CHAPTER

# 1

# Hedonic Hotspots: Generating Sensory Pleasure in the Brain

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A vital question concerning sensory pleasure is how brain mechanisms cause stimuli to become pleasurable and liked. Pleasure is not an intrinsic feature of any stimulus, but instead reflects an affective evaluation added to the stimulus by the brain. That is, as Frijda expresses it (Frijda, this volume; Frijda, 2006), a pleasure gloss or hedonic value must be actively 'painted' on sweet or other sensations to make them pleasant. Brain mechanisms of pleasure, whatever they are, must take a mere sensory signal and transform it into a hedonic and 'liked' reward.

Finding the brain mechanisms responsible for painting a pleasure gloss is a major challenge for affective neuroscience (Barrett and Wager, 2006; Berridge, 2003b; Damasio, 1999; Davidson, this volume; Davidson and Irwin, 1999; Kringelbach, 2005; Kringelbach, this volume; LeDoux, 1996; Panksepp, 1991; Peciña et al., 2006). Fortunately, progress on finding hedonic generators in the brain is being made. In this chapter we focus specifically on the neuroanatomical hedonic hotspots in the brain where neurochemical signals actually contribute causally to the generation of pleasure.

We define a hedonic hotspot as a brain site where pleasure mechanisms are sufficiently concentrated together in one anatomical locus to cause pleasure enhancement when neurally activated (while recognizing that a hotspot's contribution to pleasure enhancement depends also on its participation in larger brain circuits). A hotspot might also be a site where natural pleasures are reduced below normal levels by neural suppression or damage. However, being able to enhance or stimulate pleasure is slightly different from being needed for normal pleasure, and so the contributions of 'sufficient cause' (enhancement) and 'necessary cause' (normal) need to be assessed separately. Finally, these and many other brain substrates may code the occurrence a pleasurable event by their neural activation. But for many, the neural acti-

vation may be neither necessary nor sufficient to produce pleasure (and presumably those substrates instead transfer pleasure information to cause other functions that guide decisions) (Dickinson and Balleine, this volume; Kringelbach, this volume). A particular brain substrate may have all three of these hedonic roles (code, sufficient cause, necessary cause), but alternatively it may code without causing, or it may act as a sufficient cause but not a necessary cause (Table 1). For example, as we will discuss, some sites in nucleus accumbens may enhance pleasure but may not be needed for all normal pleasures. It is an important task for affective neuroscience to assign pleasure causation to the proper brain substrates. The goal of this chapter is to identify some of the hedonic hotspots in the brain most able to cause enhancements of pleasure.

To identify a neural substrate that causes pleasure, it is often helpful to manipulate the brain and observe whether this manipulation causes a change in hedonic reactions to a sensory stimulus. Using experimental techniques to manipulate neurochemicals in focused brain locations we have recently mapped several hedonic hotspots that contribute in causal ways to pleasure. These hotspots are scattered across locations that span almost the entire brain, and are embedded in a larger pleasure circuit in the brain that operates as a whole to increase hedonic experience.

## How can we measure hedonic 'liking' in animals?

Traditional studies of pleasure 'liking' have focused on human adult subjects who can describe their feelings (Cabanac, 1971). But how can pleasure be measured in nonverbal animals like rats, in which most research on neurobiological causes must be conducted? The premise that underlies our affective neuroscience research on hedonics is that 'liking' is a basic evaluative reaction of the brain, with objective neural and behavioral indicators that can be quantified by appropriate methods in animals and humans alike.

These objective indicators include emotional facial expressions (Berridge, 2000; Darwin, 1872; Ekman, 1999). Many animals, including humans, primates, and rats exhibit homologous hedonic and aversive facial reactions to pleasant and unpleasant tastes. For example, a human infant, even on its first day of life, will rhythmically lick its lips when a drop of sugar water is placed on its tongue (Steiner, 1973). In contrast, a bitter taste like quinine elicits characteristic aversive reactions including gaping of the mouth (Steiner, 1973). Like humans, nonhuman primates and rodents display homologous 'liking' and 'disliking' reactions to sweet and bitter tastes (Steiner et al., 2001). Rats, for example, display the same rhythmic tongue protrusions as human infants, as well as paw licking and related movements when presented with a sugary solution in the mouth (Grill and Berridge, 1985; Grill and Norgren, 1978a) (Figure 1). Similarly, in response to a bitter taste, rats emit the same aversive gaping reactions that human infants show, along with headshakes and frantic wiping of the mouth (Figure 1).

Importantly, these animal affective reactions fluctuate in similar ways to human subjective pleasure when relevant circumstances change (Berridge, 2000). For example, just as food is more pleasant to us when hungry, sweet tastes elicit more 'liking' reactions when rats are hungry than when full (Berridge, 2000; Cabanac, 1971). Such homeostatically-induced changes in sen-

**Types of Roles in Pleasure**

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| **'Sufficient Cause'**<br>Example<br>Nucleus Accumbens<br>  | **Neural stimulation is sufficient to cause increase in pleasure**<br>Caveat: Causation is distributed beyond stimulated substrate<br>*The stimulated substrate doesn't contain all causation itself, but rather interacts with other distributed components of a larger brain circuit to cause pleasure. Condition of other brain substrates and external events may modulate impact of neural activation.* |
| **'Necessary Cause'**<br>Example<br>Ventral Pallidum<br>  | **Neural blockade/lesion produces loss of pleasure**<br>Caveat: Deficit may not always be mirror image of normal function<br>*Loss of pleasure after a lesion may mean that the substrate was the pleasure generator, but alternatively could mean that its function was to facilitate pleasure generation in other structures that still remain (e.g. removal of a transistor may make a radio squeal, but the transistor's function was not merely a 'squeal suppressor').* |
| **'Code'**<br>Example<br>Orbitofrontal Cortex<br>  | **Neural activation during pleasure**<br>Caveat: Code may or may not be cause<br>*Some neural activations may cause the pleasure they code. Other neural activations may be instead a consequence of a hedonic reaction generated elsewhere in the brain, rather than cause the hedonic reaction themselves (and presumably help cause some other psychological function).* |

