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Review

'Liking' and 'wanting' in eating and food reward: Brain mechanisms and clinical implications

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ABSTRACT

It is becoming clearer how neurobiological mechanisms generate 'liking' and 'wanting' components of food reward. Mesocorticolimbic mechanisms that enhance 'liking' include brain hedonic hotspots, which are specialized subregions that are uniquely able to causally amplify the hedonic impact of palatable tastes. Hedonic hotspots are found in nucleus accumbens medial shell, ventral pallidum, orbitofrontal cortex, insula cortex, and brainstem. In turn, a much larger mesocorticolimbic circuitry generates 'wanting' or incentive motivation to obtain and consume food rewards. Hedonic and motivational circuitry interact together and with hypothalamic homeostatic circuitry, allowing relevant physiological hunger and satiety states to modulate 'liking' and 'wanting' for food rewards. In some conditions such as drug addiction, 'wanting' is known to dramatically detach from 'liking' for the same reward, and this may also occur in over-eating disorders. Via incentive sensitization, 'wanting' selectively becomes higher, especially when triggered by reward cues when encountered in vulnerable states of stress, etc. Emerging evidence suggests that some cases of obesity and binge eating disorders may reflect an incentive-sensitization brain signature of cue hyper-reactivity, causing excessive 'wanting' to eat. Future findings on the neurobiological bases of 'liking' and 'wanting' can continue to improve understanding of both normal food reward and causes of clinical eating disorders.

1. Introduction

Several decades of neuroscience studies have advanced understanding of how the brain generates behavior related to food reward, motivation, and hunger. A fundamental question that remains is how mesocorticolimbic and hypothalamic circuitry interact to produce reward and the motivation to eat [1–7].

Work in our lab has focused on understanding how mesocorticolimbic systems generate 'wanting' and 'liking' for food rewards, which have turned out to be somewhat separable. Here we describe how various brain mechanisms produce those two components of food reward. 'Wanting' and 'liking' usually cohere together, but also can dissociate in particular brain conditions to come apart. Findings have revealed a distributed network of brain hedonic 'hotspots' that can amplify hedonic impact or 'liking' for food rewards. These 'liking' mechanisms differ from larger mesocorticolimbic circuitry that generates incentive salience or 'wanting' as motivation to eat. We focus on mechanisms for 'liking' and for 'wanting', and how these interact with homeostatic hypothalamic circuitry in controlling eating and food reward.

1.1. 'Liking' and 'wanting' as separate psychological processes

The words liking and wanting are often used interchangeably in ordinary life when talking about rewards. For example, people may want a palatable piece of chocolate because they like the flavor and other sensations of consuming it. In ordinary use, liking means conscious pleasure and wanting means conscious desire, which typically involve cognitive appraisals and declarative goals mediated by cortically-weighted circuitry. But here we use quotations for 'wanting' and 'liking in order to distinguish specific psychological processes from ordinary use [8]. 'Wanting' here refers to the particular psychological process of incentive salience, which can occur either consciously or unconsciously, generated by brain mesolimbic circuitry in the form of cue-triggered motivation. When rewards such as palatable foods and their predictive cues are imbued with incentive salience by mesocorticolimbic circuitry, those cues and foods become attractive, and in conscious form able to elicit subjective cravings. Whether conscious or not, incentive salience triggered by cues can also generate behavioral urges to seek and consume their associated rewards [9,10]. In the laboratory, 'wanting' is typically measured in humans by subjective craving ratings, and in animals by how much food is pursued,

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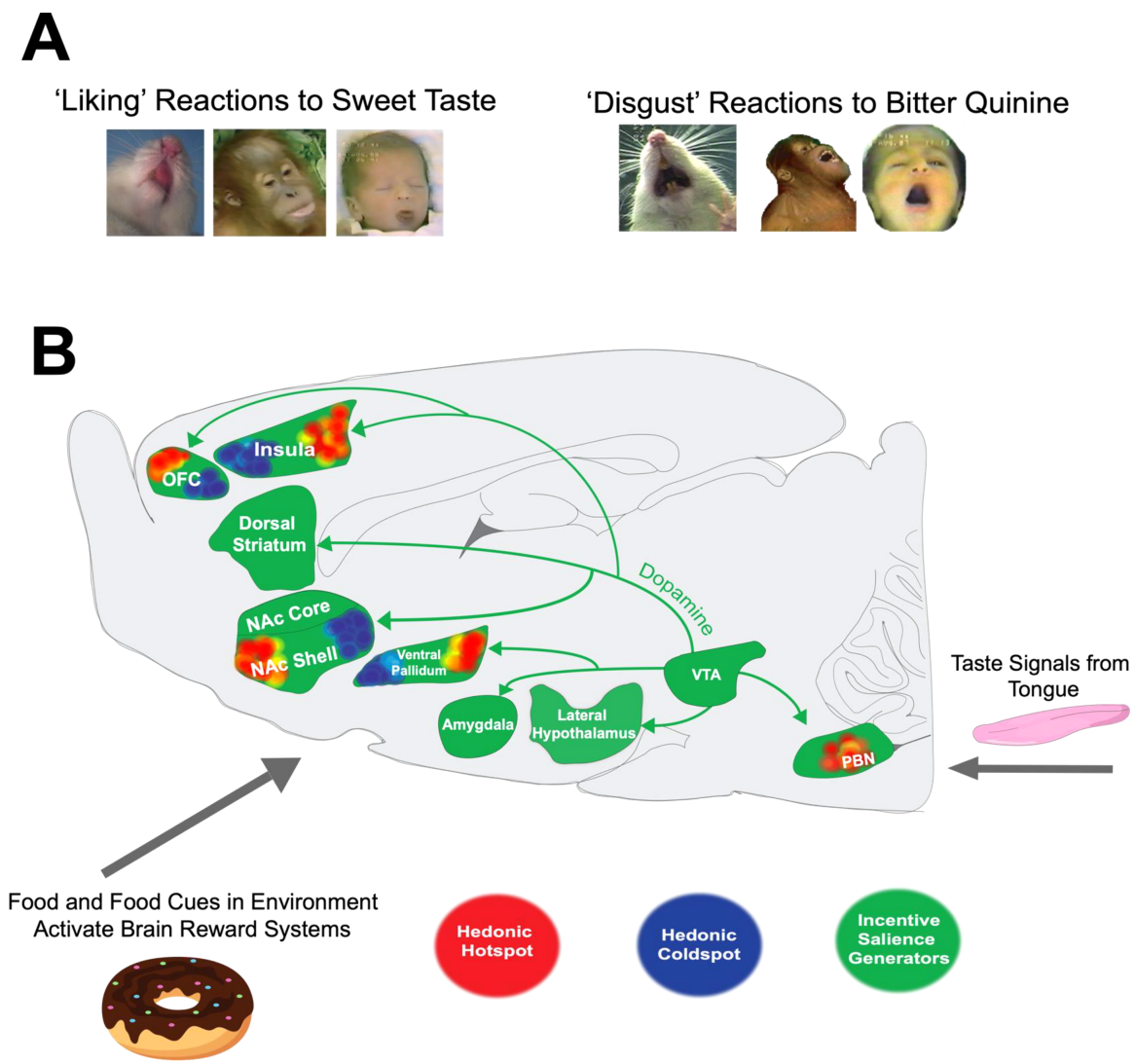


Fig. 1. Brain systems of 'wanting' and 'liking'. A) Positive hedonic expressions ('liking') elicited in response to palatable sucrose solutions (left). Negative aversive orofacial expressions ('disgust') in response to bitter quinine solutions (right). Orofacial expressions to palatable and aversive solutions are homologous across various mammalian species that include human infants, nonhuman primates, rodents, and horses. B) Palatable foods and their predictive cues activate mesocorticolimbic reward systems. Sagittal view of a rat brain depicting brain systems of 'wanting' and 'liking'. 'Wanting' is generated by mesolimbic dopamine systems originating from the midbrain that project to various limbic structures (pictured in green) to generate incentive salience. 'Liking' is mediated by hedonic hotspots (pictured in red) where opioid, orexin, endocannabinoid, and optogenetic manipulations enhance positive orofacial expressions to sucrose taste. By comparison, the same manipulations within the hedonic coldspots (pictured in blue) oppositely suppress 'liking' reactions to sucrose solutions.

consumed, or preferred over an alternative. 'Liking' refers to the hedonic impact of pleasant rewards, which when surfaced into consciousness can result subjective pleasure ratings in adult humans, but which in animals and infant humans can be assessed via objective measures of hedonic orofacial expressions elicited to taste in the affective taste reactivity test [11–15]. 'Liking' and 'wanting' can become separated in some conditions, as discussed below.

1.2. Measuring hedonic 'liking' with the taste reactivity test

The hedonic taste reactivity task measures affective orofacial reactions to tastes of sucrose, quinine, water, etc., and the reactions to any given taste can also be shifted by a variety of relevant physiological, learning, and brain manipulation factors that alter its palatability. Originally pioneered by Steiner for use in human infants [11], the test was adapted for rodents by Grill and Norgren [13]. Orofacial responses to taste are grouped into positive, neutral, and aversive categories. Positive hedonic or 'liking' evaluations (Fig. 1a) are reflected in tongue protrusions, paw licks, and lateral tongue protrusions, typically elicited by tastes such as sucrose. By comparison, negative aversive or 'disgust' evaluations are reflected by gapes, forelimb, flails, headshakes, paw treading and face washes, and typically elicited by bitter quinine. Many of these orofacial expressions to taste are homologous, or evolutionarily conserved, across mammalian species ranging from human infants to non-human primates, rodents, and horses [14–16]. In our laboratory, rodents are implanted with bilateral oral cannula, which allow taste solutions to be directly infused into their mouths without them having to engage in any appetitive activity to obtain them, and allowing experimenter control of stimulus intensity and duration. Independence from appetitive or instrumental decisions to consume is important in allowing taste reactivity to provide a relatively pure measure of taste-elicited 'liking', without being altered by changes in 'wanting' that can influence most other behavioral measures of food reward [15,17].

Tastants with very different sensory properties like sucrose, saccharin, salt, and fats can all evoke similar positive 'liking' responses, indicating that hedonic reactions are palatability-specific rather than sensory-specific [14,18–21]. Accordingly, taste reactivity behaviors are not simple inflexible reflexes to a particular sensation, but rather reflect

a hedonic evaluation that also depends on the internal state of the organism, including physiological appetite and satiety states, neurobiological states, as well as learned associations carried from previous experiences with the taste. Physiological states like hunger and satiety can shift subjective ratings of palatability for a particular taste in humans, in a phenomenon known as alliesthesia [22–24]. In rodents too, caloric hunger magnifies hedonic 'liking' reactions to palatable sweet taste, whereas satiety conversely reduces 'liking' [25,26]. Similarly, salt appetite modulates the hedonic impact of the intense saltiness taste of concentrated NaCl. For example, hypertonic concentrations of salt are normally aversive, in the sense that rats mostly display 'disgust' reactions when a seawater concentration of NaCl is placed into their mouths. However, when a hormonal state of sodium deficiency or salt depletion is induced, orofacial reactivity to the same intensely salty taste shifts to mostly positive 'liking' [20,27–31]. Conversely, modulation by learned associations can be induced by pairing a novel 'liked' sweet taste of saccharin as a Pavlovian conditioned stimulus (CS+) with an injection of lithium chloride, which induces malaise, as an unconditioned stimulus (UCS), to produce a conditioned taste aversion (CTA) so that subsequent exposures to saccharin taste instead elicit negative gapes and related 'disgust' reactions [32–37].

