Interaction of taste and place coding in the hippocampus

Running title: Taste and place coding in the hippocampus

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Abstract

An animal's survival depends on finding food, and the memory of food and contexts are often linked. Given that the hippocampus is required for spatial and contextual memory, it is reasonable to expect related coding of space and food stimuli in hippocampal neurons. However, relatively little is known about how the hippocampus responds to tastes, the most central sensory property of food. In this study, we examined the taste-evoked responses and spatial firing properties of single units in the dorsal CA1 hippocampal region as male rats received a battery of taste stimuli differing in both chemical composition and palatability within a specific spatial context. We identified a subset of hippocampal neurons that responded to tastes, some of which were place cells. These taste and place responses had a distinct interaction: taste-responsive cells tended to have less spatially specific firing fields, and place cells only responded to tastes delivered inside their place field. Like neurons in the amygdala and lateral hypothalamus, hippocampal neurons discriminated between tastes purely on the basis of palatability, and never coded taste quality in a "value-free" manner; these responses did not reflect movement or arousal. However, hippocampal taste responses emerged several hundred msec later than responses in other parts of the taste system, suggesting that the hippocampus does not influence real-time taste decisions, instead associating the hedonic value of tastes with a particular context. This incorporation of taste responses into existing hippocampal maps could be one way that animals use past experience to locate food sources.

Significance statement

Finding food is essential for animals' survival, and taste and context memory are often linked. While hippocampal responses to space and contexts have been well characterized, little is known about how the hippocampus responds to tastes. Here, we identified a subset of hippocampal neurons that discriminated between tastes based on palatability. Cells with

stronger taste responses typically had weaker spatial responses, and taste responses were confined to place cells' firing fields. Hippocampal taste responses emerged later than in other parts of the taste system, suggesting that the hippocampus does not influence taste decisions, but rather, associates the hedonic value of tastes consumed within a particular context. This could be one way that animals use past experience to locate food sources.

Introduction

The hippocampus is essential for spatial learning and memory, and is thought to provide a cognitive map of animals' experience. The central data for this view come from studies of place cells that respond to specific locations as animals explore their environments (O'Keefe and Nadel, 1978; Moser et al., 2008).

Given that one of the most obvious uses for such a mental map is to aid in the finding of food, it is surprising how little is known about how the hippocampus processes taste, the most central sensory property of food. It is reasonable to expect that taste information reaches the hippocampus; although not traditionally considered to be part of the taste system, anatomical studies show that the hippocampus receives projections, either directly or indirectly through the entorhinal cortex, from several brain regions in which taste information is processed, including the gustatory cortex (GC), orbitofrontal cortex, and amygdala (Suzuki and Amaral, 1994; von Bohlen und Halbach and Albrecht, 2002). Functional imaging studies in humans also indicate that the hippocampal formation is active during taste ingestion and discrimination (Zald et al., 1998; Haase et al., 2009; Spetter et al., 2010), and rodent lesion studies suggest that the hippocampus plays a role in taste learning (Reilly et al., 1993; Stone et al., 2005; Chinnakkaruppan et al., 2014).

72 A great deal is known about taste responses in other parts of the taste system: in cortex,
73 these responses evolve dynamically, reflecting taste presence, identity and palatability in
74 distinct epochs preceding the decision to consume or expel a given taste (Katz et al., 2001;
75 Sadacca et al., 2012; Sadacca et al., 2016). However, it remains unclear if or how hippocampal
76 taste responses co-exist and interact with representations of space. While hippocampal neurons
77 are known to respond to tastes in a context-dependent manner (Ho et al., 2011), no studies to
78 date have directly measured single unit responses to tastes in the hippocampus alongside
79 spatial firing properties, or examined the dynamics of these responses.
80
81 Hippocampal place cells are certainly capable of encoding non-spatial information such
82 as odors (Wood et al., 1999), visual cues (Fried et al., 1997), textures (Shapiro et al., 1997),
83 tones (Moita et al., 2003) and time (Kraus et al., 2013). Place cells typically respond to these
84 stimuli by modulating their firing rate ("rate remapping," Leutgeb et al., 2004; Allen et al., 2012)
85 or firing location ("global remapping," Leutgeb et al., 2005; Fyhn et al., 2007). A new cognitive
86 map can also be formed based on the parameters of a behaviorally relevant non-spatial
87 stimulus (Kraus et al., 2013; Aronov et al., 2017). The difficulty inherent in dissociating spatial
88 from non-spatial influences in behaving rodents (O'Keefe, 1999), however, has led some
89 researchers to propose that seeming responses to non-spatial stimuli may simply reflect
90 changes in animals' movement or attentive state, rather than sensory stimuli (Shan et al., 2016).
91 To establish that non-spatial responses are genuine, it is necessary to show that spatially tuned
92 neurons can discriminate between sensory stimuli.
93
94 Here, we did just this, recording single-unit activity in the dorsal CA1 region of awake
95 rats while exposing them to four taste solutions. We identified subsets of place cells and
96 interneurons that discriminated between tastes based purely on palatability; this pattern was
97 consistent with those observed in basolateral amygdala (BLA; Fontanini et al., 2009) and lateral

98 hypothalamus (LH; Li et al., 2013), although hippocampal taste dynamics evolved much more
99 slowly. Neurons classified as taste-responsive place cells responded exclusively to tastes
100 delivered within their place field, and tended to have lower spatial selectivity than non-taste-
101 responsive place cells. Together, these results establish that hippocampal responses to sensory
102 stimuli do not simply reflect changes in arousal state, and can encode sensory parameters
103 relevant for behavior. Further, they suggest that hippocampal taste responses may be used to
104 form value-related associations between tastes and contexts, which can facilitate using past
105 experience to locate food sources.
106
107 **Materials and Methods**
108 Animals and surgery
109 Five adult (450-550 g) male Long-Evans rats (Charles River Laboratories) were used as
110 subjects in this study. Rats were kept on a 12 h light/dark cycle, with all sessions taking place
111 around the same time during the light period. All surgical and experimental procedures were
112 conducted in accordance with the National Institutes of Health guidelines and approved by the
113 Brandeis University Institutional Animal Care and Use Committee.
114
115 After several weeks of habituation to daily handling, animals were chronically implanted
116 with a microdrive array consisting of 25-30 independently moveable tetrodes in the right dorsal
117 hippocampal region CA1 (-3.6 mm AP, 2.2 mm ML), and an intra oral cannula (IOC). Each IOC
118 consisted of a polyethylene tube inserted beneath the temporalis muscle and terminating
119 anterolateral to the first maxillary molar, allowing for the precise delivery of taste solutions onto
120 the rat's tongue (Grill and Norgren, 1978; Travers and Norgren, 1986; Katz et al., 2001).
121
122 Following recovery from the implantation surgery (~7-8 days), rats were water-deprived
123 to 85-90% of their *ad libitum* weight to ensure taste consumption during the recording sessions.

124 At ~14 d after implantation, animals were habituated for at least 3 days to the behavioral
125 chamber, sleep box, and the delivery of taste solutions through the IOC. Following habituation,
126 we performed daily recording sessions in which rats were exposed to pseudo-randomized
127 sequences of four standard taste stimuli (see **Figure 1A**, **1B** and *Passive taste administration*
128 *paradigm*). Following the conclusion of experiments, we made electrolytic lesions through each
129 electrode tip to mark recording locations. Brains were sectioned into 50 μm slices and stained
130 with cresyl violet to confirm electrode placement in the hippocampal cell layer (see **Figure 1C**).
131

132 <u>Passive taste administration paradigm</u>

133 Each recording session typically lasted between 2 and 3 hours, and consisted of three sessions
134 in a ~30 x 35 x 40 cm Plexiglass behavioral chamber (J. Green, Charles River Maker Lab)
135 interleaved with four 15-20 minute sleep sessions in a ~30 x 30 x 40 cm black box (rest box).
136 The first and last sessions in the behavioral chamber consisted of 15-20 minute periods in which
137 animals were habituated to the behavioral chamber in the absence of tastes. During the middle
138 experimental session (depicted in **Figure 1A**), rats received a pseudo-randomized sequence of
139 four standard taste stimuli [sweet: 4 mM saccharin (S); salty: 100 mM sodium chloride (N);
140 neutral: distilled water (W); and bitter: 5 mM quinine hydrochloride (Q)] that varied in hedonic
141 value and fell within the range of concentrations typically used by other groups (3-20 mM
142 saccharin, 10-300 mM sodium chloride, and 1-10 mM quinine; for review, see Frank and Brown,
143 2003; Kobayakawa et al., 2005; Accolla and Carleton, 2008; Geran and Travers, 2009; Chen et
144 al., 2011; Sadacca et al., 2016). Taste solutions were delivered directly onto the tongue in ~40
145 μL aliquots via four polyamide tubes inserted into the IOC, with a separate tube for each
146 solution to prevent the mixing of tastes. Rats received 50 pseudo-randomized repeats of each of
147 the four taste stimuli, for a total of 200 taste deliveries. The interval between taste deliveries was
148 randomized to 13-17 seconds, allowing sufficient time for the taste system to reset between

149 presentations (A. Fontanini and D.B. Katz, unpublished observations). The total amount of fluid
150 delivered in each ~50 minute taste administration period was 8 mL, after which animals had
151 access to an additional 15-20 mL of water in their home cage.
152
153 Electrophysiology

154 Electrophysiological recordings were conducted using a SpikeGadgets system (Tang et al.,
155 2017). Spikes were sampled at 30 kHz and bandpass filtered between 600 Hz and 6 kHz. Local
156 field potentials (LFPs) were sampled at 1.5 kHz and bandpass filtered between 0.5 and 400 Hz.
157 During recording sessions, the animal's position and speed were recorded using an overhead
158 monochrome CCD camera (30 fps) and tracked by LEDs affixed to the headstage.
159
160 Over ~14 d following surgery, tetrodes were gradually advanced to the CA1 hippocampal
161 cell layer, as identified by characteristic EEG patterns (sharp-wave ripples, or SWRs; theta
162 rhythm) as previously described (Jadhav et al., 2012; Jadhav et al., 2016; Tang et al., 2017).
163 Tetrodes were readjusted after each day's recordings. Each animal had one hippocampal
164 reference tetrode in corpus callosum, which was also referenced to a ground screw installed in
165 the skull overlying cerebellum.
166
167 Single units were isolated offline based on peak amplitude and principal components
168 (Matclust, M.P. Karlsson). Only well-isolated units with stable waveforms that fired at least 100
169 spikes per session were included in our analysis. Putative interneurons (*Int*) were identified on
170 the basis of firing rate (> 8.5 Hz) and spike width (< 0.35 ms) parameters (**Figure 1D**), as
171 characterized previously (Jadhav et al., 2016; Tang et al., 2017). All other isolated units were
172 classified as pyramidal cells (*Pyr*). We isolated a total of 482 neurons from five rats, conducted
173 across nine experiments. **Table 1** shows the distribution of cells across all five animals.