**Table 1. Types of pleasure mediation:** *Sufficient cause, Necessary cause, and Code. The phrase 'brain structure X mediates pleasure' has three different possible meanings, which may or may not coincide, though they are often meant together. It is useful to distinguish between cause and code, and even to distinguish among different ways of causing (caveats apply to each shorthand distinction). Examples are neither exhaustive nor exclusive (e.g. VP also codes pleasure, and orbitofrontal cortex may turn out to cause pleasure); see text for discussion.*

sory pleasure have been called 'alliesthesia' (Cabanac, 1971; this volume; Leknes and Tracey, this volume). Similarly, the intense taste of salt at concentrations higher than seawater is not pleasant to either people or rats, and normal rats accordingly respond to this taste with gapes and other aversive reactions. However, if one physiologically depletes a rat of sodium, thus eliciting a state of 'salt appetite,' affective reactions to this very same salty taste suddenly flip from negative to positive, and hedonic tongue protrusions are observed instead of aversive gapes (Berridge et al., 1984; Schulkin, 1991; Tindell et al., 2006). Thus 'liking' facial reactions to tastes reflect not simply sensory properties of the stimulus, but rather a hedonic evaluation of it that incorporates physiological needs. 'Liking' reactions also incorporate psychological influences on hedonic impact, such as preference learning, as well as many neural factors (Berridge, 2000). For these reasons, we and other neuroscientists have been able to use such affective reactions in rodents as an index of core 'liking' or hedonic impact. By measuring how

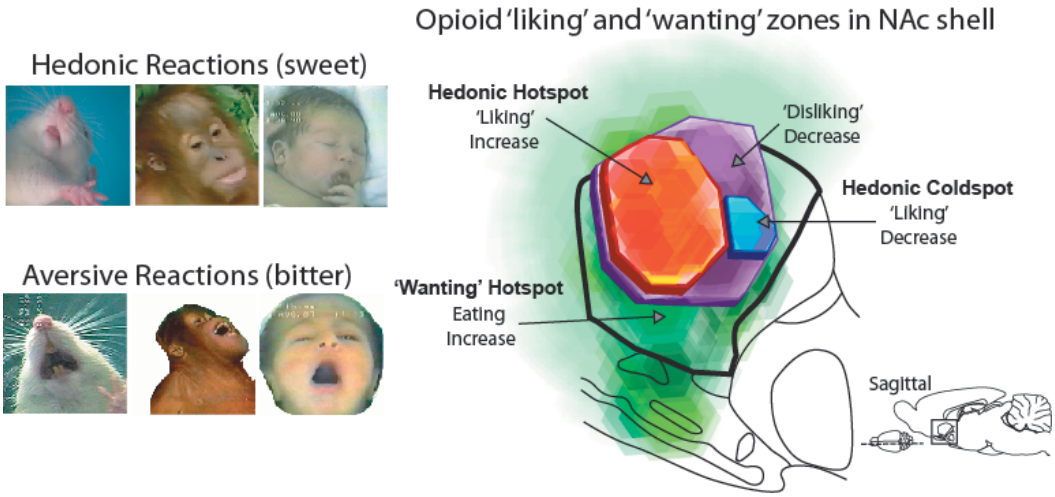


**Figure 1. Taste 'liking' reactions and contrast map of nucleus accumbens hotspots.** *Positive 'liking' reactions to pleasant sweet tastes shared by human newborn, young orangutan, and adult rat (tongue protrusion; left top), and aversive 'disliking' reactions to unpleasant bitter tastes (gape; left bottom). Affective facial expressions like these provide an objective index of 'liking' and 'disliking' reactions to the hedonic impact of tastes. Opioid hotspots and coldspots for hedonic 'liking', 'disliking', and motivational 'wanting' are mapped and stacked within the nucleus accumbens (medial shell region shown in sagittal view; right). Virtually the entire medial shell stimulates 'wanting' for reward (e.g., increased food intake) in response to opioid stimulation (green hexagons represent individual microinjection Fos plumes), and so do other nearby structures including the core of nucleus accumbens as well as parts of the ventral neostriatum above the accumbens, and the olfactory tubercle beneath the accumbens. The much smaller hedonic hotspot for 'liking', where opioid stimulation actually increases positive hedonic reactions to sucrose taste (red), is contained within the anterior and dorsal quarter. 'Liking' reactions to sucrose are reduced by opioid stimulation in a small posterior hedonic coldspot (though still stimulating 'wanting'; purple), whereas an intermediate region that contains both hotspot and coldspot mediates opioid suppression of aversive 'disliking' for bitter quinine. The hotspot zone map is modified from Peciña and Berridge (2005).*

'liked' or 'disliked' a particular taste is, we can then experimentally manipulate 'liking' and 'disliking' to reveal the neural mechanisms responsible for adding pleasure to gustatory sensation.

## Neuroscience tools for identifying hedonic hotspots: microinjections and Fos plumes

One way to reveal brain substrates that cause 'liking' is to activate a mechanism in a neuroanatomically and neurochemically focused fashion in order to observe increased hedonic reactions characteristic of pleasure impact. A useful technique is microinjection of a tiny droplet of drug directly into the brain, because it can painlessly activate a neural system in a fashion that is highly specific both neuroanatomically and neurochemically (it is painless because it is made via cerebral cannulae that were previously implanted under anesthesia). If a microinjection boosts pleasure processes, then the brain site must contain a neuro-

chemically-coded mechanism sufficient to cause amplification of hedonic impact.

