

1 **RHYTHMIC ACTIVITY IN THE MEDIAL FRONTAL CORTEX ENCODES**  
2 **RELATIVE REWARD VALUE**

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16 Abbreviated title: Value coding by the medial frontal cortex

17 Conflict of Interest: None

18 Financial Support: NSF grant 1121147, NIH grant DK099792-01A1, and the Klarman Family

19 Foundation to ML and a NSF Graduate Research Fellowship to LMA.

20 **Abstract**

21 How do we know the reward value of a given food or fluid? The item must first be consumed  
22 and only then can its relative value be computed. Rodents consume fluids by emitting rhythmic  
23 trains of licks and reward value is likely encoded by neuronal activity entrained to the lick cycle.  
24 Here, we investigated the relationship between licking and reward signaling by the medial  
25 frontal cortex (MFC), a key cortical region for reward-guided learning and decision-making. Rats  
26 were tested in an incentive contrast procedure, in which they received alternating access to  
27 higher and lower value sucrose rewards. Neuronal activity in the MFC encoded the relative value  
28 of the ingested fluids, showing stronger entrainment to the lick cycle when animals ingested  
29 higher value rewards. The signals developed with experience, encoded the reward context, and  
30 depended on neuronal processing within the MFC. These findings suggest that consummatory  
31 behavior drives reward signaling in the MFC.

## 32 **Introduction**

33 The medial frontal cortex (MFC) is a crucial brain region for the adaptive control of behavior.  
34 Across species, the MFC monitors behavioral outcomes and enables adjustments in  
35 performance (Shidara and Richmond, 2002; Ito et al., 2003; Amiez et al., 2006; Narayanan and  
36 Laubach, 2006; Luk and Wallis, 2009; Sul et al., 2010; Narayanan et al., 2013). In behavioral  
37 neuroscience studies, information about behavioral outcomes must be generated by the act of  
38 consuming foods and fluids given as rewards for correct responding. However, interpretations  
39 of MFC processing have largely been drawn from experiments in which reward-related signaling  
40 was measured in responses to reward predictive stimuli (e.g. Otis et al., 2017) or during the  
41 period of reward consumption without regard to the animal's ongoing ingestive behavior (e.g.  
42 Jezzini et al., 2013; Donnelly et al., 2014).

43 A recent study from our laboratory (Horst and Laubach, 2013) reported that licking  
44 influences neural activity in the pregenual MFC. Neuronal firing rates were modulated around  
45 bouts of licks, which were further denoted by phase-locking of field potentials in the theta range  
46 (4-8 Hz). These signals might be expected given the anatomy of the pregenual MFC. The medial  
47 part of the pregenual MFC, called the prelimbic cortex (aka area 32), is reciprocally connected  
48 with the agranular insular cortex (Gabbott et al., 2003), which contains taste-responsive neurons  
49 (e.g. Stapleton et al., 2006). Moreover, the most prominent subcortical projections of the  
50 prelimbic cortex are to subcortical autonomic centers such as the hypothalamus, periaqueductal  
51 gray, and nucleus of the solitary tract (Floyd et al., 2000; Floyd et al., 2001; Gabbott et al., 2006;  
52 Reppucci and Petrovich, 2015). These connections may mediate the ability of the prelimbic  
53 cortex to regulate breathing (Hassan et al., 2013), which must be adjusted with regard to  
54 consummatory actions.

55 The more lateral part of the rostral MFC, called the medial agranular cortex (AGm or M2),  
56 has been described as "jaw opening" motor cortex (Yoshida et al., 2009; Haque et al., 2010) and  
57 projects to the trigeminal motor (Yoshida et al., 2009) and sensory (Iida et al., 2010) nuclei. A  
58 number of studies have recently examined the caudal (peri-callosal) part of this region, and

59 established that it controls head movements (Erlich et al., 2011), whisking (Brecht et al., 2004),  
60 and action-based value selection (Kargo et al., 2007; Sul et al., 2011). This caudal part of the MFC  
61 may play a general role in adaptive choice behavior, specifically in mapping or integrating  
62 sensory signals into motor outputs (Barthas and Kwan, 2017). No study has examined the  
63 functional properties of the more rostral MFC, where Horst and Laubach (2013) reported  
64 prominent licking-related neuronal activity, with regard to reward-guided decisions.

65 Therefore, the goal of the present study was to address the role of the rostral MFC  
66 (prelimbic and AGm areas) in the control of reward-guided behavior. We used a simple take-it-  
67 or-leave decision-making task, called the Shifting Values Licking Task (Parent et al., 2015a,b), to  
68 study reward signaling in relation to ongoing consummatory actions. Rats lick on a spout to  
69 receive liquid sucrose rewards and the relative value of the fluids alternates between a better  
70 and worse option every 30 sec. Rats learn to persistently lick for the better option and suppress  
71 licking when the worse option is available. They show incentive contrast effects when tested  
72 with only single levels of rewards (i.e. the duration of licking bouts is prolonged when rats lick  
73 for a higher value fluid when it is presented in alternation with a lower value fluid compared to  
74 when only the higher value fluid is available). Bilateral reversible inactivations of the rostral MFC  
75 impair performance in this task (Parent et al., 2015a): With MFC inactivated, rats fail to show  
76 incentive contrast effects and demonstrate temporally fragmented licking (i.e. the duration of  
77 licking bouts is reduced). Opposite effects were found when rats are tested with drugs that  
78 enhance neuronal excitability, such as the hunger hormone ghrelin (Parent et al., 2015b).

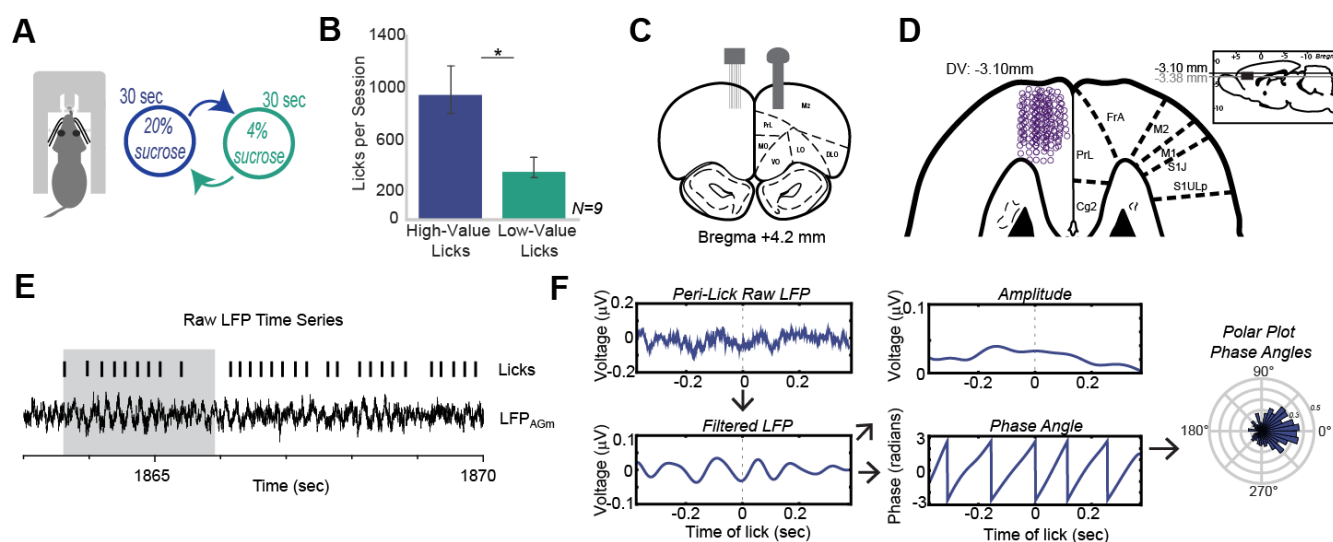
79 To examine how the rostral MFC encodes relative reward values and controls value-  
80 guided consumption, we recorded spike activity and local field potentials (LFPs) as rats  
81 performed the Shifting Values Licking Task. We analyzed neuronal activity in relation to the  
82 animals' ongoing licking behavior and as a function of the relative reward value of the ingested  
83 solutions. We found that neuronal activity in the MFC encoded the relative value of the ingested  
84 fluids, showing stronger entrainment to the lick cycle when animals ingested higher value  
85 rewards. In some of the rats, we recorded neuronal activity as the rats progressed through the

86 initial sessions of operant training, and found that these signals developed with experience.  
87 Next, we modified the task to include periods of non-reinforced licking, so we could determine if  
88 the signals reflected the receipt of reward (perhaps driven by sensory information from the  
89 taste system). Surprisingly, we found that the neuronal coding of relative value persisted  
90 throughout the periods when the higher and lower value fluids were available, suggesting that  
91 the signals encode the reward context. Finally, we used unilateral reversible inactivations (via  
92 muscimol) to determine if the reward signals depended on processing by neurons in the MFC.  
93 The unilateral reversible inactivations had minimal effects on licking behavior (compared to  
94 Parent et al., 2015a), but reduced the differential encoding of reward value for neuronal signals  
95 recorded in the opposite hemisphere. Together, our findings suggest that consummatory  
96 behavior drives signaling in the MFC that is used to compare the relative reward values of  
97 ingested foods and fluids.

## 98 **Results**

99 To investigate the role of the frontal cortex in reward-related consummatory behaviors,  
100 we assessed licking behavior in rats while performing simultaneous recordings in the rostral  
101 MFC. We trained rats in the shifting values licking task (Parent et al., 2015a), in which they licked  
102 at a drinking spout to receive 0.025 ml of a liquid sucrose reward (Figure 1A). The reward value  
103 of the fluid switched between higher (20% sucrose wt/vol) and lower (2 or 4%) levels every 30  
104 seconds. After only three to five 30 minute sessions, rats show increased licking for the high-  
105 value reward relative to their licking for the lower value solution (Figure 1B; paired t-test  
106 between high-value and low-value licks:  $t_{(8)} = 4.29$ ,  $p < 0.005$ ).

107 Eleven rats were implanted with multi-electrode arrays in the rostral MFC. In four of the  
108 rats, a drug cannula was implanted in the opposite hemisphere using the same stereotaxic  
109 coordinates (Figure 1C). Figure 1D shows the placement of where each electrode terminated in  
110 the MFC (specifically, within the medial agranular and prelimbic cortices).

