

Pleasure Systems in the Brain

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Pleasure is mediated by well-developed mesocorticolimbic circuitry and serves adaptive functions. In affective disorders, *anhedonia* (lack of pleasure) or *dysphoria* (negative affect) can result from breakdowns of that hedonic system. Human neuroimaging studies indicate that surprisingly similar circuitry is activated by quite diverse pleasures, suggesting a common neural currency shared by all. Wanting for reward is generated by a large and distributed brain system. Liking, or pleasure itself, is generated by a smaller set of hedonic hot spots within limbic circuitry. Those hot spots also can be embedded in broader anatomical patterns of valence organization, such as in a keyboard pattern of nucleus accumbens generators for desire versus dread. In contrast, some of the best known textbook candidates for pleasure generators, including classic pleasure electrodes and the mesolimbic dopamine system, may not generate pleasure after all. These emerging insights into brain pleasure mechanisms may eventually facilitate better treatments for affective disorders.

The English word “hedonic” comes originally from the ancient Greek for pleasure (*ἡδονή*; in Latin script: *hédoné*), in turn derived from the word for “sweet” (*ἡδύς* or *hédús*). Today hedonic refers to sensory pleasures as well as many higher types of pleasure (e.g., cognitive, social, aesthetic, and moral).

Some goals of affective neuroscience are to understand how brain mechanisms generate pleasures, and also displeasures, and eventually find more effective treatments for affective disorders (Anderson and Adolphs, 2014; Damasio and Carvalho, 2013; Haber and Knutson, 2010; Heller et al., 2013; Kringelbach and Berridge, 2010; Panksepp, 2011). Capacity for normal pleasure is essential to healthy psychological function or well-being. Conversely, affective disorders can induce either the pathological absence of pleasure reactions (as in clinical anhedonia) or the presence of excessive displeasure (dysphoric emotions such as pain, disgust, depression, anxiety, or fear).

But is a neuroscience of pleasure feasible? Doubts that pleasure might be scientifically understood have been expressed for over a century. Early doubts stemmed from behaviorist convictions that only objective behavioral-neural reactions were eligible for scientific study and never subjective experiences (including the experience of pleasure). However, progress in the past 50 years proves that many complex psychological processes involving subjective experience can be successfully studied and related to underlying brain mechanisms. Still, some objections persist today. For example, LeDoux’s recent recommendation that affective neuroscientists should focus only on behavioral affective reactions, rather than on subjective emotions, shares those earlier concerns (LeDoux, 2014).

In our view, a neuroscience of pleasure can be pursued as successfully as the neuroscience of perception, learning, cognition, or other well-studied psychological functions. The crucial test of this proposition is: can affective neuroscience produce

important new conclusions into how brain systems mediate hedonic impact? Evidence in support of this, we think, now exists in the form of recent findings. In this article we discuss some of these new findings, including (1) separation of reward liking, wanting, and learning mechanisms in mesocorticolimbic circuitry; (2) identification of overlap in neural circuitry underlying sensory pleasures and higher pleasures; (3) identification of particular sites in prefrontal limbic cortex that encode pleasure impact; (4) mapping of surprisingly localized causal hedonic hot spots that generate amplifications of pleasure reactions; (5) discovery that nucleus accumbens (NAc) hot spot and cold spot mechanisms are embedded in an anatomically tuned keyboard organization of generators in NAc that extends beyond reward liking and wanting to negative emotions of fear and disgust; and (6) identification of multiple neurochemical modes within NAc mechanisms that can retune keyboard generators into flipping between oppositely valenced motivations of desire and dread.

A Neuroscience of Pleasure

In a sense, pleasure can be thought of as evolution’s boldest trick, serving to motivate an individual to pursue rewards necessary for fitness, yet in modern environments of abundance, also inducing maladaptive pursuits such as addictions. An important starting point for understanding the underlying circuitry is to recognize that reward involves a composite of several psychological components: liking (core reactions to hedonic impact), wanting (motivation process of incentive salience), and learning (Pavlovian or instrumental associations and cognitive representations) (Berridge and Robinson, 2003). These component processes also have discriminable neural mechanisms. The three processes can occur together at any time during the reward-behavior cycle, though wanting processes tend to dominate the initial appetitive phase, while liking processes dominate the subsequent consummatory phase that

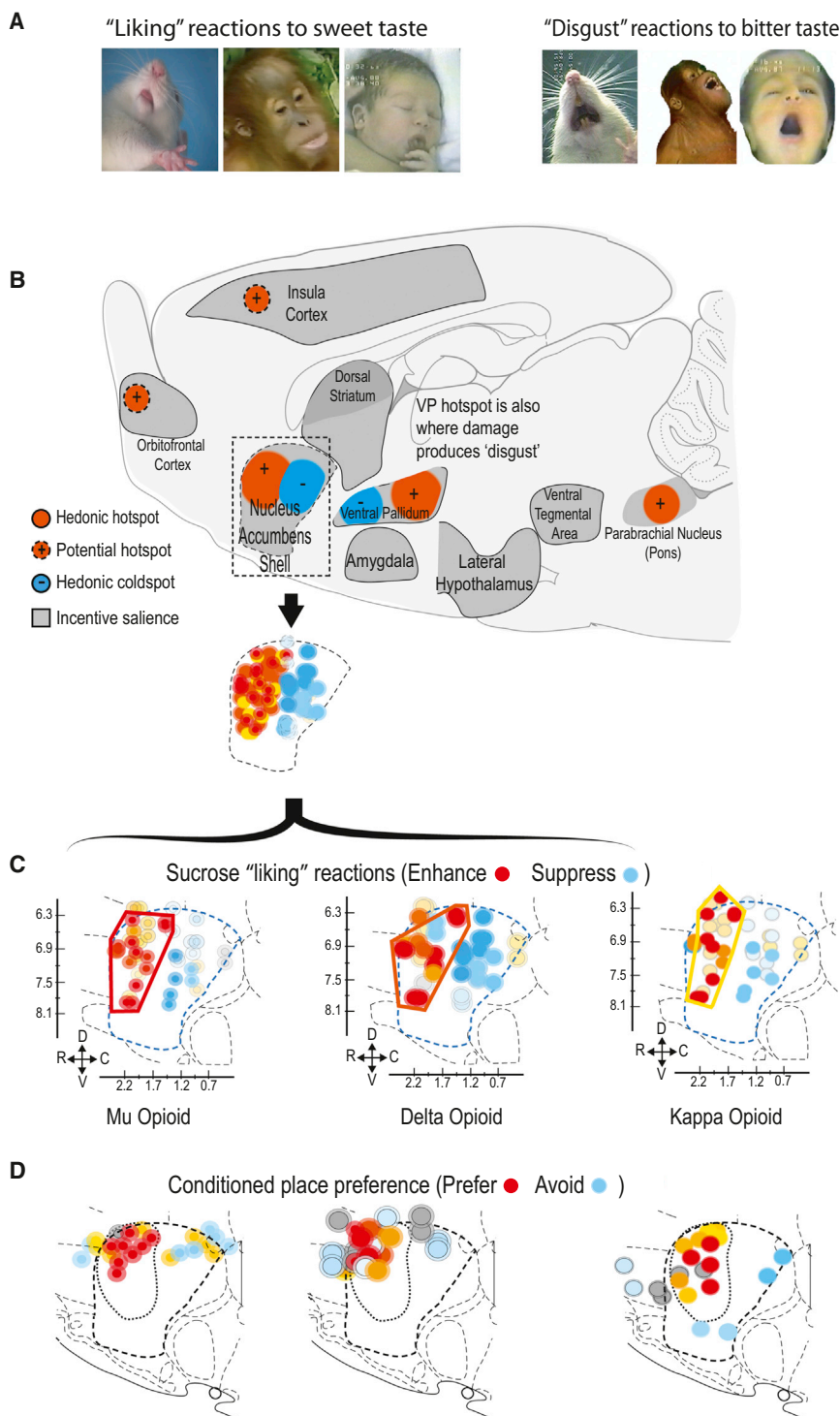


Figure 1. Causal Hedonic Hot Spots and Cold Spots in the Brain

(A) Top shows positive hedonic orofacial expressions ("liking") elicited by sucrose taste in rat, orangutan, and newborn human infant. Negative aversive ("disgust") reactions are elicited by bitter taste.

(B) Middle shows sagittal view of hedonic hot spots in rat brain containing the NAC, VP, and prefrontal cortex. Hot spots (red) depict sites where opioid stimulation enhances "liking" reactions elicited by sucrose taste. Cold spots (blue) show sites where the same opioid stimulation oppositely suppresses "liking" reactions to sucrose.

(C) NAC blow-up of the medial shell shows effects of opioid microinjections in the NAC hot spot and cold spot (red/orange dots in hot spot = > 200% increases in "liking" reactions to sucrose. Cold dots in cold spot = 50% reductions in "liking" reactions to sucrose). Panels show separate hedonic effects of mu opioid, delta opioid, and kappa opioid stimulation via microinjections in the NAC shell on sweetness "liking" reactions. Bottom row shows effects of mu, delta, or kappa agonist microinjections on establishment of a learned place preference (i.e., red/orange dots in hot spot) or place avoidance (blue dots). Surprisingly similar patterns of anterior hedonic hot spots and posterior suppressive cold spots are seen for all three major types of opioid receptor stimulation. Modified from [Castro and Berridge \(2014\)](#).

(D) Bottom row shows effects of mu, delta, or kappa agonist microinjections in NAC medial shell on establishment of a learned place preference (i.e., red/orange dots in hot spot) or place avoidance (blue dots). Surprisingly similar patterns of anterior hedonic hot spots and posterior suppressive cold spots are seen for all three major types of opioid receptor stimulation. Modified from [Castro and Berridge \(2014\)](#).

may lead to satiety. Learning, on the other hand, happens throughout the cycle. A neuroscience of reward seeks to map these components onto necessary and sufficient brain networks (see [Figure 1](#)).

To study pleasure comprehensively, good human neuroimaging studies are needed to explore correlative encoding of

reactions (with quotes) to distinguish them from the subjective experience of liking (in the ordinary sense, without quotes). Objective hedonic reactions can be measured in both human and animal neuroscience studies, which together allow some comparisons across species and can lead to a more complete causal picture of how brain systems mediate hedonic impact.

Evolutionary Origins of Brain Systems for Hedonic Reactions

The ultimate explanation for why pleasure encompasses both objective and subjective levels of reaction likely lies in evolutionary history. Darwin (1872) originally suggested that affective reactions were selected by evolution for their useful functions, which were adapted into emotional expressions. Following Darwin's logic, modern affective neuroscience also posits brain mechanisms of emotional reactions to mediate evolved "survival functions" (LeDoux, 2012), with emotional "core features that can form the basis for studies of emotion across phylogeny" (p. 198) (Anderson and Adolphs, 2014), which can be usefully exploited by objective studies.

