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# The Neural Encoding of Cocaine-Induced Devaluation in The Ventral Pallidum

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**Abstract:** Cocaine experience affects motivation structures such as the nucleus accumbens (NAc) and its major output target, the ventral pallidum (VP). Previous studies demonstrated that both NAc activity and hedonic responses change reliably as a taste cue comes to predict cocaine availability. Here we extended this investigation to examine drug-experience induced changes in hedonic encoding in the VP. VP activity was first characterized in

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adult male Sprague–Dawley rats in response to intraoral infusions of palatable saccharin and unpalatable quinine solutions. Next, rats received 7 daily pairings of saccharin that predicted either a cocaine (20 mg/kg, ip) or saline injection. Finally, the responses to saccharin and quinine were again assessed. Of 109 units recorded in 11 rats that received saccharin–cocaine pairings, 71% of responsive units significantly reduced firing rate during saccharin infusions and 64% increased firing rate during quinine exposure. However, as saccharin came to predict cocaine, and elicited aversive taste reactivity, VP responses changed to resemble quinine. After conditioning, 70% of saccharin-responsive units increased firing rate. Most units that encoded the palatable taste (predominantly reduced firing rate) were located in the anterior VP, while most units that were responsive to aversive tastes were located in the posterior VP. This study reveals an anatomical complexity to the nature of hedonic encoding in the VP.

**Keywords:** Ventral pallidum; Cocaine; Hedonics; Learned aversion; Electrophysiology

# 1. Introduction

Drug addiction is a neurological disorder that burdens societies with a significant economic cost and individuals with profound suffering. One of the hallmarks of addiction is the high rate of chronic relapse observed in individuals attempting to remain abstinent. For addicts, stressors and dug-associated cues can spark episodes of drug craving and aversive physiological responses, fueling cycles of relapse following periods of abstinence (Fox et al., 2008, Newton et al., 2003 and Paliwal et al., 2008). Therefore, understanding the neural systems that mediate both drug associations and affective responses are likely to be necessary steps in understanding how to effectively disrupt this cycle.

The measurement of a conditioned change in the affective state of a nonhuman is extremely difficult, but some animal models allow for the study of neural systems that regulate affective state. One such design pairs an otherwise palatable taste with investigator-delivered cocaine administration or availability (self-administration) to generate taste aversion (Colechio and Grigson, 2014 and Grigson, 1997). Using this design, the patterned neuronal activity in the nucleus accumbens (NAc) has been shown to encode not only the observed change in hedonic state but also the motivation to seek cocaine (Wheeler et al., 2008 and Wheeler et al., 2015). Specifically, while the predominant

neuronal response to palatable taste stimuli is generally a decrease in firing rate, aversive stimuli evoked largely increased firing rates, regardless of whether the aversive stimulus is innately aversive (Roitman, Wheeler, & Carelli, 2005) or devalued by a drug of abuse (Wheeler et al., 2008 and Wheeler et al., 2015).

The NAc participates in a network of nuclei that modulate both hedonic perception and motivated behavior. The recipient of the majority of GABA-ergic output projections from the NAc is the ventral pallidum (VP), which also has functional microcircuits that regulate hedonic processing and motivated behavior (Smith & Berridge, 2007). In humans, functional imaging studies have shown that the activity of the VP is strongly associated with positive affective responses (Childress et al., 2008, Pessiglione et al., 2007 and Simmons et al., 2014). In rodents, several studies have demonstrated that the VP not only plays a critical role in the normal expression of hedonic responses, but also in ingestive behavior (Gong et al., 1997 and Stratford and Wirtshafter, 2013), and drug seeking (Kemppainen et al., 2012, Mahler et al., 2014 and Stefanik et al., 2013). Furthermore, *in vivo* electrophysiological experiments have aligned specific patterns of VP neuronal activity with hedonic processing and drug-seeking behavior ( Root et al., 2010, Root et al., 2012, Root et al., 2013 and Smith et al., 2011). Based on this intimate relationship, and coincident function, we hypothesized that VP neurons encode hedonic information and are sensitive to changes of hedonic values as a result of cocaine-induced conditioned taste aversion.

An objective of this study was to characterize the neural encoding of appetitive and aversive tastants throughout the VP. Pharmacological manipulations at various sites in the VP indicate that it is a functionally heterogeneous structure, similar to the NAc (Ho and Berridge, 2013 and Ho and Berridge, 2014), which receives relevant NAc input throughout its rostral–caudal extent (for review see Root, Melendez, Zaborszky, & Napier, 2015). Therefore, recordings were conducted with an attempt to cover as much of the VP as possible along this axis. Initial recordings were conducted to characterize the neuronal responses to palatable saccharin and aversive quinine intraoral infusions. Then, we examined a potential change in the encoding of the saccharin solution, reflective of a change in the perceived palatability, as saccharin was devalued through association

with cocaine. Our results indicate that the VP encodes the drug-induced devaluation of natural rewards, and illustrate a regional organization of hedonic encoding.

