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Ventral Pallidum Roles in Reward and Motivation

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Abstract

In recent years the ventral pallidum has become a focus of great research interest as a mechanism of reward and incentive motivation. As a major output for limbic signals, the ventral pallidum was once associated primarily with motor functions rather than regarded as a reward structure in its own right. However, ample evidence now suggests that ventral pallidum function is a major mechanism of reward in the brain. We review data indicating that 1) an intact ventral pallidum is necessary for normal reward and motivation, 2) stimulated activation of ventral pallidum is sufficient to cause reward and motivation enhancements, and 3) activation patterns in ventral pallidum neurons specifically encode reward and motivation signals via phasic bursts of excitation to incentive and hedonic stimuli. We conclude that the ventral pallidum may serve as an important ‘limbic final common pathway’ for mesocorticolimbic processing of many rewards.

Author Keywords

Substantia Innominata; Pleasure; Limbic; Addiction; Obesity; Liking; Wanting; Learning

Ventral Pallidum Function: Moving Beyond Movement

The ventral pallidum was recognized as a distinct anatomical structure only a few decades ago. Heimer and Wilson first identified the ventral pallidum in 1975 as the primary output for the ventral striatum (nucleus accumbens), and suggested it served a role similar to globus pallidus in the striatal-pallidal circuitry for dorsal striatum (caudate-putamen) [1]. Previously the ventral pallidum often had been lumped with adjacent areas including the globus pallidus, substantia innominata, extended amygdala system, lateral preoptic area of hypothalamus (far rostral and lateral hypothalamus), or the polymorph layer of the olfactory tubercle. Today, however, its distinctive limbic-thalamocortical anatomical connectivity, histochemical and neuronal makeup (e.g. high levels of substance P, enkephalins, and iron; heterogeneous cell types

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including cholinergic and GABAergic projection neurons; basal firing rates that are generally slower than dorsal pallidal but faster than striatal projection neurons) are recognized to distinguish ventral pallidum from other surrounding structures [1–16].

Notions of the ventral pallidum as a striatal output for movement, comparable to globus pallidus, contributed originally to a view that it functioned as a motor expression site [17,18]. For example, based on a series of behavioral studies, Mogenson and colleagues proposed that nucleus accumbens projections to the ventral pallidum translated limbic motivation signals into motor output [18,19]. This account attributed “limbic-motor integration” [19] to accumbens-pallidal systems, and specifically identified ventral pallidal projections to brainstem (e.g. pedunclopontine tegmentum) as a primary motor output for limbic motivation signals. However, transferring input from accumbens to brainstem motor-related targets is only one feature of ventral pallidum connectivity. The ventral pallidum is also a central convergent point for input from orbitofrontal, prefrontal and infralimbic cortex, the amygdala, lateral hypothalamus, ventral tegmental area, parabrachial nucleus, subthalamic nucleus, and other structures related to reward [20–35]. Conversely, the ventral pallidum projects back to nearly all of its input sources including the nucleus accumbens for reciprocal information exchange [8,13,36–41]. Further, ventral pallidum outputs re-enter corticolimbic loops via direct projections to medial prefrontal cortex, and dense projections to mediodorsal nucleus of thalamus, which relays in turn to prefrontal cortex [6,10,11,13,36,38,42,43]. Such limbic-related anatomical connectivity sets the stage for the ventral pallidum to mediate reward and motivation functions at many levels in the brain, beyond merely aiding translation to movement [35,40,44–54].

The most crucial evidence that ventral pallidum mediates reward, however, must come from actual functional demonstrations that ventral pallidum manipulations have consequences for reward. That is, do manipulations of ventral pallidum actually alter reward-related measures of neural activation and reward-directed behavior? Many such studies have now been conducted, which we review below. Together they provide strong evidence that the ventral pallidum is needed for normal reward, that it can add new reward value to stimuli, and that its neurons can encode reward and incentive motivation to gain external rewards.

The Ventral Pallidum is Necessary for Reward

Necessary for motivation to eat and hedonic impact

Perhaps the earliest experiments to implicate ventral pallidum in reward and motivation functions were a set of studies by Morgane that pushed the boundaries of food reward functions beyond the lateral hypothalamus to include the ventral pallidum and globus pallidus [55]. Morgane reported that electrolytic lesions to the globus pallidus (which now can be recognized to have damaged ventral pallidum), caused aphagia (failure to voluntarily eat) and adipsia (failure to drink) in rats, similar to lesions of the lateral hypothalamus [55–61], despite not damaging the lateral hypothalamus (the pallidal lesions being anterior, further lateral or dorsal to the hypothalamus). This early lesion study did not distinguish between globus pallidus and ventral pallidum, but rather damaged both, and used the name of globus pallidus for the entire damaged region. However, our own inspection of Morgane’s lesions, as well as early lateral hypothalamic lesions, in published histological figures indicates the aphagia-inducing lesions damaged ventral pallidum as well as their intended target structure. These data, together with a later study that found that aphagia can be produced by lesions of the posterior ventral pallidum that do not invade globus pallidus or lateral hypothalamus [60], confirmed a role for the ventral pallidum as a key component of the neural system for eating and food ‘wanting’ [62].

The ventral pallidum may play an even more unique role in mediating reward beyond being necessary for motivated eating: it is the only structure known to us in which local lesions also

eliminate normal ‘liking’ for sucrose, and replace it with ‘disliking’ [60]. ‘Liking’ is a second core component of reward, in addition to ‘wanting,’ and for many the most crucial. For natural food rewards, ‘liking’ has objective consequences in affective reactions patterns, such as orofacial reactivity patterns in response to tastes that are homologous across species [63–66].

Lesion studies of ventral pallidum and lateral hypothalamus have attempted to map the locus for a particular affective change in reward that often accompanied aphagia-producing lesions: the loss of acceptance or positive hedonic reactions to the taste of palatable food (such as tongue protrusions and lip licking), and replacement by active aversion reactions (such as gapes or headshakes). In the late 1970s, studies by Schallert and Whishaw [59] and Stellar, Brooks, and Mills [61] found that active avoidance of food (e.g. withdrawal from a food- or chocolate-containing spoon) and aversion to intraorally infused food (e.g. ejection of the reward followed by aversion reactions like face washing) was produced by what was described as damage to the anterior portion of lateral hypothalamus [59,61]. That damage encroached on what is now known to be ventral pallidum. Active avoidance-aversion was not produced by damage to more posterior subregions in the lateral hypothalamus (which caused aphagia without active aversion) [59]. A later mapping study actually contrasted ventral pallidum, globus pallidus or lateral hypothalamic excitotoxin lesions, and found that active aversion to sucrose was caused only if a lesion damaged the ventral pallidum (specifically its posterior end, overlapping with part of the adjacent substantia innominata) [60] (Figure 1) ¹. Of note, the posterior and medial edge of ventral pallidum abuts the anterior and lateral edge of the lateral hypothalamus, and in fact, many classical electrolytic lesions of the lateral hypothalamus that produced aphagia with aversion also damaged the ventral pallidum as well as lateral hypothalamus [59,60]. This positioning may be important, given evidence for a ‘hedonic hotspot’ in the posterior ventral pallidum that we will describe below where ‘liking’ can actually be enhanced by neurochemical activity.

