

Published in final edited form as:

Neurosci Biobehav Rev. 2013 November ; 37(0): . doi:10.1016/j.neubiorev.2012.12.008.

Mapping brain circuits of reward and motivation: In the footsteps of Ann Kelley

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Abstract

Ann Kelley was a scientific pioneer in reward neuroscience. Her many notable discoveries included demonstrations of accumbens/striatal circuitry roles in eating behavior and in food reward, explorations of limbic interactions with hypothalamic regulatory circuits, and additional interactions of motivation circuits with learning functions. Ann Kelley's accomplishments inspired other researchers to follow in her footsteps, including our own laboratory group. Here we describe results from several lines of our research that sprang in part from earlier findings by Kelley and colleagues. We describe hedonic hotspots for generating intense pleasure 'liking', separate identities of 'wanting' versus 'liking' systems, a novel role for dorsal neostriatum in generating motivation to eat, a limbic keyboard mechanism in nucleus accumbens for generating intense desire versus intense dread, and dynamic limbic transformations of learned memories into motivation. We describe how origins for each of these themes can be traced to fundamental contributions by Ann Kelley.

Keywords

Eating; Pleasure; Fear; Incentive salience; Nucleus accumbens; Neostriatum; Ventral pallidum; Opioid; Dopamine; Rat

1. Introduction

Our thesis here is that discrete psychological components of motivation and reward affect are to some degree assignable to discrete neurochemical and neuroanatomical mechanisms within brain mesocorticolimbic circuitry. Neural manipulations especially can dissociate and reveal these components, sometimes in surprising ways. For example, some particular psychological components that seem closely interconnected in common experience, such as 'wanting' and 'liking' for the same reward, may actually be less similar in neural mechanisms than other motivational components that seem psychologically opposite, such as fear and desire. We describe such components here, and highlight how neuroscience studies of motivation and reward can benefit from combining careful behavioral analyses with neural manipulations and mapping of brain mechanisms. Work by the late Ann Kelley and colleagues began many of these efforts, and inspired related studies in our and others'

laboratories aimed at identifying the psychological nature of motivation components and the specific neural systems involved.

2. Nucleus accumbens in eating and 'liking'

Ann Kelley was a leading pioneer in the neuroscience of reward and motivation. For example, she and her colleagues were among the first to combine research on the anatomy of mesocorticostratial systems, the role of opioid signals in striatal systems, and their interactions with hypothalamic regulatory circuits in controlling motivated behavior. Those investigations by her laboratory followed her earlier collaborative studies with Iversen and colleagues on classic mesolimbic microinjection effects, and her elegant collaborative neuroanatomical studies with Nauta and colleagues in the late 1970s and early 1980s (Kelley et al., 1980, 1982; Kelley and Iversen, 1978).

One important later theme for the Kelley lab concerned reward circuitry underlying generation of the motivation to eat. By the early 1990s, Bakshi and Kelley (1993b) had shown that microinjections of morphine into either nucleus accumbens (NAc; ventral striatum) or ventromedial regions of neostriatum (dorsal striatum or caudate-putamen) caused robust increases in eating behavior and food intake. Following this discovery, Kelley and colleagues went on to demonstrate that eating induced by mu opioid stimulation of NAc was sensitive to the palatability of the food eaten, preferentially enhancing intake of palatable sweet or high fat foods more than other foods, rather than merely instigating a general drive to ingest or engage in oromotor consummatory acts (Kelley et al., 1996; Zhang et al., 1998; Zhang and Kelley, 1997). Those results from the Kelley lab helped develop the idea that mu opioid signaling in NAc might enhance the hedonic impact of palatable foods to stimulate ingestion (Baldo and Kelley, 2007).

Another important issue for Ann Kelley's work was anatomical heterogeneity and localization of function within subregions of striatal structures. To determine which opioid circuits worked to enhance palatable eating, Zhang and Kelley (2000) conducted an extensive opioid microinjection mapping study of behavioral effects on stimulated eating, comparing regions of NAc and neostriatum. They found that opioid stimulation of eating was supported by the entire NAc shell (both medial shell and lateral shell) and entire NAc core, plus ventrolateral regions of neostriatum. In addition, they showed that mu opioid receptor stimulation in the NAc increased Fos expression in other limbic brain structures, such as lateral hypothalamus and ventral tegmental area, indicating recruitment of distributed brain networks to motivate feeding.

3. Pinpointing opioid hedonic enhancement in NAc: discovery of a 'liking' hotspot

Such findings by Ann Kelley and colleagues, together with related work by others (Gosnell and Majchrzak, 1989; Islam and Bodnar, 1990; Simone et al., 1985), inspired many labs to further investigate the role of opioid circuitry in the NAc in palatability. In particular, our lab set out to identify whether and where opioid stimulation would enhance basic positive hedonic reactions of 'liking' to palatable tastes, such as sucrose. Initial taste reactivity experiments found that systemic injections of morphine increased hedonic reactions to sucrose solutions (Doyle et al., 1993; Rideout and Parker, 1996) and decreased aversive behaviors to bitter quinine (Doyle et al., 1993; Parker et al., 1992; Rideout and Parker, 1996). The taste reactivity test of orofacial reactions was developed for rodents receiving intra-oral infusions of taste solutions (Grill and Norgren, 1978; Pfaffmann et al., 1977), and was based originally on earlier demonstrations by Steiner (1973) of distinct positive versus negative affective facial expressions in newborn human infants elicited by sweet (e.g.,

rhythmic lip-licking) versus bitter or sour tastes (e.g., gapes, headshakes). The microstructure of affective orofacial reactions of 'liking' versus 'disliking' is systematically homologous between rodents, monkeys, apes, and human infants, making taste reactivity a useful tool to empirically study hedonic experiences (Berridge, 2000, 2003; Steiner, 1973; Steiner et al., 2001).

Pecina and Berridge (1995, 2000) approached the localization question for opioid pleasure mechanisms by examining the effects of morphine microinjections on hedonic reactions to sucrose as assessed by the taste reactivity test. First, Pecina and Berridge (1995) found that intracerebroventricular microinjections of morphine into the forebrain lateral ventricles increased hedonic 'liking' reactions to a sweet sucrose taste, confirming that opioids promote eating by acting on central brain mechanisms to enhance the sensory pleasure of food. To more directly investigate the localization of substrates for hedonic enhancement, Pecina and Berridge (2000) subsequently made microinjections of morphine directly into brain sites within the medial shell of NAc, one of the areas where Kelley's studies had found mu opioid receptor stimulation to most potently increase eating (Zhang et al., 1998; Zhang and Kelley, 1997, 2000). Peciña and Berridge found that opioid stimulation of the NAc medial Pecina shell was sufficient to enhance hedonic 'liking' reactions to sucrose. But not all sites of medial shell were equally effective: a localized hotspot seemed to exist that doubled or tripled 'liking' reactions, whereas morphine microinjections at other shell sites did not, even though those sites just as powerfully stimulated eating. This grouping of sites turned out to be clumped in the anterior half of medial shell, as viewed by today's understanding of NAc anatomy.

4. Changing criteria for rostrocaudal boundaries in NAc shell

Peciña and Berridge initially adopted the same stereotaxic coordinates as Kelley and colleagues to target the medial shell (Basso and Kelley, 1999; Kelley and Swanson, 1997; Maldonado-Irizarry et al., 1995; Zhang and Kelley, 2000). Most of their sites were located in what we would now classify as the rostral half of medial shell, even sites intended to be relatively caudal. Indeed, most microinjection studies from many labs through the 1990s focused primarily on the rostral half of NAc (for example: Burgdorf et al., 2001; Carlezon and Wise, 1996; Duvauchelle et al., 1992; Hyttia and Koob, 1995; Sills and Vaccarino, 1996; Sokolowski and Salamone, 1998). The caudal half was left relatively unexplored until after 2000.