174

175 **Table 1.**

176 Cell distribution across animals

177

Animal	CA1 cells					
	All	Pyr	Int	Taste responsive	Pyr	Int
EM5	162	155	7	24	18	6
LH36	41	39	2	7	5	2
EM6	136	118	18	52	35	17
LP1	91	79	12	11	6	5
LH42	52	50	2	2	1	1
Total	482	441	41	96	65	31

178

179 SWR detection

180 SWRs were detected as previously described (Jadhav et al., 2016; Tang et al., 2017) using the
181 ripple-band (150-250 Hz) filtering of LFPs from multiple tetrodes. A Hilbert transform was used
182 to determine the envelope of band-passed LFPs, and events that exceeded a threshold (mean
183 + 3 SD) were detected. SWR events were defined as the times around initially detected events
184 when the envelope exceeded the mean. SWR periods were excluded from place field analysis,
185 similar to previous studies (Jadhav et al., 2016; Tang et al., 2017).

186

187 Palatability/preference data

188 Taste palatability was assessed using a brief-access task (BAT, Davis Rig Gustometer, Med
189 Associates; for details, see Sadacca et al., 2016) in a separate cohort of adult male rats (n = 7)
190 that underwent the same water restriction protocol as the rats used in the recording experiment.

Consumption data were averaged across two testing days for each animal. The palatability rank order determined by the brief-access test (S > N > W > Q, see **Figure 5C**) matches what has been observed in numerous studies across a broad range of stimulus delivery methods and assessment techniques (Travers and Norgren, 1986; Breslin et al., 1992; Clarke and Ossenkopp, 1998; Fontanini and Katz, 2006; Sadacca et al., 2016).

Experimental design and statistical analysis

Spatial maps:

To characterize the spatial firing properties of neurons, two-dimensional occupancy-normalized firing rate maps (**Figure 2**, **3A**, **4A**, **4B**) were made using 0.5 cm square bins and smoothed with a 2D Gaussian (σ = 3 cm; Tang et al., 2017). Data from taste delivery (500 ms before to 2500 ms after) and SWR periods (see *SWR detection and modulation*) were excluded from spatial map analysis. Peak rates for each cell were defined as the maximum firing rate across all spatial bins in the spatial map.

Spatial specificity was determined by calculating the spatial information content, or amount of information that a single spike conveys about the animal's location in bits/spike using the formula:

Spatial information content = $\sum P_i(R_i/R)log_2(R_i/R)$,

where *i* is the bin number, P_i is the probability of occupancy for bin *i*, R_i is the mean firing rate for bin *i*, and R is the overall mean firing rate of the cell (Skaggs et al., 1993).

215 Unpaired t-tests were used to determine whether the average spatial information content
216 differed significantly between taste-responsive and non-taste-responsive neurons of each cell
217 type (**Figure 3B**; pyramidal cells: n = 65 taste-responsive cells, n = 376 non-taste-responsive
218 cells; interneurons: n = 31 taste-responsive cells, n = 10 non-taste-responsive cells).
219
220 *In-field vs. out-of-field analysis*:
221 To analyze how place cells responded to tastes delivered inside or outside of their place fields
222 (**Figure 4**), only pyramidal cells exhibiting place-specific activity (n = 395 cells, defined as
223 neurons whose peak rate exceeded 1 Hz and spatial information content exceeded 0.2
224 bits/spike, similar to Moita et al., 2003) were considered. The in-field region of each cell's place
225 field was defined as the largest cluster of neighboring bins with a firing rate exceeding 20% of
226 the peak rate, with all other bins defined as out-of-field (Brun et al., 2002). Only place cells that
227 contained at least ten in-field and out-of-field taste delivery trials were included in this in-field vs.
228 out-of-field analysis (n = 26 taste-responsive cells, n = 153 non-taste-responsive cells). A one-
229 way ANOVA was used to assess differences between the average in-field and out-of-field eta-
230 squared values (see *Taste selectivity*) of taste-responsive and non-taste-responsive cells
231 (**Figure 4C**).
232
233 *Taste response properties*:
234 The pseudo-randomized taste delivery paradigm used to characterize hippocampal responses
235 to tastes is described above (see *Passive taste administration paradigm*). Taste responses were
236 characterized separately for each of the 482 isolated neurons, focusing on the 2500 ms of
237 spiking activity following each taste delivery, a time period that includes previously identified
238 taste-related responses, but precedes swallowing behaviors that remove tastes from the tongue
239 and make neural responses difficult to interpret (Travers and Norgren, 1986; Katz et al., 2001).
240 We analyzed a set of response properties ranging from general to specific, as have been

241 identified in other parts of the taste system, including the GC (Katz et al., 2001; Sadacca et al.,
242 2012), BLA (Fontanini et al., 2009; Piette et al., 2012), and LH (Li et al., 2013). Neurons were
243 classified as "taste-responsive" (see **Table 1** for summary) if they exhibited responses to taste
244 presence, identity and/or palatability, as described below. All other neurons were classified as
245 "non-taste-responsive." All statistical tests were performed in MATLAB and evaluated at a level
246 of p = 0.05 unless otherwise specified, with a Bonferroni correction applied for multiple
247 comparisons.
248
249 First, non-specific responses to taste presence (**Figure 5B**, light gray lines), which are
250 common across all four types of taste delivery and thought to originate from somatosensory
251 responses detecting a taste on the tongue, were determined by assessing whether evoked
252 responses differed significantly from the baseline firing rate in responses collated across all 200
253 taste delivery trials (Katz et al., 2001). The significance of the difference was first established
254 using the main effect for time in a two-way, mixed-effect ANOVA (taste [saccharin, NaCl, water,
255 quinine) x time [successive 500 ms bins of firing rate]).
256
257 Next, responses to taste identity (**Figure 5B**, dark gray lines), in which at least one taste
258 can be discriminated from the others, were assessed by determining if the evoked responses to
259 the four tastes (this time, collated across the 50 deliveries of each unique taste) differed from
260 each other. We employed a similar strategy as the one used to evaluate taste responsiveness,
261 except in this case, the main effect for taste was considered.
262
263 Finally, responses to taste palatability (**Figure 5D**), which reflected the relative hedonic
264 value of tastes as assessed in the BAT (see **Figure 5C** and *Palatability/preference data*) were
265 computed using a rank correlation (R^2) between the evoked response and the palatability of the
266 associated taste. Specifically, neurons whose evoked firing rates matched the ranking of taste

preference (S > N > W > Q) in increasing or decreasing order had higher palatability index scores.

Taste selectivity:

The magnitude of taste responsiveness for each cell was quantified using eta-squared (η^2), a standard measure of ANOVA effect sizes that describes the proportion of variance in a dependent variable explained by each factor:

$$\eta^2 = SS_{(factor)}/SS_{(total)},$$

where SS is the sum of squares (Maier et al., 2015). In our analysis, we used the summed SS of the two main factors (time + taste) to calculate η^2. The Pearson correlation (R^2) between spatial information content and eta-squared was computed separately for place cells (n = 395 cells) and interneurons (n = 41 cells). As described above (see *In-field vs. out-of-field analysis*), a one-way ANOVA was used to assess differences in η^2 for the in-field and out-of-field regions of taste-responsive (n = 26 cells) and non-taste-responsive (n = 153 cells) place cells that fit our analysis criteria (**Figure 4C**).

