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Current Opinion in Neurobiology

Neuroscience of affect: brain mechanisms of pleasure and displeasure

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Affective neuroscience aims to understand how *affect* (pleasure or displeasure) is created by brains. Progress is aided by recognizing that affect has both objective and subjective features. Those dual aspects reflect that affective reactions are generated by neural mechanisms, selected in evolution based on their real (objective) consequences for genetic fitness. We review evidence for neural representation of pleasure in the brain (gained largely from neuroimaging studies), and evidence for the causal generation of pleasure (gained largely from brain manipulation studies). We suggest that representation and causation may actually reflect somewhat separable neuropsychological functions. Representation reaches an apex in limbic regions of prefrontal cortex, especially orbitofrontal cortex, influencing decisions and affective regulation. Causation of core pleasure or 'liking' reactions is much more subcortically weighted, and sometimes surprisingly localized. Pleasure 'liking' is especially generated by restricted hedonic hotspot circuits in nucleus accumbens (NAc) and ventral pallidum. Another example of localized valence generation, beyond hedonic hotspots, is an affective keyboard mechanism in NAc for releasing intense motivations such as either positively valenced desire and/or negatively valenced dread.

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Current Opinion in Neurobiology 2012, **23**:xx–yy

This review comes from a themed issue on **Social & emotional neuroscience**

Edited by **Ralph Adolphs** and **David Anderson**

0959-4388/$ – see front matter,

http://dx.doi.org/10.1016/j.conb.2013.01.017

Introduction

Affect, the hedonic quality of pleasure or displeasure, is what distinguishes emotion from other psychological processes. Affect therefore distinguishes affective neuroscience from other branches of neuroscience, and in a sense, all affective neuroscience could be viewed as a search for affect in the brain. Yet to search for affect itself, as a core process of pleasure or displeasure, has rarely been the explicit goal of affective neuroscience studies. Consequently, the degree of understanding of how affect *per se* is created by brain mechanisms has remained relatively undeveloped even as brain studies of emotion have multiplied [1•]. Yet fortunately, substantial progress has begun to be made in the past few years in understanding brain mechanisms of pleasure and displeasure [2••,3,4,5].

We will focus here on the prototypical affect of pleasure as sensory reward. Pleasure and reward are important, both today and in evolutionary history. Healthy well-being requires capacity for normal pleasure reactions. Dysfunction in reward circuitry can produce affective psychopathologies ranging from depression to addiction. Evolutionarily, selected pleasure reactions shape behavior toward adaptive goals.

Reward involves multiple neuropsychological components together: first, the hedonic affect of pleasure itself ('liking'); second, motivation to obtain the reward ('wanting' or incentive salience); and third, reward-related learning. Each component likely played key roles in optimizing the allocation of brain resources necessary for evolutionary survival, by helping to initiate, sustain and switch behavior adaptively among different available options [5–7]. Here, we concentrate on describing the progress made in uncovering brain mechanisms involved in 'liking' or core pleasure reactions, but note that 'wanting' and learning components involve overlapping neural systems.

Pleasure arises from hedonic brain systems: subjective and objective features

What is pleasure or core 'liking'? First, pleasure is never merely a sensation. Even a sensory pleasure such as a sweet taste requires the co-recruitment of additional specialized pleasure-generating neural circuitry to add the positive hedonic impact to the sweetness that elicits 'liking' reactions (described in details below) [4,5,8]. Without that pleasure gloss, even a sweet sensation can remain neutral or actually become unpleasant.

Second, pleasure has not only subjective, but also objective features. Although the conscious experience of pleasure is its most striking feature, brain systems naturally evolved as objective mechanisms to produce behavior. Pleasure mechanisms were selected and conserved by the same natural evolutionary pressures that shape any

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psychological function. Hedonic mechanisms require millions of neurons arranged into patterns of mesocorticolimbic circuitry, a combination constituting substantial biological investment that was unlikely to have evolved if affective reactions did not convey significant objective benefits [3,9•,10,11].

Our focus on objective affective reactions to identify core hedonic processes takes its lead from Darwin's original book on emotion over a century ago [12]. Darwin noted distinctive affective expressions (facial, bodily, and autonomic) in humans and animals in various emotional situations. Darwin's approach is also echoed by Joseph LeDoux's recent proposal: ''By focusing on survival functions instantiated in conserved circuits, key phenomena relevant to emotions and feelings are discussed with the natural direction of brain evolution in mind (by asking to what extent are functions and circuits that are present in other mammals are also present in humans)...'' (p. 654) [9•]. We similarly suggest that considering animal and human studies together allows the best progress to be made in understanding how affective reactions are mediated by brain systems.

