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Neural Coding Mechanisms for Flow Rate in Taste-Responsive Cells in the Nucleus of the Solitary Tract of the Rat

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Di Lorenzo PM, Victor JD. Neural coding mechanisms for flow rate in taste-responsive cells in the nucleus of the solitary tract of the rat. *J Neurophysiol* 97: 1857–1861, 2007. First published December 20, 2006; doi:10.1152/jn.00910.2006. When a taste stimulus enters the mouth, intentional movement of the stimulus within the oropharyngeal cavity affects the rate at which taste receptors are exposed to the stimulus and may ultimately affect taste perception. Early studies have shown that stimulus flow rate, the experimental equivalent of the effects of these investigative movements, modulates the portion of the peripheral nerve response that occurs when behavioral assessments of tastants are made. The present experiment studied the neural coding mechanisms for flow rate in the nucleus of the solitary tract (NTS), the first central relay in the taste pathway. Responses to NaCl (0.1 M) presented at high (5 ml/s) and low (3 ml/s) flow rates, sucrose (0.5 M), quinine HCl (0.01 M), and HCl (0.01 M) were recorded extracellularly from single NTS units in multiple replications. Information conveyed by evoked responses was analyzed with a family of metrics that quantify the similarity of two spike trains in terms of spike count and spike timing. Information about flow rate was conveyed by spike timing and spike count in approximately equal proportions of units (each ~1/3), whereas information about taste quality was conveyed by spike timing in about half of the units. Different subsets of units contributed information for discrimination of flow rate and taste quality.

INTRODUCTION

Flow rate is an important aspect of a taste stimulus because it impacts the magnitude of the initial phasic component of the neural response (Smith and Bealer 1975), the portion of the response corresponding to the interval when behavioral decisions based on taste quality (sweet, sour, salty, or bitter) are made (Halpern and Tapper 1971). In the natural setting, variation in flow rate is a reflection of the active process of exploration associated with gustation. For example, when an animal licks a fluid from a sipper tube, the flow rate of the stimulus, i.e., the rate at which the stimulus flows across the tongue, depends on the rate at which the animal swipes its tongue across the opening of the tube as well as the turbulence created by tongue and jaw movements as the animal moves the stimulus around the oropharyngeal cavity. Changes in flow rate resulting from these investigative movements may intensify the taste sensation in preparation for further taste reactivity, e.g., swallowing, gaping, etc., and are known to affect perception of taste intensity in humans (Meiselman et al. 1972). Further, both flow rate and taste stimulus concentration modulate the magnitude of the early transient of the chorda tympani nerve (CT,

a branch of the facial nerve innervating taste buds on the rostral 2/3 of the tongue) response, suggesting that both characteristics may share common coding mechanisms.

In the present study, we describe the coding mechanisms for stimulus flow rate in the nucleus of the solitary tract (NTS), the first relay in the central gustatory neuraxis and the target of CT projection. In the context of recent work showing that information about taste quality can be conveyed by the temporal characteristics of the early NTS response (the same portion of the response that would be predicted to reflect flow rate) (Di Lorenzo and Victor 2003), the influence and potential interaction of taste quality and flow rate on temporal coding was a special focus of this study.

Twenty-two male Sprague-Dawley rats (250–350 g) were used in these experiments. Animals were housed individually in stainless steel cages, maintained on a 12-h light-dark cycle with ad libitum food and water. Rats were anesthetized with urethan (1.5 g/kg ip, administered in 2 equal doses spaced 30 min apart) and pentibarbital sodium (Nembutal; 25 mg/kg ip) and prepared surgically for electrophysiological recording in the NTS (see Di Lorenzo and Victor 2003) with core temperature maintained at 37°C via a thermistor-controlled heating pad. Single units in the taste-responsive portion of the NTS were located and recorded with tungsten microelectrodes (18–20 MΩ @ 1 kHz; FHC) using standard electrophysiological recording techniques described previously (Di Lorenzo and Victor 2003).