Taste response dynamics:

To determine the timing of presence-, identity-, and palatability-related responses in single neurons, Student's t-tests were conducted on successive time windows of each neuron's evoked response (window size, 500 ms; step size, 50 ms; span, 0-2500 ms after taste delivery; Sadacca et al., 2012; Li et al., 2013). To analyze taste-related dynamics on a population-wide level, we constructed a histogram showing what percentage of the total 482 recorded neurons exhibited responses to taste presence, identity and palatability at each time point following

292 stimulus delivery (**Figure 6A**). To investigate the timing of different aspects of the taste
293 experience present in hippocampal responses, we compared response onset times of
294 presence- and identity-related firing (**Figure 6B**) as well as identity- and palatability-related firing
295 (**Figure 6C**) in the subset of cells that exhibited both (n = 19 and 14 cells, respectively).
296 Principal component analysis (PCA, see Briggman et al., 2005; Harvey et al., 2012) was
297 conducted on the pooled subset of 36 identity-responsive cells to determine when discriminative
298 firing emerged in the population response following taste delivery, with significance assessed at
299 the p = 0.01 level comparing the neural data to 10,000 instances of firing-rate-shuffled controls
300 (**Figure 6D**).
301
302 *Speed and position controls*:
303 To ensure that hippocampal responses to tastes were not actually caused by overall differences
304 in movement following taste delivery or in response to different tastes, we used a one-way
305 ANOVA to compare the average speed and distance traveled during the pre- vs. post-taste
306 period (2.5 seconds before or after taste delivery, segmented into 500 ms bins with a 50 ms
307 step size) across all tastes (n = 1800 total trials across 9 sessions), as well as separately for
308 each of the four tastes (n = 450 trials of each taste across 9 sessions).
309
310 **Results**
311
312 **Hippocampal place cells and interneurons respond to tastes.**
313 We examined taste responses in a total of 482 CA1 neurons recorded across nine sessions in
314 five rats (mean ± SEM: 53.6 ± 5.34 neurons/session) that received a battery of four standard
315 tastes *via* IOC (**Figure 1A**). Tastes were delivered in random order and timing as rats explored
316 the behavioral chamber, leading to a varied distribution of taste delivery locations (**Figure 1B**).
317 Histology confirmed that the majority of our tetrodes were located intermediately along the

318 proximodistal axis of dorsal CA1 (**Figure 1C**; Henriksen et al., 2010). Isolated single neurons
319 were classified as either pyramidal cells (91.5%, 441/482) or interneurons (8.5%, 41/482) on the
320 basis of baseline firing rates and action potential shape (**Figure 1D**).
321
322 In total, 395 of the 441 pyramidal neurons were classified as place cells using standard
323 analysis of the spatial specificity of firing rate responses (see Materials and Methods, Moita et
324 al., 2003). The spatial firing maps of four representative place cells and interneurons (all of
325 which were computed with taste delivery periods omitted from the analysis) are shown in the top
326 row of **Figure 2**. As expected (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978), only
327 the pyramidal cells had place fields (**Figure 2A, 2B**)—interneurons (**Figure 2C**, **2D**) typically
328 exhibited high spontaneous firing rates regardless of the rat's position.
329
330 A cell was considered "taste-responsive" if significant firing rate modulations were
331 evoked by taste presence, identity, and/or palatability (see **Figure 5** for more details). In total,
332 96/482 (19.9%) cells were classified as taste-responsive, which is similar to the proportion
333 reported in the only previous study to assess taste responses in individual hippocampal neurons
334 (Ho et al., 2011). We found taste-responsive and unresponsive units on tetrodes across the
335 proximodistal axis of dorsal CA1 (n = 50/60 tetrodes with taste-responsive units). **Table 1** shows
336 the distribution of taste-responsive cells across animals.
337
338 The peri-stimulus time histograms (PSTHs) for an example taste-responsive place cell
339 and interneuron are depicted in the bottom row of **Figure 2B** and **2D**. The place cell in **Figure**
340 **2B** responded to tastes from 500-1000 ms following taste delivery, while the interneuron in
341 **Figure 2D** responded to tastes from 1200-2500 ms following taste delivery (light gray lines). In
342 contrast, the PSTHs for non-taste-responsive cells (**Figure 2A**, **2C**) show no differences in
343 evoked activity from baseline (black dashed line) or between tastes (colored lines).

344

345 Since hippocampal activity is affected by animals' location and movement, one possible
346 explanation of these results is that different tastes have different impacts on animals' motor
347 behavior, and that therefore any perceived "taste"-evoked responses can simply result from
348 changes in the animal's speed or position (O'Keefe, 1999; Shan et al., 2016). To control for this
349 possibility, we assessed differences in rats' pre- and post-taste speed and position, both overall
350 and between each of the four tastes. We found no differences in the average speed (before
351 taste delivery: 1.07 ± 0.031 cm/s, after taste delivery: 1.12 ± 0.029 cm/s; one-way ANOVA, p =
352 0.29) or distance traveled (before taste delivery: 1.57 ± 0.050 cm, after taste delivery: 1.59 ±
353 0.045 cm; one-way ANOVA, p = 0.74) in the 2.5 seconds preceding and following taste
354 deliveries; the same was true when trials were split up by taste identity (post-pre taste delivery
355 speed: saccharin: -0.081 ± 0.063 cm/s, NaCl: 0.037 ± 0.061 cm/s, quinine: 0.11 ± 0.061 cm/s,
356 water: 0.12 ± 0.070 cm/s; one-way ANOVA, p = 0.10; post-pre taste delivery distance:
357 saccharin: -0.0026 ± 0.11 cm, NaCl: -0.029 ± 0.11 cm, quinine: 0.093 ± 0.093 cm, water: 0.027
358 ± 0.11 cm; one-way ANOVA, p = 0.86). Therefore, it is unlikely that hippocampal responses to
359 tastes were caused by changes in animals' position or locomotion; rather, they reflected sensory
360 responses to some aspect of the taste experience itself.

361

362 **Taste responses are gated by the spatial firing properties of hippocampal neurons.**
363 We found that 14.7% of place cells (n = 58/395 cells) had significant responses to tastes; a far-
364 higher percentage of interneurons (75.6%; n = 31/41 cells) were taste-responsive (**Figure 2**).
365 The significance of this larger likelihood of taste-responsiveness amongst spatially diffuse
366 interneurons than in spatially-specific place cells (chi-square test, $\chi^2 = 84.87$, p = 3.19e-20)
367 suggests that taste responsiveness depends on the spatial firing properties of hippocampal
368 neurons. To further investigate the relationship between place- and taste-specific firing, we
369 compared the spatial information content (Skaggs et al., 1993) and eta-squared values (a

standard measure of ANOVA effect size, used here to quantify the magnitude of a cell's response to tastes; see Maier et al., 2015) of taste-responsive and non-taste-responsive hippocampal neurons.

Figure 3A depicts the firing fields of 12 example non-taste-responsive and taste-responsive place cells and interneurons, all of which were computed with taste delivery periods (extending from 500 ms before to 2500 ms after taste delivery) omitted from the analysis. As expected, place cells had a much higher average spatial information content (1.30 ± 0.034 bits/spike; higher values = smaller, more concentrated regions of enhanced firing) than interneurons (0.12 ± 0.034 bits/spike; unpaired t-test, p = 2.61e-25). Therefore, taste responses (which were found predominately in interneurons) were associated with lower spatial information contents.

This same pattern was found to hold even within each cell type, however: cells with stronger taste-evoked responses tended to exhibit weaker spatial responses (**Figure 3B**) in analyses restricted to place cells (taste-responsive: 0.91 ± 0.050 bits/spike; non-taste-responsive: 1.37 ± 0.038 bits/spike; unpaired t-test, p = 1.03 e-06) and interneurons (taste-responsive: 0.065 ± 0.040 bits/spike; non-taste-responsive: 0.29 ± 0.015 bits/spike; unpaired t-test, p = 0.0027), as illustrated by the larger place fields and more evenly distributed interneuron firing maps in **Figure 3A**. There was a negative correlation between spatial information content and magnitude of taste responsiveness (eta-squared, or η^2) within each cell type (place cells: Pearson correlation, R= -0.18, p = 3.27e-04; interneurons: Pearson correlation, R= -0.58, p = 5.95e-05), confirming that hippocampal neurons that respond strongly to taste delivery tend to have more diffuse firing in space.

The above analysis implies that while place cells tended to exhibit fewer and lower-magnitude taste responses than interneurons, a subset of place cells exhibited taste-specific firing (n = 58/395 cells; example in **Figure 2B**). Thus it is important to ask how place and taste responses interact when an animal receives familiar tastes in a specific spatial context: can place cells acquire sensory responses regardless of location, or are responses to tastes gated by spatial firing, as suggested for other sensory modalities (Moita et al., 2003; Shan et al., 2016)? To investigate this question, we compared the specificity of taste responses inside and outside each place cell's firing field.

Only place cells (n = 58 taste-responsive cells, n = 337 non-taste-responsive cells) were considered for in-field vs. out-of-field analysis. We defined a cell's place field as the largest area in which the firing rate exceeded 20% of the peak rate (Brun et al., 2002). To ensure sufficient sampling of taste responses, only cells that contained at least ten in-field and out-of-field trials were included in our analysis (n = 26 taste-responsive cells, n = 153 non-taste-responsive cells). Eta-squared was then determined separately for trials taking place within and outside each cell's place field.