1.3. Hedonic hotspots: brain mechanisms of 'liking'

Our laboratory has studied brain generators of taste 'liking' by combining central neural manipulations of hedonic circuitry with the taste reactivity measure of 'liking' versus 'disgust'. In brief, pharmacological microinjections, excitotoxin lesions, optogenetic brain stimulation or inhibitions, etc. are used to systematically turn on or turn off particular neural systems in various brain locations during the taste reactivity test. This is coupled with an analysis of local Fos protein expression that allows us to more directly determine the spread of neuronal changes induced by a manipulation that alters 'liking', to identify localization of function, and map subregional localization of hedonic mechanisms within a brain structure. These studies have revealed a distributed network of limbic hotspots or small sites within subregions of cortical and subcortical structures in the rat that are capable of amplifying the hedonic impact (Fig. 1b) of sucrose taste [19,38–40]. Brain hedonic hotspots appear to be restricted to particular subregions of limbic structures such as rostrodorsal quadrant of medial shell of nucleus accumbens (NAc), caudolateral half of ventral pallidum (VP), a rostromedial portion orbitofrontal cortex (OFC), a far posterior zone of insula cortex (IC), and the parabrachial nucleus of the brainstem pons (PBN). Brain hedonic hotspots that generate 'liking' are embedded within larger mesocorticolimbic circuitry (spanning several entire structures) that is capable of generating incentive salience 'wanting', underlying the close interconnection between 'liking' and 'wanting' functions in reward [38,41–48]. In the following sections we discuss roles of these hedonic hotspots and mesocorticolimbic motivation circuitry in food reward, describe recent findings, and consider their potential roles in normal appetite and in clinical eating disorders and obesity.

2. Hindbrain structures compute early hedonic evaluations

Rudimentary hedonic processing of tastes begins to occur in the brainstem early in pathway of ascending gustatory signals [11,49–52]. For example, brainstem (4^{th}-ventricle) microinjections of a benzodiazepine drug that promotes GABA signaling enhanced positive 'liking' reactions to sweet taste, as did microinjections limited to the parabrachial nucleus of the pons, revealing that site as a brainstem hedonic hotspot [53,54]. Brainstem capacity for early hedonic-related processing was also revealed by classic studies of taste reactions in decerebrate rats and in anencephalic infants, both of which lack a functioning forebrain, yet are able to adequately respond to sucrose taste with positive affective reactions, and to quinine with aversive reactions [11,50]. Similarly, decerebrate rats show increases in positive 'liking' reactions to intra-oral sucrose after systemic administration of a benzodiazepine drug [55]. For humans and other primates, the causal role of PBN in food hedonics has sometimes been questioned [56,57] on the basis that in primates, gustatory neuroanatomical projections may ascend directly from the hindbrain nucleus of the solitary tract to forebrain thalamus and limbic structures, rather than making an obligatory intermediary relay in PBN as in rodents [58,59]. However, very little data actually exists yet on PBN roles in food reward functions in primates, including humans.

A crucial need for forebrain hierarchical contributions to normal 'liking' exists even in rats, evident from observations that many features of normal physiological and associative modulation of 'liking' reactions that occur in normal rats are missing in decerebrate rats. For example, decerebrate rats that are transected above the midbrain cannot learn or retain behavioral conditioned taste aversions to a nausea-paired sweet flavor that normally would switch 'liking' to 'disgust' reactions, suggesting that higher order affective processing involving experience and learning requires forebrain control and cannot be fully mediated by the brainstem on its own [32,35,37,50]. Caloric hunger similarly is reported to fail to enhance positive hedonic reactions to sweet tastes in decerebrate rats [60] unlike in normal rats [25,61], and inducing a hormonal salt appetite state fails to not enhance positive orofacial reactions to the taste of salt [62] again unlike in normal rats [20,27–31]. Those decerebrate failures suggest that the brainstem by itself cannot integrate physiological state or learned associations with tastes to modulate alliesthesia changes in hedonic orofacial reactions, even though some rudimentary processing of such modulating inputs has been reported in brainstem based on electrophysiological measures of neural activity [63–67].

3. The nucleus accumbens medial shell- hotspot for hedonic enhancement

Several decades of research have implicated the nucleus accumbens (NAc) as especially important in food motivation, and the NAc also plays important roles in controlling 'liking' reactions. Relevant to 'wanting', opioid, dopamine, and GABA/glutamate drug microinjections in the nucleus accumbens, especially in medial shell, can robustly enhance motivation to pursue and eat palatable foods [19,68–82]. Importantly however, the nucleus accumbens is a heterogenous structure with multiple anatomical subregions [83–89] that differentially mediate 'liking' and 'wanting', at least in response to particular manipulations [19,70,71,75,88]. Beyond the anatomical components of core and shell, there also are important subregional hedonic specializations within the shell, such as the hedonic hotspot within the rostrodorsal quadrant of medial shell. The rostrodorsal quadrant of NAc medial shell was first identified as an important hedonic hotspot (Fig. 1b) for 'liking' enhancement by Peciña and Berridge [19]. That hedonic mapping study used microinjections of the mu-opioid receptor agonist (DAMGO) to show that, only in the 1 mm^3 rostrodorsal subregion of medial shell did mu opioid stimulation enhance 'liking' reactions to sucrose taste, even though opioid stimulation anywhere throughout the entire NAc shell generated robust 'wanting' to eat reflected in increased food intake. Opioid stimulations at NAc shell sites other than the rostrodorsal hotspot completely failed to enhance sweetness 'liking' reactions at all, even decreasing sucrose 'liking' at a hedonic 'coldspot' site in caudal shell, despite still increasing 'wanting' to eat [19]. That and subsequent mapping studies revealed a clear NAc subregional dissociation between amplification of 'liking', which is limited to the rostral medial shell hotspot, versus of 'wanting', which can be generated by opioid and some other neurochemical manipulations throughout the entire medial shell as well as NAc core [19,68]. Further illustrating the unique hedonic features of this NAc hotspot, delta opioid and even kappa opioid agonists can enhance sucrose 'liking' similarly to mu opioid stimulations when microinjected within

the 1 mm^3 hotspot in rostrodorsal shell, although kappa opioid stimulation is known to produce negative aversive effects at many other brain sites [70].

Beyond opioid stimulation, orexin and endocannabinoid microinjections within the NAc rostrodorsal shell hotspot also can enhance sucrose 'liking' reactions (endocannabinoid enhancements might possibly also extend to caudodorsal shell) [90,91]. Endocannabinoids bind to presynaptic receptors on axonal terminals of NAc neurons, and influence the release of other postsynaptic neurotransmitters [92]. The ability for endocannabinoids in the NAc hotspot to enhance sucrose 'liking' appears to require local endogenous opioid mediation [93]. For example, if opioid-blocking naloxone is mixed in the same microinjection into NAc hotspot that contains the endocannabinoid anandamide, the simultaneous opioid blockade prevents the endocannabinoid stimulation from enhancing 'liking' reactions to sucrose at all. These findings seem in accordance with research showing that opioid and cannabinoid receptors often co-localize on the same neurons to form heterodimers, and that the two neurochemical signals can functionally interact together to influence motivation for food and drug rewards [94–96].

While opioid, endocannabinoid, orexin, and a few other neurotransmitters act in the NAc hotspot to enhance 'liking'[38,75,91,93,97–99], mesolimbic dopamine is notably missing from the list of hedonic neurochemical signals. Even in the NAc hotspot of rostrodorsal shell, synaptic dopamine stimulations, such as by amphetamine microinjection or genetic knockdown of the dopamine transporter that boosts dopamine levels in NAc synapses, completely fail to enhance 'liking' at all (although potently stimulating cue-triggered 'wanting' for sweet reward)[100,101]. Conversely, removing NAc dopamine signals via permanent 6-OHDA lesions or through pharmacological blockade can suppress 'wanting' during consuming and instrumental responding tasks [102–113], but fails to impair 'liking' reactions [107,114,115].

3.1. Desire versus dread from the nucleus accumbens shell

Another reflection of rostrocaudal differentiation of affective valence functions within the medial shell of NAc is an anatomical gradient of oppositely-valanced appetitive 'desire' vs fearful 'dread' motivations, revealed by localized microinjections that alter amino acid signaling in inhibitory ways along the anterior to posterior anatomical axis of NAc (Fig. 2a) [88]. For example, these opposite motivations can be produced by microinjections of either the glutamate AMPA antagonist DNQX, which block excitatory glutamate signals, or the $GABA_a$ agonist muscimol, which inhibit neuronal activity by opening Cl- ion gates. Microinjections of either drug at sites in rostral shell generate appetitive increases in food intake and can establish conditioned place preference [71,80,116–118]. By comparison, at sites in caudal shell the same pharmacological microinjections can promote active forms of negatively-valenced fearful behaviors such as distress vocalizations or escape attempts and bites when touched, or induce conditioned place avoidance, and elicit spontaneous defensive treading-burying (an antipredator reaction), while often simultaneously reducing appetitive food intake [75,88,119–121]. Intermediate sites between rostral and caudal poles of the NAc shell can produce a mixture of appetitive behavior and fearful behaviors (Fig. 2).

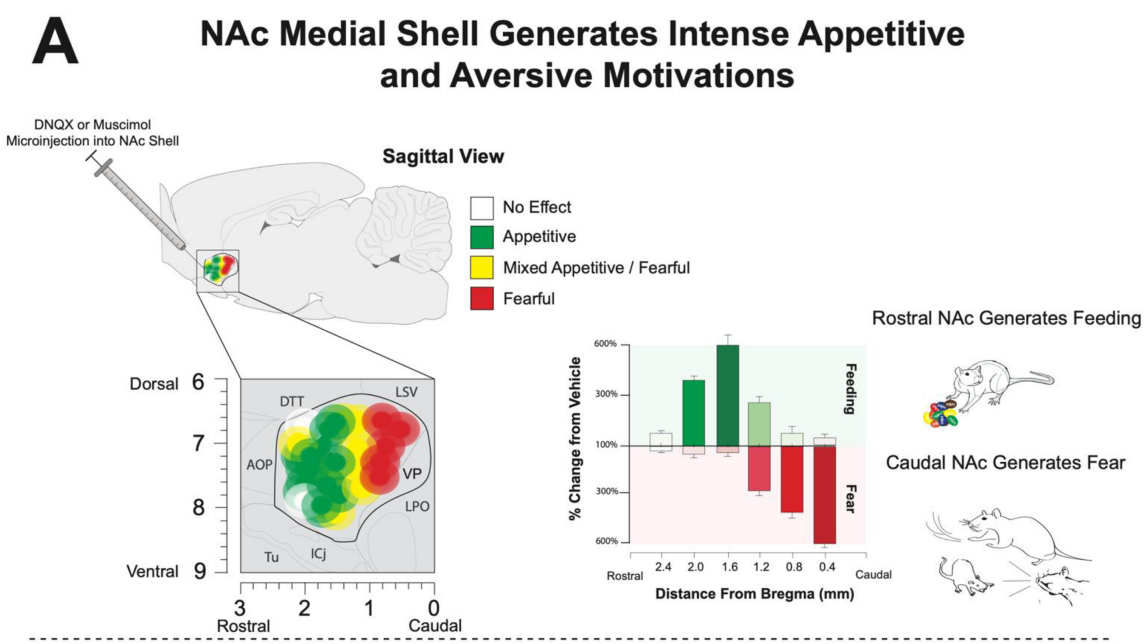
Importantly, the valence tuning of rostral vs caudal sites of medial shell is not static, or determined by anatomical position alone, but instead also can be altered to some extent by shifting the emotional ambience of the testing environment [116,119,120]. For example, rats that receive DNQX microinjections in a calm dark and quiet environment resembling their home cage, which rats prefer over standard laboratory conditions, show enhanced appetitive generation at more widespread sites that extend throughout most of the NAc shell, including caudal portions that otherwise generated fear. Conversely, DNQX microinjections in a more stressfully loud and bright environment shift many NAc shell sites from generating appetitive behavior into instead generating predominantly fearful behaviors [119,121].