Caudal neglect of NAc until the 21st century may have arisen in part because popular stereotaxic atlas representations of the caudal portion of medial shell were relatively compressed until the year 2000 by comparison to expanded representations in recent years. For example, the entire rostrocaudal extent of NAc shell has grown from under 2 mm in a popular atlas of the 1960s (Pellegrino and Cushman, 1967) to approaching 3 mm in one atlas often used today (Paxinos and Watson, 2007). Even in successive editions of the Paxinos and Watson atlas, the representation NAc shell has grown by nearly half a millimeter from front to back, as represented in serial coronal sections. Most of this apparent growth has been in the caudal half of shell: more sections and a greater anterior–posterior span is now covered by coronal maps for caudal shell, whereas the rostral shell has remained relatively stable. As a result, the represented distance has grown between the anteroposterior (AP) midpoint of medial shell to the caudal edge of medial shell by about 0.5 mm for Paxinos and Watson from 1998 to 2007. The AP midpoint corresponds functionally to the caudal edge of the hedonic hotspot (Fig. 1). An anatomical marker for that AP level for a person inspecting a coronal section is visible in the lateral septum dorsal to the shell: in more rostral sections through the hotspot the septum is penetrated by vertical streaks of the indusium griseum of the hippocampus, but those streaks disappear as one reaches the caudal edge of the hotspot

(midpoint of medial shell), and are no longer visible in more posterior sections. An additional midpoint marker is the transition from the genu to the body of the corpus callosum.

Perhaps even more important to early caudal neglect of shell and subsequent correction has been the rostral migration of stereo-taxic coordinates that can be seen in coronal sections of successive Paxinos and Watson editions. For example, an intermediate site in medial shell corresponding to caudal border of hotspot fell in coronal plane that was described as 1.2 mm anterior to bregma in 1998, but is more recently marked as 1.68 mm ahead of bregma in the 2007 edition—a move of nearly half a millimeter. By contrast, sagittal plane maps and coordinates have remained essentially unchanged in Paxinos and Watson since 1998 (e.g., their Figure 165 of Paxinos and Watson, 2007). What this means is that a person looking at a coronal brain slice at the AP midpoint, perhaps marked anatomically by the disappearance of the indusium griseum and the transition from the genu to the body of the corpus callosum (Fig. 1), would conclude that they were 1.2 mm ahead of bregma in 1998, but at 1.68 in 2007. If they plotted the 1.2 mm ahead of bregma position on the sagittal map of Figure 165 in the 1998 edition, their site appears to be in the caudal half of medial shell. But in 2007, plotting the same location as 1.68 mm ahead of bregma on the essentially unchanged corresponding sagittal map moves the site a half-millimeter forward and it is no longer in posterior shell. Thus sites taken as posterior in the 1990s can be recognized now to be only in the center of medial shell. Of course the medial shell has not actually expanded anatomically, nor have these markers moved in the brain, but the change in coronal atlas representations allows a reassessment, and more recent studies have probed caudal zones of shell that once went unmapped in coronal sections.

As a consequence of all this, studies that ostensibly included caudal regions of medial shell (Basso and Kelley, 1999; Kelley and Swanson, 1997) may have actually focused on mid-rostral or central locations (between 1.6 and 2.2 mm rostral to bregma), leaving more caudal regions of medial shell relatively untouched (e.g., 0.45–1.6 mm ahead of bregma).

This rostral NAc tilt applied to Pecina and Berridge in 2000. To map the site of functional hedonic enhancement, Pecina and Berridge used a Fos plume mapping technique, which measures the diameter of drug impact on local neurons surrounding a microinjection. They found that morphine microinjections in a circumscribed area of medial shell generated robust increases in hedonic 'liking' responses elicited by sucrose taste, more than doubling control levels, and enhanced chow consumption. Other sites in shell only increased eating but not hedonic responses to taste. The hedonic 'liking' enhancements were mapped particularly in what Pecina and Berridge then considered to be the caudal region of medial shell (but actually was only the caudal portion of the rostral half of shell). Indeed, in their 2000 paper they called the hedonic site a caudal shell site. At least, it constituted the caudal grouping of their NAc sites (which now would be considered mid-rostral, the other sites being far-rostral).

However, with the emerging realization after 2000 that the NAc medial shell also extended more caudally, it became necessary to remap the hedonic site again including more caudal regions of and Berridge therefore completed a subsequent medial shell. Pecina and Berridge therefore completed a subsequent mapping study using microinjections of the selective mu-opioid agonist, DAMGO, to examine the entire medial shell, including far caudal sites (Pecina and Berridge, 2005). In that second study they found that the hedonic enhancement site (remaining unmoved anatomically) did not extend into the true caudal half of shell after all (though the eating-stimulation zone did), but was rather by our current standards located in the rostral half of medial shell, particularly the midrostral zone (and also positioned in the dorsal half of shell). By measuring the diameters of localized Fos plumes surrounding DAMGO microinjections, and using that as an index of spread of impact for opioid

stimulation, Peciña and Berridge calculated the volume of the 'liking' enhancement hotspot to be approximately 1 mm³. Therefore the hedonic hotspot was redefined as a cubic millimeter volume in the rostradorsal quadrant of medial shell, a definition that has persisted to the present (Fig. 2). Beyond locating the hedonic hotspot, another major lesson our lab took from this re-mapping was to always represent localization of function by graphically mapping behavioral effects onto the sites of drug microinjection where they were actually produced. This creates atlas-based pictorial maps of hotspots, gradients or other anatomical distributions of function, rather than rely solely on words to describe neuroanatomical position (because the meaning of words can change regarding anatomical features: such as rostral versus caudal applied to NAc). Showing the mapped position of hotspots graphically, in relation to landmarks and stereotaxic coordinates, may help act as safeguard against having to revise descriptions of a hotspot location in future, even if terms change to designate a particular region.

5. Anatomical bases of hotspot functional uniqueness

What anatomical basis exists for why the NAc hotspot might be uniquely able to amplify hedonic impact? This issue has recently begun to be explored by neuroanatomists using sensitive tracing techniques. Recent studies by Thompson and Swanson (2010) and by Zahm et al. (2012), have indicated that the NAc hotspot in the rostradorsal quadrant of medial shell may be distinct anatomically as well as functionally. Both anatomical studies reported the NAc rostradorsal hotspot to have unique connectivity features that are at least quantitatively and perhaps sometimes qualitatively different from all the rest of NAc (including the rest of medial shell; Fig. 3).

For example, Thompson and Swanson reported that the NAc hotspot (rostradorsal quadrant of medial shell) receives unusually specific inputs from infralimbic cortex (homologous to Brodmann's area 25 or subgenual anterior cingulate cortex in humans) (Barbas et al., 2003; Ongur and Price, 2000; Uylings et al., 2003). Similarly, they reported that the NAc hotspot sends outputs in a unique pattern to restricted subregions of hypothalamus and ventral pallidum, different from the targets of other shell subregions (Thompson and Swanson, 2010). Based on additional mapping of thalamic and prefrontal cortex connections, Thompson and Swanson concluded that the NAc hotspot was embedded in its own special closed-circuit corticolimbic-thalamocortical loop (separate from other segregated loops passing through different NAc shell sub-regions).

