to stores in ERC compared to
10 hippocampus and amygdala (Chi square test, $\chi^2(2)=6.2$, $p < .05$, Figure 3b). The clustering of
11 landmark-responsive neurons in the ERC during navigation and retrieval comports well with our
12 previous findings of landmark responsive neurons clustering in the parahippocampal region (ERC
13 and parahippocampal gyrus) during navigation (Ekstrom et al., 2003).
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27 We then performed identical analyses with our simultaneously recorded LFPs to look for
28 changes in LFP power to specific items during navigation and retrieval. In contrast to neurons,
29 broadband LFPs did not show significant selectivity for items (Figure 2 b,d,f; raw traces in
30 Supplementary Figure 1); only 4% (3/87) of channels with LFP signal responded significantly to
31 a particular item, which did not exceed the Type I error rate ($\chi^2(1)=.1$, $p = \text{n.s.}$; Figure 3a and
32 Table 1). Theta and gamma-band LFPs, however, showed item selectivity compared to the
33 broadband LFP (Figure 3a and Table 1). The theta-band LFP modulated power to specific items
34 in 13% (11/87) of channels while gamma-band LFP modulated power to specific items in 17%
35 (15/87) of channels. Both of these responses exceeded the type I error rate (theta: $\chi^2(1)=7.2$, $p <$
36 $.01$; gamma: $\chi^2(1)=28$, $p < .00001$). The responses of theta and gamma band LFPs to stores and
37 passengers are shown in Table 2; we did not observe regional differences for item-specific LFP
38 responses. Item-specific neural responses exceed item-specific theta responses (neurons vs. theta
39 $\chi^2(1)=5.3$, $p < .01$) but not item-specific gamma responses ($\chi^2(1)=3.0$, $p = \text{n.s.}$).
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LFP responses during retrieval

Previous LFP recordings found greater oscillatory power during retrieval compared to encoding while patients with implanted electrodes navigated a virtual environment (Kahana et al., 1999). Because our experiment involved encoding during navigation and retrieval of these items following navigation, we hypothesized that we might also observe changes in LFPs or firing rate for the different experimental contexts that were not specific to items. LFPs that showed a significant effect of experimental context (navigation vs. retrieval but not to items; see methods) were then subjected to additional post-hoc tests ($p < .05$, corrected) in which LFP power during a specific experimental context (navigation, recognition, or associative recognition) was compared with LFP power during the other experimental contexts.

In representative examples, the mean LFP power on MTL channels showed significant experimental context-related changes, increasing in power across frequencies during retrieval compared to navigation (Figure 4 b,d,h). Twenty percent (17/87) of broadband LFP responses showed modulations to experimental context, which significantly exceeded the Type I error rate ($\chi^2(1)=26$, $p < .00001$; Figure 3a). We observed significantly more experimental context-related broadband LFP responses than broadband LFP item responses (20% vs. 4%). Theta and gamma-band LFPs responded in comparable numbers to experimental context (theta: 13%; gamma 12%, Table 3), although the number of electrodes showing theta and gamma-band LFP context responses was not significantly different from the number of electrodes showing theta and gamma-band LFP item responses (Figure 3a, Table 3).

We then determined during which experimental context(s) LFPs responded with a change in power. The majority of broadband, theta, and gamma LFP responses increased during retrieval compared to encoding (Table 3 and Figure 3c); a small number of gamma-band LFPs also responded with greater power during encoding (Table 3). In all frequency bands, however, there were significantly more electrodes active during retrieval compared to encoding (broad-band: 17

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3 vs. 0, [$\chi^2(1)=17$, $p < .0001$]; theta-band, 11 vs. 0, [$\chi^2(1)=11$, $p < .001$]; gamma-band, 8 vs. 2,
4 [$\chi^2(1)=5$, $p < .05$]. Experimental context-related LFP responses were evenly distributed
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6 throughout the hippocampus, ERC, and amygdala (Table 3). The broadband LFP, but not the
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8 theta and gamma LFP, showed greater power during associative recognition compared to item-
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10 recognition (9 LFPs were significantly greater during associative recognition compared to 1 LFP
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12 significantly greater during item-recognition ($\chi^2(1)=6.4$, $p < .01$, Table 3). Also, greater numbers
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14 of electrodes showed increased power during associative recognition in hippocampus and ERC
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16 compared to the amygdala ($\chi^2(1)=9$, $p < .01$).
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22 The broadband LFP therefore showed the least selectivity for items (4%) and the greatest
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24 selectivity for experimental context (20%). Broadband LFP responses showed significantly
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26 greater amplitude during retrieval compared to navigation, and showed the greatest amplitude
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28 during associative recognition compared to item recognition. Broadband LFPs responding
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30 significantly during associative recognition were present to greater degrees in hippocampus and
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32 ERC than amygdala. While both gamma and theta bands showed some selectivity for items (13%
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34 and 17%), gamma and theta bands also responded significantly to experimental context (13% and
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36 12%). Similar to the broadband LFP, we found the greatest number of theta and gamma LFP
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38 responses during retrieval compared to navigation.
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Neural firing rate changes during encoding