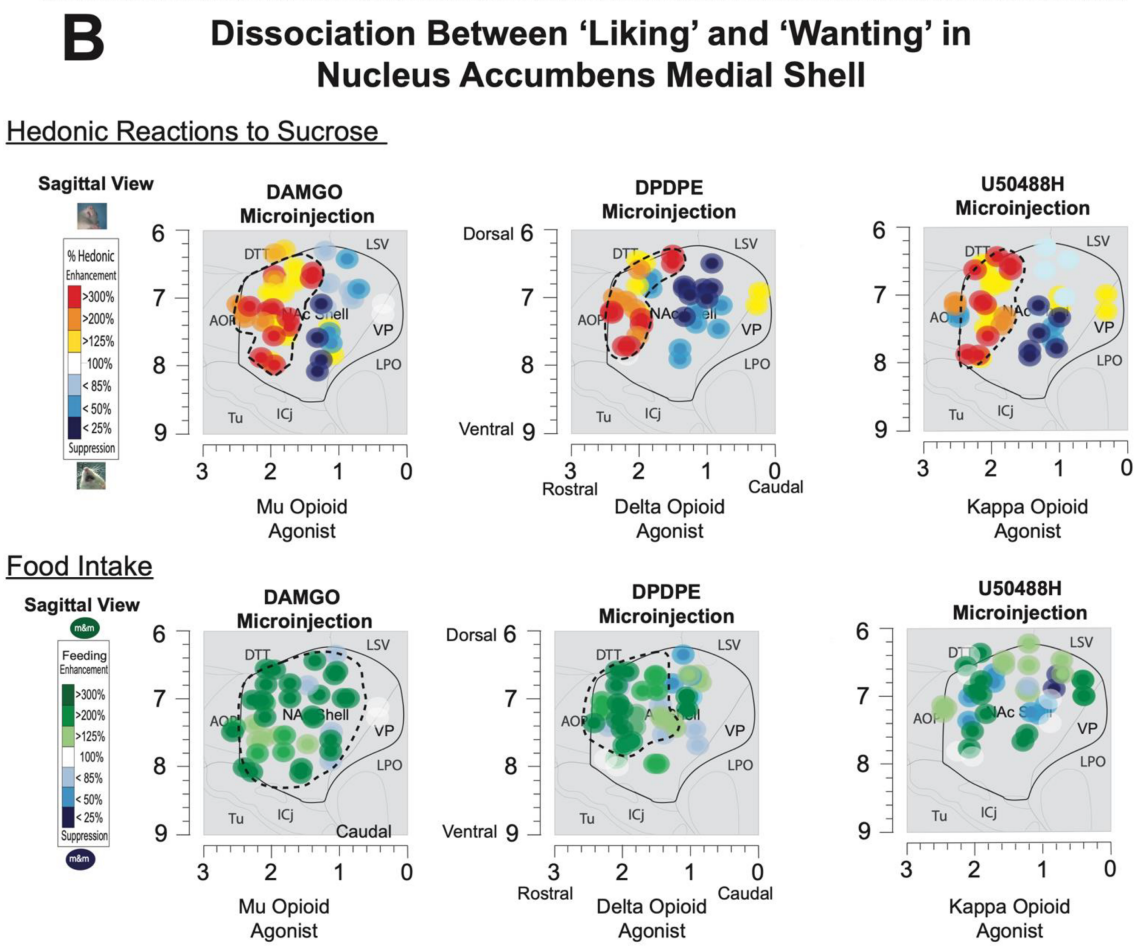
Precisely how do DNQX and muscimol actions in NAc shell elicit such intense motivations? A prominent hypothesis of NAc function has been that neuronal inhibitions in NAc medium spiny neurons generate reward motivation [122–131]. By this hypothesis, local NAc neuronal inhibitions suppress axonal release of GABA by output projections of NAc medium spiny neurons onto downstream structures including ventral tegmental area (VTA), lateral hypothalamus (LH), and VP, which consequently disinhibits those target structures into relative excitation [89,132–137]. This NAc inhibition hypothesis is supported by electrophysiological reports that NAc neurons often are phasically inhibited by presentations of reward stimuli, including drugs or palatable foods [124,127,128,138], (although c.f. [41,139-144]). Conversely, aversive bitter tastes and their cues have been reported by some investigators to typically evoke excitatory increases in NAc neuronal firing [128,138]. Similarly, learning a new aversive motivational value for a previously positive reward may shift the electrophysiological response of NAc neurons to tastes from inhibition to excitation. For example, inducing a learned Pavlovian taste aversion to a normally 'liked' saccharin solution, by pairing it with nausea, was reported to shift subsequent NAc neuronal responses to that taste from original inhibitions when still rewarding to predominately excitations when 'disgusting' [145]. Conversely, appetite states can induce alliesthesia to raise the incentive value of relevant tastes. For example, physiological sodium depletion that shifts affective reactions of intensely hypertonic NaCl tastes from 'disgust' to positive 'liking', was reported to simultaneously switch the NAc neuronal response to saltiness from excitation to inhibition [146].

By comparison, NAc output targets such as VP or VTA typically encode reward stimuli with electrophysiological excitations, so that as a taste becomes more positively 'liked', the greater the neuronal excitation in the posterior VP hotspot [29,147].Therefore, one hypothesis to explain how microinjections of DNQX or muscimol in NAc shell generate intense motivations is that they inhibit the activity of local NAc neurons, shutting off axonal GABA release, and so disinhibit or activate downstream VP, LH and VTA targets [126]. DNQX would merely reduce NAc activity relative to normal levels by blocking excitatory glutamate inputs onto local neurons, whereas muscimol would act on GABA-A receptors to directly open Cl- gates to more powerfully inhibit NAc neurons.

The neural difference in degree of NAc inhibition can create some categorical psychological consequences. Accordingly, DNQX microinjection in rostral shell increases food intake as a form of 'wanting' to eat, but does not enhance 'liking', whereas muscimol in the rostral shell hotspot increases both 'wanting' and 'liking' together [99]. Similarly, DNQX in caudal shell only increases motivated 'fear' behaviors, whereas muscimol in caudal shell both increases 'fear' motivation and induces excessive 'disgust' affective reactions to sucrose. Consistent with the idea that NAc inhibition releases projection targets into activation, such NAc drug microinjections increase neuronal activity reflected in Fos expression in downstream structures, including LH, VTA, VP, and paraventricular thalamus (PVT) [116,148,149].

To test whether local neuronal inhibition is actually necessary for DNQX microinjections in NAc shell to cause intense motivations, Hannah Baumgartner, Shannon Cole, and Jeffrey Olney in our laboratory recently tested whether opposing DNQX-induced inhibitions in NAc with optogenetic channelrhodopsin (ChR2) stimulation at the same site would reverse the desire or dread motivations otherwise produced by the DNQX microinjection [116]. They found that the answer was yes: exciting NAc neurons at the same local site as a DNQX microinjection reversed the ability of the microinjected DNQX drug to induce increases in appetitive eating behavior and food intake at rostral shell sites, and similarly reversed the elicitation of defensive or fearful behavior at caudal sites [116]. Further, in support of the hypothesis that





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NAc neuronal inhibition may be sufficient by itself to generate an intense motivation, Shannon Cole and Jeffrey Olney have also found preliminary evidence that acute inhibition of local neurons in NAc shell, such as by optogenetic inhibitory opsins, may directly elicit increases in motivated behavior [150,151]. For example, rats who received inhibitory viruses targeted at rostral NAc shell sites showed laser-bound increases in eating behavior. These pilot observations support the hypothesis that neuronal inhibitions in NAc shell can be a sufficient cause of increased motivation, as well as being a necessary part of the mechanism by which NAc DNQX microinjections elicit desire or dread [116].

Fig. 2. 'Liking', 'wanting', desire, and dread in the nucleus accumbens medal shell. A) Top shows amino acid disruptions (via glutamate AMPA receptor antagonist DNQX or $GABA_A$ agonist muscimol) in the medial shell of the nucleus accumbens reveal a rostral to caudal organization of intense motivations. Manipulations into anterior sites produce voracious feeding (shown in green). The same microinjections at posterior sites generate fearful motivations (depicted in red) such as distress calls, bites, escape attempts, and defensive treading. DNQX or muscimol in mid NAc medial shell produce a mix of appetitive and aversive motivations. B) Bottom-top panel shows dissociations between 'liking' and 'wanting' in the nucleus accumbens medial shell following microinjections of mu-opioid agonists (DAMGO), delta-opioid agonists (DPDPE), and kappa-opioid agonists (U50488H). Similar patterns of hedonic enhancements were found after mu, delta, and kappa opioid agonists. While microinjections into anterior dorsal (in red) sites magnified 'liking' expressions to sucrose solutions, posterior manipulations oppositely suppress 'liking' expressions (in blue). Bottom panels shows the dissociable effects of mu, delta, and kappa manipulations in the nucleus accumbens medial shell on free-feeding. Mu-opioid agonists generated feeding throughout the entire medial shell. By comparison, delta opioids generate feeding within anterior sites overlapping with the hedonic hotspots. Finally, kappa opioid stimulation did not reliably generate feeding at any site despite generating intense 'liking' expressions in the rostrodorsal quadrant. Adapted from Castro & Berridge (2014).

