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Patterns of single-neuron activity during associative recognition memory in the human medial temporal lobe

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ABSTRACT

Electrophysiological activity in medial temporal lobe (MTL) structures is pivotal for declarative long-term memory. Single-neuron and microcircuit findings capitalizing on human microwire recordings from the medial temporal lobe are still fragmentary. In particular, it is an open question whether identical or different groups of neurons participate in different memory functions. Here, we investigated category-specific responses in the human MTL based on single-neuron recordings in presurgical epilepsy patients performing an associative long-term memory task. Additionally, auditory beat stimuli were presented during encoding and retrieval to modulate memory performance. We describe the proportion of neurons in amygdala, entorhinal cortex, hippocampus and parahippocampal cortex belonging to different response classes. These entail neurons coding stimulus-familiarity, neurons coding successful item memory, and neurons coding associated source memory, as well as the overlap between these classes. As major results we demonstrate that neurons responding to stimulus familiarity (old/new effect) can be identified in the MTL even when using previously known rather than entirely novel stimulus material (words). We observed a significant overlap between familiarity-related neurons and neurons coding item retrieval (remembered/forgotten effect). The largest fraction of familiarity-related neurons was found in the parahippocampal cortex, and a considerable fraction of all parahippocampal neurons was related to successful item retrieval. Neurons related to successful source retrieval were different from the neurons coding the associated information. Most importantly, there was no overlap between neurons coding item memory and those coding associated source memory strongly suggesting that these functions are facilitated by different sets of neurons.

1. Introduction

Declarative long-term memories crucially depend on electrophysiological activity in medial temporal lobe (MTL) structures (e.g. Eichenbaum, 2000; Rugg and Vilberg, 2013). Thanks to intracranial EEG recordings in presurgical epilepsy patients, system-level patterns accompanying successful memory encoding and retrieval have been well described in humans (e.g. Jacobs and Kahana, 2010; Fell and Axmacher, 2011). Recently, memory-related single-neuron and microcircuit patterns have also been reported capitalizing on human microwire recordings from the MTL (for reviews see e.g. Viskontas, 2008; Rutishauser, 2019). However, these findings are still fragmentary. In particular, it is not clear whether the same or distinct groups of neurons participate in different functions related to memory processing. Such knowledge would be very important, for instance, to understand the patterns of memory decline in aging and neurodegenerative diseases (e.g. Bowman and Dennis, 2015; Kapogiannis and El Haj, 2018).

There are basically two major approaches to investigate memory functions. The first is to contrast neural responses for new (firstly presented) versus old (repeatedly presented) items and identify neural correlates of familiarity processing (neurons with a significant contrast are henceforth referred to as familiarity-related neurons). The second is to differentiate neural responses for (subsequently) remembered versus forgotten items/associations during encoding or retrieval, respectively (neurons with a significant contrast are henceforth referred to as memory-related neurons). This approach identifies item and source memory-related processing in a narrow sense. Of course, familiarity processing and item memory-related processing are closely interrelated,

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since presence/absence of a memory signal is a prerequisite for identifying an item as old/new.

Most single-neuron investigations of memory functions in the MTL have focused on familiarity processing (e.g. Fried et al., 1997; Viskontas et al., 2006; Rutishauser et al., 2006, 2008; Wixted et al., 2014, 2018). In the human hippocampus, for old stimuli more neurons exhibited decreases in firing rate relative to baseline, but for new stimuli more neurons showed increases (Viskontas et al., 2006). Rutishauser and colleagues (2006, 2008) categorized neurons into novelty and familiarity detectors depending on whether their firing rate was higher for new versus old stimuli and vice versa, respectively. In the human hippocampus and amygdala, more novelty than familiarity neurons were detected (together about 1/4 of all recorded neurons in the hippocampus and 1/6 in the amygdala). However, Wixted et al. (2014) reported no evidence for neurons responding to stimulus novelty/familiarity and attributed this discrepancy to the fact that they used previously known concrete words as stimuli, whereas Rutishauser et al. (2006, 2008) presented previously unknown images. Therefore, the first goal of our study is to put the notion to the test that familiarity-related neurons cannot be identified in the MTL when using previously known stimulus material by using previously known words.

Up to now, few single-neuron studies have addressed firing rate characteristics related to successful vs. unsuccessful memory encoding and retrieval, i.e. memory-related processing in a narrow sense (e.g. Cameron et al., 2001; Rutishauser et al., 2008; Staresina et al., 2019). As expected, Rutishauser et al. (2008) found that during retrieval, firing rates increased for remembered versus forgotten stimuli (images) in familiarity neurons and decreased in novelty neurons. Moreover, they reported that successful vs. unsuccessful memory retrieval of associated source information (image location) was coded by the same familiarity/novelty neurons. Though not directly investigated by Rutishauser et al. (2008), this finding may be interpreted as implying that familiarity-based item memory and recollection-based source memory are facilitated by the same neurons. Consequently, the second aim of our study was to test whether neurons coding remembered vs. forgotten items (i.e., item memory-related neurons) and those coding remembered vs. forgotten associations (i.e., source memory-related neurons) are the same.

For this purpose, we investigated category-specific responses in the human MTL during an associative long-term memory task (Staresina et al., 2012) based on human single-neuron recordings. Patients were asked to memorize object words (item memory) and their associations with colors or scenes (source memory). The chosen paradigm is particularly suited to disentangle familiarity-based item recognition from recollection-based source recognition. Additionally, auditory beat stimuli were presented during encoding and retrieval to influence memory performance (Derner et al., 2018). Auditory beats are amplitude-modulated tones with modulation frequencies in the range of typical EEG rhythms. We used this brain stimulation technique as it is non-invasive, reversible and its impact on memory performance has been reported in several studies (for overviews, see Chaieb et al., 2015; Garcia-Argibay et al., 2019). In-depth analyses addressing the question as to whether the effects of beat-stimulation on firing rates are interrelated with memory performance, will be described in another report.

Following spike detection and sorting, units were categorized into different classes according to their response characteristics. These classes comprised, for instance, units showing firing rate changes after stimulus presentation during encoding (stimulus-responsive units), units responding differentially to novel versus familiar stimuli (familiarity-related units) or units exhibiting different firing rates for remembered vs. forgotten items or associations (memory-related units). Next, we determined the proportions of units belonging to these classes within different MTL regions (Mormann et al., 2008). Finally, we evaluated whether these classes overlapped above chance level.