This elimination of normal food reward (suppressed ‘liking’ and ‘wanting’, with enhanced aversion) that follows posterior ventral pallidum lesions may also be achieved with temporary neurochemical inactivation of ventral pallidal activity by excessive GABAergic inhibition. Microinjection of the GABA_A agonist muscimol in the ventral pallidum was recently reported to attenuate intake of saccharine-flavored water or of bitter quinine-water, and to replace positive hedonic taste reactions to saccharine taste with aversive reactions [78]. These GABA microinjections that enhanced aversion did not explicitly distinguish subregions of the ventral pallidum, and reported effects were averaged for the entire ventral pallidum (though placements fell within the posterior lesion-aversion zone and extended anteriorly too).

Some evidence from humans also supports the idea that the ventral pallidum may be needed for normal motivation and hedonics. A recent clinical report describes a drug-addicted human

¹The only other neural lesion known to cause active aversion to sweet tastes is the classic ‘thalamic preparation’, in which the entire telencephalon composed of all structures anterior to the thalamus is removed by suction ablation or similar surgery, leaving intact thalamus, hypothalamus, midbrain and brainstem [67,68]. Importantly, the ‘thalamic preparation’ may damage the ventral pallidum, which is part of the telencephalon, raising the possibility that ventral pallidum damage might similarly be responsible for the thalamic animal’s aversion to sucrose. The importance to positive hedonic reactions of a ventral telencephalic structure such as ventral pallidum is emphasized by the consideration that basic hedonic reactions to taste are preserved in decerebrate animals transected above the superior colliculus but below most of the hypothalamus (with only the brainstem functioning) [68–70]. This presents a rather curious scenario: removing the ventral pallidum by itself or with the rest of the telencephalon, while leaving the diencephalic hypothalamus and thalamus as well as the brainstem, dramatically reduces hedonic reactions. But removing the ventral pallidum and telencephalon, *plus* the diencephalic hypothalamus and thalamus, fails to have much of an effect on hedonics. How can this be? For many behavioral functions, the brain contains a hierarchical organization such that brainstem signals are regulated by forebrain structures [71–74]. The taste pathway traverses through brainstem structures, such as nucleus of the solitary tract and parabrachial nucleus in rodents, then through the forebrain in bifurcating gustatory sensory paths (e.g. to gustatory thalamus then gustatory cortex) and limbic paths (e.g. to ventral pallidum) [75, 76]. We have argued that basic affective and emotional reactions can be generated by the brainstem (e.g. in parabrachial nucleus: [77]), but in the normal intact brain these signals are under inhibitory control by forebrain hedonic structures like the ventral pallidum. This may be why we can observe relatively normal hedonics in decerebrated animals but impaired hedonics in animals with localized ventral pallidal lesions. See [74] and [54] for more detail.

patient with partial lesions to the ventral pallidum (overlapping with globus pallidus) who, after the lesions, “reported the disappearance of all drug cravings and remained abstinent from all recreational drugs other than an occasional glass of wine with dinner,” and “reported that he no longer experienced pleasure from drinking alcohol” (p. 786) [79]. The patient also “endorsed a depressed mood” and doctors noted a general “anhedonia” (p. 786) [79]. However, the patient also gained weight throughout this period, contrary to the lesion-induced aphagic effects in rodents described above, which may perhaps reflect spared parts of the ventral pallidum in the patient (the extent of damage is not clear from the published report of the still-living patient). In a second recent case [80], a patient with bilateral damage to the globus pallidus (the lesion is described by the authors as perhaps extending into the ventral pallidum) reported an “inability to feel emotions”, and was noted by analysts to have a flat affect and “a profound lack of motivation” (p. 413). In a reward task, the patient worked much less than normal to increase viewing time of pleasant pictures like food (by pressing a keyboard key), and reported less arousal from the pictures. His ratings of picture pleasantness were normal, and he worked normally to decrease viewing time of unpleasant pictures. The lesions thus appear to have impaired his ability to motivate behavior towards positive visual stimuli, though the extent of ventral pallidum damage is again not clear.

Necessary for reward learning and performance

Lesion or inactivation studies have further shown the ventral pallidum to be crucial for learning or performing learned responses related to rewards, in addition to generating the impact of unconditioned rewards. In operant and place preference conditioning studies, for example, ventral pallidum excitotoxin lesions or temporary inactivation (by microinjection of GABA or glutamate drugs, or lidocaine to block sodium channels) reduce baseline or primed lever pressing for alcohol, i.v. cocaine, and electrical stimulation to the medial forebrain bundle [81–88]. Rats with ventral pallidum GABAergic inactivation also have diminished willingness to work hard on an instrumental task to obtain sucrose reward, and instead shift their choice toward normal chow that can be obtained more easily, an effort shift similar to that produced by depletion of mesolimbic dopamine [89]. Ventral pallidum inactivation also reduces Pavlovian incentive learning about rewards, such as acquiring and expressing learned preferences for environments paired with sucrose, amphetamine, and morphine reward [90–92], and additionally impair performance in a variety of discrimination or matching tasks [93–104].

Thus, in total, features of normal reward learning and memory, motivational ‘wanting’, and hedonic ‘liking’ all appear to depend critically on the ventral pallidum. Among these reward components, normal hedonics may quite specifically require the ventral pallidum in a relatively unique way, whereas the other components can also be impaired by damage to other brain structures.

Ventral Pallidal Mechanisms for Enhancing Reward Impact

Beyond being necessary for normal reward, as reflected by impairments induced by lesion or inactivation, specific neurobiological activations in the ventral pallidum may also be sufficient to cause increases in the hedonic or motivational impact of stimuli. That is, it may be possible to enhance reward ‘liking’ or ‘wanting’ by chemical or other stimulation of the ventral pallidum. *Necessary* and *sufficient* causations are distinct forms of reward mediation, and do not always converge on the same reward substrates [54,105], but they may do so in the ventral pallidum.

Perhaps the first evidence suggesting that ventral pallidum activations can enhance the rewarding impact of stimuli and actions came from brain stimulation studies in the 1990s, which demonstrated that animals would repeatedly press a lever to self-stimulate through

electrodes implanted in ventral pallidum [53,106,107], similarly to electrodes in the lateral hypothalamus and medial forebrain bundle [106,108–110]. This finding indicated that circuit activation through ventral pallidal stimulation was sufficient to activate a reward for instrumental pursuit, and placed the ventral pallidum as part of a larger network of limbic sites where reward might actually be generated in neural activity. More recent studies have begun to characterize the ventral pallidal neurotransmitters systems that play a role in enhancing reward ‘liking’ versus ‘wanting’, with some intriguing chemical and anatomical compartmentalizations.

