Neuron. Author manuscript; available in PMC 2016 May 6.
Published in final edited form as:
Neuron. 2015 May 6; 86(3): 646–664.
doi: 10.1016/j.neuron.2015.02.018

PMCID: PMC4425246
NIHMSID: NIHMS664561
PMID: 25950633

Pleasure systems in the brain

Kent C. Berridge[1] and Morten L. Kringelbach[2,3]

[1]Department of Psychology, University of Michigan, Ann Arbor, MI 48109-1043 USA
[2]Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, OX3 7JX, UK
[3]Centre for Functionally Integrative Neuroscience, University of Aarhus, 8000 Aarhus C, Denmark
[1]*Corresponding author*: berridge@umich.edu

Abstract

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 rewards is generated by a large and distributed brain system. Liking, or pleasure itself, is generated by a smaller set of hedonic hotspots within limbic circuitry. Those hotspots 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.

Introduction

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

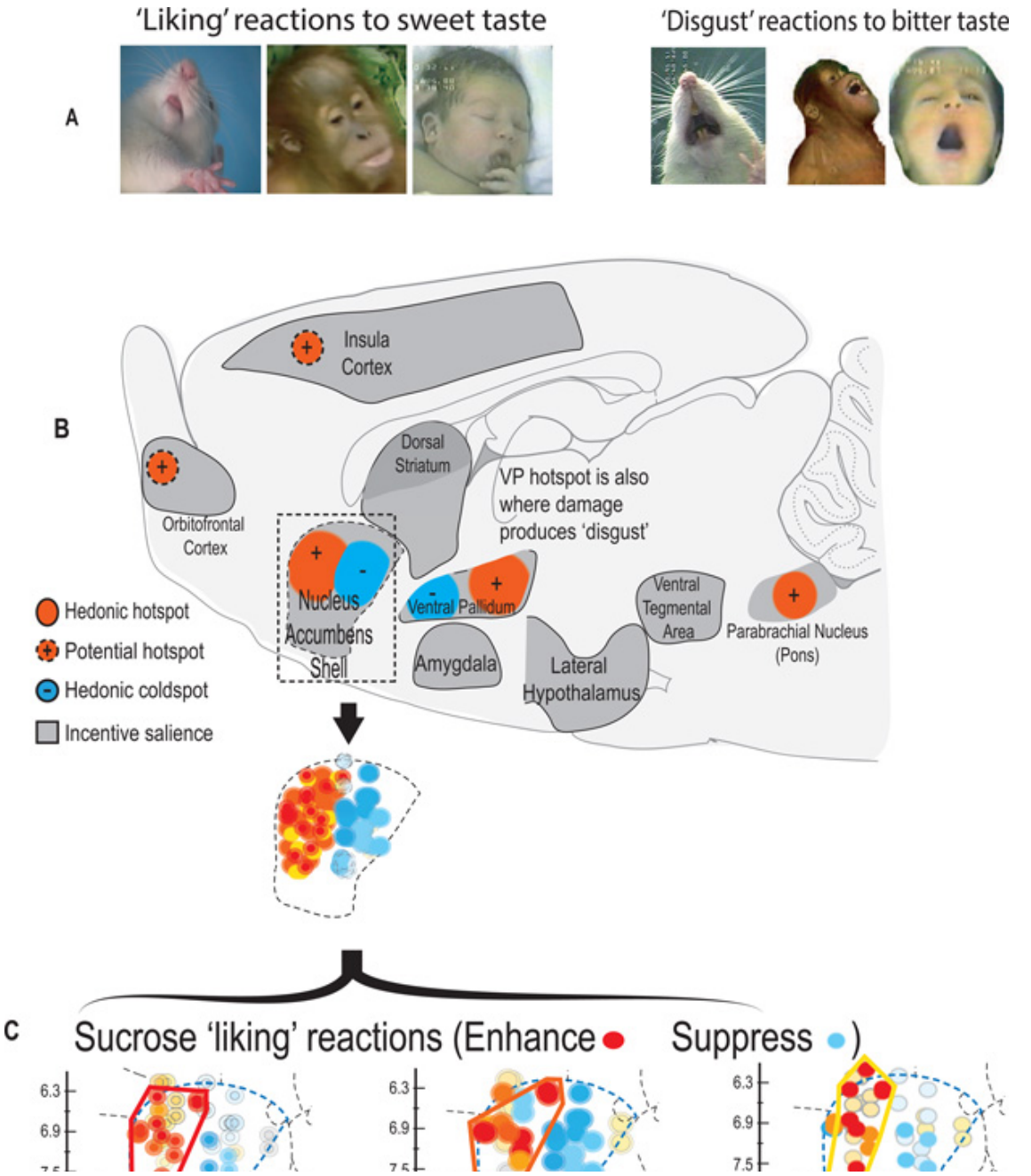
A goal of affective neuroscience is to understand how brain mechanisms generate pleasures, and also displeasures, and eventually find more effective treatments for affective disorders (Anderson and Adolphs, 2014; Damasio and Carvalho, 2013; Haber and Knutson, 2010; Heller et al., 2013; Kringelbach and 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 hotspots that generate amplifications of pleasure reactions; 5) discovery that nucleus accumbens (NAc) hotspot and coldspot mechanisms are embedded in an anatomically-tuned keyboard organization of generators in nucleus accumbens 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 rewards involve 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 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).



Open in a separate window

Figure 1

Causal hedonic hotspots and coldspots 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) shows sagittal view of hedonic hotspots in rat brain containing nucleus accumbens, ventral pallidum, and prefrontal cortex. Hotspots (red) depict sites where opioid stimulation enhances 'liking' reactions elicited by sucrose taste. Coldspots (blue) show sites where the same opioid stimulation oppositely suppresses 'liking' reactions to sucrose. C) Nucleus accumbens blow-up of medial shell shows effects of opioid microinjections in NAc hotspot and coldspot. (red/orange dots in hotspot = >200% increases in 'liking' reactions; blue dots in coldspot = 50% reductions in 'liking' reactions to sucrose). Panels show separate hedonic effects of mu opioid, delta opioid and kappa opioid stimulation via microinjections in 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 hotspot) or place avoidance (blue dots). Surprisingly similar patterns of anterior hedonic hotspots and posterior suppressive coldspots are seen for all three major types of opioid receptor stimulation. Modified from (Castro and Berridge, 2014).

To study pleasure comprehensively, good human neuroimaging studies are needed to explore correlative encoding of pleasant experiences, and good animal studies are needed to explore causation of underlying hedonic reactions. This two-pronged approach exploits a fundamental duality in hedonic processes, related to the objective versus subjective faces of pleasure (Damasio and Carvalho, 2013; Kringelbach and Berridge, 2010; Schooler and Mauss, 2010; Winkielman et al., 2005). Pleasure is sometimes assumed to be a purely subjective feeling. But pleasure also has objective features in the form of measurable hedonic reactions, both neural and behavioral, to valenced events. In this review we denote objective hedonic reactions as 'liking' 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 (Darwin, 1872). 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. One 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). ost 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; Peciña 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 lickometer in animal studies) and the simple brainstem decision to swallow food in the mouth. But consummatory reactions are highly heterogeneous. In particular, affective reactions taste reactivity patterns have a uniquely specific relation to 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 blockade (Peciña et al., 1997), nor 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 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, romantic or sexual pleasures, 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 Kringelbach, 2012; Kringelbach et al., 2012; Parsons et al., 2010; Salimpoor et al., 2011; Vartanian and Skov, 2014; Veldhuizen et al., 2010; Vuust and Kringelbach, 2010; Xu et al., 2011; Zeki and Romaya, 2010). These shared reward networks include anatomical regions of prefrontal cortex, including portions of orbitofrontal, insula, and anterior cingulate cortices, as well as often subcortical limbic structures such as nucleus accumbens (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.

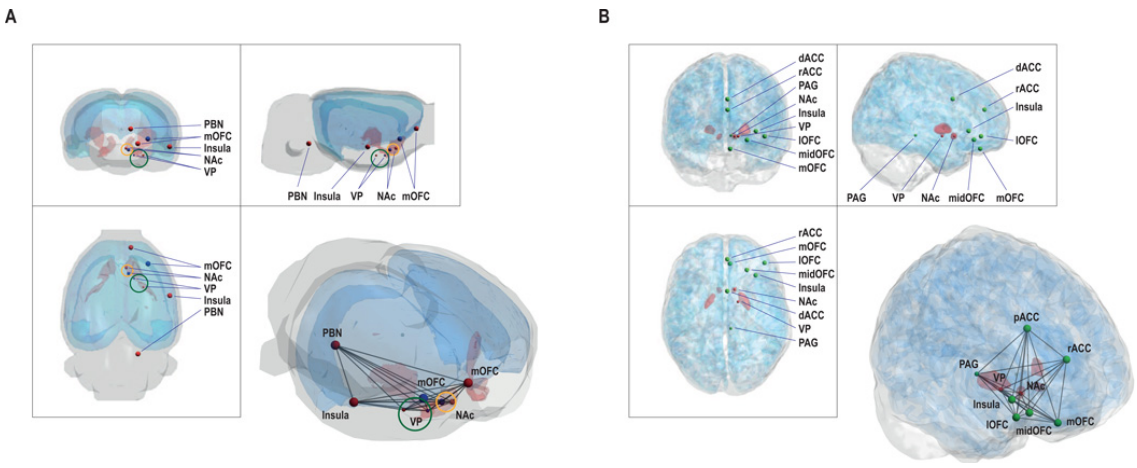


Figure 2

Three-dimensional comparison of hedonic sites in rat brain (left) and human brain (right)

A. Rat brain shows hedonic hotspots (red) and coldspots (blue) in coronal, sagittal, horizontal planes and in 3D fronto-lateral perspective view (clockwise from top left). B. Human brain shows extrapolation of rat causal hotspots to analogous human sites in NAc and VP (red), and shows fMRI coding sites for positive affective reactions in green (from text). Human views are also in coronal, sagittal, horizontal and 3D perspective (clockwise from top left of B). The tentative functional networks between the different hotspots and coldspots 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. Abbreviations: VP, ventral pallidum; NAc, nucleus accumbens; PBN, parabrachial nucleus; mOFC, medial orbitofrontal cortex; lOFC, lateral orbitofrontal cortex; midOFC, mid-anterior orbitofrontal cortex; dACC, dorsal anterior cingulate cortex; rACC, rostral anterior cingulate cortex; PAG, periaqueductal gray.

