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Ventral Pallidum Firing Codes Hedonic Reward: When a Bad Taste Turns Good

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Tindell, Amy J., Kyle S. Smith, Susana Peciña, Kent C. Berridge, and J. Wayne Aldridge. Ventral pallidum firing codes hedonic reward: when a bad taste turns good. *J Neurophysiol* 96: 2399–2409, 2006. First published August 2, 2006; doi:10.1152/jn.00576.2006. The ventral pallidum (VP) is a key structure in brain mesocorticolimbic reward circuits that mediate "liking" reactions to sensory pleasures. Do firing patterns in VP actually code sensory pleasure? Strong evidence for hedonic coding requires showing that neural signals track positive increases in sensory pleasure or even reversals from bad to good. A useful test is the salt alliesthesia of physiological sodium depletion that makes even aversively intense NaCl taste become palatable and "liked." We compared VP neural firing activity in rats during aversive "disliking" reactions elicited by a noxiously intense NaCl taste (triple-seawater 1.5 M concentration) in normal homeostatic state versus in a physiological salt appetite state that made the same NaCl taste palatable and elicit positive "liking" reactions. We also compared firing elicited by palatable sucrose taste, which always elicited "liking" reactions in both states. A dramatic doubling in the amplitude of VP neural firing peaks to NaCl was caused by salt appetite that matched the affective switch from aversive ("disliking") to positive hedonic ("liking") reactions. By contrast, VP neural activity to "liked" sucrose taste was always high and never altered. In summary, VP firing activity selectively tracks the hedonic values of tastes, even across hedonic reversals caused by physiological changes. Our data provide the strongest evidence yet for neural hedonic coding of natural sensory pleasures and suggest, by extension, how abnormalities in VP firing patterns might contribute to clinical hedonic dysfunctions.

INTRODUCTION

Salt is crucial to survival and can be a potent hedonic stimulus. Ordinarily, hypertonic concentrations of NaCl (such as seawater) taste unpleasant to humans and elicit "disliking" gape reactions from rats (although lower concentrations of salt are often pleasant) (Schulkin 1993; Stellar 1980). However, even the unpleasant valence of intense salty tastes can be reversed from negative to positive by physiological sodium deficiency states, in a hedonic phenomenon called taste "alliesthesia" (Cabanac 1971). For example, physiological sodium depletion reverses "disliking" reactions to hypertonic NaCl taste into "liking" reactions in rats (e.g., tongue protrusions) and increases the perceived pleasantness of salt for humans (Beauchamp et al. 1990; Berridge et al. 1984; Clark and Bernstein 2004, 2006; Kochli et al. 2005; Leshem and Rudoy 1997; Richter 1936; Roitman et al. 2002; Wilkins and Richter 1940).

How are hedonic impact reversals coded in the brain? The ventral pallidum (VP) is an especially likely candidate to code sensory pleasure because it receives converging inputs from gustatory circuits and limbic circuits that mediate natural and drug rewards (Kalivas et al. 1999; Swanson 2005; Zahm 2006). Sucrose rewards elicit increased firing in VP neurons in rats (Tindell et al. 2004), suggesting that positive hedonic signals might be encoded in neural firing rates. Indeed, the VP mediates reward in the sense that direct manipulations of the VP cause changes in the hedonic impact of sweet tastes and reward value of other incentives (June et al. 2003; Shimura et al. 2006; Skoubis and Maidment 2003; Smith and Berridge 2005; Tang et al. 2005). For example, opioid receptor stimulation in a posterior VP "hedonic hotspot" causes increases in the number of hedonic "liking" reactions elicited by sucrose taste (Smith and Berridge 2005). Conversely, lesions of the VP cause hedonic "liking" reactions to be lost and replaced by aversive reactions, even to sucrose (Cromwell and Berridge 1993).

If VP neurons truly code hedonic impact, then they should track enhanced hedonic impact in a manner that is specific to the stimulus that gains value (i.e., not stimuli in general) and their hedonic code should be separable from codes for movement and sensory features. Ideally, a true hedonic code should even track a reversal in the valence impact of a stimulus from negative ("disliked") to positive ("liked"). To test the idea that the VP encodes positive hedonic impact, we recorded neural activity in the VP while assessing the changing hedonic impact of intense salt (triple-seawater concentration, 1.5 M NaCl) versus sweet tastes (0.5 M sucrose) by affective "liking" and "disliking" reactions (controlling stimulus sensory properties by delivering taste solutions directly into the mouth by oral cannulae). We selectively altered the positive/negative valence of salt taste by inducing physiological sodium need and compared the neuronal and behavioral changes in reaction to salt versus sucrose tastes. Our results demonstrate that VP firing rates selectively track the positive hedonic impact of tastes, reversing from negative to positive to salt while constantly responding positively to sucrose. Thus VP neuronal firing passes the most stringent possible test for encoding sensory pleasantness, providing the strongest evidence yet for hedonic neuronal coding in a brain limbic structure.

METHODS

Animals

Eight male Sprague–Dawley rats (300–450 g) were housed individually on an 8 AM to 8 PM reversed light–dark schedule, and provided with unrestricted access to a sodium-free diet, distilled water, and 3% NaCl (0.5 M) solution (except during the sodium-depletion phase of the experiment, when no NaCl was available). The
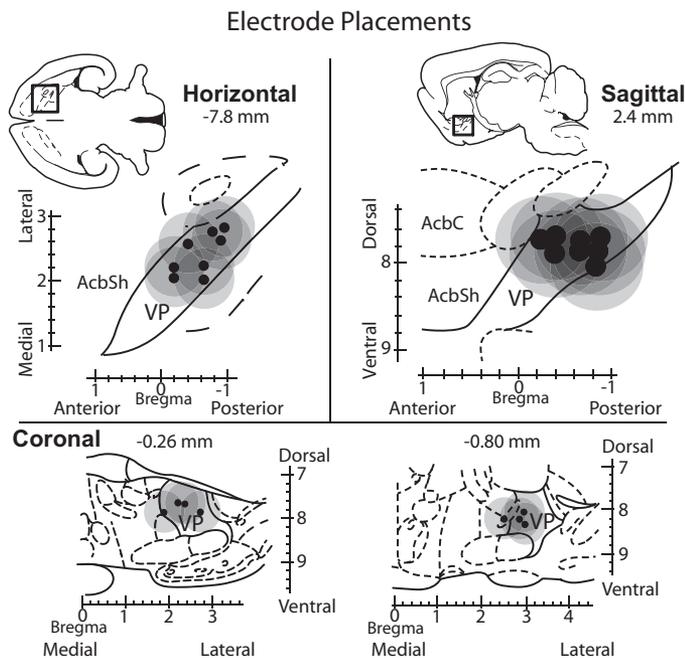
Electrode Placements

FIG. 1. Recording sites in the ventral pallidum (VP). Coronal, sagittal, and horizontal views. Dark dots show center of each electrode bundle and gray halos show maximum spread of individual electrode wires.