Taste stimuli included NaCl (0.1 M), HCl (0.01 M), quinine HCl (0.01 M), and sucrose (0.5 M) presented at room temperature. NaCl was delivered at two flow rates, 3 and 5 ml/s. The other tastants were presented at 5 ml/s. Although these flow rates are relatively high, they were chosen to correspond to those used by Smith and Bealer (1975) to facilitate direct comparisons of NTS responses with those in the CT nerve. Tastants were bathed over the tongue through a specially designed stimulus delivery system described in detail elsewhere (Di Lorenzo and Victor 2003). Flow was regulated by a pinch valve positioned on the tube leading from the reservoir to the mouth. Flow rates were calibrated daily prior to each experiment. For variations in flow rate for NaCl, the output of the NaCl reservoir was directed through two different solenoids and two different pinch valves (each imposing a different flow rate) to the same mouth tube. Calibration tests confirmed that this system produced an even flow rate across the entire 5-s stimulus presentation, including the initial portion, for all taste

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stimuli including NaCl presented at both high and low flow rates.

Taste stimulation trials consisted of a 10-s baseline, 10-s distilled water (for tactile adaptation), 5-s stimulus, 10-s wait, and 20-s distilled water rinse. Interstimulus intervals were ≥ 2 min. To begin, each of four standard taste stimuli were presented in individual trials, all at the high flow rate. Next, for nine cells, NaCl trials were presented repeatedly in alternate trials at the low and high flow rates for as long as the cell was isolated. For the remaining 13 cells, blocks of tastants consisting of NaCl (high flow rate), NaCl (low flow rate), and sucrose, quinine, and HCl (all at the high flow rate) were presented repeatedly for as long as the unit remained well isolated.

Isolation of single units was accomplished using specialized software (Spike2, CED). Action potentials were stamped with the time of occurrence (resolution = 1 ms) relative to the beginning of each stimulus trial. Response magnitude was measured as the rate of firing in spike/second (sps) in the first 2 s of the response minus the firing rate in the final 5 s of water presentation. A change in the average firing rate over the first 2 s of stimulus presentation that differed from the average firing rate during water presentation (last 5 s) by ≥ 2.54 SD was defined as a significant response. To assess the breadth of tuning of taste-responsive NTS cells, an uncertainty measure (Smith and Travers 1979) was calculated for each unit using the response magnitudes across taste stimuli presented at the high flow rate; a value close to 1.0 indicated that the cell responded nearly equally well to all tastants tested (broad tuning), whereas a value close to 0 indicated that the cell responded to a single taste stimulus (narrow tuning).

To characterize the contribution of the temporal structure of a response to coding of flow rate or taste quality, spike trains were analyzed by the metric space method of Victor and Purpura (1996, 1997; recently reviewed in Victor 2005). This analysis is based on a family of metrics that measure "distance" (i.e., dissimilarity) between spike trains. Each of these metrics represents the minimum "cost" of transforming one spike train into another by changing a different aspect of the spike trains to be compared. Here, these included the number of spikes and the precise timing of spikes. The simplest metric, D^{count}, compares the number of spikes contained in two spike trains associated with two responses. In this case, adding or deleting a spike incurs a cost of 1 and shifting the time of spikes incurs no cost. That is, D^{count} is simply the arithmetic difference between the number of spikes in each response.

To measure the difference between two spike trains in terms of the arrangement of spikes in time, the metric $D^{spike}[q]$ was used. $D^{spike}[q]$ is a parametric family of metrics in which the parameter q determines how close in time two spikes need to occur to be considered equivalent. The cost of adding or deleting a spike is set at "1" as in D^{count}, and in addition, the cost of moving a spike by an amount of time t is set at qt where q is in units of 1/s. Each metric provides for a classification (clustering) of responses. The extent to which this clustering faithfully reflects the stimulus is quantified by transmitted information, H. The transmitted information was calculated at a range of values of q. The maximum value of $H(q)$ is denoted H_{max}, and the value of q at which H_{max} is achieved is denoted q_{max}.

In the present experiment, we analyzed the NaCl responses when NaCl was presented at high and low flow rates separately from the dataset of responses to NaCl, sucrose, quinine, and HCl presented at the high flow rate. Thus the maximum possible value of H for discrimination of flow rate was 1 ($\log_2 2 = 1$) and the maximum possible value of H for the discrimination of taste quality was 2 ($\log_2 4 = 2$). For both datasets, the relative contribution of spike count and spike timing to the information conveyed by taste responses were quantified using these methods.

Two auxiliary analyses were carried out as detailed by Victor and Purpura (1996). The first analysis ("surrogate shuffled") controlled for well-known upward bias in the estimation of H due to chance correlations in limited data (Treves and Panzeri 1995). Briefly, values of H calculated by classifying the observed responses were compared with values H_0 obtained from 10 to 40 surrogate datasets in which the tastants associated with each response were randomly scrambled. Only values of H that exceed the range (mean $\pm$ 2 SD) of values of H_0 can be considered to represent better-than-chance classification.

