Title: Hippocampal neurons code individual episodic memories in humans

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Abstract:

The hippocampus is an essential hub for episodic memory processing. However, how human hippocampal single neurons code multi-element associations remains unknown. Some argue that each hippocampal neuron codes for an invariant element within an episode. Instead, others have proposed that hippocampal neurons bind together all elements present in a discrete episodic memory. Here, we provide evidence for the latter. We show that individual neurons, which we term Episode Specific Neurons (ESNs), code discrete memory episodes. These ESNs do not reflect the coding of a particular element in the episode (i.e., concept or time). Instead, they code for the conjunction of the different elements that make up the episode.

One-Sentence Summary:

Individual neurons in the hippocampus code for discrete episodic memories.

Introduction:

Episodic memory refers to our ability to reinstate the what, where and when of past experiences (Tulving, 2002). This ability is thought to depend on the reinstatement of neural activity that was present at memory encoding (Pacheco Estefan et al., 2019). It is undisputed that the hippocampus plays an integral role in episodic memory processing (Lisman et al., 2017; Marr, 1971; Squire, 1992) and the binding of multimodal information (Cooper and Ritchey, 2020). However, how it codes episodic memories remains controversial.

One important open question is whether neurons in the hippocampus code for specific content elements or an entire episode. Concept Neurons in the hippocampus fire in response to specific invariant elements independent of the context (Gelbard-Sagiv et al., 2008; Mormann et al., 2008; Mormann et al., 2011; Quiroga et al., 2005). One contemporary idea is that the diverse elements that make up an episode are coded by the simultaneous activity of a set of these Concept Neurons (Quiroga, 2012; 2020) or by expanding the selectivity of existing Concept Neurons (Ison et al., 2015). Alternatively, single units in the hippocampus might sparsely encode a specific set of elements within an individual episode and act as pointers to cortical modules during memory reinstatement (Teyler and DiScenna, 1986; Teyler and Rudy, 2007). Unlike Concept Neurons, these Episode Specific Neurons (ESNs) would fire in response to the conjunction of all the diverse information within an episode and not in response to individual content elements (such as a specific face or a specific place; Figure 1A). Despite simulations

pointing towards the existence of ESNs (see Bowman Wyble, 2007 Parish et al., 2021), to this day there is no evidence for such a sparse conjunctive code in humans.

In search of an answer to this issue, we leveraged intracranial microwire recordings to investigate the firing patterns of neurons in the human hippocampus. We hypothesized that a significant number of hippocampal neurons reinstate their firing rate within a specific episode (i.e., fire during encoding and retrieval). Importantly, these ESNs would code for the conjunctive elements present within an episode and are not tuned to individual elements within the episode. elements As control analyses, we investigated whether this firing activity can be explained by a firing response to specific invariant elements, as occurs in Concept Neurons (CN; Quiroga et al., 2005), or by a time preference, as occurs in Time Cells (TC; Reddy et al., 2021; Umbach et al., 2020).