The selection of hedonic reactions has required the evolution of mammalian brains to dedicate millions of developing neurons into mesocorticolimbic patterns of reward circuitry (Haber and Knutson, 2010). Such neural investment was subject to the same selection pressures that shaped evolution of any other function. Hedonic circuitry was therefore unlikely to have been shaped into its present form, or to have persisted throughout evolution, unless objective affective reactions actually conveyed significant consequences in terms of benefits for survival and fitness (Anderson and Adolphs, 2014; Damasio, 2010; Kringelbach and Berridge, 2010; LeDoux, 2012; Panksepp, 2011). Objective affective reactions likely appeared first during evolution, with subjective affective reactions following in some species, via the evolution of more elaborate and hierarchical brain mesocorticolimbic circuitry to translate core "liking" reactions into conscious feelings of pleasure (Damasio and Carvalho, 2013).

Objective Hedonic Reactions

A useful example of an objective hedonic reaction is the orofacial affective expression of "liking" elicited by tastes in newborn human infants (Steiner, 1973). Positive taste "liking" versus negative "disgust" expressions can be elicited on the first post-natal day (Figure 1). Sweet tastes elicit positive hedonic "liking" expressions comprising relaxed facial muscles and a contented licking of the lips, whereas bitter tastes elicit "disgust" expressions. Homologous "liking" orofacial expressions can be elicited also in apes and monkeys and even in rats and mice (e.g., rhythmic tongue protrusions and lateral lip licking to sweetness versus gapes and headshakes to bitterness) (Berridge, 2000; Grill and Norgren, 1978a; Steiner et al., 2001). The basic sensorimotor circuitry of these affective expressions resides in the brainstem (Grill and Norgren, 1978b; Steiner, 1973), but such affective expressions are not mere brainstem reflexes, but rather are hierarchically controlled by forebrain structures. Forebrain circuitry exerts powerful descending control over brainstem and behavioral output. A consequence is that "liking" expressions elicited by a given taste are appropriately modulated physiologically by relevant appetite versus satiety states (Cabanac and Lafrance, 1990; Kaplan et al., 2000), as well as associatively by learned preferences and aversions (Delamater et al., 1986). Most strikingly, "liking" reactions are powerfully controlled by discrete neural manipulations located in several limbic forebrain structures, as will be discussed (Castro and Berridge, 2014; Mahler et al., 2007; Pecina and Berridge, 2005; Smith and Berridge, 2005).

"Liking" facial expressions also belong to the consummatory class of motivated behaviors, which typically occurs after an initial appetitive phase of flexible seeking behavior (Craig, 1918; Sherrington, 1906). Those hedonic reactions co-occur with several other ingestive consummatory reactions, including voluntary consumption of food, the microstructure of consumption movements (often measured as spout-lick patterns by lickometers in animal studies), and the simple brainstem decision to swallow food in the mouth. But consummatory reactions are highly heterogeneous. In particular, affective taste reactivity patterns most closely track the hedonic evaluation of taste "liking" and sometimes for that reason dissociate from all other consummatory reactions (Berridge, 2000). Dissociation is most commonly induced by manipulations that alter motivational (i.e., "wanting"), but not hedonic aspects ("liking") of the value of a food incentive. For example, dopamine suppressions reduce the incentive value of sweetness similar to sucrose dilution, as reflected in changes in lickometer measures of ingestive microstructure (Galistu and D'Aquila, 2012; Smith, 1995), as well as suppressing appetitive seeking and sometimes food intake (Wise and Raptis, 1986). Yet, taste reactivity "liking" expressions are not diminished by such pharmacological dopamine blockades (Pecina et al., 1997), or even by complete destruction of mesolimbic dopamine projections. Such dissociations have indicated that dopamine is not actually needed for the hedonic impact of food pleasure, but rather only for their incentive motivation value, as described further below.

Subjective versus Objective Levels of Hedonic Reaction

As mentioned above, to avoid confusion it is useful to use "liking" (in quotes) to specifically refer to behavioral or neural hedonic reactions, whether or not those objective "liking" reactions are accompanied by a corresponding conscious liking or feeling of pleasure (which may require additional neural mechanisms). A similar distinction applies to conscious wanting versus the mesolimbic motivation process of incentive salience or "wanting" and its objective consequences. The subjective versus objective distinction is based also on evidence that, even in humans, the two forms of hedonic reaction can be independently measured. For example, objective hedonic "liking" reactions can sometimes occur alone and unconsciously in ordinary people without any subjective pleasure feeling at all, at least in particular situations (e.g., evoked by subliminally brief or mild affective stimuli) (Childress et al., 2008; Fischman and Foltin, 1992; Winkielman et al., 2005). Unconscious "liking" reactions still effectively change goal-directed human behavior, though those changes may remain undetected or be misinterpreted even by the person who has them (Bargh et al., 2012; Childress et al., 2008; Pessiglione et al., 2007; Winkielman et al., 2005). More commonly, "liking" reactions occur together with conscious feelings of liking and provide a hedonic signal input to cognitive ratings and subjective feelings. However, dissociations between the two levels of hedonic reaction can still sometimes occur in normal people due to the susceptibility of subjective ratings of liking to cognitive distortions by framing effects, or as a consequence of theories concocted by people to explain how they think they should feel (Gilbert and Wilson, 2009; Schooler and Mauss, 2010). For example, framing effects can cause two people exposed to the

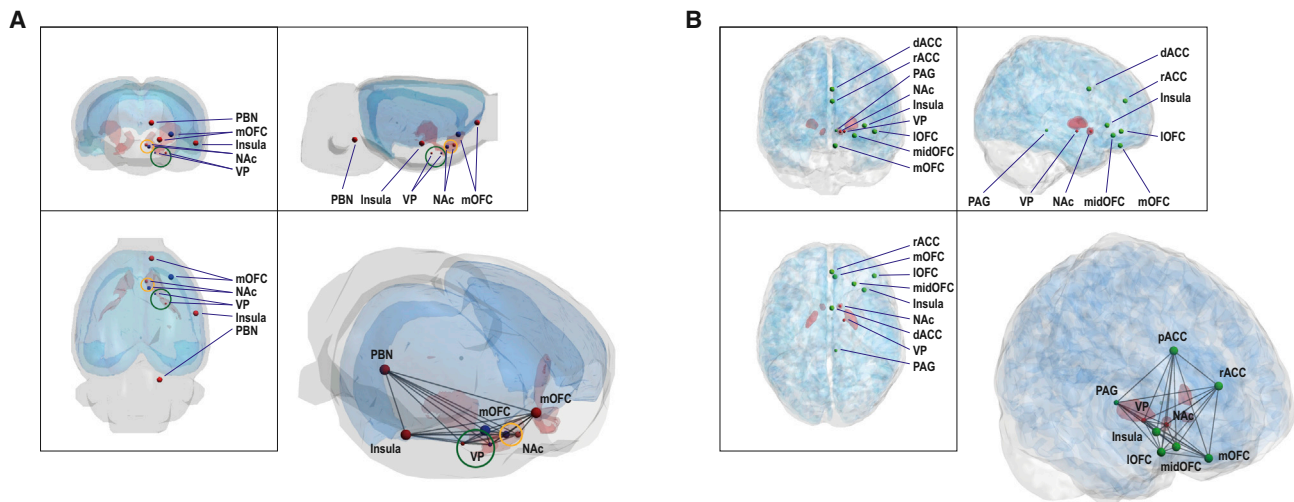


Figure 2. 3D Comparison of Hedonic Sites in Rat Brain and Human Brain

(A) Rat brain shows hedonic hot spots (red) and cold spots (blue) in a glass-brain view seen from the front, the side, 3D fronto-lateral perspective, and from the top (clockwise from top left). (B) Human brain shows extrapolation of rat causal hot spots to analogous human sites in the NAc and VP (red) and shows fMRI coding sites for positive affective reactions in green (from text). Human views are also from front, side, 3D perspective, and top (clockwise from top left of B). The tentative functional networks between the different hot spots and cold spots have been added to give an impression of the topology of a pleasure network. The functional connection lines are not meant to imply direct anatomical projections between two connected structures, but rather a functional network in mediating hedonic “liking” reactions and subjective pleasure ratings. Parabrachial nucleus (PBN); medial OFC (mOFC); lateral OFC (lOFC); mid-anterior OFC (midOFC); dorsal anterior cingulate cortex (dACC); rostral anterior cingulate cortex (rACC); and periaqueductal gray (PAG).

same stimulus to report different subjective ratings, if one of them had a wider range of previously experienced hedonic intensities (e.g., pains of childbirth or severe injury) (Bartoshuk, 2014). In short, there is a difference between how people feel and report subjectively versus how they objectively respond with neural or behavioral affective reactions. Subjective ratings are not always more accurate about hedonic impact than objective hedonic reactions and the latter can be measured independently of the former.

Mapping Pleasure in the Brain

The experience of one pleasure often seems very different from another. Eating delicious foods, experiencing romantic or sexual pleasures, using addictive drugs, listening to music, or seeing a loved one: each feels unique. The only psychological feature in common would seem that all are pleasant. However, the difference in one’s subjective experiences is not necessarily a good guide to the underlying neural mechanisms. Those neural mechanisms may overlap to a surprising degree.

Over the last decades, a growing set of results from neuroimaging studies have suggested that many diverse rewards activate a shared or overlapping brain system: a “common currency” reward network of interacting brain regions. Pleasures of food, sex, addictive drugs, friends and loved ones, music, art, and even sustained states of happiness can produce strikingly similar patterns of brain activity (Cacioppo et al., 2012; Georgiadis and Krangelbach, 2012; Krangelbach et al., 2012; Parsons et al., 2010; Salimpoor et al., 2011; Vartanian and Skov, 2014; Veldhuizen et al., 2010; Vuust and Krangelbach, 2010; Xu et al., 2011; Zeki and Romaya, 2010). These shared reward networks include anatomical regions of prefrontal cortex, including por-

tions of orbitofrontal, insula, and anterior cingulate cortices, as well as often subcortical limbic structures such as NAc, ventral pallidum (VP), and amygdala (shown for rats and humans in Figure 2). An implication of the common currency hypothesis is that insights into brain hedonic substrates gained by experiments using one kind of pleasure, such as food “liking”, may apply to many other pleasures too.