Figure 4 shows the spatial firing maps of representative taste-responsive (top) and non-taste-responsive (bottom) place cells, as well as PSTHs for trials taking place in- and out-of-field. For the taste-responsive cell (**Figure 4A**), virtually all responses occurred within the cell's place field (middle panel), with very little taste-evoked firing out of field (right panel). On the other hand, no taste-evoked responses were observed in- or out-of-field for the non-taste-responsive cell (**Figure 4B**). This trend was representative of the entire population of place cells (**Figure 4C**): the in-field region of taste-responsive cells had a higher average eta-squared value than the out-of-field region, or either region of non-taste-responsive cells (eta-squared values, taste-responsive cells, in-field: 0.036 ± 0.0042; taste-responsive cells, out-of-field: 0.023 ±

421 0.0027; non-taste-responsive cells, in-field: 0.025 ± 0.0013; non-taste-responsive cells, out-of-
422 field: 0.0208 ± 0.0011; 1-way ANOVA, p = 3e-05). Together, these results indicate that
423 hippocampal taste responses are gated by the spatial firing properties of place cells—a finding
424 that is consistent with previous studies investigating tone-evoked sensory responses during
425 auditory fear conditioning (Moita et al., 2003; Shan et al., 2016).
426
427 **Hippocampal taste-specific responses purely reflect taste palatability, at a relatively long**
428 **delay.**
429 Previous work has shown that taste-specific firing in GC neurons evolves through three stages:
430 following an initial, nonspecific response to taste presence, a discriminative response conveys
431 information about taste identity starting at approximately 200 ms after stimulus administration;
432 after approximately 500 ms, responses then change to reflect palatability, specifically
433 anticipating an animal's decision to consume or expel a particular taste between 600 and 1600
434 ms after taste delivery (Katz et al., 2001; Piette et al., 2012; Sadacca et al., 2012; Maier and
435 Katz, 2013; Li et al., 2016; Sadacca et al., 2016). Brainstem taste responses in the parabrachial
436 nucleus (PbN) are similarly organized (Baez-Santiago et al., 2016). Other nodes of the taste
437 CNS, however, such as the BLA and LH, appear instead to respond primarily and immediately
438 to the hedonic value of tastes, regardless of identity (Fontanini et al., 2009; Li et al., 2013). To
439 determine which components are present in hippocampal taste responses (and when), we
440 performed analyses similar to those brought to bear on firing in these other structures.
441
442 Many hippocampal neurons responded nonspecifically to taste presence, providing
443 information that could allow for the detection of tastants on the tongue (**Figure 5A**). In a subset
444 of these cells, responses were more discriminative, providing information about taste identity
445 and/or palatability. Two such neurons are shown in **Figure 5B**—one of which (top) rapidly
446 developed a response primarily to quinine, and one of which (bottom) produced a longer-latency

447 response that differentiated each of the four tastes, and that notably involved a sudden change
448 of firing rate to sucrose.
449
450 Closer examination revealed that the patterning of both of these responses reflected
451 taste palatability across the entirety of the periods of taste-specific firing (**Figure 5D**).
452 Responses to taste palatability were assessed, as is typical in studies of taste temporal coding
453 (Li et al., 2013; Baez-Santiago et al., 2016; Sadacca et al., 2016), in terms of the correlation
454 between neuronal firing rates and the order of taste preference, which was assayed in a brief-
455 access task (Li et al., 2013; Monk et al., 2014; Sadacca et al., 2016) run on a separate cohort of
456 experimental rats (**Figure 5C**). The observed order of taste preference (S > N > W > Q) shown
457 in **Figure 5C** is consistent with that observed across a broad range of stimulus delivery methods
458 and assessment techniques (Travers and Norgren, 1986; Breslin et al., 1992; Clarke and
459 Ossenkopp, 1998; Fontanini and Katz, 2006; Sadacca et al., 2016).
460
461 **Figure 5D** reveals that palatability correlations for the example neurons shown in **Figure**
462 **5B** developed as the taste-specific responses themselves developed: the place cell's responses
463 (**Figure 5B**, top) were significantly correlated with taste palatability between 600 and 2100 ms
464 (**Figure 5D**, top), while the interneuron's responses (**Figure 5B**, bottom) were palatability-
465 related between 2000 and 2500 ms (**Figure 5D**, bottom; compare these periods with the dark
466 gray line in **Figure 5B**, which marks the period of significantly taste-specific firing).
467
468 Again, the examples shown in **Figure 5** suggest that, like responses observed in limbic
469 structures (i.e., BLA and LH; Fontanini et al., 2009; Li et al., 2013) but unlike those in the main
470 taste axis (i.e., GC and PbN; Sadacca et al., 2012; Baez-Santiago et al., 2016), hippocampal
471 taste responses do not go through a period of "pure" taste specificity prior to becoming
472 palatability-related. These appearances were borne out in an analysis of the entire neural

473 dataset. **Figure 6A** shows, similar to what has been observed in all other parts of the taste
474 system (Katz et al., 2001; Sadacca et al., 2012; Baez-Santiago et al., 2016; Fontanini et al;
475 2009; Li et al., 2013), that totally non-specific responses to taste presence emerged first in
476 hippocampus, followed by responses to taste identity and palatability. However, both taste
477 specificity and palatability-relatedness appeared in hippocampal taste responses at similarly
478 long latencies (average onset, presence: 1032.5 ± 55.73 ms; identity: 1443.1 ± 108.07 ms;
479 palatability: 1797.2 ± 118.51 ms).
480
481 Direct within-neuron comparisons strongly supported the group analysis. Presence-
482 related responses reliably arose before identity-related responses in cells that responded to
483 both properties (n = 19 cells, paired t-test, p = 7.55e-05), as also evidenced by the cloud of
484 points above the unity line (**Figure 6B**; regression slope: 0.079, p = 0.79). A plot of the onset
485 latency of identity- and palatability-related responses in cells where both properties were
486 present, meanwhile, revealed tight clustering around the unity line (**Figure 6C**; n = 14 cells;
487 regression slope: 0.92, p = 8.68e-06) with no significant differences between onset times
488 (paired t-test, p = 0.83), suggesting that these properties arose simultaneously in single-unit
489 responses.
490
491 Finally, we performed PCA by pooling responses of identity-responsive cells (n = 36
492 cells) to examine population dynamics. This analysis revealed that tastes are discriminated
493 based on palatability, as shown by significant encoding of palatability rank (here, in reverse
494 order as shown in **Figure 5C**) by the principal components starting at ~1.4 s after stimulus
495 delivery (**Figure 6D**). PCA of the palatability-responsive cells (n = 18 cells) showed the same
496 trend, with principal components for each of the four tastes separating at ~1.4 s following taste
497 delivery.
498

We therefore conclude that hippocampal “taste codes” do not contain the purely identity-related component found in gustatory brainstem and cortex; rather, tastes are discriminated solely based on hedonic value. In this regard, hippocampal responses are similar to those observed in other non-cortical parts of the taste system, such as the BLA (Fontanini et al., 2009) and LH (Li et al., 2013); notably, however, palatability coding appears in hippocampus much later than it appears in these other limbic structures—a difference that likely has strong implications for the potential roles of the hippocampus in taste (see Discussion below).

508 **Discussion**

509 Our findings suggest that place and taste responses can co-exist within the same hippocampal
510 neurons, and that these two response modalities influence one another. Taste-responsive cells
511 tended to have less spatially specific firing fields (**Figure 2**, **3**). On the other hand, place cells
512 that responded to tastes did so in a spatially specific manner (**Figure 4**), with responses only
513 occurring within that cell's place field. Hippocampal neurons discriminated between tastes at
514 relatively long latencies and purely on the basis of palatability (**Figure 5**, **6**); these findings
515 confirm additional analyses suggesting that these responses likely do not simply reflect changes
516 in animals' movement or attentive state, as has been suggested (O'Keefe, 1999; Shan et al.,
517 2016). Our observations add to an expanding view of the hippocampal cognitive map as a
518 representation that encompasses both spatial and non-spatial aspects of an animal's
519 environment (Shapiro et al., 1997; Eichenbaum et al., 1999; Wood et al., 1999; Moita et al.,
520 2003; Kraus et al., 2013; Aronov et al., 2017).
521
522 In total, about 20% of recorded hippocampal cells in our study were classified as taste-
523 responsive (**Figure 2**), which is similar to the proportion reported in the only previous study to
524 assess taste responses in individual hippocampal neurons (Ho et al., 2011). This result confirms
525 that the hippocampus contains a smaller fraction of taste-responsive neurons than that
526 observed in brain regions traditionally considered to be part of the taste system, including the
527 GC (Katz et al., 2001), BLA (Nishijo et al., 1998; Fontanini et al., 2009; Moran and Katz, 2014),
528 LH (Li et al., 2013), and PbN (Baez-Santiago et al., 2016). Hippocampal taste responses were
529 also about an order of magnitude smaller than those in GC, both in terms of eta-squared
530 (**Figure 3C, 4C**) and palatability correlations (**Figure 5D**, Maier et al., 2015; Sadacca et al.,
531 2016).
532

533 Unlike what has been observed in GC (Katz et al., 2001; Sadacca et al., 2016) and PbN
534 (Baez-Santiago et al., 2016), we found little evidence of pure sensory coding in the
535 hippocampus in this passive administration paradigm. Instead, hippocampal neurons distinguish
536 between tastes based on palatability (**Figure 6**), similar to other limbic structures belonging to
537 the taste system such as the BLA (Fontanini et al., 2009) and LH (Li et al., 2013). However,
538 palatability-related hippocampal coding emerges much later than that observed in BLA or LH
539 (Fontanini et al., 2009; Li et al., 2013), and quite likely after the time (although more direct
540 measurements must be taken to ascertain this) that animals make decisions about palatability-
541 related orofacial behaviors (Li et al., 2016; Sadacca et al., 2016). These results support the idea
542 that the hippocampus does not contribute to an animal's decision to consume or expel a given
543 taste; rather, it responds to the hedonic value of tastes consumed within a particular context.
544 This could serve as a means of associating tastes and places, allowing animals to use past
545 experience to locate food sources.
546
547 While spatial learning is indisputably considered to be a hippocampal-dependent
548 process (Morris, 1984; Burgess et al., 2002; Moser et al., 2008), the role of the hippocampus in
549 non-spatial taste learning is less clear-cut. Forms of taste learning such as conditioned taste
550 aversion (the process by which a pleasant taste becomes aversive following its association with
551 gastric distress) and latent inhibition (the reduction of conditioned aversion following safe pre-
552 exposure to a taste) were once considered to be hippocampal-independent because these
553 behaviors can persist following permanent hippocampal lesions (Gallo and Candido, 1995;
554 Yamamoto et al., 1995; Molero-Chamizo and Moron, 2015). Other studies reveal a role for
555 hippocampus in taste learning, for instance, during social transmission of food preferences
556 (Bunsey and Eichenbaum, 1995; Countryman et al., 2005), but report a variety of specific
557 behavioral effects depending on the method of perturbation used (Miller et al., 1986; Reilly et
558 al., 1993; Stone et al., 2005; Chinnakkaruppan et al., 2014). Future studies in which individual