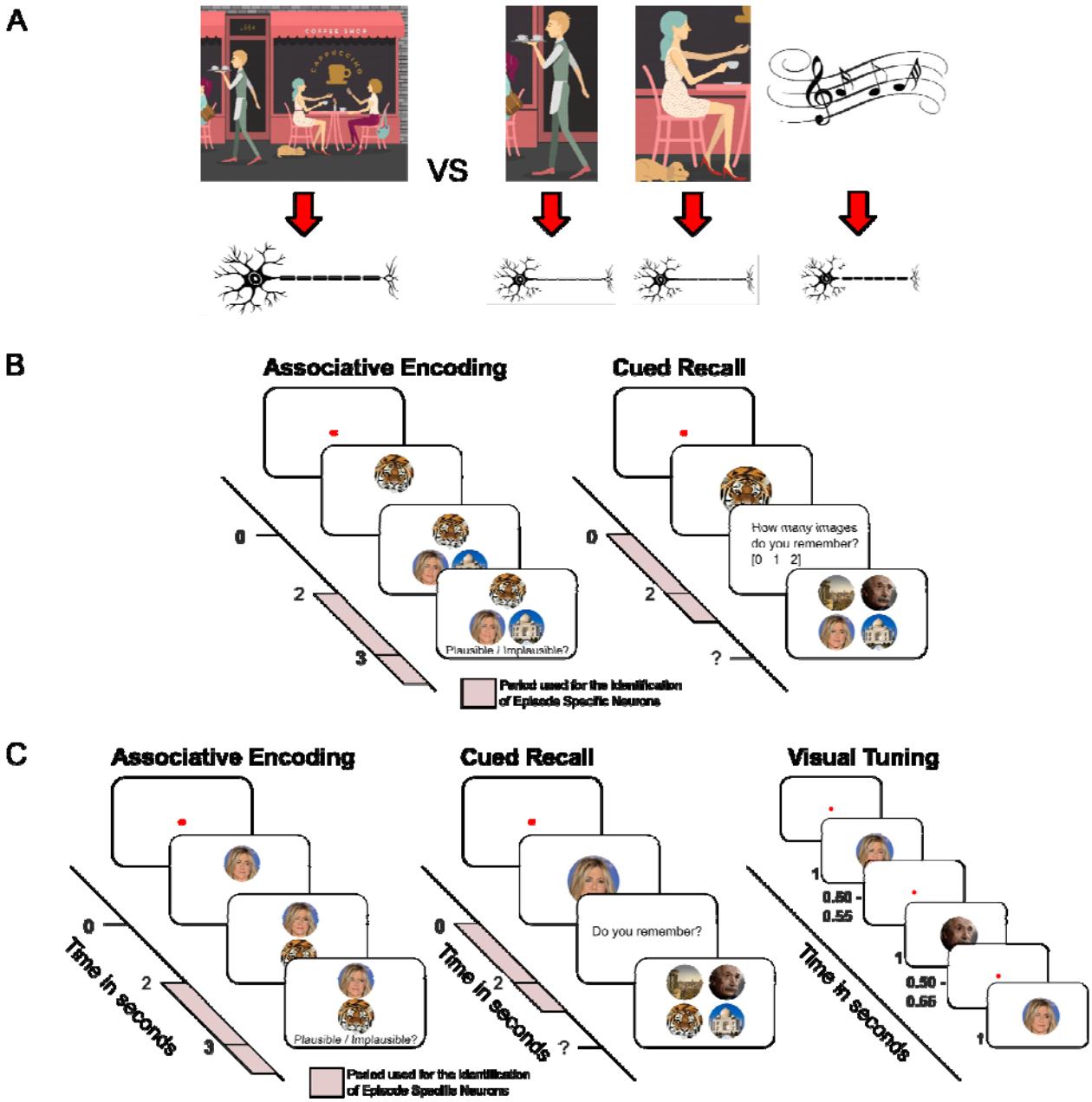

Figure 1. Difference between Indexing Theory and Concept Neuron based hippocampal coding of episodic memories, experiment procedure for experiments 1 & 2.

(A) Left: The classic indexing theory (Teyler and DiScenna, 1986) proposes that neurons in the hippocampus represent a conjunctive code that binds together all the elements that make up the episode in the form of an index. Within this framework, neurons do not directly code for the elements themselves (i.e., the smell of the coffee, your friend, the background music, the café, etc.), but rather act as pointers to these different elements which themselves are coded elsewhere (i.e., the neocortex). Right: However, some hippocampal neurons are thought to code for specific elements or concepts, which is why they are called Concept Neurons (Mormann et al., 2008; Mormann et

al., 2011; Quiroga et al., 2005). Within this framework, a group of neurons collectively code an episodic memory, with each neuron representing a specific element involved in that episode (i.e., a neuron coding for the coffee, another neuron coding for your friend, etc. (Quiroga, 2012; 2020)). It is important to note that one index or one concept is likely to be coded by an assembly of neurons, not a single neuron.

(B) Outline of the procedure for experiment 1. During encoding, all participants were instructed to imagine a vivid episode involving an animal cue and two associate images (two faces, two places or a face and a place) and rated its plausibility. This approach is suitable for investigating episodic memory as originally defined by Tulving in 1972 (Tulving, 1972). During recall, participants were asked to retrieve the associated images when cued with the animal cue. The experiment was self-paced and every episode was learned and tested only once. Following each encoding block of roughly 20 episodes, participants performed a short distractor task. The pink areas represent the time windows used for subsequent analyses (see Methods).

(C) Outline of the procedure for experiment 2. Left: The memory task was largely the same as in experiment 1 (see Figure 1B). However, events consisted of one cue (either an animal, a face or a place) and one associate image (either an animal, a face or a place). Right: After the memory task, patients performed a visual tuning task where the previously used stimuli were shown multiple times in quick succession without a memory component. This approach has been traditionally used to identify putative Concept Neurons.