For precision mapping of hedonic mechanisms, however, it is not enough to know where a drug has been microinjected in the brain. Drugs diffuse from the site of injection, which makes pinpointing functional 'liking' effects imprecise unless one knows exactly how far the impact spreads. To help pinpoint 'liking' mechanisms, we have developed a microinjection 'Fos plume' mapping tool based on the ability of many drugs to activate local protein production in neurons they impact (Mahler et al., 2007; Peciña and Berridge, 2000; 2005; Peciña et al., 2006; Smith and Berridge, 2005). A drug that activates neurotransmitter receptors on a neuron can trigger intracellular second messengers and cascades of molecular signals to the cell nucleus to quickly make proteins that influence the neuron's function.

As a step to altering neuronal function, several reward-related drugs trigger transcription of the c-fos gene on neuronal chromosomes into RNA, and its translation into Fos protein. Thus, looking to see which neurons produce more Fos protein is a useful way to see which neurons are most activated by a drug microinjection. The functional spread of Fos activation can be seen as a plume of dark-stained neurons around a drug microinjection site, when a slice of brain tissue is chemically processed in a way that stains Fos-containing neurons. The size of this Fos plume reveals where in the brain a drug microinjection has acted when it elevates 'liking' reactions to sweet taste. By assigning the behavioral 'liking' enhancements we observe to the particular microinjection Fos plumes that cause them, we can map objective and precise plots of hedonic hotspots in the brain (Mahler et al., 2007; Peciña and Berridge, 2000; 2005; Peciña et al., 2006; Smith and Berridge, 2005).

## Hedonic Hotspots

It turns out that several brain limbic structures have tiny pleasure-generating sites tucked within them — hedonic hotspots. These hotspots combine together to form a distributed causal circuit to add pleasure to sensory experience.

### *An opioid hedonic hotspot in the nucleus accumbens*

We have identified an opioid hedonic hotspot of approximately 1 cubic millimeter volume within the medial shell of the nucleus accumbens in rats. If hotspot size is proportional to whole brain size, then in humans, the hotspot will be roughly 750 times bigger in volume than in the rat, or between 0.7 and 1-cubic centimeter (Figure 1, 2). The nucleus accumbens has long been linked to affective processes (Balleine, 2005; Berridge, 2003b; Cardinal et al., 2002; Kelley et al., 2002; Knutson and Cooper, 2005; Leyton, this volume; Panksepp, 1991; Petrovic, this volume; Roitman et al., 2005; Shizgal, this volume; Small and Veldhuizen, this volume; Taha and Fields, 2005; Yamamoto, 2006). However, the existence within it of localized hotspots specialized to amplify hedonic impact was not previously known. At most, distinctions have been made between the large shell and core subregions of nucleus accumbens, but the shell has generally been presumed to act as a whole in generating hedonic impact.

The discovery of a specialized hotspot shows that reality is more complex. The specialized opioid hedonic hotspot constitutes only a third of the medial portion of

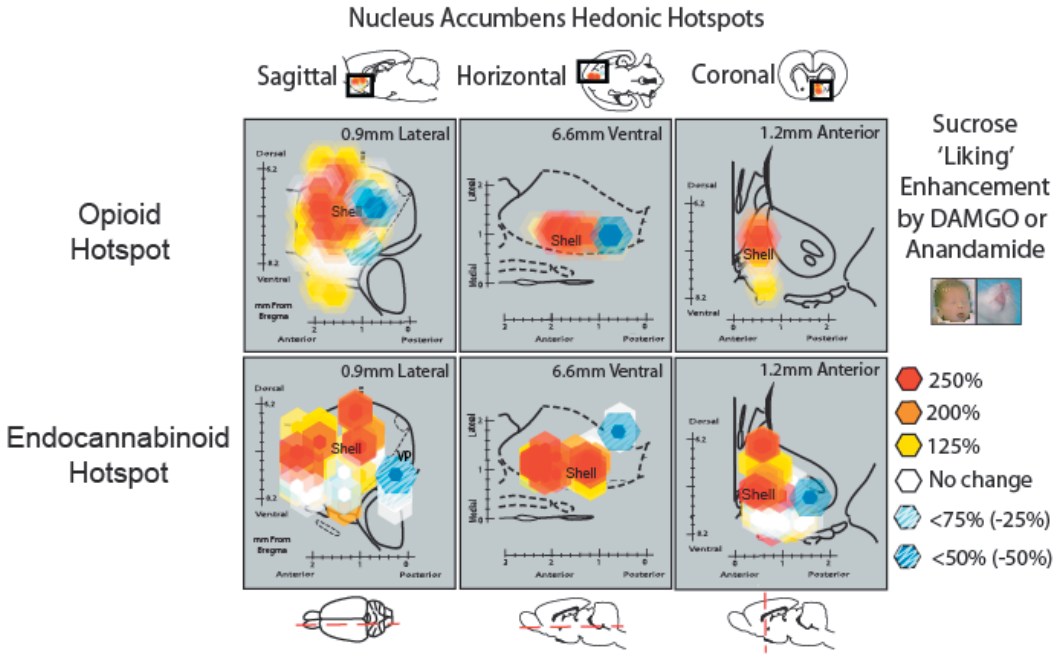


**Figure 2. Opioid and endocannabinoid hedonic hotspots in the nucleus accumbens.** *In these Fos plume maps, symbol color denotes the intensity of sucrose 'liking' amplification by opioid microinjection (yellow-to-red = increase above normal), and symbol size denotes estimated drug functional spread based on Fos plumes. Top row depicts the medial shell containing the opioid hedonic hotspot in sagittal, horizontal and coronal views (modified from Peciña and Berridge, 2005). The hedonic hotspot for 'liking' is revealed in the anterior shell, whereas a smaller coldspot for 'liking' suppression is revealed behind it (blue = decrease below normal). Bottom row depicts the endocannabinoid hedonic hotspot that overlaps the same location (modified from Mahler et al., 2007). The endocannabinoid hotspot covers the entire opioid hotspot and may be larger, but anatomically both accumbens hedonic hotspots are roughly similar.*