Concerning human affect, not only can subjective pleasure ratings (liking in the ordinary sense) be assessed in adults, but also objective 'liking'-related reactions exist that can be measured in adults and even infants. In adults, objective affective reactions alone, without any subjective feelings, can occur as unconscious pleasures under limited circumstances (e.g. as unfelt but behaviorally biasing affective reactions to subliminally brief stimuli) [13–15]. The translation of objective 'liking' reaction into subjective pleasure feeling probably requires recruitment of additional brain mechanisms specialized for cognitive appraisal and conscious experience. An implication of the objective-subjective distinction is that subjective ratings of felt pleasure, while crucial signatures of human affective experience, are interpretive readouts of underlying affective processes, not always infallible windows into core pleasure reactions themselves. Indeed, 'liking' can sometimes occur unconsciously, and at other times even conscious pleasure ratings sometimes detach substantially from core affective reactions (as people concoct explanations to themselves for how they think they should feel) [16–19]. Therefore objective measures can be equally as useful as subjective measures for probing pleasure and displeasure mechanisms.

Comparing limbic systems: affect circuitry in humans and animals

The brain's circuitry for affective reactions spans from front to back of nearly the entire brain (Figure 1). Much of this circuitry is remarkably similar between humans and other mammals [20–22]. Even some apparent differences between humans and other species in limbic circuits may be more exaggerated in name than in fact. For example, essentially the same homologous region of deep ventral anterior cingulate cortex exists in both, but is called the subgenual anterior cingulate cortex (Area 25) in humans, and called infralimbic cortex in rodents.

Still, some real differences do exist between limbic brains of humans and other animals. The most obvious difference is the massive expansion of prefrontal cortex in humans, reflecting greater encephalization. Anatomically, encephalization also creates greater differentiation among prefrontal subregions. This may produce a few human cortex subregions that lack any clear homologue in nonprimates, such as dorsal anterior insula [23•]. This may also produce some neuronal differences, such as the granular layer in anterior orbitofrontal cortex of humans, that is, missing in rats.

Encephalization may also foster greater invasion by descending projections from prefrontal cortex into subcortical structures and functions. A possible human feature is greater 'freeway' connectivity, or direct projections between cortex and deep subcortical structures. By comparison, other animals might rely a bit more on 'local' road connections, which make more frequent intermediate stops. For example, descending projections from orbitofrontal cortex make more clearly defined connections to hypothalamus and brainstem structures in primates than in rats [24]. Conversely, ascending sensory pain and taste signals toward cortex from the brainstem primary visceral/sensory relay, the nucleus of the solitary tract in the medulla, may leap directly to the thalamus in primates, but make an obligatory stop at the pontine parabrachial nucleus in rats [23•,25]. Psychologically, human encephalization may consequently result in a greater cortical involvement of affect and emotion, expressed as top-down regulation of affective reactions. Still, mesocorticolimbic circuits for mediating core affective reactions are largely similar across all mammals.

Many pleasures: one hedonic brain system to mediate them all?

The sensory pleasure of a delicious-tasting food feels different from pleasures of sex or drugs. Even more different seem social or cognitive pleasures of seeing a loved one or listening to music. But does each psychological pleasure have its own neural circuit? Perhaps not. Instead there appears heavy overlap, with a shared mesocorticolimbic circuit or single common neural currency, involved in all those diverse pleasures [6,7,26–35]. Neuroimaging studies often implicate the same list of usual culprits as activated by various pleasures. The list includes cortical regions (e.g. orbitofrontal, anterior cingulate, and insula cortices) and subcortical structures (nucleus accumbens (NAc), ventral pallidum, amygdala, and mesolimbic tegmentum). This overlapping pattern opens the possibility that the same hedonic generating circuit, embedded in larger mesocorticolimbic systems,