3.2. Neurobiological mechanisms of hedonic hotspots

What neurobiological features of the hedonic hotspots may explain their unique capacities for hedonic enhancement? For example, in rats the NAc hedonic hotspot is a 1 mm^3 quadrant of rostrodorsal medial shell, and is the only NAc shell or core site where opioid, endocannabinoid, and orexin stimulations amplify 'liking reactions to sweet taste [70,75,97,99,152]. Neurobiological evidence suggests that the rostrodorsal subregion of NAc medial shell that contains the hotspot may also have unique neuroanatomical features that differ from other subregions of medial shell [85,86]. For example, one anatomical connectivity tracing study reported that the rostrodorsal subregion of NAc medial shell receives inputs from a distinct subregion of infralimbic cortex in rats, corresponding to Area 25 of the anterior cingulate cortex in humans; those infralimbic inputs to the rostrodorsal hotspot differ from the cortical inputs to other subregions of medial shell [85]. Similarly, the NAc hotspot in rostrodorsal shell sends outputs to distinct subregions of LH and VP that are different from the LH/VP output targets of other NAc shell subregions [85]. Finally, the VP target in turn sends its projections to a particular anterior thalamus subregion that finally projects back to the original infralimbic/A25 cortical subregion, forming a closed-circuit loop that runs through the NAc hotspot. In other words, the NAc hedonic hotspot appears to belong to a distinct cortical-striatal-pallidal-hypothalamic-thalamic-cortical circuit loop that is segregated from other loops running through different subregions of medial shell [85]. Another neuroanatomical study reported that the rostrodorsal hotspot of NAc medial shell has additional distinct features, such as dense projections to subregions of lateral hypothalamus that other NAc subregions may not project to [86]. The rostral hotspot of NAc medial shell also has distinct neurochemical features, such as a higher incidence of parvalbumin neurons than in the caudal coldspot of medial shell [153], and distinct neurochemical responsiveness to mu opioid stimulation [154]. By contrast, the caudal subregion of medial shell, which contains the hedonic coldspot where mu opioid stimulation by DAMGO microinjection (as well as delta or kappa opioid stimulations) oppositely suppresses 'liking' (although still increasing 'wanting' to eat, at least for mu stimulation), instead has transitional features shared with extended amygdala structures [86]. Which, if any, of these neurobiological features underlie the hotspot's special ability to enhance 'liking' reactions, or rostrocaudal gradients in affective functions of medial shell? The answer to that question is not yet known, but such evidence at least shows that it has a number of unique neuroanatomical and neurochemical features which could eventually be part of that explanation.

4. Ventral pallidum hedonic hotspot

The ventral pallidum receives the densest output projections from nucleus accumbens [132,133,155,156], and ventral pallidum is important in both reward and aversion [29,38,157–174]. The posterior half of the ventral pallidum of rats contains another 0.8 mm^3 hedonic hotspot where microinjections of the mu-opioid agonist DAMGO more than doubles hedonic 'liking' reactions to sucrose [38,98]. Similar to NAc, though reversed in front to back valence polarity, the VP appears organized along a bivalent anatomical gradient [38]. For example, local opioid stimulation by DAMGO microinjection in the posterior (the same subregion is also lateral and dorsal in VP) half of VP enhanced sucrose 'liking' reactions (and increased food intake), whereas the same opioid stimulation in anterior (which is also medial and ventral) VP oppositely suppressed positive 'liking' reactions (and suppressed food intake), revealing a rostral VP hedonic coldspot. It may be related that a human neuroimaging study found similar rostrocaudal bivalence, in that anterior VP was reported to activate in response to disgusting images, whereas posterior VP activated to images of palatable foods [170,175]. However, anterior VP still can participate in generating incentive motivation or 'wanting' for rewards. A different manipulation of anterior VP, namely local GABA blockade induced via bicuculine antagonist microinjections to disinhibit or excite anterior VP neurons, caused increases in food intake [38]. Similarly, anterior VP has also been shown by others to be important in motivation to pursue drug and foods rewards [166,169].

Within the hedonic hotspot of posterior VP, orexin microinjections also have been found to enhance 'liking' reactions to sucrose, just as opioid microinjections do [90]. Furthermore, recent pilot studies using optogenetic stimulation suggest that directly exciting VP neurons via channelrhodopsin in the posterior hotspot similarly enhances positive 'liking' expressions, as well as increasing 'wanting' to eat [176–178]. By comparison, optogenetic stimulation of LH neurons adjacent to VP, increased only food intake but not hedonic reactions to sucrose, indicating it is possible to increase 'wanting' without increasing 'liking' [176–179]. Similarly implicating these subregional differences for VP in reward, others have reported that frequency thresholds for electrical self-stimulation in VP are lower in posterior subregions of VP than anterior subregions supporting a special role for caudal ventral pallidum in some reward-related functions [180]. However, as mentioned, anterior VP neurons also contribute to motivation to seek reward, at least in some neurobiological modes and in some situations [38,98,166,169,172]. The functional flexibility and multiple roles of VP subregions is a topic that deserves further investigation.

4.1. Hotspots recruit each other to unanimously enhance 'liking' as an integrated hedonic circuit

Some evidence suggests that stimulating one hedonic hotspot (e.g., in either VP, NAc, OFC, or insula) recruits neural activation of other hotspots in different structures, activating the entire array of distributed hotspots as a unitary hedonic circuit to enhance 'liking' reactions [1,17,39,98,176,178]. For example, opioid stimulation of the NAc hotspot via NAc DAMGO microinjection recruits distant Fos activation in the VP hotspot when enhancing 'liking' reactions to sucrose taste [98], and similarly amplifies electrophysiological firing patterns of neurons in the VP hotspot that encode hedonic 'liking' for sucrose [147]. Conversely, local opioid stimulation in the VP hotspot reciprocally recruits Fos activation in the NAc hotspot when enhancing sucrose 'liking' [98]. Similarly, in the cortical hedonic hotspots in OFC or insula, DAMGO or orexin microinjections that enhance 'liking recruit distant Fos increases in subcortical VP and NAc hotspots [39]. Furthermore, evidence suggests that mutual recruitment among hotspots

may be causally *necessary* for any hotspot stimulation to enhance 'liking' reactions. Blocking opioid receptors with a naloxone microinjection in one hotspot (either NAc or VP) while simultaneously stimulating the other hotspot, prevents any hedonic enhancement that otherwise would be generated by the DAMGO microinjection in the other hotspot [98]. All in all, these studies suggest that the hedonic hotspots act together as a unified functional circuit for hedonic enhancement, and that disruption of that full circuit recruitment can prevent opioid hotspot stimulation from enhancing affective responses to palatable tastes.

However, while hedonic hotspots recruit each other into action, the exact neuroanatomical connections by which they do so remains as yet unknown. Anatomical tracing evidence suggests that the hotspots do not directly project to each other [85,86]. For example, although NAc and VP as whole structures are heavily interconnected, the NAc subregion of rostrodorsal medial shell that contains the hedonic hotspot primarily projects to the anterior VP that contains the hedonic coldspot and not to the posterior VP hotspot [85,86]. Conversely, the posterior VP hotspot sends reciprocal efferents primarily to the lateral core of the NAc, not to the rostral medial shell that contains the NAc hotspot [85,86,136,155]. In addition, while NAc projects to PBN, which may be a brainstem hedonic hotspot [40], NAc-PBN projections primarily arise from the ventral quadrant of the medial shell, not the rostrodorsal shell quadrant that contains the NAc hedonic hotspot [136]. Similarly, the subregion of prefrontal cortex that projects directly to the NAc shell hotspot is the infralimbic region of ACC (equivalent to Area 25 in humans), and not the anteromedial OFC that contains its cortical hedonic hotspot [85]. A lack of point to point projections among hedonic hotspots indicates that intermediary anatomical relay sites must exist to functionally connect hedonic hotspots together, but the precise identity of these relay sites and connections is not yet known.

4.2. Ventral pallidum hotspot: crucial to normal 'liking'

Although all hedonic hotspots can produce *gains* in hedonic 'liking' reactions when appropriately stimulated, damage to most hotspots does not produce *loss* of normal 'liking' reactions. The posterior VP hotspot is the only known brain region where excitotoxic or electrolytic neuron-destroying lesions can result in loss of normal 'liking' reactions and replacement by excessive 'disgust' reactions even to sweet taste (Fig. 3). These effects can persist for weeks, underlining the special importance of VP hotspot to normal hedonic function [168,181]. For example, after VP lesions, normally 'liked' sucrose taste instead elicits 'disgust' reactions such as gapes, headshakes, paw treading, etc., as though the sweet taste had become bitter or otherwise strongly unpalatable [168,181].

Classic studies in the 1960s using large electrolytic lesions originally attributed lesion-induced 'disgust' to damage to the LH [182,183]. However, subsequent more precise mapping using smaller excitotoxin lesions indicated that the crucial 'disgust-induction' lesion site was not in LH, but was actually the hedonic hotspot of posterior VP [168]. The large electrolytic lesions to LH of earlier studies typically also damaged posterior VP in addition to the LH, which may account for the negative affective reactions reported by early LH studies [1]. In other words, only damage to the VP hotspot produces dramatic loss of hedonic function. Both LH lesions and VP lesions can cause loss of 'wanting' to eat or drink, producing severe adipsia and aphagia, so that lesioned rats require intragastric feeding and hydration to be kept alive. But if they receive that intense nursing for days to weeks, rats slowly begin to independently feed again on soft palatable food, eventually progressing to normal eating and then drinking behavior, although some subtle ingestive functions still remain impaired [183–186].

Beyond 'disgust' induction by posterior VP lesions, pharmacological inhibition of posterior VP hotspot neurons, such as by microinjections of GABA agonists, also can induce temporary excessive 'disgust' to sweetness that lasts at least for hours [181,187]. Excessive 'disgust' induced by pharmacological muscimol/baclofen microinjections in the VP hotspot, as well as by posterior VP lesions, has been interpreted as a 'release phenomenon' [181,187], a century-old concept from the early neurologist Hughlings-Jackson for explaining how a neuronal dysfunction produces an active behavioral disorder [188]. That is, the excessive disgust probably results from negative-affect generating circuitry in other brain structures outside the VP, which is released or disinhibited by damage to the positively-valenced hedonic hotspot of posterior VP [181,187].

Our lab is currently testing whether direct optogenetic inhibition of VP neurons can similarly cause loss of hedonic function. Our recent pilot results, using the modified inhibitory channelrhodopsin (SwiChR + +) opsin, which opens negative Cl- ion gates in the neuronal membrane, allowing influx of Cl- ions to make the neuron more negative and less able to fire (similar to an IPSP) [189], suggest that optogenetic inhibition of neurons in the posterior VP hotspot may suppress positive 'liking' reactions elicited by sucrose taste, and possibly also increase negative 'disgust' reactions to an already aversive quinine solution (Morales & Berridge, 2019 and personal observations). Optogenetic induction of neuronal inhibition may be less intense than that induced by pharmacological GABAergic microinjections, producing weaker behavioral consequences, but results so far suggest that optogenetic inhibition may be enough to suppress positive hedonic valence or increase negative valence under some conditions.

4.3. Potential neurobiological basis of hedonic differences between posterior VP vs anterior VP: 'liking' hotspot vs coldspot

What accounts for differences in reward functions between anterior and posterior subregions of VP? One answer may lie in distinct neurobiological features of their neurons, as the ventral pallidum contains multiple types of neurons which can differ in their electrophysiological signatures [191,192], and in their neurochemical identities across anterior-posterior subregions [173,193–196]. For example, electrophysiologically, VP is thought to contain either Type I or Type II cells. The anterior VP contains a mixture of Type I and Type II cells, whereas posterior VP hotspot contains predominantly Type II cells [192]. Type I cells are easily excitable, tonically active, and larger than Type II cells. Type II neurons by contrast exhibit low basal firing rates, require higher thresholds for stimulation, and share some morphological features with NAc MSNs.

Neurochemically, approximately ~74% of VP neurons are GABAergic, ~11% are cholinergic, and ~15% are glutamatergic, in mostly separate and non-overlapping populations [173,195,197]. VP glutamate neurons are concentrated in anterior VP [173,197], near the site of the hedonic coldspot [38], whereas posterior VP is more heavily GABAergic. A number of studies have suggested that VP GABAergic neurons contribute primarily to reward-related motivation, whereas VP glutamatergic neurons contribute to aversive motivation, by oppositely modulating the activity of their overlapping downstream targets such as LH, VTA, and lateral habenula (LHb) [162,171,173,197–201].