2. Material and methods

2.1. Participants

Recordings from five presurgical epilepsy patients (3 female (age: 26/42/47 years), 2 male (age: 36/48 years), mean age: 40 ± 9 years) with implanted microwires were analyzed. These patients represent a subset of a group of 13 patients (microwires had only been implanted in this subset), for whom results from macro-electrode recordings were previously reported (Derner et al., 2018). All patients gave informed written consent. The study was conducted according to the Declaration of Helsinki, and was approved by the ethics committee of the Medical Faculty of the University of Bonn.

2.2. Experimental paradigm

Subjects were asked to perform an associative memory task (see Fig. 1) as previously described (e.g. Staresina et al., 2012). During the encoding phase of the task, 50 German nouns (per run; on each run different nouns) were presented together with a color patch (red/blue) or a scene image (office/nature; one office and one nature image used throughout the experiment) for 3.5 s each. Presentation of red and blue patches (color runs) or office and nature images (scene runs) randomly alternated across trials. During a jittered inter-trial interval of 700–1300 ms (mean=1000 ms) a fixation cross was presented. Subjects were asked to indicate with a button press whether the association between the color/scene and noun was plausible or not, i.e., whether it was possible for this word/color or word/scene combination to exist in real life/nature or not. The retrieval phase started after a 1-minute break. The 50 nouns previously presented during the encoding phase were shown together with 25 previously unstudied nouns. The response options were 1) “new”, 2) the two possible color/scene sources (indicating an “old” response with source memory) and 3) a question mark (indicating an “old” response without source memory). Each response trial was displayed for a maximum of 5 sec. In each experimental run only one source category (color or scene) was used.

In addition, auditory beat stimuli (the term “beat” refers to the interference of two tones with close frequencies) or a control tone were presented to the subjects across six experimental runs, either during the encoding phase (for color source runs only) or the retrieval phase (for scene source runs only) (see also Derner et al., 2018). The stimulation conditions were: binaural beats (5 Hz), monaural beats (5 Hz), control tone (220 Hz – no beat). Beat stimulation was presented at stimulus onset for the duration of each trial (encoding: 3.5 s, retrieval: 5 s). Auditory beats were composed of two sine waves with frequencies of 217.5 Hz and 222.5 Hz. Monaural beats resulting from the physical superposition of the two sine waves were presented to both ears simultaneously. In the case of binaural beats, one sine wave (e.g. 217.5 Hz) was presented to one ear, while the other sine wave (e.g. 222.5 Hz) was presented to the opposite ear. Each of the five subjects completed six runs each comprising 50 encoding trials and 75 retrieval trials (i.e. 300 encoding and 450 retrieval trials per subject). The order of beat stimulation conditions across the six runs had been counterbalanced within the original group of 13 patients.

2.3. Data recording and preprocessing

Action potential recordings were obtained from a bundle of nine microwires (eight high-impedance recording electrodes, one low-impedance reference, AdTech, Racine, WI) protruding from the end of each depth electrode targeting hippocampus, entorhinal cortex, amygdala and parahippocampal cortex. The differential signal from the microwires was amplified using a Neuralynx ATLAS system (Bozeman, MT), filtered between 0.1 and 9000 Hz, and sampled at 32 kHz. These recordings were stored digitally for further analysis. The num-