Independently, Zahm et al. (2012) recently reported the NAc hotspot of rostral shell to differ from caudal shell, and specifically to share some connection patterns with the lateral septum. Zahm and colleagues suggested the NAc hotspot to be an anatomical transitional zone that merges NAc shell features with features of lateral septum (again, different from the caudal half of medial shell, which they suggest may instead be a transitional zone of NAc with the extended amygdala, including bed nucleus of stria terminalis and central nucleus of amygdala) (Zahm, 2006). While Zahm and colleagues differ from Thompson and Swanson on some points that remain to be resolved, taken as a whole both studies provide initial confirmation that the NAc rostradorsal quadrant of medial shell is a relatively distinct anatomical entity as well as a functional hotspot.

6. Other hedonic opioid receptors?

Recent work in our lab on the NAc hotspot has further explored the role of the hotspot in determining effects of delta and kappa opioid receptors in the enhancement of hedonic 'liking'. This work also follows in the footsteps of Ann Kelley. Bakshi and Kelley (1993a) examined opioid receptor roles in the generation of eating by microinjecting specific agonists for mu, delta or kappa opioid receptors into the NAc and ventral neostriatum. They

found that mu agonist microinjections most greatly potentiated feeding, whereas the delta agonist only moderately potentiated feeding, and the kappa agonist failed to stimulate intake. Similar patterns have been replicated (Ragnauth et al., 2000; Zhang and Kelley, 1997). However, recent findings in our lab indicate that the medial shell hotspot may modulate the role of kappa and delta stimulation in 'liking' and 'wanting', just as it modulates the hedonic role of mu opioid stimulation. Our most recent preliminary results suggest that within the rostradorsal hotspot kappa and delta receptors also may enhance hedonic impact, though neither do so outside the hotspot (Castro and Berridge, 2012). Further, increased motivation to eat may also be more localized to the hotspot for kappa or delta stimulation than it is for mu opioid stimulation, which can spur intake throughout the entire shell and core. We expect these intriguing possibilities will soon be resolved.

7. Striatopallidal hedonic circuitry: roles of ventral pallidum opioids

The ventral pallidum is the chief anatomical output target of the NAc (Groenewegen et al., 1999), and has emerged recently as an important structure in its own right for the generation of motivation and affect (Inui et al., 2009; Kalivas et al., 1999; Lim et al., 2004; Napier and Mickiewicz, 2010; Smith et al., 2009). Regarding 'liking' enhancements in particular, the ventral pallidum has also been shown to contain a hedonic 'hotspot', located in its posterior half (Cromwell and Berridge, 1993; Ho and Berridge, 2009; Smith and Berridge, 2005).

Clues that a hedonic hotspot existed in ventral pallidum were first seen in classic 1960s–1970s reports suggesting that lesions to the tissue surrounding and including lateral hypothalamus were sufficient to produce aphagia and disliking behaviors to sucrose (Morgane, 1961; Schallert and Whishaw, 1978; Stellar et al., 1979; Teitelbaum and Epstein, 1962). Those large electrolytic lesions can be seen in retrospect to have damaged ventral pallidum as well as lateral hypothalamus (Berridge, 1996; Smith et al., 2008). In a 1990s excitotoxin lesion study, Cromwell and Berridge (1993) sought to more precisely map the putatively hypothalamic 'disliking' region by examining sucrose 'disliking' produced by small, discrete cell body lesions in either lateral hypothalamus, globus pallidus, or ventral pallidum. To map the aversion effects, Cromwell measured the diameter of each excitotoxin lesion by quantifying the degree of neuronal death at multiple locations in and near the lesion center. Cromwell and Berridge found that lesions to lateral hypothalamus did indeed produce aphagia, but never 'disliking' to sweet solutions, whereas loss of 'liking' reactions and replacement with 'disliking' gapes only occurred if lesions damaged the ventral pallidum. This ventral pallidum site for damage-induced 'disliking' was recently confirmed by Chao-Yi Ho in another excitotoxin study in our lab, and indicated to reside specifically in the posterior half of ventral pallidum (Ho, 2010).

Smith and Berridge (2005) originally identified the hedonic hotspot and mapped its boundaries via opioid enhancements of sensory pleasure, similar to the NAc hotspot. They found that microinjections of DAMGO into the ventral pallidum had bivalent effects on 'liking' reactions and eating, depending on the precise site within ventral pallidum. In the roughly cubic-millimeter hotspot within caudal half of ventral pallidum, opioid stimulation doubled hedonic 'liking' reactions to sucrose taste as well as increased appetitive eating of chow, again like the NAc hotspot. Conversely, in the rostral half of ventral pallidum mu-opioid stimulation actually decreased 'liking' reactions to sucrose and decreased eating and chow intake. Thus, the caudal ventral pallidum contains a distinct opioid hedonic/incentive hotspot that is functionally similar to the NAc hotspot in dorsomedial shell of NAc, plus an oppositely valenced rostral hedonic coldspot for 'liking' suppression.

What anatomical basis exists for why the rostral versus caudal subregions of ventral pallidum have opposite opioid effects on hedonic impact and motivation? A potential

answer has been suggested by a recent anatomical and electrophysiological study of rostrocaudal differences among neurons within ventral pallidum by Kupchik and Kalivas (2012). Their careful morphological and patch clamp analysis suggested that the caudal ventral pallidum containing the hotspot may comprise mostly neurons that have long aspiny dendrites and are relatively excitable. By comparison, the rostral ventral pallidum (especially rostromedial quadrant) contains neurons with shorter spiny dendrites that are more similar to nucleus accumbens neurons, and are more hyperpolarized and silent (Kupchik and Kalivas, 2012). Such neuronal differences might possibly underlie why opioid hedonic enhancement is functionally localized in ventral pallidum to the caudal hotspot.

The NAc and ventral pallidum are heavily interconnected, with each structure sending GABAergic projections to the other. Although the hotspots may not be directly interconnected anatomically (Thompson and Swanson, 2010), they functionally interact together (Smith and Berridge, 2007; Smith et al., 2011). To explore this interaction, Smith and Berridge (2007) examined whether the two hotspots functionally interacted as a single unit or integrated circuit in enhancing 'liking'. They found that recruitment of neurobiological activation occurred after DAMGO microinjection into one hotspot increased local Fos expression, as well as recruiting distant Fos expression in the other structure's hotspot (Smith and Berridge, 2007). Similarly in a later study, NAc hotspot DAMGO microinjection enhanced firing by ventral pallidum hotspot neurons to the taste of sucrose in a sustained pattern that appears to code hedonic impact of the sweet sensation (Smith et al., 2011). Additionally, the hedonic circuit required unanimous opioid participation by the dual hotspots in simultaneous cooperation, further indicating that NAc-VP circuits act together as a single unit to enhance 'liking'. When DAMGO was infused into one hotspot, and the opioid antagonist naloxone was simultaneously infused into the other, the endogenous opioid blockade of the second hotspot completely prevented the hedonic enhancement normally produced by opioid stimulation of the first (Smith and Berridge, 2007). Thus blockade in either hotspot vetoes the hedonic enhancement induced by stimulation of the other, presumably by preventing full recruitment of the hedonic circuit as a whole unit. Intriguingly, while 'liking' enhancement caused by DAMGO in the NAc hotspot was blocked by ventral pallidum microinjection of naloxone, 'wanting' stimulation by the NAc hotspot DAMGO was still preserved: the rats still ate more food. This dissociation indicates that opioid signals that act within the NAc can work to enhance motivational 'wanting' for food independently of 'liking' under some conditions, even when the source of enhancement begins anatomically in the hotspot, just as opioid stimulation at all NAc sites outside the hotspot selectively stimulates 'wanting' without 'liking' under all conditions tested so far. The cooperation between NAc-VP may help explain why there are two distinct hedonic hotspots in the brain: the two function together within an integrated circuit that conforms to classic striatopallidal organization. The two hotspots work together in tandem as an integrated functional unit that generates intense hedonic impact for food.