# 2. Materials and methods

## *2.1. Animals*

Male, adult Sprague–Dawley rats (Harlan Laboratories, IN) weighing between 300 and 350 g were used in this study. Animals were individually housed in AAALAC-accredited vivarium on a 12 h reversed light/dark cycle. All experimental procedures and testing took place during the dark phase, which is the naturally active phase of rats. Every animal had *ad libitum* access to food and water throughout the entirety of the study. A total of 16 animals were used in this study (11 from the Cocaine group and 5 from the Saline group) for both electrophysiological recordings and taste reactivity behavior. All experimental procedures were approved by the Institutional Animal Care and Use Committee at Marquette University in accordance with the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health.

## *2.2. Surgical procedures*

Animals were deeply anesthetized with ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (20 mg/kg) and intraoral catheters were implanted as previously described (Wheeler et al., 2008). The catheters were implanted bilaterally, lateral to the first maxillary molar and exteriorized on the top of the animal's head. Plastic washers were used to secure catheter placement. Microelectrode arrays (NB Labs, TX) were implanted bilaterally at AP +0, ML ±0.8 relative to bregma, and DV −7.8 relative to brain surface. Each array contained 2 rows of 4 microwires (diameter 50 μm, 0.25 mm between wires, rows separated by 0.5 mm). During surgeries, the ground wire for each microelectrode was wrapped around a skull screw and inserted approximately 1 mm into the brain. The stereotaxic coordinates were chosen to ensure array placement across the VP. The implanted arrays were held in place using acrylic dental cement. For all surgical procedures, rats were treated with the

anti-inflammatory meloxicam (1% oral suspension) the day of, and for three days following surgery to reduce inflammation and postoperative pain. Animals were allowed to recover for a minimum of 7 days prior to the initiation of experimental procedures.

## *2.3. Apparatus*

Both electrophysiological recording and taste-drug pairings took place in a 43 × 43 × 53 cm Plexiglass chamber (Med. Associates, VT) housed within a sound-attenuating box. An infusion line connecting to a 20 ml syringe in a syringe pump was installed and passed through a swivel and a commutator (Crist Instruments, MD) located above the Plexiglass chamber. The infusion pump was controlled by MedPC computer program to allow for the automated delivery of tastants, and the generation of event-related timestamps that were coordinated with electrophysiological recording equipment. Under each chamber, a camera was positioned to allow for recording behavioral responses (taste reactivity).

## *2.4. Taste-drug pairings*

Following recovery from surgery, electrophysiological responses to saccharin (0.15%), and quinine (0.001 M), were initially recorded to establish a baseline population response. In each recording session, 45 intraoral infusions of each tastant (0.2 ml/6 s) were delivered with randomized intertrial intervals (30–90 s) within a maximum of 52 min for a given session. After baseline responding was established, animals received 7 days of daily saccharin–cocaine (Cocaine group), or saccharin–saline (Saline group) pairings. During each training session, rats in the Cocaine-paired condition received 45 infusions of saccharin followed by a cocaine injection (20 mg/kg, ip). Following daily saccharin exposure, animals in the Saline-paired condition received an injection of saline of equivalent volume. Following conditioning, a test session occurred in which electrophysiological and behavioral responses to both saccharin and quinine were again assessed using the same parameters. The design of the test session was identical to baseline testing.

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## *2.5. Taste reactivity scoring/analysis*

Taste reactivity was analyzed in a frame-by-frame analysis using digital video recorded on the test sessions before and after conditioning. The appetitive and aversive responses were counted using the technique described in Grill and Norgren (1978). Instances of rhythmic tongue protrusions and paw-licking behavior were counted as appetitive responses. Aversive behavioral responses include gaping (mouth movements that matched a triangle shape for a duration exceeding 90 ms), paw flailing, wet dog shakes, and passive drips. The rates of aversive and appetitive events (per trial) were computed for each animal. Taste reactivity data were analyzed with mixed ANOVA and subsequent planned comparisons of appetitive and aversive taste reactivity (events/trial) in the Cocaine and Saline groups.

