Experience-induced drift in the neural coding of individual differences in perception

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Abstract

Like humans, no two rodents like precisely the same tastes. Here, we ask whether these individual differences determine cortical taste responses, late epochs of which "code" palatability. We show that rats' individual preferences match late-epoch responses with a fidelity significantly higher than that expected on the basis of canonical palatability rankings. A single tasting session, however, induces "neural drift," such that previously-assessed preferences are no longer reflected in cortical activity.

Main Text

The basic task of an animal's sensory system—processing input such that the animal can generate appropriate behavioral output—is particularly vital when said input is a gustatory stimulus, because consumption decisions must be made when the potentially dangerous substance is already in the animal's mouth. Palatability (the hedonic value associated with a taste) is the primary variable informing the selection of appropriate responses (swallowing or rejection) to such stimuli.

Primary gustatory cortex plays a major role in this process. Mammalian cortical taste responses[1-3] unfold through three firing-rate epochs[4], with palatability-relatedness—higher firing in response to desirable tastes and lower in response to undesirable tastes (or vice-versa)—emerging in the 3rd of these epochs, 700-1200ms after taste delivery. This emergence predicts[5,6] and drives[7] appropriate consumption behaviors.

Analyses supporting the above findings have been founded on the fact that certain tastes are typically much more desirable (sucrose) than others (quinine), ignoring individual differences. Such differences abound, however—just as human preferences vary from individual to individual[8,9], different rats prefer different tastes[10,11]. It is reasonable to hypothesize that individual variability in cortical responses should accurately track that individual's current taste preferences. To our knowledge, however, tests of such hypotheses have never been attempted.

To fill this gap, we used lick bout analysis of Brief-Access Task data[12] to quickly assess individual taste preferences in 10 rats (Figure 1A). As predicted, palatabilities were very different from rat to rat (Figure 1B); even the orders of preferences sometimes differed from well-established canonical ranks (sucrose>NaCl>citric acid>quinine; Figure 1C).

We then implanted these same rats with electrode bundles and intra-oral cannulae (Figure 2A), and, following recovery and habituation, recorded the spiking responses of cortical single neurons (15.9±6.83 units/session, total n=255) to the same tastes that had been offered in the preference tests. Figure 2B shows a typical cortical response; this neuron's firing became taste-specific before 200msec, then became significantly palatability-related (i.e., correlated with canonical preferences) only later. This pattern was consistent with those of previous studies[4,5]. When we used each rat's own taste preference data in place of canonical ranks, the correlation of palatability with firing significantly increased (Figure 2C). This effect was reliable across animals (Figure 2D) and localized to the response epoch devoted to palatability coding (Figure 2E). Note that this increase emerged despite the use of vastly different taste administration methods in the preference test (licking) and electrophysiology session (intra-oral cannula)—a fact that highlights the significance of the result—and that the correlation survived an 11-day separation between preference tests and recording sessions. We conclude that a rat's individual taste preferences drive individual variability in their cortical taste responses, and that this relationship is stable across almost 2 weeks.

This stability contrasts strikingly with the "neural drift" induced by the tasting session itself. When we performed a second such session, just 24 hours after the first, changes emerged in the taste responses of many neurons held across both sessions—changes that reduced the correlation of late-epoch firing with that rat's previously-evaluated individual taste preferences (Figure 3A). When we separated data by recording session, the late-epoch correlation with canonical palatability ranks was apparent in both sessions 1 & 2, but the enhancement in that correlation realized when the rat's individual preferences were used was specific to session one (Figure 3B-C).

We reach a pair of conclusions: First, the dynamics of cortical taste responses, and in particular the late emergence of palatability-related firing, are a valid characterization of the taste processing being done by the rat; the GC responses specifically reflect that rat's individual taste preferences. Second, a single taste session suffices to change taste responses that were apparently stable across the preceding 2 weeks; this result, which is consistent with work on taste experience[13,14], suggests that "neural drift"[16] is highly sensitive to a rat's experience with the sensory stimuli under study.

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Materials and Methods

Subjects

Female Long Evans rats single-housed in independently-ventilated cages on a 12h/12h light/dark schedule are acclimated to the facility and handled for 1 week before any experimental procedures. Unless otherwise specified, animals in home cages have ad lib access to chow and water. All experiments were conducted in accordance with the Brandeis Institutional Animal Care and Use Committee (IACUC).