Are VP GABAergic neurons important in amplifying 'liking' and 'wanting' for food rewards? To better answer this question, pilot studies in our lab have recently begun to explore this issue via selective optogenetic stimulation of GABA neurons in VP using a Cre-dependent promoter to express ChR2 in the ventral pallidum of GAD-Cre rats [202]. Our preliminary experiments indicate that optogenetic stimulation of VP GABA neurons generates robust feeding, biases and narrows preference for a laser-paired sucrose reward, and promotes self-stimulation [178,190]. Most interestingly, optogenetic stimulation of posterior VP GABA neurons additionally appears to enhance 'liking' reactions to sucrose taste, as well as 'wanting' to eat [190]. By contrast, inhibiting the same posterior VP GABA neurons with a Cl- ion channel opsin (iC + +) may suppress 'liking' reactions [190]. Thus, our preliminary results so far support the hypothesis that it is GABAergic neurons in the posterior VP hotspot that are responsible for both gain of function and loss of function changes in hedonic 'liking' reactions.

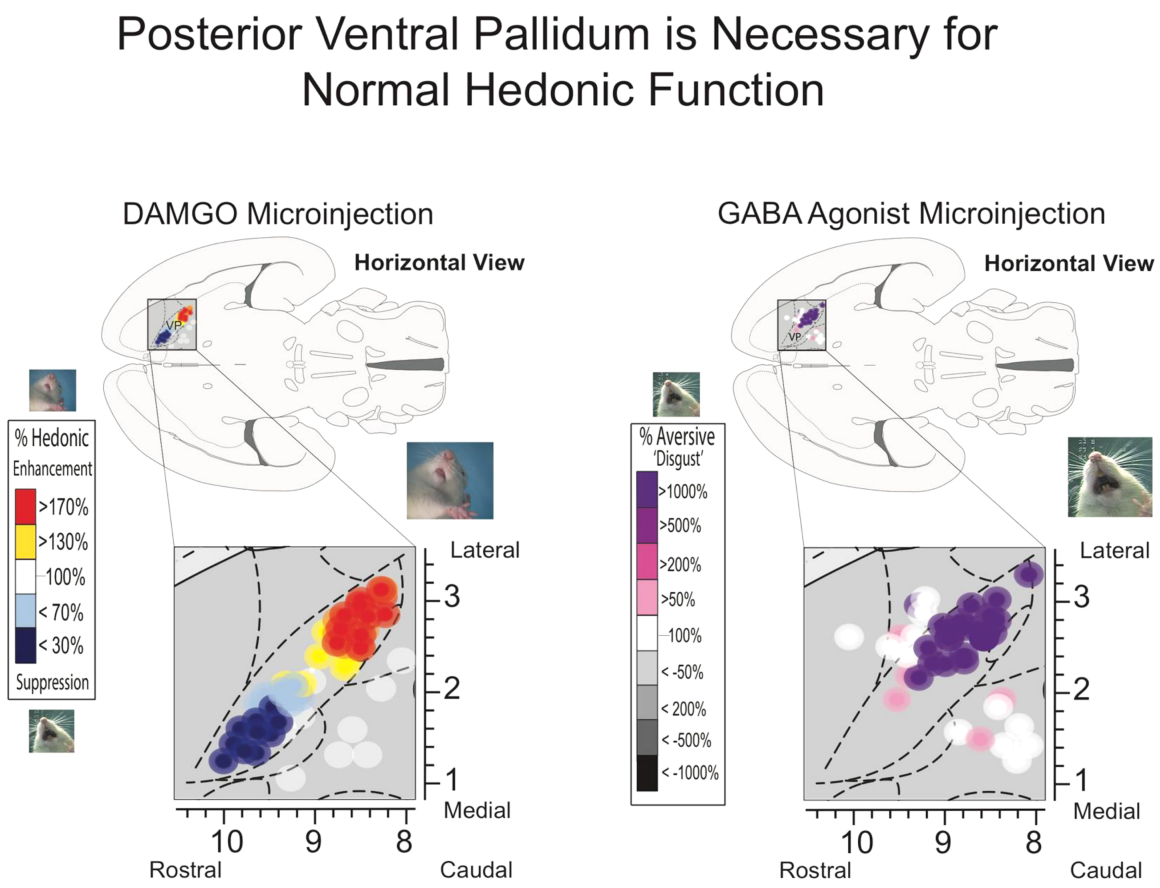

Fig. 3. The posterior ventral pallidum is necessary for normal hedonic function. Microinjections of mu-opioid and orexin agonists (left) into the pallidum revealed a rostral to caudal organization of hedonic function. Stimulation of the posterior ventral pallidum 'hotspot' causally amplifies sucrose orofacial expressions ('liking') while the same manipulations in the caudal hedonic 'coldspot' suppress them. Temporary inactivation of posterior VP via GABA agonists generates a reversal of hedonic function so that normally 'liked' sucrose solutions elicit aversive 'disgust' reactions. Adapted from Smith & Berridge (2005) and Ho & Berridge (2014).

Additionally, GABA neurons throughout the entire VP may more generally participate in motivation 'wanting' for rewards [38,171,173,181].

5. Cortical hedonic hotspots – insula and orbitofrontal cortex

Beyond subcortical hedonic hotspots, two hotspots in cortex were recently discovered by our lab: one in the anteromedial orbitofrontal cortex, and another in the far-posterior insula cortex of rats. Both of these cortical hedonic hotspots similarly caused hedonic gains of function in sucrose 'liking' reactions in response to drug microinjections that deliver mu opioid stimulation or orexin stimulation to local neurons [39]. By contrast, the same opioid/orexin microinjections in other limbic cortex sites outside these hotspots, even in other regions of OFC or insula, fail to enhance sucrose 'liking' (and some sites suppress 'liking'), even if they stimulate 'wanting' to eat [39].

The finding that hedonic hotspots exist in the cortex was surprising in one sense, because lesions in cortical areas do not reliably reduce hedonic reactions in either rats or humans [203–208]. That is, damage to the orbitofrontal cortex or insula does not necessarily cause loss of 'liking' reactions to foods or other pleasant events. However, gain of hedonic function is different from loss of hedonic function, and in a neural hierarchy a superior structure such as cortex might plausibly cause hedonic gains by activating subcortical hedonic circuitry, without causing hedonic losses when damaged, if the subcortical circuitry is capable on its own of generating basic hedonic reactions. In any case, human neuroimaging data and animal electrophysiological studies have also reported that orbitofrontal cortex and insula at least encode hedonic values of food and other rewards [3,209–215].

In keeping with the hierarchical triggering and cross-hotspot recruitment notions, DAMGO or orexin into the OFC or insula hotspot that enhanced 'liking' caused distant increases in neural activation measured by Fos expression in the hedonic hotspots in NAc and VP. This supports the hypothesis that 'liking' enhancements caused by neurochemical stimulation of a particular hotspot are mediated by recruiting the entire hedonic circuitry across the brain to activate all hotspots together [1,39,98,147]. The two cortical hedonic hotspots were also shown to bookend a long 'hedonic coldspot' strip between them where orexin and DAMGO microinjections oppositely suppressed sucrose hedonic reactions (i.e., stretching from lateral orbitofrontal cortex through insula). Orexin or opioid microinjections in the coldspot strip produced a pattern of Fos changes across the brain quite different from cortical hotspot microinjections, suggesting activation of a separate anti-'liking' neural circuitry that dampens positive hedonic reactions [39]. It is interesting that an overlapping subregion of posterior insula (posterior to gustatory sensory cortex) also appears crucial to taste aversion learning [216].Increases in motivational 'wanting' to eat, measured as increased consumption of chocolate M&M candies were also produced by all OFC hotspot microinjections and some insula hotspot microinjections, and were also produced by a number of non-hedonic sites in infralimbic cortex, prelimbic cortex, or anterior cingulate cortex (ACC), and even by some sites in the intervening hedonic coldspot strip of posterior-lateral OFC and anterior insula [39].

Current pilot studies in our lab are investigating whether optogenetic ChR2 excitation of neurons in these cortical OFC and insula hedonic hotspots can drive 'liking' enhancements, similarly to opioid or

orexin neurochemical stimulations of those same OFC or insula subregions. Our preliminary data suggest that optogenetic excitation of neurons in either the anteromedial OFC hotspot or in the far-posterior insula hotspot may indeed double 'liking' reactions to sucrose taste [190,217]. However, more mapping may be needed given that a recent report suggested that optogenetic stimulation in anterior insula of mice promotes positive affective reactions whereas posterior insula stimulation evoked 'disgust' reactions [218,219]. We also note that some others have reported optogenetic laser self-stimulation of glutamate neurons in insula regions, or of insula-to-amygdala projections [218,220], although others report avoidance of laser-stimulation at some insula sites [218,220,221], suggesting the insula picture in particular may need further clarification.

6. Distributed brain mechanisms of 'wanting': nucleus accumbens core, neostriatum, amygdala, lateral hypothalamus and beyond

The mesocorticolimbic brain system that generates incentive salience or 'wanting' is anatomically larger than the hedonic hotspot network, including entire structures of NAc, central nucleus of amygdala and parts of neostriatum, etc. Neurochemically it includes dopamine and glutamate, as well as opioid orexin, and endocannabinoid transmitters so that its functionally more robust than the 'liking' network (Fig. 1b). [222–231]. This robust network can generate intense incentive motivation and appetite, even without enhancing hedonic 'liking'.

6.1. Nucleus accumbens core

Incentive motivation to eat can be amplified by manipulations such as opioid-stimulating microinjections throughout the entire nucleus accumbens, including both core and shell. Regarding simple (unconditioned) food intake, some studies have reported that various manipulations in the core as well as shell can enhance free-feeding in rodents, albeit many report less robust effects from the core compared to shell [73,80,81,152,232–236]. However, both core and shell have been shown to potently alter learned instrumental responding for palatable rewards in rats [237–239], which may be due specifically to enhanced cue-triggered 'wanting' or incentive salience as shown in an elevated Pavlovian-instrumental transfer (PIT) paradigm after DAMGO or amphetamine microinjections in NAc [239]. Interestingly, lesions to the core, but not shell prevent reallocation of food-related responses in a decision-making task where rats are given the option to lever press for a preferred palatable sucrose reward vs. eating normal laboratory chow that is freely available within the chamber [240].

Overall, the NAc medial shell is especially important for its role in generating intense incentive motivation, whereas the core has been reported to be preferentially activated by reward-predictive cues [1,70,97,146,241–246]. For example, previously drug-associated cues can trigger drug-seeking [247]. Conditioned instrumental responding may be associated with Fos expression in D1 and D2 core medium spiny neurons [143], and specific forms of PIT, which depend upon association of cues with the learned identities of specific foods, are especially reliant on NAc core [248]. Conversely, decreasing dopamine signaling in the core can suppress sign-tracking behavior in rats [249,250].

