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Neural Activity in Human Hippocampal Formation Reveals the Spatial Context of Retrieved Memories

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In many species, spatial navigation is supported by a network of place cells that exhibit increased firing whenever an animal is in a certain region of an environment. Does this neural representation of location form part of the spatiotemporal context into which episodic memories are encoded? We recorded medial temporal lobe neuronal activity as epilepsy patients performed a hybrid spatial and episodic memory task. We identified place-responsive cells active during virtual navigation and then asked whether the same cells activated during the subsequent recall of navigation-related memories without actual navigation. Place-responsive cell activity was reinstated during episodic memory retrieval. Neuronal firing during the retrieval of each memory was similar to the activity that represented the locations in the environment where the memory was initially encoded.

When one encounters an old friend and remembers the time they last met, often the place of meeting and surrounding circumstances come to mind. This is the hallmark of episodic memory: the capacity to store and later retrieve memories that are bound to a particular place and time (*1*). Theories of episodic memory posit that the brain supports this ability by continually maintaining an updated representation of the current spatiotemporal context, which is a neural representation of space, time, and other aspects of one's current cognitive milieu (*2*). When the brain forms a new episodic memory, these theories predict that the content of the experience becomes associated with the current spatial and temporal context. When the memory is retrieved, this prior context is partially reinstated, focusing one's thoughts on the time and place of the remembered episode. This reinstatement not only provides the phenomenological experience of remembering, but also helps to cue other memories experienced within the same or related contexts.

Although it is well established that the hippocampus and surrounding medial-temporal-lobe (MTL) structures play a central role in the formation and retrieval of context-mediated memories (*3*–*5*), we know far less about how these memory processes manifest in the activities of individual MTL neurons. Much of what is known about the neural coding properties of hippocampal and MTL neurons comes from studies of rodent spatial navigation, where individual neurons respond preferentially at specific locations within a given contextually defined spatial environment (*6*, *7*). Similar neuronal responses have also been identified in the human hippocampus during virtual spatial navigation (*8*, *9*). The context-dependent firing of these neurons (*10*, *11*) and their dependence on the animal's goal state or past history of experienced cues (*12*, *13*) have led some to speculate that the neural representation of space in the hippocampus is part of a broader network of neurons that encode episodic memories more generally (*14*–*17*). This hypothesis suggests that the same neural structures and computations that enable the learning of a spatial layout via place-cell activity also facilitate the encoding of episodic memories. However, according to a prominent alternative account, the spatial coding functions of the hippocampus are part of a context module that operates independently of the computations that encode the content of a memory (*18*, *19*).

We designed a virtual-reality memory game in which participants played the role of a delivery person, driving through a virtual town and delivering items to stores. Our participants were patients with drug-resistant epilepsy who were implanted with depth electrodes to localize the focus of their seizures and to map cognitive function in surrounding healthy tissue. In an initial phase of the game, participants explored the town using a computer controller to navigate from store to store as they attempted to learn the layout of the environment illustrated in Fig. 1A. After this initial familiarization phase, during which participants visited each store twice, a series of "delivery days" began. On each delivery day, participants were instructed to travel from store to store, visiting 13 randomly chosen stores (of the 16 total) in a randomly determined order. Upon their arrival at each store, participants were presented with an item [either visually for 2 s for participants one to five or aurally for participants six and seven (*20*)]. Upon arrival at the final (13th) store, no item was presented. Instead, the screen

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went black and participants were prompted to vocally recall as many of the 12 delivered items as they could remember in any order (participants recalled 5.2 items, on average). After being given 90 s for free recall, participants could advance to a new delivery day, in which they would deliver a distinct but randomly determined set of items to a random sequence of 13 stores and then attempt to recall the new set of items. Consistent with earlier work (*21*), participants exhibited a significant ($P = 0.008$) tendency to consecutively recall items delivered to more spatially proximate locations (see supplementary text).