Brief Access Task and Individual Preference Testing

Individual taste preferences were measured using brief-access-task (BAT). The BAT rig (Davis MS-160 Lickometer apparatus (MedAssociates Instruments)) measures each lick to a tastant while permitting control over maximum latency to lick (set to 60s), maximum access time(10s), and inter-trial intervals (10-30s) and delivering tastants in a pseudo-randomized order to ensure that identical tastants did not immediately follow each other and that multiple aversive tastants were not delivered sequentially. Each tastant was presented 8 times, for a total presentation count of 56 taste presentations per session. A fan was present above the rig to reduce odor cues during task participation. All experiments were run between 10:00-14:00.

Before preference testing, rats underwent three days of 45-minute dry habituation within the BAT rig to familiarize the rat to the experimental chamber. Following habituation, rats were placed on water restriction and underwent two days of water habituation, with 30 presentations of two alternating water tubes. Water habituation data were used to ensure no bottle preference (no rats showed significant preference for one bottle). For preference test assessment, rats were tested for 3 (taste set 1, 2 and 3) or 5(set 4) consecutive days and each received one of three tastant sets which remained consistent throughout testing. The three tastant sets were as follows (in canonical preference rank order):

Set 1: 0.1M NaCl, 0.05M NaCl, Water, 0.009M Citric Acid, 7.8E-5M Quinine HCl (QHCl)

Set 2: 0.3M Sucrose, 0.1M NaCl, Water, 0.1M Citric Acid, 0.001M QHCl

Set 3: 0.3M Sucrose, Water, 0.001M QHCl

Set 4: 0.3M Sucrose, 0.005M Saccharine, 0.1M NaCl, Water, 0.1M Citric Acid

All tastants were dissolved in deionized water and formulated the day of each experiment.

Several lick behaviors are measured for each tastant presentation, including lick count and bout count (cumulative licks before a 500ms pause takes place). Trials in which the animal did not lick were considered no-participation and excluded from analysis. Mean licks per 10 second access period were calculated as the average over all tastant experiment days. Mean bout length is the average of all bout lengths for that taste for all experiment days when no-participation trials are excluded (referred to as bout data). Bout ranks are the rank order as determined from the order of the bout mean values.

Computational analysis of BAT data

Data captured during the BAT component of the experiment was processed and analyzed in python. Libraries integral to the analysis included: pandas, numpy, pingouin, matplotlib, and seaborn. Presentations which resulted in 0 licks were deemed ‘no participation’ and were excluded from any analysis.

Surgical implantation of GC electrode and Intra-Oral Cannula

After Rats recovered their weight from water deprivation, they underwent implantation surgery. Rats were anesthetized with an intraperitoneal injection of xylazine and ketamine dosed appropriately to body weight (100mg/kg and 5mg/kg respectively). The electrode, a bundle of 32 25µm microelectrode wires attached to a mini-Microdrive, was implanted into GC (A/P = +1.4, M/L = -5.0, D/V = -4.4). Rats also received an intra-oral cannula (IOC); a polyethylene cannula implanted behind the maxillary molars, through the left masseter muscle and through the opening of the scalp. Rats recover for 7 days before next experimental procedures.

Electrophysiological recording and passive tastant delivery experiment

Rats habituated for 2 days for 30 minutes to the electrophysiological recording rig. The rats are placed on a mild water restriction and the following 2 days they are habituated to liquids delivered through the IOC (60 trials on day 1 and 120 trials on day 2; 22s inter-trial-intervals (ITI)). Finally, data are collected for each rat over at least 2 consecutive testing days where each rat received 30 presentations of three or four tastants in random order with 22s ITI (~1 hour for each session). These tastes were selected from the taste set they received during the BAT task formulated the same as above:

Set 1: 0.1M NaCl, 0.05M NaCl, 0.009M Citric Acid, 7.8E-5M QHCl
Set 2: 0.3M Sucrose, 0.1M NaCl, 0.1M Citric Acid, 0.001M QHCl
Set 3: 0.3M Sucrose, Water, 0.001M QHCl
Set 4: 0.3M Sucrose, 0.005M Saccharine, 0.1M NaCl, 0.1M Citric Acid

The gas-powered rig was calibrated to deliver 30 microliters of each stimulus during a single presentation (total session volume: ~4mL) through the IOC. All deliveries were controlled by a Raspberry-Pi microcomputer. Spiking data was collected via Intan RHD2132 analog-to-digital chip amplifier. Recordings were taken at a sampling rate of 30 khz and cleaned immediately using a software High-Pass filter and 60hz notch filter. Electrodes were driven down (~0.25mm) after each session to capture new cells with each session. The entire recording rig was enclosed in a faraday cage to reduce latent electromagnetic interference during recordings.