559 neurons are recorded during taste learning, which have been informative when focused on other
560 nodes of the taste system (Grossman et al., 2008; Lavi et al., 2018), may help to decipher how
561 the hippocampus encodes tastes and contexts to guide future food choices.
562
563 Hippocampal taste responses are almost entirely gated by the neurons' spatial firing
564 properties (**Figure 3**, **4**). Our finding that place cells only respond to tastes delivered within their
565 place field (**Figure 4**) is consistent with previous studies (Moita et al., 2003; Shan et al., 2016),
566 indicating that taste responses can best be understood as a rate code overlaid on existing
567 representations of space. Since place fields can be modulated by food reward (Dupret et al.,
568 2010; Allen et al., 2012), it seems likely that taste responses could arise as a consequence of
569 place cell remapping. However, we could not address this question in the current study, since
570 rats did not explore the behavioral chamber in the absence of tastes, making it difficult to
571 calculate place fields. Future studies that incorporate place-specific taste delivery will be able to
572 explore whether taste experience can modify animals' hippocampal representation of a
573 particular environment through rate or global remapping, as has been shown for other sensory
574 modalities (Moita et al., 2004; Fyhn et al., 2007; Zhang and Manahan-Vaughan, 2015).
575
576 Whatever the relationship between spatial and gustatory firing, more hippocampal
577 interneurons—by their very nature, non-place cells—respond to non-spatial stimuli than place
578 cells (**Figure 3**). This result is consistent with studies that measured responses to tones during
579 fear conditioning (Moita et al., 2003) or odors in anesthetized rats (Deshmukh and Bhalla,
580 2003). This finding may reflect the intrinsic properties of each cell type: place cells have lower
581 firing rates on average and rarely respond outside of their place field, while interneurons exhibit
582 high firing rates regardless of location (see **Figure 2**), making it much easier to obtain statistical
583 significance in the latter. Further, if spatial responses gate taste responses, non-specific spatial
584 responses of interneurons may enable taste responses. Another (though not mutually

585 exclusive) possibility is that interneurons modulate place cell taste responses via long-range
586 projections from medial entorhinal cortex (MEC, von Bohlen und Halbach and Albrecht, 2002;
587 Melzer et al., 2012). While place cells' responses to space have been well-characterized
588 (O'Keefe and Nadel, 1978; Moser et al., 2008), recent work suggests that interneurons also
589 contribute to hippocampal representations of space (Wilent and Nitz, 2007), and disinhibit place
590 cell firing through location-specific decreases in activity (Hangya et al., 2010; Royer et al.,
591 2012). However, how non-spatial information is transmitted within hippocampal microcircuits
592 remains an open question, one that may be investigated in future studies by determining the
593 effect of cell-type-specific inhibition on hippocampal taste responses.
594
595 It has been suggested that lateral entorhinal cortex (LEC) plays a prominent role in routing non-
596 spatial information to the hippocampus (Henriksen et al., 2010; Tsao et al., 2013), with LEC and
597 MEC inputs preferentially innervating distal and proximal CA1, respectively. Our recordings
598 were predominantly in intermediate regions of CA1 (**Figure 1C**), and we observed taste- and
599 non-taste-responding cells across all of our tetrodes. The interactions of place and taste coding
600 may thus reflect a combination of spatial and non-spatial input conveyed by different entorhinal
601 sources through the hippocampal micro-circuit.
602
603 There is strong evidence that the behavioral relevance of sensory stimuli within a task
604 influences what proportion of hippocampal neurons respond to non-spatial cues. In our study,
605 rats passively received tastes via IOC, a paradigm that requires no learning, other than
606 associating tastes with a context for the first time. The total proportion of taste-responsive
607 neurons in our study (~20%, **Figure 2**) is comparable to the proportion of tone-responsive cells
608 (16%) found by one study analyzing the auditory evoked responses of hippocampal neurons
609 (Moita et al., 2003); however, this proportion increased to 52% following auditory fear
610 conditioning. Similarly, ~40% of hippocampal neurons exhibited non-spatial firing during an

odor-guided non-match-to-sample task that required working memory of spatial and non-spatial factors (Wood et al., 1999). More pronounced changes in hippocampal responsiveness are observed when reward contingencies are entirely dependent on discriminating between non-spatial cues, such as in one study where rats learned to manipulate a joystick to modulate a tone within a target frequency range (Aronov et al., 2017). During this task, about 40% of hippocampal neurons responded to specific tone frequencies, compared to only 2% during the passive playback of tones. In our study, only 8% (36/482) of CA1 neurons discriminated between tastes (**Figure 5A**), with the majority of taste-responsive cells responding nonspecifically to taste presence (77/482, 16%). These results suggest that the hippocampus forms a flexible map of spatial and non-spatial stimuli based on current behavioral demands. This ongoing mental map can be stabilized by the sequential reactivation of hippocampal place cells during SWRs (van de Ven et al., 2016; Roux et al., 2017), which is thought to contribute to the Hebbian strengthening of behaviorally relevant neuronal ensembles; future work will assess whether this is true of non-spatial experiences as well.

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806

807 **Legends**

808 **Figure 1**. Experimental design and electrophysiology.

809 ***A***, A portion of the timeline of an example taste delivery experiment. Colored bars indicate
810 individual deliveries of taste stimuli: green (S, 4 mM saccharin), yellow (N, 100 mM sodium
811 chloride), blue (W, distilled water) and red (Q, 5 mM quinine hydrochloride). Taste deliveries
812 occurred at a randomized timing of 13-17 s, with the taste identity randomized for each trial. ***B***,
813 Example session showing all 200 taste delivery locations (colored symbols) overlaid on top of
814 the rat's position in the behavioral chamber (gray circles) during one recording experiment. ***C***,
815 Histological verification of tetrode locations in intermediate dorsal CA1. Dotted lines indicate the
816 extent of recording sites across all five animals. ***D***, Classification of putative interneurons (Int,
817 gray crosses) from pyramidal cells (Pyr, black circles) based on spike width (> 8.5 Hz) and firing
818 rate (< 0.35 ms) parameters.

819

820 **Table 1**. Cell distribution across animals.

821 Summary of the number of taste-responsive and total CA1 cells recorded from each animal.
822 Only the cells meeting the inclusion criteria (see Materials and Methods) are reported. Putative
823 pyramidal cells (Pyr) and interneurons (Int) were identified on the basis of firing rate and spike
824 width parameters. Neurons were classified as "taste-responsive" if they exhibited responses to
825 taste presence, identity and/or palatability.

826

827 **Figure 2**. Subsets of hippocampal place cells and interneurons respond to tastes.

828 ***A-D***, Top panels, Example spatial firing maps of two place cells (left) and interneurons (right),
829 calculated with taste delivery periods (500 ms before to 2500 ms after taste delivery) omitted
830 from the analysis. Numbers on the bottom right of each plot denote peak spatial firing rate (FR)
831 in Hz. Bottom panels, Taste-evoked responses of each of the above neurons. Each colored
832 trace represents the mean firing rate to one of the four tastes (green: S, 4 mM saccharin; yellow:

833 N, 100 mM sodium chloride; blue: W, distilled water; red: Q, 5 mM quinine hydrochloride),
834 smoothed with a 1D Gaussian filter (σ = 5 ms), with the average of all four taste-evoked
835 responses indicated by the black dashed line. Light gray lines indicate the periods of significant
836 taste responsiveness (*p < 0.05, t-tests on successive time windows) for the place cell in **B** and
837 interneuron in **D**.
838
839 **Figure 3**. Taste-responsive hippocampal neurons exhibit weaker spatial selectivity than non-
840 taste-responsive hippocampal neurons.
841 ***A***, Example spatial firing maps of twelve non-taste-responsive (left) and taste-responsive (right)
842 place cells (Place, top row) and interneurons (Int, bottom row). Note that taste-responsive cells
843 tend to exhibit more diffuse spatial firing. All firing maps were computed with taste delivery
844 periods (500 ms before to 2500 ms after taste delivery) omitted from the analysis. Numbers on
845 the bottom right of each plot denote peak spatial firing rate (FR) in Hz. ***B***, Mean spatial
846 information content for non-taste-responsive (white bars) and taste-responsive (gray bars) place
847 cells and interneurons. Within each cell type, taste-responsive neurons had a lower spatial
848 information content than non-taste-responsive neurons (place cells: n = 337 non-taste-
849 responsive cells, n = 58 taste-responsive cells; unpaired t-test, ***p = 1.03e-06; interneurons: n
850 = 10 non-taste-responsive cells, n = 31 taste-responsive cells; unpaired t-test, **p = 0.0027).
851
852 **Figure 4**. Place cells respond to tastes delivered within their place field.
853 ***A-B***, Example in-field and out-of-field responses for a taste-responsive (**A**) and non-taste-
854 responsive (**B**) place cell. Left panels show the spatial firing maps for each cell, with place field
855 boundaries (defined as the largest region where firing exceeded 20% of the peak spatial firing
856 rate denoted on the bottom right of each plot) indicated by black lines. The colored symbols
857 represent locations of individual taste deliveries (green: S, 4 mM saccharin; yellow: N, 100 mM