8. Other hedonic mechanisms and circuitry

The magnification of hedonic 'liking' for sweet/fatty food can also be enhanced by other neuropeptides and neuromodulators in hotspots, including anandamide, an endocannabinoid (Ho, 2010; Mahler et al., 2007). Endocannabinoid manipulations have been shown to increase eating in a variety of structures, including NAc, in addition to specifically modulating the consumption of palatable food (Cooper, 2004; DiPatrizio and Simansky, 2008a,b; Harrold et al., 2002; Kirkham et al., 2002). Mahler et al. (2007) found that microinjections of anandamide, an endogenous ligand for the CB1 receptor, into the NAc hotspot increase hedonic 'liking' reactions to sucrose taste similarly to DAMGO. These results support the idea that endocannabinoids likely modulate appetite and intake in large part by modulating the palatability of food (Kirkham and Williams, 2001).

Recently, our lab has also examined another Ann Kelley theme: interactions of NAc with hypothalamic regulatory circuitry, and particularly the role of hypothalamic orexin/hypocretin in hedonic processing (Ho, 2010; Ho and Berridge, 2009). Orexin/hypocretin-containing neurons are found within a dorsally restricted zone of lateral, perifornical, and dorsomedial hypothalamus, with projections well distributed throughout the brain, including the NAc, ventral pallidum, and parabrachial nucleus (Baldo et al., 2003; Peyron et al., 1998). An anterior subregion of orexin neurons specifically in the lateral hypothalamus has been suggested by Aston-Jones and colleagues to play a special role in food and drug reward (Harris et al., 2005). Orexin neurons receive direct inputs from the orexigenic NPY- and AgRP-containing neurons in the arcuate nucleus, and orexin's role in eating was first observed following demonstrations that intracerebroventricular microinjections of an orexin 1 receptor agonist increased eating (Sakurai et al., 1998). Conversely, administration of an orexin antagonist decreased eating (Haynes et al., 2000; Rodgers et al., 2001).

Kelley and colleagues suggested several years ago a particular circuit route by which lateral hypothalamic orexin neurons might mediate alliesthesia, which is the natural enhancement of food palatability that occurs during hunger states. Kelley et al. (2005a) proposed that orexin neurons act in response to peripheral and central hunger cues via hypothalamic projections to thalamus paraventricular nucleus to activate thalamic glutamate neurons. In turn, they proposed the thalamic paraventricular neurons project to the NAc shell to excite large acetylcholine NAc interneurons. Finally they suggested the acetylcholine interneurons in medial shell then specifically activate nearby intrinsic medium spiny neurons to release enkephalin on neighboring shell neurons. Enkephalin release within the cubic-millimeter hedonic hotspot of rostromedial medial shell ought to enhance food 'liking', similarly to a DAMGO microinjection. Thus, hunger mediated by orexin activation could amplify 'liking' as well as 'wanting' for palatable food through the opioid hotspot mechanisms described above.

The circuit described by Kelley and colleagues may well exist, though our lab has additionally found evidence for a more direct circuit in which lateral hypothalamic orexin neuron activation may amplify 'liking', via a direct influence of hypothalamic orexin neurons on the ventral pallidum hotspot (Baldo et al., 2003). Ho (2010, 2009) measured 'liking' and 'disliking' reactions to tastes following microinjection of orexin directly into the ventral pallidum hotspot and found that orexin enhanced 'liking' reactions to sucrose similarly to mu opioid stimulation. Her findings indicate that orexin in ventral pallidum may amplify the sensory pleasure of food, which is relevant to orexin roles in motivating behaviors for reward (Cota et al., 2006; Kirkham and Williams, 2001; Lopez et al., 2011).

9. Opioid reward in dorsal neostriatum: above and beyond all ventral striatum

Ann Kelley's mapping of opioid stimulation of intake produced findings that support a role for motivational mechanisms in some regions of neostriatum (dorsal striatum or caudate/putamen). Kelley and colleagues found that microinjections of morphine or DAMGO in ventral regions of neostriatum produced robust eating, similar to NAc (Bakshi and Kelley, 1993a,b; Zhang and Kelley, 2000).

How far dorsal in neostriatum does motivational and eating circuitry extend? The work of Kelley and colleagues recently inspired us to re-examine this question (DiFeliceantonio et al., 2012). Bakshi and Kelley (1993b) first suggested that microinjections of opioid agonists in ventral or middle regions of neostriatum stimulated eating behavior, but that more dorsal regions of neostriatum did not. However, if one looks closely at the histology figure from Zhang and Kelley (2000), one may discern a cluster of sites within the medial dorsal region

of neostriatum that appeared to produce increases in eating. We recently probed the medial zone of the most dorsal level of neostriatum with microinjections of DAMGO. We found that DAMGO microinjections at medial sites in dorsal neostriatum can generate robust increases >200% in eating of palatable sweet food (M&M™ chocolate candies), at least in the anterior half of the dorsomedial zone (anteromedial quadrant of dorsal neostriatum) (DiFeliceantonio et al., 2012). This anterior-medial dorsal neostriatum mediation of increased 'wanting' to eat was not accompanied by any increases in hedonic 'liking' reactions to the tastes of sucrose or of M&M™ candies, as measured by taste reactivity (Fig. 2; DiFeliceantonio et al., 2012). That wanting-without-liking pattern indicates opioid stimulation of this dorsal level of anteromedial neostriatum generates pure motivation without amplifying hedonic impact, similar to other striatal-type areas outside the NAc and ventral pallidum hotspots, including the core and posterior shell of NAc, and even the central nucleus of amygdala (Mahler and Berridge, 2012; Pecina and Berridge, 2005), which has striatal-like anatomical features such as containing predominantly GABAergic neurons (Swanson, 2005).

In addition, using microdialysis techniques conducted in collaboration with Omar Mabrouk and Robert Kennedy of the Chemistry Department at the University of Michigan, we recently found that endogenous enkephalin levels in the same anteromedial quadrant of dorsal neostriatum surged >150% when rats were suddenly allowed to eat palatable chocolate M&M™ candies (DiFeliceantonio et al., 2012). This region of the neostriatum contains "patches" or "striosomes" that are rich in mu opioid receptors, and which receive cortical input projections from limbic regions of prefrontal cortex and may project directly to dopamine neurons in the substantia nigra pars compacta (Eblen and Graybiel, 1995; Fujiyama et al., 2011; Gerfen, 1984; Levesque and Parent, 1998; Ragsdale and Graybiel, 1988, 1990). Enkephalin is likely acting on these mu-opioid receptors in neostriatum patches.

Kelley and colleagues (Kelley et al., 2005a; Will et al., 2007) proposed that enkephalin levels in the NAc and ventral regions of neostriatum controlled short-term food consumption and perhaps short term motivation for food. Our results support their proposal, and suggest this striatal enkephalin role may extend to an anteromedial region even in the most dorsal level of neostriatum.

10. Beyond desire to dread in NAc: rostrocaudal keyboards of appetitive and fearful motivated behaviors in medial shell

Though perhaps somewhat surprising in light of the NAc's well-known association with reward, its medial shell has also emerged as an important neural generator of some negatively valenced motivation states of fear and disgust (Carlezon and Thomas, 2009; Levita et al., 2009, 2012; Reynolds and Berridge, 2001, 2002, 2003; Richard and Berridge, 2011a; Salamone, 1994). In particular, our laboratory has found evidence for a keyboard-like rostrocaudal gradient of motivation generators in medial shell, where localized hyperpolarizations generate intense eating at rostral sites and an equally intense form of active (defensive) fear and even disgust at caudal sites. This organization echoes the rostral hedonic hotspot versus caudal coldspot localization for opioid impact on 'liking' reactions, but with even stronger bivalent emotional tone.