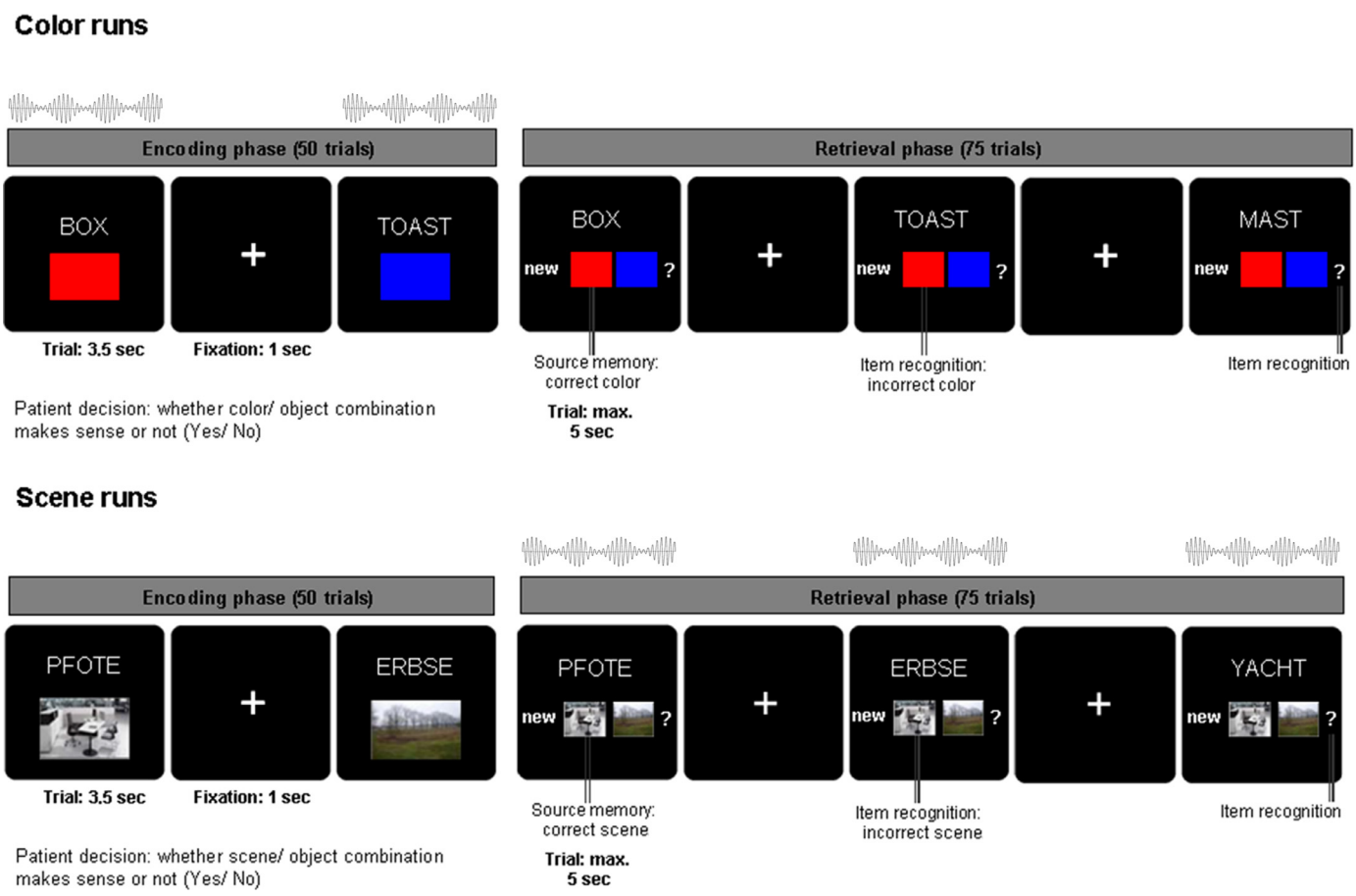

Fig. 1. Experimental paradigm: Schematic depiction of the associative memory paradigm and the beat stimulation interventions (see also Derner et al., 2018). During the encoding phase, 50 German nouns (per run) were presented together with a color patch (red/blue) or a scene image (office/nature). Subjects were asked to indicate with a button press whether the association between the color/scene and noun was plausible or not. During the retrieval phase, the 50 nouns previously presented were shown together with 25 previously unstudied nouns. The response options were 1) "new", 2) the two possible color/scene sources (indicating an "old" response with source memory) and 3) a question mark (indicating an "old" response without source memory). Across six experimental runs, auditory beat stimuli or a control tone were presented to the subjects either during the encoding phase (for color source runs only) or the retrieval phase (for scene source runs only). The stimulation conditions were: binaural beats (5 Hz), monaural beats (5 Hz), control tone (220 Hz – no beat) (for more information, see Methods).

ber of recording microwires per patient ranged from 80 to 96. Signals were band-pass filtered between 300 and 3000 Hz. Spike detection and sorting was performed using the Combinato software package (Niediek et al., 2016). After automated sorting using standard parameters, clusters in every channel were manually adjusted based on cluster shape, cross correlograms, and other features provided by the Combinato package. Sorted units were classified as single units, multi-units, or artifacts based on spike shape and variance, ratio between spike peak value and noise level, the inter-spike interval distribution of each cluster, and presence of a refractory period for the single units (Mormann et al., 2011).

Anatomical localization of microwires was determined based on the post-implantation CT scan co-registered to the pre-implantation MRI scan, both normalized to MNI space with SPM12. In detail, first the end of the corresponding depth electrode was visually identified. Then, microwire loci were inferred from a 3-mm-radius sphere placed 4 mm medial to the electrode tip (Staresina et al., 2019). Anatomical regions within the MTL were delineated visually according to segmentation protocols described by Insausti et al. (1998) and Pruessner et al. (2000, 2002). Only data from microwires unambiguously localized within amygdala, hippocampus, entorhinal cortex, or parahippocampal cortex were kept for further analysis.

Please note that pooling neurons across subjects for statistical analysis is common practice in the field of human extracellular in vivo recordings. While it would be desirable to also account for subject-related variance, the numbers of units recorded in this and other studies simply do not warrant this approach.

2.4. Evaluation of firing rates

Firing rates for each trial were calculated for non-overlapping 500 ms intervals from −500 ms to 2000 ms relative to stimulus onset. Only units with a minimal average firing rate of 2 Hz across trials in at least one interval in one of the three stimulation conditions (in encoding or retrieval) were kept for further analysis, leaving 180 units (95 single units, 85 multi units) from four brain regions (49 in the amygdala (27%), 32 in the hippocampus (18%), 63 in entorhinal cortex (35%), 36 in parahippocampal cortex (20%)).

All tests were performed across the three stimulation conditions (binaural beat/monaural beat/control tone) except for the test for differences between stimulation conditions. The following nonparametric tests were used for data analysis: Wilcoxon signed rank test (paired; for pre- vs. post-stimulus intervals), Wilcoxon rank-sum test (unpaired; old vs. new words; remembered vs. forgotten items/associations; see below), Kruskal-Wallis test for comparison of three groups (binaural beat vs. monaural beat vs. control). We chose non-parametric tests because firing rates in networks of cortical neurons are typically not normally distributed (e.g. Roxin et al., 2011).

More specifically, tests were conducted for each neuron and each of the four post-stimulus intervals. To account for multiple testing, results were Bonferroni-corrected with 4 (considered significant if $p<=0.0125$). A statistical contrast for the firing rates of a unit was considered significant if at least one interval showed significance after Bonferroni correction. Binomial tests with probability 0.05 (corresponding to the alpha level of 5%) were conducted to test if the number of units showing a significant contrast were significantly higher than expected by chance. Please note that throughout the results section p-values for binomial tests are reported independently of whether they are statistically significant or non-significant.

Further to this, the same test statistics were calculated for average firing rates across the entire 0–2 s interval to see if effects could be confirmed. All group statistics that were significant based on testing the 500 ms intervals remained significant when testing based on the 2 s interval.

2.5. Classification of units

Based on different statistical contrasts, units were categorized into the following classes:

Stimulus-responsive units: different firing rates post-stimulus vs. pre-stimulus during the encoding phase.

Familiarity-related units: different firing rates for correctly recognized old vs. new words during the retrieval phase. These units were further categorized into the following sub-classes:

a) *Familiarity units*: higher firing rates for old vs. new words.
b) *Novelty units*: higher firing rates for new vs. old words.

Furthermore, we identified units with different firing rates for old vs. new words independent of the subjects' decisions (i.e. regardless of whether words were correctly classified or misclassified). Additionally, we determined units with different firing rates depending on the subjects' behavioral responses (i.e. different firing rates for old vs. new decisions).

Memory-encoding-related units: different firing rates during the encoding phase for subsequently remembered vs. forgotten items or associations (subsequent item memory effect: hits vs. misses; subsequent source memory effect: correct vs. incorrect or unsure responses).

Memory-retrieval-related units: different firing rates during the retrieval phase for remembered vs. forgotten items or associations (item memory effect: hits vs. misses; source memory effect: correct vs. incorrect or unsure responses).

Furthermore, the following response categories were evaluated:

Units specifically responding to the associative stimulus: different firing rates for blue vs. red color associations or for indoor vs. outdoor scene associations during the encoding phase.

Units specifically responding to the auditory beat stimulation conditions: different firing rates for 5 Hz monaural vs. 5 Hz binaural vs. control stimulation.

2.6. Overlap between different classes of units

Finally, the subgroups of units that were found in combinations of the prior classes were analyzed. Here a binomial test was conducted to determine if the number of units that showed an overlap between two classes was higher than expected by chance based on the combination of their portions in the whole dataset. The probability for the binomial test was calculated accordingly as portion_class1*portion_class2 (instead of 5% for single classes).