shell (Figure 1, 2). This is only about a fifth of the whole shell (medial and lateral parts combined), and only a seventh of the entire nucleus accumbens (shell and core). Thus this opioid hotspot represents a focused area that is specialized for hedonic causation within the nucleus accumbens.

The critical finding is that within the 1 $mm^3$ hedonic hotspot, microinjection of an opioid drug that stimulates mu opioid receptors (DAMGO; mu receptors are one of several subtypes of receptors for opioid neurotransmitters) elevates hedonic 'liking' reactions to a sucrose taste by up to quadruple the usual number (Peciña and Berridge, 2005). This accumbens hedonic hotspot is located in the dorsal part in the anterior half of the medial shell. In terms of anatomical landmarks, the cubic-millimeter hotspot is just anterior to the posterior edge of the islands of Calleja but posterior to the rear edge of the dorsal tenia tecta and the lateral septum, and anterior to the level of the anterior commissure.

An equivalent nucleus accumbens hotspot might well be expected to play hedonic roles in humans, perhaps mediating the intensely rewarding effects of opiate drugs

themselves (e.g., heroin), as well as mediating the pleasure of such natural rewards as the taste of sugar – and it seems noteworthy that food pleasantness in humans is modulated by systemic administration of opioid drugs (Yeomans and Gray, 2002).

At all other parts of the nucleus accumbens tested so far in rats, microinjection of the same opioid drug fails to increase hedonic 'liking' reactions to sweetness. These other areas include the posterior or ventral subregions of medial shell, and as far as we know the core as well. In fact, DAMGO microinjections in a small cold spot in the posterior half of the medial shell actually appear to suppress 'liking' reactions to sucrose below vehicle control levels (Figure 1).

By contrast to the tight localization of 'liking' mechanisms in the hotspot, motivational 'wanting' mechanisms appear to be widely distributed throughout almost all of the medial and lateral shell, and probably also extend to cover the core of nucleus accumbens and ventral neostriatum (Figure 1). For example, DAMGO microinjection robustly stimulates increases in eating behavior and food intake at all of those accumbens sites (Bakshi and Kelley, 1993; Kelley et al., 2002; Peciña and Berridge, 2005; Zhang and Kelley, 2000). Thus, for opioid mechanisms of reward, the nucleus accumbens hotspot generates both 'liking' and 'wanting' for sweet tastes, while other areas of the nucleus accumbens can generate only 'wanting' (Figure 1).

Of course, a drug microinjection is an unnatural stimulus, and brains ordinarily would not experience such intense or localized chemical stimulation. Still, brains do experience many naturally-induced increases in normal opioid neurotransmitter release, which might have different effects in different locations. Microinjection maps essentially use an artificial manipulation to reveal brain mechanisms that paint a pleasure gloss onto sensation in ordinary life. We have focused here on enhancing the 'liking' of sweetness, because that is what we are most able to test. A number of questions remain open, such as whether the same mechanisms paint pleasure onto other sensations too, or whether pleasure would be generated even in the absence of any sensory stimulus. Current evidence suggests the nucleus accumbens participates in many rewards for people and animals, including sex, music, drugs, social rewards, humor, winning money, etc. (Carelli and Wightman, 2004; Gottfried, this volume; Insel and Fernald, 2004; Kalivas and Volkow, 2005; Knutson and Cooper, 2005; Komisaruk, this volume; Komisaruk and Whipple, 2005; Leknes and Tracey, this volume; Leyton, this volume; Menon and Levitin, 2005; Mobbs et al., 2003; Robbins and Everitt, 1996; Robinson and Berridge, 1993; Shizgal, this volume; Skov and Vartanian, this volume; Wang and Aragona, 2004). Still, more research is needed on hotspot roles in such diverse pleasures. For now we can only say that, if the brain is organized parsimoniously and uses a 'common neural currency' to mediate multiple kinds of pleasures, then the answer to questions about other pleasures may well turn out to be 'yes'.

### *An endocannabinoid hedonic hotspot in the nucleus accumbens*

Opioid signals are not the only neurochemical signals in nucleus accumbens that cause increases in pleasure. Endocannabinoids are another type of natural brain neurotransmitters, and are chemically similar to plant cannabinoids such as $^{9}$-THC, a chief psychoactive ingredient in marijuana.

An example is anandamide, a brain endocannabinoid named after the word for *bliss* in Sanskrit (an endocannabinoid is a natural brain neurotransmitter that is chemically similar to a cannabinoid drug). Cannabinoid drugs have appetite-enhancing effects, and increase intake of palatable food and sucrose-solution in rats and humans (Hart et al., 2002; Kirkham, 2005).

Endocannabinoid and opioid receptors sometimes co-exist on the same neurons in the accumbens shell, and have been found nearly side by side on the same spine of the same dendrite on neurons in striatum (Pickel et al., 2004; Schoffelmeer et al., 2006). Thus both opioid and cannabinoid receptors may exist in many of the same synapses within the hedonic hotspot and beyond (Rios et al., 2006; Schoffelmeer et al., 2006). The two signals might also interact in function. For example, opioid blockers (e.g., naloxone) have been shown to prevent many cannabinoid drug effects (including food intake enhancements), and vice versa (Tanda et al., 1997; Williams and Kirkham, 2002).