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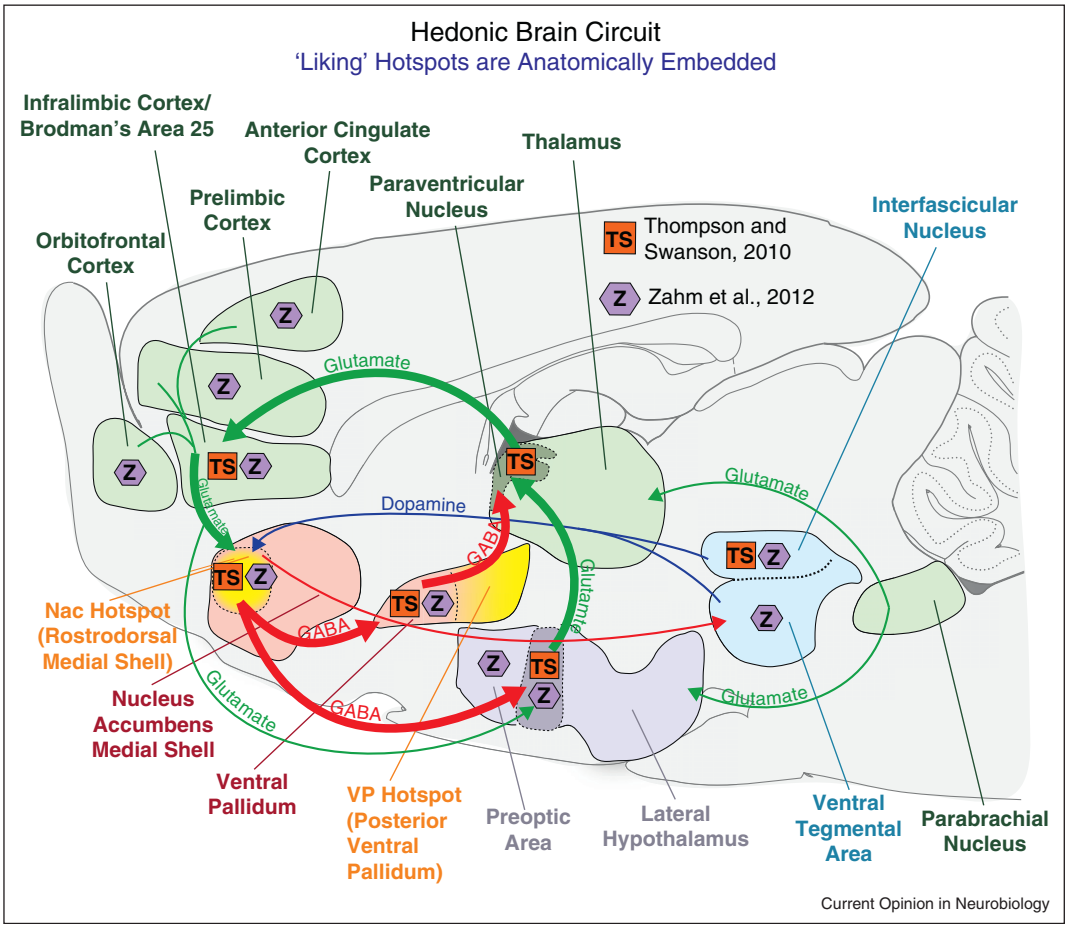
Figure 1



Hedonic hotspots and anatomical circuits that distinguish the nucleus accumbens hotspot in rostrodorsal medial shell as a unique site (anatomy based on Thompson and Swanson (TS symbol in orange boxes; 2010) and on Zahm and colleagues (Z symbol in purple hexagons; 2012). Thompson and Swanson [66••] reported that the nucleus accumbens hotspot of rostrodorsal medial shell is uniquely embedded in its own closed-circuit corticolimbicpallidal–thalamocortical loop, connecting discrete input subregions and output subregions, and segregated from other parallel loops passing through other regions of medial shell. Zahm and colleagues suggested additional unique connections for the rostrodorsal hotspot [65]. GABAergic projections are indicated in red, hedonic hotspots are marked in yellow, glutamatergic projections are green, and dopaminergic projections are marked in blue.
Figure by Daniel Castro, modified from [80].

could give a pleasurable gloss to all such rewards even when the final experience of each seems otherwise unique.

Encoding pure pleasure: apex in orbitofrontal cortex

In human neocortex, pleasure appears most faithfully represented by activity in orbitofrontal cortex, particularly in a mid-anterior subregion (Figure 2). Evidence suggests activity of this mid-anterior zone tracks changes in subjective pleasantness ratings of chocolate and delicious drinks, such as when pleasure intensity is diminished by switching the taster's state from hunger to satiety, and may also encode pleasures of sexual orgasm, drugs, and music [26,33,36,37]. Subcortically, selective hedonic changes also may be tracked by neural firing in NAc and ventral pallidum [38–41]. Such tracking gives the strongest evidence of pleasure representation (because other nonhedonic features of the experience remain constant). Additional medial regions of orbitofrontal, ventromedial prefrontal, and middle anterior insula cortices also code aspect of subjective pleasure ratings, but appear to be more concerned with monitoring and predicting reward value than in pleasure of the experience *per se*.

Some studies also indicate lateralization of affect representation, often as hemispheric differences in positive versus negative valence. Most notably, the left hemisphere of prefrontal cortex often has been implicated more in positive affect than right hemisphere [42]. For example, individuals who give higher ratings of subjective well-being may have higher activity in left than right prefrontal cortex, and activation of left subcortical