2.7. Data and code availability

In accordance with the ethics approval given by the ethics committee of the Medical Faculty of the University of Bonn and the guidelines of the German Research Foundation, pooled spiking data and program code have been made publicly available to researchers on the Github Online Repository (https://github.com/LeilaChaieb/Fell_Workspace). Further queries should be directly addressed to the corresponding author via email.

3. Results

3.1. Behavioral data

Across the group of five subjects the percentage of hits (correct old decisions) for color/scene runs was: 86/83% ± 5/4% (mean ± *s*.e.m). The percentage of false alarms (old decisions in case of new words) was: 19/19% ± 5/4%. The probability measure hits minus false alarms revealed that item recognition memory was significantly above chance (0): 67/64% ± 4/6% (effect sizes Cohen's d: 7.88/4.91; individual values: 81/85, 62/56, 69/63, 63/51, 59/65%; T-tests: $p = 0.00006/0.0004$, $t_4=17.62/10.99$; Wilcoxon signed rank tests: each $p = 0.065$; please note that the p-value of 0.065 is the lowest possible value for a two-tailed Wilcoxon test on 5 paired values). In turn, the percentages of correct, incorrect and unsure source decisions were: 63/68% ± 3/6%, 24/23% ± 7/8% and 12/9% ± 6/5%, respectively. Probability for source recognition (correct minus incorrect source decisions) was also significantly above chance (0): 39/45% ± 8/13% (effect sizes Cohen's d: 2.09/1.51; individual values: 46/81, 9/5, 43/53, 37/26, 60/60%; T-tests: $p = 0.009/0.028$, $t_4=4.68/3.37$; Wilcoxon signed rank tests: each $p = 0.065$).

3.2. Stimulus-responsive units

Application of a two-sided Wilcoxon signed rank test indicated 95 of 180 units (53%) with significantly different firing rates in pre- vs. post-stimulus intervals (most frequent interval: 500–1000 ms) during the encoding phase, which is significantly higher than the number of units expected by chance (binomial test $p = 2.34e-73$; the scientific notation "e-n" stands for "10^{-n}"; see Table 1, Fig. 2 and Supplementary Data Fig. 2). In 59% of these 95 units, firing rates increased during the post-stimulus compared to the pre-stimulus interval. In 44% of these units, firing rates decreased during the post-stimulus interval (one entorhinal unit first showed a higher, then a lower firing rate and two parahippocampal units first showed a lower, then a higher firing rate after stimulus onset).

Stimulus-responsive units were most abundant in the parahippocampal cortex (81% of all parahippocampal units; firing rate increase: 23; decrease 8). These neurons were detected in smaller proportions in the amygdala (51%; increase: 19; decrease: 6), hippocampus (47%; increase: 6; decrease: 9), and entorhinal cortex (41%; increase: 8; decrease: 19) (binomial test: all p-values < 7.64e-12). Hence, the majority of units in amygdala and parahippocampal cortex showed stimulus-related firing rate increases, whereas the majority of units in hippocampus and entorhinal cortex showed firing rate decreases.

3.3. Familiarity-related units

A two-sided Wilcoxon rank-sum test indicated 37 of 180 units (21%) with significantly different firing rates for correctly recognized old vs. new words (i.e. words shown for the second vs. words shown for the first time) in retrieval trials, which is significantly more than expected by chance (binomial test $p = 2.24e-13$, most frequent interval: 1000–1500 ms; Fig. 2 and Supplementary Data Fig. 2). In 49% of these 37 units firing rates were higher for old words (familiarity units, fam; p_binomial=0.0042). In the remaining 51%, trials with new words showed higher firing rates (novelty units, nov; $p = 0.0018$). The largest proportion of familiarity-related units was found in the parahippocampal cortex (44%; 8 fam, 8 nov; $p = 4.26e-12$) followed by hippocampus (25%; 5 fam, 3 nov; $p = 1.39e-4$), entorhinal cortex (14%; 2 fam, 7 nov: $p = 0.004$) and amygdala (8%; 3 fam, 1 nov; $p = 0.23$).

Table 1
Distribution of units in different brain regions: Number of units belonging to different classes detected in amygdala, hippocampus, entorhinal cortex and parahippocampal cortex. Percentage values refer to the total number of units in these brain regions.

	Number of units	Amygdala	Hippocampus	Entorhinal cortex	Parahippocampal cortex
Total	180	49	32	63	36
Stimulus-responsive	95	25 (51%)	15 (47%)	26 (41%)	29 (81%)
Familiarity-related	37	4 (8%)	8 (25%)	9 (14%)	16 (44%)
Memory-retrieval item	26	5 (10%)	4 (13%)	9 (14%)	8 (22%)
Memory-retrieval source	15	7 (14%)	2 (6%)	6 (10%)	0 (0%)
Associative stimulus	41	6 (12%)	6 (19%)	10 (30%)	19 (53%)
Auditory beat stimulus	83	29 (59%)	13 (41%)	26 (41%)	15 (42%)