University Committee on the Use and Care of Animals approved all methods.

Electrode implantation and oral cannula surgery

Rats were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg) for the stereotaxic placement of electrodes in VP (L: 2.6 mm, A: −0.25 to −1.10 mm; D: 7.3 mm; Fig. 1). Neural activity was recorded and monitored during surgery as the electrode cluster was lowered into the brain to facilitate accurate placement in VP (Tindell et al. 2004). Each electrode cluster consisted of eight wires (50 μm tungsten) (Jaeger et al. 1990). One wire with no spike activity was selected during recording sessions to serve as a reference channel for differential recording. Every other wire was an independent recording electrode, providing at least seven recording sites per rat clustered within a 1-mm diameter of VP. Bone screws were inserted into the skull and served as a ground reference.

In the same surgery, anesthetized rats were also implanted with bilateral intraoral cannulae for later infusion of taste solutions. Oral cannulae (PE 100 tubing) enter the mouth lateral to the first molar, travel beneath the zygomatic arch, and exit the head near the skull screws where they are attached to a stainless steel guide cannulae (19 gauge). Electrodes and oral cannulae were attached to the skull by bone screws and fixed in place with dental acrylic.

Recording

Rats were tested in a plastic 25-cm-diameter test cylinder with an open top to allow plastic tubing connections from the oral cannulae to the syringe pump, and also connections between the headstage and the commutator. A mirror under the glass bottom of the cylinder allowed video recording of behavioral orofacial affective reactions, elicited by tastes that were infused into their mouths by oral cannula, and allowed time-stamped monitoring of movements for motor coding analyses of VP firing. Two syringe pumps maintained proper rate and volume of infusions. Noise from the pump operation was masked with a white noise generator. Computer programs controlled oral infusions (Mtask, written in this laboratory) and neural recording (Recorder, Plexon,

Dallas, TX). The time-stamp clocks were synchronized for infusions, neural recordings, and videotape recordings when possible to allow for cross-comparisons. All neural (computerized analyses) and behavioral data (frame-by-frame video; observers blind) were subsequently scored and analyzed off-line as described below (Aldridge and Berridge 1998).

Oral infusion testing

Rats were tested repeatedly to blocks of 10 repetitions of the same stimuli (NaCl, sucrose, and water tastes) delivered in 0.1-ml, 1-s-pulsed infusions. Each session was repeated over 3 days in different physiological states (normal homeostasis or sodium replete; salt appetite after sodium depletion; regained normal homeostasis or re-repleted). During each session, rats were given a block of 10 infusion pulses each of three tastes: distilled water, 8.9% or 1.5 M NaCl solution, and 17.1% or 0.5 M sucrose solution. Taste pulse infusions were spaced 1 min apart. Thus rats received 10 infusions per day each of NaCl, sucrose, and water, presented in counterbalanced order between rats. Additionally, an extra infusion of distilled water was given between blocks to rinse the mouth between tastes. For infusions, a 3-ml syringe containing either water, salt, or sucrose was attached before the test session by hollow tubing (PE-50 connected to a PE-10 delivery nozzle) to a single oral cannula. The first test day served as a baseline, with all rats sodium replete in normal homeostasis.

Sodium depletion was induced by injections of furosemide (7.5 mg/kg, administered subcutaneously [sc]) and deoxycorticosterone acetate (DOCA, 5 mg/kg, sc) (Flynn et al. 2005), followed 2 h later by an additional injection of 7.5 mg/kg furosemide (Tamura and Norgren 1997). Pilot studies indicated that this combination induced a more robust behavioral salt appetite than either single hormone alone in our lab and therefore the combination was selected for this electrophysiological and taste reactivity study (personal observations). Rats continued to be maintained on sodium-free chow (Purina) and distilled water for 24 h after injection to allow salt appetite to develop. No NaCl was available between the sodium-depleting injections and the depletion test. Salt appetite induction was verified by comparing consumption of 0.5 M NaCl solution in the home cage during a 24-h period after the depletion test to baseline intake measured before the day 1 test.

Three days after the first taste infusions and VP recording test, rats received furosemide/DOCA injections and were returned to their home cage (where NaCl bottle was removed). At 24 h after hormonal injections, rats were tested for taste responses and VP recordings in a sodium-depleted state under conditions otherwise identical to those of day 1. Immediately after the sodium-depletion test, NaCl bottles were returned to the cages and rats were allowed free access to reestablish sodium balance. Three days after the sodium-depleted session, rats were tested a third and final time under identical conditions, but now in a relatively restored homeostatic balance.

Taste reactivity analysis

Taste reactions were scored off-line in a frame-by-frame video analysis by experimenters blind to taste and physiological condition. Detailed behavioral scoring procedures are described elsewhere (Berridge 2000). Briefly, the onset times of reactions during a 10-s period after each infusion were tabulated (responses typically were <15-s duration). Positive hedonic reactions included rhythmic midline tongue protrusions, lateral tongue protrusions, and paw licking (see Supplementary video 1). Aversive reaction patterns included gapes, headshakes, forelimb flails, face washing, and chin rubs. The onset and offset times of neutral rhythmic mouth movements were also recorded. The onset time stamps of taste reactions were used for comparison to VP firing.

For a behavioral assessment of taste reactivity, the number of counts for each response was summed to form ranking scores for overall hedonic, aversive, and neutral categories [modified from Berridge (2000)]. Behaviors that typically occur in discrete events (lateral tongue protrusions, gapes, chin rubs, headshakes, forelimb flails, and passive drips) received one count per occurrence. Behaviors that typically occur in continuous bouts (tongue protrusions, paw licking, rhythmic mouth movements, grooming) were timed as durations and given one count for each 1-s bout. Repeated-measures ANOVAs (day = between, taste = repeated) and Bonferroni-corrected post hoc tests evaluated taste effects (salt, sucrose, water) and physiological condition effects (baseline-replete, depletion, re-repletion) on taste reactivity scores.

To correlate behavior with VP firing, orofacial taste reactivity latencies (time to respond from taste infusion) were examined in detail on a subset of animals with neural recordings synchronized to video recordings. Latencies were tallied for each taste infusion, treatment condition, taste stimulus, and for behavioral reactions most commonly observed for hedonic, aversive, and neutral taste valuation (tongue protrusions, gapes, and rhythmic mouth movements, respectively). The relative latencies of taste reactions to VP neural responses were assessed. Two-way ANOVA (physiological condition × taste stimulus) and one-way ANOVAs (such as condition for NaCl taste) were also used to compare latencies across physiological conditions and taste stimuli.