Admittedly fMRI measures have limits in spatial and temporal resolution that might miss small or fast differences among neural subsystems that encode particular rewards. 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 rewards, 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.

One human brain site that appears especially linked to pleasure in neuroimaging studies is in orbitofrontal cortex, particularly in a mid-anterior subregion (Figures 2 and 3). Other medial regions of orbitofrontal cortex, middle anterior regions of insula cortex, and ventromedial regions of prefrontal cortex cortices also correlate with subjective pleasure ratings, but many of these 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, 2010; Kringelbach et al., 2003; O'Doherty, 2014; Schoenbaum and Roesch, 2005; Veldhuizen et al., 2010; Vuust and Kringelbach, 2010).

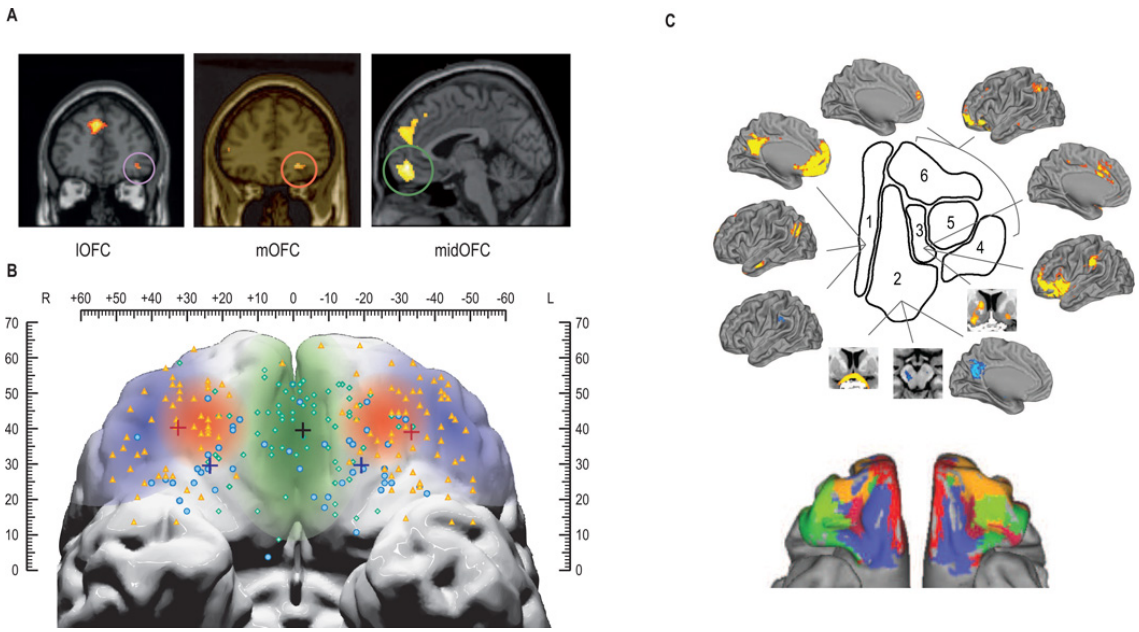


Figure 3

Hedonic coding in the human orbitofrontal cortex (OFC)

In humans, the orbitofrontal cortex is an important hub for pleasure coding, albeit heterogeneous, where different sub-regions are involved in different aspects of hedonic processing. A) Neuroimaging investigations have found differential activity to rewards depending on context in three subregions: the medial OFC (mOFC), mid-anterior OFC (midOFC) and lateral OFC (lOFC). B) A meta-analysis of neuroimaging studies showing task-related activity in the OFC demonstrated different functional roles for these three sub-regions. 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 lOFC region is active when punishers force a behavioural change (purple and orange triangles). Furthermore, the meta-analysis showed a posterior-axis of reward complexity such that more abstract rewards (such as money) will 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 sub-divisions 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 Fig 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 behaviour (Kringelbach and Rolls, 2004). Images in A are reproduced from (Kringelbach et al., 2004; Kringelbach et al., 2003).

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 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 orbitofrontal cortex in particular does appear to track subjective pleasure more accurately than most other limbic regions (Figure 3). One of 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 OFC has also been implicated in the encoding pleasures of sexual orgasm, drugs, and music (Georgiadis and Kringelbach, 2012; Kringelbach, 2010; 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 nucleus accumbens and ventral pallidum (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 prefrontal cortex often has been implicated more in positive affect than right hemisphere (Davidson, 2004). For example, individuals who give higher ratings of subjective well-being may have higher activity in left than right prefrontal cortex, and activity of left subcortical striatum also may be more tightly linked to pleasantness ratings than right-side (Kuhn 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 depend 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 modelling 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, and potentially help rebalance brain networks (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 hotspots that causally enhance 'liking' reactions to pleasant stimuli, and coldspots 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 revealed 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., 2012).

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. 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 (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 hotspots 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 hotspots distributed among several limbic structures throughout the brain, ranging from cortex to brainstem. Each hotspot can specifically amplify orofacial 'liking' expressions elicited by sweetness in rats, when neurochemically stimulated by an appropriate drug microinjection. Hedonic hotspots have been found in subcortical forebrain nucleus accumbens and connected ventral pallidum, in the brainstem parabrachial nucleus of the pons, and may now be emerging in limbic areas of prefrontal cortex, including orbitofrontal cortex and insula (Castro and Berridge, 2014; Castro et al., 2014; Ho and Berridge, 2013; Peciña and Berridge, 2005; Smith and Berridge, 2005; Soderpalm and Berridge, 2000).

The size of hedonic hotspots 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 hotspot is much larger. For example, the entire nucleus accumbens comprises nearly 10 mm^3 in rats, but its opioid hedonic hotspot located in the rostrodorsal quadrant of medial shell constitutes only 10% of total NAc volume (and about 30% of volume of medial shell; shown in Figures 1 & 2) (Castro and Berridge, 2012; Peciña 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 rostrodorsal hotspot of 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 (Peciña and Berridge, 2005; Smith et al., 2011). Somewhat surprisingly, delta opioid stimulation or even kappa opioid stimulation also in the same NAc hotspot will similarly enhance hedonic impact of sweetness (Castro and Berridge, 2014). At other sites in NAc medial shell, all three types of opioid stimulations fail to enhance 'liking' reactions, and indeed all oppositely suppress 'liking' reactions at a 'coldspot' site in the caudal half of medial shell. That localization suggests the NAc rostrodorsal hotspot is really quite unique as a mechanism for gating hedonic gain of function. Independently, a unique role for the NAc hotspot was confirmed using conditioned place preference tests: mu, kappa and delta stimulations all establish positive preferences for a place paired with the microinjections in hotspot, but not at other sites in 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 NAc medial shell (Mahler et al., 2007). The anatomical overlap between opioid and endocannabinoid hotspots in NAc raises the possibility that the circuitry in the same hotspot may largely mediate both neurochemical forms of pleasure enhancement.

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

Beyond NAc, the ventral pallidum (VP) is a major target of NAc projections. The VP also contains its own hotspot located at posterior end (Ho and Berridge, 2013; Smith and Berridge, 2005). The VP hotspot similarly is about $1mm^3$ in volume, constituting less than one-half of the total VP. In the VP hotspot, 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 VP, a hedonic coldspot 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 hotspot can double the number of 'liking' reactions to sweetness (Castro and Berridge, 2013). Further optogenetic confirmations would provide valuable independent validation of the hedonic function of the VP hotspot.

The circuitry connecting hotspots of nucleus accumbens and ventral pallidum remains unclear, and they may not be directly connected. Yet the two hotspots functionally interact to form an integrated circuit. For example, stimulating either hotspot 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 hotspot completely prevents mu opioid stimulation of the other one from enhancing 'liking' (Smith and Berridge, 2007; Smith et al., 2011).

Hotspots at top and bottom of the brain? In the prefrontal cortex, recent evidence indicates that orbitofrontal cortex and insula cortex may each contain their own additional hotspots (Castro et al., 2014). 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 NAc and VP hotspots (Castro et al., 2014). Successful confirmation of hedonic hotspots in orbitofrontal cortex 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, 2010; Kringelbach et al., 2003; Small et al., 2001; Veldhuizen et al., 2010).