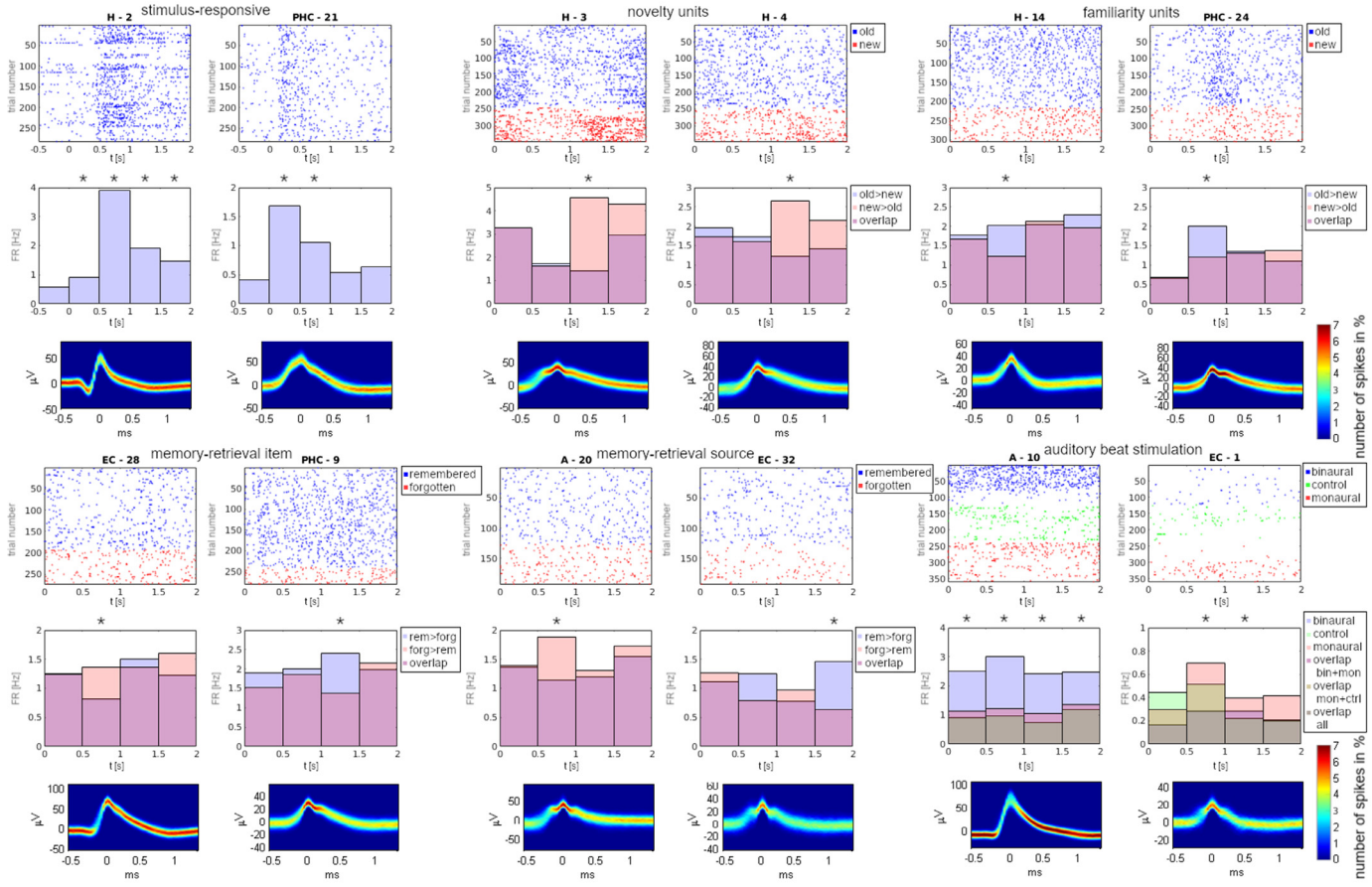

Fig. 2. Examples of units from different classes: Two example units from the classes of stimulus-responsive, novelty, familiarity, item-retrieval-related, source-retrieval-related and auditory beat stimulus-related units are shown (units are denoted by a letter (H: hippocampus, PHC: parahippocampal cortex, EC: entorhinal cortex, A: amygdala) and a consecutive number). Top: raster plots of spike times relative to stimulus onset for the conditions which were compared (see Methods). Novelty and familiarity units: old words (blue), new words (red); retrieval-related units: remembered (blue), forgotten (red); beat stimulus-related units: monaural beats (red), binaural beats (blue), control (green). Middle: Histograms of average firing rates within consecutive 500 ms windows (stimulus onset at $t = 0$). Nonparametric tests were conducted for each of the four post-stimulus intervals (Bonferroni-corrected $p<0.0125$; Wilcoxon signed rank test (paired) for pre- vs. post-stimulus intervals; Kruskal-Wallis test for binaural beat vs. monaural beat vs. control; Wilcoxon rank-sum test (unpaired) for all other comparisons). Asterisks denote significant time windows. Old vs. new /remembered (rem) vs. forgotten (forg): overlap (purple), increase (blue), decrease (red). Monaural (mon) vs. binaural (bin) vs. control (ctrl): highest firing rate for binaural (blue), for monaural (red) or control (green), overlap binaural and monaural (purple), monaural and control (light brown), binaural, monaural and control (brown). Bottom: Density plots of all spike waveforms. The plots show 2-dimensional histograms of spike voltages over time. The color code depicts the percentage of spikes (denominator: all spikes recorded for this unit) with the specified voltage at the given time point.

Average firing rates collapsed across all familiarity-related units are shown in Fig. 3 (firing rates for novelty units inverted; see also Fig. 4 in Rutishauser et al., 2008). Firing rates numerically decrease from correctly recognized old words with correct source memory (*R*+) to correctly recognized old words without source memory (R-) to correctly recognized new words (true negatives, TN) (see legend of Fig. 3 for statistical tests). Firing rates for wrongly classified old words (false negatives, FN) are smaller than for correctly recognized old words (*R*+,R-) (Wilcoxon test, $p < 0.0016$) and firing rates for wrongly classified new words (false positives, FP) are larger than firing rates for correctly classified new words (TN) ($p = 0.0024$).

Because of a statistically significant overlap between familiarity-related and item retrieval-related units (see Section 3.9.), we additionally evaluated average firing rates for the eleven units belonging to both classes. These units were found in three of five subjects and were located in parahippocampal cortex (7), entorhinal cortex (2) and amyg-

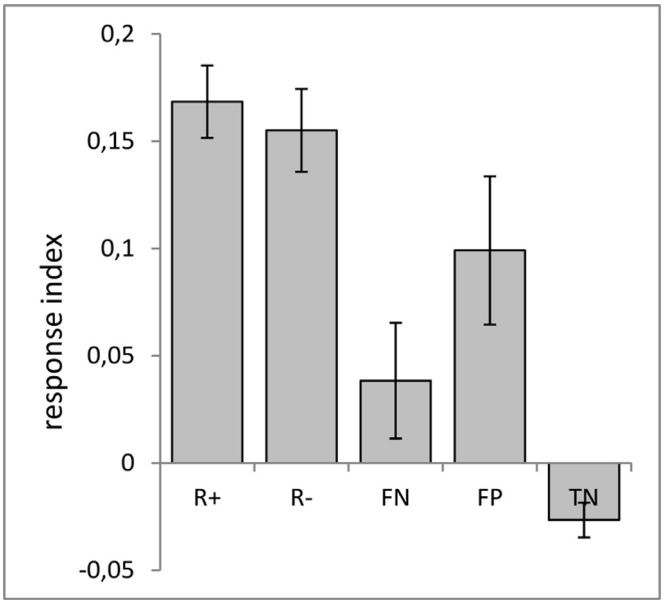

Fig. 3. Response pattern of familiarity-related units: Average normalized firing rates (averaged over mean firing rates within the 500 ms intervals) across all familiarity-related units are depicted for correctly recognized old words with correct source memory (*R+*), correctly recognized old words without source memory (R-), wrongly classified old words (false negatives, FN), wrongly classified new words (false positives, FP) and correctly recognized new words (true negatives, TN). The response index (arbitrary units) was calculated by dividing all firing rates through baseline firing rates, and subtracting average firing rates for new words. Moreover, the resulting values were multiplied by −1 for novelty units (see Rutishauser et al., 2008). Error bars depict standard error of the mean. Statistically significant differences (Wilcoxon tests, $p < 0.05$): *R+* vs. FN ($p = 5.1e\text{-}4$), R- vs. FN ($p = 0.002$), *R+* vs. FP ($p = 0.013$), R- vs. FP ($p = 0.024$), *R+* vs. TN ($p = 1.1e\text{-}7$), R- vs. TN ($p = 2.8e\text{-}7$), FN vs. TN ($p = 0.009$), FP vs. TN ($p = 0.002$).