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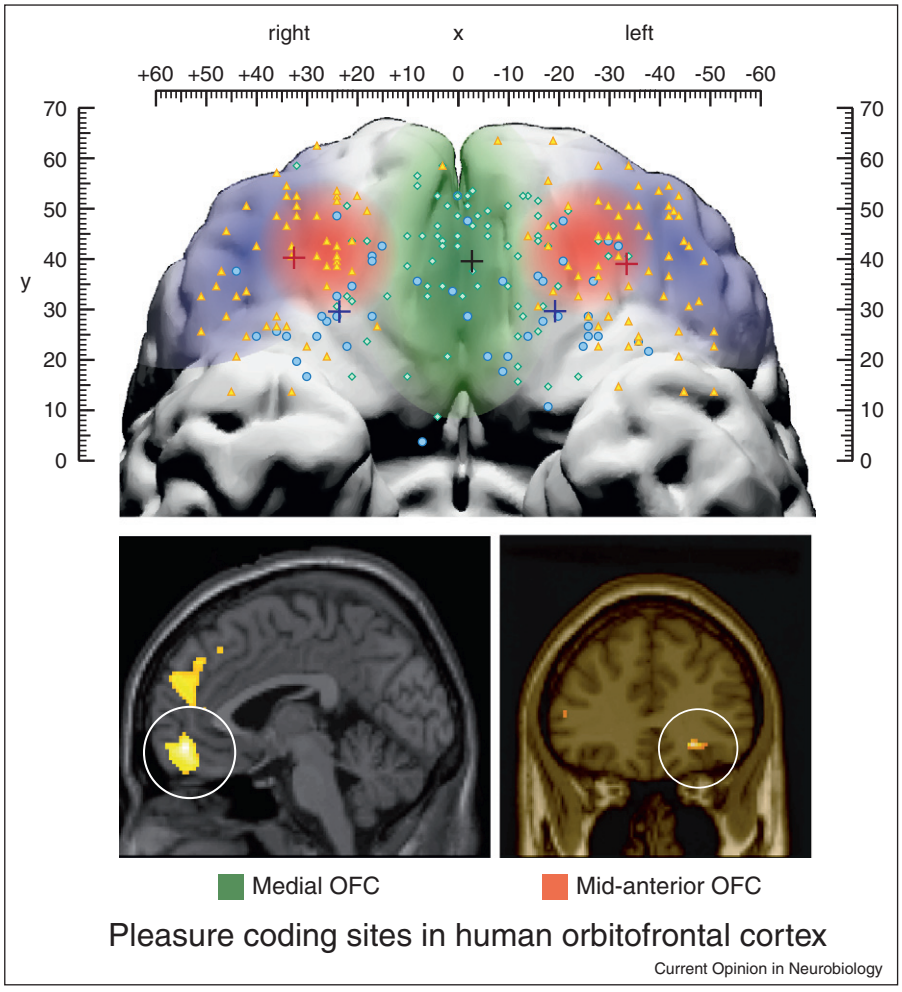
Figure 2



Subjective pleasure is faithfully coded by orbitofrontal cortex (OFC) activations in people. Sensory pleasures appear most faithfully represented especially by a mid-anterior OFC site (orange). Pleasant sensations are also coded by activation in a medial strip of OFC (green), but the medial strip may not as faithfully track changes in pleasure as the orange mid-anterior site [37]. Smaller symbols show results of a large meta-analysis of 267 orbital areas, which indicated that a medial subregion of orbitofrontal cortex monitored learning and memory of reward values (green area and round blue dots), whereas a lateral orbitofrontal subregion monitored punishers (purple and orange triangles) [81]. Independently, posterior subregions of OFC represented complex or abstract reinforcers (such as money) whereas anterior subregions represented sensory rewards such as taste [81].

striatum also may be more tightly linked to pleasantness ratings than right-side [43–45]. However, other studies have found more equal or bilateral activity patterns, and so the precise role of lateralization in pleasure still needs further clarification.

Subcortical weighting of brain pleasure generators

The weight of evidence from research on *causation* of affect suggests that affective reactions may be generated chiefly in subcortical brain structures rather than by any of the cortical regions discussed above [3,46••]. Causation may be more anatomically restricted than representation of affect, because only a few of structures that represent an affective reaction need also cause that reaction. The other structures may represent affect as a step to generating their own different functions, such as cognitive appraisal, memory, decision making, and so on.

Much cortical representation of affect may fit into this 'other causal' category. Evidence from humans that cortex is not needed to cause affect includes, for instance, persistence of relatively normal affective reactions such as pleasure even after massive damage to prefrontal cortex. For example, thousands of lobotomy patients in the 1950s retained most feelings as far as could be discerned (albeit showing impairment in cognitive judgment), despite having lost most contributions from their prefrontal cortex. More recent strong evidence comes from a beautifully detailed analysis of apparently normal pleasure (and other emotions) remaining in a man who lost most of