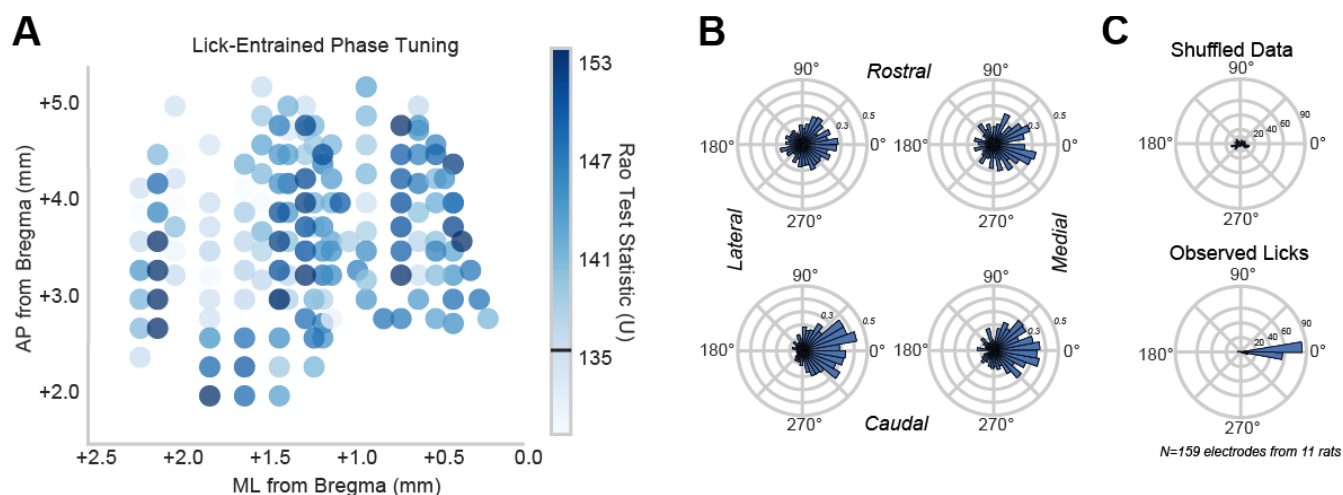


**Figure 1: Behavioral task and neuronal recordings.** A. Rats were tested an incentive contrast procedure called the shifting values licking task (Parent et al., 2015a). They were required to lick on a spout to receive liquid sucrose rewards. Reward values shift between relatively high (20% wt/vol) and low (4% or 2% wt/vol) concentrations of sucrose every 30 seconds. B. Experienced rats (fourth training session) licked more for the high-value sucrose than for the low-value sucrose. Asterisk denotes  $p < 0.005$  (paired  $t$ -test;  $t(8) = 4.29$ ,  $p < 0.005$ ). C. All 11 rats were implanted with a microwire array targeting the rostral medial frontal cortex (MFC) in one hemisphere and a subset of rats ( $N=4$ ) had a drug cannula implanted in the opposite hemisphere. D. Locations of recording sites are depicted on a horizontal section from a standard rat atlas (Paxinos and Watson, 1997). E. An example of a local field potential (LFP) recording shows lick-entrained rhythmic activity. Gray box denotes delivery of fluid. F. Relationships between LFP signals and licking was assessed by bandpass filtering the LFPs around the licking frequency (defined by the inter-quartile range around the medial inter-lick interval) and applying the Hilbert transform to measure the amplitude and phase of licking-related neuronal activity. Instantaneous phase was measured, plotted using polar coordinates, and analyzed with standard methods for circular statistics (Agostinelli and Lund, 2013). See methods for details.

## 111 Lick-entrained neuronal activity in the medial frontal cortex

112 We recorded local field potentials (LFP) from the MFC in rats as they ingested liquid  
 113 sucrose in the shifting values licking task. Figure 1E shows a raw LFP trace from one electrode as  
 114 one of the rats licked at the drinking spout for liquid sucrose. To measure entrainment between  
 115 the LFPs and the animal's licking, we bandpass filtered the LFPs around the licking frequency  
 116 and averaged the resulting peri-event data. This revealed rhythmic fluctuations in the LFPs  
 117 synchronized to the lick cycle (Figure 1F, left panel). We then applied the Hilbert transform to the  
 118 LFP signals, which allowed us to analyze the amplitude and phase of the LFPs (Figure 1F, middle

119 panel) and represent the phase of LFPs using circular histograms (also known as polar plots).  
120 These plots revealed tuning of the phase angles of the LFPs at the onset on licking (Figure 1F,  
121 right panel).



**Figure 2: Neuronal activity in the MFC was entrained to the lick cycle.** A. Spatial plot of phase tuning using the test statistic from Rao's spacing test of uniformity. Individual electrode locations are plotted according to their location in reference to Bregma (N=159 electrodes). Recording sites are depicted as circles colored by the strength of their Rao test statistic (U). The colorbar shows values of U from the 5th to 95th percentile range over all recording sites. Values above the black bar (near 135) were not uniform ( $p < 0.05$ ). B. Polar plots represent phase tuning examples from four spatial extremes of the graph in (A). The most rostral/lateral (top left;  $U=134.48$ ,  $p > 0.05$ ), rostral/medial (top right;  $U=152.30$ ,  $p < 0.001$ ), caudal/medial (bottom right;  $U=153.51$ ,  $p < 0.001$ ), and caudal/lateral (bottom left;  $U=147.44$ ,  $p < 0.001$ ) electrodes were chosen. There was no drastic difference among the four locations with regard to phase tuning. C. Group summaries of the mean phase angle at the time of licking from all 11 rats reveal significant phase tuning toward 0 degrees (i.e. peak or trough of the rhythm). These results were compared with phase angles measured from surrogate data (shuffled inter-lick intervals), which did not show evidence for significant phase entrainment.

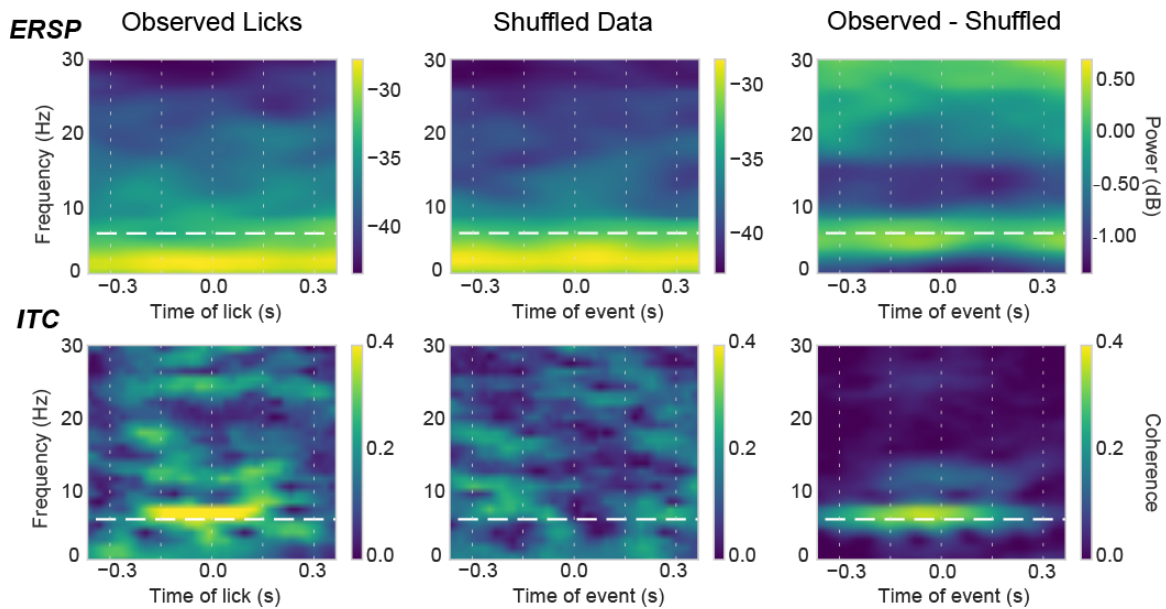
122 To further investigate the relationship between licking and the phase angle of LFPs, we  
123 used circular statistics to measure the consistency of the phase angles at the time of licking  
124 from the LFPs (Figure 2). We used Rao's spacing test for uniformity, which assesses the  
125 directional spread of circular data. Each LFP was bandpass filtered near the licking frequency ( $\pm 2$   
126 inter-lick intervals) and the Hilbert transform was used to measure the phase angles, as shown  
127 in the example in Figure 1F. We plotted each electrode's location in MFC and shaded them by the  
128 intensity of the test statistic from the Rao test (Figure 2A). The black horizontal line in the

129 colorbar on the right denotes a Rao test statistic that corresponds to a level for the Rao statistics  
130 at  $p=0.05$ . All shades above this line denote significant directional non-uniform tuning of the lick-  
131 entrained phase angles for that given electrode. Polar plots for four example electrodes (from  
132 four different rats) located in each extreme of MFC space (rostral/lateral, rostral/medial,  
133 caudal/lateral, and caudal/medial) are shown in Figure 2B. Remarkably, the electrodes had a  
134 mean phase angle near 0 degrees, i.e. at the peak or trough of the neural oscillation. While  
135 there was no anatomical specificity of phase tuning in MFC, the region as a whole showed a  
136 relatively similar phase that is suggestive of tuning to the lick cycle.

137         These results showing lick-entrained phase tuning of LFPs were significantly different  
138 from those obtained with surrogate data (based on shuffled inter-lick intervals). Figure 2C shows  
139 polar plots of the average angle from each electrode's lick-entrained LFPs (500 observed licks in  
140 the session) and from 500 randomly shuffled data points from the same session. Lick-entrained  
141 LFPs from each of the 11 rats in the study showed significant phase tuning towards the  $0^\circ$   
142 direction, as opposed to 500 randomly sampled data points, which do not show any significant  
143 phase tuning in any direction. This suggests that LFP phase angles are tuned in a specific  
144 direction at the onset of licking, at the peak or trough of the neural oscillation.

145         While the polar plots revealed the phase angle at the onset on licking, it was still unclear  
146 of what frequency range the LFP's amplitude and phase were occurring. To do so, we used  
147 standard time-frequency analysis measures from human EEG research (eeglab toolbox in  
148 Matlab). We low-pass filtered the LFPs below 100 Hz and measured lick-related changes in  
149 spectral power (event-related spectral power or ERSP) and phase consistency at the times of the  
150 licks (inter-trial phase coherence or ITC). The ERSP analysis showed increased power below 10  
151 Hz (Figure 3A, top row). We compared the results at lick-onset to randomly shuffled data that  
152 had the same time structure as the licks (shuffled data from inter-lick intervals, Figure 3 middle  
153 panel; see methods). Power at the lowest frequencies in the 2-4 Hz "delta" range) was also  
154 apparent in ERSP plots made with shuffled events, and was not evident in the difference plot  
155 (Figure 3, top right ERSP plot). This finding suggests that LFP power near the licking frequency





**Figure 3: Time-frequency analysis of lick-entrained LFP data.** Event-Related Spectral Power [ERSP] (top) and Inter-Trial Coherence (ITC) are shown for a typical LFP recording aligned to the time of licking in the behavioral task. The white horizontal dashed line depicts the median licking frequency. The white vertical dashed lines depict the median inter-lick intervals. ERSP and ITC measures were computed using observed licks (left) and surrogate data (middle), created by shuffling inter-lick intervals. Persistent elevated ERSP was notable at very low frequencies (~2 Hz, or delta) for both the observed (upper left) and shuffled (upper middle) events, i.e. was not entrained to the lick cycle. Subtraction of the shuffled ERSP matrix from the observed ERSP matrix revealed elevated power at the licking frequency (horizontal dash line). ITC was apparent near the licking frequency over a period of two lick cycles for the observed licks (lower left), but not the shuffled licks ((lower middle). Subtraction of the shuffled ITC matrix from the observed ITC matrix revealed elevated power at the licking frequency (horizontal dash line).