Finally, in brainstem, a hindbrain site near the parabrachial nucleus of dorsal pons also appears able to contribute to hedonic gains of function (Soderpalm and Berridge, 2000). A brainstem mechanism for pleasure may seem more surprising than forebrain hotspots to anyone who views 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 roles 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 hotpot site and neurochemical stimulation Hotspots 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 hotspot in rostrodorsal 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 hotspot (Castro and Berridge, 2014; Mahler et al., 2007; Peciña and Berridge, 2005). But in the same NAc hotspot, neither dopamine stimulation or glutamate 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 hotspot, the particular neurochemical mode determines whether 'liking' for sweetness will be enhanced or not, as well controlling 'wanting' to eat. Neurochemical mode is clearly as important as anatomical site. Yet outside the hotspot at other sites in NAc shell, even mu opioid and endocannabinoid stimulations fail to enhance 'liking' at all (Castro and Berridge, 2014; Mahler et al., 2007; Peciña and Berridge, 2005). In fact, NAc microinjections of mu, delta or kappa opioid agonists in the posterior hedonic coldspot of 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 hotspot (Castro and Berridge, 2014; Pecina and Berridge, 2013). Thus

anatomical site gates the hedonic effectiveness of those neurochemical modes. Clearly, it is the *interaction* between hotspot site and mode of neurochemical stimulation that determines hedonic impact.

Ventral pallidum hotspot: sufficient to enhance and needed for normal 'liking' Prefrontal cortex and nucleus accumbens do share one interesting quirk regarding causation of hedonic impact. Both contain hotspots 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 hotspot of posterior ventral pallidum 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 hotspot appears more crucial than any other known brain site 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 ventral pallidum (Ho and Berridge, 2014; Smith et al., 2010).

Besides lesions, temporary pharmacological inactivation in the posterior VP hotspot also causes intense 'disgust' (Ho and Berridge, 2014; Shimura et al., 2006). By comparison in 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 'coldspot' (not rostrodorsal 'hotspot') (Ho and Berridge, 2014). That difference between VP and NAc suggests that NAc segregates hedonic gain of function versus loss of function into different anatomical sites of medial shell, whereas the VP hotspot combines both forms of hedonic causation together(Ho and Berridge, 2014). The VP hotspot 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 is also produced by large ablations of the entire telencephalon that include the ventral pallidum 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 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 (Hughlings Jackson, 1958).

Desire to dread: an affective keyboard in NAc shell

The anterior NAc opioid hedonic hotspot and posterior suppressive coldspot fit within a broader anatomical NAc pattern of front-to-back valence organization in shell that generates additional emotions beyond 'liking' and 'disgust'. This NAc pattern resembles an *affective keyboard* arranged rostrocaudally within 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 medial shell. At its anterior end, it generates predominantly positive-valenced motivations in response to localized neural events such as microinjections of a GABA agonist (muscimol) or of a glutamate AMPA antagonist (DNQX): eating more than twice normal amounts of food, increasing appetitive seeking for food rewards (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 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).

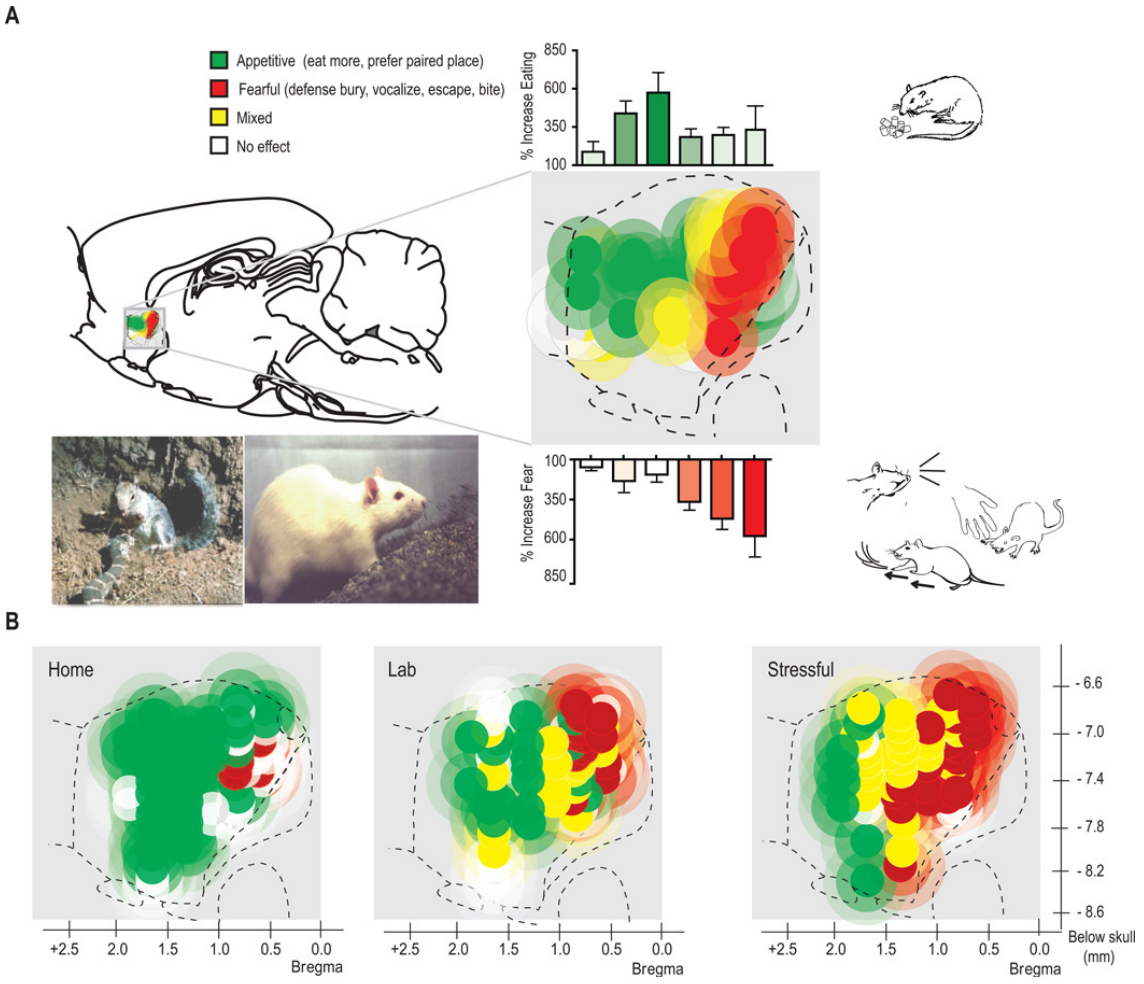


Figure 4

Affective keyboard in nucleus accumbens for desire and/or dread

Top: A rostrocaudal keyboard pattern of generators in NAc for appetitive versus fearful behaviors, showing consequences of microinjections of either glutamate AMPA antagonist or GABA agonist microinjections at rostrocaudal sites in medial shell. Rostral green sites produced 600% increases in food consumption (desire only). Caudal red sites generated purely increased fearful reactions at levels up to 600% over normal (escape attempts, distress calls, defensive bite attempts; spontaneous anti-predator treading/burying e). Photos show examples of antipredator treading/burying behavior elicited by threat stimuli: ground squirrel toward rattlesnake predator, rat toward electric-shock prod in lab. The same antipredator behaviors occurs 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 rostrocaudal location in medial shell (appetitive desire to eat at top; fearful dread reactions at bottom). Bottom: 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 zoned 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; Richard and Berridge, 2011).

Of course, several other brain structures, from amygdala to hypothalamus, ventral pallidum or brainstem also known to mediate various aversive emotional reactions, including fear, pain or disgust (Baliki 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' 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 rostrocaudal keys contained in the nucleus accumbens 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 vs negative valence: two keys would generate only two outputs, but the NAc shell generates many different incremental outputs of gradual variation depending on precise site. Just as a musical keyboard generates many distinct notes, the rostrocaudal 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 moving a brick 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 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., via DNQX blocks glutamate AMPA receptors).

Both drugs produce similar motivation keyboard patterns of intense appetitive-fearful behaviors when microinjected in 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 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 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 caudal shell expands in a stressfully bright and loud environment to invade rostral shell, while simultaneously shrinking the desire-generating zone to only the far-rostral tip of 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 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 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 mostly 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 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 prefrontal limbic cortex (Richard and Berridge, 2013). For example, raising local cortical excitations in infralimbic cortex, a medial prefrontal region homologous to 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 orbitofrontal cortex tilted valence in a positive desire direction: at least in the sense of expanding the appetitive zone that generates eating into caudal areas of NAc that otherwise produce negative 'fear' reactions (Richard and Berridge, 2013). Thus corticolimbic regulation adjusts both the intensity and valence of motivations produced by 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 amygdala, prefrontal cortex and 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'."(Wise, 1980) (p. 94). Conversely, the 'dopamine pleasure hypothesis' postulated that reduction of dopamine neurotransmission caused loss of pleasure. This inverse hypothesis is known as the 'dopamine *an*hedonia 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 of a series of problems that arose in the past two decades. The first problem specifically applied to the *an*hedonia versions that posited loss of pleasure. Evidence began to emerge that loss of dopamine doesn't 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 of schizophrenia. Closer inspection has suggested that many patients with conditions 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 rewards (e.g., higher runway performance of hyper-dopaminergic 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')(Pecina and Berridge, 2013; Peciña et al., 2003; Smith et al., 2011; Wyvell and Berridge, 2000). In people, 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 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 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 more '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 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 nucleus accumbens 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 hotspot could amplify 'liking' as described above, resulting in a more genuinely pleasurable experience. Similarly, GABA signals in the far rostral strip of 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 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, 2011; Wolf and Ferrario, 2010), even if opioid hedonic mechanisms underwent down-regulation 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 rewards (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 comes 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 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 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 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 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). One 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 (Hoebel, 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 to whether ‘pleasure electrodes’ lived up to their name, we have reexamined 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 septum, anterior hypothalamus, nucleus accumbens, ventral pallidum, ventromedial neostriatum, pyriform cortex and ventromedial neocortex (Figure 5)(Heath, 1972; Heath, 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). One of Heath’s most dramatic ‘pleasure electrode’ cases was known as B-19: a young man implanted with stimulation electrodes in 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"(Heath, 1972) (p. 6). 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.