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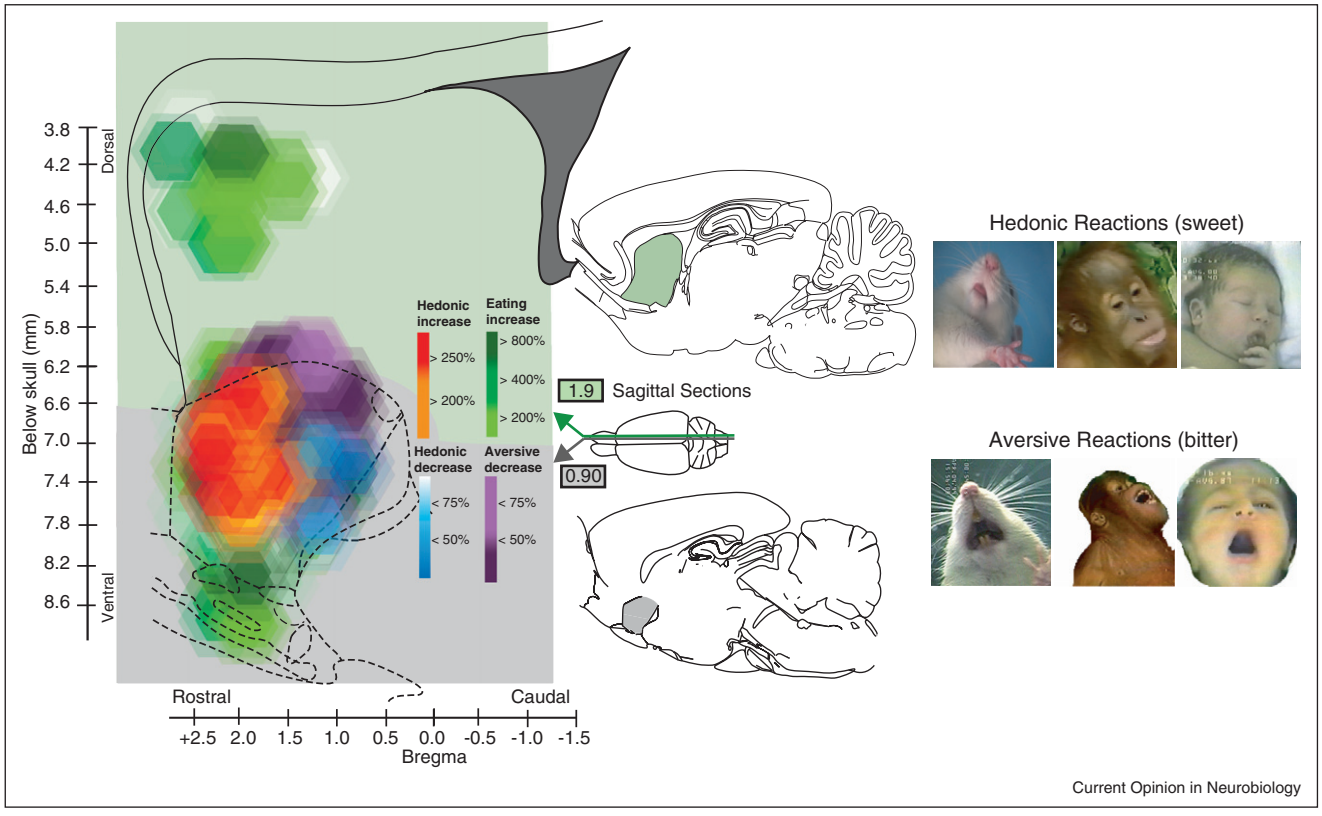
limbic prefrontal cortex due to encephalitis destruction of bilateral medial orbitofrontal cortex, insula, and ventral anterior cingulate (plus hippocampus and amygdala) [46••]. Despite pronounced memory and cognitive deficits, this patient retained a rich emotional life for 20 years as far as could be told, including remarkable capacity to talk about his feelings. Asked about himself, the patient reported, ''I have a strong feeling of happiness, that we are here together working on these wonderful games and feeling happy together. I am glad to be here with you''. He was also able to develop new Pavlovian learned fears of medical syringe needles and noisy fMRI machines and socially learned to prefer a friendly caretaker to a grumpy one. The most parsimonious interpretation of all this is that even in humans, pleasures and fears are generated primarily by subcortical systems that continue to function strikingly well in the absence of limbic neocortex [3,46••]. Affective reaction remaining despite prefrontal loss is one reason to suggest that cortical representation is a quite different function from subcortical causation of affect.

Pleasure generators identified through objective 'liking' reactions

Subcortical brain machinery for actually generating or causing a 'liking' reaction to core pleasure can be probed more extensively via brain manipulations in animals. Studies in our laboratory have identified neural pleasure generators by focusing on the sensory pleasure of sweetness. Sweet 'liking' is useful because affective facial expressions of taste pleasure 'liking' exist in newborn humans and in some animals, aiding the objective measure of hedonic impact. For example, parents often know when their baby expresses a 'liking' judgment of the deliciousness of a meal. Sweet foods elicit a contented licking of the lips, but bitter tastes instead elicit disgust gapes and headshakes. Homologous 'liking' orofacial expressions are elicited also in apes and monkeys, and even in rats and mice [47]. We have used brain manipulations of 'liking' reactions to identify brain mechanisms that generate and enhance such pleasures as sweetness (Figure 3).

Figure 3



Detail of hedonic hotspot in nucleus accumbens for pleasure generation (sagittal view of medial shell and of neostriatum). This is a causation map: colors reflect hedonic or motivation consequences (on 'liking' reactions or on food intake) of mu opioid agonist microinjections at each site (based originally on Peciña and Berridge [51]). Red/orange symbols in the rostrodorsal hotspot show sites that caused doubling or higher levels of hedonic 'liking' reactions to sucrose taste. By comparison, at caudal sites the same opioid microinjections only suppressed aversive 'disgust' reactions to bitter quinine (purple; e.g. suppressed gapes), or bivalently suppressed both 'liking' and 'disgust reactions (blue). Green sites denote increases in motivation 'wanting' to eat without any hedonic change in either 'liking' or disgust (enhanced motivation also extended through all red/purple/blue sites in nucleus accumbens).Modified from [80], based on data from [51].