We first sought to identify patterns of neuronal activity that represented participants' location within the virtual town. We identified place-responsive cells as the neurons that exhibited significantly increased firing at a particular location in the virtual environment (*20*). Figure 2A depicts the activity of one example place-responsive cell, which increased its firing rate when the participant was positioned at a location on the left side of the virtual environment and facing north. The majority of the identified place-responsive cells were direction-dependent (72%) and did not exhibit significant place fields when direction of traversal was not taken into account. This is similar to earlier findings of directionally oriented place cells in environments with clearly defined routes, in contrast to open environments, where omnidirectional place cells are prevalent (*8*, *22*). These directionally oriented place cells were not generally responsive to place-invariant view information (see supplementary text). Figure 2B shows the firing rate of a place-responsive cell from the entorhinal cortex, which activated at a location in the south part of the environment during eastward movements. In total, we identified 95 place-responsive cells, making up 25.6% of all observed neurons. There were significant numbers of place-responsive cells in the hippocampus, entorhinal cortex, and amygdala and in anterior MTL regions of ambiguous localization (*20*) (binomial test with $P < 0.01$ for each region) (Fig. 2C and tables S1 and S2).

To determine whether spontaneous retrieval of items during free recall reinstated the spatial context associated with the item's encoding, we calculated the neural similarity between ensemble place-responsive cell activity during navigation and during item retrieval [see (*20*) and fig. S1 for further details]. We partitioned the environment into three regions for each recalled item: regions close to the delivery location, regions of intermediate distance, and regions that were far from the delivery location. We then asked whether the ensemble place-cell activity at the time of retrieval was more similar to navigational epochs that were closer to the delivery location. A high degree of similarity would indicate the reinstatement of the spatial context associated with the item. To protect against potential confounding between item and spatial context, we excluded navigational epochs surrounding the delivery of an item.

We found significant spatial context reinstatement surrounding the time of item vocalization (time course illustrated in Fig. 3A). The level of neural similarity between recall activity and navigation activity was ordered such that areas of the environment near an item's encoding location exhibited the highest similarity scores, intermediate spatial distances exhibited middling similarity scores, and far spatial distances exhibited the lowest similarity scores (this effect was strongest over the interval of –300 to 700 ms, illustrated