We then performed the same experimental context-related analyses we reported for LFPs on neural firing rate (see Methods). We found that 25% (30/119) of neurons responded significantly to experimental context (Figure 3a, Table 1). To compare our experimental context-related LFP amplitude and power changes with our experimental context-related firing rate changes, we compared neural responses with LFP responses on the same channel (e.g., Figure

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3 4b,d,f,h). In contrast to LFP responses, neurons often showed increased firing during navigation
4 compared to retrieval (Figure 4a,c,e,g). Post-hoc comparisons, identical to those previously
5 performed on LFPs, revealed that the majority of these context-related neurons increased their
6 firing rate during navigation compared to retrieval (77% [23/30] vs. 23% [7/30]; $\chi^2(1)=8.5$, $p <$
7 $.01$; Figure 3c). We found a significant dissociation for neurons responding during encoding and
8 LFPs responding during retrieval. This effect was most pronounced for the broadband LFP
9 compared to neural firing rate (neurons, encoding vs. retrieval: 23 vs. 7, broadband LFP, 0 vs. 17,
10 Fischer's exact test, $p < .00001$) but was also significant for theta-band (Fischer's exact test, $p <$
11 $.005$, Table 3) and gamma-band LFPs (Fischer's exact test, $p < .0001$, Table 3). Our results for
12 experimental context-related neurons thus show the opposite trend to context-related LFPs: more
13 experimental context-related neurons were active during encoding than retrieval.

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29 No correlation between neural firing rate and LFPs over population of responses
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34 Despite the dissociations we observed between neurons and LFPs for experimental
35 context, it could still be the case that neural firing rate changes and LFP changes were closely
36 related in time. We also wished to address whether neural firing rate and LFP power changes
37 were coupled for item responses, because neuron, theta-band LFPs, and gamma-band LFPs all
38 showed significant item-responses. If neurons and LFPs were associated, we would expect firing
39 rate and LFP power changes to correlate on the same channels. To address this issue, we
40 computed the correlation between the mean firing rate with the mean broad-band wavelet-
41 transformed LFP power between 300 and 1500 msec post-stimulus using methods identical to
42 Krieman et al 2006. This analysis was done separately for channels showing significant changes
43 in firing rate to items (44/119) and experimental context-selective changes in firing rate (e.g.,
44 during encoding or retrieval, 30/119). The mean correlation across the population of cellular and
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3 LFP channels did not differ from zero for items (Figure 5; $r=-.01 \pm .02$; $t(43)=-.85$; $p = n.s.$) or
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5 experimental context ($r=-.06 \pm .06$, $t(29)=.73$, $p=n.s.$).
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8 Although classic hippocampal LFPs are seen between 1-100 Hz (Halgren and Smith,
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10 1987; McCarthy et al., 1995; Fernandez et al., 1999), correlations between firing rate and LFPs
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12 have typically been reported above the gamma band (Mukamel et al., 2005), e.g., 40-100 Hz. We
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14 thus redid our population correlation analysis for LFP power separately in the theta (4-8 Hz) and
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16 gamma band (40-100 Hz). Correlations between cellular firing rate for item and experimental
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18 context responses and theta band power were not significantly different from zero (Figure 5; item:
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20 $r=-.01 \pm .02$, $t(43)=-.90$, $p = n.s.$; context: $r=.05 \pm .03$, $t(29)=1.8$, $p = n.s.$), and neither were
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22 correlations between cellular firing rate for item and experimental context responses and gamma
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24 band power (Figure 5; item: $r=-.02 \pm .05$, $t(43)=.3$, $p = n.s.$; context: $t(29)=-.8$, $p = n.s.$). To ensure
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26 there were no regional, frequency band, or behaviorally induced differences in these correlation,
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28 we conducted a 3 x 3 x 2 region (amygdala vs. hippocampus vs. ERC) x band (broadband vs.
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30 theta vs. gamma) x behavioral variable (item vs. experimental context) ANOVA. There were no
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32 main effects of any variable and no significant interactions (see Tables 2 and 3 for correlations
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34 broken down by region).
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51 DISCUSSION