6.2. The dorsal neostriatum

Parts of the neostriatum, sometimes called dorsal striatum, also participates in generating incentive motivation. Human imaging studies have long shown that food-related cravings are associated with activation of the dorsal striatum [251,252]. This human striatal response to food has been reported to become blunted in those who frequently eat a specific type of food. For example, people who frequently eat ice cream may show suppressed dorsal striatal activation to a milkshake [253]. Similarly, rodent studies have shown that prolonged exposure to a high sugar and fat diet resembling a western diet can alter glutamate, opioid, and dopamine transmission in the dorsal striatum [254]. Lack of dopamine in the dorsal striatum is associated with severe aphagia that ultimately results in death, further implicating neostriatum role in feeding and appetite [255–257].

The dorsomedial part of the neostriatum (DMS) is known for a role in goal-directed learning and motivation [258–265], but it may also play a role in directly generating appetite. For example, microinjection of mu-opioid stimulating DAMGO directly into the dorsomedial neostriatum causes rats to increase food intake [43]. Similarly, levels of the endogenous opioid neurotransmitter enkephalin within dorsomedial neostriatum surge spontaneously when rats begin to eat a palatable food, consistent with an appetite-promoting mechanism [43]. Dorsmedial participation in generating motivation to eat is consistent with evidence that opioid-stimulating microinjections throughout much of the neostriatum can cause increases in food intake [43,68,73,77,266]. However, DAMGO microinjection in the dorsomedial neostriatum that enhances 'wanting' to eat sweet food is not accompanied by any enhancement orofacial 'liking' reactions to sweetness, suggesting a specific incentive motivation but not hedonic contribution [43]. Finally, selective inhibition in dorsomedial neostriatum of the dopamine D2 'stop' pathway, while preserving the D1 'go' pathway, invigorates motivation to work for a palatable reward during a progressive ratio task [267]. Overall, these results suggest that opioid and dopamine signals in the dorsomedial neostriatum play an important role in modulating incentive motivation to eat.

By comparison, the dorsolateral part of the neostriatum (DLS) has traditionally been described for roles in habit formation [262,268–272], model-free stimulus-response associations [273–277], motor sequences and direct movement control [278–283]. However, DLS also plays a role in motivation for reward. For example, optogenetic stimulation of the direct-path (D1 dopamine receptor expression) and indirect (D2 receptor expressing) neostriatal neurons can promote place-based self-stimulation and avoidance, respectively [284].

The DLS also helps generate incentive salience for learned food cues, visible in an autoshaping or sign-tracking paradigm [42]. Microinjections of DAMGO or of amphetamine into the DLS can enhance attraction to sucrose-related cues. In this situation, rats learn that the insertion of a metal lever into the chamber (Pavlovian CS+) predicts a free sucrose pellet (UCS) [42]. Typically, one group of rats, known as sign-trackers (STs), attribute high incentive salience directly to the predictive lever, and approach and nibble the CS+ lever [285–287]. Another group of rats, known as goal-trackers (GTs), instead are attracted to the sucrose-pellet dish or goal, approaching and nibbling the metal dish. When mu-opioid or dopamine signaling was enhanced in the dorsolateral neostriatum by microinjection of DAMGO or amphetamine, 'pure' ST rats that always go to the lever CS+ became even more attracted towards their CS+ lever than before, suggesting intensified incentive salience that is even more narrowly-focused on the CS+ [42]. Similarly, GTs became selectively even more attracted toward their dish, again suggesting intensified and motivation focused on their preferred stimulus. In Pavlovian parlance, the dish is also a type of Pavlovian CS+, but one that is *contiguous* to sucrose UCS in space and time, whereas the lever is a *predictive* CS+ whose presentation is correlated with UCS delivery; both CS+ types are traditionally recognized by Pavlovian learning theory.

Further evidence from the same study supported the conclusion that these enhancements of conditioned responding were due to increased motivational attraction to the respective CS+s, rather than to intensified habits. For example, DLS microinjections of DAMGO also increased sign-trackers willingness to learn and work on a new instrumental nosepoke task in order to earn presentations of their lever CS+ (i.e., increased instrumental conditioned reinforcement of an entirely new behavioral response, showing magnified 'wanting' for the CS+ as a feature of incentive salience) [42]. Similarly, sign-trackers flexibly followed their lever to a new location in the chamber if it moved after

DAMGO microinjections in DLS, rather than repeating the same habitual response of going to the old location.

Amphetamine microinjections that promoted dopamine release in dorsolateral neostriatum made 'mixed sign-trackers', which previously mostly went to lever CS+ but sometimes made a 'goal-tracking' defection toward the dish CS+, actually switch to become instead purer goal-trackers, again replacing the more habitual response with a different one. That is, DLS dopamine stimulation appeared to enhance motivated attraction to the UCS-proximal dish CS+ at the expense of the predictive lever CS+'s attractiveness for those individuals [42]. Thus, the dorsolateral neostriatum may have important roles in both amplifying incentive motivation and in selecting which competing cues for food reward become most attractive.

A different view of the dorsal neostriatum's role in eating was recently suggested by Ivan de Araujo, Mark Schatzker, and Dana Small [288], but may possibly be reconciled with our own view expressed above. De Araujo et al. argue that less reliant are the hedonic properties of foods like flavor, taste, and aroma in their ability to generate excessive overeating [288]. They note that vagal sensory projections from the viscera to the hindbrain sensory nucleus of the solitary tract carry signals about caloric content arising from food digestion, and show vagal signals may trigger dopamine release from substantia nigra axons in the dorsal neostriatum [288]. Strikingly, direct optogenetic stimulation of vagal-to-medulla projections supports laser self-stimulation, which they suggest reveals a response-reinforcing signal [289]. Nutrient conditioning of flavor preferences similarly relies on intact dopamine signaling in the dorsal striatum [290,291]. The vagal-neostriatal dopamine reinforcement signal, De Araujo et al. suggest, does not enhance food hedonic palatability but rather strengthens behavior more directly, similar to traditional stimulus-response (S-R) habit stamping-in theories. As de Araujo et al. put it "In other words, reinforcement and habit acquisition can occur seamlessly in the absence of any consciousness-borne flavor appreciation." (p. 153, [288]).

The hypothesis of de Araujo et al. that vagal nutrient signals act in neostriatum without any "consciousness-borne flavor appreciation" is consistent with our view that neostriatal dopamine fails to enhance 'liking'. The hypothesis that vagal signals promote learned attraction to foods is also consistent, as de Araujo et al. point out, with many earlier demonstrations by Anthony Sclafani, Kevin Myers and colleagues that intra-gastric calories are able to act as a UCS to establish a conditioned preference for a paired CS flavor in rats, increasing 'wanting' to eat that food whether or not it also increases 'liking' for the more 'wanted' CS flavor [290,292–295]. For example, nutrient conditioning can enhance 'wanting' without enhancing 'liking' reactions for a bitter/sour CS+ flavor [295], although it can enhance both 'wanting' and 'liking' together if the CS+ flavor was initially sweet or palatable [294]. Thus, enhanced 'liking' is a possible accompaniment but not an obligatory component of nutrient conditioned taste preferences.

Based on all this, we would suggest a possible alternative interpretation to S-R habit reinforcement for the role of vagal-evoked dopamine in neostriatum. That is, given that dopamine in dorsal neostriatum can enhance the incentive salience of specific food cues, as described above [42], vagal-evoked dopamine release in dorsal neostriatum might similarly promote 'wanting' to eat evoked by particular food cues associated with vagal stimulation. This would be an incentive motivation mechanism, probably maximally triggered by particular foods that are both caloric and palatable, rather than a behaviorist response stamping-in mechanism, and would not be confined to habits but could promote eating even if food seeking required novel responses or if the food cues moved to new settings.

6.3. The amygdala

The focus of 'wanting' onto particular targets is a function in which amygdala also plays an important role. The amygdala is composed of multiple nuclei, including the basolateral nucleus of amygdala (BLA), the medial nucleus of the amygdala (MeA), and the central nucleus of amygdala (CeA) [296–303], and of these, the CeA is particularly important to generating intense incentive salience. The CeA has 'striatal-level' status within a cortico-striatal-pallidal macrosystem organization of forebrain structures (in which the BLA has cortical status, and the bed nucleus of stria terminalis (BNST) holds 'pallidal status' within the extended amygdala complex [297]). The striatal-level status of the CeA may be relevant to its ability to amplify appetitive motivation. For example, the CeA contains many GABAergic neurons that receive BLA glutamate inputs and mesolimbic dopamine inputs (glutamate-dopamine convergence similar to NAc and neostriatum), and project primarily to BNST as a pallidal-type target [304].

Eating palatable food causes increases in Fos expression in the central amygdala [305,306] and direct manipulations that alter opioid, glutamate, GABA, and several peptides within CeA can potentiate unconditioned food intake [45,307–320]. Conversely, GABAergic inactivation of the CeA or dopamine blockade in CeA suppresses food intake [321,322]. Some recent optogenetic studies have similarly reported that ChR2 activation of various CeA neuronal types amplifies food intake and drinking of palatable sweet solutions [323–326].

The CeA may also play a special role in targeting enhanced 'wanting' on to particular learned cues for food rewards. For example, in a sign-tracking/goal-tracking situation, CeA mu-opioid stimulation by DAMGO microinjection selectively enhances the incentive salience of the sucrose-predicting lever CS+ in sign-trackers, but selectively enhances the incentive salience of the sucrose-contiguous dish CS+ in goal-trackers. In both cases it enhances approach towards, and consummatory bites and nibbles to the individual's preferred metal lever or dish cue [44,45,307]. That suggests the CeA can amplify incentive motivation and focus 'wanting' specifically on an already preferred CS + stimulus [44]. Similarly, in a Pavlovian-to-instrumental transfer situation (PIT), CeA opioid stimulation specifically enhances cue-triggered 'wanting' by increasing bouts of instrumental lever pressing for sucrose reward when the CS+ is presented, and not in its absence [307]. In addition to its role in food motivation and appetite, CeA signaling has also been shown to be important for cue-induced motivation for drug rewards [327–332]. Conversely, lesion studies suggest that loss of CeA function impairs cue-induced 'wanting', suppressing PIT, and other forms of motivation [333–336].

Recently, optogenetic CeA stimulations have been used to amplify and control the direction of 'wanting' for a particular target, such as sucrose, cocaine, or even a noxious shock-rod stimulus that delivers electric shocks if touched [46,47,337]. The CeA role is powerful enough to make a rat 'want what hurts it' when laser stimulation is paired with voluntary encounters of the noxious shock rod, so that rats paradoxically become compulsively attracted to the shock-rod and subject themselves to shocks again and again [337]. This CeA-driven attraction is mediated in part via recruiting activation of distributed mesocorticolimbic circuitry for incentive motivation [337].

Regarding food in particular, studies by Mike Robinson and Shelley Warlow in our lab showed that pairing such CeA optogenetic stimulation with a sucrose target could make the rat exclusively pursue that laser-paired sucrose target while ignoring an equally good sucrose alternative. CeA stimulation also amplified breakpoint incentive motivation to obtain sucrose in a progressive ratio task [47]. Another study by Robinson and colleagues showed that rats will withstand a painful foot shock in order to gain access to the laser-paired sucrose, and pursue it even when the alternative non-laser paired sucrose reward is 10 times larger [338]. However, Robinson and Warlow found that CeA ChR2 stimulation did not appear to enhance orofacial 'liking' reactions for sucrose, despite making rats 'want' sucrose more [47]. Pilot results in our lab suggest that pairing optogenetic CeA ChR2 stimulation specifically of CRF neurons in CeA with a particular sucrose target can similarly make that target exclusively preferred over an alternative sucrose option, and so mimic at least some of the CeA ChR2 effects described above [339–341].