VP firing analysis: spike discrimination

Waveforms of single neurons were discriminated from other neurons and from noise using an interactive computer program (Off-line Sorter; Plexon). Single units were verified by their refractory periods in an autocorrelation histogram (NeuroExplorer, Nex Technologies). As a final discrimination procedure, we performed a cross-correlation analysis (NeuroExplorer) on all units to ensure that any unit recorded simultaneously on two electrode sites was counted only once in the analysis. Any remaining units that could not be separated from other neurons or noise were discarded. The neural constituents differed from day to day on most electrode wires, and thus we made comparisons across groups rather than individuals.

Perievent rasters and histograms

Discriminated spikes were used to construct perievent rasters and histograms for visual inspection and quantitative analyses of responses to tastes and evoked movements. Histogram bins and raster trials from these compiled data were used for firing rate analyses (below).

Responsive populations

A VP neuron was defined as responsive to a taste if the firing rate during the 1-s infusion was significantly different ($P < 0.05$ in Bonferroni-corrected paired t-test) from the firing rate during background (5 s before infusion). Numbers of responsive neurons for the 1-s infusions were tallied and compared across tastes and physiological conditions using ANOVA.

Firing rates

VP firing rates of responsive neurons were normalized by dividing a neuron's absolute firing rate during the 1-s infusion by its firing during the 5-s period immediately before that infusion. Normalization reduces baseline variation caused by neurons that naturally fire slower or faster than others and allows us to focus analyses on the relative changes in response magnitude elicited by taste infusions. Analysis of firing rate trends across blocks of trials revealed that neural responses changed across trials within blocks (F = 8.623, $P < 0.0001$; thus our firing rate analysis of tastes across physiological conditions in individual cells included trial as a covariate). We performed a repeated-measures ANOVA on the normalized firing rates in SPSS (Chicago, IL) with taste as the within-subjects repeated measure and physiological condition as the between-subjects factor. Bonferroni-corrected post hoc tests were performed for other comparisons. Because we were not able to complete all three taste tests on some cells, and these cells were therefore not included in the repeated-measures analysis, we performed a separate between-subject analysis (ANOVA) to verify statistical conclusions (between-subject results are reported only where the two produced different results).

All responsive neurons, whether excitatory or inhibitory, were included in the computations of overall rate changes. This approach is conservative because it does not use a priori criteria to screen out any group of neurons and best reflects the net output of the responsive neural population (allowing inhibitions to cancel excitations). Overall, the waveforms and other characteristics of neuronal activity suggested that different units were being recorded over different test days (Tindell et al. 2004, 2005). Therefore comparisons between normal homeostatic and sodium-depleted physiological states (different test days) were always done using between-subjects ANOVAs and Bonferroni-corrected post hoc tests, whereas tastes tested within one session could be compared with a within-subject design.

Histology

After all recordings were completed, rats were given an overdose of pentobarbital and perfused transcardially with saline and formaldehyde. Brains were removed, sliced in 40-μm coronal sections, and stained with cresyl violet. Slices were examined under light microscopy to verify electrode placement in VP. Coronal electrode site coordinates were further converted into horizontal and sagittal atlas planes to facilitate three-dimensional mapping of site placements. We mapped the full anatomical spread of electrodes contained in each bundle (Fig. 1).

RESULTS

Latency of taste movement responses

Infusion pulses of 1.5 M NaCl, 0.5 M sucrose, or distilled water delivered by cannula into the mouth typically elicited an immediate behavioral response (0.61 ± 0.034 s latency, mean ± SE) of a brief burst of neutral reactions lasting about 1 s (e.g., rhythmic mouth movements; neutral latency did not change across physiological conditions [$F(1,127) = 0.16$, $P = 0.683$[). Either positive ("liking") or negative ("disliking") affective reactions usually followed within 0.5–1.5 s later and then lasted 10 to 15 s (see Supplementary video 1), with valence depending on the taste and physiological condition (sample latencies: tongue protrusions = 1.23 ± 0.23 s; gapes = 2.08 ± 0.19 s).

Behavioral "liking" and "disliking" reactions to taste palatability

Sucrose taste elicited strongly positive hedonic reactions regardless of whether rats were in normal homeostasis or sodium depleted. The number of positive hedonic reactions elicited by 0.5 M sucrose never changed over test days (all comparisons: $P > 0.05$; Fig. 2). By contrast, concentrated 1.5 M NaCl normally evoked overwhelmingly aversive "disliking" reactions on the first baseline test day in sodium homeostasis (Fig. 2). When rats were in a salt appetite state induced by sodium depletion, however, aversive reactions to NaCl fell to
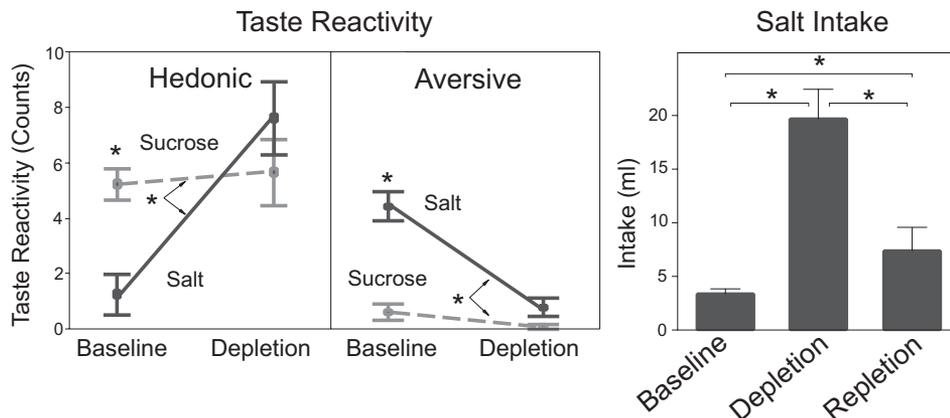
Taste Reactivity

Salt Intake

FIG. 2. Behavioral "liking" reactions to salt increase after sodium depletion (*left*). NaCl infusions into the mouth elicited more positive hedonic ("liking") reactions and fewer negative aversive ("disliking") reactions when rats were sodium depleted than when in normal homeostasis. Sucrose always elicited "liking" reactions and NaCl became similar to sucrose during sodium depletion. Salt appetite was later confirmed by increased 24-h free consumption of salt solution in home cage after sodium depletion (*right*). Intake was higher after sodium depletion and recovered mostly but not completely in re-repletion, and remained slightly higher than baseline after sodium repletion. *$P < 0.05$.

$<25\%$ of their original levels (interaction: $F = 3.983$, $P = 0.009$). Aversive reactions to NaCl fell to near zero on the sodium-depleted test ($P < 0.0001$), becoming similar to sucrose levels on that day (Fig. 2).