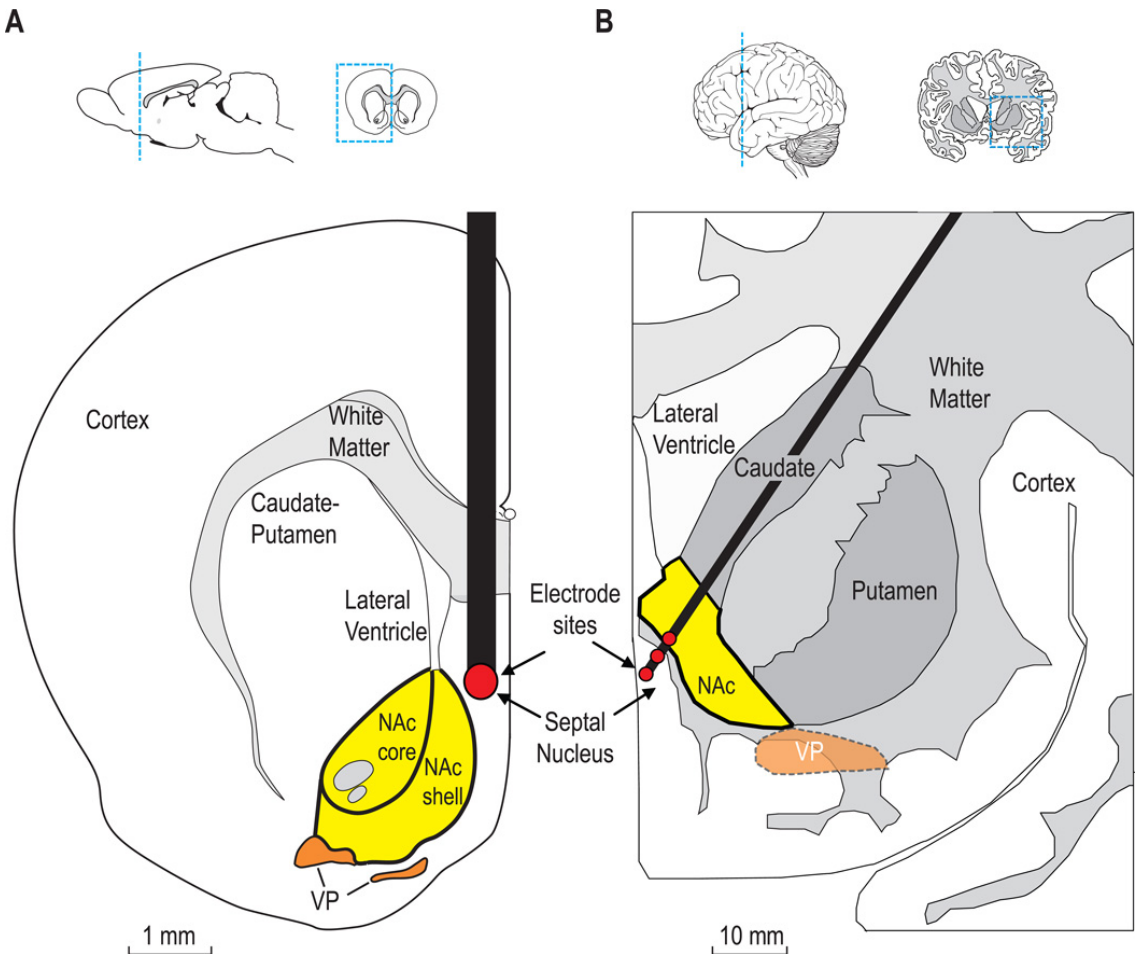


Figure 5

False pleasure electrodes?

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

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 nucleus accumbens and the subthalamic nucleus, the subgenual cingulate cortex, and fibers descending from 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.1383)(Herzog et al., 2003).

At sites in the nucleus accumbens, 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 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). One of us (MLK) 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 NAc or prefrontal cortex, resulting in positive engagement in social or leisure activities (Bewernick 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 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 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 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 orbitofrontal cortex; identification of hotspots 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 wellbeing. 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.

Acknowledgements

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, 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 helpful anonymous reviewers for suggestions on the manuscript. Research in our laboratories has been supported by grants from the NIH to KCB (MH63644 and DA015188), and from the TrygFonden Charitable Foundation and ERC Consolidator Grant to MLK (CAREGIVING n. 615539).

Footnotes

References

1. Anderson DJ, Adolphs R. A Framework for Studying Emotions across Species. Cell. 2014;157:187–200. [PMC free article] [PubMed] [Google Scholar]
2. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting Value of Pain and Analgesia: Nucleus Accumbens Response to Noxious Stimuli Changes in the Presence of Chronic Pain. Neuron. 2010;66:149–160. [PMC free article] [PubMed] [Google Scholar]
3. Barch DM, Treadway MT, Schoen N. Effort, anhedonia, and function in schizophrenia: Reduced effort allocation predicts amotivation and functional impairment. J Abnorm Psychol. 2014;123:387–397. [PMC free article] [PubMed] [Google Scholar]
4. Bard P. A diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. Am J Physiol. 1928;84 [Google Scholar]
5. Bargh JA, Schwader KL, Hailey SE, Dyer RL, Boothby EJ. Automaticity in social-cognitive processes. Trends Cogn Sci. 2012;16:593–605. [PubMed] [Google Scholar]
6. Barrett LF, Mesquita B, Ochsner KN, Gross JJ. The experience of emotion. Annu Rev Psychol. 2007;58:373–403. [PMC free article] [PubMed] [Google Scholar]
7. Bartoshuk L. The Measurement of Pleasure and Pain. Perspectives on Psychological Science. 2014;9:91–93. [PubMed] [Google Scholar]
8. Berridge KC. Measuring hedonic impact in animals and infants: microstructure of affective taste reactivity patterns. Neurosci Biobehav Rev. 2000;24:173–198. [PubMed] [Google Scholar]
9. Berridge KC. From prediction error to incentive salience: mesolimbic computation of reward motivation. European Journal of Neuroscience. 2012;35:1124–1143. [PMC free article] [PubMed] [Google Scholar]
10. Berridge KC, O'Doherty JP. From experienced utility to decision utility. In: Glimcher PW, Ernst F, editors. Neuroeconomics. Second Edition. San Diego: Academic Press; 2014. pp. 335–351. [Google Scholar]
11. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev. 1998;28:309–369. [PubMed] [Google Scholar]
12. Berridge KC, Robinson TE. Parsing reward. Trends Neurosci. 2003;26:507–513. [PubMed] [Google Scholar]
13. Berridge KC, Valenstein ES. What psychological process mediates feeding evoked by electrical stimulation of the lateral hypothalamus? Behav Neurosci. 1991;105:3–14. [PubMed] [Google Scholar]
14. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, Axmacher N, Lemke M, Cooper-Mahkorn D, Cohen MX, et al. Nucleus Accumbens Deep Brain Stimulation Decreases Ratings of Depression and Anxiety in Treatment-Resistant Depression. Biol Psychiatry. 2010;67:110–116. [PubMed] [Google Scholar]
15. Boccard SG, Fitzgerald JJ, Pereira EA, Moir L, Van Hartevelt TJ, Kringelbach ML, Green AL, Aziz TZ. Targeting the affective component of chronic pain: a case series of deep brain stimulation of the anterior cingulate cortex. Neurosurgery. 2014a;74:628–637. [PubMed] [Google Scholar]