Disinhibition of ventral pallidum from GABA suppression: stimulation of food ‘wanting’ (but not ‘liking’)

The use of intracranial drug microinjection to manipulate neurotransmission in limbic circuits has been particularly important for evaluating the natural chemical signals that mediate reward enhancement. This work has indicated the possibility that release of ventral pallidum neurons from tonic inhibitory GABA inputs from nucleus accumbens, central amygdala, and other areas (i.e. disinhibition), is a chief ‘downstream’ mechanism by which hyperpolarizations in nucleus accumbens stimulate motivation and reward [44,111–114]. Microinjections in nucleus accumbens of GABA agonists, glutamate AMPA antagonists, or opioid or cannabinoid agonists all stimulate eating behavior and pursuit of drugs and other rewards, through mechanisms that have been suggested to include local accumbens inhibition and disinhibition of ventral pallidum [48,50,113,115–122].

In an early study addressing chemical mechanisms of reward enhancement within the ventral pallidum, microinjection of a GABA_A receptor antagonist (bicuculline) in ventral pallidum was shown to dramatically increase eating behavior and food intake [52], which has also been observed subsequently [78,123] (Figure 1). In order to test whether this stimulation of the motivation to eat involved enhancement of hedonic impact of food, we and others have conducted taste reactivity tests of ‘liking’ changes induced by bicuculline in the ventral pallidum [123] (Figure 1). Taste reactivity results indicated that GABA blockade in the ventral pallidum completely fails to elevate hedonic reactions to taste rewards. Neither in the posterior area where lesions produce aversion nor in any other area did bicuculline microinjection cause any detectable elevation of normal hedonic reactions to sucrose [78,123]. This has led us to conclude that ventral pallidal GABA disinhibition appears to be a mechanism of enhancing ‘wanting’-without enhancing ‘liking’-for food reward [50,54].

Such a pattern of ‘wanting’ without ‘liking’ augmentation is similar to the effect previously shown to result from activating mesolimbic dopamine systems by several manipulations: electrical stimulation of the medial forebrain bundle, systemic amphetamine or cocaine administration, microinjection of amphetamine into nucleus accumbens, neural sensitization induced by repeated psychostimulant exposure, or elevation of synaptic dopamine levels by genetic knockdown of the dopamine transporter [124–128]. In all of these cases of pure ‘wanting’ enhancement, dopaminergic stimulation enhanced motivated behavior to obtain or consume reward but failed to enhance hedonic reactions to tastes. Similarly in humans psychostimulant exposure that elevates dopamine levels and subjective ratings of drug or food reward ‘wanting’ has been reported in several studies to fail to also enhance subjective ratings of pleasure liking or euphoria [129,130]. It is not yet known how ventral pallidum GABA and mesolimbic dopamine interact in such cases, but there are several possibilities. For example, dopamine neurons also innervate ventral pallidum directly [25,26] and appear to have an important, but as yet unspecified, role in reward. For example, psychostimulant microinjection into the ventral pallidum is sufficient to condition a place preference [131] and increase eating behavior [132], while D1 receptor antagonist microinjection reduces intake [78] and dopaminergic terminal lesions block the development of a preference for cocaine-paired

environments [133]. Local dopamine release can suppress the inhibitory influence of GABA transmission on ventral pallidum firing [134], indicating a modulatory role in GABAergic disinhibition of neural activity that may be important for motivation enhancements. Additionally, direct ventral pallidal modulation of midbrain dopamine activity via projections to ventral tegmental area [135–138] is another possible mechanism by which ventral pallidal GABAergic disinhibition might stimulate ‘wanting’ without ‘liking’.

However, while GABAergic disinhibition of ventral pallidum neurons does not increase hedonic impact, GABA_A receptor activation by the agonist muscimol into the central ventral pallidum reduces normal hedonic reactions to sucrose and elevates aversive reactions [78, 139], which may parallel the aversion consequence of ventral pallidum lesions [60]. Additionally, normal avoidance and aversion to a taste previously paired with lithium-chloride sickness can be reduced by ventral pallidal GABA_A activation with bicuculline [140]. One possibility is that baseline neuronal activity in ventral pallidum has a necessary role in normal hedonic valuation, although depolarization induced by GABAergic disinhibition is not sufficient to cause enhancement of food’s hedonic valuation (despite enhancing the motivation to eat and reducing the expression of learned aversions).

Ventral pallidum opioids: ‘liking’ and ‘wanting’ stimulation in a posterior hotspot

Opioid neurotransmission is a more potent substrate for hedonic reward in ventral pallidum. Mu opioid stimulation is capable of enhancing hedonic ‘liking’ as well as motivational ‘wanting’, at least in a cubic millimeter hotspot of posterior ventral pallidum. Brain opioids have long been linked to hedonic and motivational properties of food, drugs and other incentives [141–147]. The ventral pallidum has abundant mu opioid receptors [148–151], and ventral pallidum opioid transmission is centrally involved in conditioned place preference and drug self-administration [30,152–156].

In contrast to GABA blockade, it turns out that increase in opioid transmission in the ventral pallidum is sufficient to enhance hedonic ‘liking’ reactions to sucrose as well as motivational ‘wanting’ to eat, but only in a restricted subregion of posterior ventral pallidum (Figure 1). In a recent study, we identified this posterior subregion as an opioid hedonic hotspot where microinjections of the mu opioid agonist DAMGO more than doubled taste ‘liking’ (hedonic reactions to sucrose) and quadrupled food ‘wanting’ (eating behavior) [123]. Fos plume mapping of drug functional spread helped reveal that the opioid hedonic hotspot was contained in the posterior half of the ventral pallidum and was roughly a cubic millimeter in size. Interestingly, the hedonic hotspot overlaps with the area where lesions abolish food reward and cause sucrose aversion [60], although an explicit comparison mapping of these opposite manipulations has yet to be made.

The special reward features of the posterior hotspot are underscored by observations that mu opioid stimulation of a more central and anterior coldspot location in ventral pallidum actually suppresses taste ‘liking’ reactions and eating behavior below normal levels, instead of enhancing them [123]. This difference reveals that opioid ‘liking’ and ‘wanting’ enhancement mechanisms are both highly localized to the hotspot in the posterior ventral pallidum. By contrast, the same reward functions are suppressed by the opioid coldspot in the anterior ventral pallidum.