Results:

We analyzed recordings from two separate experiments (experiment 1: 585 neurons in the hippocampus, 16 participants, 7 female; age mean = 36.125 years, from 26-53 years; experiment 2: 86 neurons in the hippocampus, 8 participants, 4 female; age mean = 34.375 years, from 19-58 years) where patients were implanted with stereotactic Behnke-Fried depth electrodes in the hippocampus (Figure S1), while they performed a memory association task (Figure 1B & Figure 1C).

During encoding of experiment 1 participants created a vivid mental story consisting of an animal cue and two associate images (two faces, two places or a face and a place). By contrast, experiment 2 consisted of one cue and one associate image (both either an animal, face, or

place). During recall, the animal cue was presented again and participants were asked to retrieve the associate image(s). The experiments were self-paced and every episode was learned and retrieved only once.

Identifying Episode Specific Neurons (ESNs)

For every neuron, we determined the firing rate during each correctly remembered episode at encoding and retrieval. We then z-scored the firing rate across all encoding and retrieval episodes. This was done independently for encoding and retrieval to account for general differences in firing rates. We measured episode-specific firing reinstatement as the product of the standardized firing rates at encoding and retrieval (Figure 2A). Due to the self-paced nature of the experiment, we expected no consistent temporal firing pattern to emerge and instead assumed that a rate code contained enough information to represent an event.

Using a trial-shuffling procedure, we generated a distribution of reinstatement values expected by chance. A neuron was considered an ESN if (i) the empirical reinstatement value exceeded the 99th-percentile of the shuffled distribution for at least one episode and (ii) the standardized firing rate for encoding and retrieval of that episode each exceeded 1.645 ($\triangleq p_{\text{right-tailed}} < 0.05$). The second criterion prevented the identification of ESNs which would excessively fire at only one phase of the task (i.e., encoding or retrieval). It could be argued that ESNs identified in this manner could reflect the firing of cells tuned to the image of the animal cue, rather than the conjunction of all elements since the cue is episode-unique and presented during encoding and retrieval. To address this issue, in experiment 1, we excluded neurons that showed a significant firing increase during the first second after the encoding of the animal cue for episodes that were later reinstated (see Methods). This procedure has traditionally been used to identify putative concept neurons (Quiroga et al., 2005; Mormann et al., 2008; Mormann et al., 2011). This

approach revealed that in experiment 1 a significant number of hippocampal neurons were ESNs (141 out of 585 neurons ≙ 24.10%; $p < 0.001$; permutation test; Figure 2B). In experiment 1 117 out of 141 ESNs (≙82.98%) coded for a single episode. Two example ESNs are shown in Figure 3. These ESNs are unlikely to be concept cells tuned to the animal cue as the firing rate during encoding reaches its maximum only after the presentation of the associate stimulus (see Figure 4A). It is of note that the proportion of neurons that can be classified as ESNs is proportional to the number of events learned and retrieved (the same is the case for Concept Neurons). As such it is not suitable to determine the sparseness of the hippocampal code. The proportion of ESNs of all recorded neurons is useful as an estimation of how many ESNs we can expect in future analyses.

ESNs do not code for the (content of the) associate images

To rule out that ESNs are firing in response to a stimulus category (such as faces or places) we repeated the ESN identification analysis, but only included ESNs that showed reinstatement in at least one episode with two face associate images and at least one episode with two place associate images. Such neurons would be very unlikely to code for a specific stimulus category or concept because the stimulus material in these episodes does not overlap. Again, we found a significant number of ESNs (7 out of 585 single units ≙ 0.012%; $p = 0.0004$). It is important to note, that this is a very conservative analysis, as only a few ESNs reinstate two or more episodes (24 out of 141 ESNs ≙ 17.02%).