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One surprising finding has been that neural generators of intense pleasure are much more restricted neurochemically than was previously envisioned [48•,49,50,51]. For instance, mesolimbic dopamine, probably the most popular brain neurotransmitter candidate for pleasure two decades ago, turns out not to cause pleasure or 'liking' at all. Rather dopamine more selectively mediates a motivational process of incentive salience, which is a mechanism for 'wanting' rewards but not for 'liking' them [48•,52,53•,54–57]. When amplified by addictive drugs or by endogenous factors, dopamine helps generate intense levels of 'wanting', characteristic of drug addiction, eating disorders, and related compulsive pursuits [44,53•,58–61]. Why, then, are dopamine-promoting drugs such as cocaine or methamphetamine reportedly so pleasant? One possibility is that some psychostimulant euphoria comes from the 'wanting' component of reward: a world that seems more attractive may well carry an aura of euphoria. Another potential mechanism is that, distinct from raising dopamine in the synapse, such drugs might also induce secondary recruitment of additional neurobiological mechanisms that more directly cause hedonic pleasure. For instance, there is evidence to suggest that elevation of endogenous opioid signals may be recruited in limbic structure [62,63]. Such opioid recruitment in accumbens-pallidal hotspots described below would plausibly generate pleasure 'liking' [64]. Conceivably, the secondary recruitment of hedonic mechanisms might become somewhat sluggish with continual drug-taking, therefore requiring higher doses for the sought-after pleasurable high, even if dopamine-related sensitization enhanced circuit reactivity to produce more and more intense 'wanting' [60].

Hedonic hotspot network

Another surprising finding has been that pleasures generators are much more anatomically restricted than previously envisioned, localized to particular subregions. We have identified several pleasure generators as small hedonic hotspots, nestled in subcortical structures [48•,49–51]. Opioid and endocannabinoid neurochemical signals do more effectively generate intense pleasures than dopamine — but only within the boundaries of such hotspots. For example, mu opioid stimulation by DAMGO microinjection within a hotspot of NAc (localized in the rostrodorsal quadrant of medial shell), or in another hotspot of ventral pallidum (in the posterior half of ventral pallidum), more than doubles the intensity of 'liking' reactions elicited by sweetness. But the same DAMGO microinjections elsewhere in the remaining 90% of NAc outside the hotspot generate only 'wanting' without enhancing 'liking' — much like dopamine (i.e. remaining 60% of medial shell and probably entire lateral shell and core; and even regions of dorsal striatum) [48•,49–51] (Figures 1 and 3). In addition, in the anterior half of ventral pallidum, DAMGO microinjection actually causes opposite suppression of 'liking' reactions. So far, no hedonic hotspots have yet been found in neocortex (though the search continues), but rather only in these subcortical structures. Continued failure to find a hedonic-enhancing hotspot in prefrontal cortex would be another reason to distinguish between cortical representation and subcortical causation of pleasure as different functions.

Each accumbens-pallidum hotspot is only a cubic-millimeter in volume in rats (a human hotspot equivalent should be approximately a cubic-centimeter, if scaled to whole-brain size). Functionally, hedonic hotspots seem quite specialized for intense pleasure generation compared to regions around them. Neurobiologically, hotspots may have unique anatomical or neurobiological features that distinguish them from the rest of their containing structure, and which perhaps permit the functional specialization for pleasure causation [65•,66••,67•] (Figure 1).

Integrating neurochemical and anatomical findings, what makes opioid neurotransmitters more hedonic than dopamine is not that limbic opioid signals always generate 'liking'. In most of NAc, neither does. Rather opioid stimulation has the special capacity to enhance 'liking' only if the stimulation occurs within an anatomical hotspot — whereas dopamine never does anywhere [48•,68,69]. Beyond NAc and ventral pallidum, opioid stimulation in all regions tested so far for other structures, such as neostriatum, amygdala, and so on, at best generate enhancement only of motivation 'wanting' without enhancing hedonic 'liking' [51,70,71]. Overall, the pattern indicates not only strong localization of hedonic function, but also neurochemical specificity of pleasure neurotransmitters.