156 was phase-locked to the lick cycle. By contrast, delta power was not entrained to the lick cycle.  
157 We also found significant levels of ITC around the onset of licking (Figure 3, bottom row),  
158 specifically in the 6-8 Hz theta range. This level of phase-locking was significantly different from  
159 that obtained from the same analysis applied to LFPs at the times of randomly shuffled events  
160 (Figure 3, middle panel).

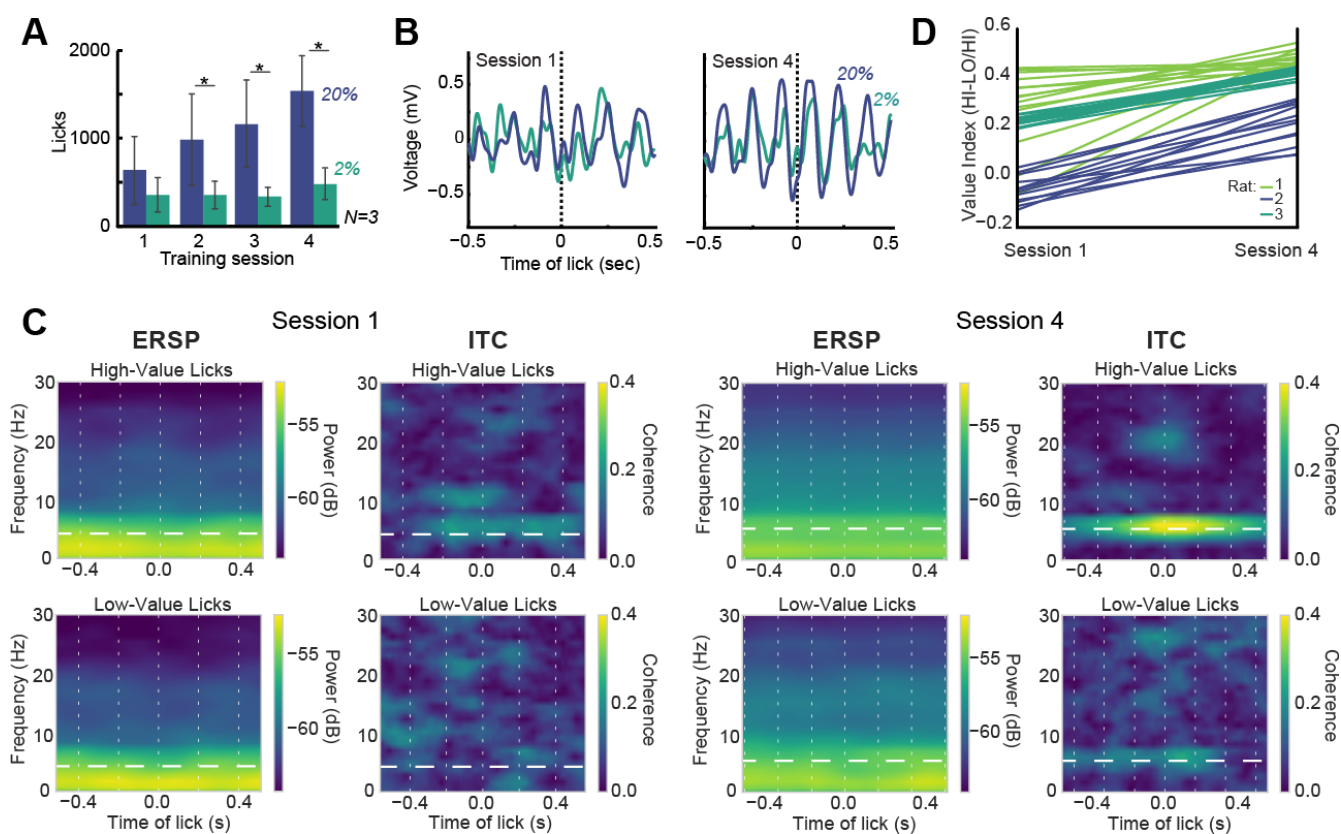
### 161 **Rhythmic activity develops with experience and encodes reward value.**

162 The previous results found lick-entrained neural activity in the MFC. The results in Figure  
163 4 and in subsequent figures reveal within-session dynamics specifically associated with the rats  
164 experiencing two different concentrations of liquid sucrose. We chose to compare data from the

165 first and fourth training sessions based on a previous study from our lab showing asymptotic  
166 licking behavior by day 4 in the same task (Parent et al., 2015a). When trained in the shifting  
167 values licking task, rats quickly came to lick more for the high-value sucrose over days, and  
168 licked less for the low-value sucrose (Figure 4A). Median inter-lick intervals (ILIs) were reduced  
169 from session 1 to session 4 (Wilcoxon rank-sum test from three rats individually:  $p < 0.0001$ ),  
170 indicating that rats increased their licking frequency with experience in the task.

171 Repeated measures ANOVA found a main effect of reward value on licking ( $F_{(1,14)} = 32.20$ ,  
172  $p < 0.001$ ). Tukey's posthoc test found evidence for a difference between the number of licks for  
173 the high-value versus low-value reward in session 4 ( $p = 0.013$ ), but not session 1 ( $p = 0.935$ ). Event-  
174 related potentials (ERPs) showed lick-entrained rhythmic activity in the fourth training session  
175 that was not apparent in the rats' first day of the training (Figure 4B). Notably, there was a  
176 distinction between high-value and low-value phase-locking to the onset of licking evident in LFP  
177 data from session 4, but this signal was not apparent during session 1. To capture effects of  
178 reward value on the LFPs, we calculated a "value index" for each electrode's ITC value index  
179 (Figure 4D, see methods) for sessions 1 and 4. (The value index was derived from difference  
180 between the high-value and low-value ITC values divided by the high-value ITC.) All electrodes  
181 from all rats showed an increase in the ITC value index, suggesting there was an increase in the  
182 difference between the phase-locking for high-value versus low-value licks by session 4 (paired t-  
183 test:  $t(39) = -12.085$ ,  $p < 0.001$ ).

184 Additionally, ITC and ERSP spectral plots showed evidence for the development of lick-  
185 entrained phase-locking, specifically for the high-value licks, and a decrease in delta power for  
186 both types of licks, respectively (Figure 4C). While there were very low levels of phase-locking for  
187 high-value licks in session 1, a much stronger ITC developed by session 4 for the high-value licks.  
188 To measure changes in the signals associated with the two reward values over sessions, we  
189 performed a repeated-measures ANOVA with the maximum ITC values as the dependent  
190 variable and the values of the licks and the training sessions as predictors. This analysis found a  
191 significant interaction between session and value ( $F_{(1,164)} = 10.45$ ,  $p < 0.005$ ), and Tukey's posthoc



**Figure 4: Rhythmic activity develops in MFC with experience and encodes reward value.** A. Recordings were made in a subset of three rats as they learned the behavioral task. The rats showed increased licking for the high-value sucrose compared to the low-value sucrose after the first training session and the relative difference in licking increased over the first four training sessions. Asterisk denotes  $p < 0.05$ . B. Neuronal entrainment to the lick cycle developed with experience in the task. For example, Event-Related Potentials (ERP) increased in size and apparent rhythmicity between the first and fourth training session (blue = higher-value 20% sucrose; green = lower value 2% sucrose). C. Increased entrainment to the lick cycle was also apparent in Inter-Trial Coherence (ITC), which was not apparent in session 1 and specific to licks that delivered high-value sucrose in session 4. (White vertical lines = average inter-lick intervals across the session. White horizontal dashed line = average licking frequency across the session.) D. To capture differences in ITC values for the two types of licks across all recordings, we used a value index, defined as  $(ITC-HI - ITC-LO)/ITC-HI$ . The index was based on the maximum ITC values in a temporal window ranging from one inter-lick interval before lick onset up to 50 ms after the lick and for all frequencies between 4 and 12 Hz (“theta”). As shown in the parallel line plot, in which each line denotes a LFP recording from a distinct electrode, this index was larger in session 4 compared to session 1 (paired  $t$ -test:  $t(39) = -12.085$ ,  $p < 0.001$ ).

192 test revealed differences between session 1 versus session 4 ITC values ( $p < 0.05$ ) and between  
 193 high-value lick ITC and low-value lick ITC in session 4 ( $p < 0.001$ ). There was no difference