Admittedly, fMRI measures have limits in spatial and temporal resolution that might miss small or fast differences among neural subsystems that encode a particular reward. It remains possible that more fine-grained spatial and temporal multivariate pattern analysis techniques (Haynes and Rees, 2006; King and Dehaene, 2014) will identify subsets of limbic neural circuitry particular to just one type of reward (Chikazoe et al., 2014). Consistent with this, subtle differences may be found in neuronal firing in animal studies between different sensory rewards, such as tasty foods versus addictive drugs (though some neural differences may be due to accompanying confounds, such as different movements required to obtain the different reward, or sensory accompaniments, rather than to unique reward encoding per se) (Cameron and Carelli, 2012). Still, so far, the balance of evidence suggests rather massive overlap between neural systems that mediate rewards of different types. The overlap is far more extensive than many might have expected based on the subjective differences in experiences.

A human brain site that appears especially linked to pleasure in neuroimaging studies is in the orbitofrontal cortex (OFC), particularly in a mid-anterior subregion (Figures 2 and 3). Other medial regions of the orbitofrontal cortex, middle anterior regions of the insula cortex, and ventromedial regions of the prefrontal cortex also correlate with subjective pleasure ratings, but many of these

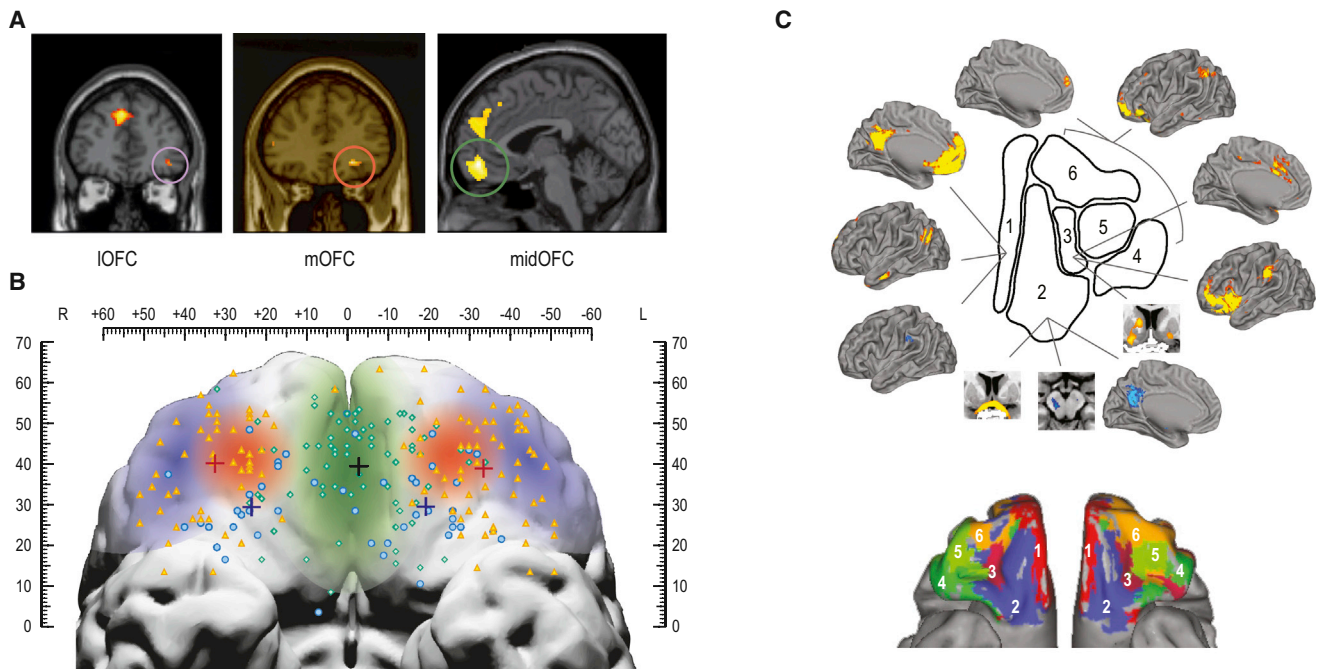


Figure 3. Hedonic Coding in the Human Orbitofrontal Cortex

In humans, the OFC is an important hub for pleasure coding, albeit heterogeneous, where different subregions are involved in different aspects of hedonic processing (Kringelbach, 2005).

(A) Neuroimaging investigations have found differential activity to reward depending on context in three subregions: the medial OFC (mOFC), mid-anterior OFC (midOFC), and lateral OFC (IOFC).

(B) A meta-analysis of neuroimaging studies showing task-related activity in the OFC demonstrated different functional roles for these three subregions. In particular, the midOFC appears to best code the subjective experience of pleasure such as food and sex (orange), while mOFC monitors the valence, learning, and memory of reward values (green area and round blue dots). However, unlike the midOFC, activity in the mOFC is not sensitive to reward devaluation and thus may not so faithfully track pleasure. In contrast, the IOFC region is active when punishers force a behavioral change (purple and orange triangles). Furthermore, the meta-analysis showed a posterior-axis of reward complexity such that more abstract rewards (such as money) would engage more anterior regions to more sensory rewards (such as taste).

(C) Further investigations into the role of the OFC on the spontaneous dynamics during rest found broadly similar subdivisions in terms of functional connectivity (Kahnt et al., 2012) with an optimal hierarchical clustering of four to six OFC regions. This included medial (1), posterior central (2), central (3), and lateral (4–6) clusters with the latter spanning an anterior-posterior gradient (bottom of Figure 3B) and connected to different cortical and subcortical regions (top of Figure 3B). Taken together, both the task-related and resting-state activity provides evidence for a significant role of the OFC in a common currency network. It is also compatible with a relatively simple model where primary sensory areas feed reinforcer identity to the OFC, where it is combined to form multi-modal representations and assigned a reward value to help guide adaptive behavior (Kringelbach and Rolls, 2004). Images in (A) are based on Kringelbach et al. (2003, 2004).

other regions appear to be more concerned with monitoring or predicting reward values than with generating the pleasure *per se* (Georgiadis and Kringelbach, 2012; Kahnt et al., 2010; Kringelbach, 2005; Kringelbach et al., 2003; O'Doherty, 2014; Schoenbaum and Roesch, 2005; Veldhuizen et al., 2010; Vuust and Kringelbach, 2010).

It is important to remember that neuroimaging studies are correlational in nature rather than causal, and that the physiological bases of underlying signals (such as the blood-oxygen-level-dependent [BOLD] signal measured with fMRI) are only partly understood (Winawer et al., 2013). Interpreting correlational signals is complicated. Some correlational neuroimaging activity may of course reflect causal mechanisms for pleasure, while other activity may be a consequence, rather than cause. That is because many brain regions that become active during a normal pleasure may not actually generate that pleasure *per se*, but rather activate as a step to causally generating their own different functions, such as cognitive appraisal, memory, attention, and decision making about the pleasant event.

However, the mid-anterior subregion of the orbitofrontal cortex in particular does appear to track subjective pleasure more accurately than most other limbic regions (Figure 3). Among the strongest tests for pleasure coding is to hold the pleasant stimulus constant across successive exposures, but vary its hedonic impact by altering other input factors, such as relevant physiological states. For example, evidence suggests that mid-anterior orbitofrontal activity tracks sensory satiety, involving selective declines in the subjective pleasantness of a given food's taste after consuming a lot of it, compared to another food which is not devalued (Gottfried et al., 2003; Kringelbach et al., 2003). Tracking a *change* in pleasure of a stimulus is the strongest possible correlational evidence, because it shows the activity is not coding mere sensory features (e.g., sweetness) or other stable confounds. The same region of orbitofrontal cortex has also been implicated in the encoding pleasures of sexual orgasm, drugs, and music (Georgiadis and Kringelbach, 2012; Kringelbach, 2005; Kringelbach et al., 2003; Salimpoor et al., 2011; Veldhuizen et al., 2010; Vuust and Kringelbach, 2010).

Subcortically, there is evidence from other animals that such selective hedonic changes also may be tracked by activity in the NAc and VP (Krause et al., 2010; Loriaux et al., 2011; Roitman et al., 2010; Tindell et al., 2006).

Some studies also indicate lateralization of affect representation, often as lateralized hemispheric differences in coding positive versus negative valence. Most notably, the left hemisphere of the prefrontal cortex often has been implicated more in positive affect than the right hemisphere (Davidson, 2004). For example, individuals who give higher ratings of subjective well-being may have higher activity in the left than the right prefrontal cortex, and activity of left subcortical striatum also may be more tightly linked to pleasantness ratings than the right-side (Kühn and Gallinat, 2012; Lawrence et al., 2012; Price and Harmon-Jones, 2011). However, other studies have found more equal or bilateral activity patterns, and so the precise role of lateralization in pleasure still needs further clarification.

An important caveat of human neuroimaging studies is that these have traditionally compared a hedonic activation with a baseline at rest. Recently, it has become clear that the brain is never truly resting, but rather spontaneously active and constantly switching between different resting state networks (Cabral et al., 2014). The switching between different networks depends on the state of the brain, and so one way to think about the pleasure system is to facilitate the state transition between different points in the pleasure cycle to optimize survival. Plausibly, the so-called *default mode network* may play an essential role in this, and thus problems in orchestrating the state transitions may manifest as anhedonia in affective disorders (Kringelbach and Berridge, 2009). With advanced computational modeling of human neuroimaging data, this is now becoming a testable hypothesis (Cabral et al., 2012). New efforts have given birth to computational neuropsychiatry as a way to discover novel biomarkers for affective states and in neuropsychiatric disorders (Deco and Kringelbach, 2014).

Mapping Brain Pleasure Generators

Mapping causal generators of pleasure in the brain is a challenge because it can require invasive brain manipulations, needed to establish evidence for causation, which are ruled out by legitimate ethical constraints in human studies. However, evidence from animal studies is revealing a network of hedonic hot spots that causally enhance “liking” reactions to pleasant stimuli and cold spots that diminish the “liking” reactions (Figure 2).

A useful starting distinction is between causation of *loss* versus *gain* of function. In loss of function, lesions or neural dysfunctions reveal mechanisms that are necessary for normal function. In gain of function, neurobiological stimulations reveal mechanisms that are sufficient to cause higher levels of hedonic impact. While some neural structures mediate both forms of causation for hedonic function, other neural mechanisms may mediate only one, for example, able to produce gains of function that enhance pleasure reactions without being needed for normal pleasure. Brain structures able to cause gains in hedonic function may be more widely distributed than structures needed for normal pleasure reactions, which are more anatomically restricted and subcortically weighted. Further, both forms of causation may be more restricted than the coding activity re-

vealed by neuroimaging correlations with pleasure described above.