16. Boccard SG, Pereira EA, Moir L, Van Hartevelt TJ, Kringelbach ML, FitzGerald JJ, Baker IW, Green AL, Aziz TZ. Deep brain stimulation of the anterior cingulate cortex: targeting the affective component of chronic pain. Neuroreport. 2014b;25:83–88. [PubMed] [Google Scholar]
17. Brauer LH, De Wit H. High dose pimozide does not block amphetamine-induced euphoria in normal volunteers. Pharmacol Biochem Behav. 1997;56:265–272. [PubMed] [Google Scholar]
18. Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A. Synaptic and Behavioral Profile of Multiple Glutamatergic Inputs to the Nucleus Accumbens. Neuron. 2012;76:790–803. [PMC free article] [PubMed] [Google Scholar]
19. Britt JP, McGehee DS. Presynaptic Opioid and Nicotinic Receptor Modulation of Dopamine Overflow in the Nucleus Accumbens. J Neurosci. 2008;28:1672–1681. [PubMed] [Google Scholar]
20. Cabanac M, Lafrance L. Postingestive alliesthesia: the rat tells the same story. Physiol Behav. 1990;47:539–543. [PubMed] [Google Scholar]
21. Cabral J, Hugues E, Kringelbach ML, Deco G. Modeling the outcome of structural disconnection on resting-state functional connectivity. Neuroimage. 2012;62:1342–1353. [PubMed] [Google Scholar]
22. Cabral J, Kringelbach ML, Deco G. Exploring the network dynamics underlying brain activity during rest. Prog Neurobiol. 2014;114:102–131. [PubMed] [Google Scholar]
23. Cacioppo S, Bianchi-Demicheli F, Frum C, Pfaus JG, Lewis JW. The Common Neural Bases Between Sexual Desire and Love: A Multilevel Kernel Density fMRI Analysis. The Journal of Sexual Medicine. 2012;9:1048–1054. [PubMed] [Google Scholar]
24. Callesen MB, Scheel-Kruger J, Kringelbach ML, Moller A. A systematic review of impulse control disorders in Parkinson's disease. Journal of Parkinson's disease. 2013;3:105–138. [PubMed] [Google Scholar]
25. Cameron CM, Carelli RM. Cocaine abstinence alters nucleus accumbens firing dynamics during goal-directed behaviors for cocaine and sucrose. The European journal of neuroscience. 2012;35:940–951. [PMC free article] [PubMed] [Google Scholar]
26. Carlezon WA, Jr, Thomas MJ. Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. Neuropharmacology. 2009;56(Suppl 1):122–132. [PMC free article] [PubMed] [Google Scholar]
27. Castro D, Berridge KC. Mu opioid, delta or kappa opioid receptor activation in nucleus accumbens hotspot enhances 'liking' reaction to hedonic impact of tastes. Society for Neuroscience Abstracts. 2012 [Google Scholar]
28. Castro DC, Berridge KC. Optogenetic enhancement of food ‘liking’ versus ‘wanting’ in the ventral pallidum hotspot and lateral hypothalamus; Society for Neuroscience Conference (San Diego); 2013. [Google Scholar]
29. Castro DC, Berridge KC. Opioid hedonic hotspot in nucleus accumbens shell: Mu, delta, and dappa maps for enhancement of sweetness “liking” and “wanting” J Neurosci. 2014;34:4239–4250. [PMC free article] [PubMed] [Google Scholar]
30. Castro DC, Chesterman NS, Wu MKH, Berridge KC. Two cortical hedonic hotspots: orbitofrontal and insular sites of sucrose 'liking' enhancement; Society for Neuroscience Conference (Washington, D.C.); 2014. [Google Scholar]
31. Chikazoe J, Lee DH, Kriegeskorte N, Anderson AK. Population coding of affect across stimuli, modalities and individuals. Nat Neurosci. 2014;17:1114–1122. [PMC free article] [PubMed] [Google Scholar]

32. Childress A, Ehrman R, Wang Z, Li Y, Sciortino N, Hakun J, Jens W, Suh J, Listerud J, Marquez K, et al. Prelude to passion: limbic activation by "unseen" drug and sexual cues. PLoS ONE. 2008;3:e1506. [PMC free article] [PubMed] [Google Scholar]
33. Colasanti A, Searle GE, Long CJ, Hill SP, Reiley RR, Quelch D, Erritzoe D, Tziortzi AC, Reed LJ, Lingford-Hughes AR, et al. Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. Biol Psychiatry. 2012;72:371–377. [PubMed] [Google Scholar]
34. Collins AG, Frank MJ. Opponent actor learning (OpAL): modeling interactive effects of striatal dopamine on reinforcement learning and choice incentive. Psychol Rev. 2014;121:337–366. [PubMed] [Google Scholar]
35. Cone JJ, McCutcheon JE, Roitman MF. Ghrelin Acts as an Interface between Physiological State and Phasic Dopamine Signaling. J Neurosci. 2014;34:4905–4913. [PMC free article] [PubMed] [Google Scholar]
36. Coss RG, Owings DH. Snake-Directed Behavior By Snake Naive and Experienced California Ground Squirrels in a Simulated Burrow. Zeitschrift Fur Tierpsychologie-Journal of Comparative Ethology. 1978;48:421–435. [Google Scholar]
37. Coss RG, Owings DH. Rattler Battlers. Nat Hist. 1989:30–35. [Google Scholar]
38. Craig W. Appetites and aversions as constituents of instincts. Biological Bulletin of Woods Hole. 1918;34:91–107. [PMC free article] [PubMed] [Google Scholar]
39. Cromwell HC, Berridge KC. Where does damage lead to enhanced food aversion: the ventral pallidum/substantia innominata or lateral hypothalamus? Brain Res. 1993;624:1–10. [PubMed] [Google Scholar]
40. Damasio A, Carvalho GB. The nature of feelings: evolutionary and neurobiological origins. Nat Rev Neurosci. 2013;14:143–152. [PubMed] [Google Scholar]
41. Damasio A, Damasio H, Tranel D. Persistence of feelings and sentience after bilateral damage of the insula. Cereb Cortex. 2012 [PMC free article] [PubMed] [Google Scholar]
42. Damasio AR. Descartes' error : emotion, reason, and the human brain. New York: GP Putnam; 1994. [Google Scholar]
43. Damasio AR. Self comes to mind : constructing the conscious brain. 1st edn. New York: Pantheon Books; 2010. [Google Scholar]
44. Darwin C. The Expression of the Emotions in Man and Animals (1998 edition: revised and with commentary by P Ekman) Oxford: Harper Collins - Oxford University Press; 1872. [Google Scholar]
45. Davidson RJ. Well-being and affective style: neural substrates and biobehavioural correlates. Philos Trans R Soc Lond B Biol Sci. 2004;359:1395–1411. [PMC free article] [PubMed] [Google Scholar]
46. Dayan P, Berridge KC. Model-based and model-free Pavlovian reward learning: revaluation, revision, and revelation. Cogn Affect Behav Neurosci. 2014;14:473–492. [PMC free article] [PubMed] [Google Scholar]
47. Deco G, Kringelbach Morten L. Great Expectations: Using Whole-Brain Computational Connectomics for Understanding Neuropsychiatric Disorders. Neuron. 2014;84:892–905. [PubMed] [Google Scholar]
48. Delamater AR, LoLordo VM, Berridge KC. Control of fluid palatability by exteroceptive Pavlovian signals. J Exp Psychol [Anim Behav] 1986;12:143–152. [PubMed] [Google Scholar]
49. Difeliceantonio AG, Berridge KC. Which cue to 'want'? Opioid stimulation of central amygdala makes goal-trackers show stronger goal-tracking, just as sign-trackers show stronger sign-tracking. Behav Brain Res. 2012;230:399–408. [PMC free article] [PubMed] [Google Scholar]

50. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. Biol Psychiatry. 2010;67:902–911. [PMC free article] [PubMed] [Google Scholar]
51. Eisenegger C, Naef M, Linssen A, Clark L, Gandamaneni PK, Muller U, Robbins TW. Role of dopamine D2 receptors in human reinforcement learning. Neuropsychopharmacology. 2014;39:2366–2375. [PMC free article] [PubMed] [Google Scholar]
52. Ettenberg A, McFarland K. Effects of haloperidol on cue-induced autonomic and behavioral indices of heroin reward and motivation. Psychopharmacology. 2003;168:139–145. [PubMed] [Google Scholar]
53. Evans AH, Pavese N, Lawrence AD, Tai YF, Appel S, Doder M, Brooks DJ, Lees AJ, Piccini P. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. Ann Neurol. 2006;59:852–858. [PubMed] [Google Scholar]
54. Faure A, Reynolds SM, Richard JM, Berridge KC. Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens. J Neurosci. 2008;28:7184–7192. [PMC free article] [PubMed] [Google Scholar]
55. Faure A, Richard JM, Berridge KC. Desire and dread from the nucleus accumbens: cortical glutamate and subcortical GABA differentially generate motivation and hedonic impact in the rat. PLoS One. 2010;5:e11223. [PMC free article] [PubMed] [Google Scholar]
56. Fischman MW, Foltin RW. Self-administration of cocaine by humans: a laboratory perspective. In: Bock GR, Whelan J, editors. Cocaine: Scientific and Social Dimensions, CIBA foundation symposium No 166; Chichester, UK. Wiley; 1992. pp. 165–180. [Google Scholar]
57. Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, Akers CA, Clinton SM, Phillips PE, Akil H. A selective role for dopamine in stimulus-reward learning. Nature. 2011;469:53–57. [PMC free article] [PubMed] [Google Scholar]
58. Friedman JH, Chang V. Crack cocaine use due to dopamine agonist therapy in Parkinson disease. Neurology. 2013;80:2269–2270. [PMC free article] [PubMed] [Google Scholar]
59. Galistu A, D'Aquila PS. Effect of the dopamine D1-like receptor antagonist SCH 23390 on the microstructure of ingestive behaviour in water-deprived rats licking for water and NaCl solutions. Physiol Behav. 2012;105:230–233. [PubMed] [Google Scholar]
60. Gallistel CR. Dopamine and reward: comment on Hernandez et al. (2006) Behav Neurosci. 2006;120:992–994. [PubMed] [Google Scholar]
61. Georgiadis JR, Kringelbach ML. The human sexual response cycle: brain imaging evidence linking sex to other pleasures. Progress in neurobiology. 2012;98:49–81. [PubMed] [Google Scholar]
62. Georgiadis JR, Kringelbach ML, Pfaus JG. Sex for fun: a synthesis of human and animal neurobiology. Nat Rev Urol. 2012 advance online publication. [PubMed] [Google Scholar]
63. Gilbert DT, Wilson TD. Why the brain talks to itself: sources of error in emotional prediction. Philos T R Soc B. 2009;364:1335–1341. [PMC free article] [PubMed] [Google Scholar]
64. Gottfried JA, O'Doherty J, Dolan RJ. Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science. 2003;301:1104–1107. [PubMed] [Google Scholar]
65. Grill HJ, Norgren R. The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res. 1978a;143:263–279. [PubMed] [Google Scholar]
66. Grill HJ, Norgren R. The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. Brain Res. 1978b;143:281–297. [PubMed] [Google Scholar]
67. Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35:4–26. [PMC free article] [PubMed] [Google Scholar]