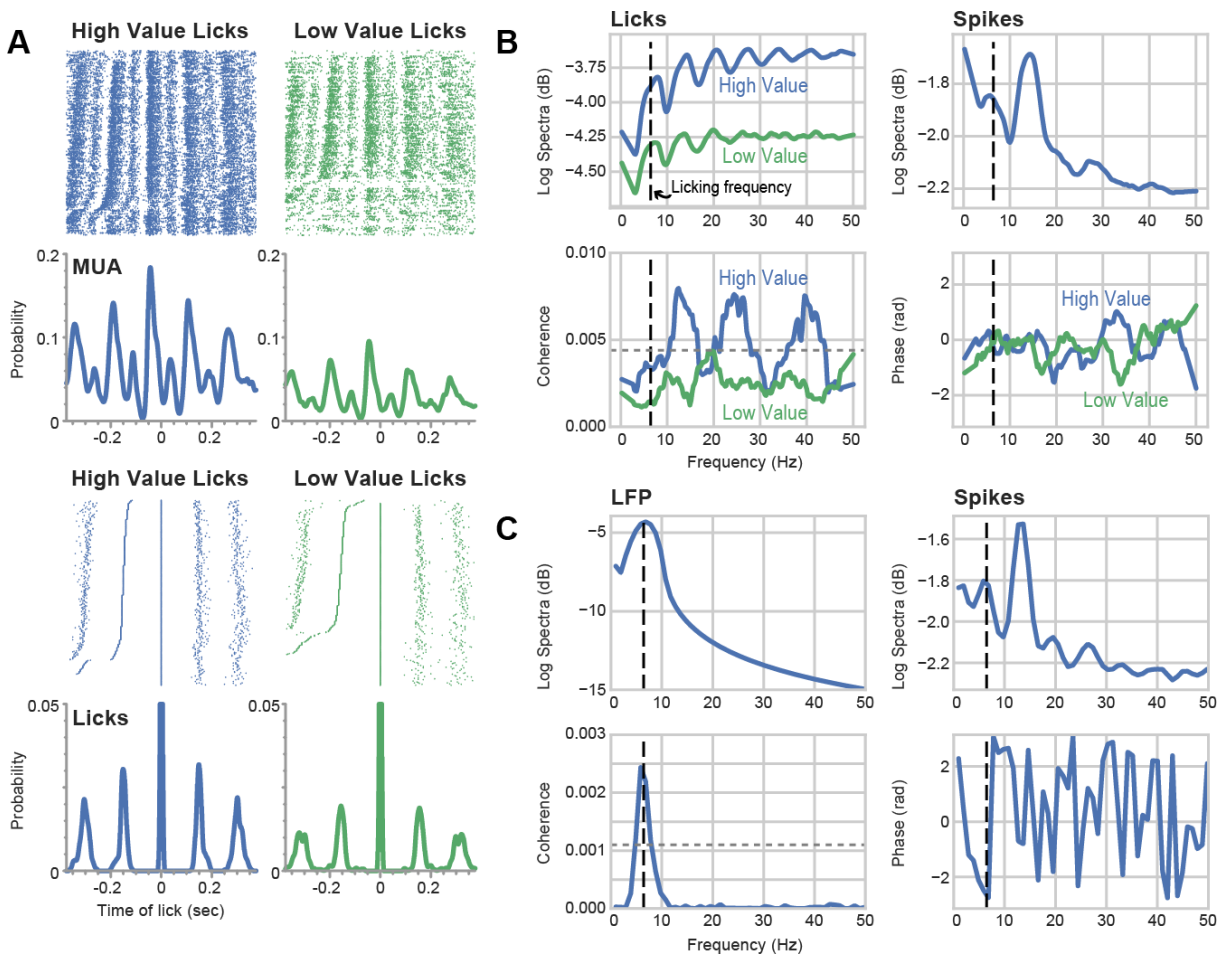
194 between high-value and low-value ITCs ( $p=0.14$ ) in session 1. The difference in lick-entrained ITC  
195 strength that developed over days is evidence for an experience-dependent encoding of reward  
196 value by the rostral MFC.

197 We also assessed changes in LFP power by performing a repeated-measures ANOVA with  
198 the individual maximum ERSP values as the dependent variable and the value of the licks and  
199 training session as predictors, which revealed significant changes to the maximum ERSP values  
200 across sessions. There was a significant interaction between session and reward value  
201 ( $F_{(1,163)}=15.43$ ,  $p<0.001$ ). Tukey's post-hoc analyses showed a difference in power from session 1  
202 to session 4 high-value licks ( $p<0.0001$ ), as well as power for session 4 high and low value licks  
203 ( $p<0.0001$ ), yet there was no difference in power between session 1 high-value and low-value  
204 licks ( $p=0.99$ ). These findings suggest that both the power and phase of LFPs in the MFC are  
205 sensitive to experience in the licking task, and a distinction of both measures emerged over  
206 days, suggesting a role for the rostral MFC in encoding relative reward value.

### 207 **Lick-entrained spike activity**

208 While the previous results showed evidence for lick-entrained rhythmic activity and an  
209 encoding of reward value through LFPs in MFC, it was unclear if spike activity would show  
210 similar results. Spike recordings revealed strongly modulated activity synchronized to the lick  
211 cycle (Figure 5A). Multi-unit activity [MUA] ( $N=44$ , recorded from 3 rats in the 4<sup>th</sup> training session)  
212 was enhanced when rats licked for the high-value sucrose relative to the low-value sucrose  
213 ( $t(43)=3.78$ ,  $p<0.001$ ; Figures 5A and upper plot in 6A). The probability of spiking at the licks was  
214 below 0.3 for all multi-units, and was below 0.1 for instances when single units were isolated  
215 from the same recording sites. (For this reason, we focused on MUA in the present study.)

216 Neuronal entrainment to the lick cycle was measured using lick-spike coherence (using  
217 routines from Neurospec 2.0; see Methods). An example of lick-spike coherence for a unit that  
218 was selective to the higher value licks is shown in Figure 5B. Spectral power is shown for the  
219 licks (upper left plot) and spikes (upper right plot). The licks had a peak near the frequency

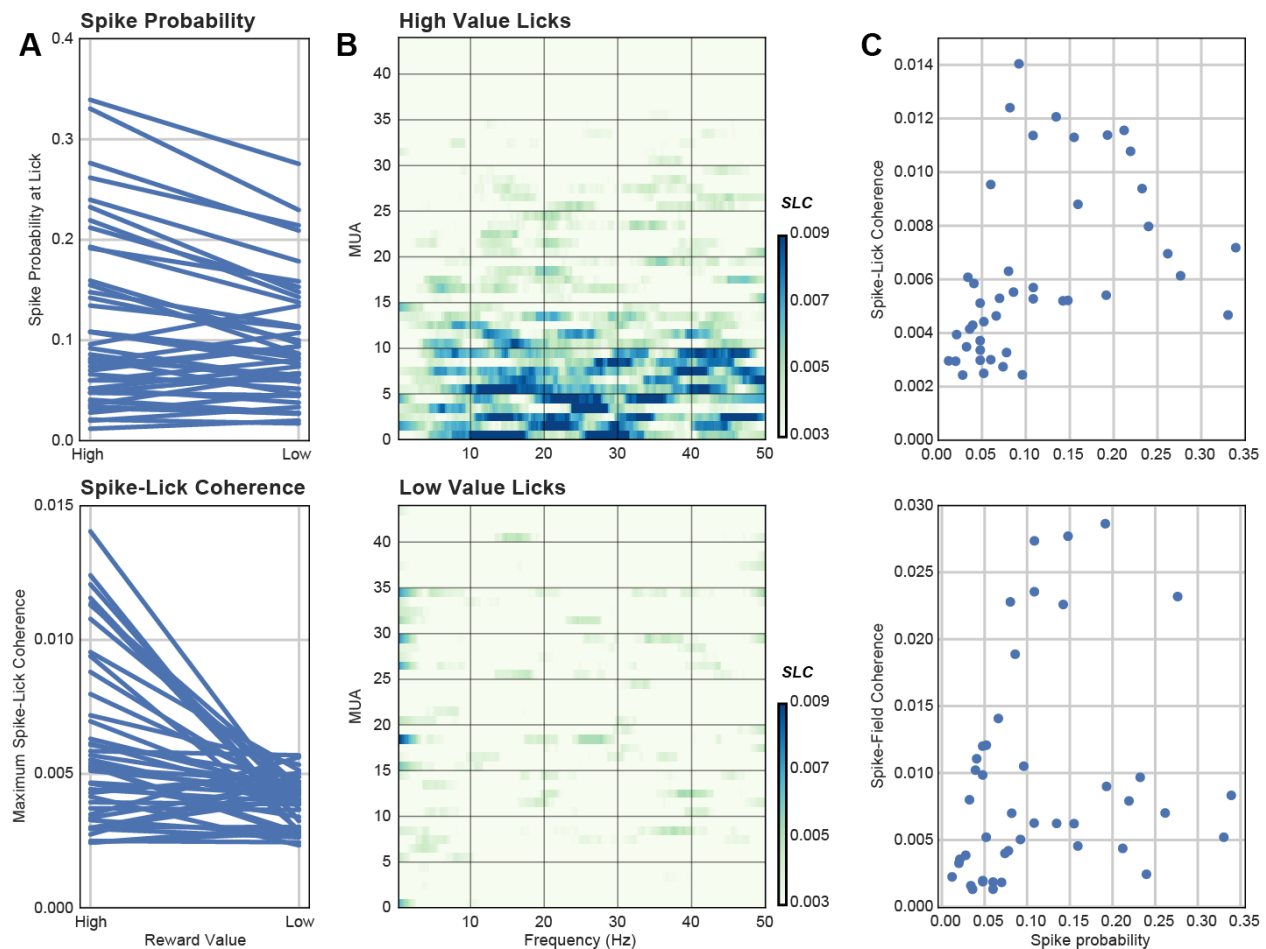


**Figure 5: Spike activity in MFC was entrained to the lick cycle.** A. Example of multi-unit spike activity (top) and licks (bottom) entrained to the lick cycle when a rat consumed the higher (blue) and lower (green) value sucrose rewards. Raster plots show clear rhythmic spiking and licking. The rasters were sorted by the latency to the last lick before the lick at time 0, with the shortest preceding intervals at the top of the raster. The high value licks were sub-sampled for this plot so that neural activity and licking could be compared for the same number total licks (at time 0). Peri-event histograms (bin: 1 ms, 10-point Gaussian smoothing) denote the probability of spiking around the times of the licks. B. Example of spike-lick coherence (MUA from panel A). Spectral analysis of the licking point processes showed peaks at the licking frequency (black dashed line) and higher harmonics of that frequency (left). By contrast, the spike train had its largest spectral peak at ~15 Hz, in the low beta range. A smaller peak was also apparent at the licking frequency. Spike-lick coherence showed multiple peaks in the low beta (12-16 Hz), high beta (22-27 Hz), and gamma (38-43 Hz) ranges for the high value licks. No peaks were above the 95% confidence interval (gray dashed line) for the low value licks. Phase was near 0 for these signals. C. Example of spike-field coherence. Spectral analysis of a bandpass filtered LFP (as in Figure 1) showed a single broad peak at the licking frequency. The spectral plot for the simultaneously recorded spike train is the same as in panel C. Spike-field coherence was apparent at the licking frequency (5.96 Hz), at a level approximately twice the 95% confidence interval. The phase between the spikes and fields was near  $-P$  at the licking frequency (lower right plot).

216 defined by the median inter-lick interval (black dash line), and harmonics at higher intervals of  
217 that frequency. The blue and green traces depict the spectral power for the higher and lower  
218 value licks, respectively. The spikes had a major peak at ~14 Hz and minor peaks at the licking  
219 frequency and in the high beta and gamma ranges. Coherence values at frequencies up to 50 Hz  
220 are shown in the lower left plot in Figure 5B. The unit was not coherent with the licks at the  
221 licking frequency but had multiple significant peaks in the low (~14 Hz) and high (~25 Hz) beta  
222 and gamma (~40 Hz) ranges for the high value, but not the low value, licks. Phase was near zero  
223 at the licking frequency (lower right plot in Figure 5B). Over all units, 33 of 44 units (75%) fired in  
224 phase with licks that delivered the higher value fluid. Only 19 of these units (43%) fired in phase  
225 with licks that delivered the lower value fluid. Similar to the effect of relative value on spike  
226 probabilities, spike-lick coherence was greater for the higher value licks compared to the lower  
227 value licks (lower plot in Figure 6A; proportions test: Chi square = 7/9, df = 1,  $p < 0.01$ ).