As illustration, entire limbic regions of human prefrontal cortex appear surprisingly unnecessary for the causal generation of normal pleasure. For example, the surgical procedure of prefrontal lobotomy, performed on thousands of patients during the 1950s, removed or disconnected most of their prefrontal lobe (Valenstein, 1986). Yet lobotomy patients retained most hedonic feelings as far as could be discerned (albeit showing impairments in cognitive judgment), as do other human patients with similarly large prefrontal cortex lesions arising from stroke, tumor, or injury (Damasio, 1994; Szczepanski and Knight, 2014). A dramatic recent report confirmed that even more massive cortical damage, destroying not only prefrontal orbitofrontal and ventromedial cortex, but also frontal insula and ventral anterior cingulate cortex (plus hippocampus and amygdala in the rostral temporal lobe), left intact normal behavioral affective reactions to preferred social partners or frightening syringes, and even verbal hedonic reports such as “I have a strong feeling of happiness, that we are here together working on these wonderful games” (Damasio et al., 2013).

Stark examples of subcortical causation of normal hedonic reactions in people also include hydranencephalic children, who essentially lack a telencephalic forebrain and have virtually no cortex, yet may still show complex emotional responses to social caregivers and music. For example, Shewmon et al. (1999) described complex behavioral hedonic reactions in hydranencephalic children, such as in a 6-year old boy born with congenital “absence of cerebral tissue rostral to the thalamus, except for small mesial temporal-lobe remnants” (p. 364), who still “smiled when spoken to and giggled when played with. These human interactions were much more intense than, and qualitatively different from, his positive reactions to favorite toys and music,” (p. 366) (Shewmon et al., 1999). Similarly, Merker reported that other hydranencephalic children “express pleasure by smiling and laughter, and aversion by ‘fussing’, arching of the back, and crying (in many gradations), their faces being animated by these emotional states. A familiar adult can employ this responsiveness to build up play sequences predictably progressing from smiling, through giggling, to laughter and great excitement on the part of the child,” (p. 79) (Merker, 2007). Such cases of human emotional reaction without (or with hardly any) cortex indicate that subcortical structures may be surprisingly competent to generate many normal hedonic reactions and are consistent with many animal studies.

Causal Hedonic Hot Spots for Hedonic Enhancements

Yet hedonic gains of function can be produced by neural events in several forebrain structures, resulting in intense pleasure reactions. Animal affective neuroscience studies have recently identified a network for generating hedonic enhancement of “liking” reactions, embedded as a set of small hedonic hot spots distributed among several limbic structures throughout the brain, ranging from the cortex to the brainstem. Each hot spot can specifically amplify orofacial “liking” expressions elicited by sweetness in rats, when neurochemically stimulated by an appropriate drug microinjection. Hedonic hot spots have been found in the subcortical forebrain NAc and connected VP, in the brainstem

parabrachial nucleus of the pons, and may now be emerging in limbic areas of prefrontal cortex, including OFC and insula (Castro and Berridge, 2014; D.C. Castro et al., 2014, Soc. Neurosci., abstract; Ho and Berridge, 2013; Pecifia and Berridge, 2005; Smith and Berridge, 2005; Söderpalm and Berridge, 2000).

The size of hedonic hot spots mapped so far is each about 1 cubic millimeter in volume in rats (which might be extrapolated to a cubic centimeter in humans, if proportional to brain size). By comparison, each structure that contains a hot spot is much larger. For example, the entire NAc comprises nearly 10 cubic millimeters (mm^3) in rats, but its opioid hedonic hot spot located in the rostradorsal quadrant of the medial shell constitutes only 10% of total NAc volume (and about 30% of volume of the medial shell; shown in Figures 1 and 2) (Castro and Berridge, 2014; Pecifia and Berridge, 2005). In other words, as far as is known, nearly 90% of the remaining NAc may lack capacity to enhance “liking” reactions, even for mu opioid stimulation.

In more detail, inside the rostradorsal hot spot of the medial shell in NAc, mu opioid stimulation via agonist microinjections can at least double the hedonic impact of sucrose, as reflected in more “liking” reactions (Pecifia and Berridge, 2005; Smith et al., 2011). Somewhat surprisingly, delta opioid stimulation or even kappa opioid stimulation also in the same NAc hot spot will similarly enhance hedonic impact of sweetness (Castro and Berridge, 2014). At other sites in the NAc medial shell, all three types of opioid stimulations fail to enhance “liking” reactions and indeed all oppositely suppress “liking” reactions at a cold spot site in the caudal half of the medial shell. That localization suggests the NAc rostradorsal hot spot is really quite unique as a mechanism for gating hedonic gain of function. Independently, a unique role for the NAc hot spot was confirmed using conditioned place preference tests: mu, kappa, and delta stimulations all establish positive preferences for a place paired with the microinjections in a hot spot, but not at other sites in the NAc medial shell (Castro and Berridge, 2014). Beyond opioid signals, endocannabinoid stimulation by microinjections of anandamide similarly enhances “liking” reactions in an overlapping subregion of the NAc medial shell (Mahler et al., 2007). The anatomical overlap between opioid and endocannabinoid hot spots in NAc raises the possibility that the circuitry in the same hot spot may largely mediate both neurochemical forms of pleasure enhancement.

What makes the NAc hot spot so special? The full answer remains for the future, but some insights are emerging from recent reports that the NAc hot spot in the rostradorsal medial shell has unique neuroanatomical features, and also unique neurochemical features, different from other subregions of the medial shell and NAc core (Britt and McGehee, 2008; Kupchik and Kalivas, 2013; Thompson and Swanson, 2010; Zahm et al., 2013).

Beyond the NAc, the VP is a major target of NAc projections. The VP also contains its own hot spot located at the posterior end (Ho and Berridge, 2013; Smith and Berridge, 2005). The VP hot spot similarly is about 1 mm^3 in volume, constituting less than one-half of the total VP. In the VP hot spot, either mu opioid or orexin-A stimulating microinjections more than

double the level of “liking” reactions elicited by sweetness (Ho and Berridge, 2013; Smith and Berridge, 2005). Conversely, more rostrally in the VP, a hedonic cold spot of similar volume exists where mu opioid stimulation oppositely reduces sweetness “liking” (Smith and Berridge, 2005). Recent optogenetic studies have also begun to help confirm this hedonic gain of function capacity, by indicating that optogenetic excitation (channelrhodopsin) of neurons within the VP hot spot can double the number of “liking” reactions to sweetness (D.C. Castro and K.C. Berridge, 2013, Soc. Neurosci., abstract). Further optogenetic confirmations would provide valuable independent validation of the hedonic function of the VP hot spot.

The circuitry connecting hot spots of the NAc and VP remains unclear, and they may not be directly connected. Yet the two hot spots functionally interact to form an integrated circuit. For example, stimulating either hot spot can recruit activation of the other and mutual recruitment into simultaneous participation appears necessary to enhance “liking” reactions, in the sense that blocking opioid activation in either hot spot completely prevents mu opioid stimulation of the other one from enhancing “liking” (Smith and Berridge, 2007; Smith et al., 2011).

Hot Spots at the Top and Bottom of the Brain?

In the prefrontal cortex, recent evidence indicates that the OFC and insula cortex may each contain their own additional hot spots (D.C. Castro et al., Soc. Neurosci., abstract). In specific subregions of each area, either opioid-stimulating or orexin-stimulating microinjections appear to enhance the number of “liking” reactions elicited by sweetness, similar to the NAc and VP hot spots. Successful confirmation of hedonic hot spots in the OFC or insula would be important and possibly relevant to the orbitofrontal mid-anterior site mentioned earlier that especially tracks the subjective pleasure of foods in humans (Georgiadis et al., 2012; Kringelbach, 2005; Kringelbach et al., 2003; Small et al., 2001; Veldhuizen et al., 2010).

Finally, in the brainstem, a hindbrain site near the parabrachial nucleus of dorsal pons also appears able to contribute to hedonic gains of function (Söderpalm and Berridge, 2000). A brainstem mechanism for pleasure may seem more surprising than forebrain hot spots to anyone who views the brainstem as merely reflexive, but the pontine parabrachial nucleus contributes to taste, pain, and many visceral sensations from the body and has also been suggested to play an important role in motivation (Wu et al., 2012) and in human emotion (especially related to the somatic marker hypothesis) (Damasio, 2010). Further, a brainstem contribution to pleasure circuitry is quite consistent with a hierarchical view of brain organization, which would suggest hedonic functions to be reiteratively represented at multiple levels of the brain.

Interaction between Hot Spot Site and Neurochemical Stimulation

Hot spots generate hedonic enhancement through an interaction between their specific anatomical site and their particular neurochemical state or mode of stimulation. Neither alone is sufficient to enhance “liking”. For example, in the NAc hot spot in the rostradorsal medial shell, microinjections of mu, delta, or kappa

opioid agonists all double the “liking” reactions elicited by sucrose taste, as does endocannabinoid stimulation in its overlapping hot spot (Castro and Berridge, 2014; Mahler et al., 2007; Pecifia and Berridge, 2005). But in the same NAc hot spot, neither dopamine stimulation nor glutamate α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) blockade alter hedonic “liking” for sucrose at all, even though both elevate “wanting” to eat as effectively as opioid stimulation (Faure et al., 2010; Smith et al., 2011). In other words, in the NAc hot spot, the particular neurochemical mode determines whether “liking” for sweetness will be enhanced or not, as well as controlling “wanting” to eat. The neurochemical mode is clearly as important as the anatomical site. Yet outside the hot spot at other sites in the NAc shell, even mu opioid and endocannabinoid stimulations fail to enhance “liking” at all (Castro and Berridge, 2014; Mahler et al., 2007; Pecifia and Berridge, 2005). In fact, NAc microinjections of mu, delta, or kappa opioid agonists in the posterior hedonic cold spot of the shell all oppositely suppress “liking” reactions elicited by sweetness to just half normal levels, even though mu stimulation at that posterior NAc site still enhances cue-triggered “wanting” to obtain reward and stimulates “wanting” to eat as much as in the anterior hot spot (Castro and Berridge, 2014; Pecifia and Berridge, 2013). Thus, anatomical site gates the hedonic effectiveness of those neurochemical modes. Clearly, it is the *interaction* between hot spot site and mode of neurochemical stimulation that determines hedonic impact.