Positive hedonic reactions to NaCl tastes more than tripled when rats were sodium depleted compared with rats in normal homeostasis on the first and third test days ($F = 3.995$, $P = 0.008$). With sodium depletion, the number of hedonic "liking" reactions elicited by NaCl taste rose from a near-zero first-day baseline ($P < 0.0001$) to a level that equaled the number of positive reactions elicited by sucrose ($P = 0.165$). On the same sodium-depleted day, the first NaCl-elicited positive hedonic reactions (rhythmic tongue protrusions) appeared earlier than on the normal homeostatic day (latency to first mouth movement: $F = 14.51$, $P < 0.001$; one-way ANOVA on condition: $F = 13.77$, $P = 0.001$), although sucrose-elicited latencies for these positive hedonic reactions were unaffected by physiological condition (one-way ANOVA on condition: $F = 2.19$, $P = 0.145$).

Finally, on the third test day after sodium re-repletion by overnight free access to salt, reactions to salt taste infusions returned again to aversive "disliking" patterns (baseline vs. re-replete: $P > 0.05$). Water infusions never changed the pattern of positive hedonic, negative aversive, or neutral taste reactions across baseline-replete, depletion, or re-repletion tests ($P > 0.05$). Typically water elicited mostly neutral reactions plus low numbers of either hedonic or aversive reactions [e.g., fewer hedonic reactions than sucrose ($P = 0.042$) and fewer aversive reactions than NaCl in normal homeostatic days (baseline: $P < 0.0001$; re-repletion: $P = 0.007$)].

In voluntary 24-h intake tests conducted beginning overnight after sodium-depleted recording sessions, rats drank three times more of 0.5 M NaCl solution than they had when in normal homeostasis, which confirmed the efficacy of salt appetite induction by furosemide/DOCA administration ($F = 21.695$, $P < 0.0001$; Fig. 2, *right*). On the night after the re-repletion test, after rats had been allowed to substantially recover from sodium deficiency, rats drank much less NaCl solution than they had when sodium depleted, but still nearly 50% more than they had on the first test in normal homeostasis [paired-samples *t*-test; $t(16) = 3.24$; $P < 0.05$].

Ventral pallidum neuronal firing

We recorded activity from 167 neurons in VP, of which roughly 60% responded to at least one or more of the infused

tastes (100 of 167 neurons; Fig. 1). Our principal finding was that taste-elicited firing rates rise in correlation to positive hedonic impact. VP neural firing rates to NaCl taste increased selectively during sodium depletion to high firing rates that equaled sucrose (Fig. 3), an increment that paralleled the behavioral shift from aversive salt "disliking" to hedonic "liking" reactions to taste. Indeed, a regression analysis revealed that neural firing in response to NaCl (Fig. 3) was positively correlated to behavioral hedonic scores of the same rats, comparing across normal homeostatic versus sodium depletion test days [$F(1,65) = 6.52$, $P = 0.014$, Spearman's correlation: $P = 0.007$].

In a comparison of firing rates during the 1-s taste infusion to firing rates during 5-s baseline before the taste infusion, sucrose always evoked large increases in firing rates ($>66\%$ in responsive VP neurons). Sucrose firing remained high regardless of test day or physiological state (repeated-measures analysis where every cell was fully tested with all taste solutions: $F = 0.052$, $P = 0.82$; Fig. 3). NaCl taste, by contrast, elicited firing less than half in amplitude of sucrose on the first test day when rats were in normal homeostasis (29% over baseline; $P < 0.0001$ compared with sucrose; Fig. 3). When sodium depleted, however, NaCl-elicited firing peaks more than doubled in
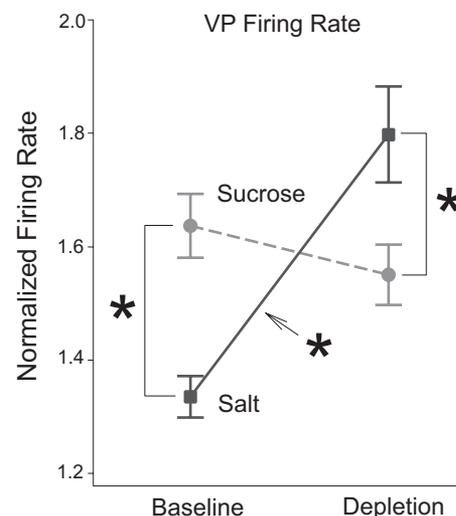
VP Firing Rate

FIG. 3. VP firing rates code taste hedonic impact (averaged over first 1 s after taste infusion; within-subject data). Normalized rate peaks (mean and SE) elicited by 1.5 M NaCl are normally much lower than sucrose, but physiological sodium depletion causes NaCl-elicited peak rates to increase to levels equivalent to sucrose or even higher. *$P < 0.05$.

TABLE 1. *VP unit responses across 1-s taste infusions*

	Salt (*n* = 67)		Sucrose (*n* = 78)		Water (*n* = 67)		Total Responsive Neurons	
Test	Excite	Inhibit	Excite	Inhibit	Excite	Inhibit	Excite	Inhibit
Baseline-replete (*n* = 32/44)	19 (59%)	2 (6%)	21 (66%)	1 (3%)	21 (66%)	2 (6%)	28 (88%)	4 (12%)
Depletion (*n* = 31/54)	17 (55%)	2 (6%)	22 (71%)	6 (19%)	17 (55%)	5 (16%)	23 (74%)	8 (26%)
Re-repletion (*n* = 35/67)	20 (57%)	3 (9%)	22 (63%)	2 (6%)	19 (54%)	2 (6%)	29 (83%)	6 (17%)

Rows show the number of responsive neurons (out of a total of 165 neurons tested) and in parentheses the percentage that these responsive neurons represented.

amplitude compared with the earlier homeostatic NaCl test (*P* < 0.0001). NaCl-elicited firing rates exceeded sucrose-elicited firing rates (*P* = 0.002; Fig. 3) in the within-subjects analysis and equaled sucrose rates (*P* > 0.05) in a between-subjects analysis that included all cells, irrespective of whether they had data for all three tastes. By either analysis, the interaction between NaCl taste and physiological depletion state for VP firing rate was robust and significant; furthermore, it was clear that NaCl firing was no longer lower than sucrose firing on the sodium-depleted day (interaction: F = 32.154, *P* < 0.0001; Fig. 3).

Finally, after rats were provided with free access to NaCl in their home cages to regain sodium balance, some elevation of VP firing to NaCl taste persisted into the re-replete test (depletion vs. re-repletion: *P* = 0.663; baseline-replete vs. re-repletion: *P* < 0.0001). Previous studies reported persistence of behavioral intake of elevated hypertonic NaCl for days or months after (Sakai et al. 1989; Tang and Falk 1979), and we note that a slight increase in voluntary intake of NaCl persisted into the re-replete test in our results. Persistence in VP neural firing might conceivably be a mechanism of elevated appetitive motivation to ingest salt even after a substantial return to homeostatic balance. With respect to hedonic palatability, VP persistence in firing might indicate that VP neurons remain hedonically biased toward NaCl taste for some time after sodium depletion. The dissociation of NaCl firing from taste reactivity on the re-repletion day suggests the intriguing possibility that the brain may be capable of multiple different evaluations of intense NaCl taste after recovery from depletion. A possible explanation for the dissociation between aversive taste reactions and hedonically positive signals in VP is that negative hedonic signals might have been generated elsewhere in the brain on the re-replete day, which overruled the hedonically positive VP signal. Multiple hedonic signal sources could produce short-term conflicts between hedonic processing and physiological needs. In the future, it would be of interest to compare firing in other structures in re-replete conditions and to compare VP firing and taste reactivity parametrically after longer recovery periods to resolve whether they reconverge (Bernstein 2003; Lucas et al. 1999; Wolf et al. 1984).