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55 Our task, which required encoding of items and associations between items during
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57 navigation as well as recognition of those items and their associations, provided an opportunity to
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3 contrast the neural basis of item-related and experimental context-related representations. Our
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5 paradigm also permitted us to contrast representations formed during navigation with
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7 representations accessed during retrieval. It is thus notable that a high percent (29%) of neurons
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9 showed changes in firing rate for viewing specific items during encoding which persisted through
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11 retrieval, despite differences in experimental context between the different tasks. These
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13 responses were typically specific to a few items, suggesting that item-specific representations are
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15 formed in the hippocampal area. While selective, item-specific neural responses have been
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17 reported previously in the MTL during viewing of famous people and other objects (Heit et al.,
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19 1988; Kreiman et al., 2000; Quiroga et al., 2005), we show here that these representations are
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21 invoked during both item-learning and during learning of episodes involving formation of item-
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23 context associations.
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27 We also found greater numbers of neurons responding during viewing of stores in the
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29 ERC compared to the hippocampus and amygdala. We previously described neurons present in
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31 the ERC and parahippocampal gyrus (parahippocampal region) that increased firing during
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33 viewing of landmarks during navigation (Ekstrom et al., 2003). Because we did not find
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35 significant numbers of store-responsive neurons firing during a control task in which subjects
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37 viewed stores and read their names out loud prior to navigation (Ekstrom et al., 2003), our results
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39 suggest that ERC neurons were specifically involved in encoding spatial landmarks. Our current
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41 results extend our previous findings to show that neurons in the ERC increase firing rate to
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43 specific stores and maintain their firing during both simple recognition of these objects and
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45 during retrieval of these objects along with the context in which they were encoded. Thus, our
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47 results show that the same ERC neurons that encode spatial landmarks during navigation
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49 maintain their altered firing rates when these stores are viewed during retrieval.
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53 In contrast to the significant changes in neural firing rate for items encountered during
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55 navigation and retrieval, we did not find significant numbers of item-specific broadband LFPs
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57 changing during navigation and retrieval. These data suggest that during navigation and retrieval,
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3 the broadband LFP does not convey information about specific stimuli. We did, however,
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5 observe item-specific responses in theta and gamma-band. Previous work demonstrated
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7 increased theta and gamma amplitude during encoding of items that are subsequently recalled
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9 (Sederberg et al., 2003; Mormann et al., 2005). Because we did not find a significant correlation
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11 between neural item responses and theta-band and gamma-band LFP responses, our results
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13 suggest that theta-band and gamma-band LFPs do not directly relate to neural firing rate changes.
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16 We did observe significant LFP power changes to experimental contexts in all frequency
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18 bands. A significantly greater number of broadband, theta-band, and gamma-band LFPs were
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20 active while subjects viewed passengers and stores during retrieval compared to encoding. In
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22 contrast, we found significantly greater numbers of neurons active while subjects viewed stores
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24 and passengers during encoding compared to retrieval. It is notable that we again dissociated
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26 neurons and LFPs based on encoding vs. retrieval. It is possible that the self-timed nature of
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28 navigation led to a greater dissociation of LFPs during encoding (while navigating) compared to
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30 retrieval. Previous scalp EEG recordings, however, during a timed, continuous recognition task
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32 demonstrate greater ERP amplitude during retrieval compared to encoding (Finnigan et al., 2002).
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34 Also, Kahana et al, (1999) observed greater theta oscillatory power during retrieval of a spatial
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36 locations while recalling learned navigational routes than during encoding of these routes
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38 (Kahana et al., 1999). Thus, given that previous studies have also reported greater LFP power
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40 during retrieval compared to encoding we believe that our finding of greater broadband, theta,
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42 and gamma-band LFP power during retrieval compared to encoding is therefore not specific to
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44 the self-paced nature of navigation.
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49 While we found greater numbers of electrodes active during retrieval compared to
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51 encoding in all frequency bands, we also observed greater numbers of broadband LFPs
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53 responding during associative compared to item recognition. This finding further argues that the
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55 greater broadband LFP power we observed during retrieval when compared to encoding relates to
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57 retrieval-specific processes. Because we found greater numbers of electrodes responding during
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associative compared to item recognition in the hippocampus and ERC compared to the amygdala, our data further argue that retrieval-specific increases in LFPs during associative retrieval may be unique to memory processing in these two regions. Given that we observed this effect in the LFP, a reflection of synaptic input (Mitzdorf, 1985; Logothetis, 2003), but not in neural firing rate, our data further suggest that retrieving associations requiring both item and source information leads to greater input of synaptic activity in the hippocampus and ERC compared to item recognition.

A final question we wished to address was the simultaneous relation between neurons and LFPs during memory processing. Previous recordings from human auditory cortex suggest a high correlation between neural firing rate and gamma-band LFPs during listening to complex sounds (Mukamel et al., 2005). In the Mukamel et al. (2005) experiment, however, large numbers of neurons were simultaneously active during the task, suggesting coordinated input and output processes (Logothetis, 2003). In our experiment, few neurons responded at any given time to items due to their selectivity for certain items and not others. It is thus not surprising that we observed little or no population correlation between neurons and LFPs for items in any frequency band. Although we observed significant theta and gamma band responses to items, cellular responses to items did not correlate with either theta or gamma-band LFPs. These data suggest that neural and theta/gamma band LFP responses were not associated in time, and that theta/gamma band LFP responses were to different objects at different times than cellular responses. Based on our dissociation for neural responses during encoding and LFP responses during retrieval, we tentatively suggest that our item-related neural responses relate to item-maintenance, while LFP responses may relate to attentional process involved in processing specific objects in memory.