VP Hot Spot: Sufficient to Enhance and Needed for Normal “Liking”

The prefrontal cortex and NAc do share one interesting quirk regarding causation of hedonic impact. Both contain hot spots able to cause gains of hedonic function for intense “liking”, but neither when damaged cause loss of hedonic function: neither reducing positive “liking” reactions nor increasing negative “disgust” reactions. By contrast, the hedonic hot spot of posterior VP combines causation for gain of function with necessity for normal baseline levels of “liking”: that necessity is revealed after caudal VP lesion by loss of positive “liking” for sweetness and replacement by intense “negative disgust” reactions (e.g., gapes and headshakes elicited by sucrose) (Cromwell and Berridge, 1993; Ho and Berridge, 2014). In short, the posterior VP hot spot appears more crucial than any other known brain sites for loss of hedonic function after damage, at least for taste pleasure. Even classic lateral hypothalamic lesions that once were thought to induce intense food disgust (Teitelbaum and Epstein, 1962), may have done so actually only by additionally damaging the posterior VP (Ho and Berridge, 2014; Smith et al., 2010).

Besides lesions, temporary pharmacological inactivation in the posterior VP hot spot also causes intense “disgust” (Ho and Berridge, 2014; Shimura et al., 2006). By comparison in the NAc shell, intense “disgust” is caused by only temporary inactivations (not lesions, suggesting disruptions must act to impair hedonic impact before circuitry compensations can occur) and only in the posterior cold spot (not rostradorsal hot spot) (Ho and Berridge, 2014). That difference between the VP and NAc suggests that the NAc segregates hedonic gain of function versus loss of function into different anatomical sites of the medial shell, whereas the VP hot spot combines both forms of

hedonic causation together (Ho and Berridge, 2014). The VP hot spot thus appears unique among brain sites for hedonic loss of function.

The excessive disgust that follows these VP disruptions may be viewed as a release phenomenon, produced by disinhibition of negative-valenced circuitry in the remaining forebrain diencephalon (Ho and Berridge, 2014). Similar intense “disgust” and other aversive emotions are also produced by large ablations of the entire telencephalon that include the VP as well as other telencephalic forebrain structures, but leave intact the diencephalic hypothalamus and thalamus (Bard, 1928; Grill and Norgren, 1978b), whereas positive reactivity is spared by lower transections of the brain, such as the midbrain decerebration (which eliminates all forebrain circuitry, including NAc, VP, and hypothalamus) (Grill and Norgren, 1978b). A disinhibition interpretation also fits a hierarchical view of how pleasure and displeasure are organized in the brain (Jackson, 1958).

Desire to Dread: An Affective Keyboard in NAc Shell

The anterior NAc opioid hedonic hot spot and posterior suppressive cold spot fit within a broader anatomical NAc pattern of front-to-back valence organization in the shell that generates additional emotions beyond “liking” and “disgust”. This NAc pattern resembles an *affective keyboard* arranged rostrocaudally within the medial shell, which can generate intense desire or even dread as well as hedonic impact (Reynolds and Berridge, 2001; Richard and Berridge, 2011) (Figure 4). The keyboard pattern is arranged from anterior to posterior ends of the medial shell. At its anterior end, it generates predominantly positive-valenced motivations in response to localized neural events such as microinjections of a γ -aminobutyric acid (GABA) agonist (muscimol) or of a glutamate AMPA antagonist (DNQX): eating more than twice normal amounts of food, increasing appetitive seeking for food reward (Stratford and Kelley, 1997; Stratford and Wirtshafter, 2012; Wirtshafter et al., 2012), inducing a conditioned preference for a place paired with the microinjection, and (for GABA microinjections) even increasing “liking” reactions to sweet tastes (Reynolds and Berridge, 2002). However, as the microinjection site moves more caudally in the NAc shell, appetitive behaviors decline. Instead, negative “fearful” behavior becomes increasingly intense, and (for GABA) sweet tastes become also disgusting (Faure et al., 2010; Ho and Berridge, 2014; Reynolds and Berridge, 2002; Richard et al., 2013b).

Of course, several other brain structures, from amygdala to hypothalamus, VP or brainstem, are also known to mediate various aversive emotional reactions, including fear, pain, or disgust (Baliiki et al., 2010; LeDoux, 2012; von dem Hagen et al., 2009). The amygdala is especially crucial for fear-related learning of passive responses to threats, such as freezing to a Pavlovian cue that predicts footshock (LeDoux, 2012; Maren et al., 2013). The posterior NAc instead produces a more active set of fearful coping reactions (Faure et al., 2010; Reynolds and Berridge, 2002; Richard et al., 2013b). For example, these include distress calls and frantic escape leaps by a normally tame rat when approached or touched by a human hand, and even defensive bites directed toward the offending hand, as active unconditioned “fearful” responses. Or when left alone after a microinjection, the rat spontaneously often emits “fearful”

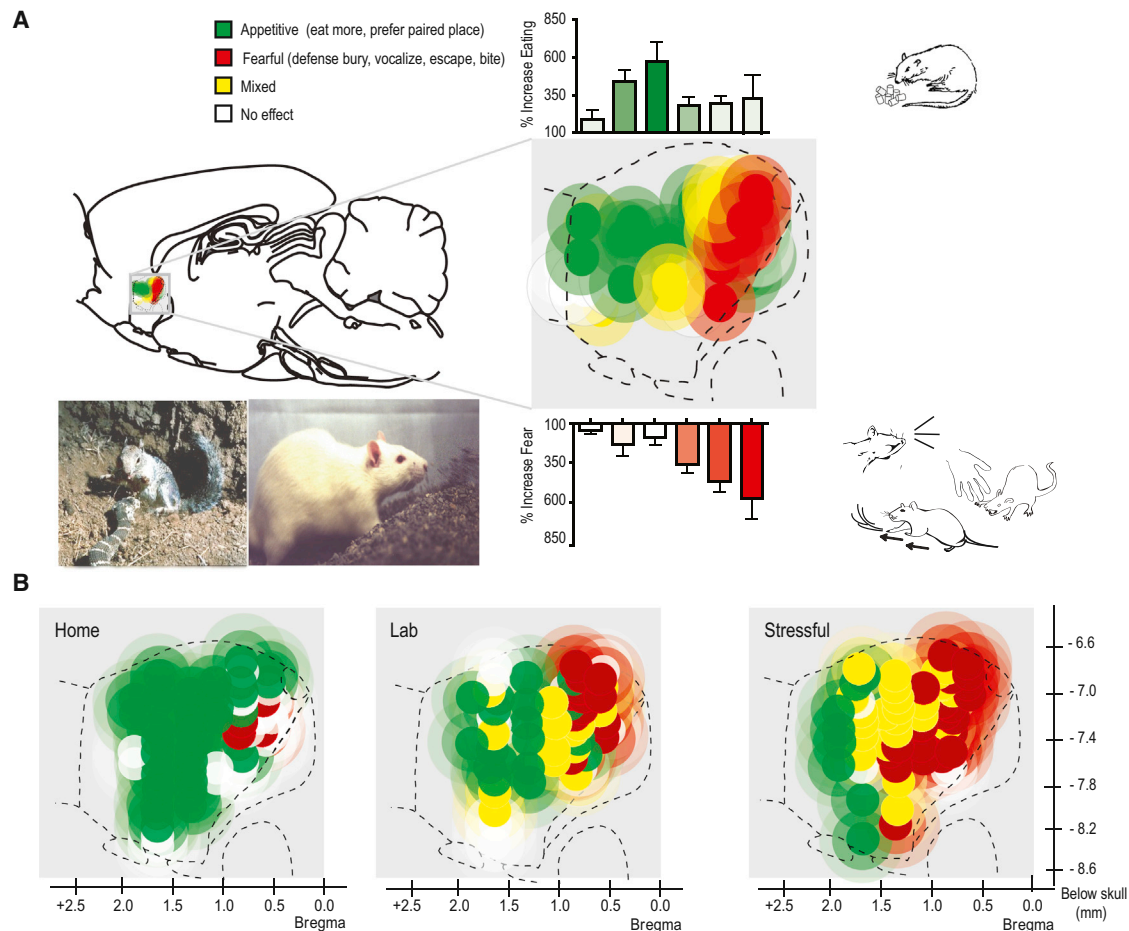


Figure 4. Affective Keyboard in NAc for Desire and/or Dread

(A) A rostral-caudal keyboard pattern of generators in the NAc for appetitive versus fearful behaviors, showing consequences of microinjections of either glutamate AMPA antagonist or GABA agonist microinjections at rostrocaudal sites in the medial shell. Rostral green sites produced 600% increases in food consumption (desire only). Caudal red sites generated increases purely in fearful reactions at levels up to 600% over normal (escape attempts, distress calls, defensive bite attempts, and spontaneous anti-predator treading/burying). Photos show examples of antipredator treading/burying behavior elicited by threat stimuli: ground squirrel toward rattlesnake predator and rat toward electric-shock prod in the laboratory. The same antipredator behaviors occur without any specific threat stimulus after DNQX or muscimol microinjections in posterior NAc: denoted by red dots. Yellow sites released both desire and fearful behaviors in the same rats during the same 1 hr test. Just as a keyboard has many notes, bars reflect the many graded mixtures of affective desire-dread released as microinjection sites move to rostral-caudal locations in the medial shell (appetitive desire to eat at top and fearful dread reactions at bottom).

(B) Environmental ambience retuned the NAc keyboard. A comfortable "home environment" (the rat's own home room: dark, quiet, smell, and sound of conspecifics in the room) suppressed fearful behaviors and expanded zone for appetitive behaviors, produced by microinjections that block glutamate AMPA receptors (DNQX). A standard laboratory environment rebalances the keyboard into nearly equal halves for desire versus dread. A stressfully over-stimulating sensory environment (bright lights plus loud rock music) tilted the causal keyboard toward dread and shrank the zone that generated appetitive desire. Squirrel photo by Cooke from [Coss and Owings \(1989\)](#). Figure data modified from [Richard et al. \(2013a\)](#), based on data from [Reynolds and Berridge \(2008\)](#) and [Richard and Berridge \(2011\)](#).

antipredator reactions that rodents typically use in the wild to defend against natural threats (e.g., defensive burying toward a rattlesnake) ([Coss and Owings, 1978](#)). These defensive reactions are usually targeted toward stimuli the affected rat may perceive as potentially threatening, such as glittering transparent corners of the cage or experimenters visible beyond the transparent wall ([Coss and Owings, 1978](#); [Reynolds and Berridge, 2002](#)).