68. Haynes JD, Rees G. Decoding mental states from brain activity in humans. Nat Rev Neurosci. 2006;7:523–534. [PubMed] [Google Scholar]
69. Heath RG. Pleasure and brain activity in man. Deep and surface electroencephalograms during orgasm. Journal of Nervous and Mental Disease. 1972;154:3–18. [PubMed] [Google Scholar]
70. Heath RG. Exploring the mind-brain relationship. Baton Rouge, LA: Moran Printing Inc.; 1996. [Google Scholar]
71. Heller AS, van Reekum CM, Schaefer SM, Lapate RC, Radler BT, Ryff CD, Davidson RJ. Sustained striatal activity predicts eudaimonic well-being and cortisol output. Psychol Sci. 2013;24:2191–2200. [PMC free article] [PubMed] [Google Scholar]
72. Hernandez G, Rajabi H, Stewart J, Arvanitogiannis A, Shizgal P. Dopamine tone increases similarly during predictable and unpredictable administration of rewarding brain stimulation at short inter-train intervals. Behav Brain Res. 2008;188:227–232. [PubMed] [Google Scholar]
73. Herzog J, Reiff J, Krack P, Witt K, Schrader B, Muller D, Deuschl G. Manic episode with psychotic symptoms induced by subthalamic nucleus stimulation in a patient with Parkinson's disease. Mov Disord. 2003;18:1382–1384. [PubMed] [Google Scholar]
74. Hnasko TS, Perez FA, Scouras AD, Stoll EA, Gale SD, Luquet S, Phillips PE, Kremer EJ, Palmiter RD. Cre recombinase-mediated restoration of nigrostriatal dopamine in dopamine-deficient mice reverses hypophagia and bradykinesia. Proc Natl Acad Sci U S A. 2006;103:8858–8863. [PMC free article] [PubMed] [Google Scholar]
75. Ho C-Y, Berridge KC. Excessive disgust caused by brain lesions or temporary inactivations: mapping hotspots of the nucleus accumbens and ventral pallidum. European Journal of Neuroscience. 2014 n/a-n/a. [PMC free article] [PubMed] [Google Scholar]
76. Ho CY, Berridge KC. An orexin hotspot in ventral pallidum amplifies hedonic 'liking' for sweetness. Neuropsychopharmacology. 2013;38:1655–1664. [PMC free article] [PubMed] [Google Scholar]
77. Hoebel BG. Neuroscience and motivation: pathways and peptides that define motivational systems. In: Atkinson RC, Herrnstein RJ, Lindzey G, Luce RD, editors. Stevens' Handbook of Experimental Psychology. New York: John Wiley & Sons; 1988. pp. 547–626. [Google Scholar]
78. Holtzheimer PE, 3rd, Mayberg HS. Deep brain stimulation for treatment-resistant depression. Am J Psychiatry. 2010;167:1437–1444. [PMC free article] [PubMed] [Google Scholar]
79. Hughlings Jackson J, editor. Selected writings of John Hughlings Jackson. London: Staples Press; 1958. [Google Scholar]
80. Humphries MD, Prescott TJ. The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward. Progress in Neurobiology. 2010;90:385–417. [PubMed] [Google Scholar]
81. Kahnt T, Chang LJ, Park SQ, Heinzle J, Haynes J-D. Connectivity-Based Parcellation of the Human Orbitofrontal Cortex. J Neurosci. 2012;32:6240–6250. [PubMed] [Google Scholar]
82. Kahnt T, Heinzle J, Park SQ, Haynes JD. The neural code of reward anticipation in human orbitofrontal cortex. Proc Natl Acad Sci U S A. 2010;107:6010–6015. [PMC free article] [PubMed] [Google Scholar]
83. Kaplan JM, Roitman M, Grill HJ. Food deprivation does not potentiate glucose taste reactivity responses of chronic decerebrate rats. Brain Res. 2000;870:102–108. [PubMed] [Google Scholar]
84. Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, Lozano AM. Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years. Am J Psychiatry. 2011 [PubMed] [Google Scholar]

85. King JR, Dehaene S. Characterizing the dynamics of mental representations: the temporal generalization method. Trends Cogn Sci. 2014;18:203–210. [PMC free article] [PubMed] [Google Scholar]
86. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35:217–238. [PMC free article] [PubMed] [Google Scholar]
87. Krause M, German PW, Taha SA, Fields HL. A Pause in Nucleus Accumbens Neuron Firing Is Required to Initiate and Maintain Feeding. J Neurosci. 2010;30:4746–4756. [PMC free article] [PubMed] [Google Scholar]
88. Kringelbach ML. The hedonic brain: A functional neuroanatomy of human pleasure. In: Kringelbach ML, Berridge KC, editors. Pleasures of the brain. Oxford, UK: Oxford University Press; 2010. pp. 202–221. [Google Scholar]
89. Kringelbach ML, Berridge KC. Towards a functional neuroanatomy of pleasure and happiness. Trends Cog Sci. 2009;13:479–487. [PMC free article] [PubMed] [Google Scholar]
90. Kringelbach ML, Berridge KC, editors. Pleasures of the Brain. Oxford: Oxford University Press; 2010. [Google Scholar]
91. Kringelbach ML, de Araujo IE, Rolls ET. Taste-related activity in the human dorsolateral prefrontal cortex. Neuroimage. 2004;21:781–788. [PubMed] [Google Scholar]
92. Kringelbach ML, Green AL, Aziz TZ. Balancing the brain: resting state networks and deep brain stimulation. Frontiers in integrative neuroscience. 2011;5:8. [PMC free article] [PubMed] [Google Scholar]
93. Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex. 2003;13:1064–1071. [PubMed] [Google Scholar]
94. Kringelbach ML, Pereira EAC, Green AL, Owen SLF, Aziz TZ. Deep brain stimulation for chronic pain. Journal of Pain Management. 2009;3:301–314. [Google Scholar]
95. Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol. 2004;72:341–372. [PubMed] [Google Scholar]
96. Kringelbach ML, Stein A, van Hartevelt TJ. The functional human neuroanatomy of food pleasure cycles. Physiol and Behav. 2012;106:307–316. [PubMed] [Google Scholar]
97. Kuhn S, Gallinat J. The neural correlates of subjective pleasantness. NeuroImage. 2012;61:289–294. [PubMed] [Google Scholar]
98. Kupchik YM, Kalivas PW. The rostral subcommissural ventral pallidum is a mix of ventral pallidal neurons and neurons from adjacent areas: an electrophysiological study. Brain Struct Funct. 2013;218:1487–1500. [PMC free article] [PubMed] [Google Scholar]
99. Lawrence NS, Hinton EC, Parkinson JA, Lawrence AD. Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. NeuroImage. 2012;63:415–422. [PubMed] [Google Scholar]
100. LeDoux J. Rethinking the emotional brain. Neuron. 2012;73:653–676. [PMC free article] [PubMed] [Google Scholar]
101. LeDoux JE. Coming to terms with fear. Proc Natl Acad Sci U S A. 2014;111:2871–2878. [PMC free article] [PubMed] [Google Scholar]
102. Leyton M, aan het Ro M, Booij L, Baker G, Young S, Benkelfat C. Mood-elevating effects of d-amphetamine and incentive salience: the effect of acute dopamine precursor depletion. J Psychiatry Neurosci. 2007;32:129–136. [PMC free article] [PubMed] [Google Scholar]

103. Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A. Amphetamine-Induced Increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. Neuropsychopharmacology. 2002;27:1027–1035. [PubMed] [Google Scholar]
104. Leyton M, Vezina P. Striatal ups and downs: their roles in vulnerability to addictions in humans. Neurosci Biobehav Rev. 2013;37:1999–2014. [PMC free article] [PubMed] [Google Scholar]
105. Liggins J, Pihl RO, Benkelfat C, Leyton M. The dopamine augmenter L-DOPA does not affect positive mood in healthy human volunteers. PLoS One. 2012;7:e28370. [PMC free article] [PubMed] [Google Scholar]
106. Lodge DJ, Grace AA. Divergent activation of ventromedial and ventrolateral dopamine systems in animal models of amphetamine sensitization and schizophrenia. The International Journal of Neuropsychopharmacology FirstView. 2011:1–8. [PMC free article] [PubMed] [Google Scholar]
107. Loriaux AL, Roitman JD, Roitman MF. Nucleus accumbens shell, but not core, tracks motivational value of salt. J Neurophysiol. 2011;106:1537–1544. [PMC free article] [PubMed] [Google Scholar]
108. Mahler SV, Berridge KC. What and when to "want"? Amygdala-based focusing of incentive salience upon sugar and sex. Psychopharmacology. 2012;221:407–426. [PMC free article] [PubMed] [Google Scholar]
109. Mahler SV, Smith KS, Berridge KC. Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. Neuropsychopharmacology. 2007;32:2267–2278. [PubMed] [Google Scholar]
110. Maren S, Phan KL, Liberzon I. The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci. 2013;14:417–428. [PMC free article] [PubMed] [Google Scholar]
111. Mayer DJ, Wolfle TL, Akil H, Carder B, Liebeskind JC. Analgesia from electrical stimulation in the brainstem of the rat. Science. 1971;174:1351–1354. [PubMed] [Google Scholar]
112. Medic N, Ziauddeen H, Vestergaard MD, Henning E, Schultz W, Farooqi IS, Fletcher PC. Dopamine Modulates the Neural Representation of Subjective Value of Food in Hungry Subjects. J Neurosci. 2014;34:16856–16864. [PMC free article] [PubMed] [Google Scholar]
113. Meredith GE, Baldo BA, Andrezjewski ME, Kelley AE. The structural basis for mapping behavior onto the ventral striatum and its subdivisions. Brain Struct Funct. 2008;213:17–27. [PMC free article] [PubMed] [Google Scholar]
114. Merker B. Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. Behav Brain Sci. 2007;30:63–81. discussion 81–134. [PubMed] [Google Scholar]
115. Meyers C, Amick MA, Friedman JH. Ice cream preference in Parkinson's disease. Medicine and health, Rhode Island. 2010;93:91–92. [PubMed] [Google Scholar]
116. O'Sullivan S, Evans A, Lees A. Dopamine dysregulation syndrome: an overview of its epidemiology, mechanisms and management. CNS Drugs. 2009;23:157–170. [PubMed] [Google Scholar]
117. O'Doherty JP. The problem with value. Neurosci Biobehav Rev. 2014 [PMC free article] [PubMed] [Google Scholar]
118. Olds J. Pleasure centers in the brain. Sci Am. 1956;195:105–116. [Google Scholar]
119. Olds J. Drives and reinforcements: behavioral studies of hypothalamic functions. New York: Raven Press; 1977. [Google Scholar]
120. Olds J, Milner P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative and Physiological Psychology. 1954;47:419–427. [PubMed] [Google Scholar]