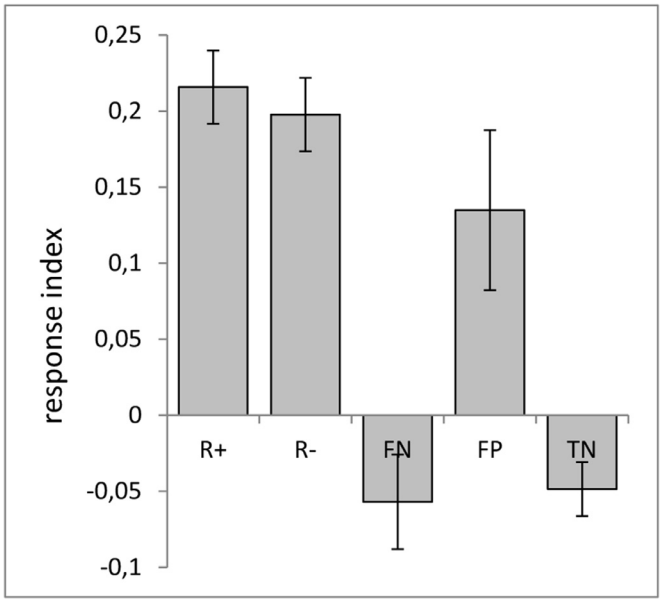

Fig. 4. Response pattern of units being both familiarity-related and item retrieval-related: Average normalized firing rates (averaged over mean firing rates within the 500 ms intervals) across all familiarity-related units are depicted for correctly recognized old words with correct source memory (*R+*), correctly recognized old words without source memory (R-), wrongly classified old words (false negatives, FN), wrongly classified new words (false positives, FP) and correctly recognized new words (true negatives, TN). The response index (arbitrary units) was calculated by dividing all firing rates through baseline firing rates, and subtracting average firing rates for new words. Moreover, the resulting values were multiplied by −1 for novelty units (see Rutishauser et al., 2008). Error bars depict standard error of the mean. Statistically significant differences (Wilcoxon tests, $p < 0.05$): *R+* vs. FN ($p = 0.002$), R- vs. FN ($p = 0.001$), *R+* vs. TN ($p = 0.001$), R- vs. TN ($p = 0.001$), FN vs. FP ($p = 0.019$), FP vs. TN ($p = 0.024$).

dala (2). Their firing pattern appears similar to the firing pattern of all familiarity-related units with one exception (see Fig. 4). Across all familiarity-related units firing rates for wrongly classified old words (FN) are larger than for correctly classified new words (TN) (Wilcoxon test, $p = 0.0089$). In contrast, for the units being both familiarity-related and item retrieval-related, average firing rates for wrongly classified old words (FN) are numerically close-by and do not statistically differ from firing rates for correctly classified new words (TN). Moreover, firing rates for wrongly classified old words (FN) significantly differ from firing rates for wrongly classified new words (FP) in these units (Wilcoxon test, $p = 0.019$), which is not the case for all familiarity-related units. Hence, firing rates for units being both familiarity-related and item retrieval-related seem to more closely mirror subjects' decisions (FN, TN: "new" responses; FN, FP: "new" vs. "old" response) than firing rates of all familiarity-related units.

3.4. Classification of old/new responses dependent and independent of the subjects' decisions

Independent of the subjects' decisions, 32 units of all units (17%) showed different firing rates for old vs. new words (15 old>new, 17 new>old; $p = 4.58e\text{-}10$). These units were most common in the parahippocampal cortex (33%; 6 old>new, 6 new>old; $p = 9.87e\text{-}8$), followed by the hippocampus (28%; 4 old>new, 5 new>old; $p = 1.91e\text{-}5$), amygdala (10%; 3 old>new, 2 new>old; $p = 0.097$) and entorhinal cortex (10%; 2 old>new, 4 new>old; $p = 0.095$).

Based on the behavioral responses, we found that 42 units of the total number (18%; $p = 4.76e\text{-}17$) showed different firing rates for words that were classified as old vs. new. Of these, 25 units also showed different firing rates for old vs. new words independent of the subjects' decisions ($p = 1.4255e\text{-}7$). In 19 of 42 (45%) units firing rates were higher for words classified as old (familiarity units), in the remaining 55% words classified as new showed higher firing rates (novelty units). Again, the largest proportion was located in the parahippocampal cortex (50%; 9 fam, 9 nov, $p = 1.45e\text{-}14$), followed by hippocampus (28%; 5 fam, 4 nov, $p = 1.91e\text{-}5$), entorhinal cortex (17%; 2 fam, 9 nov, $p = 2.68e\text{-}4$) and amygdala (8%; 3 fam, 1 nov, $p = 0.229$). Thus, about one third more units showed different firing rates based on the subjects' familiarity decisions compared to based on old/new stimulus properties.

3.5. Memory-encoding-related units

Firing rates during encoding trials were compared for subsequently remembered vs. forgotten words (hits vs. misses), i.e. with regard to item memory, using a two-sided Wilcoxon rank-sum test. 9 units of all units (5%) showed significant differences for subsequent item memory (most frequent time window: 0–500 ms), which is not more than the number of units expected by chance (binomial test: $p = 0.548$).

Moreover, subsequent memory was tested for source associations (correct vs. incorrect or unsure responses). 13 units of the total number (7%) showed significant differences for subsequent source memory (most frequent time window: 500–1000 ms). Again, this number was not significantly higher than expected by chance ($p = 0.119$).

3.6. Memory-retrieval-related units

Similar to the search for memory-encoding-related units, firing rates during retrieval trials were compared for successful vs. unsuccessful item and source memory using a two-sided Wilcoxon rank-sum test.