Our experiments on the NAc generation of desire and fear stemmed originally as confirmation and hedonic probing of Ann Kelley and colleagues' demonstration of intense eating generated by the rostral-to-middle zones of medial shell after amino acid hyperpolarizations caused by microinjections of an AMPA glutamate antagonist (such as DNQX) or a GABA-A agonist (such as muscimol) (Basso and Kelley, 1999; Kelley et al.,

2005b; Kelley and Swanson, 1997; Maldonado-Irizarry et al., 1995; Stratford, 2005; Stratford and Kelley, 1997, 1999; Stratford et al., 1998; Stratford and Wirtshafter, 2011, 2012).

In our lab, Reynolds and Berridge (2001) first confirmed that muscimol microinjection in rostral-to-middle zones of medial shell generated intense eating, and that progressively more caudal microinjections stopped eliciting eating. Yet Reynolds and Berridge also found that caudal microinjections in NAc shell were not behaviorally 'silent'. Instead caudal sites elicited intense levels of fearful anti-predator behavior known as defensive treading or defensive burying, in which wild rodents use rapid forepaw movements to throw dirt or debris at a threatening stimulus or predator (i.e. rattlesnake or scorpion) (Coss and Owings, 1978; Londei et al., 1998; Reynolds and Berridge, 2001; Treit et al., 1981), and which lab rats emit to a stationary electrified shock prod or in response to predator odor (De Boer and Koolhaas, 2003; Treit et al., 1981). This anti-predator behavior requires the presence of support stimuli: dirt, sand, wood shavings, cob bedding or some similar loose substrate on the floor of the test chamber for the rat to engage with its forepaws and use in throwing or pushing motions. In a cage empty aside from food, the rat cannot readily display the naturalistic fearful response. That stimulus requirement, plus dependence on caudal sites for generation, is probably why the fearful treading behavior was never reported in NAc studies prior to our lab's findings. Defensive treading generated by caudal shell sites (generally between 0.48 and 1.4 mm ahead of bregma) tends not to be emitted randomly in all directions, but instead is targeted upon a particular location or perceived stimulus that the rat apparently defends itself against: treading and throwing bedding toward the front of the transparent cage (e.g., toward the experimenter, cameras, and lights visible beyond the cage) or toward cage corners where light tends to reflect brightly back into the cage from the curved surface of transparent plastic (Reynolds and Berridge, 2001). Additionally, supporting the interpretation that caudal NAc shell sites release motivated fear, if the experimenter attempts to touch a rat showing defensive treading after a caudal shell microinjection of muscimol or DNQX, the rat is likely to emit other fearful or defensive reactions, such as audible distress vocalizations, frantic leaps and attempts to escape, and even to defensively bite the experimenter's approaching hand, though the same rat at all other times is highly tamed and docile (Reynolds and Berridge, 2001, 2002, 2003).

Microinjections of either AMPA glutamate antagonist DNQX or GABAergic agonist muscimol, both of which likely induce localized inhibitions (disinhibiting downstream targets via release from tonic GABAergic inhibition), generate this same rostrocaudal keyboard pattern of intense eating versus intense fear (Fig. 4) (Faure et al., 2008; Reynolds and Berridge, 2001, 2002, 2003). Importantly, only muscimol's GABAergic inhibition, which likely mimics signaling from intrinsic subcortical GABA-releasing circuitry, generates corresponding changes in pleasure versus disgust along a similar rostrocaudal gradient. Muscimol microinjection in a small vertical strip of rostradorsal shell enhances "liking" reactions elicited by bittersweet sucrose-quinine taste, whereas more caudal microinjections produce "disliking" or disgust reactions such as gapes (Faure et al., 2010; Reynolds and Berridge, 2002). In contrast, corticolimbic glutamate blockade with DNQX has no effect at any shell site on either "liking" or "disliking" for tastes, despite generating intense motivations related to eating or fear, potentially indicating that top-down cortical glutamate inputs have less access to subcortically generated hedonic processes mediated by intrinsic GABAergic processing within medial NAc shell (Faure et al., 2010).

The valence of motivated behavior generated by medial shell hyperpolarizations is anatomically biased, such that rostral versus caudal amino acid disruptions typically generate positive versus negative motivational salience, but the behavior produced at a given rostrocaudal site is not absolutely fixed in valence. Environmental and corticolimbic

neurobiological factors can retune (or “flip”) the valence of behavior produced from most sites (Reynolds and Berridge, 2008; Richard and Berridge, 2012). Testing in an aversive, stressful environment, with very bright lights and loud rock music (e.g., Iggy Pop sound track; 80–86 decibels) expands the fear-generating zone, such that microinjections at more rostral locations generate fear (Reynolds and Berridge, 2008). Conversely, testing in a familiar and comfortable home-like environment nearly eliminates fear generation from most sites except in the most posterior rim of caudal shell, and expands the appetitive zone, such that more caudal locations generate only eating (Reynolds and Berridge, 2008). However, eating and fear induced by GABAergic muscimol microinjections that mimic intrinsic subcortical NAc circuits are more resistant to environmental retuning than DNQX glutamatergic microinjections: rostral GABA inhibitions always generate intense eating without fear and caudal GABA inhibitions generate fear without eating, regardless of the current emotional environment (Richard et al., 2012). Therefore, in the small rostral NAc shell area where GABA inhibitions increase hedonic ‘liking’ reactions (Faure et al., 2010), GABA inhibitions never generated fear, even in a stressful environment. This perhaps indicates that separate neuronal ensembles or circuits are responsible for positively valenced ‘liking’/appetitive behaviors versus negatively valenced ‘disgust’/fear.

Endogenous dopamine also plays a role in the glutamatergic generation of appetitive and fearful motivation by corticolimbic AMPA blockade via DNQX microinjection in NAc shell, as well as in the environment-induced shifts of valence mapping and retuning of particular keyboard sites. Adding a combination of D1 and D2 dopamine antagonists to the DNQX microinjection prevents it from generating either eating or fear (Faure et al., 2008). Importantly, when separately compared, D1 and D2 signals play different roles in enabling motivation generation by NAc glutamate disruption. Eating generated by DNQX in rostral medial shell requires only D1 endogenous dopamine transmission, whereas fearful behavior generated by caudal DNQX requires both D1 and D2 transmission (Richard and Berridge, 2011b). Further, the dopamine receptor requirements for a given site in NAc shell can reverse if a change in environmental ambience shifts the valence of motivation generated by AMPA blockade at the site (Richard and Berridge, 2011b). That is, appetitive eating generated by DNQX never requires D2 dopamine transmission, even when generated by caudal shell in a home-like familiar environment. Conversely, defensive behavior generated by DNQX always requires D2 dopamine transmission, even when generated by rostral shell in a stressful environment (Richard and Berridge, 2011b). This D1 versus D2 dopamine receptor difference may indicate differing recruitment of parallel output pathways from NAc. Dopamine D1 receptors are associated with neurons that give rise to direct pathway projections which target ventral tegmentum, whereas D2 receptors are only associated with ‘indirect path’ projections to ventral pallidum and potentially lateral hypothalamus (Humphries and Prescott, 2010; Lu et al., 1998; Richard and Berridge, 2011b; Zhou et al., 2003). D1 versus D2 dopamine receptors also may differently alter glutamatergic inputs from hippocampus, amygdala, and prefrontal cortex origins (Bamford et al., 2004; Charara and Grace, 2003; Nicola et al., 1996; Pennartz et al., 1992; Richard and Berridge, 2012). These differences in inputs and outputs are consistent with the notion that somewhat separate ensembles of neurons or segregated circuits might be recruited in the NAc generation of desire versus dread.