Electrophysiology data processing

Bandpass filtering and common average referencing were employed to further clean data and increase signal quality. Discriminable action potentials of no less than 3:1 signal-to-noise ratio were isolated on-line from each signal and saved digitally. Prior to analysis of taste-related activity, cells are clustered using 3-D cutting techniques alongside supervised verification of inter-spike interval plots. All spikes included in analysis had at least 2000 waveforms and met our criteria of <0.5% 1ms violations and <2% 2ms inter-spike interval violations. For a comprehensive explanation of the protocol used for spike sorting in this project, refer to Mukherjee et al., 2017. By driving down the mini-microdrive between sessions, new cells were captured each day, which was verified by comparing waveform shapes.

Semi-processed spiking arrays were then exported to an analysis framework built in python. After processing, each 7000ms (2s pre stimulus, 5s post stimulus) recording window was binned using a sliding window average with window size of 250ms and step size of 25ms. Peri-stimulus time histograms (PSTHs) were constructed out of each single neuron's binned activity activity with lines smoothed with gaussian filter (sigma = 1.5).

Next, canonical and preference-based rank orders gathered during BAT (referred to as bout ranks) were tested for rank correlation (Pearson) against spiking data for each time bin, epoch-wise. Individual rat's bout data was also correlated against spiking data for that rat (Spearman). Epochs were defined as follows: Baseline: -700ms:-250ms; detection: 1ms:250ms; identity: 250ms:0ms; palatability: 750ms:1250ms; Canonical rank and bout rank spiking correlation values were then compared using a two-tailed student's T test for each epoch. The effect was considered significant if $p<0.05$.

Histology

Following the experimental sessions, subjects were deeply anesthetized with ketamine/xylazine mix (200, 20 mg/kg respectively, delivered via intraperitoneal injection) and perfused via intra-ventricular perfusion of saline, followed by 10% formalin. Brains were then extracted for histological verification of electrode placement. As the canula of electrodes are painted with a fluorescent cell-labeling dye to verify electrode location slices were stained with a Nissl stain to highlight regional markers and confirmed cannula track is above and the electrode tip sits in GC. One animal was excluded from electrophysiology data processing for electrode misplacement (BAT data included in Figure 1).

Data availability

The data within this study can be made available from the corresponding author upon reasonable request.

Code availability

Analyses were conducted in python. The scripts used for these data analyses are available at https://github.com/kmaigler/blech_indiv_pref for review. It will be uploaded to a permanent repository (Zenodo) upon acceptance.