Firing rates to water infusions were low on the first test day in normal homeostasis, similar to NaCl (*P* = 0.344) and lower than sucrose (*P* < 0.0001). Sodium depletion induced a mild increase in water firing rates, which became similar to sucrose rates on that day (*P* = 0.095), although water rates still remained lower than the high NaCl rates (*P* < 0.0001; we note that furosemide/DOCA treatment increased water intake in addition to salt appetite). Overall, the pattern of water-elicited firing remained low on all days compared with other tastes, but

rates moderately increased over successive normal, depletion, and re-repletion tests (*P* < 0.0001).

Background or baseline firing rates measured 5 s before taste infusions remained constant across trials (average: 11.37 spikes/s; F = 1.899, *P* = 0.168). Baseline VP rates appeared not to be affected by sodium depletion or physiological homeostasis, showing no variation over test days (F = 0.729, *P* = 0.509), nor was there any interaction between trials or days (F = 0.483, *P* = 0.618). Baselines also did not change systematically between taste blocks within a day (F = 0.210, *P* = 0.811).

Overall, therefore physiological shifts in sodium balance/depletion selectively caused firing rates of responsive VP units to double in magnitude for salt taste, but remain constantly high for sucrose taste (interaction: F = 7.832, *P* < 0.0001). These changes in VP firing directly paralleled the hedonic changes in behavioral taste reactivity patterns from salt "disliking" to "liking" (with constant sucrose "liking"). We conclude that taste-elicited peak amplitudes of VP neuronal firing rates reflect the relative hedonic impacts of sucrose and intense NaCl tastes, shifting dynamically and appropriately according to current physiological state.

Sensory coding versus hedonic coding?

Although the dramatic shift in NaCl firing indicates that overall VP firing does not code stable sensory properties of sweet versus intense salt tastes that are preserved across physiological state changes, we conducted further analyses into potential sensory-coding properties of individual neurons. The majority of VP neurons recorded were found to respond to at least some taste infusions (60%, *n* = 100/167). Excitations or inhibitions were observed in different neurons to particular sucrose, NaCl, and water tastes (Table 1), and excitation was more common than inhibition (*n* = 183/208 responses or 88%; Table 1). The excitation bias in the populations of responsive neurons did not change with tastes or with physiological state across test sessions (F = 0.123, *P* = 0.884; F = 2.063, *P* = 0.130, respectively).

To further assess sensory coding of sweet versus salty gustatory signals, we asked whether neurons coded a single taste distinctly on any given day. Overall across the 3 days, 35% of 99 neurons responded to a single taste, 29% of neurons to two tastes, and 37% to all three tastes. However, physiological sodium depletion appeared to expand the sensory focus of the population of VP neurons on a day-by-day basis. For example, on day 1 in normal homeostasis, nearly half the neurons (46%; 13/28) responded to a single taste, whereas only a quarter of the population (25%; 7/28) fired to all three tastes. On the sodium-depleted day, however, this ratio roughly re-

versed so that only 19% (7/36) responded to single taste, whereas 52% (19/36) responded to all three tastes. Further, there were no differences in the number of responsive neurons activated by different tastes (salt, sucrose, water) or significant patterns across test days (taste: F = 2.269, P = 0.105; day: F = 1.367, P = 0.257; interaction: F = 0.780, P = 0.539). Thus this pattern of VP responses clearly cannot be explained by straightforward sensory coding without positing that sodium depletion made intense salt sensation no longer distinguishable from sweet sensation. However, rats remain able to identify taste sensations under these physiological changes, including being able recognize particular Pavlovian sour/bitter taste labels during sodium depletion that previously were paired with either NaCl or sucrose during normal homeostasis, and to respond to each taste appropriately (Berridge and Schulkin 1989; Fudim 1978). Thus a sensory reversal from salty to sweet is unlikely to explain our results, even if subtle changes in intensity coding of moderate NaCl concentrations in brain stem gustatory relay sites of anesthetized rats occur during depletion (e.g., increasing responsiveness to dilute NaCl) (Berridge and Schulkin 1989; Berridge et al. 1984; Cho et al. 2004; Jacobs et al. 1988; Symonds et al. 2002; Taha and Fields 2005; Tamura and Norgren 1997); rather, we conclude that the hedonic impacts of salty, sweet, and water tastes are represented in VP firing separately from pure sensory coding and dynamically modulated by the current physiological state.

Movement coding versus hedonic coding

It is also important to separate coding of stimulus hedonic impact from coding of movements elicited close in time to the stimulus as part of behavioral affective reactions. To scrutinize the potential relationship of VP firing to movement events, we conducted analyses of unit firing correlations to corresponding behavioral events identified in a frame-by-frame video analysis. The time stamps of the behavioral events were compared against simultaneously correlated VP neuronal firing.

Taste stimuli that elicited positive hedonic "liking" reactions (NaCl on sodium-depleted day and sucrose on all days) each triggered initial rises in VP firing that typically began within 200 ms of infusion pump onsets, reached 50% maximum within 500 ms, and peaked between 600 and 800 ms of pump onset (Fig. 4). The increase in firing lasted about 1 s (Fig. 4), which is similar to the physical taste stimulus duration of the 1-s infusion by the computer-controlled pump. On the first test day when rats were in normal homeostasis, NaCl tastes elicited a similar temporal pattern of VP activation, although peak size was much reduced (less than one third that of sucrose on that day, or of NaCl or sucrose on the sodium-depleted day), and even though the behavioral reactions were very different.