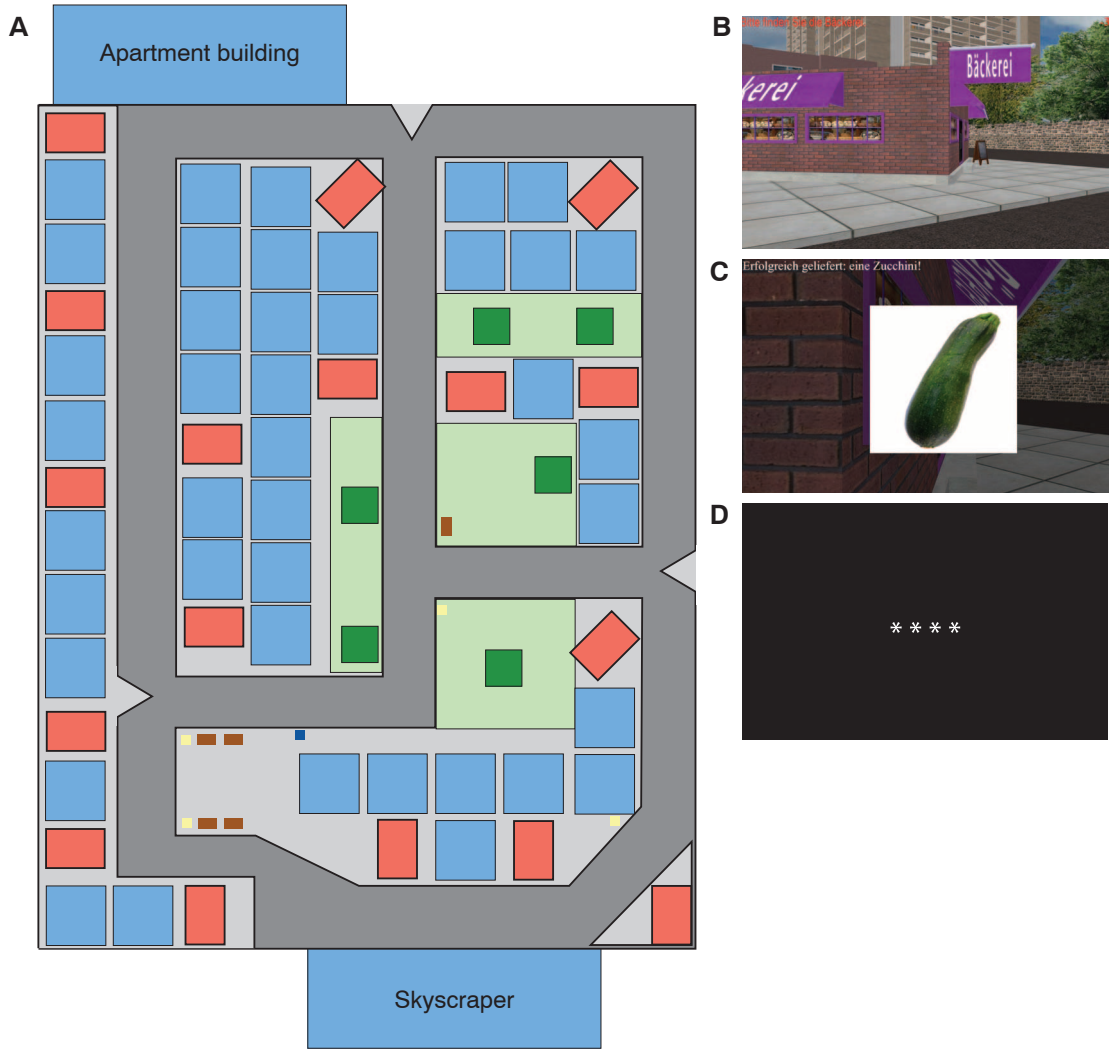

Fig. 1. The behavioral task. (**A**) Overhead map of the virtual environment. Red rectangles, store locations; blue squares, locations of nonstore buildings; green areas, grass and trees; small dark blue, brown, and yellow boxes; mailboxes, benches, and street lights. (**B**) An example storefront that a participant might encounter. (Translation of text at top left: "Please find the bakery.") (**C**) The presentation of an item (a zucchini) upon arrival at the target store (bakery). (Translation of text at top left: "Successfully delivered: a zucchini.") (**D**) The initiation of the recall period, as indicated by a black screen with asterisks.

in Fig. 3B). An analysis of variance (ANOVA) indicated a significant effect of distance on the level of neural similarity ($F_{2,300} = 7.6$, $P < 0.001$). Performing this latter analysis across participants rather than recall events revealed that neural similarity within the near distance bin was significantly greater than that within the far distance bin (Fig. 3C) [$t(5) = 4.0$, $P = 0.009$].

During the spontaneous recall of an item, place-responsive cells exhibited firing patterns similar to those shown during exploration of the region of the town where the item was previously delivered. Thus, recalling an episodic memory involves recovery of its spatial context, as seen in the activity of place-responsive cells in the human hippocampal formation and surrounding MTL regions. If the item delivery occurred in or near a cell's place field, characterized by a firing rate that is significantly higher than the baseline level, then recalling the item should also produce an increase in firing rate. We calculated the firing rate of place-responsive cells when participants were navigating inside and outside of each cell's place field, as well as the firing rate when participants recalled items that were presented near to or far from each cell's respective place field (Fig. 4) [see (*20*) and fig. S2 for further details]. The average in-field firing rate (3.8 Hz) was substantially higher than the out-of-field firing rate [1.9 Hz; $t(32) = 5.9$, $P < 10^{-5}$]. The average firing rate during the recall of items presented near a place field was 2.2 Hz, which was significantly higher than the 1.8-Hz firing rate during recall of items presented far from a place field [$t(32) = 2.2$, $P = 0.03$].

Unlike traditional list-recall studies of episodic memory, in which items unfold only in time, the present experiment provided a distinct spatial context for each item. This allowed us to leverage the spatial-coding properties of hippocampal neurons in the study of the neural basis of episodic recollection. Spatially sensitive neural activity in the hippocampal formation became reactivated during episodic retrieval, when no visual cues were present. At the time of recall, participants simply vocalized the names of the delivered items in the order in which they came to mind, yet the neurons responsive to spatial information reactivated during the time just before and during vocalization. This reactivation implies that each experienced item is bound to its spatial context, which in turn may be reinstated when the item comes to mind during recall.