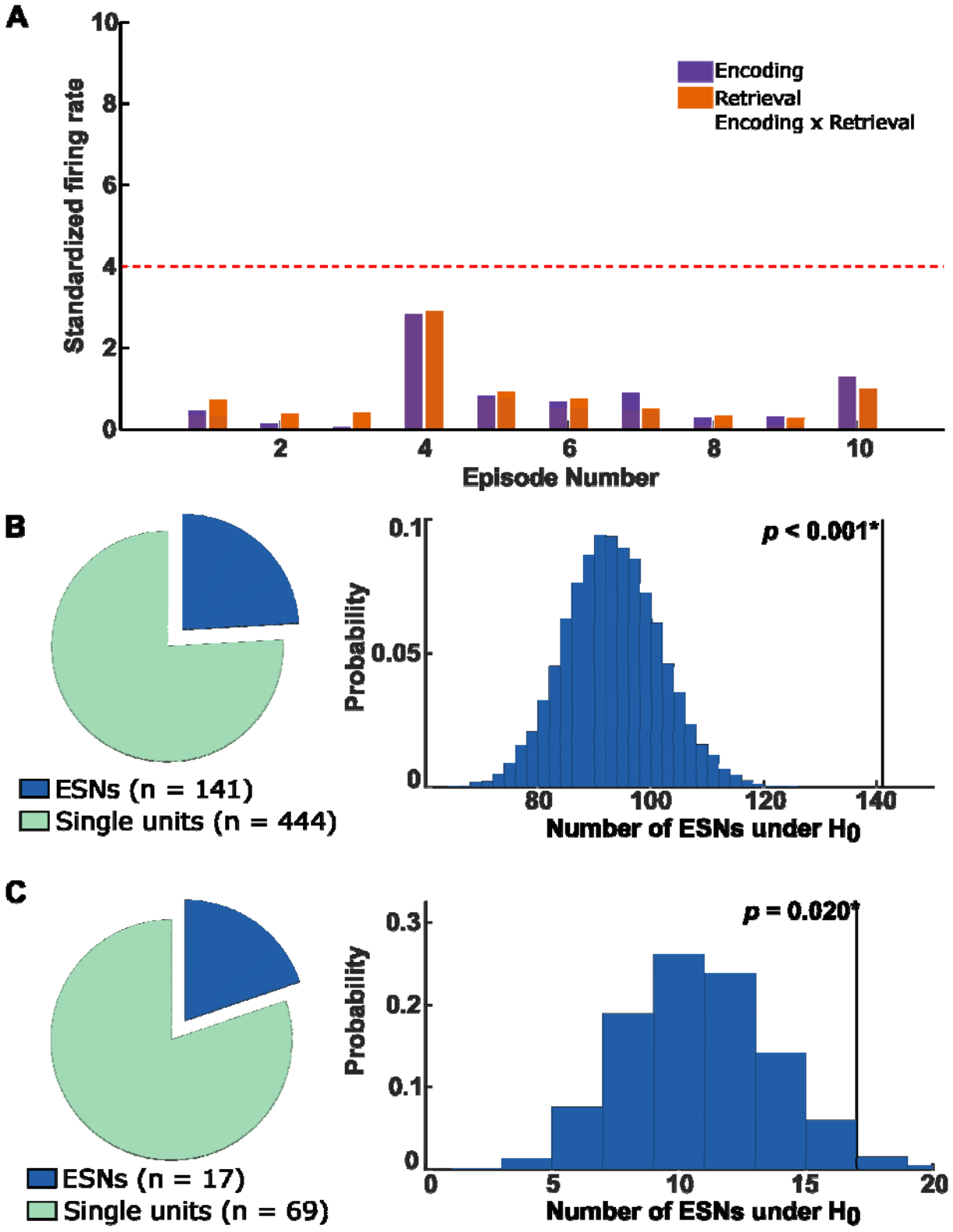

Figure 2. Analysis schematic and number of ESN identified in experiments 1 & 2.

(A) A schematic for identifying Episode Specific Neurons (ESNs) is shown. The diagram shows the z-scored firing rate on the y-axis for ten simulated episodes on the x-axis color-coded for encoding and retrieval (purple and orange, respectively). The transparent bars encompassing encoding and retrieval indicate the product of encoding and retrieval firing rates, which is used as the measure of episode-specific reinstatement. The dotted red line shows the threshold (derived from a shuffling procedure, see Methods). Because of the way ESNs are defined, they are required to fire substantially above their average firing rate during encoding and retrieval, which rules out neurons that generally show an increased firing rate in remembered episodes.

(B) Resulting ESN during experiment 1. Left: The pie chart depicts the number of ESNs that show significant firing reinstatement to at least one episode (dark blue) and the number of neurons that showed no firing reinstatement (green). Right: The number of ESNs as expected by chance and the empirical number of ESNs (141 out of 585 neurons; $p < 0.001$; permutation test).

(C) Same as (B) but for experiment 2. Out of a total of 86 hippocampal neurons, we identified 17 ESNs ($p = 0.0202$; permutation test).