Anandamide signals in the nucleus accumbens participate in generating sensory pleasure, similar to opioid signals. We have identified an endocannabinoid hedonic hotspot in the nucleus accumbens for enhancing sweetness 'liking', which seems to completely cover the opioid hotspot described above (and possibly extend beyond it) (Mahler et al., 2007) (Figure 2). Microinjections of anandamide directly into this 1.6 $mm^3$ hotspot, located in the dorsal portion of the medial nucleus accumbens shell, doubled hedonic 'liking' reactions to sucrose above normal levels (Figure 2).

The endocannabinoid hotspot for 'liking' may be slightly larger than the opioid hotspot, although differences in the experiments that mapped them make it difficult to compare size directly. In any case, in the same endocannabinoid hotspot anandamide also doubled the amount of food eaten and the time spent engaged in eating behavior. These results indicate that anandamide signals, like mu opioid signals in its overlapping hotspot in medial shell of accumbens, enhance both hedonic 'liking' of tasty rewards and 'wanting' to consume those rewards.

The enhancement of affective 'liking' reactions by anandamide appears specific to positive 'liking', and not negative 'disliking'. By contrast to its amplification of positive hedonic reactions to sucrose, anandamide failed to change affective reactivity to a bitter taste of quinine. Selective amplification of sweet 'liking' may possibly suggest a hedonic explanation of why the 'marijuana munchies' are often directed towards especially palatable foods, as well as reveal an endogenous brain mechanism for generating the pleasure gloss for natural sensations.

### *An opioid hedonic hotspot in the posterior ventral pallidum*

One of the major output structures for nucleus accumbens reward signals is the ventral pallidum, a forebrain structure located just posterior to the nucleus accumbens near the bottom of the brain (Heimer and Wilson, 1975). The ventral pallidum is a limbic 'final common pathway'. It receives projections from a host of reward-related brain areas in addition to the nucleus accumbens, such as amygdala, orbitofrontal cortex, anterior cingulate cortex and infralimbic cortex, lateral hypothalamus, ventral tegmental area, and parabrachial nucleus. In turn, the ventral pallidum projects reciprocally to many of them, including the nucleus accumbens, and projects upwards to the forebrain's me-

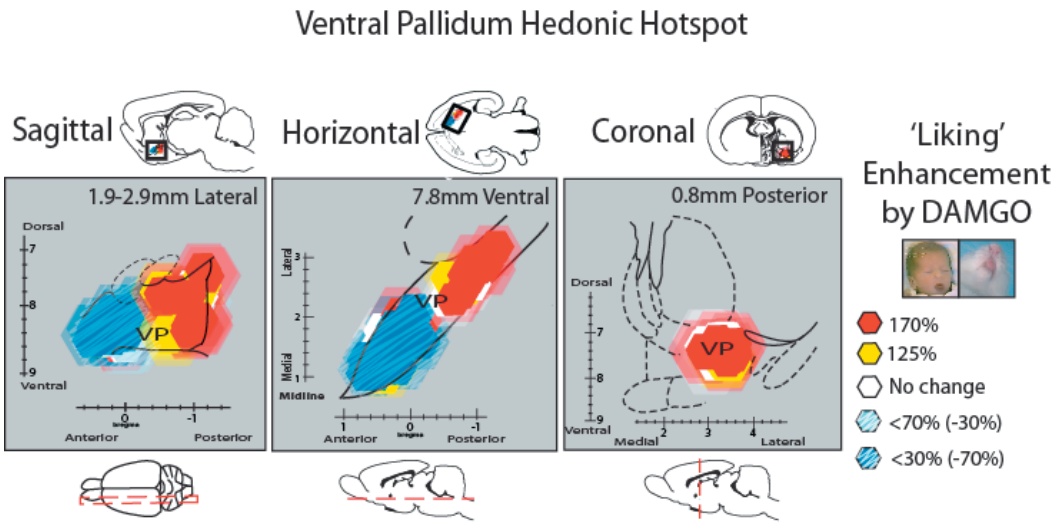


**Figure 3. Opioid hedonic hotspot in the ventral pallidum.**
*The ventral pallidum (VP) hedonic hotspot is contained in the posterior one-third of VP, represented in 3 planes by red and yellow shading (modified from Smith and Berridge, 2005). The Fos plume map shows the intensity of 'liking' amplification caused by opioid microinjections (DAMGO), similar to Figure 2. Both 'liking' and 'wanting' are increased simultaneously by opioid stimulation in the hedonic hotspot, whereas both are suppressed together by microinjections in an anterior coldspot (blue area).*

diodorsal nucleus of the thalamus to form a limbic-cortico-limbic loop, connecting to limbic prefrontal cortex and back down to accumbens and ventral pallidum (Aldridge and Berridge, this volume; Grove, 1988a; b; Haber et al., 1985; Kalivas and Nakamura, 1999; Mogenson and Yang, 1991; Price, this volume; Zahm, 2000). Thus, anatomically, the ventral pallidum is in a key position to mediate pleasure signals in the brain.

In fact, it does. In mapping sites where microinjections cause 'liking' enhancement, we have found that the ventral pallidum contains its own opioid hedonic hotspot. The ventral pallidum's hedonic hotspot is an approximately 0.80 $mm^3$ area in its posterior end where mu opioid stimulation magnifies hedonic 'liking' (Smith and Berridge, 2005) (Figure 3). This hotspot is slightly smaller than the 1 $mm^3$ nucleus accumbens opioid 'liking' hotspot, but it is roughly equal in the proportion of the structure that it fills. The ventral pallidum is only about two-thirds the size of the accumbens medial shell, so both hotspots fill approximately one-third to one-half of their containing structure.