Because human neural recordings are rarely possible, little is known about the neural substrates of spontaneous verbal recall. Nonetheless, several recent studies have established the general phenomena of content reinstatement, whereby the attributes of an item at encoding become reinstated just before recall. This has been shown for human hippocampal neurons that are selective for taxonomic categories, or possibly individual items (*23*), and also for distributed patterns

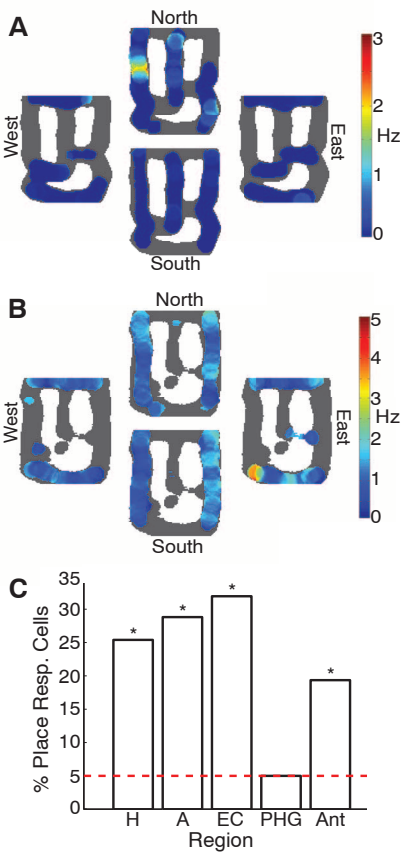

Fig. 2. Place-responsive cells. (**A**) Firing-rate map for a cell responsive to northward traversals located in participant six's hippocampus, shown separately for each cardinal direction. Gray represents all areas traversed by the participant, regardless of the direction of travel. (**B**) A cell responsive to eastward traversals recorded from participant one's entorhinal cortex. (**C**) Regional distribution of place-responsive cells in the entire data set of 371 single units (H, hippocampus; A, amygdala; EC, entorhinal cortex; PHG, parahippocampal gyrus; Ant, anterior medial temporal lobe). The red dashed line indicates the false-positive rate of 5%. Asterisks denote brain regions where the number of place-responsive cells significantly exceeded chance levels.

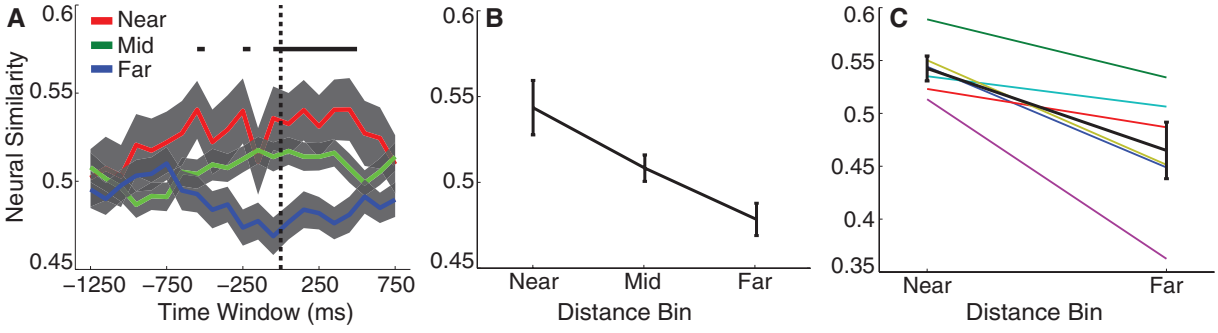

Fig. 3. Spatial context reinstatement. (**A**) Time courses of neural similarity between ensemble place-cell activity during navigation and during item recall are shown for near, middle, and far spatial distance bins. Time courses, shown relative to recall onset, were computed in overlapping 500-ms windows (*x* values indicate the center of the window). Similarity is defined as the cosine of the angle between ensemble activity during recall and navigation, normalized as a rank score (*20*). Shaded regions indicate SEM across recalled items. The horizontal bar indicates statistically significant time points, as determined by ANOVA with a false-discovery rate–adjusted significance threshold of 0.017. The vertical dotted line at 0 ms denotes the onset of the vocalization. (**B**) Average neural similarity for near, middle, and far spatial distance bins is shown for the time period of −300 to 700 ms relative to recall onset. Error bars indicate SEM across recalled items. (**C**) Neural similarity for near and far spatial distance bins for each of the included participants (thin colored lines) and the participant average (thick black line) is shown for the time period of −300 to 700 ms relative to recall onset. Error bars indicate SEM across participants.