The second analysis ("exchange resampling") determined the extent to which the rate envelope, i.e., changes in firing rate during the time course of the response, could account for the observed contribution of temporal firing pattern to H. Here surrogate data sets were created that matched the poststimulus time histograms of the observed responses in terms of the rate envelope and that had the same number of spikes in each response but which differed from the observed response in the precise arrangement of spikes in time. We then compared values of H_{max} obtained from the recorded data with values H_{max}(exchange) obtained from the same analysis on 10–40 exchange-resampled datasets using $D^{spike}[q_{max}]$. If H was above the range (mean $\pm$ 2 SD) of values of H_{max}(exchange), we concluded that the observed temporal coding is not merely due to the rate envelope of the response to each tastant (with the overall variability in spike count taken into consideration) and that the arrangement of spikes in time in individual trials contributes additional information.

Responses from 22 cells to NaCl presented in repeated trials at both flow rates were recorded from single units in the NTS. In 13 of those units, responses to repeated presentations of the other three tastants were also recorded. The number of stimulus repetitions ranged between 10 and 40. Across all units, the mean spontaneous rate was 2.38 $\pm$ 0.62 (SE) sps, and the order of effectiveness for all tastants tested was NaCl>HCl>sucrose>quinine. Sixteen units (73%) responded best to NaCl, 6 (37%) to HCl, and none to sucrose or quinine. In general, taste units were broadly tuned with 8 cells (36%) responding to all 4 taste stimuli, 10 (46%) to 3 stimuli, 3 (14%) to 2 stimuli, and 1 (4%) to a single taste stimulus. Average Uncertainty measure across units was 0.80 $\pm$ 0.02 SE. Table 1 shows the spontaneous rates, breadth of tuning and response magnitudes for all units.

Results of the analysis of temporal coding for flow rate, summarized in Table 2, indicate that spike count, the rate envelope, and spike timing may all contribute to encoding differences in flow rate. H_{max}, representing the information conveyed by temporal coding, did not exceed the value of H_{count}, representing the contribution of spike count alone, in eight units (8 of 22, 36%). That is, in these units, we did not detect any contribution of temporal coding to signaling of flow rate. [Perhaps a footnote: In 2 of these units (FR13 and FR14),

TABLE 1. *General characteristics of NTS taste-responsive units*

| | | | | Response (Mean Firing Rate in spikes/s over 2 s) | | | | |
| | | | | *n* | | | | |
Cell	No. of Trials	Spontaneous Rate	Best	Breadth of Tuning	High	Low	H	Q	S
FR10	17	3.1	HCl	0.76	25.3 ± 0.7	25.4 ± 1.0	24.1	12.9	−0.3
FR11	23	2.7	NaCl	0.67	21 ± 3.6	22.1 ± 4.2	5.9	6.9	−0.7
FR12	14	0.9	NaCl	0.55	25.5 ± 2.3	18.7 ± 3.4**	2.4	3.2	1.6
FR13	12	0.54	NaCl	0.71	10.2 ± 0.7	−0.1 ± 0.2**	3.4	−0.1	2.2
FR14	12	1	NaCl	0.97	8.3 ± 0.7	1.0 ± 0.4**	5.5	6.3	6.2
FR21	40	0.5	NaCl	0.92	38.6 ± 1.1	39.1 ± 0.9	10.4	6.4	13.3
FR22	23	1.2	NaCl	0.68	13.6 ± 1.6	10.7 ± 1.6**	1.5	2.8	1.9
FR23	12	6.2	NaCl	0.54	3.1 ± 0.5	1.2 ± 0.6**	0.2	1.2	−0.4
FR24	11	0.2	HCl	0.67	15.8 ± 1.7	17.3 ± 1.7	10.8	2.8	−0.1
FR30	11	3	HCl	0.79 ± 0.02	16.1 ± 1.4	15.3 ± 1.2	59.7 ± 1.7	51.4 ± 1.4	3.3 ± 0.8
FR31	10	1	NaCl	0.76 ± 0.04	47.7 ± 2.4	45.3 ± 1.7	15.8 ± 1.1	17.2 ± 0.8	0.2 ± 0.4
FR42	14	0.6	NaCl	0.70 ± 0.08	5.7 ± 0.8	1.8 ± 0.6**	4.4 ± 0.7	4.7 ± 1.4	0.1 ± 0.1
FR44	12	1.7	NaCl	0.90 ± 0.07	13.0 ± 1.6	14.4 ± 1.3	9.0 ± 0.8	7.1 ± 0.5	1.2 ± 0.4
FR45	15	0.54	NaCl	0.77 ± 0.08	8.1 ± 0.6	7.0 ± 0.8	2.5 ± 0.3	1.0 ± 0.3	4.5 ± 0.7
FR48	18	0.44	HCl	0.88 ± 0.01	74.0 ± 2.0	60.4 ± 2.1**	75.1 ± 2.9	60.7 ± 1.7	9.7 ± 0.9
FR49	10	7.1	NaCl	0.91 ± 0.02	64.8 ± 7.2	53.9 ± 8.0	52.3 ± 15.5	62.7 ± 11.0	17.6 ± 2.3
FR50	12	1.97	NaCl	0.82 ± 0.03	56.5 ± 1.8	44.6 ± 2.1**	53.0 ± 1.4	47.3 ± 1.3	3.5 ± 0.8
FR51	11	12.4	HCl	0.91 ± 0.01	5.9 ± 1.3	2.7 ± 1.2	9.9 ± 1.3	9.2 ± 1.0	6.0 ± 0.8
FR54	10	1.44	NaCl	0.66 ± 0.04	1.5 ± 0.5	1.9 ± 0.4	1.0 ± 0.2	0.9 ± 0.3	04 ± 0.2
FR55	10	1.46	HCl	0.88 ± 0.01	12.5 ± 0.8	13.0 ± 1.3	14.3 ± 1.0	10.4 ± 1.0	2.1 ± 0.4
FR57	15	0.14	NaCl	0.86 ± 0.02	2.3 ± 0.5	2.2 ± 0.2	0.9 ± 0.2	1.2 ± 0.3	1.9 ± 0.3
FR58	16	4.13	NaCl	0.65 ± 0.04	18.5 ± 3.7	14.0 ± 3.4	8.8 ± 1.6	5.2 ± 0.8	1.4 ± 0.8