The hedonic features of the ventral pallidum hotspot are similar to those of the nucleus accumbens. In the posterior hotspot, microinjections of the mu opioid agonist DAMGO roughly double the number of hedonic 'liking' reactions to a sucrose taste compared to control vehicle microinjections (Smith and Berridge, 2005) (Figure 3). Opioid receptor activation in the ventral pallidum hedonic hotspot also stimulates food 'wanting' (eating behavior) as well as 'liking' (Shimura et al., 2006; Smith and Berridge, 2005). By contrast to these positive effects on 'liking' and 'wanting', a negative suppression of 'liking' and 'want-

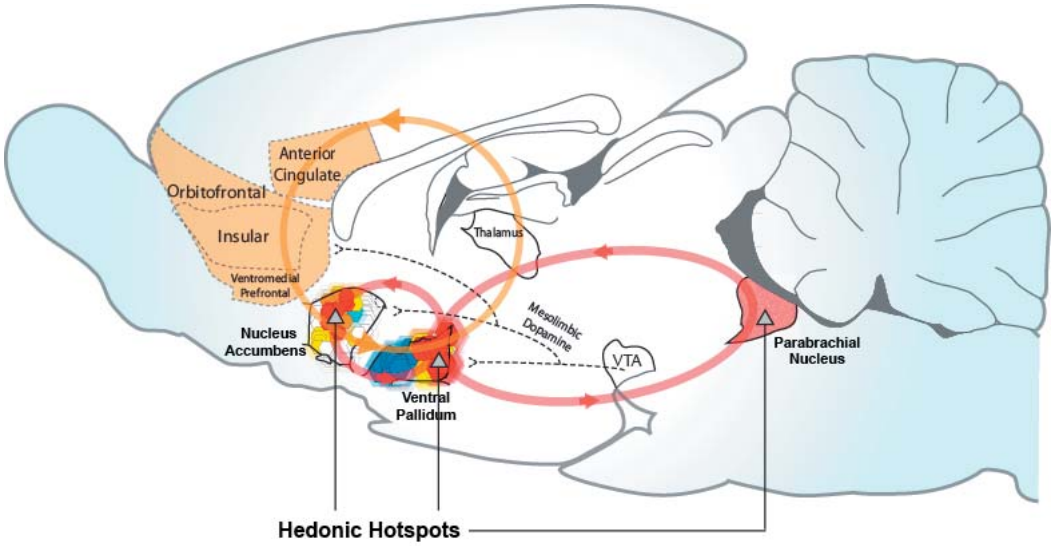


**Figure 5. Hedonic hotspots and hedonic circuits of the brain.**
*Opioid hedonic hotspots are shown in nucleus accumbens, ventral pallidum, and brainstem parabrachial nucleus. Neurochemical signals in each hedonic hotspot can cause amplification of core 'liking' reactions to sweetness. Hedonic circuits connect hotspots (red) into integrated loops for causation of 'liking' (orange and red loops). Additional forebrain loops relay 'liking' signals to limbic regions of prefrontal cortex and back to hotspots, perhaps for translation of core 'liking' into conscious feelings of pleasure and cognitive representations (dotted, orange cortex). Dashed, black subcortical lines show mesolimbic dopamine projections, which we suggest fail to cause 'liking' after all.*

ing' is produced if the same DAMGO microinjections are made in a more anterior coldspot of the ventral pallidum (Figure 3). Recently, exciting evidence has emerged that humans might share the same ventral pallidum hotspot and coldspot for food pleasure. Calder and colleagues found that the posterior hotspot of ventral pallidum was activated in people who looked at appetizing pictures of foods like chocolate cake, whereas their anterior coldspot was activated when looking at disgusting pictures of rotten food (Calder et al., 2007).

The ventral pallidum hotspot uses multiple neurochemical signals to generate motivational 'wanting', but not all generate hedonic 'liking' as well. For example, microinjections of a drug (bicuculline) that blocks $GABA_A$ signals from accumbens causes increases in 'wanting' just as opioid stimulation does, and so makes rats robustly eat more food (Shimura et al., 2006; Smith and Berridge, 2005; Stratford et al., 1999). The GABA-related 'wanting' site extends everywhere in the ventral pallidum (roughly two cubic millimeters), not just the posterior third, and so is much larger than the opioid hotspot. But GABA-related 'wanting' never causes an increase in hedonic 'liking' reactions to sugar taste, not even in the posterior hotspot, even though the GABA motivational enhancement of food 'wanting' is as powerful as the opioid enhancement (Smith and Berridge, 2005). Instead bicuculline-stimulated eating for ventral pallidum always appears as pure 'wanting' without 'liking'.

Why should blocking GABA receptors in ventral pallidum ever cause increases in 'wanting'? One explanation favored by some neuroscientists is that GABA ordinarily is itself inhibitory (suppressing activity in neurons that receive it), and is released by neurons projecting from the nucleus accumbens to cause inhibition of ventral pallidum neuronal activity. Some nucleus accumbens neurons inhibit their own firing during a reward or incentive cue, and direct *neural inhibition* of some accumbens neurons (e.g., by microinjection of a GABA agonist that inhibits neurons) causes *psychological excitation* of 'wanting' and 'liking' reward functions (Berridge, 2007a; Day and Carelli, 2007; Kelley et al., 2005; Reynolds and Berridge, 2002). It is possible that accumbens inhibition would shut off the release of GABA in ventral pallidum, and thus free the ventral pallidum neurons to become more active. Our GABA-blocking microinjection would similarly free neurons and might mimic this particular aspect of incentive motivation.