Multiple Anatomical Modules in NAc Shell

The number of differently valenced rostral-caudal keys contained in the NAc shell is difficult to estimate and in practice is defined somewhat arbitrarily by the size of the microinjections used to tap the keyboard. But probably it contains more than two keys

corresponding to mere positive versus negative valence: two keys would generate only two outputs, but the NAc shell generates many different incremental outputs of gradual variation depending on the precise site. Just as a musical keyboard generates many distinct notes, the rostral-caudal affective keyboard generates multiple distinct quantities of appetitive versus fearful behaviors. For example, as sites move from front to back, intense behaviors become gradually less appetitive, and incrementally more fearful, so that many different ratio mixtures are produced, just as your hand along a piano keyboard would generate many different mixtures of notes changing gradually in pitch.

However, a causal caveat may be needed here. To say an appetitive mechanism is densest in the anterior half of the NAc shell may really be to say that the anterior half is densest in neural mechanisms which ordinarily *inhibit* appetitive behavior, and which themselves must be inhibited by the rostral microinjection that produces the intense appetitive behavior. This disinhibition interpretation arises because of the inhibitory nature of the GABA_A agonist or glutamate antagonist microinjections that produce the intense behaviors. The drug microinjections either hyperpolarize NAc neurons (i.e., muscimol stimulates GABA receptors) or at least block excitatory depolarizations of NAc neurons (i.e., DNQX blocks glutamate AMPA receptors).

Both drugs produce similar motivation keyboard patterns of intense appetitive-fearful behaviors when microinjected in the medial shell, and the GABA agonist adds a corresponding hedonic keyboard of “liking-disgust” effects (Faure et al., 2010; Richard and Berridge, 2011). A disinhibition interpretation suggests that reduced activity of NAc projection neurons, which themselves release mostly GABA, would release or disinhibit recipient neurons in target structures into relative excitation (e.g., in VP, hypothalamus, or ventral tegmentum) (Carlezon and Thomas, 2009; Meredith et al., 2008; Roitman et al., 2005). Target excitations could be the final active mechanism to produce intense motivations. Output projections from particular rostrocaudal sites in the NAc shell appear partly segregated from each other in target structures (Thompson and Swanson, 2010; Zahm et al., 2013), which might help tune the valence of intense desire/dread motivations produced at different NAc sites. Although some contrary evidence suggests that local NAc excitations also generate motivated behaviors (Britt et al., 2012; Taha and Fields, 2005), this disinhibition hypothesis at least does potentially account for many features of the NAc in motivation (Carlezon and Thomas, 2009), including the NAc keyboard production of “desire” versus “fear”.

Retuning the Affective Keyboard

Strikingly, the valence of desire-dread motivations generated by the NAc keyboard is not necessarily fixed by anatomical location, but can be powerfully retuned psychologically for many sites by emotional factors such as the valenced ambience of an environment (Figure 4). At least, dramatic psychological retuning occurs for the glutamate-related DNQX gradient that merely blocks local NAc excitation (Reynolds and Berridge, 2008; Richard and Berridge, 2011). By comparison, the GABA-related muscimol gradient is more resistant to retuning, perhaps because it involves stronger neuronal NAc hyperpolarization (Richard et al., 2013b). Retuning can completely reverse the valence generated at a site from desire to dread or back from dread to desire. For example, the fear-generating zone of the caudal shell expands in a stressfully bright and loud environment to invade the rostral shell, while simultaneously shrinking the desire-generating zone to only the far-rostral tip of the medial shell (Reynolds and Berridge, 2008; Richard and Berridge, 2011). Conversely, a quiet home-like environment (which rats prefer) causes the NAc keyboard to expand its rostral desire-generating zone into the caudal half of shell and shrink the fear-generating zone into merely the far-caudal tip. Such remapping can actually flip many intermediate sites of the shell into releasing opposite motivations in the different environments.

Speculatively, it can be hypothesized that some pathological human conditions might induce more permanent retuning of the NAc valence generators. For example, post-traumatic stress disorder might persistently retune NAc generation in a fearful direction in human patients, similarly to a stressful ambience. Conversely, human addiction and mesolimbic sensitization might retune NAc generators in an appetitive direction, potentiating desire for addicted rewards. These possibilities could be explored by future research.

For the glutamatergic keyboard in rats, the neurobiological mechanism of psychological retuning appears to rewire local neurobiological modes of neurochemical activation within the local NAc microdomain. For example, generation of “fear” behaviors by NAc AMPA blockade requires endogenous dopamine activity at both D1 and D2 receptors simultaneously within the local microinjection site; the defensive motivation can be prevented by adding an antagonist for either dopamine receptor to the eliciting DNQX microinjection (Faure et al., 2008; Richard and Berridge, 2011). By contrast, generation of appetitive desire, even at the same NAc site, requires only D1 activity, not D2 activity (Richard and Berridge, 2011). That pattern suggests that direct and indirect output paths of NAc may have different roles in this desire-dread generation. Dopamine D1 receptors occur on NAc neurons belonging to the “direct” output path that includes a projection directly to ventral tegmentum, whereas D2 receptors occur mostly on neurons belonging to the “indirect” output path that projects only to the VP and hypothalamus (Humphries and Prescott, 2010). Thus, both paths may be equally important in producing the intense “fearful” reaction, whereas positive “desire” generation may be dominated by the direct path (Richard and Berridge, 2011). If so, that would be consistent with suggestions from others that a NAc D1 direct path dominates in appetitive motivation (Xiu et al., 2014).

Finally, NAc keyboard tuning is regulated by corticolimbic top-down inputs from the prefrontal limbic cortex (Richard and Berridge, 2013). For example, raising local cortical excitations in the infralimbic cortex, a medial prefrontal region homologous to the human subgenual anterior cingulate cortex (area 25), broadly suppressed the intensity of motivations otherwise produced by simultaneous NAc microinjections, regardless of valence (Richard and Berridge, 2013). By comparison, excitation of the OFC tilted valence in a positive desire direction, at least in the sense of expanding the appetitive zone that generates eating into caudal areas of the NAc that otherwise produce negative “fear” reactions (Richard and Berridge, 2013). Thus corticolimbic regulation adjusts both the intensity and valence of motivations produced by the NAc circuitry.

Pruning False Candidates: Mesolimbic Dopamine and “Pleasure Electrodes”?

Beyond identifying brain mechanisms that cause subjective feelings of pleasure or objective hedonic reactions, progress in affective neuroscience is also aided by pruning away previous candidates for pleasure generators that have failed to live up to their initial hedonic promise. In our view, two of the most famous brain candidates for pleasure mechanisms featured in textbooks of the past few decades turn out in the end to lack sufficient evidence needed to maintain their hedonic claim: (1) mesolimbic

dopamine systems that are activated by many reward-related stimuli, and (2) most so-called pleasure electrodes for deep brain stimulation that supported behavioral self-administration (i.e., animals or people were willing to work to stimulate the electrodes, such as by pressing a button). As discussed next, our view is that neither dopamine nor most pleasure electrodes actually caused hedonic reactions or pleasure after all, but rather more specifically increased motivation components of reward such as incentive salience, producing “wanting”, without causing “liking” or true hedonic impact.

Mesolimbic Dopamine and the (An)hedonia Hypothesis

The mesolimbic dopamine system has been the most famous neurochemical candidate in the past half century for a pleasure generator in the brain. The mesolimbic system contains dopamine neurons originating in or near the ventral tegmental area (VTA) of the midbrain, which chiefly ascend to the NAc or ventral striatum, as well as to the amygdala, the prefrontal cortex, and the neostriatum. Mesolimbic dopamine systems clearly do play an important role in reward, but that role may not be as hedonic as once thought.

The idea that dopamine was a mechanism for pleasure is known as the “dopamine hedonia” or “dopamine pleasure” hypothesis, and was originally proposed by Roy Wise, “dopamine junctions represent a synaptic way station...where sensory inputs are translated into the hedonic messages we experience as pleasure, euphoria, or ‘yumminess’,” (p. 94) (Wise, 1980). Conversely, the “dopamine pleasure hypothesis” postulated that reduction of dopamine neurotransmission caused loss of pleasure. This inverse hypothesis is known as the “dopamine anhedonia hypothesis” (Ettenberg and McFarland, 2003; Hnasko et al., 2006; Smith, 1995; Wise and Colle, 1984; Wise et al., 1978).

However, today relatively few neuroscientists who study dopamine in reward appear to assert in print that dopamine causes pleasure. Even original proponents are no longer so enthusiastic. For example, by the mid-1990s Wise had retracted the dopamine hedonia hypothesis: he was quoted to say, “I no longer believe that the amount of pleasure felt is proportional to the amount of dopamine floating around in the brain,” (p. 35) (Wickelgren, 1997) and more recently concluded that “pleasure is not a necessary correlate of dopamine elevations” (p. 179) (Wise, 2008).

The decline in advocacy of the dopamine pleasure hypothesis stems from several problems that arose in the past two decades. The first problem specifically applied to the anhedonia versions that posited loss of pleasure. Evidence began to emerge that loss of dopamine does not necessarily reduce pleasure after all. For example, in rats, even near complete destruction of nigrostriatal and mesolimbic dopamine neurons to approximately 1% normal levels, via extensive 6-hydroxydopamine neurotoxin lesions, turns out to leave orofacial “liking” reactions to sweetness completely intact and unimpaired (Berridge and Robinson, 1998). Similarly for human ratings of subjective pleasure, Parkinson’s patients who have extensive dopamine depletion due to their disease still give normal hedonic ratings of liking to the sensory pleasure of a sweet taste (Meyers et al., 2010; Sienkiewicz-Jarosz et al., 2013). And human subjective ratings of drug

pleasure (e.g., cocaine) are not reduced by pharmacological disruption of dopamine systems, even when dopamine suppression does reduce wanting ratings (Brauer and De Wit, 1997; Leyton et al., 2007).

Related questions have arisen recently about whether other types of clinical “anhedonia” truly live up to their lack-of-pleasure label, such as in depression or in schizophrenia. Closer inspection has suggested that many of these patients may not be anhedonic any more than Parkinson’s patients: at least sensory pleasures may persist virtually intact (Barch et al., 2014; Dowd and Barch, 2010; Sienkiewicz-Jarosz et al., 2005; Treadway and Zald, 2011). This has given rise in some cases to a reinterpretation of anhedonia as “avolition” or more specific impairment of incentive motivation.

Dopamine Elevations Produce Higher “Wanting” without Higher “Liking”?