Values are means ± SE. NTS, nucleus of the solitary tract. ** $P < 0.01$ for *t*-test comparison of NaCl response at high and low flow rates

$H_{max} = 1$. We counted these units among those for which rate envelope or temporal pattern did not contribute to coding of flow rate. However, it is quite possible that temporal aspects of the response might have further boosted the fidelity of coding of flow rate had we tested flow rates that were closer together than 3 and 5 ml/s.] In seven (7 of 22; 32%) of the remaining 14 units, precise spike timing added a significant amount of information about flow rate [H_{max} was greater than H_{count}, and $H_{max} - H_{max}$(exchange) was statistically significant ($P < 0.05$)]. In the remaining seven units (7 of 22, 32%), information conveyed by the rate envelope, but not spike timing, contributed information above and beyond spike count to discriminating high and low flow rates [H_{max} was greater than H_{count} but not significantly larger than H_{max}(exchange)].

TABLE 2. *Analyses of temporal coding of flow rate and taste quality*

| | Flow Rate | | | | Taste Quality | | | |
Cell	H_{count}	$H_{max} - H_{count}$	q_{max}	Information From Spike Timing	H_{count}	$H_{max} - H_{count}$	q_{max}	Information From Spike Timing
FR10	0.064							
FR11	0.006	0.439	32	*				
FR12	0.408	0.403	16	*				
FR13	1							
FR14	1							
FR21	0	0.152	16	*				
FR22	0.016	0.043	16					
FR23	0.161							
FR24	0.007	0.327	8					
FR30	0.161	0.613	16		0.850	0.607	2	*
FR31	0	0.758	16		1.011	0.476	64	*
FR42	0.561				0.745	0.114	2	
FR44	0.013	0.205	16	*	0.806	0.165	2	
FR45	0.003				0.840	0.565	4	*
FR48	0.013	0.729	11.3		0.956	0.563	16	
FR49	0.049	0.051	128		0.330	0.543	16	*
FR50	0.788				0.993	0.627	11.3	*
FR51	0.155	0.179	2.8	*	0.224	0.466	4	*
FR54	0.047	0.249	16	*	0.365	0.106	8	*
FR55	0.029	0.282	2		0.642	0.486	4	
FR57	0.218				0.224	0.294	2	
FR58	0.001	0.352	64	*	0.447	0.200	8	

*, indicates H_{max} exceeds 95% confidence limit for exchange resampling analysis. Missing values under "Flow Rate" indicates that H_{max} did not exceed H_{count}. Missing values under "Taste Quality" indicates no data available.