228 Most of the units with significant spike-lick coherence showed peaks in the beta and  
229 gamma ranges, and there was no consistent frequency associated with lick-spike coherence  
230 (Figure 6B). (This might be expected given the multi-unit nature of the spike data.) There was no  
231 simple relationship between spike probability and spike-field coherence (upper plot in Figure  
232 6C), except that units with low spike-lick coherence tended to have low spike probabilities.

233 Given the general lack of spike-lick coherence at the licking frequency, despite the  
234 common finding of beta and gamma coherence, we examined spike-field coherence using the  
235 same bandpass filtered LFPs used to analyze for lick-entrainment (Figure 1,2). This analysis  
236 revealed all 44 MUA recordings exhibited significant levels of spike-field coherence at  
237 frequencies associated with the licking cycle. An example of spike-field coherence is shown in  
238 Figure 4C. Similar to the phase measurements of the LFPs (Figure 2), spikes and fields tended to  
239 be in phase near the peak of the LFP rhythm (lower right plot in Figure 5D). Similar to spike-field  
240 coherence, there was no simple relationship between spike probability at the time of the licks  
241 and spike-field coherence (lower plot in Figure 6C). Overall, these analyses show clear  
242 relationships between spike activity, the lick cycle, and LFP fluctuations that encode relative



**Figure 6: Spike activity in MFC encoded relative reward value.** A. Parallel line plot for spike probability and spike-lick coherence at times of higher and lower value licks. Each line denotes a recording of multi-unit activity. Both measures were greater for the higher value licks compared to the lower value licks over all recordings (spike probability:  $t(43)=3.78$ ,  $p<0.001$ ; spike-lick coherence:  $t(43)=4.60$ ,  $p<0.001$ ). B. Frequencies associated with spike-lick coherence (SLC) are shown in a matrix plot for coherence plotted as false color over the range of frequencies (2-50 Hz) for the 44 units. Results were complex, as no single frequency was associated with the relative difference in reward value. However, many units that fired in phase with licking were coherent at frequencies in the beta (10-30 Hz) and/or gamma ranges (>30 Hz). C. There was no simple relationship between spike probability (at the time of the licks) and spike-lick coherence (upper plot) or spike-field coherence (lower plot). That is, units with the highest likelihoods of spiking during the licks were not necessarily entrained to the lick cycle (SLC) or the ongoing LFP rhythms near the licking frequency (SFC).

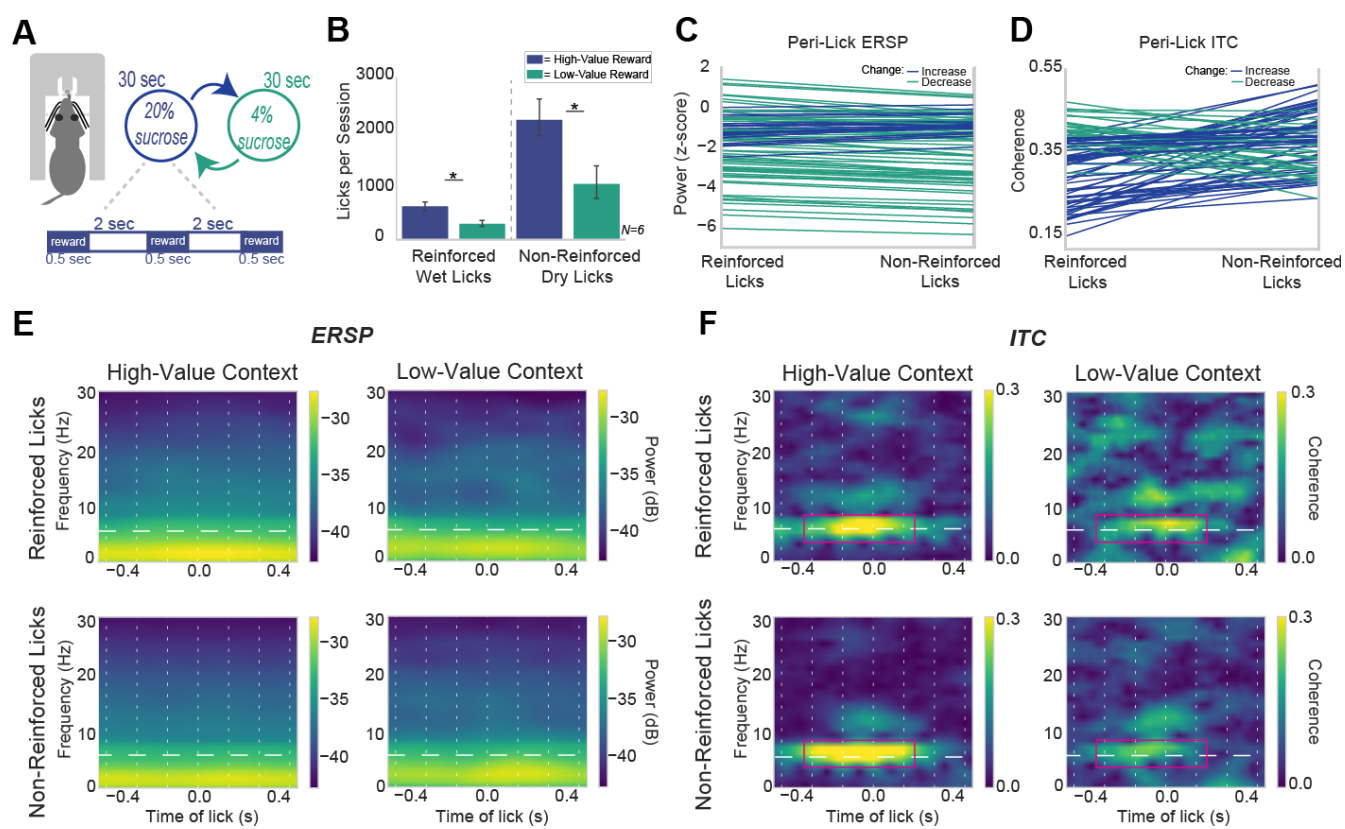
243 reward value. However, the relations between these variables were complex and could not be  
 244 reduced to a single cortical rhythm linking the behavioral and neuronal measures.

## 245 **Reward context, not reinforcement, drives licking-related theta entrainment**

246           The signals described above could simply reflect an encoding of the taste properties of  
247 the ingested solutions by the rostral MFC. To examine this issue, we modified the shifting values  
248 licking task to include a 2 second period of non-reinforced licking between periods of fluid  
249 delivery (Figure 7A). This procedure resulted in rats continuously licking during the non-  
250 reinforced blocks of the task (Figure 7B). All rats continued to lick more during these non-  
251 reinforced blocks when they could receive the high-value fluid compared to when they could  
252 receive the low-value fluid ( $t_{(5)} = 4.25$ ,  $p < 0.005$  for all high-value context licks against all low-value  
253 context licks;  $t_{(5)} = 4.87$ ,  $p < 0.005$  for non-reinforced high-value context licks versus non-reinforced  
254 low-value context licks;  $t_{(5)} = -4.92$ ,  $p < 0.005$  for reinforced high-value context licks versus  
255 reinforced low-value licks). Additionally, LFP signals synchronized to reinforced and non-  
256 reinforced licks were similar, with the main differences between high-value licks and low-value  
257 licks still evident despite the adjustment to the task. Figures 7C and D show group summaries of  
258 the differences in ERSP and ITC values at the onset of the reinforced and non-reinforced high-  
259 value licks. Of all electrodes from 6 rats trained in the adjusted task, there are minimal  
260 differences in ERSP values (Figure 7C). LFP activity also showed no major change in maximum  
261 ERSP between each lick value's reinforced versus non-reinforced licks ( $F_{(1,359)} = 2.52$ ,  $p > 0.05$  for  
262 interaction between lick type and reward type), which is evident in the spectral plots from one  
263 channel in an example rat in Figure 6E.

264           However, the majority (60 of 91) of the electrodes (from all rats) showed increases in  
265 phase-locking for the non-reinforced high-value licks (Figure 7D). We performed a repeated-  
266 measures ANOVA with factors for lick type (reinforced or non-reinforced) and reward value (high  
267 or low) with maximum ITC values as the dependent variable. This analysis found evidence for a  
268 significant interaction between lick type and reward value ( $F(1,359) = 31.94$ ,  $p < 0.001$ ). The non-  
269 reinforced licks had slightly greater ITC values at the onset of licking (high-value reinforced licks  
270 = 0.48, SD = 0.069; high-value non-reinforced licks = 0.51, SD = 0.063), which was also confirmed  
271 using Tukey's posthoc test (reinforced versus non-reinforced high-value licks,  $p < 0.05$ ). Spectral





**Figure 7: Reward context, not reinforcement per se, drives neuronal entrainment to the lick cycle.**

A. The shifting values licking task was modified to include a 2 second period between pump activations. The 2 second “inter-pump interval” allows for non-reinforced licks (dry licks at the spout) to be recorded within the 30 second states of high or low value sucrose availability. B. Group summary of total licks ( $N=6$  rats) showed that rats licked during the non-reinforced blocks and licked more in the higher-value blocks. Asterisk denotes  $p<0.05$ . C. Parallel line plots of maximum ERSP values for reinforced versus non-reinforced licks during the high-value blocks. Lines are colored by their direction (increase or decrease in power). There was no difference in power for reinforced versus non-reinforced licks ( $F(1,359)=2.52$ ,  $p>0.05$ ). D. Parallel line plots of maximum ITC values for reinforced versus non-reinforced licks during the high-value blocks. The majority of LFPs showed increased phase-locking to non-reinforced licks (blue lines), while electrodes from two rats show a slight decrease in phase-locking for non-reinforced licks (green lines). Overall group summaries show an increase in phase-locking for the non-reinforced licks ( $F(1,359) = 31.94$ ,  $p<0.001$ ). E,F. Example of time-frequency analysis of a LFP from a rat that showed decreased ERSP and ITC (magenta box) when the rat licked in the lower-value context. ITC was higher near the licking frequency when the higher value reward was available, regardless if the licks were reinforced or not. Horizontal white lines indicate the within-session licking frequencies and vertical white lines indicate the inter-lick intervals for each session.