An intriguingly similar segregation of positive affect to the posterior half ventral pallidum has recently been observed in human brain activations. In functional MRI studies, posterior ventral pallidum was reported to become more active during the presentation of images depicting appetizing food like chocolate cake, perhaps corresponding to the rat posterior hotspot above [157,158]. By contrast, negative pictures of disgusting and rotten food were reported to

stimulate activity in more anterior regions of the ventral pallidum, perhaps corresponding to the rat anterior coldspot [158].

The posterior opioid hotspot additionally may be the best location for stimulating instrumental seeking for brain stimulation reward. In perhaps the first foreshadowing of the hedonic hotspot, microinjection of an opioid agonist in the posterior ventral pallidum was reported to increase the amount a rat will work to self-stimulate through electrodes implanted in the medial forebrain bundle, while the same microinjection in anterior ventral pallidum suppressed self-stimulation below normal levels [46]. That bivalent pattern seems quite similar to the more precisely mapped effects on taste 'liking' reactions and spontaneous food intake [123]. Also, the posterior ventral pallidum has an advantage for brain stimulation facilitation by microinjections of a delta opioid agonist [159]. Further, self-stimulation of an electrode in the ventral pallidum itself also appears to have an anterior-posterior gradient, as electrical current thresholds required for maintaining self-stimulation decline from the anterior to posterior ends, indicating that stimulation in the posterior hotspot is a more potent reward to animals even at low intensities [106].

Why would the hotspot in posterior ventral pallidum have more positive reward functions than the anterior ventral pallidum? There are a few known neurobiological features of the hotspot in the posterior ventral pallidum that might be involved. The posterior ventral pallidum appears to have higher enkephalin levels than anterior ventral pallidum [160,161], a higher ratio of noncholinergic to cholinergic cells [162], and a less dense concentration of presynaptic mu opioid receptors [149] compared to anterior ventral pallidum. Lastly, marked differences in anatomy have been noted for dorsal and lateral versus ventral and medial subregions of ventral pallidum in a plane at the anteroposterior level of the anterior commissure [14–16,37], which may be relevant as posterior ventral pallidum is more laterally placed in the brain (though the functional role of medial-lateral or dorsal-ventral subdivisions in reward is not yet clear).

Accumbens-pallidum opioid interaction: asymmetric paths for 'liking' and 'wanting'

The ventral pallidum hotspot forms a functional circuit with another cubic-millimeter hedonic hotspot in medial shell of nucleus accumbens that similarly uses mu opioid signals to control 'liking' and 'wanting' [50,54,163]. To evaluate interactions between hotspots and structures, we pitted opioid activation of the ventral pallidum hotspot against simultaneous opioid suppression of the accumbens hotspot, and vice versa [164]. We found that opioid inactivation in the nucleus accumbens (via microinjection of naloxone in nucleus accumbens hotspot) blocked the elevation of 'liking' normally caused by opioid activation in the posterior ventral pallidum (via microinjection of DAMGO in ventral pallidum hotspot). Similarly, 'liking' elevation from opioid stimulation of the accumbens hotspot was blocked by opioid inactivation of the ventral pallidum hotspot. In addition, opioid activation in either hotspot also increased distant Fos protein expression in the other hotspot (and naloxone suppressed distant Fos), showing that opioid activation in one site recruits the other into activation as a neurobiological circuit. Thus, 'liking' elevation appears to require simultaneous participation of both opioid hotspots in ventral pallidum and accumbens (Figure 4).

These results imply that a traditional anatomical view of the ventral pallidum as purely a serial output for ventral striatal signals is only partially true. The ventral pallidum can equally influence the functional reward output of upstream accumbens as be influenced as a downstream consequence of accumbens activation, indicating a bidirectional interaction in which opioid-related information flows both ways. This possibility is also consistent with known bidirectional physiological interactions and reciprocal anatomical connections [1,39, 44,165–168].

The circuit dynamics for controlling ‘wanting’ turn out to be a bit different from those controlling ‘liking’. Elevation of food ‘wanting’ appears to be asymmetrically dominated by opioid activation of the accumbens hotspot [164]. We found that eating elevation after opioid activation in the accumbens hotspot was not blocked by opioid blockade of the ventral pallidum hotspot. However, accumbens opioid blockade prevented any eating stimulation by opioid activation of the ventral pallidum hotspot. For motivation to eat (food ‘wanting’), opioid activation in the nucleus accumbens seems able to stimulate food intake in the absence of endogenous opioid recruitment in ventral pallidum (perhaps through connections with other motivation sites like the lateral hypothalamus[164,169–174]).

Neuronal activity in Ventral Pallidum Hotspot Codes Reward

How are reward ‘liking’ and ‘wanting’ encoded by neuronal firing within the ventral pallidum hotspot? A neural reward code must represent features of a sensory reward in profiles of neural activity, and the information in this neural representation is available for communication to efferent targets [175]. We have found evidence in recent behavioral electrophysiology experiments that the firing patterns of neurons in the ventral pallidum hotspot code reward and associated stimuli, and may discriminate learning, ‘liking’ and ‘wanting’ components of reward.

Ventral pallidal neurons fire with a phasic burst of excitation to a sucrose pellet reward [176]. If that sucrose pellet is paired associatively as an unconditioned stimulus (UCS) with a tone conditioned stimulus (CS+), ventral pallidum neurons develop an anticipatory excitation response to the auditory Pavlovian CS+ that predicts future sucrose reward as rats learn [176]. When multiple serial CS+ cues are presented, ventral pallidum neurons fire to each cue, and with extended training develop a more prominent phasic excitation to the first predictive cue (CS+1) compared to a subsequent cue (CS+2) that occurs closest to reward [127,176] (Figure 3). This pattern is similar to mesolimbic dopamine neurons [177](but see: [178]), and maximal firing to the first predictor has been taken to imply representation of cue predictive value [127,177,179]. Unlike dopamine neurons, however, neurons in the ventral pallidum hotspot continue to be strongly activated by sucrose rewards even long after they are predicted (when the Pavlovian association is well established), suggesting that the firing can represent hedonic information in addition to the predictive value of cues.

However, firing to reward properties of stimuli is confounded with sensory stimulus identity (e.g. sweetness of reward), arousal, and motor reactions, making their functional interpretation difficult. More focused experiments are required to pinpoint the coded neuronal representation for the hedonic value of reward and incentive value of a cue. Recently, we have conducted a series of studies designed explicitly to isolate hedonic, motivation, and learning features in excitatory bursts of ventral pallidum firing.