ESNs do not code for the content/visual properties of the cue or associate image

Traditionally, visually responsive neurons have been identified using the repeated presentation of a stimulus. In the above analysis, we only present the animal cue once, which is suboptimal for ruling out Concept Neurons tuned to the animal cue. To ameliorate this shortcoming, in experiment 2 we added a visual tuning task (Figure 1C) after the memory association task. During the visual tuning task, images from the memory task were repeatedly shown in quick succession. This approach has typically been used to identify putative Concept Neurons that respond to one of the images independently of any memory processes (Mormann et al., 2008; Mormann et al., 2011; Quiroga et al., 2005). When excluding Concept Neuron activity in this independent dataset, we replicated our previous results and identified a significant number of ESNs (17 out of 86 neurons ≙ 19.77%; $p = 0.0202$; permutation test; Figure 2C). In experiment 2 16 out of 17 ESNs (≙94.12%%) coded for a single episode.

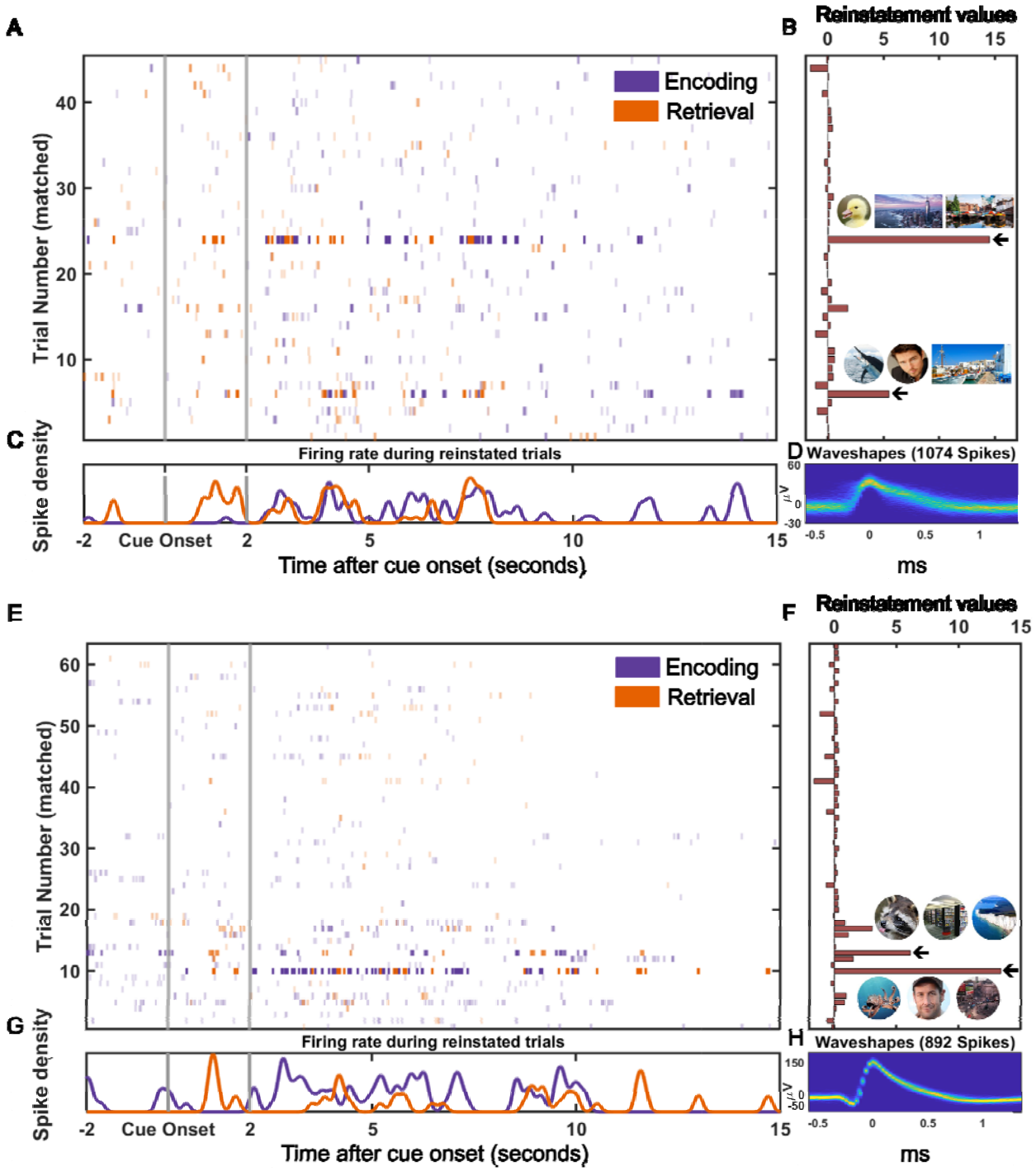

Figure 3. Firing patterns for two example Episode Specific Neurons.