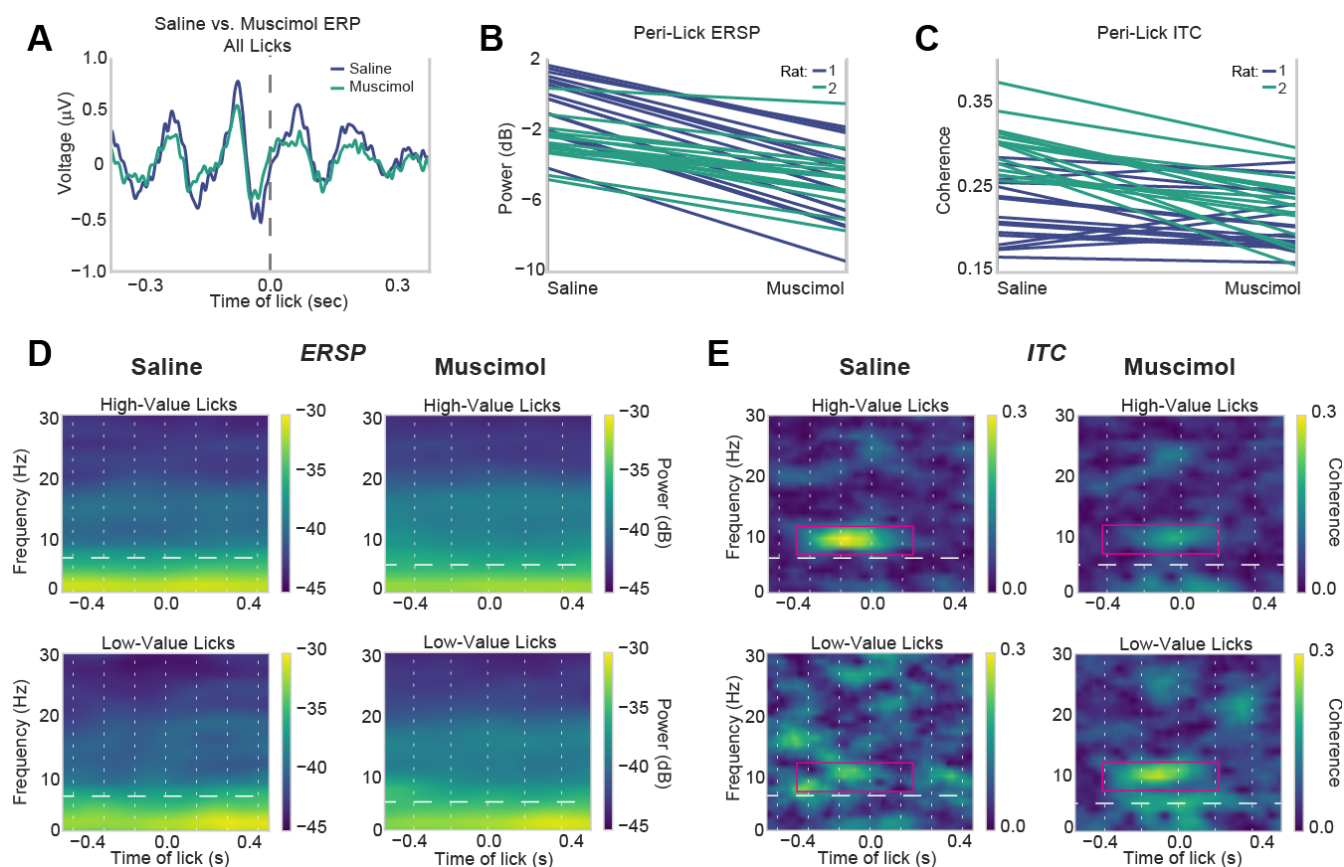
272 plots, shown in Figure 7F, revealed modest increases in phase-locking for the non-reinforced  
 273 high-value licks, and minimal differences in the phase-locking for the reinforced versus non-

274 reinforced low-value context licks. These findings suggest that the reward context, rather than  
275 the properties of the delivered fluids, drives reward signaling in the rostral MFC.

### 276 **Reward signaling depends on the medial frontal cortex**

277 While the previous results implicate the MFC in lick-entrained rhythmic activity,  
278 specifically in encoding reward value, it was unclear of the specific role the MFC has in reward-  
279 based behaviors, or if the signals encoding reward value are due to or generated by other brain  
280 regions. We investigated if perturbing MFC activity would thus alter the encoding of relative  
281 reward value. Using the design described in Figure 1C, we recorded LFP activity from one  
282 hemisphere and infused muscimol, a GABA-A receptor agonist, into the opposite hemisphere via  
283 a drug cannula in four rats. Two of these rats had aligned electrode arrays and drug cannula  
284 (same cytoarchitectural area and layer). Two other rats were not precisely aligned, and  
285 electrophysiological data from those animals were not considered further. In all four rats, we  
286 did not observe any major behavioral change in the number of licks emitted during the  
287 muscimol sessions. (This is in contrast to our previous study with bilateral inactivations (Parent  
288 et al., 2015a), which clearly alter performance of the task.) The lack of behavioral effects of  
289 muscimol allowed us to assess potential electrophysiological changes without overt effects of  
290 the inactivations on the animals' licking behavior. There was a marginal decrease in the overall  
291 inter-lick intervals under muscimol (Wilcoxon rank-sum test,  $p < 0.05$ ), but no other effects of  
292 inactivation were apparent (e.g. duration of licking bouts).

293 In the two rats with aligned electrode arrays and drug cannulas, LFP activity during  
294 muscimol inactivations was dramatically altered. Muscimol infusions decreased the magnitude  
295 and rhythmicity of event-related potentials (ERP) during licking (Figure 8A), and decreased  
296 power (ERSP) during both high-value and low-value licks (Figure 8B, all electrodes plotted from  
297 two rats). This was confirmed in the spectral plots, shown from one example electrode from one  
298 rat (Figure 8D), where there is specifically a decrease in the low-frequency delta power. A  
299 repeated measures ANOVA on maximum ERSP values around the onset of licking revealed a



**Figure 8: Reward signaling depends on neuronal activity in the MFC.** Rats were tested with an electrode array in the MFC in one hemisphere and an infusion cannula in the other hemisphere, and after infusions of either PBS or muscimol were made via the infusion cannula. A. Event-related potentials (ERP) from an electrode in the saline (blue line) and muscimol (yellow line) sessions. MFC inactivation had minor effects on the overall evoked signal in the MFC from the opposite hemisphere. B. However, parallel line plots revealed a decrease in power at the licking frequency (ERSP) at the onset of licking for the higher value fluid during the muscimol session compared to the saline session ( $F(1,123) = 96.09, p < 0.001$ ). C. Likewise, there was a reduction in phase entrainment (ITC) at the licking frequency for 28 of 32 electrodes ( $F(1,123) = 18.17, p < 0.001$ ). D,E. Example of time-frequency analysis of a LFP that showed reduced ERSP and ITC at the licking frequency (magenta box) in the muscimol test sessions. Effects were specific to licks for the high value reward. Horizontal white lines indicate the within-session licking frequencies and vertical white lines indicate the inter-lick intervals for each session. Note that muscimol in MFC slightly reduced the licking frequencies.

300 decrease in power at lick-onset from saline to muscimol sessions ( $F(1,123) = 96.09, p < 0.001$ ).

301 Muscimol infusions also decreased the lick-entrained phase-locking in the theta  
 302 frequency range. As seen in Figure 8C, 28 of 32 electrodes showed decreased phase-locking  
 303 around the onset of licking. A repeated measures ANOVA revealed a significant difference in ITC

304 values for the saline and muscimol sessions ( $F_{(1,123)} = 18.17, p < 0.001$ ). Spectral plots from an  
305 example electrode (Figure 8E) show diminished phase coherence in the theta frequency range  
306 for the high-value licks. The decrease in phase-locking therefore disrupted the previously  
307 evident differential signaling of reward value, suggesting that adequate reward signaling for  
308 relative rewards depends on the MFC.

## 309 **Discussion**

310 The goal of the present study was to investigate the neural representation of  
311 consummatory rewards in rat frontal cortex. We found lick-entrained neural activity of both local  
312 field potentials (Figure 1-3) and spikes (Figures 5-6) in the medial frontal cortex, specifically in  
313 the rostral prelimbic and medial agranular (AGm) regions. These signals developed with  
314 experience and encoded the relative reward value of the ingested liquid sucrose rewards (Figure  
315 4). By modifying the behavioral task to include periods of non-reinforced licking, we found that  
316 this neuronal coding of relative value persisted beyond the period of reward delivery and  
317 suggest that it encodes the reward context (Figure 7). Finally, inactivation of the MFC diminished  
318 the encoding of reward value, establishing that the reward signals described in this study were  
319 generated, at least in part, by neurons in the MFC (Figure 8). Together, our results provide the  
320 first evidence that the rodent MFC tracks engagement in consummatory behavior and encodes  
321 the expected reward value of ingested foods and fluids.

## 322 **Reward-related activity & encoding of relative reward value**

323 Many previous studies have reported reward-related neural activity in the frontal cortex  
324 of humans (Glascher et al., 2009; Levy and Glimcher, 2011), primates (Watanabe, 1996; Roesch  
325 and Olson, 2004; Shidara and Richmond, 2002; Amiez et al., 2006; Padoa-Schiappa and Assad,  
326 2006; Hayden et al., 2009; Luk and Wallis, 2009; Bouret and Richmond, 2010; Cai and Padoa-  
327 Schiappa, 2012), and rodents (Gutierrez et al., 2006; Petyko et al., 2009; Horst and Laubach,  
328 2013; Petyko et al., 2015). However, all of these studies focused on the more medial and caudal

329 parts of the frontal cortex and did not assess reward signaling with respect to ongoing ingestive  
330 behavior. Our findings are the first to show that the most rostral area of MFC has a direct role in  
331 signaling the value of ingested foods and fluids, and does so in direct register with the animal's  
332 ongoing ingestive behavior. Activity from both LFPs and spikes in this region is entrained to the  
333 action of licking, and the two types of reward (high-value / high-concentration sucrose or low-  
334 value / low-concentration sucrose) are encoded differently by the extent of phase entrainment  
335 of the neuronal signals to the animal's lick cycle. Our findings also suggest that these MFC  
336 reward signals are generated by the taste of the liquid rewards, as the signals persist  
337 throughout blocks of time when licking is not reinforced and animals expect to receive relatively  
338 higher or lower value rewards (Figure 7). As such, the signals appear to reflect the reward  
339 context, representing the valued reward state that the animal is currently acting within. This  
340 idea is similar to previous concepts for prefrontal cortex which is involved in the "active  
341 maintenance" of behavior (Miller and Cohen, 2001) and represents the behavioral context  
342 (Hyman et al., 2012; Euston et al., 2012).