VP rates do not code kinematic details of neutral mouth movements

Within 200 ms of stimulus onset, VP firing rates increased concurrently with neutral mouth movements, which were therefore subjected to special attention in our motor analysis. We compared which of two events best correlated to the rise in VP firing: the onset of taste stimulus or the onset of the first neutral mouth movement (Figs. 5 and 6). Movement-aligned histograms were more dispersed in time with peaks that were
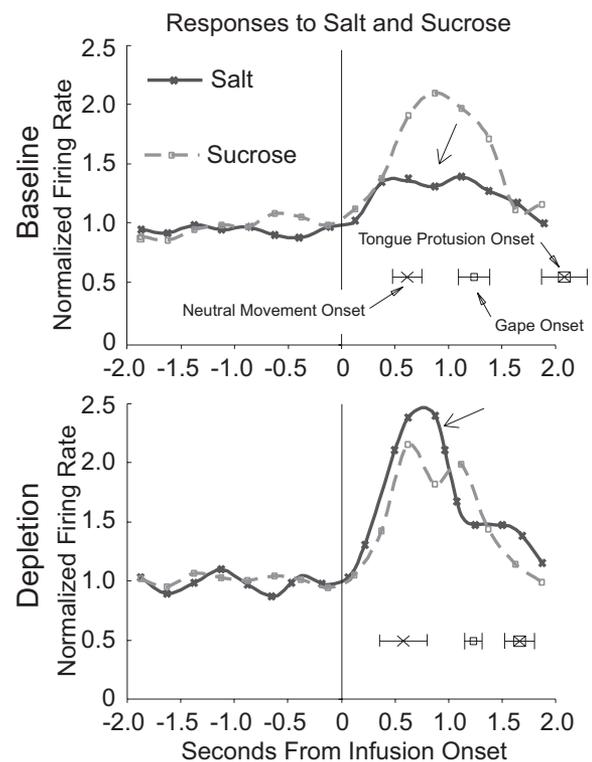

FIG. 4. Pattern changes in firing rate with physiological sodium depletion (within-subject data). Time course of VP normalized neural firing rates are aligned with respect to taste infusions averaged in 250-ms bins across responsive neurons during normal sodium homeostasis (*top*) and depletion (*bottom*). Sucrose firing rates (dashed line, box marks) were higher than salt (solid line, cross marks) during normal homeostasis, but with sodium depletion, firing rates to salt rose to exceed sucrose. Mean onset times of movements (neutral, hedonic, and aversive) are indicated below the histograms along with bars demarcating ±1 SE. Positive hedonic tongue protrusions and aversive gapes typically occurred >500 ms after VP firing rise and persisted much longer than VP firing. Firing was not time-locked to individual repetitive movements. Arrows highlight change in salt-induced firing between normal and depleted states.

less well defined than stimulus-aligned perievent histograms (compare *right* and *left* columns in Figs. 5 and 6), that is, timing relationships of neural firing were linked more rigidly to sensory stimuli than to movements. If neurons code sensory pleasure, then one might expect timing correlated best to the onset of taste stimuli (and not to movements), whereas if neurons code movement then timing should correlate most clearly to movements (and not stimuli).

Most neurons fired to only one or two tastes (62%), even though similar neutral movements typically occurred with the onset of all three taste stimuli. Similarly, neutral movements were elicited by NaCl on all test days, although VP firing changed dramatically depending on physiological state. Failure to respond to all neutral movements argues against pure movement coding by VP neurons.

Conversely, we also found that VP firing could occur in the absence of mouth movements. On occasional trials, rats omitted neutral mouth movements as initial reactions. Even in these cases where neutral mouth movements did not occur, VP firing onset was essentially similar as long as the taste and physiological condition remained the same (Figs. 5 and 6). Thus all together, VP firing was neither necessary nor sufficient to cause the neutral movements that initiated responses to taste infusions.
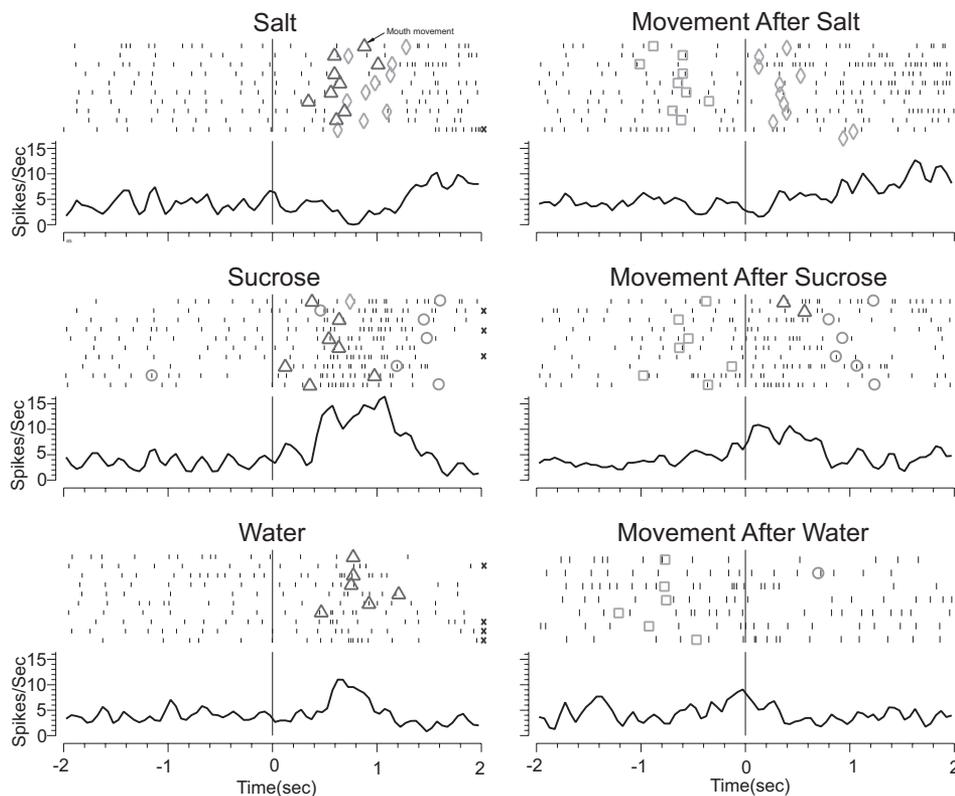
FIG. 5. VP neuronal response examples: decoupling taste hedonic impact from movements. Responses of a single neuron (Day 1, normal physiological state) to taste infusions (*left column*) and associated neutral mouth movements (*right column*) are shown for salt (*top row*), sucrose (*middle row*), and water (*bottom row*) tastes. Raster has a dash for each spike and one row for each taste trial. *Bottom trace*: smoothed average histogram (50-ms bins) with firing rate indicated on *y*-axis. Each raster and histogram is aligned to onset (at *time = 0*) of the taste infusion (*left column*) or neutral mouth movement onset (*right column*). This neuron had a vigorous response to the sucrose taste, a weaker response to water, and no response (weak inhibition) to salt. Triangle mark on each raster in the *left column* showed the time at which neutral mouth movements occurred in that trial. Diamond symbol indicates onset of aversive gape movement (Salt infusion, *top*; and one Sucrose trial). Circle indicates time of hedonic tongue protrusion (Sucrose trials, *middle*). Trials marked with an × at the end of the raster had no neutral or other mouth movement within the 2-s time frame of the taste infusion and therefore these trials do not contribute to movement aligned rasters and histograms. When firing is aligned to the onset of neutral mouth movements (*right*, time of taste infusion marked by square), peak amplitudes of neural responses decreased and the slope of the rise in firing was relatively flattened, suggesting that VP firing does not code the movements.
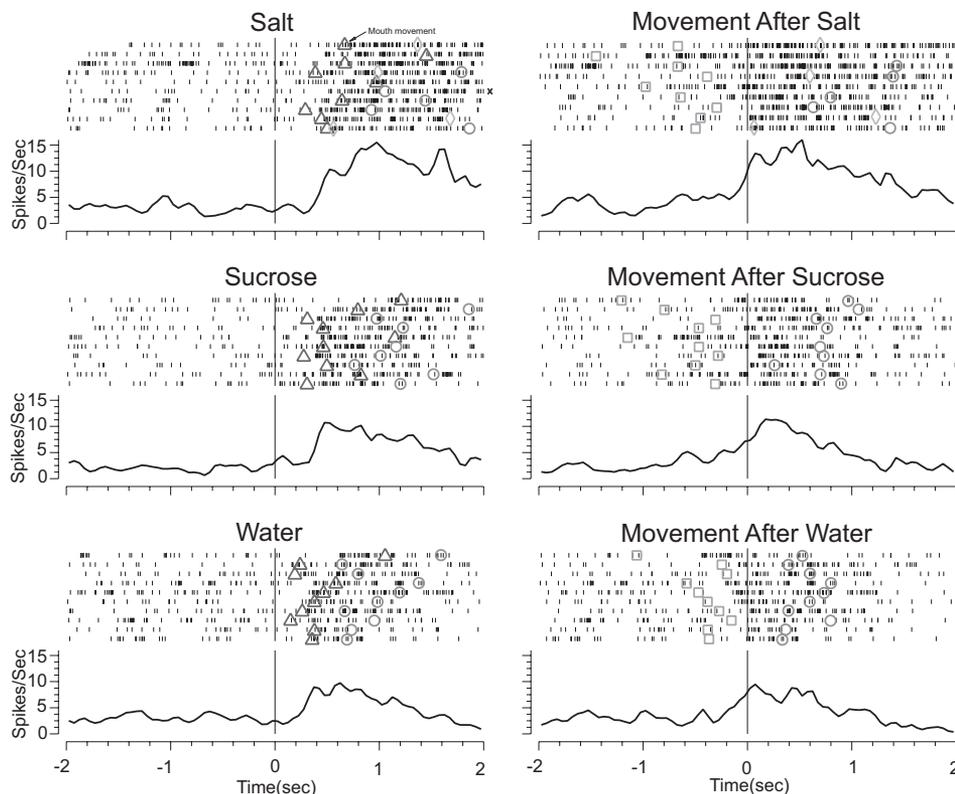