11. Limbic transformations of memories into motivation

Beyond the generation of motivation by mesocorticolimbic circuits, Ann Kelley and colleagues also explored the interaction between motivation and learning within NAc. She notably explored the role played in appetitive instrumental conditioning by NMDA receptors (Kelley et al., 1997) and protein synthesis (Hernandez et al., 2002), and interactions with dopamine in NAc circuits (Kelley and Delfs, 1991).

On the surface, motivation triggered by Pavlovian cues for reward may often appear to simply be learned (e.g., purely due to conditioned associations or memories triggered by a cue) (Schultz et al., 1997; Wise, 2012). However, learned Pavlovian associations account for only half the input required for the generation of the Pavlovian motivation process of incentive salience (Zhang et al., 2009). The other half comes from the neurobiological state of mesocorticolimbic circuits at the moment of cue re-encounter (Zhang et al., 2009), which is influenced by pharmacological/physiological drug states, appetite/satiety states, stress states, etc. An individual's mesocorticolimbic state combines synergistically with learned CS-UCS associations to generate motivation on the fly, and the result of the combination can raise, lower, or even completely reverse the previously learned motivational value (Zhang et al., 2009).

The strongest proof of principle comes from complete reversal by a shift in neurobiological state of motivation valence for a previously learned cue, from attractive to repulsive or from repulsive to attractive (Fig. 5). For example, we have found that an appropriate physiologically induced state shift within mesocorticolimbic circuitry can dynamically convert Pavlovian cue-triggered motivation from repulsion to incentive salience for a CS associated with disgustingly intense saltiness (Robinson and Berridge, 2010; Tindell et al., 2009). This makes that CS into an instant motivational magnet, even if it was always avoided and learned to be aversive on every previous encounter. Our lab recently demonstrated this psychological transformation in practice by first training a Pavlovian association between a CS (sudden appearance of a noisy metal lever in chamber) with the disgusting UCS experience of tasting a salt solution similar to that of the Dead Sea (9% NaCl; 300% more salty than ordinary sea water) directly into the mouth. Subsequently, a combination of hormone and diuretic drug injections was used to produce a novel physiological state of strong salt appetite. In the new appetite state, we found that the salt CS was suddenly transformed into an attractive motivational magnet, as reflected by the rat's behavior: the earlier-avoided CS now elicited behavioral approach and consummatory nibbles and sniffs upon its very first presentation in extinction, with no re-learning about its salty UCS. The CS transformation occurred to the first re-encounter, without the triple seawater salt solution having ever been experienced as anything other than disgusting. We also found that this dramatic motivation transformation from repulsive to attractive was mediated neurobiologically by intense activation of mesocorticolimbic circuits, as reflected by up to 10-times elevations in expression of Fos protein in neurons belonging to NAc (especially rostral shell), prefrontal cortex, ventral pallidum and ventral tegmentum, triggered by the combination of cue re-encounter with novel physiological appetite state (Robinson and Berridge, 2010).

Similar, if not as dramatic, instant re-computations and enhancements of CS motivation value can be accomplished by directly manipulating mesocorticolimbic structures with opioid or dopamine stimulation to alter neurobiological state. Typically, rather than reverse value, this suddenly raises an already moderately high and positive CS motivation value from the level that was previously learned to a new even higher peak that was never learned or experienced prior to the recombination. For example, microinjections of amphetamine or DAMGO into NAc shell or core produces robust increases in cue-triggered 'wanting' for sugary rewards as measured in Pavlovian to instrumental transfer (PIT) or in neuronal incentive salience signals (Pecina and Berridge, 2008; Wyvell and Berridge, 2000). Similarly, microinjections of DAMGO or amphetamine raise conditioned reinforcement value or breakpoint values in instrumental tests that might reflect incentive salience (Cunningham and Kelley, 1992; Kelley and Delfs, 1991; Zhang et al., 2003). We have found that DAMGO microinjections in other striatal-type structures such as the central amygdala also increase cue-triggered 'wanting' in PIT and likewise increase the motivational magnet strength of an individual's favorite reward cue in a sign-tracking versus goal-tracking test

(autoshaping) (DiFeliceantonio and Berridge, 2012; Mahler and Berridge, 2009, 2012). Conversely, microinjections of a dopamine antagonist into NAc core immediately suppress the motivational magnet features of a CS for sugar in sign-tracking rats (Saunders and Robinson, 2012).

The power of a motivational magnet consists of the intensity and frequency of behaviors directed at a cue. Importantly, it is computed on line and is transferable to other reward cues. When in the absence of a goal, for example with intra-oral sucrose delivery, rats that might have ordinarily have been goal-trackers instead engage in sign-tracking behavior (Robinson and Berridge, 2010). Both sign and goal cues can transform into motivational magnets for goal-trackers with certain neurobiological or environmental manipulations (DiFeliceantonio and Berridge, 2012; Mahler and Berridge, 2012; Robinson and Berridge, 2010). In addition, sign-trackers can flip to goal-tracking behavior after some mesolimbic-related pharmacological stimulations or sensitization (Doremus-Fitzwater and Spear, 2011; Holden and Peoples, 2009; Simon et al., 2009), which might boost the incentive salience of UCS-proximal cues such as the goal at the expense of UCS-distal cues such as the Pavlovian CS sign (Smith et al., 2011; Tindell et al., 2006).

Therefore, it seems clear that neurobiological state modulations of mesocorticostratial circuitry can synergistically combine with previously learned Pavlovian CS-UCS associations to produce sudden changes in psychological incentive salience attributed to the CS at the moment it is re-encountered. These modulations can flexibly change the temptation power of a learned Pavlovian cue for reward either up or down, depending on the neurobiological modulation, and do so even when all learned associations remain unchanged. In other words, there is more to Pavlovian motivation than learning per se.

12. Relation of affective neuroscience functions to brain mechanisms of decisions and learning

Our discussion has focused on the generation of intense levels of motivation (e.g., 'wanting' and fear) and hedonic reactions ('liking' and 'disgust') by NAc circuitry interacting with related structures such as ventral tegmentum, neostriatum, amygdala and neocortex. How do these topics relate to other psychological functions such as cognitive decision making or to learning of reward predictions or habits? And how do anatomical features such as localized hedonic hotspots or rostrocaudal desire-fear keyboards relate to other features of mesocorticostratial circuits, such as spiraling connections between midbrain and striatal targets that ascend dorsally from nucleus accumbens to neostriatum (Haber et al., 2000)? We believe that larger perspectives can eventually accommodate all of these functions and features. For example, the generation of 'liking' and 'wanting' components of reward considered here ordinarily must interact with learning components of reward and related functions (e.g., Pavlovian, instrumental and cognitive mechanisms of learning) to produce real behavior.

Motivational processes such as incentive salience contribute even to cognitive decision making in the sense that subcortically generated 'wanting' can bias decisions, including decisions ordinarily controlled by cortex-based circuitry. At intense extremes, motivational processes such as mesolimbic incentive salience or fearful salience can substantially take control of decision-making, producing compulsive forms of addictions or of fearful paranoia. The affective neuroscience functions discussed here co-exist alongside whatever other psychological functions turn out to be mediated by striatal-related circuitry, which by some views would also include prediction error or habit-learning functions (Graybiel, 2008; Schultz et al., 1997).

Neuroanatomically, the distinctive neurobiological substrate features responsible for giving unique hedonic-generating functions to the NAc hotspot or VP hotspot, or responsible for creating rostrocaudal keyboards in NAc shell for generating desire versus fear (Thompson and Swanson, 2010; Zahm et al., 2012), similarly must co-exist with other mesocorticostratial anatomical wiring features, which include ascending spirals of progressive ventral-to-dorsal information flow (Haber et al., 2000). Although we have focused purely on features underlying the generation of intense motivation and affect, eventually more fully informed perspectives will be able to incorporate all such features and additional functions.