The lack of a correlation between experimental context-related neurons and LFPs is somewhat more surprising because these experimental context-related responses were active over an entire block of the experiment (e.g., during navigation or retrieval). Given, however, that

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3 neurons and LFP power (across all bands) increased during complementary phases of the
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5 experiment, with neurons increasing firing during encoding, and LFPs increasing in power during
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7 retrieval, this lack of a correlation is not surprising based on our behavioral results. In support of
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9 our finding of a dissociation between LFP power and neural firing during navigation, a recent
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11 spatial learning study in rodents by Robbe et al. 2006 similarly observed little correlation between
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13 LFP power and neural firing rate (e.g., Robbe et al, Figure 5), although the authors did not look
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15 specifically at encoding or retrieval of landmarks (Robbe et al., 2006).
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19 It is important to note here that individual neurons we recorded from may show strong
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21 coupling in the gamma frequency range even though the behaviorally-responsive population we
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23 analyzed, on average, did not. In fact, previous results suggest that subsets of neurons do in some
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25 case phase lock with the ongoing gamma oscillation in rat and human hippocampus (Bragin et al.,
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27 1995; Jacobs et al., 2006). Our findings, however, showed that over the population of item and
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29 experimental context responses, there was little correlation with gamma oscillatory power, a
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31 result bolstered by our behavioral findings. Because our primary interest was the relationship
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33 between the population of simultaneously recorded neurons and LFPs in the hippocampal area for
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35 comparison with previous studies (Buchwald et al., 1965; Wyler et al., 1982; Logothetis et al.,
36
37 2001; Logothetis, 2003; Nase et al., 2003; Mukamel et al., 2005; Kreiman et al., 2006), we did
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39 not focus on individual neurons that showed strong coupling or anti-coupling with gamma. What
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41 we wish to emphasize is that the correlation over the population of neurons and LFPs in our study
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43 was significantly lower than that observed in previous studies in other brain regions, despite the
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45 similarity of our methods to previous studies. Correlations between cellular firing rate and LFPs
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47 over the population of recording sites in auditory cortex of humans and infero-temporal cortex of
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49 monkeys, particularly in the gamma band, are typically significantly higher than what was
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51 observed in this study, reported in the range of .2-.8 (Mukamel et al., 2005; Kreiman et al., 2006).
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56 The correlations reported in this study in the hippocampal area and amygdala, in
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58 contrast, did not differ significantly from zero. These data therefore suggest that the
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3 hippocampus, ERC, and amygdala have a different functional-anatomical layout than sensory
4 regions in the brain. In support of this notion, recordings from rodent hippocampus demonstrate
5 no correlation between neighboring neurons and their behavioral correlates (Redish et al., 2001),
6 in contrast to the visual cortex, where neurons responding to the orientation of bars are arranged
7 in hypercolumns based on their preferred orientation (Mountcastle, 1997). The fact that increased
8 selectivity of neurons is often accompanied by decreases in global activity in the hippocampus
9 (Hirase et al., 2001) further supports our finding of no significant LFP change during selective
10 neural epochs in the hippocampal area.
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21 Due to the behavioral dissociations for neural firing rate and LFPs, and the non-
22 significant correlations we found between cellular firing rate and LFPs in the hippocampus
23 compared to the larger correlations reported in previous studies in other brain regions (Mukamel
24 et al., 2005; Kreiman et al., 2006), we believe the differences we observed between cellular firing
25 rate and LFPs also in part relate to differences in what these two signals represent. LFPs likely
26 reflect the input to a brain region because they largely represent the summation of excitatory
27 synaptic events (e.g., primarily EPSPs) due to afferent input (Mitzdorf, 1985). Neural firing rate
28 (e.g., action potentials), however, represents the computations and therefore the output of a region
29 (Koch and Segev, 2000; Logothetis, 2003). Our study thus provides preliminary evidence for a
30 distinction between input-related LFP responses and output-related spiking activity during
31 declarative memory processes in the human hippocampus. We suggest therefore that our
32 findings, in conjunction with previous electrophysiological studies showing stimulation-induced
33 differences between LFP-related input and neuron-related output (Mathiesen et al., 1998;
34 Mathiesen et al., 2000; Lauritzen, 2001; Lauritzen and Gold, 2003), support distinct functional
35 roles for ensemble activity (LFP and the fMRI BOLD signal) and cellular firing rate in the human
36 hippocampus during declarative memory processes.
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| Region | Neurons | | LFP broad band | | LFP theta | | LFP gamma | |
|-----------------------------|---------|---------|----------------|---------|-----------|---------|-----------|---------|
| | item | context | item | context | item | context | item | context |
| HC cells=36 LFP=28 | 7 | 10 | 1 | 7 | 4 | 2 | 9 | 3 |
| ERC cells=57 LFP=42 | 20 | 11 | 2 | 7 | 7 | 4 | 5 | 5 |
| Amyg. cells=26 LFP=17 | 7 | 9 | 0 | 3 | 0 | 5 | 1 | 2 |

Table 1: Distribution of Item and Context Responses by Anatomical Region. HC=Hippocampus, ERC=Entorhinal cortex, Amyg.=Amygdala.