FIG. 6. After sodium depletion, neural responses to tastes reflect changed hedonic impact. Responses of a single neuron on the test day after sodium depletion (Day 2) are shown with a format identical to that in Fig. 5. After sodium depletion, animals respond to salt tastes (*top*) with hedonic tongue protrusions (open circles). Neural firing rate to salt is as high as it is to sucrose (*middle*).

VP rates do not code kinematic details of strongly affective movements

VP firing peaks persisted into the more strongly positive hedonic patterns of tongue protrusions to sucrose and sodium-depleted NaCl, and with negative aversive gapes to NaCl on the homeostatic day, but the rise of VP peaks were not time-locked to the initiation or termination of any of those movements. Firing rises typically began ≤800 ms in advance of tongue protrusion or gape movements. Thus nearly a full second of delay occurred between firing and movement, suggesting that VP firing does not directly cause movements (and cannot be caused by feedback from them). Further, once evoked by a sucrose or NaCl taste, positive hedonic or negative aversive reactions typically persisted for ≤15 s, over 10 s beyond the typical 2-s time course of neural activation (because VP firing always declined within 1 s of the infusion pulse termination). VP firing appears neither necessary nor sufficient to immediately cause bouts of positive or negative affective movements.

VP rates do not code individual movement microstructure

Finally, VP firing clearly did code discrete movement microstructure, such as individual tongue protrusions or individual mouth movements. These oral movements typically occur in bouts of greater infrequency, in which the movement is rhythmically repeated faster than four times/s. The fast repetition makes it easy to ask whether VP neuronal firing was correlated to the rhythm of the movements. However, we found that VP neurons had no movement-tied rhythmic synchrony in firing and so did not correlate with the microstructure of individual movement details.

Overall, these various dissociations of VP firing from movement seem to rule out a direct or pure motor-coding role for any identifiable feature of movement, just as the analysis above rules out purely sensory coding. Instead, the overall pattern of VP firing data is most consistent with the hypothesis that firing contributes to a neural code for the hedonic impact ("liking") of sucrose and salty taste stimuli, in a fashion that integrates relevant gustatory signals with the current physiological state (alliesthesia). This does not rule out VP participation in more integrative forms of movement control (Kalivas et al. 1999; Mogenson and Yang 1991), but shows that the amplitude of taste-elicited firing peaks identified here primarily reflects the hedonic impact of the stimulus and not concomitant motor reactions.

DISCUSSION

Our principal finding was that ventral pallidal neural activity encoded the hedonic impact of tastes. VP neural activity reflected the change in hedonic value of a salty taste when salt appetite was selectively changed by physiologically induced alliesthesia (hedonic modulation). After physiological salt depletion, intensely salty tastes invoke a relative shift in palatability from "disliked" to "liked" and VP neuronal firing dynamically tracked these palatability changes. VP firing rates rose to become at least as fast to salt as it was to sucrose on the same day when behavioral reactions to salt tastes reversed from aversive "disliking" (e.g., gapes) to hedonic "liking" (e.g., tongue protrusions). In summary, VP neural firing changes specifically tracked the hedonic reversal of salt palatability, whereas VP firing to sucrose tastes remained relatively unchanged.

Identifying hedonic codes

Brain reward systems mediate the hedonic impact of natural sensory pleasures, and a fundamental goal of affective neuroscience is to identify how hedonic impact is represented by brain reward systems. However, it is difficult to tease apart positive hedonic coding from confounds with coding of simultaneous alternative factors, such as other sensory, motivational, associative, or motor processes. The current results provide potent evidence that particular VP neural signals contribute specifically to brain mechanisms of neuronal coding for positive hedonic impact.

Our study builds on and extends previous studies that have demonstrated neural activity correlated to reward value. For example, earlier studies include reports that neurons in lateral hypothalamus or other limbic areas reduced firing to the learned sight of a preferred food after eating to satiety or after reduction of sweetness concentration (Burton et al. 1975; Roitman et al. 2005; Rolls et al. 2005; Taha and Fields 2005) and reports that learned predictors of reward alter the ability to activate neurons after further learned devaluations of their reward (Baxter and Murray 2002; Rolls 2000; Schoenbaum et al. 1999; Setlow et al. 2003). However, earlier studies have generally left open whether neural activity contributed to neural representation of hedonic impact per se ("liking") or, instead, reflected some other reward-related factor such as sensation, movement, associative learning or memory and learned expectations, or motivational incentive value ("wanting") that changed simultaneously with hedonic impact.