(A) Spike raster plot. Each line indicates a spike. On the x-axis is time and on the y-axis episodes. Color-coded in purple for encoding and orange for retrieval. The transparency is adjusted according to the reinstatement values in that specific episode.

(B) Reinstatement values and the animal cues with the respective associate images for reinstated episodes (indicated by the black arrows).

(C) Spike density plot for reinstated episodes. Note that the experiment is self-paced and episode length varies. (D) 2D histogram of the waveshape of that particular unit (Niediek et al., 2016).

(E-H) same as (A-D) but for a different example ESN.

ESNs are limited to later remembered episodes

We have so far demonstrated that ESNs reinstate their firing rate when remembering a unique episode. This reinstatement cannot be explained by the semantic content or visual properties of the used image, which strengthens the notion that ESNs code for memories. Consequently, we expected to not find a significant number of ESNs when limiting our analysis to later forgotten episodes, which was indeed the case (10 out of 585 neurons ≙ 1.71%; $p = 0.4317$; permutation test). However, this result could stem from a lower number of forgotten events (see Table S1). To counter this bias, we equalized event numbers between later remembered and later forgotten events for every neuron by randomly sampling (with replacement) later remembered events as many times as participants forgot an event. If any of the sampled events were later reinstated, we considered this single neuron a miss-ESN under the null. By repeating this procedure 10,000 times we generated a distribution of how many miss-ESNs were expected if the number of later remembered and later forgotten events were equal. This analysis revealed a significantly lower empirical number of miss-ESNs compared to hit-ESNs ($p < 0.001$, bootstrapping test), demonstrating that the likelihood of finding ESNs depended on memory.

ESNs do not code for time

Recent studies in humans show that some hippocampal neurons code specific time points invariant across repetitions, which are referred to as Time Cells (Reddy et al., 2021; Umbach et al., 2020). We investigated whether our dataset contains such Time Cells (TC) using a similar

method as employed by (Umbach et al., 2020). Due to the self-paced nature of our experiment, each encoding block varied in length. To accommodate this, we used both the unaltered block length, as well as a normalized block length within one recording session (see Methods). Of all 585 recorded cells, 12 (normalized) and 9 (non-normalized) fulfilled the criteria of TCs, which is below chance level (p values > 0.8; permutation test). Critically, there was no significant overlap between neurons that behaved like TCs and ESNs (p values > 0.8; permutation test) indicating that ESNs cannot be construed as TCs.

ESNs show a wider waveshape than other neurons

Another question is if ESNs are physiologically different from other single neurons. We found some evidence that spike waveshapes of ESNs are wider than those of other units (unpaired t-test; p = 0.019; Figure S3A), possibly indicating that ESNs are physiologically different from other single neurons. In the hippocampus, a wider waveshape has previously been associated with excitatory cells (Prestigio et al., 2019). There was no significant difference in the spike height or Fano factor between ESNs and other neurons (unpaired t-tests; all p values > 0.4; Figures S3B and S4).

Recorded neurons are mostly single neurons and not multi units

Although we tried to separate multi units into single neurons as best as possible during the spike sorting procedure, some units might still represent activity from multiple neurons. We thus employed the method outlined by Tankus and colleagues (Tankus et al., 2009) to classify units into single units and multi units, using the inter-spike interval and spike waveshape variability as objective criteria. In the first experiment, 518 out of 585 units (≙ 88.55%) were classified as single units (133/141 ESNs ≙ 94.32%), while in the second experiment 59 out of 86 units (≙

68.60%) were classified as single units (12/17 ESNs ≙ 70.59%). Thus, the vast majority (i.e., 91.77%) of the reported ESNs reflect putative single units.