| region | Neurons | | LFP broadband | | | LFP theta | | | LFP gamma | | |
|-----------------------------|---------|-------|---------------|-------|-------------|-----------|-------|------------|-----------|-------|-------------|
| | store | pass. | store | pass. | r | store | pass. | r | store | pass. | r |
| HC cells=36 LFP=28 | (2,1) | (2,3) | (0,0) | (1,0) | .01+/-0.01 | (0,0) | (3,1) | .02+/-0.05 | (2,5) | (7,0) | .12+/-0.06 |
| ERC cells=57 LFP=42 | (10,4) | (4,7) | (0,0) | (2,0) | -.04+/-0.01 | (0,2) | (6,1) | .04+/-0.04 | (0,5) | (3,0) | -.05+/-0.09 |
| Amyg. cells=26 LFP=17 | (3,0) | (3,2) | (0,0) | (0,0) | .03+/-0.02 | (0,0) | (0,0) | .09+/-0.06 | (0,1) | (0,0) | .01+/-0.10 |

Table 2: Distribution of item responses by anatomical region. HC=Hippocampus,

ERC=Entorhinal Cortex, Amyg.=Amygdala. Note that a given neuron or LFP may have responded to more than one passenger (“pass.”) or store. Numbers in parenthesis indicate increasing and decreasing responses to items, respectively. “r” indicates the mean correlation coefficient for that region.

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| Region | Neurons | | LFP broadband | | | LFP theta | | | LFP gamma | | |
|-----------------------------|------------|-----------|---------------|-----------|--------------|------------|-----------|---------------|------------|-----------|---------------|
| | enc vs ret | retrieval | enc vs ret | retrieval | r | enc vs ret | retrieval | r | enc vs ret | retrieval | r |
| HC cells=36 LFP=28 | (7,3) | (0,0) | (0,7) | (1,5) | .05 +/-02 | (0,2) | (0,1) | .00 +/-03 | (1,2) | (0,1) | .07 +/-07 |
| ERC cells=57 LFP=42 | (8,3) | (0,0) | (0,7) | (0,4) | .01 +/-02 | (0,4) | (0,3) | .00 +/-02 | (1,4) | (1,2) | -.11 +/.04 |
| Amyg. cells=26 LFP=17 | (8,1) | (0,0) | (0,3) | (0,0) | .10 +/-08 | (0,5) | (1,0) | -.04 +/-02 | (0,2) | (0,2) | .05 +/-10 |

Table 3: Distribution of experiment context responses by anatomical region. HC=Hippocampus,

ERC=Entorhinal Cortex, Amyg.=Amygdala. Numbers in parenthesis for “enc vs ret”

indicate numbers of electrodes responding to encoding vs. retrieval, respectively.

Numbers in parenthesis for “retrieval” indicate significant responses during item

recognition and associative recognition, respectively. “r” indicates the mean correlation

coefficient for that region.

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For Peer Review

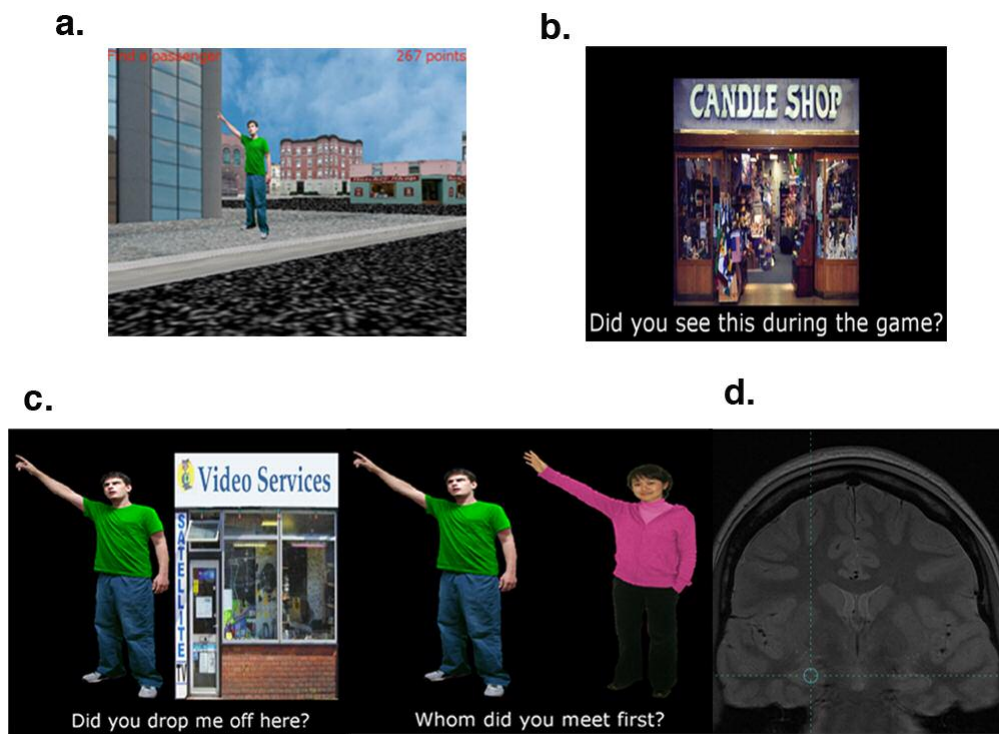


Figure 1: Methods and Electrode Placement. a) Screen shot of a passenger waiting on sidewalk from a virtual city subjects explored. Following navigation, subjects performed retrieval involving: b) item recognition, and c) associative recognition (See methods). d) Pre-implant MRI showing placement of electrode targeting the right CA region of the anterior hippocampus of a patient-subject (MRI presented in radiological convention). Green target indicates area of microwires determined by coregistering post-implant CT with pre-implant MRI (CT electrode tracts minimized to improve clarity of anatomy).