Several procedural features here helped to disentangle hedonic impact ("liking") from other confounds explained away by purely learned or cognitive factors such as altered prediction of future reward values, by motivation to consume, or by sensory or motor alternatives. They included *1*) use of reversal and positive increments for hedonic impact of an unconditioned gustatory salt stimulus (rather than either learning manipulations or relatively weak satiety devaluations), *2*) use of direct infusions of taste solutions into the mouth (to focus on unconditioned hedonic impacts rather than learned predictions, and to keep stimulation constant and avoid differential consumption), and *3*) use of careful movement assessments in frame-by-frame analyses (to tease apart hedonic coding from motor confounds). Although these dissociations do not preclude a role for VP in coding other additional functions, they provide the strongest evidence yet in any brain structure for neuronal firing specifically correlated to the hedonic impact of natural sensory pleasures.

Disentangling coding schemes

Because sensory stimulation of a taste infusion, hedonic/aversive evaluations, motor preparation, and movement execution all overlap in time, it can be difficult to disentangle which neural patterns are contributing to these different coding factors. However, several findings suggest that it is unlikely that these factors determined the VP activation patterns reported here. For example, regarding sensory coding, the "saltiness"

and "sweetness" of our suprathreshold stimuli remained essentially stable from day to day and thus VP firing changes could not have been driven by sensory gustatory signals per se.

Regarding movement, the timing of VP firing was decoupled in several ways from onset and offset of affective movements such as positive hedonic tongue protrusions or negative gapes. First, VP firing began 800 ms before those reactions, a delay that would be too long for coding movement directly but suitable for coding an intervening process such as hedonic impact that indirectly influences movements. Second, VP firing peaks lasted only 1 to 2 s (about the same duration as taste-infusion pulses), whereas positive hedonic reactions or aversive reactions typically lasted 5 to 10 s longer. Obviously, VP firing is therefore not required to drive those movements, nor is firing driven by them. Regarding the initial neutral mouth movements that preceded positive and negative affective reactions by about 1 s, which were more closely linked in time to VP firing onset than hedonic/aversive movements, there was still a clear dissociation between neutral movements and the amplitude of VP firing rate peaks. Neutral movements were generally similar in intensity for all tastes, whereas the intensity of VP firing varied dramatically across tastes in a manner consistent with positive hedonic impact. Further, on at least some trials, VP firing occurred in a hedonic-appropriate way even when there were no initial neutral mouth movements at all. Thus high VP firing variation was neither necessary nor sufficient to cause taste-elicited movements. These various dissociations suggest that VP firing rates do not directly code movement details, any more than they directly code sensation details. This does not preclude a role for VP in more complex integration of hedonic information with movement processing (Kalivas et al. 1999), but it seems clear that VP is not directly controlling basic movement as such.

Hedonic coding

It seems important to note that the VP firing increased from low to high when salt-affective palatability actually reversed in polarity from negative (aversive) to hedonically positive. Because neural firing cannot fall below zero, negative affective valence must be coded by separate neural signals for a single system to convey bivalent hedonic impact.

The relationship between bivalent affective reactions and univalent VP firing might imply that low firing reflects merely low positive hedonic impact ("liking") and says nothing about negative impact. In other words, VP rate codes identified here might represent only positive hedonic impact ("liking") and not at all negative aversion ("disliking"). If so, then negative "disliking" may be coded separately by other neural substrates or by as yet unidentified features of VP firing. This possibility implies that positive and negative affective valence might be processed independently by different limbic brain circuits. Alternatively, the relationship might mean that low levels of VP firing encode a negative "disliking" signal, whereas moderate levels might encode affective neutrality, and high levels encode positive "liking." In other words, bivalent affective dimensions might be collapsed and coded unidimensionally by neuronal firing rate. In either case, the abrupt rise in NaCl-elicited VP firing rates during sodium depletion described above would code an abrupt rise in positive "liking" reaction to intense saltiness produced by salt appetite. Future experiments will be required to explore the details of hedonic coding by parameters of VP firing rates.

Finally, we stress that besides hedonic information, VP neural networks are also likely processing nonhedonic signals, and their relative identities and interaction will need to be resolved in future studies (Tindell et al. 2004, 2005). Sensory and movement signals have already been discussed, but other functions include incentive motivation ("wanting") and reward-related learning (Tindell et al. 2004, 2005). Our results do not imply that VP firing rates code only hedonic "liking," but simply provide the strongest evidence so far that VP neural activity patterns contain a distinct representation of the hedonic impact of a natural sensory signal.

Circuitry mediating hedonic coding

Our conclusions are consistent with other evidence indicating that the ventral pallidum processes and even helps cause the hedonic impact of food and other rewards. For example, mu-opioid receptor stimulation by DAMGO microinjection in a hedonic hotspot in the caudal VP (the same VP region recorded from here) amplifies positive hedonic reactions to sucrose taste (Smith and Berridge 2005). Further, lesions that produce neuron death in the VP can actually eliminate normal "liking" reactions to sweetness and replace them by "disliking" reactions (Cromwell and Berridge 1993). Such evidence indicates that VP neurons are one of the few brain substrates identified as necessary for sensory pleasures to elicit normal positive hedonic reaction. The VP is also implicated in sex, drugs, and other incentives (Lim et al. 2004; McFarland et al. 2004; Tindell et al. 2005).

Those VP functions may arise partly from its connection with other reward structures such as amygdala (Galaverna et al. 1993; Napier 1992), orbitofrontal and insular cortex (Reep and Winans 1982; Zahm 2006), ventral tegmentum, and parabrachial nucleus (Groenewegen et al. 1993; Grove 1988a,b; Kalivas et al. 1999; Mitrovic and Napier 1998; Napier and Mitrovic 1999). VP also acts as the chief target for efferent projections from the nucleus accumbens, which itself codes reward information (Gulley et al. 2002; Peoples et al. 2004), and serves as a centripetal final common output path for mesocorticolimbic circuits (Groenewegen et al. 1999; Usuda et al. 1998; Zahm 2006). These relations place the VP in an ideal position to dynamically code reward functions such as a positive "liking" reaction to the hedonic impact of a pleasant sensation.

In conclusion, we find that neural firing in ventral pallidum participates in brain representations that encode the positive hedonic impact of sweet and salty taste rewards. VP neurons are therefore likely to be important in mediating "liking" for food pleasure and possibly other natural sensory pleasures and drug pleasures, too. Further, if VP signals code the normal hedonic impact of rewards, then pathological distortions of VP hedonic coding might cause some hedonic dysfunctions that are implicated in some eating disorders, drug addiction, and other affective disorders. The VP is thus potentially an important target for understanding both normal reward and hedonic disorders and perhaps may prove to be a useful focus for effective treatments in the future.

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