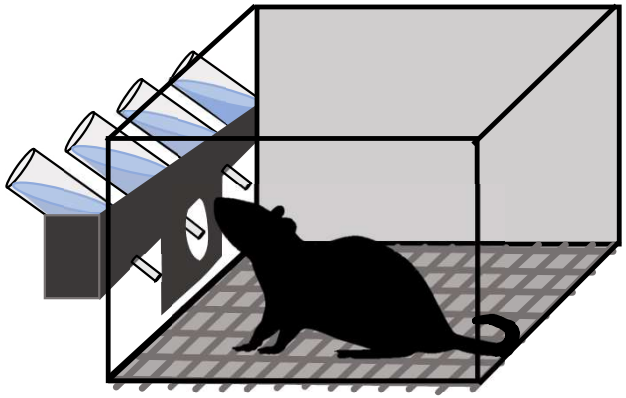
Figures

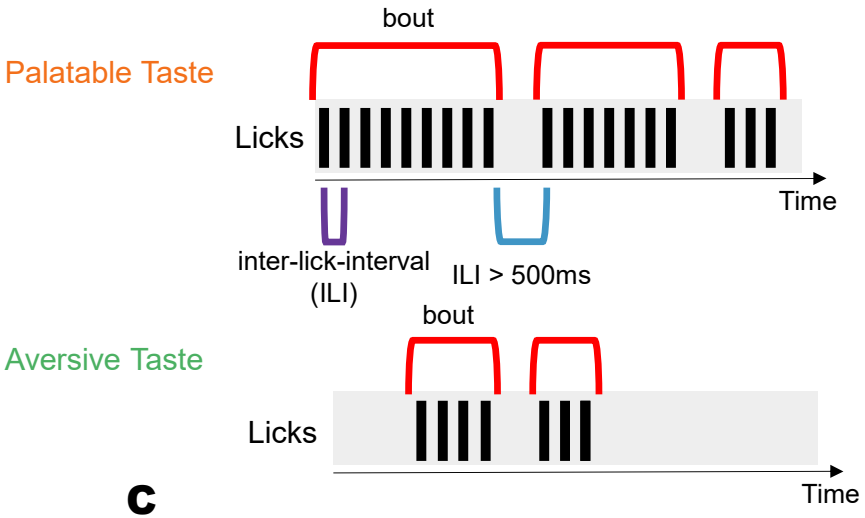
Figure 1. Individual variability in taste palatability. A. The brief-access rig—multiple bottles, each made available periodically. To the right are example data schematizing the analysis of rhythmic licking to pull out lick numbers and "bout lengths," both of which reflect palatability. See Methods for details. B. The behavioral data from the 10 rats, showing variability in preferences; each rat experienced only a subset of possible tastes. C. Left, the difference between licking to (pleasing) sucrose and NaCl by rats that correspond to 1, 2, 3, and 6 from (B); right, the difference between licking to (aversive) quinine and citric acid by rats 1, 2, 5, and 10. Note the large variability in relative preferences and change from canonical rank order.

Figure 2. Palability-relatedness of taste responses match individuals' preferences. A. Schematic of extracellular electrode placement and example coronal slice from a rat, showing canula tract (visualized by the red cell-label) localized above gustatory cortex (GC) and electrode wires sitting in GC (white dashed outline). Below, the experimental timeline (Ephys = Electrophysiological recording). B. PSTHs (see Methods) to 4 tastes for a representative cortical neuron, showing typical response dynamics; the correlation between (canonical) palatability and firing across time for this same neuron, which rises beginning at ~0.5s, and becomes significant (exceeding 1.96 SD of pre-stimulus correlations) at 0.45s (black line, right y-axis). C. Time series of palatability correlation for representative animal (n = 19 neurons), shows the rise in palatability in cortical firing using canonical palatability ranks is exceeded by the rise using that animal's individual preferences (bout data, blue). D. Across the 9 rats, the correlation difference (preference – canonical) is significantly enhanced ($t(255)>2$, $p<0.01$) beginning at the palatability epoch (0.7sec); black line denotes onset of significance. E. Grouped bar plot reveals that gustatory cortex codes rats' distinctive palatability patterns stronger than a ranked order during the palatability-related epoch ($F(255)= 5.35$, $p<0.01$).

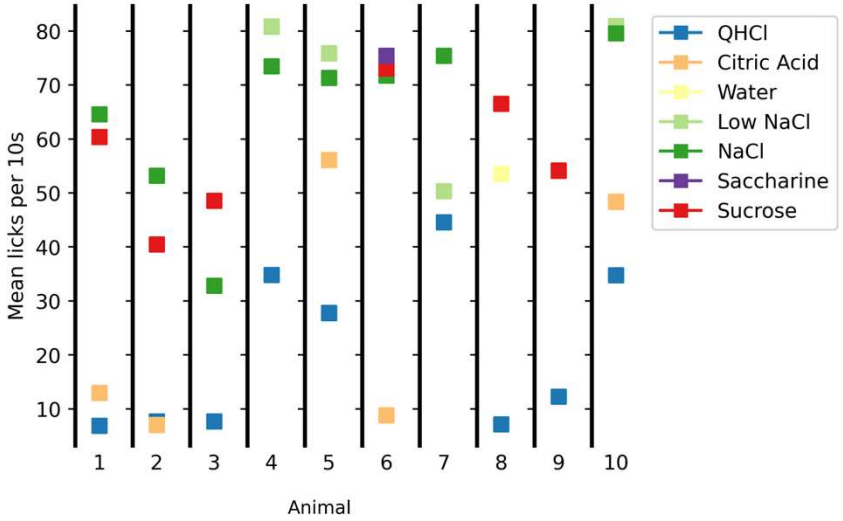
Figure 3. "Drift" of cortical palatability coding because of a single tasting session. **A1**. PSTH for a representative neuron held across the 2 recording sessions, showing palatability correlation (Pearson) overlaid in black for the first recording session. **A2.** For the second recording session, this neuron shows subtle changes in the response that caused a loss of palatability-relatedness (black, right y-axis). **B1**. The evidence that cortical coding of palatability matches rats' individual preferences is unquestionable in session 1. **B2**. Cortical coding no longer matches rats' individual preferences in session 2. **C**. A summary of the data in B1-2, showing the difference between days 1 and 2 in the palatability epoch (0.75-1.25s; ($t(101)>6$, $p<0.001$).