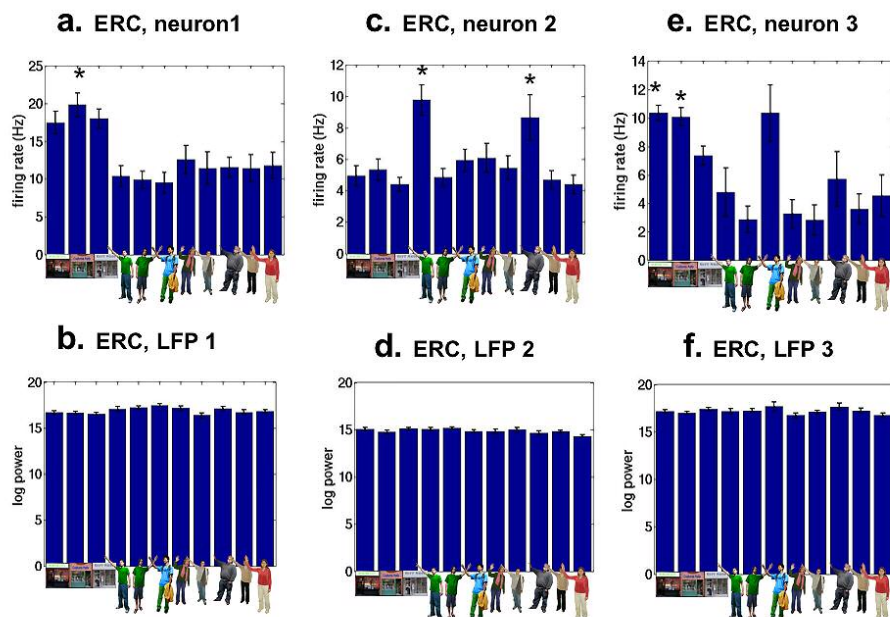


Figure 2: Entorhinal Cortex Neurons Respond to Specific Items Regardless of Experimental Context. Neurons responded to specific items seen during navigation and continued firing throughout the experiment to these items during the memory condition. Top row (a,c,e) shows the mean firing rate responses of three entorhinal cortex (ERC) neurons to items seen during navigation and retrieval; the item viewed is shown below each bar. All three ERC neurons showed significant effects of item in an ANOVA. Asterisks (*) show items for which the neurons were selective by comparing against all other items as revealed by Bonferroni corrected post-hoc t-tests; in general, ERC neurons responded to few items selectively. Note that ERC neurons responded to both stores (a,e) and passengers (c), although we observed greater numbers of responses to stores in ERC over all (Figure 3b). Bottom row (b,d,f) shows the mean broadband log LFP power (decibels) on the same recording channel to each item. Theta-band and gamma-band responses similarly did not show item-selectivity on these same channels. Only responses to items seen during navigation and retrieval are plotted.