Results of the analyses of temporal coding of taste quality, also shown in Table 2, indicated that among the 13 units for which both flow rate and taste quality data were available, seven units (7 of 13, 54%) showed a significant contribution of spike timing to information conveyed about taste quality [i.e., H_{max} greater than H_{count} and $H_{max} - H_{max}$(exchange) was statistically significant ($P < 0.05$)]. These data are consistent with a previous report indicating that about half (53%) of taste-responsive NTS units utilize spike timing to convey information about taste quality (Di Lorenzo and Victor 2003). Results from one unit (FR55; 1 of 13, 8%) suggested that the rate envelope contributed information about taste quality [H_{max} was not significantly different from H_{max}(exchange)]. Only two units (FR51 and FR54; 2 of 13, 15%) showed evidence that spike timing contributed information about both taste quality and flow rate, albeit at different levels of temporal precision (values of q).

Figure 1 shows examples of the analysis of temporal coding of flow rate (FR11) and taste quality (FR50) taken from two different units. In Fig. 1A, left, it can be seen that the average firing rates produced by NaCl presented at a high and low flow rates were approximately equivalent. This suggests that response magnitude is a poor indicator of flow rate in this unit. In Fig. 1A, right, results of the analyses of temporal coding show that spike timing contributes a significant amount of information to the discrimination of flow rate ($H_{max} - H_{count}$ $= 0.439$, $q = 32$). In Fig. 1B, left, it can be seen that the average responses magnitudes evoked by NaCl (at both high

and low flow rates), HCl, and quinine were similar across trials, suggesting that spike count alone is not sufficient to encode differences among them. Analyses of the contribution of temporal coding (Fig. 1B, right), however, show that spike timing adds a significant amount of additional information to this discrimination ($H_{max} - H_{count} = 0.627$, $q = 11.3$). In both Fig. 1, A and B, the fact that the information contributed by spike timing of the response was significantly larger than the corresponding amount of information contributed by the "exchange" surrogate data set (i.e., H_{max} was significantly larger than $H_{exchange}$) shows that spike timing per se, and not just the firing rate envelope, conveys information.

In sum, our results show that temporal coding may be utilized to encode both the flow rate of a stimulus and taste quality; however, different subsets of units may encode these characteristics. For flow rate, spike timing and spike count were each utilized in approximately a third of the units, but for taste quality, spike timing was utilized in about half of the units. Some units also utilized the rate envelope to convey information about flow rate, but this was less frequently observed for taste quality.

It is worth noting that neither spike count nor spike timing can perfectly convey differences in the flow rate of a stimulus. This is evident in the fact that the median amount of information about flow rate that was conveyed by either of these coding mechanisms was 0.34 bits (range: 0.003–0.81 bits), far short of the 1.0 bit needed for perfect discrimination. Although it is possible that information about flow rate may be encoded
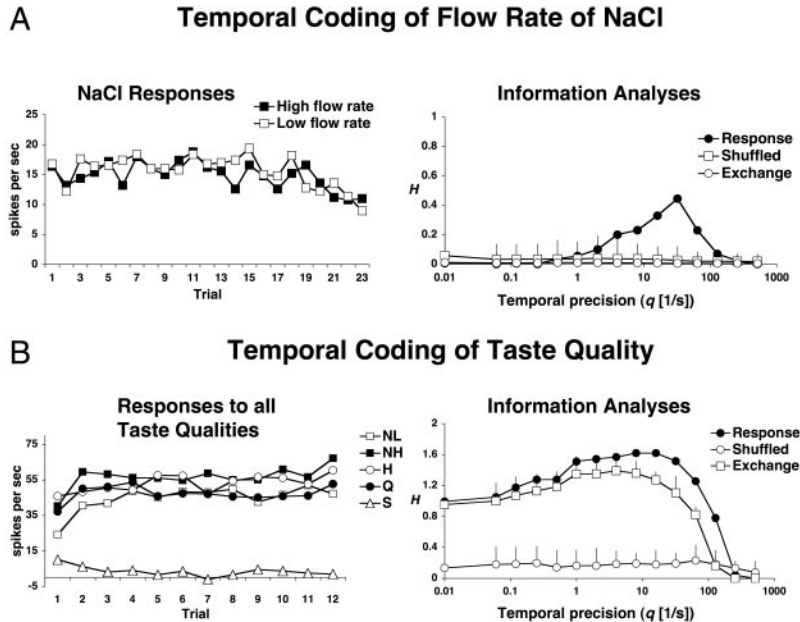