Ventral pallidum neurons encode reward hedonic ‘liking’ and incentive salience ‘wanting’

To isolate hedonic signals in ventral pallidum activity, we challenged ventral pallidum neurons with a shift in hedonic value of reward while keeping sensory identity stable [180] (Figure 2). When rats were in a normal physiological state, ventral pallidal neurons were observed to fire vigorously in response to an orally infused sucrose taste, which evoked hedonic ‘liking’ reactions in a behavioral taste reactivity test, but firing was less to an intensely salty taste (3X seawater concentration) that evoked aversive reactions. However, after animals were given diuretic injections to deplete them of bodily sodium, a sodium appetite developed and the intense salt taste evoked hedonic ‘liking’ reactions similar to sucrose. Ventral pallidal neurons then responded with an increased firing rate to the intense salt taste, equal in magnitude to the response evoked by the sucrose taste [180] (Figure 2) Additional analyses of firing during oral, grooming, and locomotion movements indicated that ventral pallidum firing did not simply

encode movements. Ventral pallidum neurons thus pass the most stringent test for hedonic coding that is dis-confounded from sensory coding: being able to track hedonic shifts of a single sensory stimulus from nasty to pleasant [116,175,180,181].

A separate but related study asked whether ventral pallidum neurons could additionally code the incentive salience of Pavlovian cues predicting salt or sucrose, in a way that could differentiate incentive ‘wanting’ from learned prediction of reward outcome [182]. Incentive salience theory posits that Pavlovian reward cues take on motivation features, which are similar in some ways to the motivation features of the unconditioned rewards they predict [183–185]. For example, reward cues become attractive and ‘wanted’ themselves. Although the incentive value of a conditioned reward cue is confounded with its predictive value, there is a way to disentangle these features in studies of neuronal coding by exploiting natural appetites. ‘Wanting’ for cues that predict sweet or salty rewards can be modulated directly by the same hunger, and sodium appetite physiological states that modulate the value of sucrose or salt UCS rewards, even if the unconditioned rewards have never been experienced in those appetite states [184,186–189]. For example, rats that have learned that a sour or bitter flavor is associated with salt, will later seek out and drink just the sour or bitter flavor by itself when they are in a physiological salt appetite state, and will show positive hedonic facial reactions to the conditioned flavor that previously was aversive [187,188,190]. In reverse, cues paired with normally pleasant sweet tastes can come to evoke aversive reactions and avoidance if the associated taste is devalued in a separate context (e.g., through pairing with lithium-chloride sickness) [190,191]. We harnessed this feature of cue incentive modulation to ask if ventral pallidum neurons code the motivation value of a learned cue, independently of what hedonic consequence the cue predicts based on its prior associative pairings with an unconditioned stimulus [182]. We paired auditory tone CS+s with either sucrose taste or intense sodium chloride taste UCSs that were infused into a rat’s mouth. Initially after training, an auditory CS+ tone predicting oral infusion of an aversive salt taste evoked virtually no firing response from posterior ventral pallidal neurons, whereas a tone predicting sucrose evoked a large firing response. After sodium depletion was induced by hormone injections, the salt and sucrose tones equally evoked intense firing from ventral pallidal neurons, even in extinction and prior to ever re-experiencing the salt taste in its new ‘liked’ state (salt ‘liking’ was confirmed in a subsequent taste reactivity test) (Figure 2). This indicates that ventral pallidum firing tracks the incentive salience of reward-predictive cues, and can integrate physiological needs to engage incentive motivation in an ‘on the fly’ manner without time spent learning new cue-reward contingencies.

The ventral pallidum may code for incentive motivation in humans as well. In one intriguing recent functional MRI study, ventral pallidal activity was elevated during the presentation of images signaling that a relatively large amount of money would be earned, which also evoked a motivated behavioral response (lever squeeze) to obtain the money [192]. Remarkably, ventral pallidal activity was even increased when the presentation of a relatively large money reward was too fast to be consciously detected, even though it still evoked a motivated behavioral response. Motivation-related activations of ventral pallidum in neuroimaging studies have similarly been observed with consciously detectable stimuli, including smells predicting tasty food or pictures depicting food [193,194].

Ventral pallidum neurons encode incentive sensitization and distinguish ‘wanting’ versus ‘liking’ enhancements

In the neural recording studies above, incentive salience ‘wanting’ and hedonic ‘liking’ were enhanced together by natural appetite, but ‘wanting’ can be separately enhanced alone by other manipulations, such as mesolimbic dopamine activation by amphetamine or psychostimulant drug-induced sensitization [105]. Can hedonic versus motivational features of reward codes in

neuronal firing be separately tracked or told apart by ventral pallidum circuits? The answer seems to be yes.

A recent study in our group found that sensitization of motivation ‘wanting’, but not ‘liking’, caused by repeated drug exposure is encoded in profiles of ventral pallidum neural activity [127] (Figure 3). First, rats were trained to associate a series of two cues (CS+1 followed by CS+2) with a sucrose reward. They were then given acute amphetamine injections, chronic intermittent amphetamine injections to cause sensitization, or both, and examined for ventral pallidum neuronal responses to reward cues in the context of elevated dopamine transmission. After sensitization, the response profile of ventral pallidum neurons shifted away from prediction coding (maximal response to initial predictor CS+1) and towards incentive coding (maximal response to a CS+2 cue that occurred subsequently just before reward when motivation was highest), even though the sensitized rats had been drug-free for two weeks prior to testing (Figure 3). This incentive magnification change was not attributable to new learning as it occurred when the animals had no opportunity to experience new cue-reward pairings after sensitization was induced. Acute administration of amphetamine on the day of test similarly shifted neural responding toward the incentive cue, and combining acute amphetamine with prior sensitization biased the profile towards incentive responding most of all.

In a further study, we separated ‘liking’ and ‘wanting’ firing codes in ventral pallidum more distinctly by enhancing them individually with different pharmacological manipulations [195]. We used neurochemically and neuroanatomically focused manipulations of the nucleus accumbens to enhance ‘wanting’ only (with dopaminergic amphetamine microinjection) or to enhance ‘liking’ as well as ‘wanting’ (with opioid DAMGO microinjection). At the same time, we assessed phasic excitations in ventral pallidum firing that encode cue incentive salience and reward hedonics. Accumbens stimulation with dopamine or opioid agonists led to a striking magnification of ventral pallidum phasic excitation peaks to an incentive CS+2 cue, without affecting excitation to the first and maximally predictive CS+1 cue (nor to a CS-minus that lacked any incentive value), and did so on the very first cue presentations in extinction prior to re-learning or reward revaluation. Both DAMGO and amphetamine also increased consumption of a tasty chocolate candy as a behavioral consequence of heightened ‘wanting’. By contrast, only opioid stimulation also enhanced hedonic ‘liking’ reactions to sucrose and caused ventral pallidum neurons to also magnify their firing response to a sucrose reward. Amphetamine by comparison completely failed to enhance either behavioral ‘liking’ reactions or ventral pallidum excitatory firing to sucrose. Our results suggested that the ventral pallidum may use separate population and firing rate activity patterns to distinguish ‘wanting’ from ‘liking’ enhancements. This would mean that ventral pallidum neurons may convey distinctly-coded signals for ‘liking’ versus ‘wanting’ features of reward enhancement to downstream structures, which might modulate decision making and behavioral reactions appropriate to the particular reward component being enhanced.