A

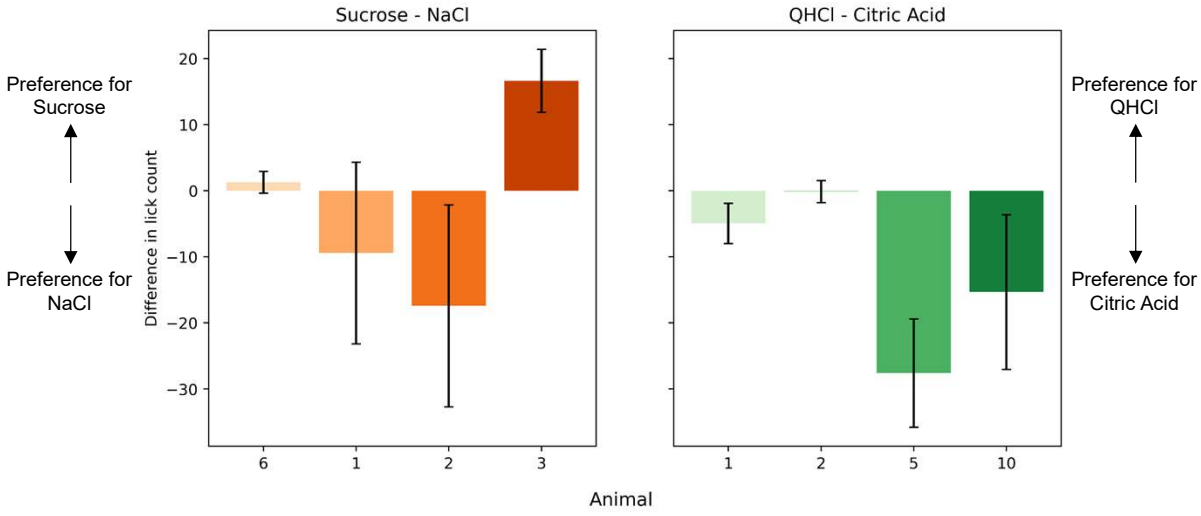


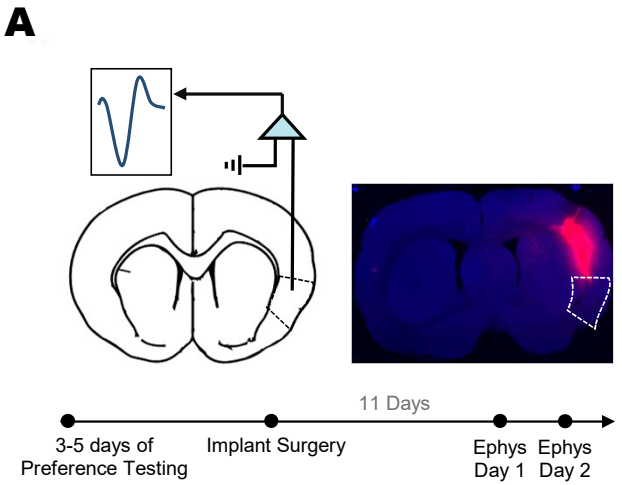

Palatable Taste
bout
Licks
Time
inter-lick-interval
(ILI)
ILI > 500ms
Aversive Taste
bout
Licks
Time