Conversely, dopamine stimulations do not reliably cause pleasure. Dopamine elevations in NAc fail to enhance “liking” for sweetness, despite increasing motivational “wanting” to obtain the same reward (e.g., higher runway performance of hyperdopaminergic mutant mice; higher peaks of cue-triggered effort to obtain sucrose reward, increases in reward consumption, and higher peaks of neural firing in NAc-VP circuits that encode cue-triggered “wanting”) (Peciña and Berridge, 2013; Peciña et al., 2003; Smith et al., 2011; Wyvell and Berridge, 2000). In people, L-3,4-dihydroxyphenylalanine (L-DOPA)-evoked surges in brain dopamine levels do not increase subjective pleasure ratings (Liggins et al., 2012). The intensity of dopamine NAc surges even when evoked by addictive drugs (e.g., amphetamine) correlates rather poorly with subjective liking ratings, but correlates much better with wanting ratings (Evans et al., 2006; Leyton et al., 2002). Examples of “wanting” (without) “liking” induced by dopamine stimulation also come from compulsive motivations induced in Parkinson’s patients treated with high-doses of dopamine agonists, especially direct D2/D3 receptor agonists (O’Sullivan et al., 2009). Those intense motivations range from gambling to shopping, pornography, Internet, hobbies, addictive drugs, or taking excessive medication in an addictive fashion (Callesen et al., 2013; Friedman and Chang, 2013; Ondo and Lai, 2008; Politis et al., 2013). Yet these cases typically do not report intense pleasure.

An important goal in the future for addiction neuroscience is to understand how intense motivation becomes narrowly focused on a particular target. Addiction has been suggested to be partly due to excessive incentive salience produced by sensitized or hyper-reactive dopamine systems that produce intense “wanting” (Robinson and Berridge, 1993). But why one target becomes more “wanted” than all others has not been fully explained. In addicts or agonist-stimulated patients, the repetition of dopamine-stimulation of incentive salience becomes attributed to particular individualized pursuits, such as taking the addictive drug or the particular compulsions. In Pavlovian reward situations, some cues for reward become “wanted” more than others as powerful motivational magnets, in ways that differ across individuals (Robinson et al., 2014b; Saunders and Robinson, 2013). The control of this narrow directional focus for intense incentive salience may involve dopamine system

interactions with learning-related structures, including amygdala-related circuitry (DiFeliceantonio and Berridge, 2012; Koob and Volkow, 2010; Mahler and Berridge, 2012; Robinson et al., 2014a). But more remains to be done to clarify how these neural mechanisms control what gets “wanted” most in addictions.

Resolving the Cocaine Puzzle?

Another puzzle has been that if dopamine does not cause sensory pleasure, why are dopamine-promoting drugs such as cocaine or methamphetamine so pleasant? There are several potential answers, both psychological and neurobiological. A psychological explanation may be that at least some of the euphoria of cocaine or amphetamine drugs comes from a “wanting” component of reward. That is, high incentive salience is just one component used to construct reward experiences (together with high hedonic impact). But on its own, elevated incentive salience induced by dopamine stimulation may to some extent be mistaken for pleasure itself. Drug enhancement of incentive salience could make other people, events, or actions in the world all seem more attractive, and be powerfully enabling of engagement with them, which might well carry an aura of euphoria even if not truly hedonic. Viewed this way, subjective reward experience may be partly synthesized from motivation and cognitive appraisal components, similar to many other emotions (Barrett et al., 2007). This mistaken appraisal explanation may also apply to the cases of electrode self-stimulation described below.

A neural explanation for why cocaine is pleasant may be that cocaine and amphetamine also stimulate secondary recruitment of endogenous opioid and related neurobiological hedonic mechanisms, beyond directly raising dopamine release. Those recruited secondary mechanisms may more directly cause “liking” reactions and subjective pleasure. For instance, dopamine-stimulating drugs recruit elevation in the NAc of endogenous opioid and GABA signals (Colasanti et al., 2012; Soderman and Unterwald, 2009; Tritsch et al., 2012). Elevated endogenous opioid release in a site such as the NAc hedonic hot spot could amplify “liking” as described above, resulting in a more genuinely pleasurable experience. Similarly, GABA signals in the far rostral strip of the NAc shell can also enhance true “liking” (Faure et al., 2010), which could occur if drugs of abuse that stimulate dopamine neurons also stimulate some of those neurons to co-release more GABA in the NAc (Tritsch et al., 2012).

However, hedonic effects might well change over time. As a drug was taken repeatedly, mesolimbic dopaminergic sensitization could consequently occur in susceptible individuals to amplify “wanting” (Leyton and Vezina, 2013; Lodge and Grace, 2012; Wolf and Ferrario, 2010), even if opioid hedonic mechanisms underwent downregulation due to continual drug stimulation, producing “liking” tolerance. Incentive-sensitization would produce addiction, by selectively magnifying cue-triggered “wanting” to take the drug again and so powerfully cause motivation even if the drug became less pleasant (Robinson and Berridge, 1993).

Dopamine and Reward Learning?

A major alternative hypothesis is that dopamine acts as a teaching signal via prediction error or temporal difference computations to cause learning about reward (Schultz et al., 1997). In

practice, it is often difficult to distinguish mesolimbic coding of reward learning from incentive motivation, because most studies rely purely on incremental learning to alter the motivation status of stimuli: learned predictive value and incentive value thus tend to co-vary together. Further, a potential experimental confound present in many dopamine tracking experiments is that physiological state control of motivation is often clamped into a narrow constant range during all phases of the study (e.g., monkeys kept always mildly thirsty in electrophysiological studies; people tested always in mild satiety). Clamping a constant state forces associative prediction to be the sole determinant of a cue’s motivational value. That’s because it excludes any dynamic modulation of incentive salience by shifts in physiological states, which often occurs in real life and which would permit experimental separation of learned versus motivation values (Berridge, 2012; Dayan and Berridge, 2014; Robinson and Berridge, 2013). The confound puts a “thumb on the scale”, in the sense that any brain activity tracking cue motivational value would appear instead to track pure reward learning. By contrast, studies that allow relevant physiological states to fluctuate often do find consequent fluctuations in the motivational value of cues and in dopamine-related activity (Cone et al., 2014; Medic et al., 2014; Robinson and Berridge, 2013; Smith et al., 2011). Future studies that incorporate fluctuation might better be able to assess if mesolimbic dopamine systems track motivational value more faithfully than learned prediction values.

Additional difficulties for the dopamine learning hypothesis come from evidence questioning whether dopamine is actually needed for any particular type of reward learning, and conversely, evidence that stimulation of dopamine does not reliably act as a causal teaching signal to establish new memories (Berridge and Robinson, 1998; Eisenegger et al., 2014; Flagel et al., 2011; Robinson et al., 2005; Saunders and Robinson, 2012; Shiner et al., 2012; Smittenaar et al., 2012). These issues have been discussed elsewhere, and no doubt will be discussed further in the future, perhaps eventually producing clearer consensus on dopamine in reward learning (Berridge, 2012; Berridge and O’Doherty, 2014; Collins and Frank, 2014; Schultz, 2013).

Pleasure Electrodes, Not-Quite-Pleasure Generators?

The search for pleasure mechanisms in the brain arguably began with the 1950s discovery by James Olds and Peter Milner of what Olds soon labeled “pleasure centers in the brain” (Olds, 1956; Olds and Milner, 1954). Those were electrode sites that rats would work to activate or self-stimulate. Self-stimulation sites typically were in the lateral hypothalamus (LH) or other points along the mesolimbic path, where electrodes can elicit surges in the NAc dopamine release (among other mechanisms) (Gallistel, 2006; Hernandez et al., 2008). Brain-stimulation reward was so potent a phenomenon that “a hungry rat often ignored available food in favor of the pleasure of stimulating itself electrically” (pp. 115–116) (Olds, 1956).

However, Olds himself later revisited the question of whether actual pleasure was produced in the final publication of his career. Posing the question, “Was there any indication of a common denominator such as the term pleasure implies?” Olds wrote in reply, “In any event the question of whether there

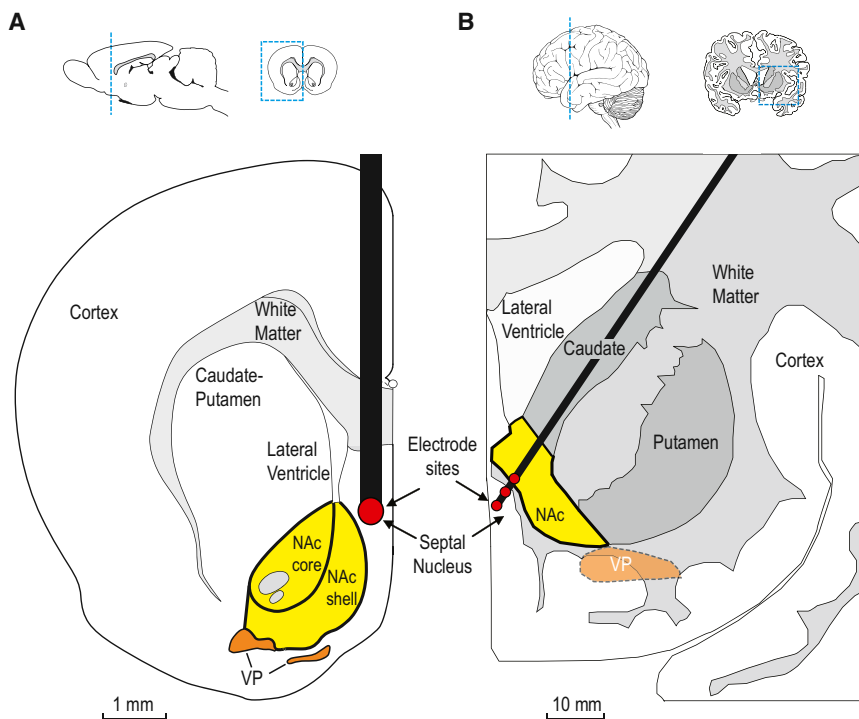


Figure 5. False Pleasure Electrodes?

Reconstruction of sites for original self-stimulation electrode locations in (A) rat of [Olds and Milner \(1954\)](#) (left) and of (B) human patient B-10 in [Heath \(1972\)](#). For both rat and humans, electrode sites would now be recognized to be located in or near the NAc. Thick line shows electrode shaft and red dots show stimulation points. In human brain, representation of the VP has been moved forward into the coronal plane of the electrode to show relative positions of the NAc and VP. Modified from [Smith et al. \(2010\)](#).

is some common denominator of positive reinforcement ... is unanswered. It deserves further study," (p. 30) ([Olds, 1977](#)). His final conclusion, therefore, appeared to leave open the entire issue of whether true pleasure or "liking" was generated by self-stimulation electrodes.