*Is the caudal ventral pallidum hotspot also necessary for 'liking'?*

Amplification of 'liking' demonstrates that opioid signals in the hedonic hotspot in ventral pallidum are a sufficient cause to increase hedonic impact of a sensory pleasure. Other evidence from brain lesions suggests that this same hotspot may also be a necessary cause for normal hedonic reactions to sweet rewards (perhaps consistent with its special role as a final common pathway for reward).

It has long been known that aversive 'disliking' reactions (e.g., gapes) to normally palatable tastes can accompany the aphagia (failure to eat) caused by very large electrolytic or excitotoxic lesions of lateral hypothalamus, at least if the lesions extend far enough anteriorly and laterally to penetrate the caudal ventral pallidum (Anand and Brobeck, 1951; Berridge, 1996; Schallert and Whishaw, 1978; Stellar et al., 1979; Teitelbaum and Epstein, 1962; Teitelbaum and Stellar, 1954).

An early lesion mapping study by Casey Cromwell in our laboratory aimed to better define the site responsible for lesion-increased aversion, and found that the only lesions that caused aversion to sucrose taste were those that damaged the ventral pallidum hotspot region, whereas lesions restricted to the lateral hypothalamus did not cause aversion (even if hypothalamic lesions caused aphagia or failure to eat as much as pallidal lesions) (Cromwell and Berridge, 1993). Hedonic reactions to a normally 'liked' sucrose taste were completely abolished after ventral pallidal lesions that included the hedonic hotspot, and replaced by aversive reactions which are normally evoked by 'disliked' tastes such as quinine (Cromwell and Berridge, 1993).

Such observations suggest that the same hedonic hotspot in ventral pallidum may contain neural substrates that are both a sufficient cause for pleasure (able to amplify above normal) and a necessary cause (needed for normal pleasure), a hypothesis that studies may test in the future. So far, the ventral pallidum is the only brain site known to be a necessary cause for normal pleasure.

Intriguingly, in a recently reported human case, bilateral partial lesions to the ventral pallidum (overlapping with external and internal globus) due to a drug overdose left the patient with "a depressed mood" and "anhedonia" (Miller et al., 2006). The patient was a drug addict prior to the lesion, but over the ensuing year "reported

the disappearance of all drug cravings and remained abstinent from all recreational drugs other than an occasional glass of wine with dinner", and "reported that he no longer experienced pleasure from drinking alcohol" (p. 786). Contrary to our description of sensory 'disliking' and aphagia above in animals with complete lesions of ventral pallidum, the patient also gained 20-lb in weight over the year. However, the extent of bilateral neuron death in ventral pallidum is not known for this patient, nor is the precise location of his damage compared with the hedonic hotspot we've identified in the rat ventral pallidum. At the moment, it simply seems striking that ventral pallidum lesions in both humans and other animals appear to induce distortions of hedonic impact and to change the consumption of rewards.

Neurons in the ventral pallidum hotspot of rats code the hedonic impact of taste pleasures in their activation patterns, as well as cause them in their effect on psychological-behavioral hedonic reactions. For example, in collaboration with the laboratory of J. Wayne Aldridge at the University of Michigan, we have found that neuronal firing rates in the hedonic hotspot of ventral pallidum code the degree of 'liking' for sweet and salty tastes (Aldridge and Berridge, this volume; Tindell et al., 2004; Tindell et al., 2006). Neurons in the ventral pallidum hotspot fire in a faster burst when a rat tastes a sugar or salt that it 'likes' than when it tastes something it 'dislikes'. Normally the neurons fire very little to a 'disliked' taste such as an intensely salty taste that is three-times saltier than seawater. But when rats are put into a physiological state of 'salt appetite' by hormone injections that deplete their bodies of salt, the same intense salty taste suddenly becomes positive and 'liked'. Simultaneously, the neurons in the ventral pallidum hotspot may suddenly fire at least as fast to the intense salt taste as they do to sugar (Aldridge and Berridge, this volume; Tindell et al., 2004; Tindell et al., 2006).

*Interaction between accumbens-pallidum opioids*

How do isolated hotspots in the nucleus accumbens and ventral pallidum combine into integrated brain hedonic circuits? Observations in our lab indicate that nucleus accumbens and ventral pallidum hotspots exchange information in both directions to form a single integrated circuit that acts to amplify the hedonic impact of a sensory reward (Smith and Berridge, 2007) (Figure 4).

'Liking' amplification by an opioid microinjection in the accumbens hotspot can be blocked if naloxone (an opioid-blocking drug) is simultaneously microinjected in the ventral pallidum hotspot (Smith and Berridge, 2007). The same microinjection of naloxone in ventral pallidum feeds back to inhibit the nucleus accumbens, where it reduces the size of the Fos plume caused by a DAMGO microinjection in the accumbens hotspot. That naloxone-induced suppression of accumbens neurons seems to reflect a suppression of the entire 'liking' circuit, and so no pleasure enhancement can be produced.

Yet, despite this suppression of 'liking' mechanisms, DAMGO microinjection in the accumbens hotspot still generates an increase in food 'wanting' that is as great as if naloxone had not been given into the ventral pallidum at all. This persistent eating enhancement may be due to alternate outgoing opioid pathways for accumbens 'wanting' signals to bypass the ventral pallidum. Accumbens projections to the lateral

hypothalamus provide one potential alternate 'wanting' circuit that might circumvent blockade of the ventral pallidum (Kelley et al., 2005; Smith and Berridge, 2007; Will et al., 2003).