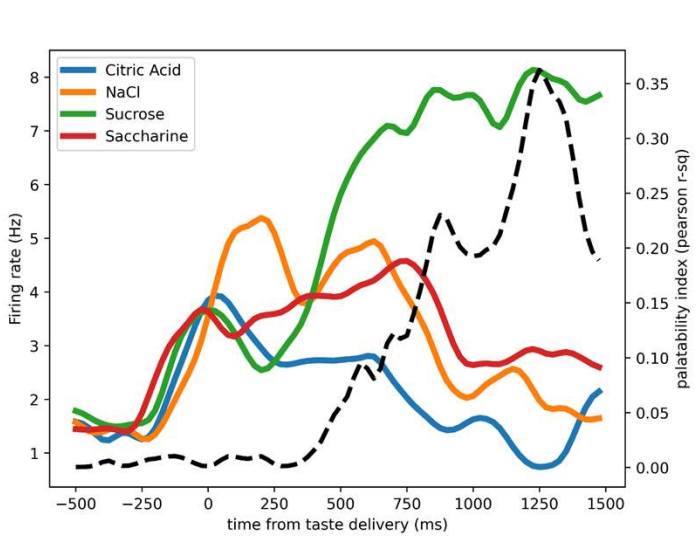
B

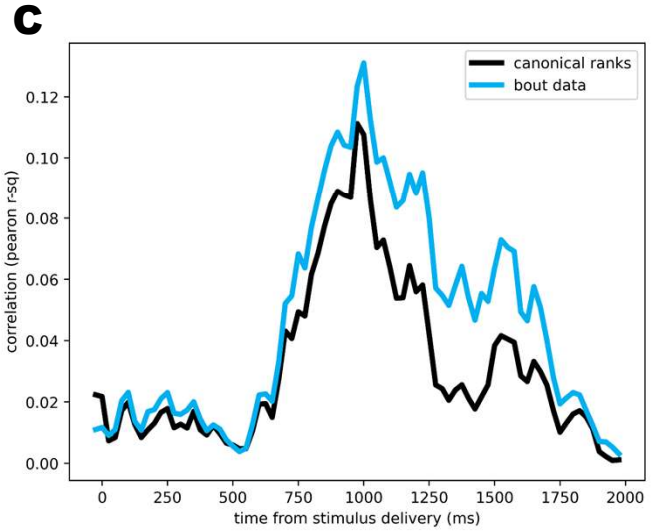

Mean licks per 10s
80
70
60
50
40
30
20
10
1
2
3
4
5
6
7
8
9
10
Animal
QHCl
Citric Acid
Water
Low NaCl
NaCl
Saccharine
Sucrose

C

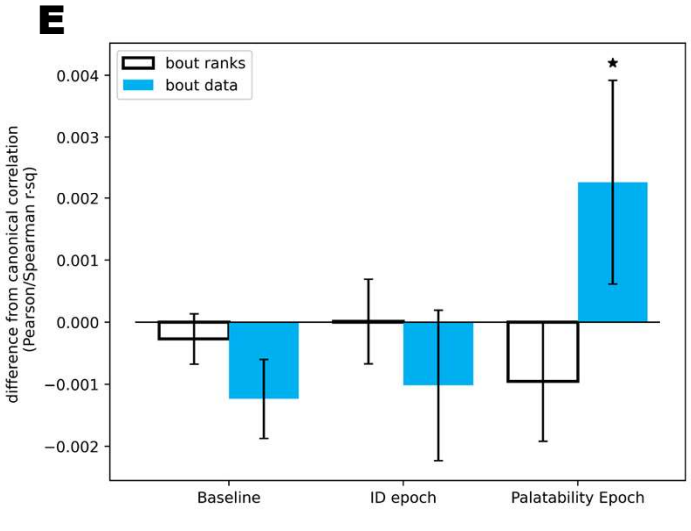

Sucrose - NaCl
QHCl - Citric Acid
Preference for
Sucrose
Preference for
NaCl
Difference in lick count
20
10
0
−10
−20
−30
6
1
2
3
1
2
5
10
Animal
Preference for
QHCl
Preference for
Citric Acid