13. Conclusions

`Liking', `wanting' and learning components of reward can be teased apart and to some degree linked to separable brain substrates. Opioid and related hedonic hotspot networks in NAc-pallidal circuits generate and amplify `liking' for sensory pleasures of food. Intense `wanting' to over-consume is generated by larger striatal networks, including even amygdala and the most dorsal levels of neostriatum. `Wanting' is also generated by corticolimbic glutamate interactions with mesolimbic dopamine, but surprisingly overlaps with NAc mechanisms that can equally generate intensely fearful motivations too. Finally, changes in the neuro-biological reactivity of mesocorticolimbic circuitry can completely transform the psychological motivation value of previously learned memories, without any new learning (a transformation potentially relevant to compulsive addictions). Each of these conclusions comes from lines of research in our lab that were originally inspired in large part by earlier ground-breaking findings of Ann Kelley and her laboratory. In short, Ann Kelley was a scientific path finder, whose impressive talent and energy opened up a number of new vistas for research on the brain and motivation. We were fortunate to follow in her scientific path, and like many others in the field we continue to be inspired by her marvelous achievements.

Acknowledgments

Some of the results described here are from work supported by National Institutes of Health grants DA015188 and MH63649 (KCB), F31 MH090602 (JMR), T32 DC00011 (DCC) and T32 DA007267 (AGD).

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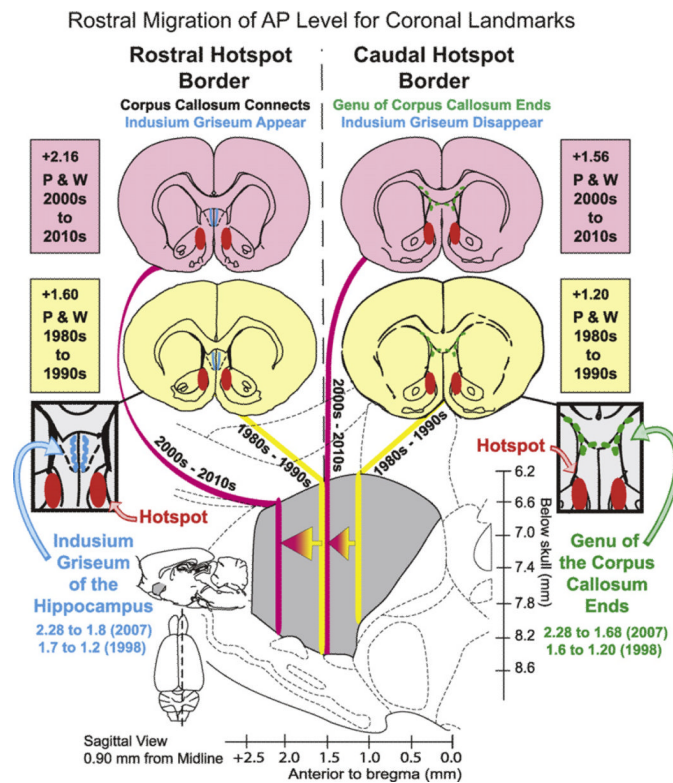


Fig. 1.

Rostral shift of anatomical markers for the NAc shell hotspot in the coronal view. Sagittal illustration of how the anteroposterior (AP) value of the rostral and caudal boundaries of the hedonic hotspot (red) have apparently shifted forward, in terms of distance from bregma, based on a comparison of coronal planes in early editions of a popular brain atlas in 1980s and 1990s (yellow; Paxinos and Watson, 1998) to the more recent 2007 edition (pink; Paxinos and Watson, 2007). As one result, anatomical markers for the rostral border of the hotspot, such as the rostral-most extent of the indusium griseum of the hippocampus (blue) where the corpus callosum is first joined, is labeled as 1.6 mm ahead of bregma in 1998 (yellow; Paxinos and Watson, 1998) but as 2.16 mm ahead of bregma in 2007 (pink; Paxinos and Watson, 2007). Concurrently, markers for the caudal border of the hotspot (a point just caudal to the genu of the corpus callosum and the indusium griseum) have changed from 1.2 mm ahead of bregma (yellow; Paxinos and Watson, 1998) to 1.56 mm ahead of bregma (pink; Paxinos and Watson, 2007). The marker referred to as indusium griseum appears as two thin vertical strips, about one mm long, of darker gray matter near the midline located in the medial portion of the dorsal peduncular cortex, extending ventrally from the corpus callosum. The more posterior marker provided by the end of the genu of corpus callosum occurs at the AP point where the rostral genu transitions to the main body of corpus callosum. At that point, the ventral (rostral) tip of indusium griseum is no longer visible in coronal section (though a small dorsal portion of indusium griseum can still be seen just dorsal to the corpus callosum). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

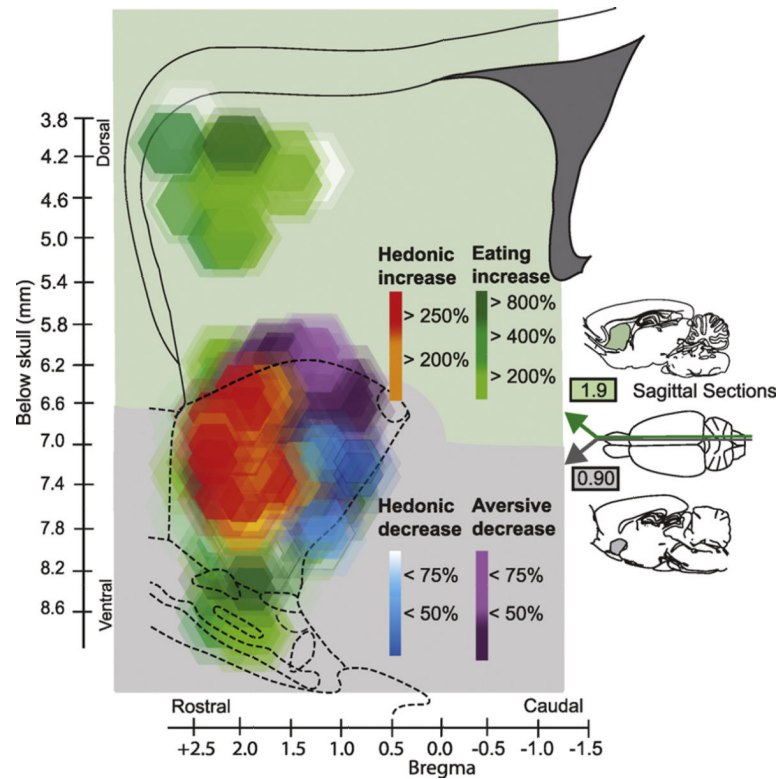
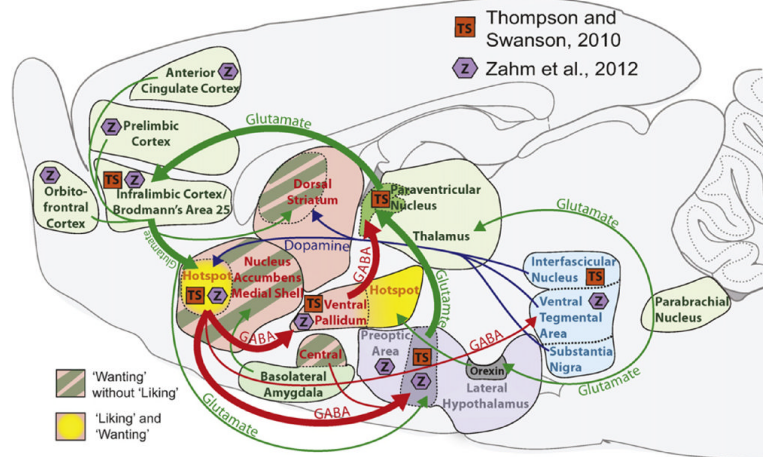