## *2.6. Electrophysiological recording procedures and neuronal response analysis*

To familiarize the rats with the recording situation, all animals were connected to a flexible recording cable (Plexon Inc., TX) attached to a commutator (Crist Instruments) for 2 h on the day before the experiment was initiated. On the following day, animals were again connected to the flexible recording cable attached to a commutator and their intraoral catheters were connected to the infusion pump. This allowed unrestrained movement in the chamber while neuronal activity in the VP was recorded. Unit activity was recorded differentially between each active wire (recording channels) and an inactive wire chosen for the absence of unit activity (reference channel).

Online isolation and discrimination were accomplished using a commercially available neurophysiological system (OmniPlex system; Plexon Inc., TX). Multiple window discrimination modules and high-speed analog-to-digital signal processing in conjunction with computer software enabled isolation of neuronal signals on the basis of waveform analysis. The neurophysiological system incorporated an array of digital signal processors (DSPs) for continuous spike recognition. The DSPs provided a continuous parallel digital output of neuronal events to a computer. Another computer controlled behavioral events of the experiment (Med Associates) and sent digital

outputs corresponding to each of these events to the OmniPlex to be time-stamped along with the neural data. Criteria for identifying different neurons on a single wire have been described in detail elsewhere (Roitman et al., 2005). Briefly, discrimination of individual waveforms corresponding to a single neuron was accomplished using template and principle component analysis procedures provided by the PlexControl software system. The template analysis procedure involves taking a sample of the waveform and building a template of that extracellular waveform. Subsequent neurons that match this waveform are included as the same neuron. Cell sorting was further accomplished after the experiment was finished using additional principle components analysis in Offline Sorter V3.3.2 (Plexon Inc., TX).

Phasic encoding of the tastants was characterized by generating perievent response histograms (100 ms bins) 10 s prior to and following intraoral infusions NeuroExplorer (Nex Technologies, MA). Each histogram was divided into a baseline epoch and an effect epoch, each 10 s in duration. A two-tailed, paired *t*-test was conducted on each unit's firing rate change to determine reliable changes in activity elicited by tastant infusion. With this analysis, unit responses were categorized as either increased cell firing, decreased cell firing, or non-responsive. After neuronal responses were characterized, Fisher's exact tests were used to detect any differences in phasic responses between Cocaine and Saline conditions as well as differences in encoding along the rostral–caudal extent of the VP.

## *2.7. Histology*

Following testing, animals were euthanized with $CO_2$, and the location of each unit was verified. A current (20 μA) was run through each implanted microwire, and brains were incubated in 4% potassium ferrocyanide, 10% formaldehyde solution. All brains were sliced into 40-μm sections and mounted. The slides were then stained with either 0.25% thionin, neutral red, or left unstained before coverslipping. Electrode placements were determined using Paxinos and Watson (2009). Fig. 1 shows electrode placements for recorded units.