858 sodium chloride; blue: W, distilled water; red: Q, 5 mM quinine hydrochloride), with in-field trials
859 denoted in pink. All firing maps were computed with taste delivery periods (500 ms before to
860 2500 ms after taste delivery) omitted from the analysis. Numbers on the bottom right of each
861 plot denote peak spatial firing rate (FR) in Hz. Right panels show the evoked responses to taste
862 deliveries taking place in-field and out-of-field for each cell. Each colored trace represents the
863 mean firing rate to one of the four tastes, smoothed with a 1D Gaussian filter (σ = 5 ms). Note
864 that taste responses are only found within the taste-responsive cell's place field (top center
865 panel). ***C***, Mean magnitude of taste responsiveness (eta-squared) for the in-field and out-of-field
866 regions of taste-responsive and non-taste-responsive place cells that fit our criteria (>10 trials
867 in- and out-of-field; n = 26 taste-responsive cells, n = 153 non-taste-responsive cells). The mean
868 eta-squared value for the in-field region of taste-responsive place cells (striped gray bar) was
869 higher than that of the in-field region of non-taste-responsive cells (striped white bar), the out-of-
870 field region of taste-responsive cells (gray bar), or the out-of-field region of non-taste-responsive
871 (white bar) cells (1-way ANOVA, ***p = 3e-05), indicating that place cells only respond to tastes
872 delivered within their place field.
873
874 **Figure 5**. Example hippocampal responses to different elements of the taste experience.
875 ***A***, Summary of the number of taste-responsive cells (n = 96/482 cells) that responded to taste
876 presence (Pres, n = 77 cells), identity (ID, n = 36 cells), and/or palatability (Pal, n = 18 cells). ***B***,
877 Example PSTHs from a taste-responsive place cell (top) and interneuron (bottom). Each colored
878 trace represents the mean firing rate to one of the four tastes (green: S, 4 mM saccharin; yellow:
879 N, 100 mM sodium chloride; blue: W, distilled water; red: Q, 5 mM quinine hydrochloride),
880 smoothed with a 1D Gaussian filter (σ = 5 ms), with the average of all four taste-evoked
881 responses indicated by the black dashed line. Light gray lines indicate periods of significant
882 responses to taste presence, while dark gray lines indicate periods of significant responses to

883 taste identity (*p < 0.05, t-tests on successive time windows). ***C***, Relative palatability of the four
884 taste stimuli as determined by a brief-access task. Palatability rank is determined by the
885 average number of licks per 15 s of exposure to the given taste. ***D***, Rank correlation (R^2)
886 between the taste-evoked firing rates and palatability rank (S > N > W > Q) for the place cell
887 (top) and interneuron (bottom) depicted in **B**. Black lines indicate periods of significant
888 palatability-relatedness (*p < 0.05, t-tests on successive time windows). Note the similarity
889 between the timing of palatability- and identity-related responses (dark gray lines in **B**).
890
891 **Figure 6**. Hippocampal neurons discriminate between tastes based on palatability.
892 ***A***, Histogram showing the percentage of hippocampal neurons that responded significantly to
893 taste presence (Pres, light gray line), identity (ID, dark gray line) or palatability (Pal, black line)
894 at each time point relative to taste delivery. Nonspecific responses to taste presence emerged
895 before responses to taste identity or palatability, which occurred at similarly long latencies. ***B***,
896 For the 19 cells that responded significantly to taste presence and identity, the onset of the
897 identity-related response (y-axis) is plotted against the onset of the presence-related response
898 (x-axis). Similar to what is seen in **A**, single-neuron responses to taste presence typically
899 preceded responses to taste identity, as evidenced by the cloud of points above the unity line
900 (black dashed line). ***C***, For the 14 cells that responded significantly to taste identity and
901 palatability, the onset of the palatability-related response (y-axis) is plotted against the onset of
902 the identity-related response (x-axis). Responses to identity and palatability tended to emerge
903 simultaneously in single units, as evidenced by tight clustering around the unity line (regression
904 slope: 0.92, ***p = 8.68e-06). ***D***, PCA of identity-responsive cells (n = 36 cells). Each colored
905 line depicts the PC of pooled responses to each of the four tastants (green: S, 4 mM saccharin;
906 yellow: N, 100 mM sodium chloride; blue: W, distilled water; red: Q, 5 mM quinine
907 hydrochloride) over time. Tastes were discriminated based on palatability, as shown by
908 significant encoding of palatability rank (S > N > W > Q, in reverse order here; **p < 0.01,

comparison to firing-rate-shuffled controls) by the PCs starting at ~1.4 s after stimulus delivery (black line).

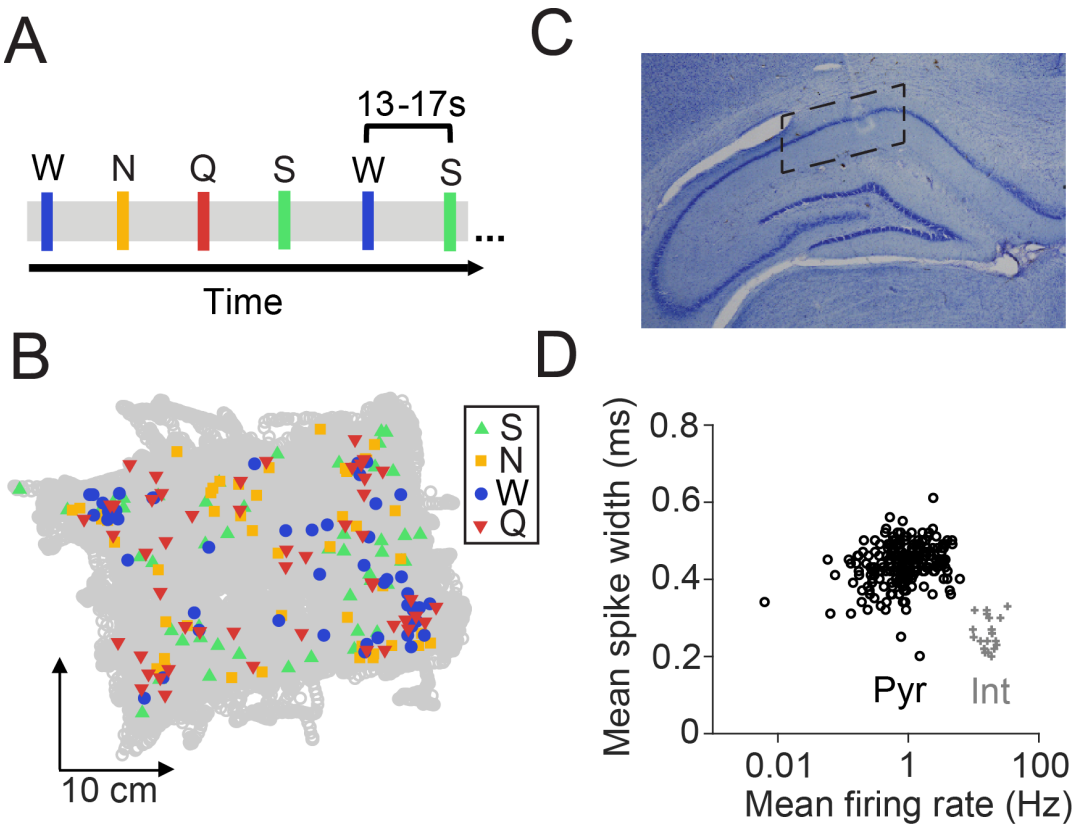

A
13-17s
W
N
Q
S
W
S
...
Time
B
S
N
W
Q
10 cm
C
D
Mean spike width (ms)
0.8
0.6
0.4
0.2
0
Pyr
Int
0.01
1
100
Mean firing rate (Hz)