Reward cues also activate ventral pallidum in humans, and we speculate that the incentive-coding patterns we have observed in rats may underlie ventral pallidum blood flow activation to drug reward cues in drug addicts that trigger motivation to take drug again. Cue-triggered ‘wanting’ for drugs may be a very basic response that does not need elaborate cognition. For example, Childress et al. [196] presented cocaine addicted subjects with pictures of drug-associated cues (e.g. images of drug taking) that could not be consciously detected. Yet the images not only triggered ventral pallidum activation (along with other limbic/cortex sites), but the intensity of ventral pallidum (and amygdala) activation predicted later positive affective reactions to the same cues when they were consciously seen (specifically, facilitated correct labeling of positive affective words). This shows that even subconsciously detected drug cues can engage ventral pallidum activation in addicts to promote motivational reactions, which

may contribute to exacerbation of drug taking in the presence of incentive cues. Indeed, there is now a wealth of evidence that the ventral pallidum is an important structure for drug seeking, taking, and relapse in animal models of addiction [81,83,90,91,111,131,154,197–200], and a key site of neuroadaptations following repeated drug exposure that may contribute to sensitization, addiction, and relapse vulnerabilities [201–207]. How incentive processing of reward cues by ventral pallidum circuits contribute to drug taking and addiction will be an important issue for future research.

Ventral Pallidum Roles in Affiliation and Sex

Another important natural reward for evolution and behavior is sex and social affiliation, and several studies have revealed a ventral pallidal involvement in those processes too. For example, in humans, ventral pallidum/ventral globus pallidus activity is reported to increase during male sexual arousal [208], and in response to subliminally presented pictures of happy human faces or sexual images [196,209]. In the *Callicebus Titi* monkey, a monogamous species of South American primate, males that are co-habiting and pair bonded with their female mate show elevated ventral pallidal glucose metabolism, which was interpreted as implying a link between ventral pallidum neural activity and the maintenance of male/female affiliation [210].

In rodents, an exciting body of work on the monogamous prairie vole has demonstrated that transmission of the hormone vasopressin in the ventral pallidum is especially critical in regulating social affiliation and pair bonding [211–214]. After cohabiting and mating with a female, monogamous male voles form a preference for that particular female over another, and vasopressin in the ventral pallidum appears to play a critical role. Monogamous male prairie voles have greater vasopressin V1a receptor binding in the ventral pallidum compared to a non-monogamous species of meadow vole in which a male may have multiple female mates but not form any pair bonds [215]. Male prairie voles contain a greater density of V1a receptors in the ventral pallidum compared to females [216], and active mating behavior by the male vole engages vasopressin-dependant mechanism that increase Fos expression in the ventral pallidum [217]. Pair bonding can even be enhanced in some prairie voles by directly stimulating vasopressin V1a receptors in the ventral pallidum via viral vector gene delivery of V1a receptors, which also causes male voles to increase their affiliative behavior towards other males [215]. Further, V1a receptor upregulation in the ventral pallidum can cause the sexually promiscuous meadow vole to behave like a prairie vole and form a preference for a single familiar female [218].

However, at present it is too early to say if the ventral pallidum mediates ‘liking’ and/or ‘wanting’, or learning, of affiliation and sex. Still, it is worth highlighting at this early stage that the ventral pallidum is a common site for enhancing at least two critical natural rewards, both sex and food, as well as drug rewards.

The Ventral Pallidum as a Limbic Final Common Pathway

To summarize, a growing body of work has demonstrated major roles for the ventral pallidum in food reward, sex, social affiliation, electrical brain stimulation reward, drugs of abuse, winning money, and other rewards. The ventral pallidum is a convergent point for limbic reward signals and an intermediate stage to diverse cognitive, affective and motor processes. It is a central site for coding and causing enhancements of reward learning, hedonics, and motivation (Figure 4).

Its centrality in reward anatomy and function might be captured most comprehensively by describing the ventral pallidum as a ‘limbic final common pathway’ for reward signals in the brain. This concept borrows from Charles Sherrington’s early formulation of “final common

pathway” to describe spinal motor nuclei as the last-stage through which signals must travel to influence movement [219]. Applied to limbic reward functions, the ventral pallidum might analogously be viewed as an essential convergent point for hedonic and motivational signaling pathways in the brain, and thus a final pathway for *reward*. This does not mean that reward functions are all contained within the ventral pallidum, nor that the ventral pallidum is necessarily the only pathway for reward to influence behavior or cognition. It simply suggests that reward pathways converge upon ventral pallidum, and that this funneling of signals plays a special role in generating major reward components. As with motor nuclei for movement, the ventral pallidum as a *limbic* final pathway passes the tests of being necessary for reward (without it, hedonics and motivation cannot be enhanced), sufficient to enhance reward (contains mechanisms that actively enhance hedonic impact and motivation), and a site of neural reward representation (represents hedonics and motivation in patterns of activity that can be sent to efferent target systems). These roles distinguish the ventral pallidum as among the most crucial sites for reward and motivation in the brain.

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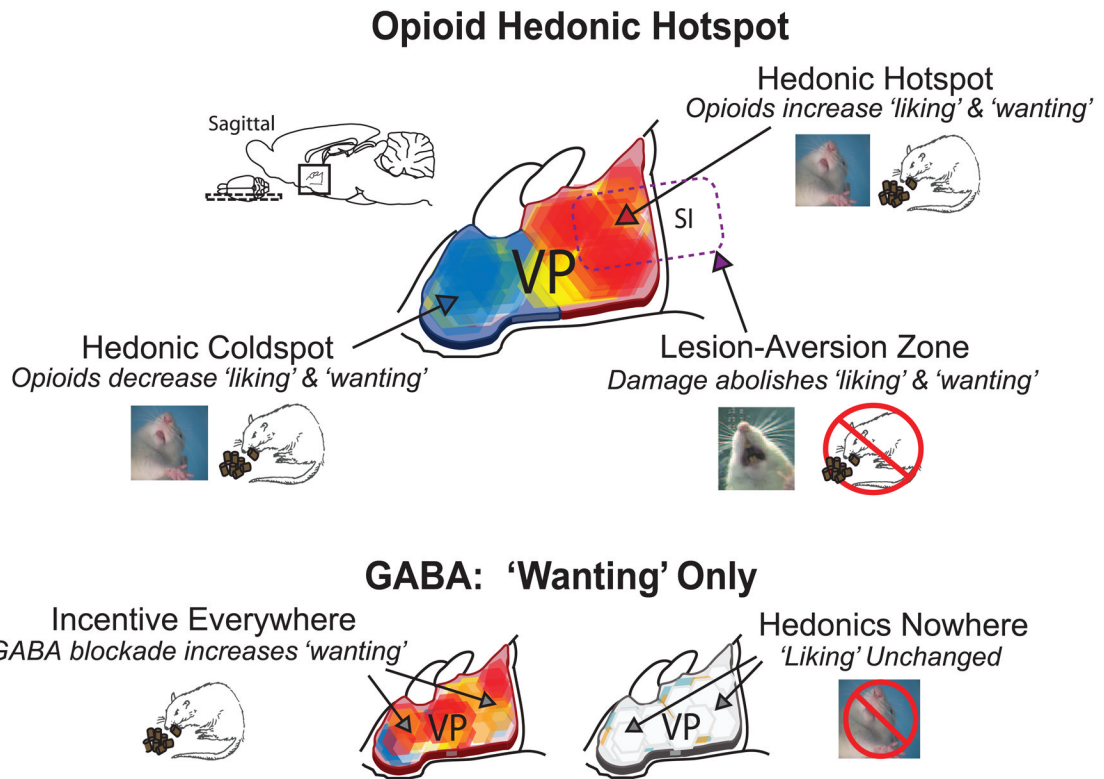
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**Figure 1.**