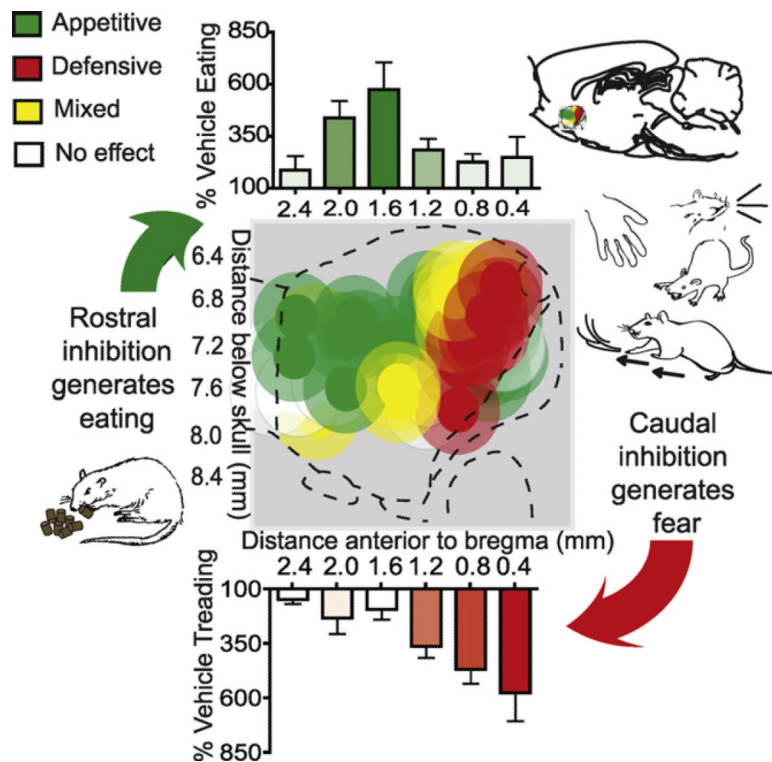
Fig. 2.

Fos plume maps of mu-opioid effects on eating and 'liking' in NAc shell. Sagittal illustration of rostral opioid hedonic hotspot in nucleus accumbens (red/orange), as mapped by consequences on hedonic impact and on intake. Symbol sizes show radius of DAMGO microinjection spread based on Fos plumes, and symbol colors indicate where microinjections only generated eating (green), or additionally generated enhanced 'liking' (the hedonic hotspot, orange to red), reduced 'disliking' or aversion (purple), or reduced 'liking' for sucrose task (coldspot, blue). The green in nucleus accumbens extends under all other colors and fills medial shell. The top of map also shows opioid eating generation site in dorsomedial neostriatum generated eating (with no impact on taste 'liking' or 'disliking'). Only a cubic-millimeter sized hedonic hotspot in NAc shell generates increased 'liking', whereas a small blue hedonic "coldspot" in caudal shell oppositely suppresses 'liking' reactions to sucrose, and a larger purple zones suppresses 'disliking' reactions to quinine. All of these sites still generate eating. Two sagittal planes of different laterality were merged to represent both dorsomedial striatum (1.9 mm from midline) and medial NAc shell (gray, 0.9 mm from midline) in one sagittal map. Based on data from Pecina and Berridge (2006) and DiFeliceantonio et al. (2012). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Mesocorticolimbic Circuits for 'Liking' and 'Wanting'

**Fig. 3.**

Neural circuits underlying motivated 'wanting' and hedonic 'liking'. A summary map showing the connections between cortical, limbic, and midbrain nuclei, with a particular focus on the unique connectivity of the NAC hotspot. Thompson and Swanson (TS, orange boxes; 2010) reported that the NAC hotspot is embedded in a closed-circuit loop, receiving corticolimbic inputs from infralimbic cortex, and projecting outputs to restricted subregions of hypothalamus (lateral preoptic area-lateral hypothalamic transition zone) and rostral ventral pallidum. These hypothalamo-pallidal afferents then project to paraventricular nucleus of the thalamus, which then completes the loop by sending efferents to infralimbic cortex. Zahm et al. (Z, purple hexagons; 2012) suggest additional connectivity in a pattern similar to lateral septum. GABAergic projections are indicated in red, hedonic hotspots are marked in yellow, potentiated 'wanting' (without 'liking') regions are indicated by dark green stripes, glutamatergic projections are bright green, and dopaminergic projections are marked in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

**Fig. 4.**

Example desire and dread gradient. Sagittal map of intense desire-dread keyboard generated by microinjections that hyperpolarize via glutamate or GABA neurotransmitter signals in NAc medial shell (example from glutamatergic AMPA blockade). DNQX microinjections produced intense appetitive (green), fearful (red) or mixed appetitive and fearful (yellow) motivated behaviors. Rostral DNQX generates purely intense eating, whereas more caudal microinjection generate intense defensive behaviors, including touch-elicited distress vocalizations, escape attempts and bite attempts, and spontaneous defensive treading. Bars above and below the maps show behavioral intensities of eating (above, green) and treading (below, red) as a percent of vehicle level in the same rats (error bars indicate SEM). From Richard and Berridge (2011a,b). Similar patterns of intense behaviors have been found after GABAergic muscimol microinjections and replicated for DNQX in other studies (Reynolds and Berridge, 2001, 2002, 2003, 2008; Faure et al., 2008, 2010). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

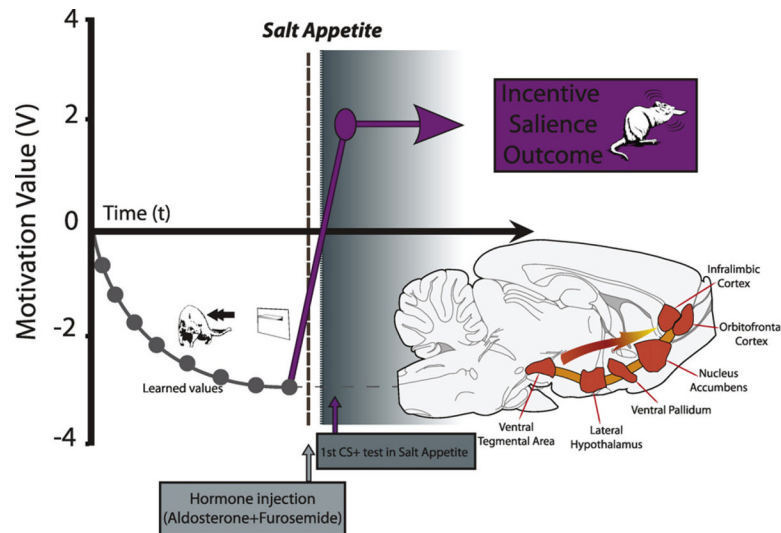


Fig. 5. Theoretical model of the synergy between learned values and mesocorticolimbic activation. The diagram displays the impact of a sudden change in internal/mesocorticolimbic state (novel salt appetite) on the progressively learned negative value of a Pavlovian CS according to the prediction made by incentive salience theory (Zhang et al., 2009). Incentive salience theory predicts that a change in internal mesocorticolimbic state would be sufficient to drastically change the reward value of a CS from negative to positive without requiring new learning (presentation of the CS alone). Upon the first presentation of the CS for intense saltiness alone (no UCS salt solution), the cue is instantly transformed from previously avoided to jumped upon and avidly nibbled, despite its associated UCS having only ever been experienced as highly disgusting and aversive.