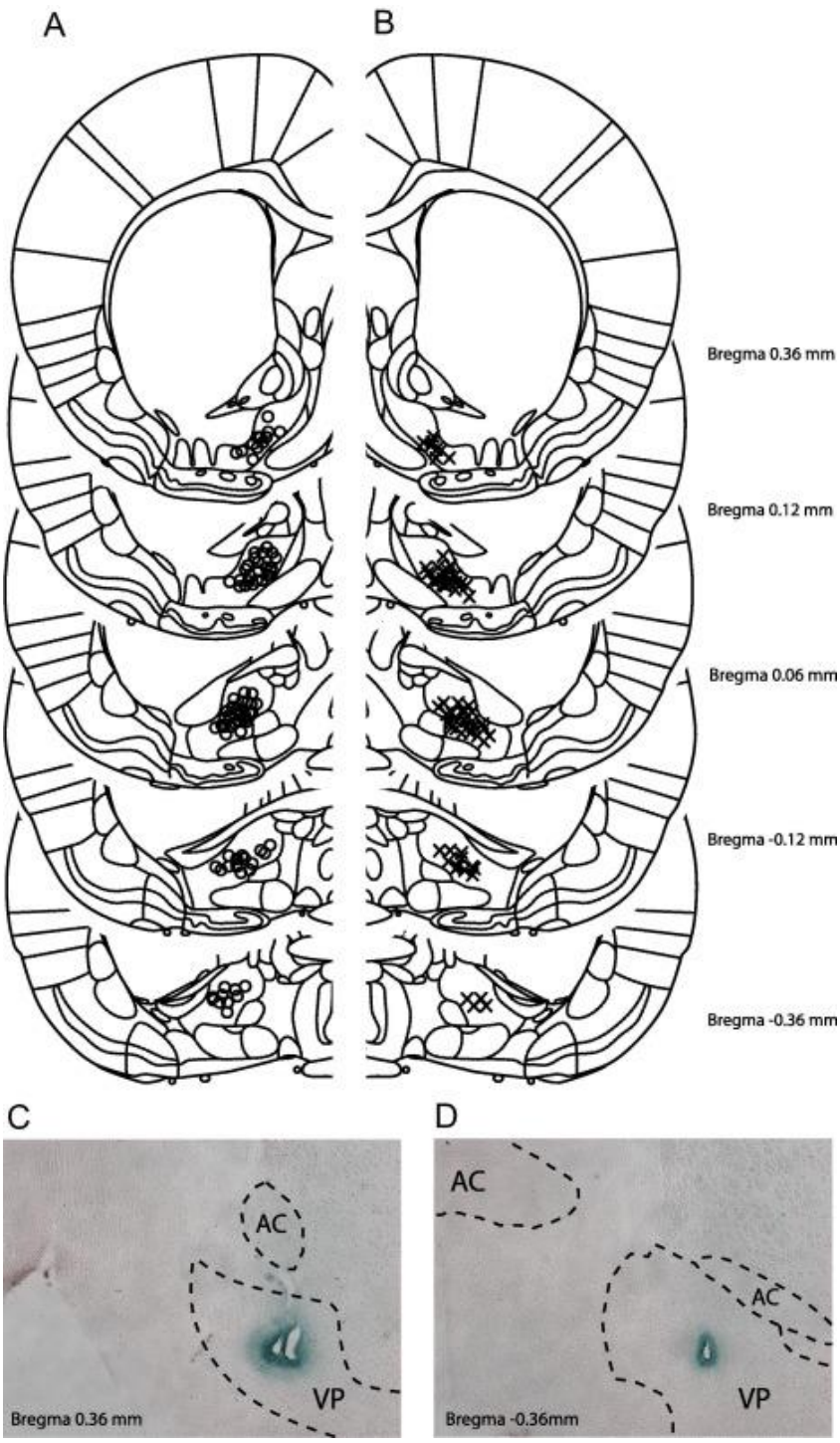


**Fig. 1.** Electrophysiological recording sites in the VP. Histologically identified placements of electrode tips are depicted as Os for animals in the Cocaine group in (A), and Xs for animals in the Saline group in (B). Histological examples of electrode placements in the anterior (C) and posterior (D) VP are presented.

# 3. Results

## *3.1. Behavioral responses to appetitive and aversive tastants*

Consistent with previous studies (Grill and Norgren, 1978, Roitman et al., 2008 and Wheeler et al., 2008), saccharin and quinine solutions evoked differential behavioral responses in rats. Upon initial exposure, saccharin elicited several appetitive responses (mean = 0.95 counts/trial, SEM = 0.20) and few aversive responses (mean = 0.08 counts/trial, SEM = 0.02) in Cocaine-paired animals. In contrast, quinine induced few appetitive responses (mean = 0.02 counts/trial, SEM = 0.01) but many aversive responses (mean = 1.74, SEM = 0.34). Similar behavioral response patterns were observed in Saline-paired animals, for both saccharin (appetitive: mean = 1.92 counts/trial, SEM = 0.40; aversive: mean = 0.07 counts/trial, SEM = 0.02) and quinine (appetitive: mean = 0.07 counts/trial, SEM = 0.02; aversive: mean = 1.08 counts/trial, SEM = 0.23). All taste reactivity data are summarized in Table 1.

**Table 1.** Hedonic behavioral responses to rewarding and aversive stimuli.

| | | **Cocaine group** | | | | **Saline group** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Pre** | | **Post** | | **Pre** | | **Post** | |
| | | **Appetitive** | **Aversive** | **Appetitive** | **Aversive** | **Appetitive** | **Aversive** | **Appetitive** | **Aversive** |
| Saccharin | Average | 0.947 | 0.076 | 0.291 | 0.397 | 1.915 | 0.074 | 1.774 | 0.080 |
| | SEM | 0.205 | 0.019 | 0.074 | 0.117 | 0.396 | 0.024 | 0.315 | 0.029 |
| Quinine | Average | 0.017 | 1.740 | 0.002 | 1.309 | 0.072 | 1.077 | 0.031 | 1.056 |
| | SEM | 0.011 | 0.338 | 0.002 | 0.119 | 0.017 | 0.233 | 0.015 | 0.100 |

Following initial behavioral assessment, the otherwise palatable saccharin solution was paired with either cocaine or saline and the resulting change in hedonic perception was evaluated. Following conditioning, results of a mixed ANOVA showed main effects of group (Cocaine vs Saline: $F_{(1,14)} = 12.92$, $p < .01$) and response type (appetitive vs aversive: $F_{(1,14)} = 42.71$, $p < .001$) as well as an interaction (Conditioning × Response type: $F_{(1,14)} = 9.70$, $p < .01$), indicating a change in the perceived palatability of saccharin in the Cocaine group. Planned comparisons of this interaction indicated that

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cocaine experience significantly reduced appetitive responses ($F_{(1,14)}$ = 12.05, $p$ < .01) and increased aversive responses ($F_{(1,14)}$ = 10.47, $p$ < .01; Fig. 2).