### 343 **A role for MFC in the reward-guided control of orolingual behaviors?**

344 Our studies (Figure 7) suggest that reward signals from the rostral MFC are driven by  
345 reward context, not by the taste properties of the liquid rewards, and these signals are phase-  
346 locked to licking behavior. As such, a major question is if this cortical region serves as a sort of  
347 "cingulate motor area" (Shima and Tanji, 1998) controlling voluntary orolingual movements  
348 based on the relative value of available rewards. Previous studies have investigated cortical  
349 regions within and near to the MFC and reported motor processing by these regions. Evidence  
350 has been reported for motor areas associated with the vibrissae (Brecht et al., 2004) and  
351 jaws/tongue (Adachi et al., 2008). These studies used intra-cortical microstimulation techniques  
352 and followed on classic studies on frontal motor maps by Hall and Lindholm (1974), Donoghue  
353 and Wise (1982), and Neafsey et al. (1986). Importantly, anatomical tract tracing studies between  
354 the AGm region of the MFC and a sensory representation of the perioral area, the trigeminal

355 mesencephalic nucleus or Vmes, reveal substantial projections from Vmes to AGm and prelimbic  
356 cortex (Yoshida et al., 2009; Iida et al., 2010). The rostral agranular cortex projects to brainstem  
357 nuclei controlling jaw-closing and jaw-opening (Haque et al., 2010). While there is not an easily  
358 defined location in rat cortex for the jaw or tongue (like there is for the forelimb area, for  
359 example), the available evidence suggests that the MFC contains an orofacial motor area. This  
360 issue should be considered when interpreting results from studies of the rostral MFC of rodents.

361         Some studies have referred to the AGm area of MFC, in rat and mouse, as the secondary  
362 motor cortex, or M2. A recent review by Barthas and Kwan (2017), and a commentary by Brecht  
363 (2011), described how the “most medial and dorsal portion of the rodent frontal cortex” goes by  
364 many names, such as AGm, M2, medial precentral cortex (PrCm), frontal orienting field (FOF),  
365 dorsomedial prefrontal cortex (dmPFC), secondary frontal area (Fr2), and primary vibrissa motor  
366 cortex (vM1). This brain region, while having some aspect of action or motor representations, is  
367 not a true M1 in rodent, as AGm / M2 lesioned animals do not have overt motor deficits (Sul et  
368 al., 2011). Regardless of the name, it is clear that this specific medial frontal area has a role in  
369 adaptive choice behavior and reward signaling (Kargo et al., 2007; Sul et al., 2010; Sul et al.,  
370 2011), specifically to map sensory input to motor actions. This interpretation applies to the  
371 present study, which is unique in that it examined sensorimotor behavior specific to the  
372 ingestive behavior of rats and found correlates of what might be a “premotor area” controlling  
373 orolingual behavior and encoding expected values of ingested foods and fluids.

374         In the mouse literature, there is an area commonly referred to as the anterior lateral  
375 motor cortex (ALM), which has been implicated in choice behavior during licking-related tasks  
376 (Guo et al., 2014, Komiyama et al., 2010). Microstimulation of the ALM in mouse impairs licking  
377 in mice, and the area also has involvement in preparatory activity and movement planning (Li et  
378 al., 2015). While it is yet unclear if our recordings are from the rat version of ALM – some studies  
379 have noted how ALM is distinct from M2 as ALM is traditionally a bit more lateral from M2  
380 (Siniscalchi et al., 2016) – there are indeed similarities between published studies of ALM in the  
381 mouse and our findings from the rostral MFC of the rat.

## 382 **Rhythmic encoding of relative reward value**

383           Two major frequencies that are prevalent in our findings are the 2-4 Hz delta rhythm and  
384 4-8 Hz theta rhythm. To summarize our frequency-specific findings, we found a prominent delta-  
385 range rhythm that occurred throughout the period when rats engaged in licking and was not  
386 phase locked to the lick cycle and did not encode the relative value of the ingested fluids (Figure  
387 3). A second rhythm occurred in the theta range (near the rats' licking frequency) that was  
388 coupled to the rats' lick cycle (Figure 3). The theta-range signal showed significant phase tuning  
389 at the onset of licking (Figures 1-3) and was enhanced when rats consumed the higher value  
390 reward in our operant incentive contrast procedure (Figure 4). Spike activity was also coupled to  
391 the lick cycle, although most prominently in the beta (10-30 Hz) and gamma (>30 Hz) ranges  
392 (Figures 5-6), and all recordings of spike activity showed coherence with the licking frequency  
393 content of the LFPs.

394           Unilateral reversible inactivations decreased theta phase tuning (Figure 8C,E) in the  
395 opposite hemisphere, established that these signals depended on neurons within the MFC. It is  
396 important to note that these inactivations were unilateral and there were no overt behavioral  
397 changes to the animals' licking behavior during inactivations. This is in strong contrast to  
398 bilateral inactivations of the same cortical area which leads to temporally fragmented licking  
399 and a failure of rats to follow learned strategies to maximize reward consumption (Parent et al.,  
400 2015a). It is not uncommon for unilateral cross-hemispheric inactivations to show less dramatic  
401 effects on behavior (Ambroggi et al., 2008), and it was necessary for our interpretations to have  
402 the rats maintain their behavior without normal MFC function. Our findings from the  
403 inactivation study bolster evidence for the role of MFC in encoding reward value and suggest  
404 that adequate signaling of reward value depends on local activity within the rostral MFC.

405           Theta rhythms are a prominent feature within the frontal cortex. Many studies have  
406 reported theta rhythmic activity that represents many different aspects of behavior, such as  
407 interval timing (Parker et al., 2014; Emmons et al., 2016), cognitive control (Cavanaugh and  
408 Frank, 2014), errors and adaptive control (Narayanan et al., 2013; Laubach et al., 2015), freezing

408 behaviors related to fear-conditioning (Karalis et al., 2016), and consummatory reward-related  
409 behavior (Horst and Laubach, 2013). The prominence of the theta rhythm in rodent frontal  
410 cortex in consummatory and reward-related studies is especially interesting because rats  
411 naturally lick within the 6-8 Hz theta range (Weijnen, 1998) and open/close their jaw in the 5-7 Hz  
412 range (Sasamoto et al., 1990). These behaviors are driven by a brainstem central pattern  
413 generator (CPG) for mastication and licking (Travers et al., 1997). However, it is not solely licking  
414 that occurs in a low-frequency rhythmic manner: many other orofacial behaviors such as  
415 chewing / mastication (Nakamura and Katakura, 1995), breathing, sniffing and whisking (Moore  
416 et al., 2013) occur in a rhythmic manner as well. These orofacial motor behaviors are controlled  
417 by CPGs in the brainstem (Moore et al., 2014), which receive projections from the rostral MFC  
418 (Yoshida et al., 2009; Haque et al., 2010; Iida et al., 2010).

## 419 **Conclusion**

420 We have shown a role for the rostral area of the rat medial frontal cortex in encoding the  
421 value of consummatory rewards in a rhythmic manner. These signals may have a key role in  
422 terminating monitoring processes associated with adaptive control (Narayanan et al., 2013;  
423 Bekolay et al., 2014), signaling outcomes during foraging behavior (Caracheo et al., 2013), and in  
424 implementing the use of learned strategies to maximize reward consumption (Parent et al.,  
425 2015a). Our study provides support for an emerging concept that the MFC contains neurons  
426 that are directly modulated by the act of consuming a reward (Petyko et al., 2009; Bouret and  
427 Richmond, 2010; Horst and Laubach, 2012; Horst and Laubach, 2013; Petyko et al., 2015). If  
428 integrated with gustatory information, which has recently been shown to be encoded by mPFC  
429 neurons (Jezzini et al., 2013), the MFC reward signals described in our study could enable control  
430 over food-based decisions and self control over eating. These issues have clinical implications  
431 given the association of the MFC with loss of control in obesity (Volkow et al., 2011) and eating  
432 disorders such as anorexia (Uher et al., 2004).



433 **Methods**

434 All procedures carried out in this set of experiments were approved by the Animal Use  
435 and Care Committees at the John B. Pierce Laboratory (where some of the experiments were  
436 conducted) and American University. All procedures conformed to the standards of the National  
437 Institutes of Health Guide for the Care and Use of Laboratory Animals. All efforts were taken to  
438 minimize the number of animals used and to reduce pain and suffering.

439 **Animals.**

440 Male Long Evans rats weighing between 300 and 325 g were purchased from Harlan or  
441 Charles River. Rats were given one week to acclimate with daily handling prior to behavioral  
442 training or surgery and were then kept with regulated access to food to maintain 90% of their  
443 free-feeding body weight. They were given ~18g of standard rat chow each day in the evenings  
444 following experiments. Rats were single-housed in their home cages in a 12h light/dark cycle  
445 colony room, with experiments occurring during the light cycle. A total of 11 rats had a  
446 microwire array implanted into medial frontal cortex. Some rats additionally had a drug cannula  
447 implanted into the opposite hemisphere using the same stereotaxic coordinates. Arrays were  
448 made by Tucker-Davis Technologies and consisted of 16 blunt-cut 50- $\mu$ m tungsten wires,  
449 insulated with Formvar, separated by 250  $\mu$ m within each row and 500  $\mu$ m between rows. In  
450 vitro impedances for the microwires were ~150 k $\Omega$ .

451 **Surgeries.**

452 Animals had full access to food and water in the days prior to surgery. Stereotaxic  
453 surgery was performed using standard methods (e.g., Narayanan and Laubach, 2006). Briefly,  
454 animals were lightly anesthetized with isoflurane (2.5% for ~2 minutes), and were then injected  
455 intraperitoneally with ketamine (100mg/kg) and either xylazine (10 mg/kg) or dexdomitor  
456 (0.25mg/kg) to maintain a surgical plane of anesthesia. Craniotomies were made above the  
457 implant location. Microwire arrays were placed into the medial frontal cortex (coordinates from

458 bregma: AP: +3.2 mm; ML:  $\pm$  1.0 mm; DV: -2.2 mm from the surface of the brain, at a 12°  
459 posterior angle). Four skull screws were placed along the edges of the skull and a ground wire  
460 was secured in the intracranial space above the posterior cerebral cortex. Electrode arrays were  
461 connected to a headstage cable and modified Plexon preamplifier during surgery and  
462 recordings were made to assess neural activity during array placement. Drug cannulas, 26-  
463 gauge PEEK (Plastics One), were implanted prior to the microwire arrays using similar  
464 procedures. Craniotomies were sealed using cyanoacrylate (Slo-Zap) and an accelerator (Zip  
465 Kicker), and methyl methacrylate dental cement (AM Systems) was applied and affixed to the  
466 skull via the skull screws. Animals were given a reversal agent for either xylazine (yohimbine,  
467 2mg/ml) or dexdomitor (Antisedan, s.c. 0.25 mg/ml) and Carprofen (5 mg/kg, s.c.) was  
468 administered for postoperative analgesia. Animals recovered from surgery in their home cages  
469 for at least one week with full food and water, and were weighed and monitored each day  
470 following surgery.