Neurochemical maps of hedonic 'liking' and motivational 'wanting' in the ventral pallidum. Microinjections of DAMGO to stimulate opioid transmission in the posterior ventral pallidum hotspot enhance reward 'liking' (increased hedonic orofacial reactions to sweet taste such as tongue protrusion shown in image insert) and also enhance 'wanting' (increased motivated eating behavior) (top; red hexagons). The same DAMGO microinjections in an anterior coldspot decrease both 'liking' and 'wanting' measures below normal (blue). The posterior hedonic hotspot overlaps with the crucial zone where ventral forebrain lesions produce aversion to palatable tastes and aphagia (purple outline). By contrast, blockade of ventral pallidal GABA with bicuculline microinjections increase food 'wanting' and eating behavior virtually throughout the ventral pallidum (bottom left; red), but fail to change normal hedonic 'liking' reactions at the same sites (bottom right; white). Maps depict data reconstructed from [60, 123]. *VP* ventral pallidum; *SI* substantia innominata.

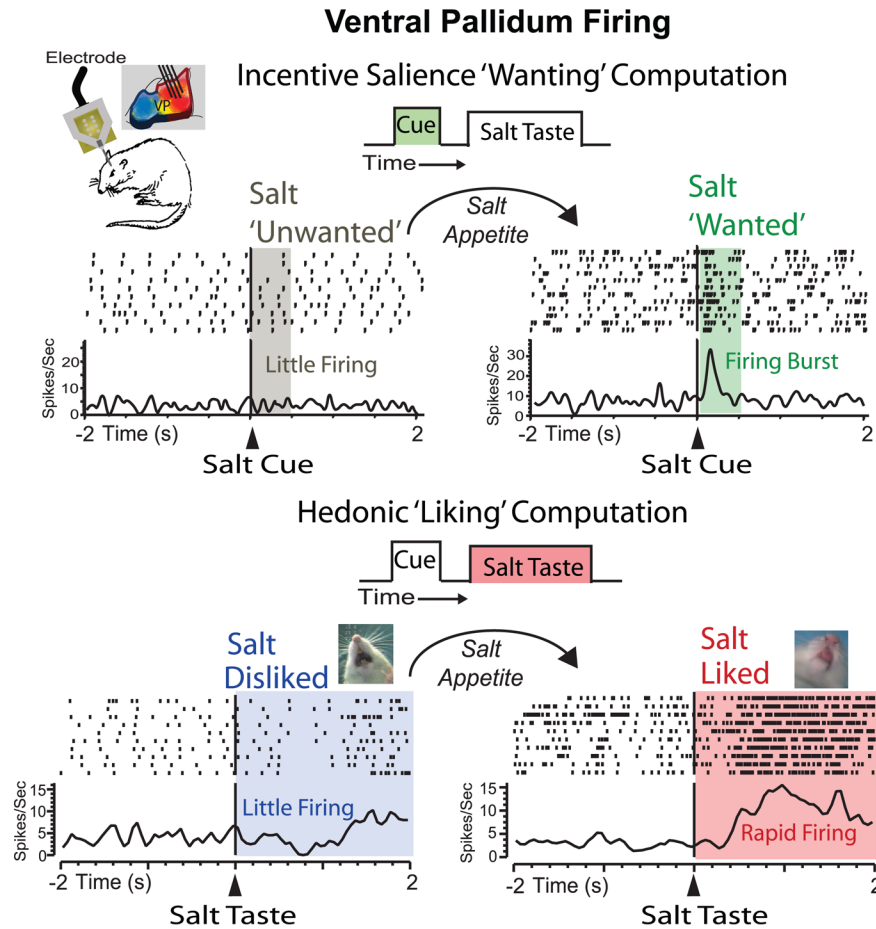


Figure 2.

Ventral pallidum hotspot neurons encode the incentive saliency of cues and hedonic value of rewards. (Top) Neurons fire little to a learned cue predicting an unpalatable salt taste, but fire in a phasic burst when the cue gains incentive value after sodium depletion and salt-appetite (raster and histogram traces show an example neuron recorded during baseline homeostasis and another neuron recorded after salt depletion firing in response to the salt cue at time zero) [182]. This dynamic computation integrates prior learned associations and physiological state to update incentive saliency 'on-the-fly' and prior to ever re-experiencing the predicted taste. (Bottom) Normally, the unpalatable salt taste evokes 'disliking' reactions (e.g. oral gaping) and evokes little ventral pallidum firing, but after sodium depletion the same taste evokes 'liking' reactions (e.g. tongue protrusions) and bursts of ventral pallidal excitatory firing to compute magnified hedonic impact [180].