A Temporal Coding of Flow Rate of NaCl

B Temporal Coding of Taste Quality

FIG. 1. A: analyses of temporal coding of flow rate in nucleus of the solitary tract (NTS) unit FR11. Left: response magnitude (mean spike/s in 1st 2 s of response minus firing rate during water presentation) across repeated trials of NaCl presented at high and low flow rates. Right: results of metric space analyses of information (H) about flow rate conveyed by spike timing. B: analyses of temporal coding of taste quality in NTS unit FR50. Left: response magnitude of responses to all taste stimuli across repeated trials. Right: results of metric space analyses of information (H) about taste quality conveyed by spike timing. NL, NaCl presented at the low flow rate; NH, NaCl presented at the high flow rate; H, HCl; Q, quinine; S, sucrose. "Response" refers to the information contributed by spike timing to the discrimination of flow rate (A) or taste quality (B) at various levels of temporal precision (q). "Shuffled" refers to an estimate of bias derived from surrogate shuffled data sets. Responses were randomly assigned different labels, e.g., NaCl responses might be re-labeled as HCl or sucrose response, etc., and the analyses of information contributed by spike timing were repeated. The graph shows the average ±2 SD of 40 such analyses of shuffled datasets for flow rate and 10 such analyses for taste quality. "Exchange" refers to exchange resampling analyses comparing H extracted from the actual responses via $D^{spike}[q]$ with H extracted from surrogate data sets that matched the time-varying firing rate, and overall spike count, of the actual data. Results of these analyses showed the information contributed by the time course of the response without regard to the pattern of individual spikes in time. The graph shows the average ±2 SD of 10 such analyses for both flow rate and taste quality.

in a structure other than, or perhaps in addition to the NTS, another explanation might be that flow rate may be encoded primarily by tactile cells. Because most taste-responsive cells in the NTS also respond to tactile stimuli (Ogawa et al. 1984) (also, as evidenced by the responses to water), they might also participate in signaling this aspect of a taste stimulus. However, because taste intensity is enhanced by flow rate (Meiselman et al. 1972), it is possible to predict that, like flow rate, changes in taste stimulus concentration will also be signaled by the temporal features of the response.

REFERENCES

Di Lorenzo PM, Victor JD. Taste response variability and temporal coding in the nucleus of the solitary tract of the rat. *J Neurophysiol* 90: 1418–1431, 2003.

Hallock RM, Di Lorenzo PM. Temporal coding in the gustatory system. *Neurosci Biobehav Rev* 30: 1145–1160, 2006.

Halpern BP, Tapper DN. Taste stimuli: quality coding time. *Science* 171: 1256–1258, 1971.

Katz DB, Simon SA, Nicolelis MA. Dynamic and multimodal responses of gustatory cortical neurons in awake rats. *J Neurosci* 21: 4478–4489, 2001.

Lestienne R. Spike timing, synchronization and information processing on the sensory side of the central nervous system. *Progr Neurobiol* 65: 545–591, 2001.

Meiselman HL, Bose HE, Nykvist WE. Effect of flow rate on taste intensity responses in humans. *Physiol Behav* 9: 35–38, 1972.

Nagai T, Ueda K. Stochastic properties of gustatory impulse discharges in rat chorda tympani fibers. *J Neurophysiol* 45: 574–592, 1981.

Ogawa H, Imoto T, Hayama T. Responsiveness of solitario-parabrachial relay neurons to taste and mechanical stimulation applied to the oral cavity in rats. *Exp Brain Res* 54: 349–358, 1984.

Smith DV, Bealer SL. Sensitivity of the rat gustatory system to the rate of stimulus onset. *Physiol Behav* 15: 303–314, 1975.

Smith DV, Travers JB. A metric for the breadth of tuning of gustatory neurons. *Chem Senses* 4: 215–229, 1979.

Treves A, Panzeri S. The upward bias in measures of information derived from limited data samples. *Neural Comput* 7: 399–407, 1995.

Victor JD. Spike train metrics. *Curr Opin Neurobiol* 15: 585–592, 2005.

Victor JD, Purpura KP. Nature and precision of temporal coding in visual cortex: a metric-space analysis. *J Neurophysiol* 76: 1310–1326, 1996.

Victor JD, Purpura KP. Metric-space analysis of spike trains: theory, algorithms and application. *Network* 8: 127–164, 1997.