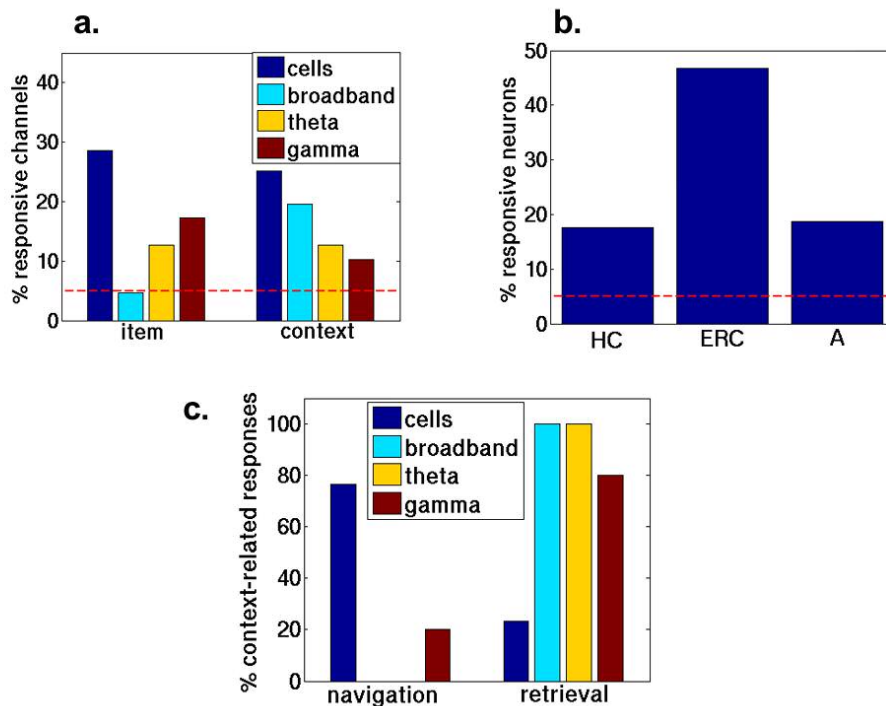


Figure 3: Response Properties over the Population of Recorded Neurons and LFPs. a) Neurons responded more to specific items (item) than they did to experimental context (context); while the broadband LFP responded to experimental context more than to items. Theta and gamma-band LFPs responded significantly to items and context. Dotted red-line indicates Type I error rate of $p = .05$. **b)** The number of neurons responding significantly to viewing stores during navigation and retrieval were significantly greater in ERC compared to hippocampus (HC) or amygdala (A); $\chi^2(2)=6.2$, $p < .05$. **c)** When we further analyzed which specific experimental context (navigation or retrieval) cellular and LFP experimental context-responsive channels responded to, we found significantly more neurons responding during navigation than retrieval and significantly more LFPs (across all bands) responding during retrieval than navigation.

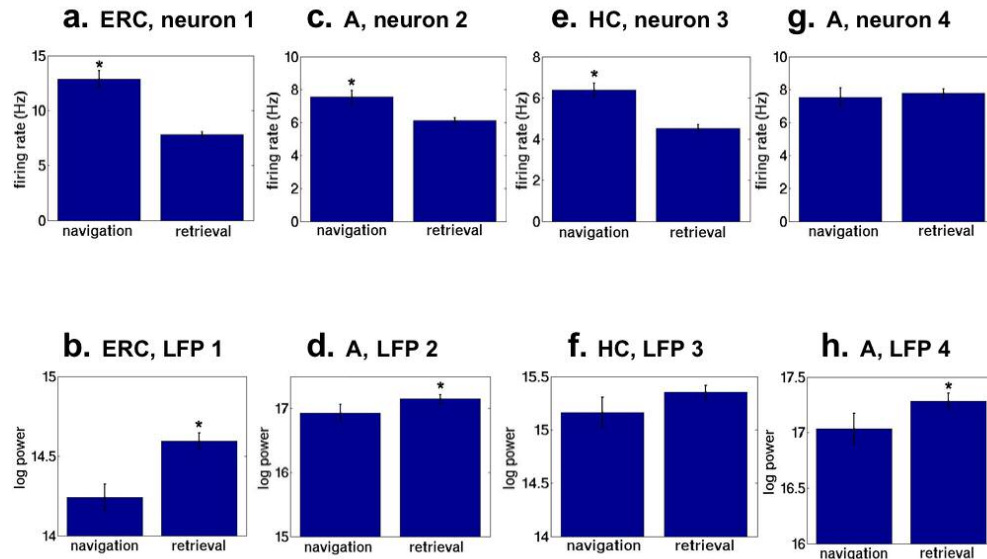


Figure 4: MTL Neurons and LFPs Showed Significant Effects of Experimental Context. Significant numbers of neurons and LFPs responded significantly to experimental context. Neurons and LFPs, however, did not change in tandem with each other. The change in mean firing rate during navigation compared to retrieval for four MTL neurons is shown in a,c,e,g; neurons were recorded in right entorhinal cortex (ERC), right amygdala (A), right hippocampus (HC), and right amygdala, respectively, and from three different patients. Panels b,d,f,h show the mean log LFP power (decibels) on the same recording channels from which neurons were isolated (y-axis on LFP plots is truncated so significant differences between conditions can be clearly visualized). Neurons a,c,e all showed greater firing during navigation, while LFP responses on these channels (b,d,f) show increases during retrieval compared to navigation.