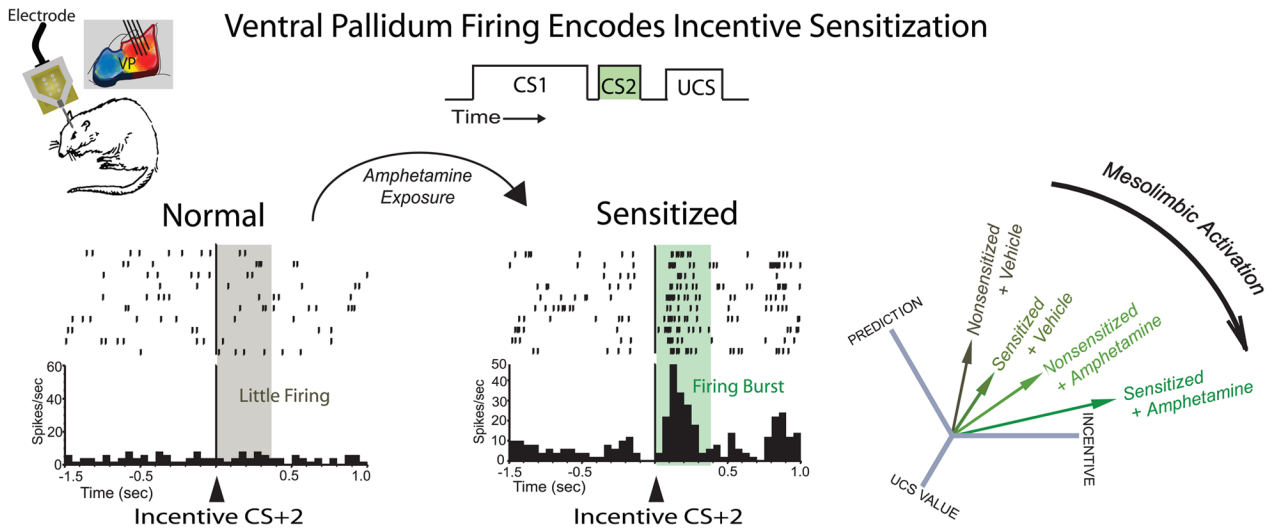


Figure 3. Ventral pallidum neurons encode incentive sensitization. Mesolimbic dopamine stimulation after acute or repeated (sensitized) amphetamine injection increases incentive salience coding in magnified phasic burst of firing of to an incentive cue (CS+2), but not maximally predictive cue (CS+1), in a cue series. When the cue sequence is learned, ventral pallidum neurons fire little to the fully predicted CS+2 (shown at left is an example neuron). After acute or repeated amphetamine exposure to increase ‘wanting’, ventral pallidum neurons fire vigorous bursts of excitation to the same CS+2 incentive cue in an extinction session (shown in center is an example neuron recorded after amphetamine sensitization) [127]. Profile analysis (Right) on responses to multiple stimuli shows that dopaminergic ‘wanting’ increases by sensitization or acute amphetamine injection shift ventral pallidum firing away from a more predictive cue (CS+1) toward a incentive cue (CS+2), and fail to increase firing to the predicted UCS reward. Similar magnification of incentive firing over prediction firing in ventral pallidum neurons occurs with dopamine or opioid stimulation directly in the nucleus accumbens [195].

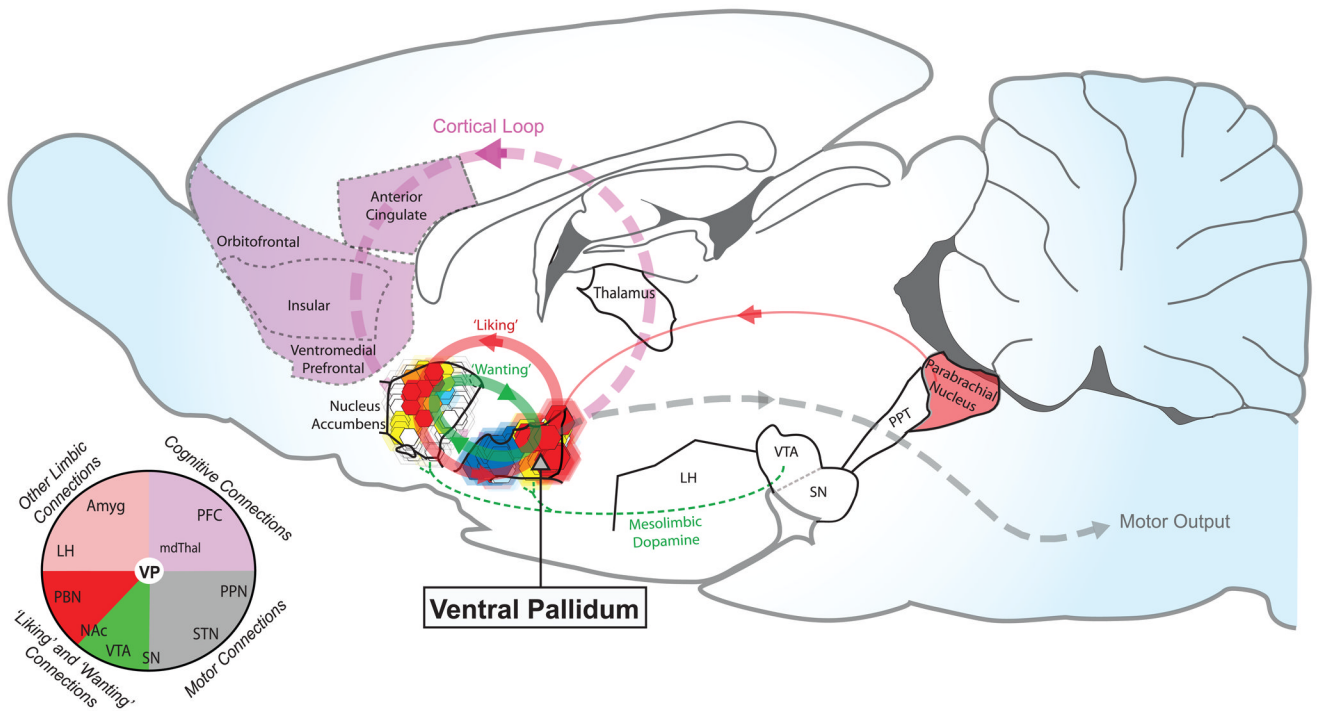


Figure 4. Sagittal rodent brain diagram highlighting the ventral pallidum as a final pathway for limbic 'liking' and 'wanting' signals. 'Liking' systems (shown in red) link together opioid hedonic hotspots in the posterior ventral pallidum and dorsal-rostral accumbens shell, and potential link with a GABAergic hedonic signal in the parabrachial nucleus. 'Wanting' systems (green) link together mesolimbic dopamine, and opioid motivational signals in the accumbens and ventral pallidum, and larger circuits. The ventral pallidum is also connected with mesolimbic-thalamocortical loops (pink) and basal ganglia or brainstem motor output (gray) to influence cognition and action. Pie chart schematic shows ventral pallidum at an intersection of limbic connections with cognitive, motor, and reward structures. *VTA* ventral tegmental area; *SN* substantia nigra; *PPT* pedunculopontine tegmentum; *LH* lateral hypothalamus; *PBN* parabrachial nucleus; *PFC* prefrontal cortex; *STN* subthalamic nucleus; *NAc* nucleus accumbens; *VTA* ventral tegmental area; *SN* substantia nigra; *mdThal* mediodorsal thalamus; *PBN* parabrachial nucleus; *Amyg* amygdala.