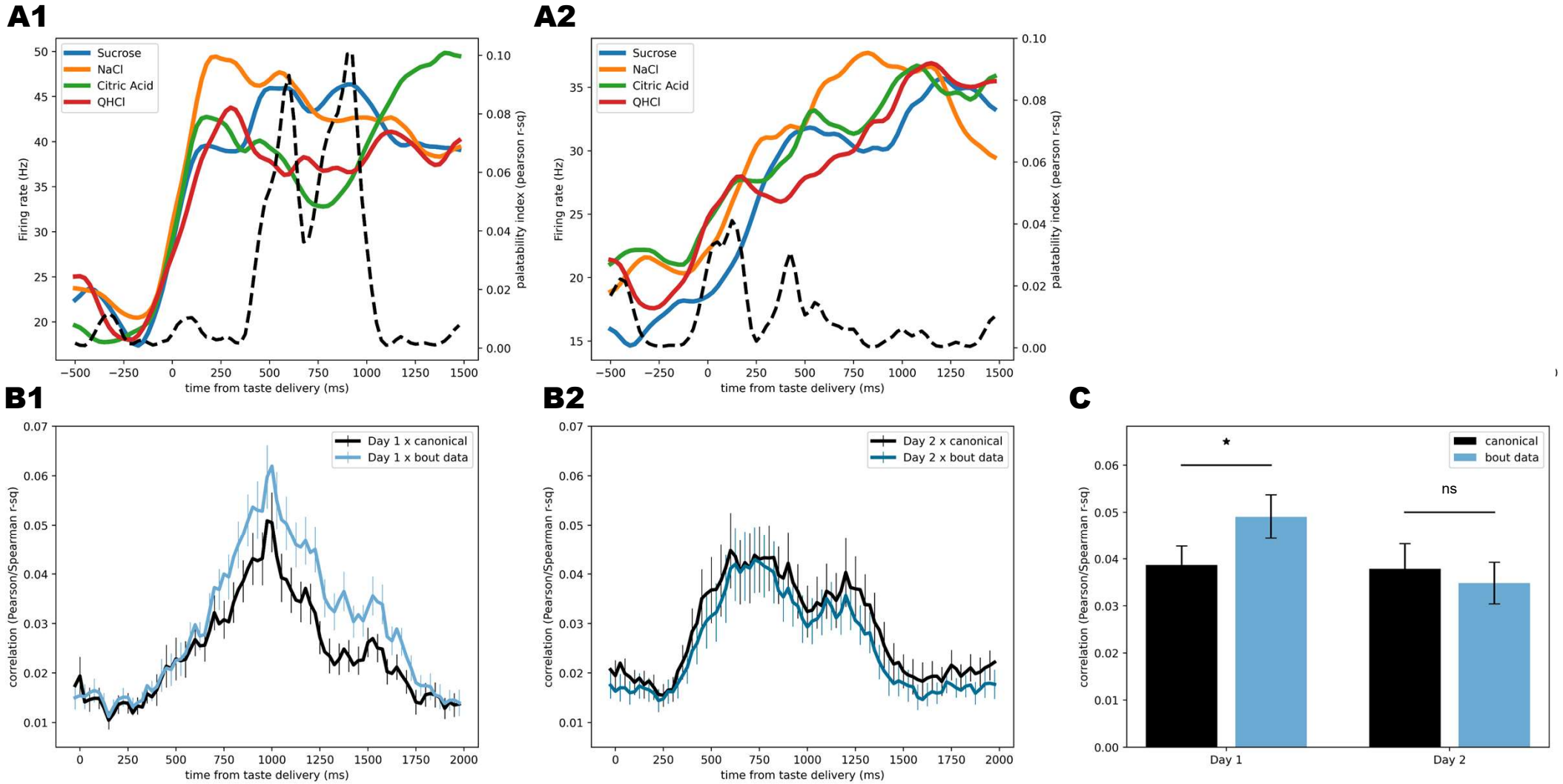

A
11 Days
3-5 days of
Preference Testing
Implant Surgery
Ephys
Day 1
Ephys
Day 2


B
Citric Acid
NaCl
Sucrose
Saccharine
Firing rate (Hz)
palatability index (pearson r-sq)
time from taste delivery (ms)


C
canonical ranks
bout data
correlation (pearon r-sq)
time from stimulus delivery (ms)


D
bout data
difference from canonical r-sq values
time from taste delivery (ms)


E
bout ranks
bout data
difference from canonical correlation
(Pearson/Spearman r-sq)
Baseline
ID epoch
Palatability Epoch


A1
A2
B1
B2
C
Sucrose
NaCl
Citric Acid
QHCl
Firing rate (Hz)
palatability index (pearson r-sq)
time from taste delivery (ms)
Day 1 x canonical
Day 1 x bout data
Day 2 x canonical
Day 2 x bout data
correlation (Pearson/Spearman r-sq)
canonical
bout data
*
ns
Day 1
Day 2