Figure 1

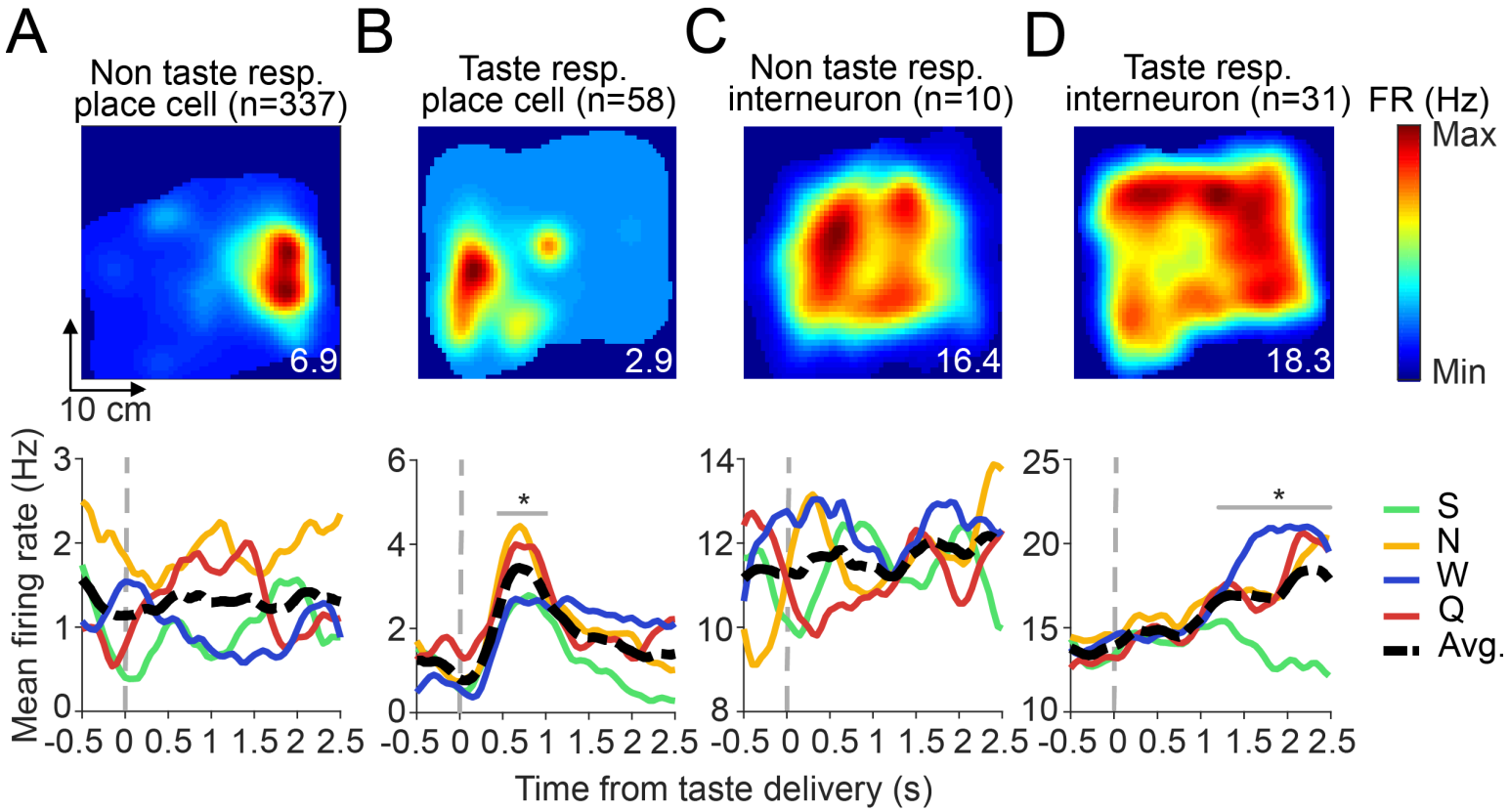

A
Non taste resp.
place cell (n=337)
6.9
10 cm
B
Taste resp.
place cell (n=58)
2.9
C
Non taste resp.
interneuron (n=10)
16.4
D
Taste resp.
interneuron (n=31)
18.3
FR (Hz)
Max
Min
Mean firing rate (Hz)
Time from taste delivery (s)
S
N
W
Q
Avg.

Figure 2

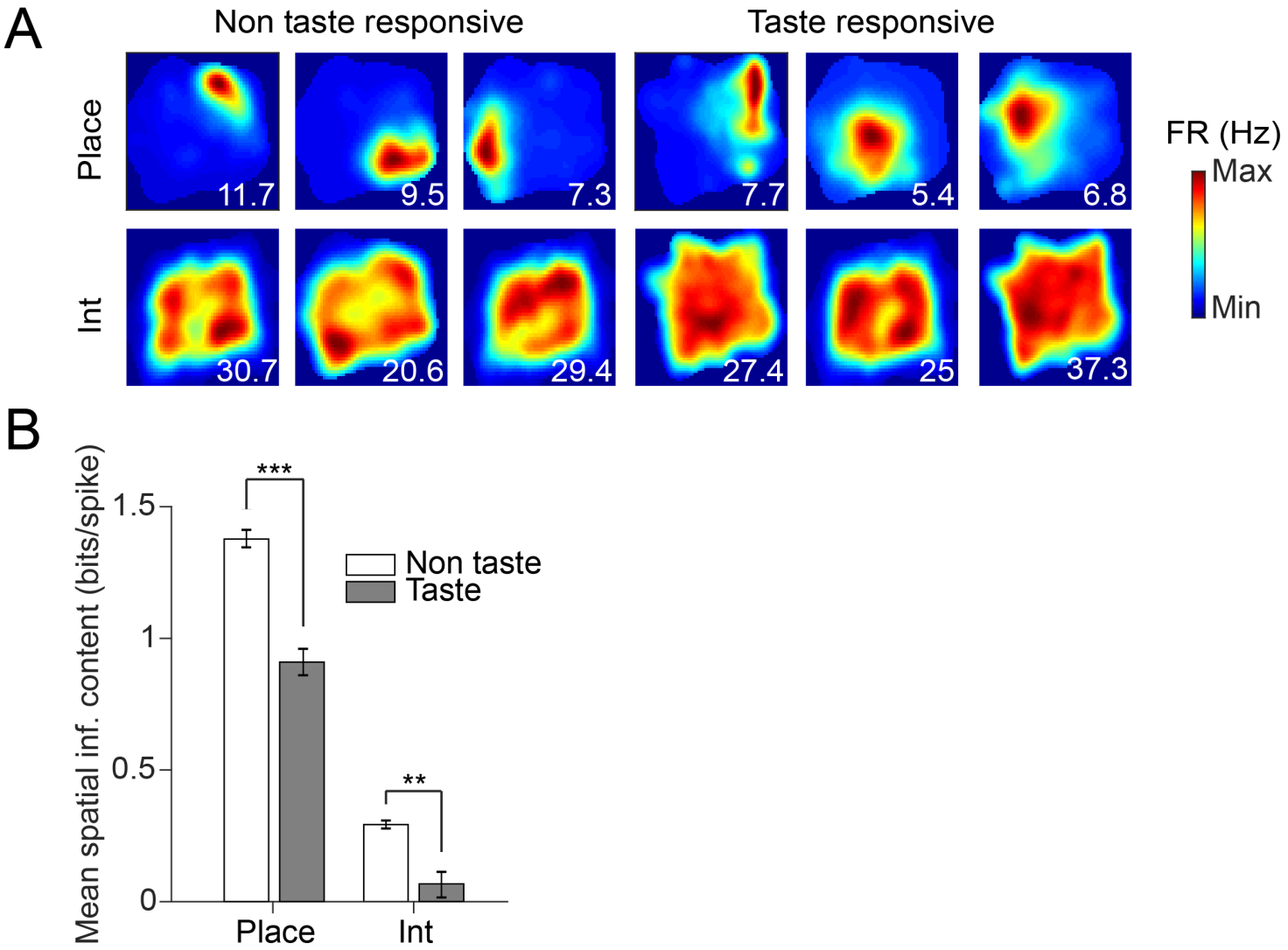
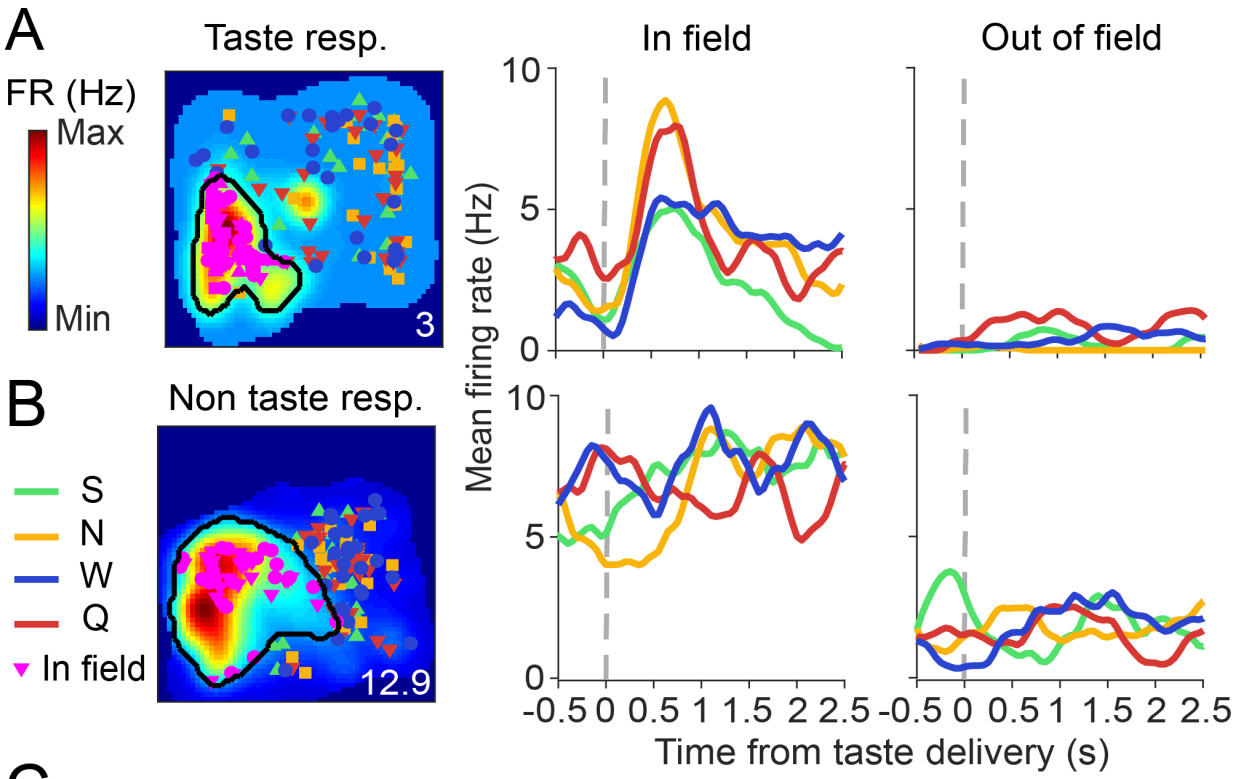

A
Non taste responsive
Taste responsive
Place
Int
11.7
9.5
7.3
7.7
5.4
6.8
30.7
20.6
29.4
27.4
25
37.3
FR (Hz)
Max
Min
B
Mean spatial inf. content (bits/spike)
1.5
1
0.5
0
***
**
Non taste
Taste
Place
Int

Figure 3


A
Taste resp.
FR (Hz)
Max
Min
3
In field
Out of field
B
Non taste resp.
S
N
W
Q
In field
12.9
Mean firing rate (Hz)
10
5
0
-0.5 0 0.5 1 1.5 2 2.5
Time from taste delivery (s)