Functionally, hotspots in NAc and ventral pallidum interact together in a single integrated circuit. The two sites act as a functional unit for mediating pleasure enhancements [48•,72]. Each hotspot seems able to recruit the other to unanimously generate amplification of 'liking'. For example, a single opioid microinjection into the NAc hotspot enhances also responsiveness of ventral pallidum hotspot neurons, reflected in neuronal firing patterns elicited by a sweet taste or in gene activation, at the same time as enhancing behavioral 'liking' reactions [48•,72]. Unanimous recruitment of both hotspots further appears to be required to magnify pleasure. Blocking either hotspot with an opioid-antagonist microinjection completely prevents opioid stimulation of the other hotspot from producing any 'liking' enhancement [72].Finally, the ventral pallidum hotspot may be especially important for maintaining normal levels of pleasure. Damage to ventral pallidum can cause even sweet sucrose taste to elicit purely negative gapes and other disgust reactions for days or weeks afterwards (C-Y Ho, The ventral pallidum as a limbic pleasure generator, PhD

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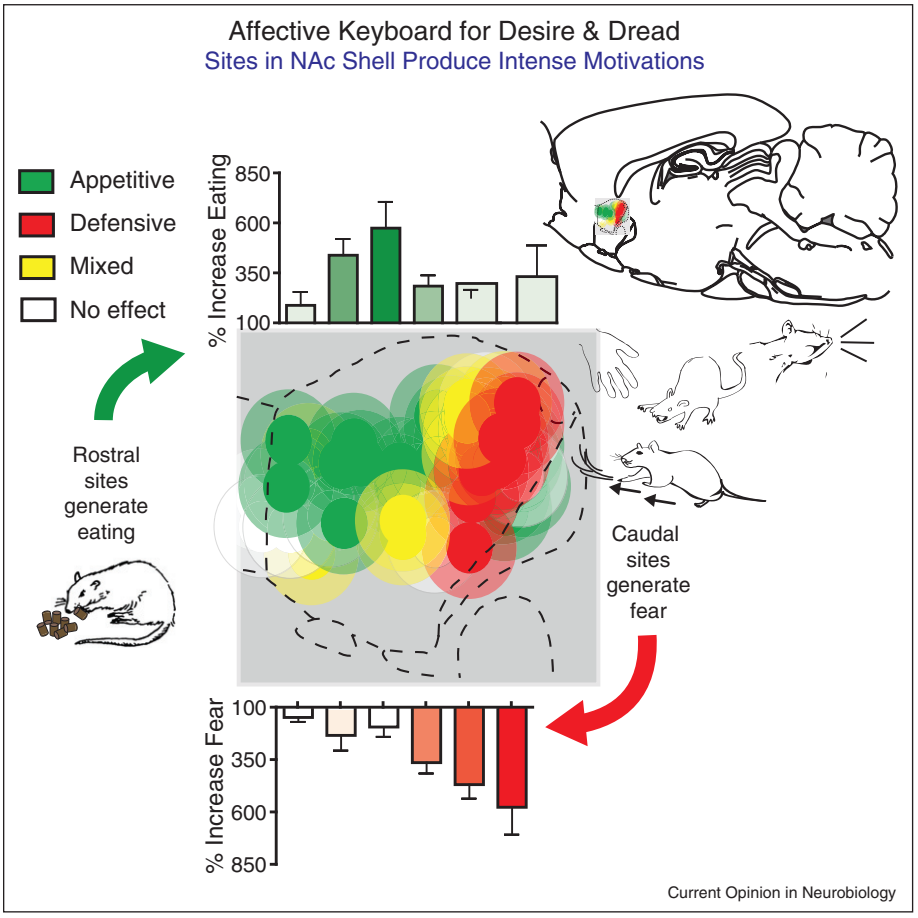
Dissertation, Ann Arbor, University of Michigan, 2010) [8,73]. No other brain lesion of a single site so potently transforms sensory pleasure into purely negative affect. Of course, other brain structures do help generate intense aversive emotions when manipulated in other ways [9•,74–77].

Affective keyboards in nucleus accumbens: beyond desire to dread

With valence reversal, we arrive at the knotty problem of how brain systems control the balance between positive versus negative emotions. Many limbic structures are implicated in both valences, and a given valence is distributed across several structures. For instance, take the negative emotion of fear. Although amygdala is best known for fear conditioning [9•], active forms of intense fear may also be generated via manipulation of NAc circuitry, operating in a different mode than for reward. Recent studies have demonstrated existence of an 'affective keyboard mechanism' in the medial shell of NAc for generating intense dread versus desire. The accumbens keyboard has remarkable anatomical orderliness in arrangement of valence generators (Figure 4). This mechanism releases intense dread-desire motivations following localized disruptions, arranged by valence along a rostrocaudal gradient in shell [76,77]. Just as a musical keyboard generates many different notes according to key location, the affective keyboard can generate many mixtures of desire versus fear, each mixture triggered at a different location. The mechanism is probably best viewed as operating via disinhibition: localized shell inhibitions that in turn release downstream efferent targets into excitation. That disinhibition interpretation arises because suppressive GABAergic neurons project from NAc to

Figure 4



Affective keyboard pattern in nucleus accumbens for releasing intense desire and/or dread. The keyboard pattern of intense motivated behaviors is revealed in the consequences of drug microinjections at various rostrocaudal sites in medial shell. Microinjections of drugs that relatively inhibit accumbens neurons via amino acid neurotransmitters (e.g. a GABA agonist or a glutamate antagonist) in turn may disinhibit or release motivation generating circuits in downstream target structures. Rostral green sites released stimulation of eating by up to 600% (desire only). Caudal red sites released purely increased fearful reactions at levels up to 600% over normal (dread only; escape attempts, distress calls, defensive bite attempts; spontaneous anti-predator treading/burying). Yellow sites released both desire and dread in the same rats during the same 1-hour 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).Modified from [80], based on data from [76,77,79].