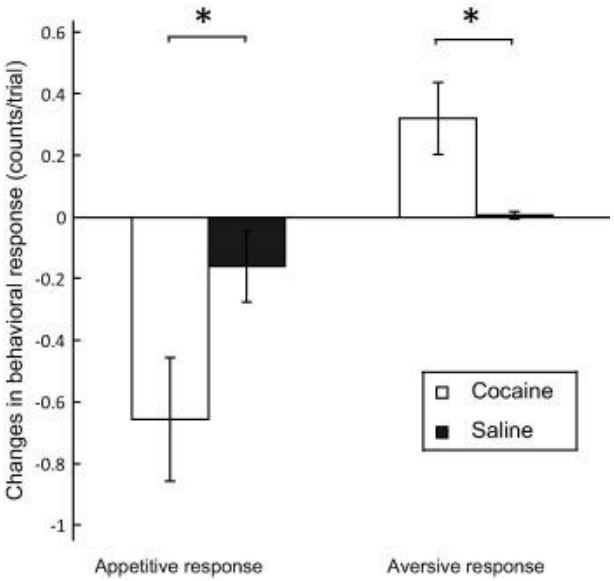


**Fig. 2.** Cocaine-predictive saccharin elicits aversive behavioral responses. The expression of appetitive (left) and aversive (right) responses was measured in Cocaine- and Saline-paired animals. Following conditioning, Cocaine-paired animals demonstrated significantly fewer appetitive and more aversive responses at test compared to Saline animals, indicating that association with cocaine resulted in conditioned taste aversion. Data are presented as mean ± SEM. Asterisks indicate significant differences ($p$ < .05).

Behavioral responses to quinine were assessed before and after saccharin conditioning as well. A separate mixed ANOVA comparing responses to quinine revealed only a main effect of response type (appetitive vs aversive: $F_{(1,14)}$ = 61.92, $p$ < .001). No other effects or interactions were observed (all $p$ values > .14), indicating that rats responded similarly to quinine at the beginning and the end of the experiment.

## *3.2. Neural encoding of unconditioned appetitive and aversive tastants in the VP*

Saccharin and quinine elicited different patterned activity in the VP. In this experiment, 109 (Cocaine) and 48 (Saline) histologically verified VP units were recorded and analyzed. Phasic responses were characterized based on the direction of change in firing rate, and most

recorded units exhibited either saccharin- or quinine-specific responses (Fig. 3A and B). A variety of neuronal responses were observed in this study, with different response onsets and durations that could reflect different aspects of gustatory, hedonic, and motor processes. This is not surprising based on the VP's position in relaying limbic information to behavioral output regions. Because of the limited number of taste-specific responses, these different responses were combined for the following analyses. Use of the 10 s pre/post infusion epochs allowed for the categorization of phasic responses (see Section 2 for more detail). Most VP units responded to saccharin with decreases in firing rate and to quinine with increases in firing rate. In saccharin-encoding neurons, 71% of the responses (12/17) from the Cocaine animals were decreases in firing rate (75% from Saline, 9/12). In all of the quinine-encoding neurons, 64% (9/14) of the responses were excitatory (100% from Saline, 3/3). All observed and categorized neuronal responses are presented in Table 2. A comparison of saccharin and quinine encoding across both groups (Cocaine and Saline) before conditioning revealed a difference in the proportions of cells that significantly increased or decreased firing rate (Fisher exact, $p < .007$).