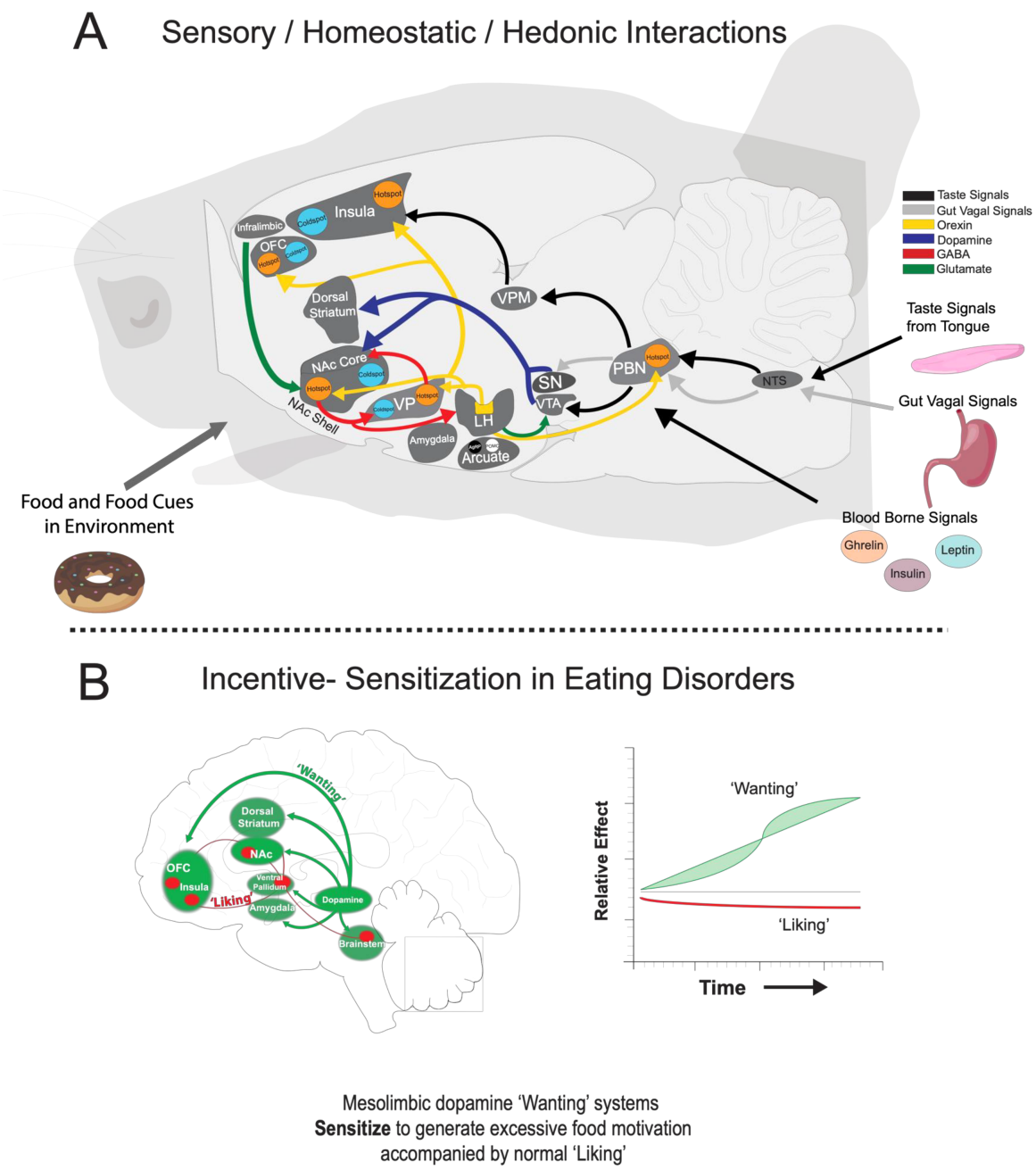

Fig. 4. Brain Systems for Appetite and Motivation. A) Top panel shows a sagittal view of a rat brain with a summary map of connections between hindbrain, hypothalamic, and mesocorticolimbic sites that mediate 'liking', 'wanting', sensory signals, and appetite. Brain hedonic hotspots (shown in orange) and coldspots (shown in light blue) in parabrachial nucleus, ventral pallidum, nucleus accumbens, orbitofrontal cortex, and insula do not share direct projections. Orexin signals from the lateral hypothalamic modulate mesocorticolimbic activity by integrating circulating signals about hunger/satiety in order to enhance or suppress 'liking' and incentive motivation during various physiological states. Additional hypothalamic systems in the arcuate nucleus of the hypothalamus may interact with mesolimbic circuitry so that their activity reflects the incentive value of food and food-related cues in the environment. Colors of arrows denote projection types. Data is based from studies described in text. B) Bottom panel is a sagittal view of mesocorticolimbic systems that mediate 'liking' and 'wanting' in humans. Individuals with eating disorders may have hyper-reactive mesolimbic dopamine systems that respond to information about food and their related cues in the environment. This enhanced dopamine release may assign excessive incentive salience that results in overconsumption of palatable foods that is independent of how much those foods are actually 'liked'.

Overall, CeA and its control over other mesocorticolimbic circuitry may be involved in sharpening the focus of amplified 'wanting' onto cues for a particular incentive target, like a high-caloric palatable food, which could contribute to intense urges to indulge in those foods, leading to overeating.

6.4. Lateral hypothalamus homeostatic interactions with mesocorticolimbic circuitry for 'liking' and 'wanting'

Understanding how 'liking', 'wanting', and hypothalamic circuitry interact to promote appetite and motivation is an enduring quest. Lateral hypothalamus (LH) may modulate the activity of mesocorticolimbic circuitry, including hedonic hotspots, by integrating homeostatic signals so that relevant hunger/satiety states can enhance or suppress

motivated and hedonic behaviors to food rewards at appropriate times [342]. But how might LH help regulate these processes? One obvious potential mechanism is orexin (Fig. 4a), given that it is both a hunger-related hypothalamic signal and an effective enhancer of 'liking' reactions in limbic hedonic hotspots [1,39,90,97,148,343,344]. Orexin/hypocretin is a neuropeptide exclusively synthesized in perifornical, lateral, and dorsomedial nuclei of the hypothalamus [345,346], and while implicated generally in arousal throughout the hypothalamus, a subset of orexin neurons in a subregion of lateral hypothalamus are also implicated in reward-related motivation [179,347–352]. LH orexin neurons project widely throughout the brain, including to nucleus accumbens, ventral pallidum, ventral tegmentum, and limbic cortex regions where the hedonic hotspots are located [83,155,349,353–358]. LH orexin is therefore an ideal candidate to help mediate alliesthesia [342,359], the phenomenon in which physiological appetite states enhance hedonic 'liking' and palatability ratings of the tastes of relevant foods [23,25,213,360]. Consistent with that hypothesis, direct microinjections of orexin-A into hedonic hotspots in VP, NAc, OFC, and insula amplify 'liking' reactions to sucrose as effectively as microinjections of mu opioid DAMGO into those sites [39,90,97].

Additional mechanisms for hypothalamic-limbic interactions include AgRP/NPY and POMC neurons in the arcuate nucleus (ARC) and LH [361–364]. ARC^{AgRP} and ARC^{POMC} neurons send robust projections to LH and their release of AgRP and POMC peptides modulate activity of LH neurons [363,364]. For most of the past 20 years, AgRP neurons have been viewed as simple homeostatic 'hunger' neurons, and POMC neurons viewed as 'satiety' neurons [365]. However, recent studies indicate that AgRP activity rapidly decreases as soon as palatable food is merely presented, or even when a cue predicting food is encountered, before any actual food has been ingested. Conversely, POMC neuronal activity can rapidly rise when triggered by these encounters or cues, in advance of any physiological satiety [366–368]. One interpretation of these rapid anticipatory changes is that AgRP and POMC neuronal activity reflects an interaction between incentive and hedonic information about available food, implying bidirectional or looping circuitry interactions between mesocorticolimbic-reward and hypothalamic-homeostatic systems [369]. That would be compatible with the increasing recognition that, rather than serving as parallel systems that promote appetite and feeding independently, hedonic and homeostatic systems may be understood as heavily interconnected, which functionally interact to control appetite and eating behavior.

7. Clinical implications of 'liking' versus 'wanting' dissociation: incentive-sensitization and obesity

The above discussion of brain mechanisms for food 'wanting' versus 'liking' may carry potential implications for human obesity and eating disorders. In the past decade, a number of obesity investigators have applied the brain-based 'wanting/liking' distinction to suggest that in some vulnerable individuals, 'wanting' for foods might dissociate and exceed 'liking' to cause excessive cue-trigged 'wants' to overeat [2,4,5,370–374]. The idea that some cases of extreme over-eating or binge-eating disorders can reflect excessive 'wanting', without excessive 'liking' invokes the incentive-sensitization theory of addiction, which was originally proposed for drug addiction but recently has been extended to behavioral addictions and to over-eating [375–377]. Incentive-sensitization applied to eating disorders suggests that some individuals may be especially vulnerable to developing neural sensitization of dopamine-related mesocorticolimbic systems of 'wanting', and consequently assign the exaggerated incentive salience that results specifically to palatable foods and the act of eating them. The result would be excessive 'wanting' to eat (Fig. 4b), typically triggered by palatable food cues or by vivid imagery about such foods, which could become especially exacerbated in moments of stress or emotional arousal that heighten mesolimbic reactivity. Evidence supporting this incentive-sensitization interpretation of overeating comes particularly from neuroimaging studies of obese or binge-eating individuals that have reported a sensitization-type brain activation signature to food cues that is remarkably similar to the signature of people who suffer from drug addiction to drug cues [2,4,370,373].

A potential incentive-sensitization brain explanation for eating disorders is also relevant to debates about the concept of food addiction [370,372,373,378–389]. That is, a legitimate 'food addiction' might exist to the degree that some over-eaters truly show incentive-sensitization signatures of brain activation to foods, in the sense that those food-sensitized individuals may experience more intense cue-triggered food cravings than other people do. The ideal brain signature for an eating addiction in the sense of incentive-sensitization would be mesocorticolimbic hyper-reactivity in nucleus accumbens or striatum, ventral tegmentum, amygdala or limbic cortical regions in over-eaters that is triggered by food cues. An incentive-sensitization signature would be hyper-reactive in both of two ways: 1) more intense brain activations triggered by food cues than by money or other reward cues in the same over-eating individual, and 2) more intense brain activations triggered by food cues in sensitized over-eaters than triggered by the same food cues in nonsensitized normal eaters.