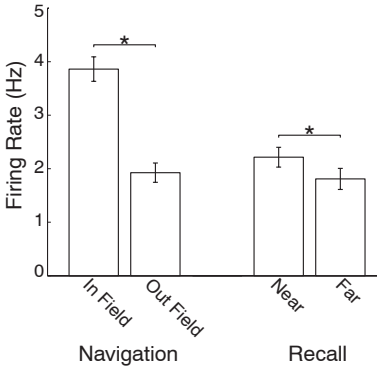

Fig. 4. Place-responsive cell activity during navigation and recall. (Left) Navigation. "In Field" indicates the average place-responsive cell firing rate when navigating within a cell's place field, whereas "Out Field" indicates the average place-responsive cell firing rate at locations outside of a place field ($*P < 10^{-5}$). **(Right)** Recall. "Near" indicates the average place-responsive cell firing rate in the time period from 1.5 s before to 1 s after recall onset of items that were initially presented in or close to the center of a place field. In contrast, "Far" represents the average place-responsive cell firing rate in the same time window for recall of items that were initially presented far from the center of a place field ($*P = 0.03$). Error bars indicate SEM.

of intracranial electroencephalography and hemodynamic activity (*24*, *25*). Reinstatement is not specific to an individual item but also activates neighboring items, as would be expected if those neighboring items provide an abstract temporal context for the recalled item (*26*, *27*). Such a temporal context signal may be reflected in the recent discovery of individual neurons in the rodent hippocampus that appear to encode the relative times of behaviorally important events (*28*, *29*).

Our finding that spontaneous recall of an item reactivates its spatial context provides direct neural evidence for theories of episodic memory that postulate context reinstatement as the basis for recollection (*2*, *30*). This result also implies that the spatial coding identified with the hippocampal place-cell system is part of a more general engine of episodic memory in which items become associated with their spatiotemporal contexts, and retrieval of items reinstates those contexts to help cue other context-appropriate memories.

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Supplementary Materials

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Supplementary Text
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Tables S1 and S2
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BTBD3 Controls Dendrite Orientation Toward Active Axons in Mammalian Neocortex

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Experience-dependent structural changes in the developing brain are fundamental for proper neural circuit formation. Here, we show that during the development of the sensory cortex, dendritic field orientation is controlled by the BTB/POZ domain–containing 3 (BTBD3). In developing mouse somatosensory cortex, endogenous Btbd3 translocated to the cell nucleus in response to neuronal activity and oriented primary dendrites toward active axons in the barrel hollow. Btbd3 also directed dendrites toward active axon terminals when ectopically expressed in mouse visual cortex or normally expressed in ferret visual cortex. BTBD3 regulation of dendrite orientation is conserved across species and cortical areas and shows how high-acuity sensory function may be achieved by the tuning of subcellular polarity to sources of high sensory activity.

Proper neural circuit development is important for the newborn animal to receive, process, and respond to information from the external sensory environment. This process critically depends on the patterning of individual neurons to shape the postsynaptic dendritic field for assembly with presynaptic axons. Dendritic remodeling is a conserved process in which postsynaptic dendrites are pruned in response to presynaptic activity during metamorphosis in *Drosophila* (*1*) and during the development of hippocampal CA1, cerebellar Purkinje cells, and retinal ganglion cells in mouse (*2*). In the rodent primary somatosensory cortex, layer IV spiny stellate neurons are concentrated around barrel walls, forming cell-sparse barrel hollows and pyramidal neuron dense septa that delineate individual barrels. In mouse somatosensory barrel cortex, spiny stellate neurons orient their dendrites toward barrel hollows during the first postnatal week to enable efficient synapse formation with thalamocortical axons from the ventrobasal thalamic nucleus (*3*). Neuronal activity and monoamine uptake in the synaptic junction contribute to this process (*4*, *5*). We pursued the mechanism of dendrite orientation by

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