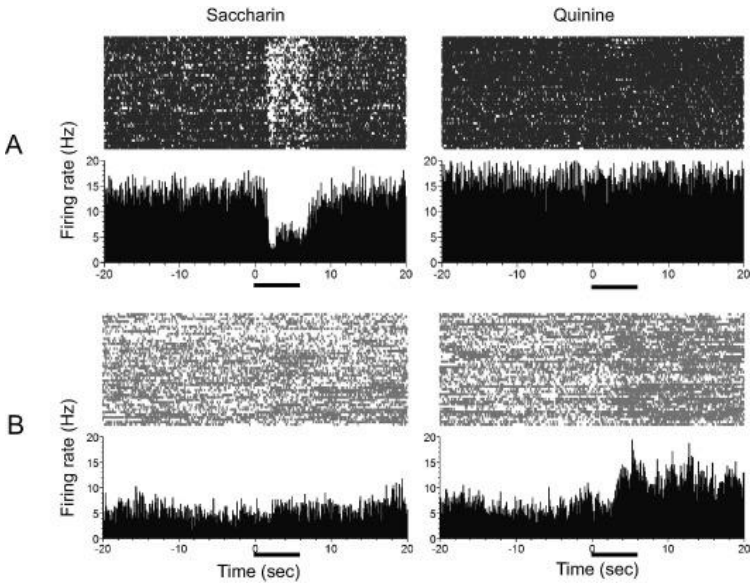


**Fig. 3.** Representative taste-selective neuronal responses in the VP. Two individual VP units are shown here as examples (A and B). Rasters and histograms depict examples of reduced (A) and increased (B) firing rate time-locked to the selective response to a presentation of saccharin (left) or quinine (right). Individual action potentials during each tastant presentation are shown in the raster, and firing rate (Hz) is shown in the

histogram below. The black bar under each histogram indicates the duration of the intraoral infusion.

**Table 2.** Electrophysiological responses to rewarding and aversive stimuli.

| Response type | | Selective | | | | Non-selective | | R | NR | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Saccharin | | Quinine | | Diff. | Same | | | |
| | | Increase | Decrease | Increase | Decrease | | | | | |
| Cocaine-Paired | Pre | 5 | 12 | 9 | 5 | 7 | 2 | 40 | 69 | 109 |
| | Post | 16 | 7 | 5 | 0 | 4 | 0 | 32 | 60 | 92 |
| Saline-Paired | Pre | 3 | 9 | 3 | 0 | 1 | 1 | 17 | 31 | 48 |
| | Post | 3 | 5 | 3 | 1 | 4 | 2 | 18 | 27 | 45 |

Note* Increase = significantly increased cell firing; Decrease = significantly decreased cell firing; Diff. = different for saccharin and quinine; R = responsive units; NR = non-responsive units.

## *3.3. Neural encoding of an aversively conditioned tastant in the VP*

As a saccharin taste was devalued by its predictive association with cocaine, it elicited different patterned activity in the VP. When saccharin was paired with saline vehicle injections, intraoral infusions of saccharin continued to elicit predominantly reductions in firing rate, (Fisher exact, $p > .64$; Fig. 4A and D). In contrast, Cocaine animals exhibited a significant shift in neuronal response pattern toward increased firing rates in the VP following conditioning, compared to baseline testing (Fisher exact, $p < .03$). Specifically, devaluation caused the number of units that responded to saccharin infusions with decreased firing rates to decrease from 71% to 30% (Fig. 4B and E), resembling the population response for quinine, (Fig. 4C). No shift was observed in the population response profile for quinine before and after the conditioning procedure in either the Cocaine group (Fisher exact, $p > .26$) or the Saline group (Fisher exact, $p > .99$). Interestingly, a greater proportion of neurons selectively encoded devalued saccharin relative to quinine before and after conditioning (Fisher exact, $ps < .03$). This raises the possibility that VP neurons are more engaged by conditioned aversive stimuli than inherently aversive stimuli.