Extreme incentive salience attributed to foods is in one sense a natural phenomenon that nearly anyone could experience – at least, under extreme conditions of prolonged starvation, but which most people in the modern world fortunately never experience. For example, during World War 2 a controlled Minnesota study of starvation was carried out using conscientious objectors as volunteers of starvation to better understand starvation consequences and treatments [390]. Gradually the volunteers began to be gripped by intense food cravings as they became extremely underweight: "Some of them (volunteers) obsessively read cookbooks, staring at pictures of food with almost pornographic interest" [390]. Despite being highly motivated, a number of volunteers could not resist succumbing to temptations to eat, and left the study. Thus, anyone can feel strong urges to eat during extreme physiological starvation that become nearly compulsive. What may be different in sensitized over-eaters is that similarly intense incentive salience is attributed to food cues, due to sensitized hyper-reactivity of mesocorticolimbic 'wanting' systems in some vulnerable individuals, even without ever being starved and despite developing obesity.

Some evidence for incentive sensitization in over-eating has come from reports that obesity and binge eating disorder is associated with heightened BOLD signals in ventral striatum, prefrontal cortex, and OFC in response to visual cues of palatable foods compared to individuals without obesity [391–393]. Similarly, individuals with obesity have been reported to have elevated brain responses in striatum, amygdala and orbitofrontal cortex to images of high calorie foods compared to foods low in calories or control images [394–401]. Using PET, one study reported elevation in striatal dopamine release in binge-eating individuals (compared to non-binge eating individuals) when they were given oral methylphenidate, which may pharmacologically prime mesolimbic dopamine reactivity, and their higher dopamine response was positively correlated with binge eating scores [402]. Heightened brain activity to palatable foods also positively correlates with self-reported subjective cravings or 'wanting' to eat [403], and individuals with binge eating are reported to have greater EEG reactivity in response to palatable chocolate pictures and increased craving ratings compared to healthy controls [404]. Elevated brain responses to food in individuals with obesity may also be associated with poorer outcomes to behavioral weight loss treatments [405]. Evidence suggests that enhanced brain limbic activity is selective to food rewards in over-eaters, as some studies have not observed increased brain activity to monetary rewards in individuals with binge-eating disorder [403,406]. Overall, these studies suggest that individuals with binge-eating disorder or obesity show incentive sensitization-like features in mesolimbic brain structures to food and food-associated cues, which could produce more intense cue-triggered 'wanting' to eat, even if not be matched by more intense 'liking'

[2,4,5,370–374].

Most telling may be prospective or longitudinal tracking studies that track individuals both before and after they develop obesity. For example, one such study reported that young women showed altered brain responses to learned food cues in ventral pallidum and neostriatum. Women who showed the greatest increase in ventral pallidum BOLD signals and greatest decrease in neostriatal signals were at greatest risk for developing excessive weight gain later in life [407].

Incentive-Sensitization contrasts to Reward Deficiency. It is worth noting that the *incentive-sensitization* hypothesis for over-eating contrasts strongly with the *reward deficiency* hypothesis, which was prominent for several decades in both obesity and drug addiction fields. This reward deficiency idea postulated that obese individuals find foods less rewarding than other individuals, and therefore eat more foods to accumulate rewarding experiences and so make up their reward deficiency. This reward deficiency hypothesis was based on reports that striatal dopamine D2 receptors appear to be down-regulated in some individuals with obesity, at least in the sense that they have reduced labeled-raclopride binding (although reduced binding to vacant receptors may not be able to distinguish between fewer receptors versus higher dopamine release and receptor occupancy). That reduced D2 binding is similar to potential D2 down-regulation in individuals with drug addiction [408–414]; although some studies fail to find D2 binding reductions in people with obesity [415].

Early reward deficiency advocates often drew on the once-popular idea that mesolimbic dopamine mediated 'liking' or food pleasure, inferring that lower D2 binding therefore meant a deficiency of pleasure. The reward deficiency hypothesis also assumed that individuals respond to reductions in food pleasure by consuming *more* food to regain a preferred pleasure level. That assumption views food pleasure reduction as similar to drug dilution, where individuals may consume a greater quantity of a dilute drug (e.g. beer) than of a concentrated drug (e.g. whiskey) to obtain the same alcohol dose. However, sensory incentives such as food obey very different empirical rules. For food rewards, making a food less 'liked', typically also makes it less 'wanted' less and therefore less consumed [9,416–418]. For example, many parents might be able to attest that putting their children on a diet of unpreferred broccoli, brussels sprouts, or spinach is unlikely to lead to weight gain. Proponents of the reward deficiency hypothesis might object to this example on grounds that reward deficiency is sometimes posited to develop later in life, and only when eating palatable energy-dense foods (e.g., sweet-fatty foods, salty-fatty foods, etc.). However, making a palatable rich food *less* palatable is still unlikely to make an individual eat more of it. In our view, there is no evidence for the reward-deficiency assumption that individuals eat more as a food becomes less tasty. Rather, people and animals instead typically eat more when the available foods are more 'liked' and consequently more 'wanted'.

Neurobiological problems may also exist for the reward deficiency hypothesis. Evidence from animal experiments where brain dopamine levels are manipulated indicates that increases in food seeking and consumption are more readily produced by *increases* of dopamine signals in the nucleus accumbens (such as after amphetamine microinjections in nucleus accumbens to promote dopamine release) than by suppression of dopamine signals [239,419–421]. Conversely, suppressing dopamine signals from the nucleus accumbens or neostriatum is most often reported to reduce eating and food seeking in animal studies, rather than cause overeating [422–424]. Similarly in people, inducing suppression of dopamine signaling in ordinary volunteers may actually cause them to eat less rather than to eat more [425]. As a caveat, however, the brain has multiple anatomical dopamine systems, and dopamine and norepinephrine signaling in the paraventricular nucleusof medial hypothalamus can oppositely suppress food intake [426,427]. Appetite-suppressing action of dopamine in the paraventricular nucleus of hypothalamus may explain why amphetamine-type drugs can be dieting aids (i.e., by stimulating hypothalamic dopamine and norepinephrine systems), and conversely why long-term exposure to neuroleptic/anti-psychotic dopamine antagonist drugs can sometimes produce weight gain [428–430].

But if reduction of accumbens/striatal dopamine signals does not cause overeating via reward deficiency, then why are obese individuals often reported to have reductions in striatal D2 receptor binding? An alternative explanation for why D2 dopamine downregulation occurs in many cases of obesity could be that D2 receptor downregulation is a *consequence* of eating palatable foods and/or weight gain, rather than being its cause. That is, encountering and eating rewarding foods may engage relatively intense mesocorticolimbic signals, possibly involving excessive or repeated dopamine release and related neurobiological over-stimulations, which eventually cause a partially compensatory down-regulation of D2 receptors just as do repeated exposures to addictive drugs.

Further, obesity is a form of extreme satiety that may induce related long-term physiological alliesthesia signals (e.g., high leptin, etc.), as negative-feedback signals that also attempt to dampen future mesocorticolimbic activation to check excessive 'wanting' to eat. All these may be viewed as *partial compensatory responses* tending to oppose the temptation power of palatable food incentives and cues that activate mesocorticolimbic dopamine systems, but which in many individuals *fail* to fully compensate because they are only partial and because other neuronal components of mesocorticolimbic incentive circuitry remain hyper-reactive to food cues. As a result, those individuals may continue to over-eat even in the face of reduced dopamine D2 receptors in nucleus accumbens or striatum. Evidence for thinking that D2 receptor downregulation is a consequence of continually eating palatable foods and of obesity, rather than a cause of over-eating, is that D2 receptor downregulation in nucleus accumbens and striatum can be induced in normal rats by giving them several weeks of free access to an array of palatably sweet and rich junk foods, on which some of them then become obese [5]. That is, the rats' D2 downregulation occurs as a consequence of continually eating sweet and fatty junk food and of any consequent obesity that develops over that prolonged period of time. Human evidence that D2 downregulation is primarily a consequence of obesity, and not the cause, is that the suppressed level of D2 dopamine receptors in severely obese humans sometimes rises after they lose weight following bariatric Roux-en-Y surgery, again as a consequence of their change in eating habits and of weight loss induced by the surgery [431,432].

In the end, future prospective human neuroimaging studies may provide the best evidence to help decide between incentive-sensitization and reward deficiency explanations of over-eating and obesity. Tracking changes in brain function in the same individuals both before they become obese and after obesity develops can provide important evidence regarding underlying causal mechanisms. For example, healthy weight adolescents who subsequently gain body fat over 2-or-3 years have been reported to show enhanced brain responses to food cues even before they gained weight [433]. Similarly, healthy weight adolescents who subsequently gain weight have been reported to have higher initial brain responses in taste and reward coding cortical regions like insula and OFC when consuming milkshakes, suggesting limbic hyper-reactivity may be a pre-existing cause of later obesity. However, after they gain weight their brain reactions to the actual taste of milkshakes declines, suggesting that that the reduction may a compensatory consequence of their weight-gain [434].

Partly as a result of many demonstrations of mesocorticolimbic hyper-reactivity to food cues in individuals with obesity, the weight of neuroimaging data may have shifted away from the reward deficiency hypothesis and toward the incentive sensitization hypothesis in the past 10 years [2,4,402,435,436]. For example, a recent meta-analysis of fMRI results concluded that "Extant data provide strong support for the incentive sensitization theory of obesity and… only minimal support for the reward deficit (deficiency) theory" [2]. Similarly, another meta-analysis review of brain imaging studies concluded that "we did not

find univocal evidence in favor of a Reward Deficit Hypothesis nor for a systematic deficit of inhibitory cognitive control. We conclude that the available brain activation data (for human obesity)… can be best framed within an Incentive Sensitization Theory" [4]. Such conclusions draw on results such as observation of fMRI hyper-reactivity to food cues in striatum, orbitofrontal cortex and insula cortex in obesity-prone human adolescents even before those individuals went on to gain weight several years later [435]. They are also consistent with reports of higher levels of dopamine release in neostriatum elicited by palatable foods in obese individuals with binge eating disorders than individuals who were not binge eaters, suggesting mesolimbic hyper-reactivity persisted in individuals who binge-eat [402]. Similarly, people who are heavier have been reported to have higher striatal dopamine release than people who were lighter, leading the authors of the study to conclude their results "suggest increase dopamine release with increasing body mass… consistent with… increasing behavioral salience of food being a risk factor for obesity" [436].

8. Conclusion

Mesocorticolimbic structures including the nucleus accumbens, ventral pallidum, orbitofrontal cortex, and insula contain localized hedonic hotspots in specific subregions, where opioid and other specific forms of stimulation can enhance 'liking' reactions to palatable foods. The same structures often also contain separable hedonic coldspots where the same neurobiological stimulations suppress 'liking'. These hotspots and coldspots are nestled within larger mesocorticostriatal 'wanting' circuitry where many of the same forms of stimulation plus others (e.g. dopamine) robustly generate intense cue-triggered incentive salience, amplifying motivation to seek and consume palatable food rewards, whether or not 'liking' is simultaneously enhanced.

The distinguishable identities of brain systems for 'liking' versus 'wanting' food rewards has implications for understanding at least some cases of human obesity, binge-eating, and related eating disorders. This particularly appears to apply in the form of incentive-sensitization signatures of hyper-reactivity of brain 'wanting' systems in some individuals with obesity or binge eating disorder, which may cause overeating without necessarily being accompanied by enhanced food 'liking'. Future research in this area will continue to extend understanding of how mesocorticolimbic systems interact with hypothalamic homeostatic signals to control normal appetite and food reward, and how specific dysregulations in motivation systems contribute to eating disorders and obesity.

Declaration of Competing Interest

The authors declare no competing financial interests.

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