26 units of all units (14%) showed significant differences between firing rates for remembered vs. forgotten words, which is significantly more than expected by chance (binomial test $p = 1.26e\text{-}6$, most frequent time window: 1500–2000 ms; Fig. 2 and Supplementary Data Fig. 2). In 31% of these 26 units firing rates were higher for remembered compared to forgotten words, whereas in the remaining 69% firing rates were lower. These units were most abundant in the parahippocampal cortex (22%; higher: 3, lower: 5, $p = 3.35e\text{-}4$), followed by entorhinal cortex (14%; higher: 2, lower: 7, $p = 0.004$), hippocampus (13%; higher: 1, lower: 3, $p = 0.074$) and amygdala (10%; higher: 2, lower: 3, $p = 0.097$).

15 units of the total number (8%) showed significant differences for source memory (most frequent time window: 500–1000 ms). These units were most common in amygdala (14%; higher: 3, lower: 4, $p = 0.011$), followed by entorhinal cortex (10%; higher: 3, lower: 3, $p = 0.095$) and hippocampus (6%; higher: 1, lower: 1, $p = 0.48$). Across all three regions, this is significantly more than the number of units expected by chance ($p = 0.037$).

3.7. Units specifically responding to the associative stimulus

In encoding trials, firing rates for different associated colors (blue vs. red) or associated scenes (indoor vs. outdoor) were compared using a two-sided Wilcoxon rank-sum test. 12 units of all units (7%) showed significant differences between firing rates for red vs. blue associations (p(color) = 0.192, most frequent time windows: 0–500 ms and 1000–1500 ms) and 32 units of the total number (18%) showed significant differences between firing rates for indoor vs. outdoor associations (p(scene)=4.58e-10, most frequent time window: 500–1000 ms). Overall, 23% of all units responded to associative stimuli (3 units specifically responded to both color and scene associations), which is significantly more than expected by chance (binomial test (probability 10%) $p = 4.27e\text{-}7$; Supplementary Data Figs. 1 and 3).

The largest proportion of associative, stimulus-specific units were found in the parahippocampal cortex (53%; 6 color, 16 scene, $p = 1.58e\text{-}10$, p(color)=0.008, p(scene)=4.26e-12), followed by entorhinal cortex (30%; 2 color, 8 scene, $p = 9.48e\text{-}2$, p(color)=0.83, p(scene)=0.013), hippocampus (19%; 2 color, 4 scene, $p = 0.094$, p(color)=0.48, p(scene)=0.074) and amygdala (12%; 2 color, 4 scene, $p = 0.365$, p(color)=0.71, p(scene)=0.229).

3.8. Units specifically responding to auditory beat stimulation conditions

Here, we compared firing rates between the three different beat stimulation conditions (binaural beat, monaural beat, control). To evaluate the effect of stimulation, trials with the same stimulation were collapsed across encoding (color runs) and retrieval phases (scene runs). A Kruskal-Wallis test was conducted to identify differences between the three stimulation conditions.

83 units of all units (46%) showed significant modulation of firing rates by different stimulation conditions (binomial test $p = 4.02e\text{-}58$, most frequent time window: 500–1000 ms, Fig. 2 and Supplementary Data Fig. 2).

These units were most abundant in amygdala (59%, 29 units), followed by parahippocampal cortex (42%, 15 units), entorhinal cortex (41%, 26 units) and hippocampus (41%, 13 units) (binomial test all p-values < 1.72e-9).

3.9. Overlap between different classes of units

Finally, we identified units that were simultaneously assigned to two of the above defined classes (see Table 2). Encoding-related units were excluded from this analysis since their number did not exceed chance level.

Firstly, there were 26 units that were both stimulus-responsive and familiarity-related. The binomial test showed a trend ($p = 0.08$) that could be confirmed when testing across the whole 2 s interval ($p = 0.091$). Thus, a large majority (70%) of the familiarity-related units were also stimulus-responsive. The overlap between stimulus-responsive and memory-retrieval related units (item or source) was below chance level (each $p \geq 0.145$).

Secondly, a significant number of 11 units were found to be familiarity-related and showed an item memory effect in retrieval trials ($p = 0.019$). Three of these units were familiarity neurons. As expected, these units exhibited higher firing rates for remembered vs. forgotten items during retrieval ($p = 0.047$). The other eight units were novelty neurons and showed higher firing rates for forgotten vs. remembered items during retrieval ($p = 0.0007$). Contrary to this, there was an overlap of only 2 units between familiarity-related units and units that showed a source memory effect in retrieval trials ($p = 0.816$). Most importantly, there was no overlap between item and source retrieval-related units ($p = 1$).

Thirdly, there were 29 units that specifically responded to associative stimuli and were also stimulus-responsive ($p = 0.062$), 24 of which were units specifically responding to associative scene stimuli ($p = 0.051$), while 8 responded to associative color stimuli ($p = 0.301$). Moreover, 13 associative, stimulus-specific units were also familiarity-related ($p = 0.082$), 12 of which were units specifically responding to associative scene stimuli ($p = 0.034$) while 2 responded to associative color stimuli ($p = 0.708$). The units specifically responding to associative stimuli did not overlap with a significant number of retrieval-related units (item: $p = 0.243$; source: $p = 0.858$).

Finally, the overlap between units modulated by the auditory stimulation condition and units responsive to visual stimuli was below chance level (46 overlapping units; $p = 0.379$). Moreover, units modulated by the auditory stimulation condition did not overlap with a significant number of units from the other classes (familiarity-related units, memory-retrieval-related units, units specifically responding to associative stimuli, all $p \geq 0.314$).

4. Discussion

In the present study, we investigated single-neuron responses in the human MTL during an associative long-term memory task. Most importantly, we report that different sets of neurons supported successful item and source memory retrieval. Furthermore, neurons coding stimulus familiarity could be detected using previously known stimulus material. These and further results are discussed below.

While Rutishauser and colleagues (2006, 2008) reported clear evidence for novelty and familiarity neurons in the human hippocampus and amygdala using previously unknown images as stimuli, Wixted and colleagues (2014) found no such evidence using previously known words as stimuli. However, on the level of population activity they reported significantly increased average firing rates for repeatedly vs. newly presented items in human hippocampus. Here, we describe evidence for novelty and familiarity neurons in the human MTL, which is in line with Rutishauser et al. (2006, 2008), but differs from Wixted et al. (2014) in spite of similar stimulus material. A likely reason for this discrepancy is a difference in statistical power since we used 75 stimuli (50/25 presented twice/once) during each of six experimental blocks yielding 450 stimuli in total, whereas Wixted et al. (2014) only used a total of 64 stimuli (32/32 presented twice/once). In addition, the average response pattern of familiarity-related neurons (see Fig. 3) for our stimulus material is in accordance with the results of

Table 2
Overlap between different classes of units: The header column and row depict the number of units belonging to each individual class. The cells of the table depict the numbers of units belonging to two classes. P-values specify statistical significance of the overlaps calculated using a binomial test (see Methods). Note that there is only one case of statistically significant overlap between classes, i.e. between familiarity-related and item retrieval-related units, and that there is no overlap at all between item and source retrieval-related units (for more information, see Results).