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targets in ventral pallidum, lateral hypothalamus or brainstem. A motivation-releasing drug microinjection inhibits NAc neurons within a local 0.5–1.0 mm diameter microdomain corresponding to a single 'key' of the keyboard (via a GABA agonist or AMPA glutamate antagonist). Thus drug inhibition of accumbens microdomains prevents the endogenous NAc inhibition of targets, and so releases particular downstream motivation generating circuits into final activation to produce the intense motivations that are observed.

The keyboard pattern is revealed by observations that, at anterior sites in NAc shell, AMPA-blocking or GABA-stimulating microinjections can double eating and food intake amounts, and increase other incentive-related behaviors (Figure 4). At more posterior sites in shell, the same drug microinjections produce increasingly fearful reactions. For example, a normally tame rat will emit frightened distress calls and frantic leaps to escape when gently touched, and even bite the hand that touches it. Spontaneously, even when not touched, the rat after posterior keyboard microinjection also emits fearful anti-predator reactions that rodents use to defend against threats in the wild (e.g. rattlesnake), using forepaws to throw debris toward objects or people seen in the room [78]. Corticolimbic inputs from the prefrontal cortex can suppressively regulate these intense motivations, by inhibiting general intensity, or by tilting the desire/dread balance in positive direction, though causal generation of the intense motivations themselves again appears to be contained more subcortically (e.g. subcortical but not cortical manipulations are known to cause the intense motivations; and even within NAc microinjection of drugs that mimic subcortical GABA signals cause a broader range of affects than drugs that disrupt corticolimbic glutamate signals [i.e. rostral GABA releases 'liking' as well as 'wanting', and caudal disgust as well as fear]) [76,77].

Though anatomical location biases the valence of desire versus dread released by the keyboard, valence at many sites can be retuned by psychological factors. The presence of a stressfully over-stimulating sensory environment (i.e. bright lights and loud Iggy Pop music) remaps the accumbens bivalent keyboard by expanding the fear-generating zone while shrinking the desire-generating zone [77,79]. Conversely, a comfortable and quiet home-like ambience remaps in opposite direction, expanding desire and shrinking fear. Such psychological top-down remapping can actually retune a single site in NAc into releasing opposite motivations in the different situations, reversing the circuit's mode of operation. The switch in operating mode may involve recruiting different neurobiological components. Fear generation demands endogenous dopamine activity at D1 and D2 receptors simultaneously within a 'key' site (implicating roles for both 'direct' output path to tegmentum and 'indirect' path to ventral pallidum and hypothalamus), whereas positive desire generation by the same site requires only its D1 dopamine signal (potentially indicating a more dominant role for neurons of its 'direct' path to ventral tegmentum) [77,79].

Neurochemical signals similarly switch the operating modes of a NAc microdomain to generate different affects and motivations. For example, in the rostral NAc hotspot, opioid stimulation generates intense 'liking' plus 'wanting' for reward, but microinjection of dopamine or glutamate-related drugs generates 'wanting' alone. Conversely, in a caudal NAc shell key, microinjections inducing opioid or dopamine stimulation generate 'wanting', whereas glutamate AMPA blockade instead generates fear, and GABA signals add disgust to the fear [74–79]. Thus quite a variety of intense affective states can be created by varying the manipulation of a single site.

Conclusion

The merit of any scientific approach can be judged by whether the approach produces important new insights. In this short review we have shared some evidence produced so far by our approach to finding pleasure in the brain. New insights are emerging into how core affective reactions of pleasure, disgust or fear are generated and represented in complex brain systems. Many of these new insights could not have been gained without aid of the approach sketched here. However, the real contribution of this approach will hopefully come in future, as the new affective neuroscience findings are applied to help addiction, depression, and other affective disorders. Our hope is that future generations may be able to use such scientific insights into brain affective mechanisms to create better lives for more people [3].

Acknowledgements

Our research is supported by grants from the NIH (MH63644 and DA015188) to KCB, and from the TrygFonden Charitable Foundation, Braveheart Charity, Novo Nordisk Foundation to MLK. We thank Daniel Castro and Dr Jocelyn Richard for redrawing Figures 1, 2 and 4.

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- •• of outstanding interest

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Please cite this article in press as: Berridge KC, Kringelbach ML. Neuroscience of affect: brain mechanisms of pleasure and displeasure, Curr Opin Neurobiol (2013), http://dx.doi.org/10.1016/j.conb.2013.01.017

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Please cite this article in press as: Berridge KC, Kringelbach ML. Neuroscience of affect: brain mechanisms of pleasure and displeasure, Curr Opin Neurobiol (2013), http://dx.doi.org/10.1016/j.conb.2013.01.017