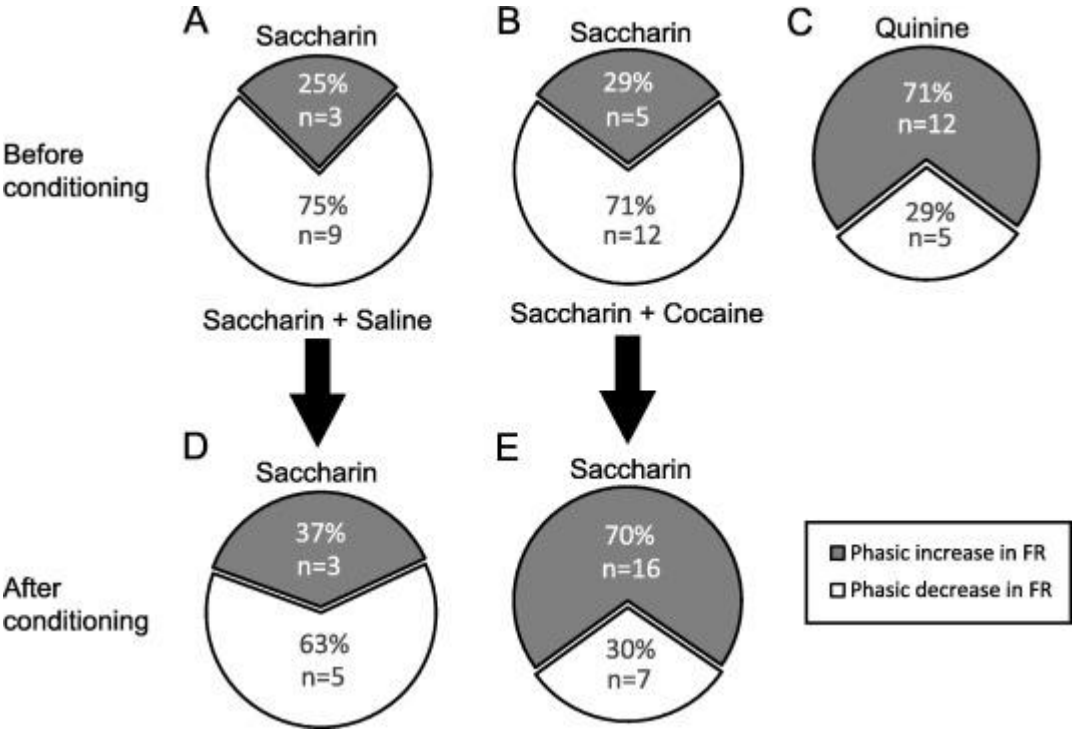


**Fig. 4.** Categorization of responses to saccharin and quinine in all phasically active neurons. (A and B) The predominant phasic response to saccharin exposure was a decrease in firing rate in VP neurons in the Saline (A) and Cocaine (B) conditions prior to conditioning. (C) The predominant response to quinine was an increase in firing rate. (D) In Saline-paired animals, the predominant response to saccharin remained decreased firing rates. (E) In Cocaine-paired animals, the response shifted to become predominantly increased firing rates ($p < .03$).

## *3.4. Regional differences in neural encoding of rewarding and aversive tastants*

One of the goals of this study was to characterize the encoding of taste responses across the rostral–caudal extent of the VP. To compare the distribution of saccharin and quinine neuronal responses, the VP was divided into anterior (rostral to bregma) and posterior VP (caudal to bregma). The VP was divided at AP = 0 because it is the approximate middle of the structure (Paxinos & Watson, 2009), and all electrode placements were histologically verified to be within the VP. For analysis purposes, units recorded prior to conditioning from the Cocaine and Saline groups were combined (Fig. 5A and B). Before conditioning, 86% (25/29) of units that selectively encoded saccharin were located in the anterior region of the VP. In contrast, 59% (10/17) of quinine-selective units were located in the posterior VP. After

conditioning, the distribution of saccharin responsive units in the Cocaine condition shifted in a manner consistent with the change in value. Following conditioning, 52% (12/23) were located in the anterior VP (Fig. 5C). Fisher exact tests revealed that both the differences in the distribution of saccharin and quinine responsive units, as well as the difference in saccharin responsive units following conditioning were significantly different (Fisher exact tests, *p*s < .02). Overall, we found that VP neurons that encode intrinsically appetitive taste reside largely anterior to bregma in the VP while responses for aversive quinine are located posterior to bregma.

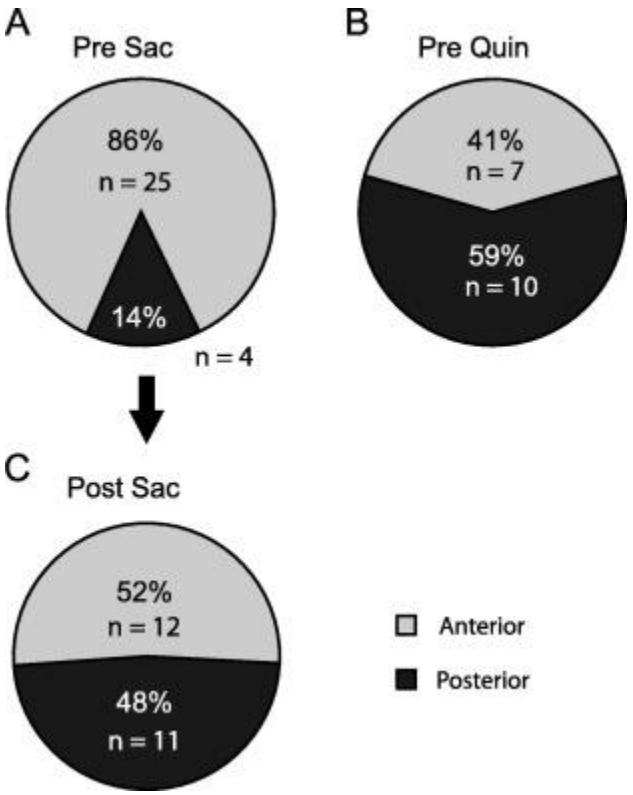


**Fig. 5.** Categorization of regionally distributed responses to saccharin and quinine. (A) An examination of all saccharin-responsive units recorded prior to conditioning indicates a regionally selective response in the anterior VP. (B) In contrast, quinine-selective responses were found predominantly in the posterior VP (C) Following saccharin–cocaine pairings, there was a significant increase in the proportion of units recorded in the posterior VP that selectively responded to the aversive saccharin tastant ($p < .02$).