121. Ondo WG, Lai D. Predictors of impulsivity and reward seeking behavior with dopamine agonists. Parkinsonism Relat Disord. 2008;14:28–32. [PubMed] [Google Scholar]
122. Panksepp J. The basic emotional circuits of mammalian brains: do animals have affective lives? Neurosci Biobehav Rev. 2011;35:1791–1804. [PubMed] [Google Scholar]
123. Parsons CE, Young KS, Murray L, Stein A, Kringelbach ML. The functional neuroanatomy of the evolving parent-infant relationship. Prog Neurobiol. 2010;91:220–241. [PubMed] [Google Scholar]
124. Pecina S, Berridge KC. Dopamine or opioid stimulation of nucleus accumbens similarly amplify cue-triggered 'wanting' for reward: entire core and medial shell mapped as substrates for PIT enhancement. Eur J Neurosci. 2013;37:1529–1540. [PMC free article] [PubMed] [Google Scholar]
125. Peciña S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: Where do mu-opioids cause increased hedonic impact of sweetness? J Neurosci. 2005;25:11777–11786. [PubMed] [Google Scholar]
126. Peciña S, Berridge KC, Parker LA. Pimozide does not shift palatability: separation of anhedonia from sensorimotor suppression by taste reactivity. Pharmacol Biochem Behav. 1997;58:801–811. [PubMed] [Google Scholar]
127. Peciña S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards. J Neurosci. 2003;23:9395–9402. [PubMed] [Google Scholar]
128. Pessiglione M, Schmidt L, Draganski B, Kalisch R, Lau H, Dolan R, Frith C. How the brain translates money into force: a neuroimaging study of subliminal motivation. Science. 2007;316:904–906. [PMC free article] [PubMed] [Google Scholar]
129. Politis M, Loane C, Wu K, O'Sullivan SS, Woodhead Z, Kiferle L, Lawrence AD, Lees AJ, Piccini P. Neural response to visual sexual cues in dopamine treatment-linked hypersexuality in Parkinson's disease. Brain. 2013;136:400–411. [PubMed] [Google Scholar]
130. Price TF, Harmon-Jones E. Approach motivational body postures lean toward left frontal brain activity. Psychophysiology. 2011;48:718–722. [PubMed] [Google Scholar]
131. Reynolds SM, Berridge KC. Fear and feeding in the nucleus accumbens shell: rostrocaudal segregation of GABA-elicited defensive behavior versus eating behavior. J Neurosci. 2001;21:3261–3270. [PubMed] [Google Scholar]
132. Reynolds SM, Berridge KC. Positive and negative motivation in nucleus accumbens shell: Bivalent rostrocaudal gradients for GABA-elicited eating, taste "liking"/"disliking" reactions, place preference/avoidance, and fear. J Neurosci. 2002;22:7308–7320. [PubMed] [Google Scholar]
133. Reynolds SM, Berridge KC. Emotional environments retune the valence of appetitive versus fearful functions in nucleus accumbens. Nat Neurosci. 2008;11:423–425. [PMC free article] [PubMed] [Google Scholar]
134. Richard JM, Berridge KC. Nucleus Accumbens Dopamine/Glutamate Interaction Switches Modes to Generate Desire versus Dread: D1 Alone for Appetitive Eating But D1 and D2 Together for Fear. J Neurosci. 2011;31:12866–12879. [PMC free article] [PubMed] [Google Scholar]
135. Richard JM, Berridge KC. Prefrontal cortex modulates desire and dread generated by nucleus accumbens glutamate disruption. Biol Psychiatry. 2013;73:360–370. [PMC free article] [PubMed] [Google Scholar]

136. Richard JM, Castro DC, Difeliceantonio AG, Robinson MJ, Berridge KC. Mapping brain circuits of reward and motivation: in the footsteps of Ann Kelley. Neurosci Biobehav Rev. 2013a;37:1919–1931. [PMC free article] [PubMed] [Google Scholar]
137. Richard JM, Plawecki AM, Berridge KC. Nucleus accumbens GABAergic inhibition generates intense eating and fear that resists environmental retuning and needs no local dopamine. Eur J Neurosci. 2013b;37:1789–1802. [PMC free article] [PubMed] [Google Scholar]
138. Robinson MJ, Berridge KC. Instant transformation of learned repulsion into motivational "wanting". Curr Biol. 2013;23:282–289. [PMC free article] [PubMed] [Google Scholar]
139. Robinson MJ, Warlow SM, Berridge KC. Optogenetic excitation of central amygdala amplifies and narrows incentive motivation to pursue one reward above another. J Neurosci. 2014a;34:16567–16580. [PMC free article] [PubMed] [Google Scholar]
140. Robinson S, Sandstrom SM, Denenberg VH, Palmiter RD. Distinguishing whether dopamine regulates liking, wanting, and/or learning about rewards. Behav Neurosci. 2005;119:5–15. [PubMed] [Google Scholar]
141. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993;18:247–291. [PubMed] [Google Scholar]
142. Robinson TE, Yager LM, Cogan ES, Saunders BT. On the motivational properties of reward cues: Individual differences. Neuropharmacology. 2014b;76(Part B):450–459. [PMC free article] [PubMed] [Google Scholar]
143. Roitman MF, Wheeler RA, Carelli RM. Nucleus Accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. Neuron. 2005;45:587–597. [PubMed] [Google Scholar]
144. Roitman MF, Wheeler RA, Tiesinga PH, Roitman JD, Carelli RM. Hedonic and nucleus accumbens neural responses to a natural reward are regulated by aversive conditioning. Learn Mem. 2010;17:539–546. [PMC free article] [PubMed] [Google Scholar]
145. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. Nature neuroscience. 2011;14:257–262. [PubMed] [Google Scholar]
146. Saunders BT, Robinson TE. The role of dopamine in the accumbens core in the expression of Pavlovian-conditioned responses. The European Journal of Neuroscience. 2012;36:2521–2532. [PMC free article] [PubMed] [Google Scholar]
147. Saunders BT, Robinson TE. Individual variation in resisting temptation: implications for addiction. Neurosci Biobehav Rev. 2013 [PMC free article] [PubMed] [Google Scholar]
148. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, Joe AY, Kreft M, Lenartz D, Sturm V. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology. 2008;33:368–377. [PubMed] [Google Scholar]
149. Schoenbaum G, Roesch M. Orbitofrontal cortex, associative learning, and expectancies. Neuron. 2005;47:633–636. [PMC free article] [PubMed] [Google Scholar]
150. Schooler JW, Mauss IB. To be happy and to know it: The experience and meta-awareness of pleasure. In: Kringelbach ML, Berridge KC, editors. Pleasures of the Brain. Oxford, UK: Oxford University Press; 2010. pp. 244–254. [Google Scholar]
151. Schultz W. Updating dopamine reward signals. Cur Opin Neurobiol. 2013;23:229–238. [PMC free article] [PubMed] [Google Scholar]
152. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997;275:1593–1599. [PubMed] [Google Scholar]
153. Sherrington CS. The integrative action of the nervous system. New York: C. Scribner's sons; 1906. [Google Scholar]