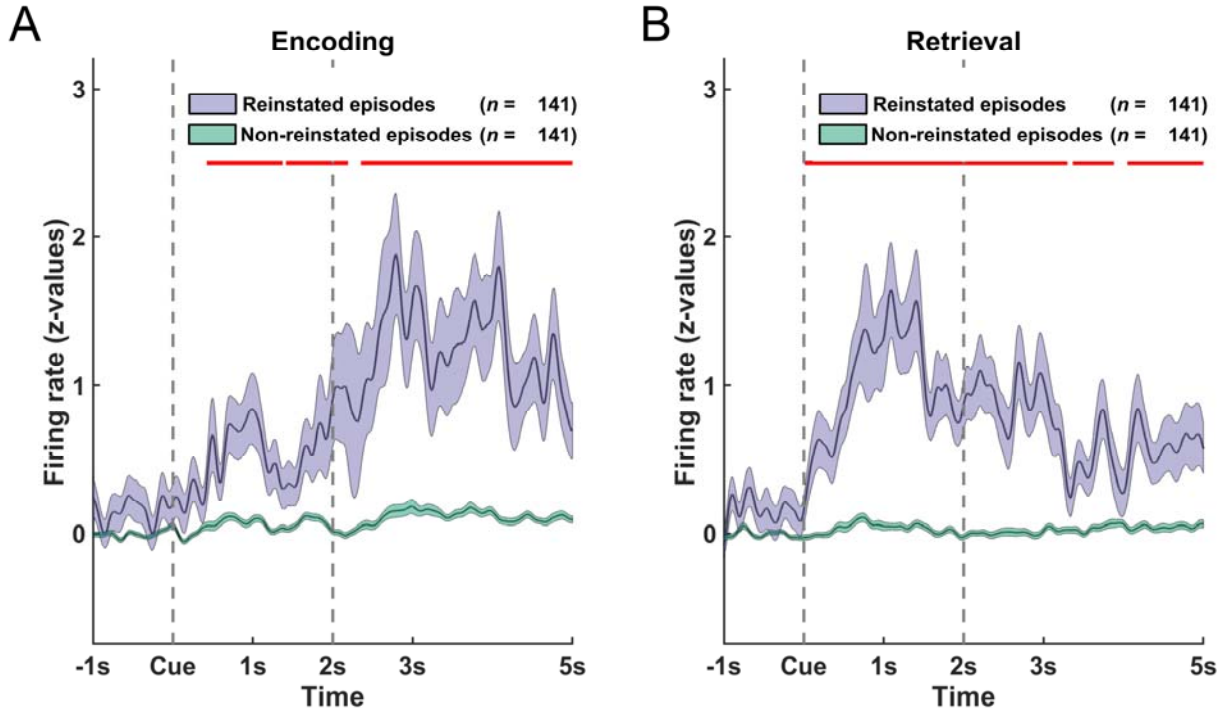

Figure 4. Firing rate of ESNs during reinstated (purple) and non-reinstated (green) episodes.

(A) Firing rate of ESNs from cue onset until five seconds later during memory encoding. The red line marks time points where the average ESN firing rate during reinstated episodes (n = 141) significantly exceeds the firing rate during average non-reinstated episodes (n =141; cluster permutation test; Maris and Oostenveld, 2007)).

(B) Same as (A) but for memory retrieval. The shaded areas indicate the SEM.

Discussion

Using an associative episodic memory paradigm in human epilepsy patients, we identified hippocampal neurons that are active during the initial encoding of a unique episode and later reinstate their firing rate when successfully remembering the same episode. The activity of these neurons could not be explained by a firing rate increase towards specific images or time points

and was dependent upon memory success. Therefore, we term these neurons Episode Specific Neurons (ESNs).

Previous studies have demonstrated that Concept Neurons increase their firing rate during memory retrieval when the image they are tuned to is part of the memory (Gelbard-Sagiv et al., 2008; Ison et al., 2015). We used three approaches to exclude that the ESNs we identified are Concept Neurons that selectively respond to visual elements or semantic concepts: (i) in experiment 1 we excluded ESNs that were visually responsive to the presentation of the animal cue at encoding. Moreover, we found a significant number of ESNs that reinstated at least one episode with two face associate images and at least one episode with two place associate images. These ESNs cannot be tuned to any specific stimulus (category) in the associate image because the associate stimuli belong to different categories (faces in one case and places in the other). (ii) We did not find a significant number of ESNs when limiting our analysis to later forgotten episodes and we found significantly fewer ESNs for later forgotten events than for later remembered events. This effectively rules out that ESNs are CNs tuned to the animal cue because the animal cue is presented independently of whether an event is later forgotten or remembered.

(iii) Following the episodic memory task in experiment 2 patients completed a visual tuning task using all stimuli presented previously. This is a standard method to identify putative Concept Neurons (Ison et al., 2015; Mormann et al., 2008; Mormann et al., 2011; Quiroga et al., 2005) and allowed us to exclude episodes where a neuron showed a visual tuning to either the cue or the associate image. Using this approach, we replicated our results from experiment 1 in a new sample of patients and found a significant number of ESNs while also verifying that these neurons do not selectively respond to visual elements or semantic concepts. Taken together these analyses reinforce the argument that ESNs are memory-related.