	Stimulus-responsive (95)	Familiarity-related (37)	Memory-retrieval item (26)	Memory-retrieval source (15)	Associative stimulus (41)	Auditory beat stimulus (83)
Stimulus-responsive (95)		26, $p = 0.080$	18, $p = 0.145$	3, $p = 0.987$	29, $p = 0.062$	46, $p = 0.379$
Familiarity-related (37)			11, $p = 0.019$	2, $p = 0.816$	13, $p = 0.082$	17, $p = 0.543$
Memory-retrieval item (26)				0, $p = 1$	8, $p = 0.243$	14, $p = 0.314$
Memory-retrieval source (15)					2, $p = 0.858$	6, $p = 0.693$
Associative stimulus (41)						19, $p = 0.527$

Rutishauser et al. (2008). As a minor difference, responses for correct versus incorrect source memory retrieval differed significantly in Rutishauser et al. (2008), but not in our data. Taken together, our findings suggest that neurons responding to stimulus familiarity can be identified in the MTL even when using previously known stimulus material.

It should be noted that our microwires did not target the perirhinal cortex, which has been suggested to specifically play a role in familiarity processing (e.g. Eichenbaum et al., 2007). Remarkably, the largest fraction of familiarity-related neurons was found in the parahippocampal cortex, a region not covered by the studies of Rutishauser et al. (2008) or Wixted et al. (2014). Moreover, about one third more units exhibited different firing rates depending on the subjects' familiarity decisions versus depending on old/new stimulus properties. This finding corroborates the idea that the observed familiarity-related firing patterns are related to memory processing and do not just reflect differences due to stimulus repetition.

Going beyond the scope of familiarity processing, we were able to identify a statistically significant number of neurons coding successful versus unsuccessful memory retrieval. Interestingly, a considerable fraction of all neurons recorded from parahippocampal cortex (22%) were related to successful item retrieval (compared to 13% from the hippocampus). This finding may appear counterintuitive since the parahippocampal cortex is mainly known for its role in the processing of contextual information, both spatial or non-spatial (e.g. Bar and Aminoff, 2003; Eichenbaum et al., 2007; Diana, 2017). Indeed, we also identified a large fraction of parahippocampal neurons (53%) showing different firing rates for the specifically associated color or scene information (Mormann et al., 2017). Diana et al. (2013) reported that activity within the parahippocampal cortex predicted successful item memory for words, when the word was presented with the same context during encoding and retrieval (but not in case of a different context). This suggests that the parahippocampal cortex also plays a role in successful item retrieval when the item context does not change, and is to some extent in line with our observation.

Regarding the question whether neurons simultaneously belong to different categories, we found a trend for an overlap between the classes of stimulus-responsive and familiarity-related neurons, as well as a significant overlap between familiarity-related and item-retrieval related neurons. This overlap was expected since novelty detection and memory retrieval of the word stimuli are closely interrelated functions (presence/absence of a memory is a prerequisite for identifying an item as old/new). There was no significant overlap between neurons specifically responding to the different auditory beat stimuli and any other category, probably because all other categories were related to the processing of visual information. It should be noted, of course, that non-significant p-values indicate failed rejection of the null hypothesis of non-overlapping categories, but cannot prove it. Interestingly, neurons responding to the auditory stimuli were most often detected in amygdala, which may be related to the fact that among the putative applications of beat stimulation most consistently effects on anxiety have been reported (e.g. Chaieb et al., 2015; Garcia-Argibay et al., 2019). The amygdala has also found to be involved in the processing of musical dissonance and musical tension (Koelsch, 2014). In line with previous studies (Mormann et al., 2008, 2017; Quian Quiroga et al., 2009), the highest portion of neurons responding to the visual stimuli was found in parahippocampal cortex.

Further to this, we observed a trend for an overlap between neurons coding the associative stimulus (blue vs. red; indoor vs. outdoor) and familiarity-related neurons. As a speculative interpretation, associative-stimulus-related neurons may interact with neurons responding to the word stimuli during the encoding phase, such that the former are co-activated when old, but not when new words are presented during retrieval.

Most importantly, we could not identify any neuron showing differential activity for successful versus unsuccessful retrieval of both item and source memory ($p_{overlap} = 1$). This finding is in accordance with dual-process models proposing that familiarity and recollection constitute two distinct processes contributing to recognition memory (e.g. Eichenbaum et al., 2007; Yonelinas, 2002). Note though that our data do not necessarily suggest two routes to recognition operating independently/in parallel and are compatible with models suggesting a single route to recognition memory with contributions from familiarity- and recollection-based processes (Weidemann and Kahana, 2019).

Moreover, there was no significant overlap between source retrieval-related neurons and associative stimulus-related neurons ($p_{overlap} = 0.858$). This outcome is in line with a recent single-neuron study investigating population activity in the MTL during retrieval of objects cued by scenes (Staresina et al., 2019). This study indicated that one set of neurons represented cue-related information and another set supported pattern completion via linking to neurons coding the associated information.

There are several open questions for future single-neuron studies, which would extend current knowledge based on intracranial EEG or functional magnetic resonance imaging studies. For instance, do the same neurons code item/source information/memory during encoding and retrieval? Do single neurons coding item/source information/memory reactivate in the time period between encoding and retrieval and if so, is post-encoding reactivation correlated with memory performance? Finally, what are the patterns of spike-based functional connectivity between the different classes of neurons (Kreuz et al., 2013)?

To summarize, we investigated neural response classes and their overlap in an associative recognition memory task. As major findings, our data indicate that a) item memory reflecting familiarity and source memory reflecting recollection are facilitated by different sets of neurons, b) the neurons critically involved in successful source memory are different from the neurons coding the associated information, c) neurons coding stimulus familiarity can be identified using previously known stimuli, d) familiarity-related neurons are most abundant in parahippocampal cortex, e) a considerable proportion of parahippocampal neurons is related to item retrieval, and f) there is a significant overlap between familiarity-related and item retrieval-related neurons.

Declaration of competing interest

The authors declare that no financial or non-financial competing interests exist.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117214.

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