## 471 **Behavioral Tasks.**

### 472 Behavioral Apparatus.

473 Rats were trained in operant chambers housed within a sound-attenuating external  
474 chamber (Med Associates, St. Albans, VT). Operant chambers contained a custom-made drinking  
475 spout that was connected to multiple fluid lines allowing for multiple fluids to be consumed at  
476 the same location. The spout was centered on one side of the operant chamber wall at a height  
477 of 5 to 6.5cm from the chamber floor. Tygon tubing connected to the back of the drinking spout  
478 would administer the fluid from a 60cc syringe hooked up to a PHM-100 pump (Med Associates).  
479 A "light-pipe" lickometer (Med Associates) detected licks via an LED photobeam, and each lick  
480 triggered the pump to deliver roughly 0.025 ml per 0.5 second. Behavioral protocols were run  
481 though Med-PC version IV (Med Associates), and behavioral data was sent via TTL pulses from  
482 the Med-PC software to the Plexon recording system.

483 Continuous-Access Shifting Values Licking Task

484           The operant licking task used here is similar to that previously described in Parent et al.  
485 (2015a,b). Briefly, rats were placed in the operant chamber for thirty minutes, where they were  
486 solely required to lick at the drinking spout to obtain a liquid sucrose reward. Licks activated the  
487 syringe pumps to deliver liquid sucrose over 0.5 second. Every 30 seconds, the reward  
488 alternated between a high concentration (20% weight per volume) and low concentration (2-4%  
489 wt/vol) of sucrose. The animal's licking behavior was constantly monitored throughout the test  
490 sessions.

491 Instrumental Shifting Values Licking Task

492           The operant licking task used above was modified slightly to allow for assessment of  
493 reinforced versus non-reinforced licks. A 2 second inter-pump interval was included between  
494 each pump activation. In other words, the rat would lick to activate a liquid sucrose reward for  
495 0.5 sec, and then once the pump stopped delivering fluid, no reward was delivered again for 2  
496 sec. The next lick after the 2 sec interval would initiate the next pump activation. Licks during the  
497 2 sec inter-trial period were *instrumental*.

498 **Electrophysiological Recordings.**

499 Multi-electrode Recordings.

500           Electrophysiological recordings were made using a Plexon Multichannel Acquisition  
501 Processor (MAP; Plexon; Dallas, TX). Local field potentials were sampled on all electrodes and  
502 recorded continuously throughout the behavioral testing sessions using the Plexon system via  
503 National Instruments A/D card (PCI-DIO-32HS). The sampling rate was 1 kHz. The head-stage  
504 filters (Plexon) were at 0.5 Hz and 5.9 kHz. Electrodes with unstable signals or prominent peaks  
505 at 60 Hz in plots of power spectral density were excluded from quantitative analysis.

## 506 Paired recordings with Muscimol infusion

507           Animals were tested with muscimol infusions in one hemisphere and recordings of  
508 neural activity in the opposite hemisphere. For control sessions, phosphate-buffered saline (PBS)  
509 was infused into MFC. The next day, muscimol (Sigma-Aldrich, St Louis, MO) was infused at 0.1  
510  $\mu\text{g}/\mu\text{l}$ . Infusions were performed by inserting a 33-gauge injector into the guide cannula, and 1.0  
511  $\mu\text{l}$  of fluid was delivered at a rate of 15  $\mu\text{l}$  per h (0.25  $\mu\text{l}$  per min) with a syringe infusion pump  
512 (KDS Scientific, Holliston, MA). The injector was connected to a 10  $\mu\text{l}$  Hamilton syringe via 0.38  
513 mm diameter polyethylene tubing. After infusion was finished, the injector was left in place for  
514 at least 4 minutes to allow for diffusion of the fluid. The injector was slowly removed and the  
515 headstage cable was subsequently plugged into the animal's implant. Rats were tested in the  
516 instrumental shifting values licking task 1 hour after the PBS or muscimol infusions. Recordings  
517 were made the day following the infusion session without any manipulation to verify recovery  
518 from the inactivation session.

## 519 **Histology.**

520           After all experiments were completed, rats were deeply anesthetized via an  
521 intraperitoneal injection of Euthasol (100mg/kg) and then transcardially perfused using 4%  
522 paraformaldehyde in phosphate-buffered saline. Brains were cryoprotected with a 20% sucrose  
523 and 10% glycerol mixture and then sectioned horizontally on a freezing microtome. The slices  
524 were mounted on gelatin-subbed slides and stained for Nissl substance with thionin.

## 525 **Data Analysis.**

### 526 Software

527           All data were analyzed using GNU Octave (<https://www.gnu.org/software/octave/> ),  
528 Python (Anaconda distribution: <https://www.continuum.io/>), and R (<https://www.r-project.org/>).  
529 Analyses were run as Jupyter notebooks (<http://jupyter.org/>). Computer code used in this study  
530 is available upon request from the corresponding author.

531 Statistical Analysis

532 Statistical testing was performed in R. Paired t-tests were used throughout the study and  
533 repeated-measures ANOVA (with the error term due to subject) were used to compare data  
534 across training sessions (Figure 4), reinforced versus non-reinforced licks (Figure 7), and PBS  
535 versus muscimol (Figure 8).

536 Data Analysis: Local Field Potentials

537 Electrophysiological data were first briefly assessed in NeuroExplorer  
538 (<http://www.neuroexplorer.com/>). Subsequent processing was done using signal processing  
539 routines in GNU Octave. Analysis of Local Field Potentials (LFP) was carried out using the EEGlab  
540 toolbox (<http://sccn.ucsd.edu/eeglab/>) (Event-Related Spectral Power and Inter-Trial Coherence)  
541 and Neurospec 2.0 (<http://www.neurospec.org/>) (spike-lick and spike-field coherence). Circular  
542 statistics were calculated using the *circular* library for R. Graphical plots of data were made using  
543 the *matplotlib* and *seaborn* library for Python. Analyses were typically conducted in Jupyter  
544 notebooks, and interactions between Python, R, and Octave were implemented using the *rpy2*  
545 and *oct2py* libraries for Python.

546 To measure the amplitude and phase of LFP in the frequency range of licking, LFPs were  
547 bandpass-filtered using eeglab's *eegfilt* function, with a fir1 filter (Widmann & Schröger, 2012),  
548 centered at the rat's licking frequency (licking frequency  $\pm$  inter-quartile range; typically around  
549 4 to 9 Hz), and were subsequently z-scored. Analyses were performed with a pre/post window of  
550 2 seconds, and the Hilbert transform was used to obtain the amplitude and phase of the LFP.

551 To measure the consistency of LFP phase, 500 licks were randomly chosen from one  
552 session from each rat along with 500 random time points that were chosen based on shuffling  
553 the inter-lick intervals from all licks in the rat's session. After creating peri-event matrices from  
554 filtered and z-scored LFP data, the Hilbert transform was applied to obtain the phase angle and  
555 amplitude for each electrode, and the phase angles were converted to circular data using the  
556 *circular* library for R (Agostinelli and Lund, 2013), and were then used in the function *rho.circular*

557 to obtain mean resultant vector length, and *mean.circular* to obtain the actual phase angle. The  
558 *rao.spacing.test* function from R's circular library was used to obtain the test statistic and  
559 corresponding p-value that tells if the phase angles at the onset of licking pointed in a specific  
560 direction or were uniformly distributed (between 0° and 360°).

561 For inter-trial phase coherence (ITC) and event-related spectral power (ERSP) spectral  
562 analyses, LFP data was preprocessed using eeglab's *eegfilt* function with a fir1 filter and was  
563 bandpass filtered from 0 to 100 Hz. For group summaries, ITC and ERSP matrices were z-scored  
564 for that given rat after bandpass filtering the data. Peri-lick matrices were then formed by using  
565 a pre/post window of 2 seconds on each side, and the *newtimef* function from the eeglab toolbox  
566 was used to generate the time-frequency matrices for ITC and ERSP up to 30 Hz. Group  
567 summaries for ITC and ERSP were performed by obtaining the maximum ITC value within a time  
568 window of  $\pm 2$  interlick intervals (typically  $\sim \pm 375$  milliseconds) around licking, and obtaining the  
569 maximum ERSP value within that same window. Each electrode's maximum ITC and ERSP value  
570 for each type of lick (high-value or low-value lick) were used in the ANOVAs for group  
571 summaries. Finally, a "value index" was calculated to assess differences in ITC and ERSP  
572 measures associated with consumption of the higher and lower value rewards. The index was  
573 defined by the difference between the measures divided by the measure for the higher value  
574 condition, e.g.  $(ITC_{Hi} - ITC_{Lo})/ITC_{Hi}$ .

575 Shuffling methods were used to compare ERSP and ITC values for observed and shuffled  
576 licks (obtained by calculating inter-lick intervals, shuffling their trial order, and adding the  
577 intervals to the first lick in each behavioral session). This gave a set of surrogate licks with  
578 random timing unrelated to the animal's behavior. Subsets of 50 licks and shuffled events were  
579 randomly chosen from each behavioral session and ERSP and ITC statistics were calculated for  
580 the subsets of observed and shuffled data.

### 581 Data Analysis: Spike Activity

582 Exploratory analysis of on-line identified single units showed spike probabilities below 0.1

583 for all single units recorded in the task. Therefore, we used multi-unit activity (MUA) to relate  
584 spike activity to the animals' lick cycles and related LFP signals. MUA was identified using the  
585 Plexon Offline Sorter v. 4.3 (Plexon, Dallas, TX). All recorded spike waveforms were thresholded  
586 ( $\pm 2.7$  times the standard deviation for the collection of waveforms) and "automatic artifact  
587 invalidation" was applied. Then, using routines in NeuroExplorer v. 5 (Nex Technologies,  
588 Madison, AL), we measured spike probabilities for all recorded MUAs around the higher and  
589 lower values licks, using 0.001 sec bins. Spike probabilities were compared for the two lick  
590 values using a paired t-test (in R). To measure Spike-Lick Coherence (SLC), we used routines  
591 (sp2\_m1.m) from Neurospec 2.0 (<http://www.neurospec.org/>). The following parameters were  
592 used: Segment power = 12 (4096 points, frequency resolution: 0.244 Hz) and Hanning filtering  
593 with 50% tapering. To measure Spike-Field Coherence (SFC), we also used routines (sp2a\_m)  
594 from Neurospec 2.0, and analyzed bandpass filtered LFP (processed as described above; licking  
595 frequency  $\pm$  inter-quartile range) and the following parameters: Segment power = 10 (1024  
596 points, frequency resolution: 0.977 Hz), Hanning filtering with 50% tapering, and line noise  
597 removal for the LFPs at 60 Hz.

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