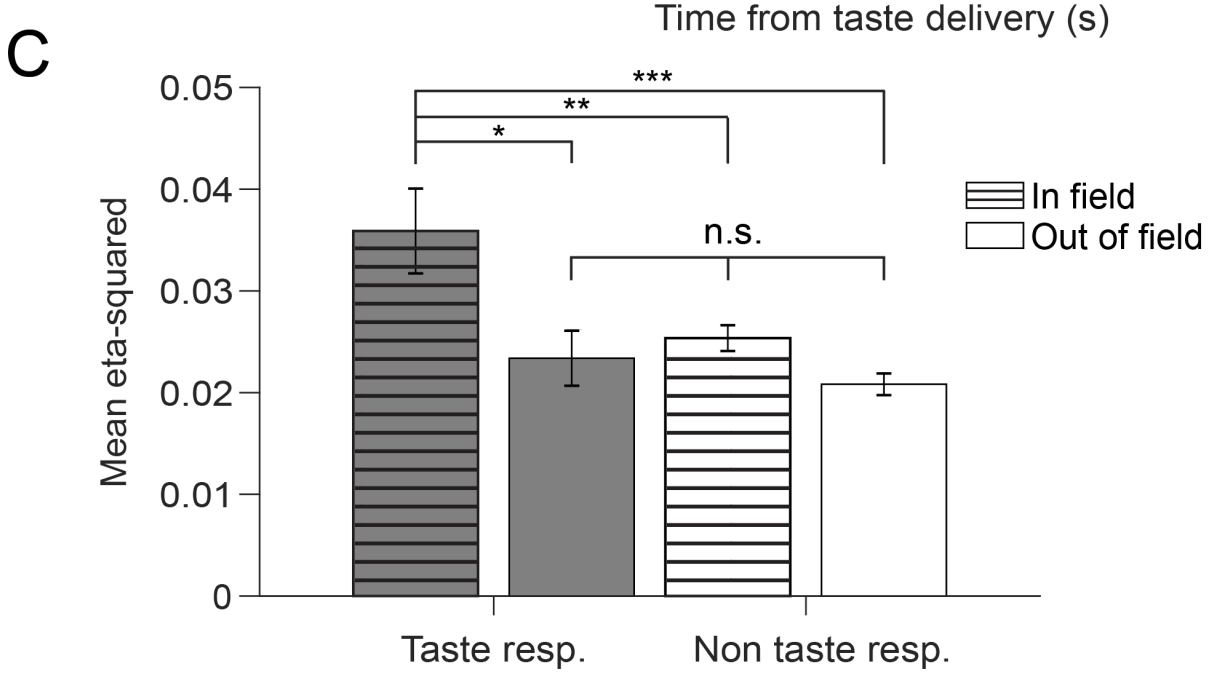

C
Mean eta-squared
0.05
0.04
0.03
0.02
0.01
0
***
**
*
n.s.
In field
Out of field
Taste resp.
Non taste resp.

Figure 4

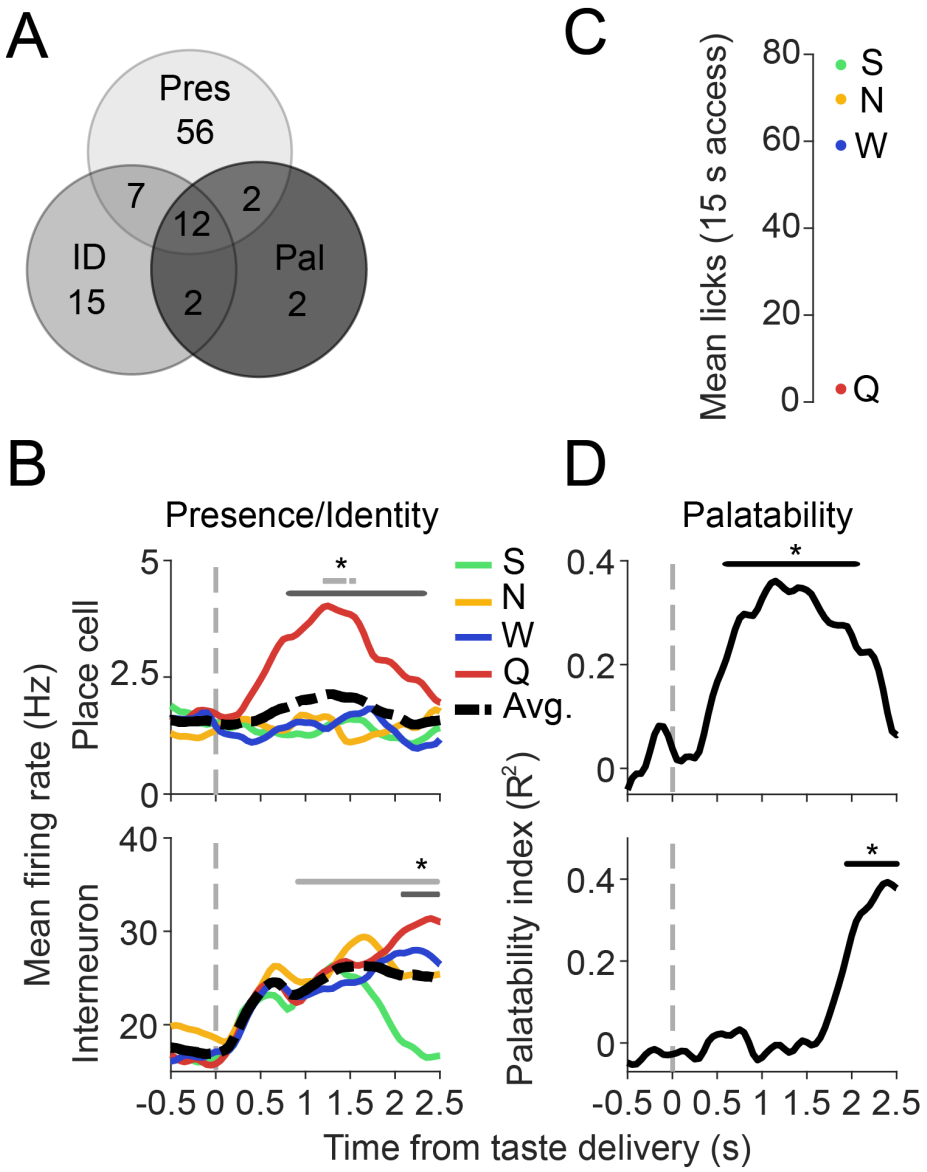

A
Pres
56
7
2
12
ID
15
Pal
2
2
C
Mean licks (15 s access)
80
60
40
20
0
S
N
W
Q
B
Presence/Identity
Mean firing rate (Hz)
Place cell
Interneuron
5
2.5
0
40
30
20
*
S
N
W
Q
Avg.
-0.5 0 0.5 1 1.5 2 2.5
Time from taste delivery (s)
D
Palatability
Palatability index (R^2)
0.4
0.2
0
*
-0.5 0 0.5 1 1.5 2 2.5

Figure 5

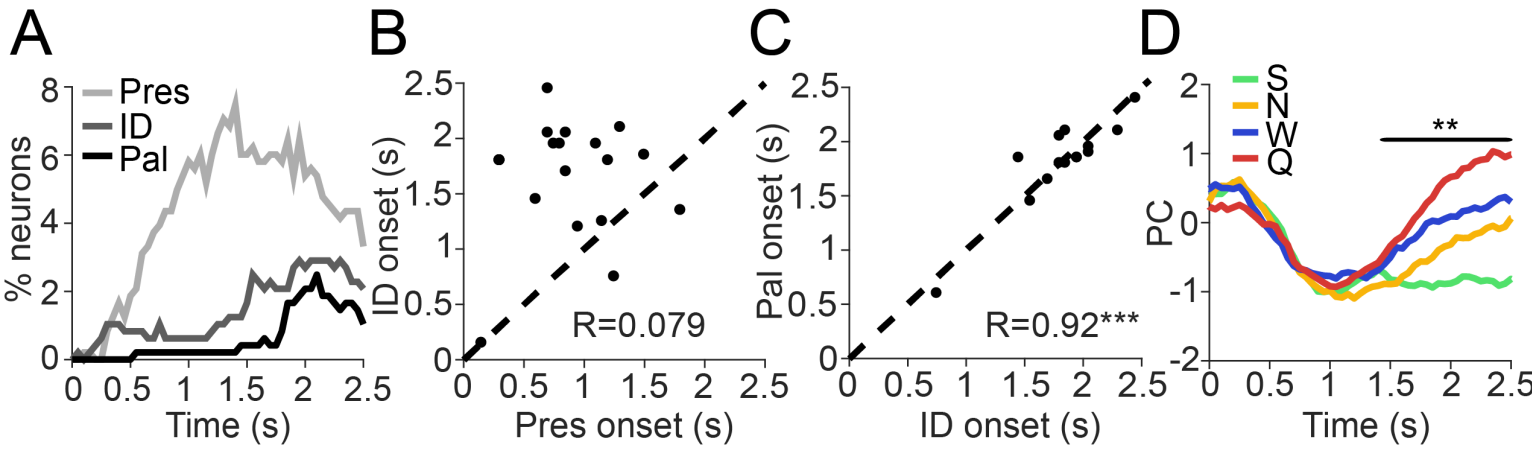

A
Pres
ID
Pal
% neurons
Time (s)
B
ID onset (s)
Pres onset (s)
R=0.079
C
Pal onset (s)
ID onset (s)
R=0.92***
D
S
N
W
Q
PC
Time (s)
**

Figure 6