154. Shewmon DA, Holmes GL, Byrne PA. Consciousness in congenitally decorticate children: developmental vegetative state as self-fulfilling prophecy. Dev Med Child Neurol. 1999;41:364–374. [PubMed] [Google Scholar]
155. Shimura T, Imaoka H, Yamamoto T. Neurochemical modulation of ingestive behavior in the ventral pallidum. Eur J Neurosci. 2006;23:1596–1604. [PubMed] [Google Scholar]
156. Shiner T, Seymour B, Wunderlich K, Hill C, Bhatia KP, Dayan P, Dolan RJ. Dopamine and performance in a reinforcement learning task: evidence from Parkinson's disease. Brain. 2012;135:1871–1883. [PMC free article] [PubMed] [Google Scholar]
157. Sienkiewicz-Jarosz H, Scinska A, Kuran W, Ryglewicz D, Rogowski A, Wrobel E, Korkosz A, Kukwa A, Kostowski W, Bienkowski P. Taste responses in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 2005;76:40–46. [PMC free article] [PubMed] [Google Scholar]
158. Sienkiewicz-Jarosz H, Scinska A, Swiecicki L, Lipczynska-Lojkowska W, Kuran W, Ryglewicz D, Kolaczkowski M, Samochowiec J, Bienkowski P. Sweet liking in patients with Parkinson's disease. J Neurol Sci. 2013;329:17–22. [PubMed] [Google Scholar]
159. Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate - From pleasure to aversion. Brain. 2001;124:1720–1733. [PubMed] [Google Scholar]
160. Smith GP. Dopamine and food reward. In: Morrison AM, Fluharty SJ, editors. Progress in Psychobiology and Physiological Psychology. New York: Academic Press; 1995. pp. 83–144. [Google Scholar]
161. Smith KS, Berridge KC. The ventral pallidum and hedonic reward: neurochemical maps of sucrose "liking" and food intake. J Neurosci. 2005;25:8637–8649. [PubMed] [Google Scholar]
162. Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci. 2007;27:1594–1605. [PubMed] [Google Scholar]
163. Smith KS, Berridge KC, Aldridge JW. Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. Proc Natl Acad Sci U S A. 2011;108:E255–E264. [PMC free article] [PubMed] [Google Scholar]
164. Smith KS, Mahler SV, Pecina S, Berridge KC. Hedonic Hotspots: Generating Sensory Pleasure in the Brain. In: Kringelbach ML, Berridge KC, editors. Pleasures of the Brain. Oxford, UK: Oxford University Press; 2010. pp. 27–49. [Google Scholar]
165. Smittenaar P, Chase HW, Aarts E, Nusselein B, Bloem BR, Cools R. Decomposing effects of dopaminergic medication in Parkinson's disease on probabilistic action selection – learning or performance? European Journal of Neuroscience. 2012;35:1144–1151. [PubMed] [Google Scholar]
166. Soderman AR, Unterwald EM. Cocaine-induced mu opioid receptor occupancy within the striatum is mediated by dopamine D2 receptors. Brain Res. 2009;1296:63–71. [PMC free article] [PubMed] [Google Scholar]
167. Soderpalm AH, Berridge KC. The hedonic impact and intake of food are increased by midazolam microinjection in the parabrachial nucleus. Brain Res. 2000;877:288–297. [PubMed] [Google Scholar]
168. Steiner JE. The gustofacial response: observation on normal and anencephalic newborn infants. Symp Oral Sens Percept. 1973;4:254–278. [PubMed] [Google Scholar]
169. Steiner JE, Glaser D, Hawilo ME, Berridge KC. Comparative expression of hedonic impact: affective reactions to taste by human infants and other primates. Neurosci Biobehav Rev. 2001;25:53–74. [PubMed] [Google Scholar]

170. Stratford TR, Kelley AE. GABA in the nucleus accumbens shell participates in the central regulation of feeding behavior. J Neurosci. 1997;17:4434–4440. [PubMed] [Google Scholar]
171. Stratford TR, Wirtshafter D. Effects of muscimol, amphetamine, and DAMGO injected into the nucleus accumbens shell on food-reinforced lever pressing by undeprived rats. Pharmacol Biochem Behav. 2012;101:499–503. [PMC free article] [PubMed] [Google Scholar]
172. Szczepanski Sara M, Knight Robert T. Insights into Human Behavior from Lesions to the Prefrontal Cortex. Neuron. 2014;83:1002–1018. [PMC free article] [PubMed] [Google Scholar]
173. Taha SA, Fields HL. Encoding of Palatability and Appetitive Behaviors by Distinct Neuronal Populations in the Nucleus Accumbens. J Neurosci. 2005;25:1193–1202. [PubMed] [Google Scholar]
174. Teitelbaum P, Epstein AN. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. Psychol Rev. 1962;69:74–90. [PubMed] [Google Scholar]
175. Thompson RH, Swanson LW. Hypothesis-driven structural connectivity analysis supports network over hierarchical model of brain architecture. Proc Natl Acad Sci U S A. 2010;107:15235–15239. [PMC free article] [PubMed] [Google Scholar]
176. Tindell AJ, Smith KS, Pecina S, Berridge KC, Aldridge JW. Ventral pallidum firing codes hedonic reward: when a bad taste turns good. J Neurophysiol. 2006;96:2399–2409. [PubMed] [Google Scholar]
177. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci Biobehav Rev. 2011;35:537–555. [PMC free article] [PubMed] [Google Scholar]
178. Tritsch NX, Ding JB, Sabatini BL. Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. Nature. 2012;490:262–266. [PMC free article] [PubMed] [Google Scholar]
179. Valenstein ES. Great and desperate cures : the rise and decline of psychosurgery and other radical treatments for mental illness. New York: Basic Books; 1986. [Google Scholar]
180. van Hartevelt TJ, Cabral J, Deco G, Moller A, Green AL, Aziz TZ, Kringelbach ML. Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's disease. PLoS One. 2014;9:e86496. [PMC free article] [PubMed] [Google Scholar]
181. Vartanian O, Skov M. Neural correlates of viewing paintings: Evidence from a quantitative meta-analysis of functional magnetic resonance imaging data. Brain Cogn. 2014;87:52–56. [PubMed] [Google Scholar]
182. Veldhuizen MG, Rudenga KJ, Small D. The pleasure of taste flavor and food. In: Kringelbach ML, Berridge KC, editors. Pleasures of the brain. Oxford, UK: Oxford University Press; 2010. pp. 146–168. [Google Scholar]
183. von dem Hagen EA, Beaver JD, Ewbank MP, Keane J, Passamonti L, Lawrence AD, Calder AJ. Leaving a bad taste in your mouth but not in my insula. Social cognitive and affective neuroscience. 2009;4:379–386. [PMC free article] [PubMed] [Google Scholar]
184. Vuust P, Kringelbach ML. The pleasure of music. In: Kringelbach ML, Berridge KC, editors. Pleasures of the Brain. Oxford, UK: Oxford University Press; 2010. pp. 255–269. [Google Scholar]
185. Wickelgren I. Neuroscience: Getting the Brain's Attention. Science. 1997;278:35–37. [PubMed] [Google Scholar]
186. Winawer J, Kay KN, Foster BL, Rauschecker AM, Parvizi J, Wandell BA. Asynchronous broadband signals are the principal source of the BOLD response in human visual cortex. Curr Biol. 2013;23:1145–1153. [PMC free article] [PubMed] [Google Scholar]

187. Winkielman P, Berridge KC, Wilbarger JL. Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value. Personality and Social Psychology Bulletin. 2005;31:121–135. [PubMed] [Google Scholar]
188. Wirtshafter D, Covelo IR, Salija I, Stratford TR. Effects of muscimol in the nucleus accumbens shell on salt appetite and sucrose intake: a microstructural study with a comment on the sensitization of salt intake. Behav Neurosci. 2012;126:699–709. [PMC free article] [PubMed] [Google Scholar]
189. Wise RA. The dopamine synapse and the notion of 'pleasure centers' in the brain. Trends Neurosci. 1980;3:91–95. [Google Scholar]
190. Wise RA. Dopamine and reward: the anhedonia hypothesis 30 years on. Neurotox Res. 2008;14:169–183. [PMC free article] [PubMed] [Google Scholar]
191. Wise RA, Colle LM. Pimozide attenuates free feeding: best scores analysis reveals a motivational deficit. Psychopharmacology. 1984;84:446–451. [PubMed] [Google Scholar]
192. Wise RA, Raptis L. Effects of naloxone and pimozide on initiation and maintenance measures of free feeding. Brain Res. 1986;368:62–68. [PubMed] [Google Scholar]
193. Wise RA, Spindler J, deWit H, Gerberg GJ. Neuroleptic-induced "anhedonia" in rats: pimozide blocks reward quality of food. Science. 1978;201:262–264. [PubMed] [Google Scholar]
194. Wolf ME, Ferrario CR. AMPA receptor plasticity in the nucleus accumbens after repeated exposure to cocaine. Neurosci Biobehav Rev. 2010;35:185–211. [PMC free article] [PubMed] [Google Scholar]
195. Wu Q, Clark MS, Palmiter RD. Deciphering a neuronal circuit that mediates appetite. Nature. 2012;483:594–597. [PMC free article] [PubMed] [Google Scholar]
196. Wyvell CL, Berridge KC. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. J Neurosci. 2000;20:8122–8130. [PubMed] [Google Scholar]
197. Xiu J, Zhang Q, Zhou T, Zhou T-t, Chen Y, Hu H. Visualizing an emotional valence map in the limbic forebrain by TAI-FISH. Nat Neurosci. 2014;17:1552–1559. [PubMed] [Google Scholar]
198. Xu X, Aron A, Brown L, Cao G, Feng T, Weng X. Reward and motivation systems: a brain mapping study of early-stage intense romantic love in Chinese participants. Hum Brain Mapp. 2011;32:249–257. [PubMed] [Google Scholar]
199. Zahm DS, Parsley KP, Schwartz ZM, Cheng AY. On lateral septum-like characteristics of outputs from the accumbal hedonic 'hotspot' of Peciña and Berridge with commentary on the transitional nature of basal forebrain 'boundaries'. J Comp Neurol. 2013;521:50–68. [PMC free article] [PubMed] [Google Scholar]
200. Zeki S, Romaya JP. The brain reaction to viewing faces of opposite- and same-sex romantic partners. PloS one. 2010;5:e15802. [PMC free article] [PubMed] [Google Scholar]