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# 4. Discussion

These results contribute to a literature characterizing the patterned activity of VP neurons in response to rewarding and aversive gustatory stimuli. Specifically, the change in encoding of an otherwise palatable saccharin taste was recorded as it was paired with, and devalued by, its association with cocaine. In general, aversive taste reactivity was accompanied by phasic increases in firing rate both inherently aversive quinine and devalued saccharin. Appetitive saccharin was encoded primarily with phasic decreases in firing rate. The observed activity in the VP is very similar to previous reports of the neural encoding of appetitive and aversive stimuli in the NAc (Roitman et al., 2005 and Wheeler et al., 2008). However, selective responses in the VP likely did not merely reflect hedonics or palatability, as devalued saccharin was encoded by a larger proportion of neurons compared to quinine.

The present finding appears to be at odds with previous research examining firing patterns of VP neurons for rewarding and aversive stimuli, as previous reports have not observed a reliable pattern of neuronal responses characterized with decreases in firing rate to rewarding or aversive gustatory stimuli (Tindell, Smith, Pecina, Berridge, & Aldridge, 2006). Specifically, it has been reported that the magnitude of the neuronal response in the VP correlates with the perceived palatability of the tastant. The most likely possible explanation for inconsistencies between this report and prior reports is the difference in electrode placement. While all of our electrodes were placed within the VP, they were predominantly represented in the more anterior aspect, not overlapping perfectly with more posterior placements from prior investigations detailing different patterns of encoding rewarding and aversive tastants (Tindell et al., 2009 and Tindell et al., 2006). It is important to note, however, that a goal of this study was to assay a significant amount of the rostral/caudal aspect of the VP, since we noted that the NAc broadly encodes rewarding and aversive tastants (Roitman et al., 2005 and Wheeler et al., 2008) and projects broadly throughout the VP (Root et al., 2015). Our analysis of differences in rostral/caudal encoding of palatability revealed that saccharin-responsive units were predominantly recorded in the anterior VP, while aversive encoding

(i.e. responses to quinine) was predominantly found in the posterior VP. Specifically, association with cocaine dramatically altered the VP neuronal response profile to saccharin, resulting in more neurons that showed increased activity in response to saccharin, and abolishing the topological difference along the rostral–caudal axis of the VP. This regional complexity of encoding is provocative and could be the focus of future studies.

The similarity between VP and NAc encoding demonstrates the complexity of the functional connection between the two structures. Because the NAc–VP projections are GABAergic, one might predict that phasic excitations in the NAc would drive a phasic decrease in firing rate in the VP (Wheeler & Carelli, 2006). In contrast to what might be expected based on this simple understanding of NAc–VP connectivity, *in vivo* studies have demonstrated that stimulation of the NAc can result in various types of responses in the VP. Lavin and Grace (1996) observed three types of neurons in the VP, which all exhibited increases in firing rates in response to accumbens stimulation. Others have characterized NAc stimulation-induced increases or decreases in firing rates, as well as biphasic responses ( Chrobak and Napier, 1993 and Mogenson et al., 1983). Heterogeneous VP responses were also observed during operant responding for cocaine. Interestingly, most phasically active VP neurons were found to reduce firing rate during approach behavior (Root et al., 2012). This response is similar to the predominant response of NAc neurons during appetitive responding (Taha & Fields, 2006), and is not the predicted result of VP disinhibition resulting from reduced GABA input by the NAc. Although in our studies, we are not examining approach behavior, it is possible that we are observing similar overlapping responses, as the animals are experiencing stimuli that would (in an instrumental design) elicit approach and avoidance, and the VP encoding could reflect the engagement of different aspects of these behaviors (Root et al., 2015). The pattern of responses of decreased cell firing characterized in the NAc and VP could reflect the involvement of other common inputs to both regions (e.g. VTA). Additionally, the neuronal activity of the VP is modulated by different neurotransmitter systems and inputs other than the NAc (Mitrovic & Napier, 1998), which can contribute to the complicated physiological response patterns observed in the VP. In sum, the current report reveals a degree of complexity to the encoding of rewarding and aversive stimuli by VP neurons and additional studies

will be necessary to reveal the critical inputs that drive motivated behavior.

## Acknowledgment

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