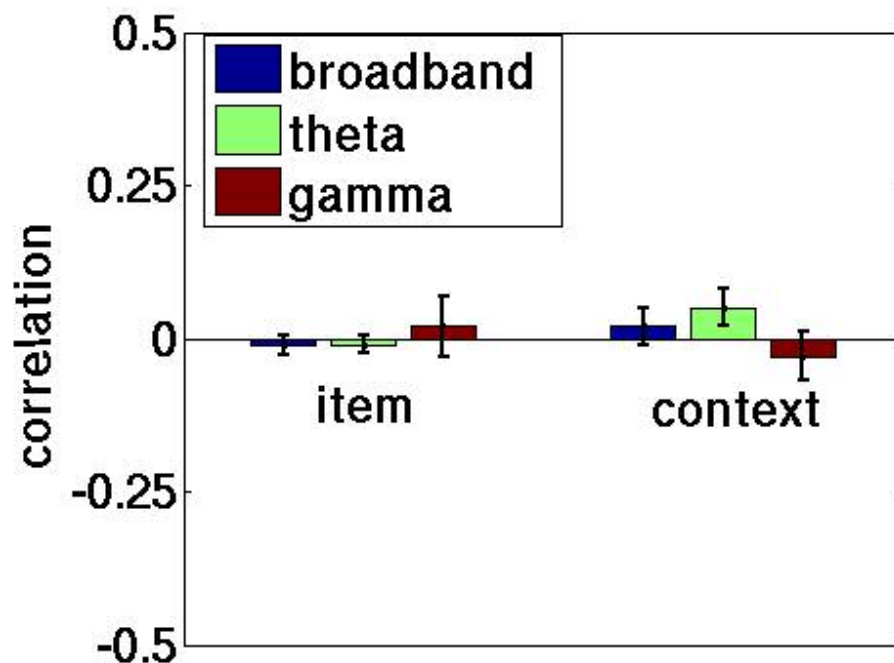
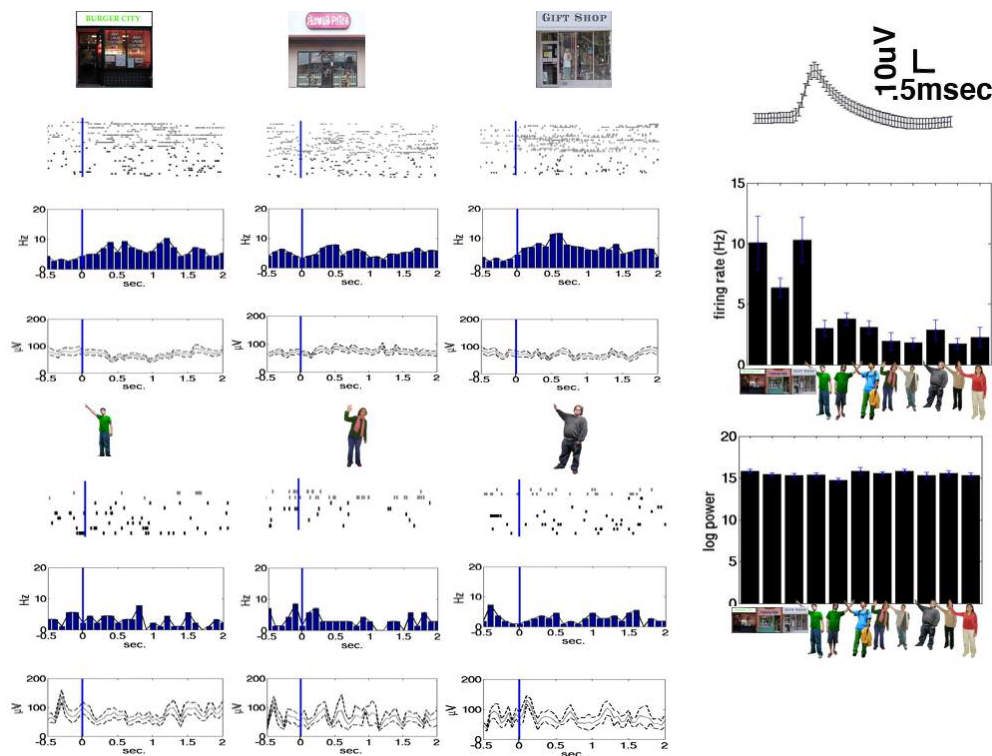


Figure 5: No Correlation Between Single Neuron Activity and Wide-band, Theta-band, and Gamma-band LFPs. Mean correlation coefficient for cellular firing rate with wide-band (1-100 Hz), theta-band (4-8 Hz), and gamma-band wavelet-transformed LFP power (40-100 Hz) averaged over neurons that showed increased firing rate to specific items (N=44) and neurons that showed increased firing for specific experimental contexts (encoding or retrieval: N=30). We observed no significant correlation between cellular firing rate and LFP power in wide-band, theta-band, and gamma-band power for items (items) and experimental context (context).



Supplementary Figure 1: MTL Neurons Respond to Specific Items Regardless of Experimental Context: Expanded Response Plot. Neurons responded to specific items seen during navigation and during the memory condition. This particular ERC neuron (not shown in Figure 2) showed selective responses to items. The item viewed is shown in the top row and fifth row, spike rasters are shown in the second row and sixth row, and peri-event time histograms are shown in the third row and seventh row. Firing rate is binned at 100msec. An ANOVA revealed a main effect of item on the firing rate for this ERC neuron as well as a main effect of experimental context. Despite the fact that the patient performed navigation and retrieval, the neuron nonetheless maintained firing for Burger City and Gift Shop regardless of the task the subject performed. Rasters in light gray show the responses during navigation; rasters in black show responses during retrieval. Far upper right panel shows the mean cellular response for all familiar items shown; items are pictured below bars representing their mean firing rate. In the fourth and eighth row, the mean raw LFP response (DC component is removed by taking the absolute value of the signal for comparison with firing rate, which cannot be negative) to the same items are shown; errorbars shown in light gray. LFP is presented at a sampling rate of 256 Hz. Far right lower panel shows the mean log LFP wavelet power for all familiar items shown averaged across a 300–1500 msec time window. The broad-band LFP did not show item-selectivity; theta and gamma band LFPs similarly did not show item-selectivity on this channel. Waveform for this neuron is shown in upper right corner; errorbars indicate small variance in waveform shape over trials.