We have been drawn to re-examine the literature on pleasure electrodes and to question whether most electrodes actually produced pleasure. Our prompt began in the 1990s with what was then a surprising finding, namely, that rewarding LH electrode stimulation tended selectively to amplify "wanting" to pursue and consume a sensory reward without actually enhancing "liking" or the hedonic impact of the same reward. This finding arose from an investigation by one of us with Elliot Valenstein on the motivation versus hedonic properties of LH electrodes ([Berridge and Valenstein, 1991](#)). An explanatory hypothesis at the time for why LH electrodes were not only self-stimulated, but also evoked intense spontaneous motivation directed at a natural reward, such as eating food, was that the stimulation essentially made the food or other reward more pleasant ([Hoebe, 1988](#)). However, contrary to that tastier food hypothesis, Berridge and Valenstein found that LH stimulation failed to enhance "liking" reactions to sweetness, even though it made the rats "want" to eat at least four times more than normal amounts ([Berridge and Valenstein, 1991](#)). Oppositely, if anything, the LH electrode made sweet tastes more disgusting during stimulation, rather than making the tastes more "liked" (e.g., evoked gapes or headshakes typical of bitterness while tasting pure sucrose).

Still, of course, the electrodes might themselves have generated an internal pleasure state, regardless of any lack of effects on external hedonic stimuli. That, after all, was the original

essence of pleasure electrode claims. To gain a better answer as to whether pleasure electrodes lived up to their name, we have re-examined the literature on human patients implanted with deep brain electrodes for self-stimulation. The first were patients implanted in the 1950s–1960s, who received electrode implants while institutionalized for depression, schizophrenia, or other psychiatric conditions. For example, the psychiatrist Robert Heath reported patients who would voraciously self-stimulate their electrodes, activating deep forebrain sites within a "septal area" that contained the septum, anterior hypothalamus, NAc, VP, ventromedial neostriatum, pyriform cortex, and ventromedial neocortex ([Figure 5](#)) ([Heath, 1972, 1996](#)). Heath's patients were often given a self-stimulation box with an activating button, with which they could control their own electrode stimulations. Typically, they self-stimulated their electrodes avidly, resulting in pleasure electrode claims (albeit the claim was usually in form of third-person descriptions by experimenters, not quoted pleasure declarations by patients themselves). Among Heath's most dramatic pleasure electrode cases was one known as B-19: a young man implanted with stimulation electrodes in the septum/accumbens region for depression and suicidal thoughts, drug abuse, and for the purpose of changing his sexual orientation (a goal now recognized as unethical; electrode site depicted in [Figure 5](#)) ([Heath, 1972](#)). Heath reported B-19's electrode to cause "feelings of pleasure, alertness, and warmth (goodwill); he had feelings of sexual arousal and described a compulsion to masturbate," (p. 6) ([Heath, 1972](#)). Yet on closer examination, despite Heath's assertions, it is not so clear that B-19's electrode ever really caused strong feelings of pleasure. B-19 was never actually quoted as saying the stimulation felt pleasurable per se. Nor was he said to show behavioral signs of pleasure or to exclaim anything like, "Oh—that feels nice!" when his electrode was stimulated. The electrode stimulation certainly never served as a substitute for sex. What it did instead was to make him want to engage more in sex, just as it made him want the stimulation more and to press the button so avidly.

Modern Deep Brain Stimulation

Deep brain stimulation has resurged in the new millennium as a therapeutic technique for disorders ranging from chronic pain to

depression, obsessive-compulsive disorder, and Parkinson's disease (Boccard et al., 2014a; Holtzheimer and Mayberg, 2010; Kringelbach et al., 2011; van Hartevelt et al., 2014). Contemporary target sites for deep brain electrodes often include the NAc and the subthalamic nucleus, the subgenual cingulate cortex, and fibers descending from the prefrontal cortex through the internal capsule. A woman with a deep brain electrode in the subthalamic nucleus was reported, upon initial activation of her electrode, to act "in love with two neurologists, and tried to embrace and kiss people" (Herzog et al., 2003). Subsequently she became motivationally focused on intense shopping, to the point of engaging in binges of "unrestrained buying of clothes." However, rather than this being a purely happy exhilaration, the continued subthalamic stimulation increasingly made her more suspicious, tense, and hostile. She developed a "delusion that her sons were conspiring against her, and she said that they tried to get her money by threat of force" (all p. 1,383) (Herzog et al., 2003).

At sites in the NAc, deep brain stimulation has been reported to produce sudden feelings of desire to engage in a particular activity, such as visiting a nearby landmark or taking up again an old hobby (Schlaepfer et al., 2008). But those human NAc electrodes explicitly failed to produce feelings of pleasure: "There were no 'liking' effects during stimulation, in contrast to findings reported by Heath," (p. 372) (Schlaepfer et al., 2008). Indeed, the patients were usually unable to tell even whether their NAc electrode was on or off. In one case, when the electrode was stimulated, the patient "was unable to identify any changes, but spontaneously reported that he realized that he was in Cologne (in Germany), that he never visited the famous Cologne Cathedral, and he planned on doing this in the immediate future, which he indeed did the day following the operation." Similarly, upon NAc electrode activation in a woman, the patient "did not report any acute changes in depressive symptomatology, but spontaneously mentioned that she wished to take up bowling again (a favorite pastime of hers 12 years ago, before onset of her depression)" (Schlaepfer et al., 2008). Whether these activities actually would be made more pleasurable by NAc stimulation remains unknown.

Beyond evoking intense "wanting", do any pleasure electrodes actually produce true "liking" too? We remain open on this question and acknowledge that a lack of evidence in the cases above does not mean that no electrode ever causes pleasure. It is just that most published cases appear to not be very pleasant in our view. It would be valuable to have more studies of contemporary deep brain stimulation effects on human pleasure.

Finally, we do not doubt that some electrodes may at least reduce negative affect, producing escape from distress or pain (Mayer et al., 1971). An author of this article (M.L.K.) has witnessed dramatic relief in chronic pain patients when deep brain stimulation is turned on in targets such as the periaqueductal gray and anterior cingulate cortex (Kringelbach et al., 2009). Similarly, relief from anxiety or depression may be produced by some deep brain stimulations of the NAc or prefrontal cortex, resulting in positive engagement in social or leisure activities (Bernick et al., 2010; Kennedy et al., 2011). Thus, it may well be that part of the mood-enhancing effects of much brain stimulation comes from the alleviation of unpleasant affective states

(Boccard et al., 2014b; Holtzheimer and Mayberg, 2010; Kringelbach et al., 2011).

Incentive Salience as Sham Reward

As mentioned at the start, reward normally contains "liking", "wanting", and learning components. Deep brain stimulation and neuropharmacological dopamine activations seem to dissociate this natural constellation, engaging only one or two of the three components. We suggest both rather specifically activate the incentive salience or "wanting" component, which interacts normally with associative learning, to produce intense motivation and focus it on a target, but without activating the pleasure or "liking" component of reward. To the external observer, and perhaps even sometimes to the experiencing person, "wanting" may be appraised as a positive reward involving eager anticipation. Such a person is likely to be confused by the unfamiliar decoupling among reward components and may fail to recognize what is happening. But dissociated "wanting" is merely a counterfeit pleasure or sham reward, which lacks a true "liking" component. This hypothesis could be probed by more sophisticated studies of pleasure during brain stimulation.

If the interpretation is correct, it is worth noting that the hedonic valence of dissociated "wanting" can easily flip from positive incentive into a negative valence of anxiety, frustration, or fear. Reversing the hedonic valence of the experience would not necessarily disrupt its motivating power. The idea that incentive motivation can be distressing is not new. After all, the word "tantalize" comes from the ancient story of the torture of Tantalus, mythical son of the Greek god Zeus, condemned for his faults to be eternally tempted by delicious food and drink held just out of reach, while remaining hungry and thirsty: painfully tantalized.

In other words, mesolimbic motivation can be plastic in hedonic valence. Motivational salience is never neutral, but its valence is not fixed. Incentive salience makes the stimulus or representation it is attributed to powerfully "wanted" as well as attention-grabbing. Fearful salience makes the percept equally attention-grabbing, yet perceived as a potential threat. Yet, the hedonic valence of the entire experience can be ambiguous. Incentive salience can occur either as eager anticipation or as negative frustration, as in Tantalus. In other situations, the overall hedonic experience of fearful salience might flip to positive, as in roller coasters or horror movies. Finally, the valence of mesolimbic motivational salience itself can be plastic, as in NAc rats that switched between "wanting" and "fear", the subthalamic-electrode woman who switched from manic shopping to suspicion, or addicts who switch from euphoric craving to the paranoia of cocaine-induced psychosis.

Conclusion: Building a Fruitful Affective Neuroscience of Pleasure

Our approach to the affective neuroscience of pleasure has combined perspectives from human and animal studies, aiming to recognize both subjective feelings and objective hedonic reactions, and to give a more accurate mapping between brain circuitry and affective processes. We began by offering to test our approach's scientific validity against the criterion of whether it produces useful new insights. We believe such new insights are emerging, as described above, to summarize: the emerging

realization that many diverse pleasures share overlapping brain substrates; better neuroimaging maps for encoding human pleasure in the OFC; identification of hot spots and separable brain mechanisms for generating “liking” and “wanting” for the same reward; identification of larger keyboard patterns of generators for desire and dread within NAc, with multiple modes of function; and the realization that dopamine and most pleasure electrode candidates for brain hedonic generators probably did not cause much pleasure after all.

Time will further assess the validity of these new conclusions, and if confirmed, we think they may aid in better understanding of both normal pleasures and affective psychopathologies. Eventually the goal is to contribute to more effective and safer treatments for affective disorders, as well as understanding of affective well-being. Finally, evidence gained may inspire future affective neuroscientists to further refine the search for the neural underpinnings of pleasure, which remains an important motivating factor for many people and without which life too often becomes meaningless.

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Our title for this article is meant as homage to that of James Olds in his 1956 article, “Pleasure centers in the brain”. While most deep brain electrodes may not have activated “pleasure centers” after all, in our view, Olds and Milner’s pioneering discovery remains a landmark that launched affective neuroscience and the search for hedonic brain mechanisms. We are grateful to Daniel Castro for help drawing [Figures 1](#) and [2](#) and to Shannon Cole, Daniel Castro, Shelley Warlow, and four anonymous reviewers for helpful suggestions on the manuscript. Research in our laboratories has been supported by grants from the NIH to K.C.B. (MH63644 and DA015188) and from the TrygFonden Charitable Foundation and European Research Council (ERC) Consolidator Grant to M.L.K. (CAREGIVING n. 615539).

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