The existence of ESNs does not mean that CNs do not play a role in episodic memory processes. Concept Neurons might code the semantic aspect of an episode (i.e., the general concept "coffee shop"). According to the indexing theory Teyler and DiScenna, 1986; Teyler and Rudy, 2007, however, hippocampal neurons that perform this indexing function should have no initial tuning and are allocated to a specific episode (i.e., the coffee shop in a specific setting) during memory formation. The behaviour of ESNs would be consistent with such an indexing function and may add the crucial event-specific information to an episode, that CNs cannot encode themselves.

Time Cells (TC) are neurons that invariantly fire at specific, reoccurring time points (Reddy et al., 2021; Umbach et al., 2020). We did not find a significant number of TCs in our study and there was no significant overlap between TCs and ESNs. This might be because the self-paced nature of the task introduced too much time variation between too few learning blocks to uncover TC dynamics. However, the absence of TCs in our paradigm corroborates ESNs as independent from TCs.

We found that ESNs have a wider waveshape than other neurons. This suggests that ESNs are likely excitatory cells (Prestigio et al., 2019). Alternatively, it is possible that ESNs and single neurons with a narrower waveshape are located in different hippocampal subfields. Unfortunately, with the current methods, we lack the precision to designate neurons to individual subfields (Quiroga, 2019).

One limitation of the current study is that every event was encoded and retrieved only once. Arguably, a repeated design would have allowed for a more reliable ESN identification. However, each memory reactivation leads to a transient plasticity of the memory trace until it is reconsolidated again. During this time window profound changes in the neurons that code for the initial memory trace might occur (Nader & Hardt, 2009). To avoid this potential confound, every episode is learned and retrieved only once in the present experiments. The stability of ESNs over

repeated reactivations and extended time periods, therefore, remains an interesting topic of research for future studies.

Previous studies using fMRI have shown item-specific activity reinstatement in the hippocampus (Chadwick et al., 2010; Mack and Preston, 2016) where similar representations are associated with distinct activity patterns (Bakker et al., 2008; Berron et al., 2016). These findings are suggestive of an episode-specific neural code, which is consistent with our results. However, due to the coarse resolution of fMRI, these previous results cannot disambiguate whether this event-specific code is driven by event-specific concept neurons, or whether it is driven by event-specific indexing neurons. We here provide evidence for the latter.

Previous work has identified a multitude of different neurons that detect novelty, familiarity (Rutishauser et al., 2006; Rutishauser et al., 2008; Rutishauser et al., 2015) as well as episode boundaries and event onsets (Zheng et al., 2022). These cell types generally fired to many episodes, whereas the here identified ESNs largely coded a single episode (experiment 1: 117/141 ESNs ≙ 82.98%; experiment 2: 16/17 ESNs ≙ 94.12%). When quantifying neural firing reinstatement between scene encoding and recognition, recent work relied on population activity (i.e., considering the activity of all recorded neurons) (Zheng et al., 2022). In contrast, we showed here that neural reinstatement takes place on the level of a single neuron. Importantly, we expect that one episode was coded by an assembly of ESNs from which we have sampled only one due to the limited number of neurons that can be recorded with the currently available methods. These findings are in line with previous work showing that episodic memories in the hippocampus are coded in a sparse distributed way (Wixted et al., 2014; Wixted et al. 2018). Moreover, in the current study, the associated image was not shown on the screen during memory retrieval. This mental reinstatement is a core feature of episodic memory which is difficult to assess with recognition-based memory paradigms.

In conclusion, we found neurons in the hippocampus that show firing reinstatement in response to a specific conjunction of elements within a unique episode. These Episode Specific Neurons did not fire in response to individual concepts (Concept Neurons) or to specific, re-occurring time points (Time Cells). We propose that during memory formation an assembly of ESNs acts as a pointer or index that initially binds the elements of an episode together, in line with the indexing theory (Bowman and Wyble, 2007; Teyler and DiScenna, 1986; Teyler and Rudy, 2007). Reactivation of this pointer allows ESNs to reinstate the episodic memory previously encoded. Importantly, because ESNs reinstate unique episodes, they contain a time and content component. However, rather than reflecting the underlying coding mechanism, this time and content aspect necessarily emerges from the conjunctive code of an episode that is unique in content and time.

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The authors declare that they have no competing interests.

Data and materials availability:

Data and analysis code is currently available in a private repository on figshare and will be made publicly available upon publication.

Supplementary Materials

Materials and Methods

Figures S1 to S5

Tables S1 and S2