*Hedonic hotspots: pleasure valuation rather than motor expression*

Does a hotspot enhancement reflect a true magnification in pleasure 'liking' rather than merely its motor expression? It is an important question, and the answer becomes quite complex. Still, several lines of clear evidence indicate an enhancement of true hedonic 'liking'.

The enhancement caused by hedonic hotspot activation does not fit any motor category: first, the enhancement is not of a single movement of the sort often produced by focused stimulation of a motor structure (because a signature hedonic configuration of several coordinated reactions is enhanced, not just one reaction); second, it does not directly activate the configuration as a fixed motor pattern (because the motor reactions are not generated by the microinjection in the absence of a palatable taste stimulus, indicating the hotspot did not simply turn on a "hedonic orofacial movement generator"; finally, it does not increase all movements as a general motor activation (because aversive reactions or other reactions are actually decreased, and because hedonic enhancement occurs at different drugs/doses from locomotor movement enhancements).

In addition, supporting evidence that hotspot neurons are truly hedonic comes from electrophysiology demonstrations that firing of neurons in the ventral pallidum hotspot tracks the hedonic value of a taste, and is not tightly associated to any motor details of reaction movements (Aldridge and Berridge, this volume; Tindell et al., 2006). Such considerations lead us to believe that hotspot maps, based on behavioral 'liking' reaction studies, truly show the location of brain substrates for hedonic valuation of pleasure, rather than simply generators of 'liking' movements.

## Levels of Pleasure in the Brain

Sensory pleasure does not arise from any one hedonic hotspot, of course. Rather, as indicated by the 'liking' circuit between accumbens-pallidum hotspots described above, pleasure results from their connection together into larger hedonic brain circuits that operate as a whole. These integrated circuits stretch across the brain from forebrain to brainstem, forming a hedonic generating system for natural pleasure.

*Brainstem hedonic roles?*

The notion that the brainstem plays any role in sensory pleasure might come as a surprise to anyone used to thinking of brainstem areas solely in terms of reflexive functions. Yet for over a century, the brainstem has been recognized to participate in the generation of basic affective reactions, as well as other psychological functions. John Hughlings Jackson, an innovative 19th century neurologist, proposed that brainstem function provided an essential first level in a neural hierarchy of 're-re-representation' of affective and other functions. According to this principle, low levels of the brain (the brainstem) generate a basic and concrete representation of events or functions, sufficient just for basic affective reactions and behavioral responses.

Examples of basic brainstem 'liking' function date back over a century ago when Goltz showed that after surgical removal of its forebrain a dog would still reject a piece

of meat soaked in bitter quinine (Goltz, 1892). Miller and Sherrington subsequently showed that decerebrated cats (surgically transected above the hindbrain) responded with ingestive "elaborate movements of the tongue" to meat-flavored water but with "retching and reflexes of rejection" to quinine (p. 167) (Miller and Sherrington, 1915). In the 1970s, Grill and Norgren showed that chronic decerebrate rats, with only a hindbrain and midbrain intact, still emitted normal positive tongue protrusions and lip licking reactions to sucrose taste, but emitted aversive gapes and other rejection reactions to quinine taste (Grill and Norgren, 1978b). In humans, Steiner showed that anencephalic infants (born missing the forebrain due to congenital malformation but with a normal brainstem) similarly emitted normal tongue protrusions to sucrose taste, but aversive gapes and headshakes in response to bitter tastes (and cried as normal infants do) (Steiner, 1973). Thus the brainstem examined in isolation seems capable of generating elemental forms of affective 'liking' or 'disliking' reactions.

In normal animals with intact brains, however, the brainstem does not react in isolation but rather is wired into a larger brain hierarchy of affect generation involving forebrain structures, including the hedonic hotspots in ventral pallidum and nucleus accumbens described earlier. Forebrain levels in a Jacksonian brain hierarchy re-represent and re-re-represent the signals that have been initially represented in brainstem, taking control of lower functions and adding new abstract features (Hughlings Jackson, 1958). By a hierarchical account, a complete affective (or other) function requires the entire system. The full affective function cannot be provided by the brainstem alone in the absence of cortex. But conversely, if 'liking' is truly organized as a Jacksonian brain hierarchy, then full-blown affective function cannot be generated by the cortex alone in the absence of brainstem.

The concept of neural hierarchy and multiple brain levels for affect generation is still present in contemporary thought on emotion, and the brainstem is still posited to make key contributions (Berridge, 2003a; Damasio, 1999; LeDoux, 1996; Panksepp, 1991). For example, Damasio has suggested that the parabrachial nucleus in the pons of the brainstem participates in generating what he calls a 'protoself', a coherent representation of the momentary state of the body used by higher brain levels to generate conscious feelings. A consequence is that brainstem lesions that disrupt generation of protoself functions may uniquely cause coma and loss of conscious awareness (Damasio, 1999).

Regarding 'liking' reactions, a surprising feature of the affective brain hierarchy is that ascending levels can be differentially balanced between positive and negative reactions (Grill and Berridge, 1985). As a consequence, less brain can sometimes actually be better affectively balanced than more brain. For example, animals with an isolated brainstem (decerebrates) generate balanced 'liking' and 'disliking' reactions to tastes: positive to sweet but negative to bitter (Grill and Norgren, 1978b). But adding one more brain layer called the diencephalon or lower forebrain (thalamus, pineal and hypothalamus) actually unbalances the hierarchy in a negative direction toward complete 'disliking'.

For example, a surgical preparation that creates this brainstem-plus-lower-forebrain has sometimes been called a 'thalamic' animal, involving ablation of everything above

the thalamus. It lacks not only neocortex but also the subcortical upper forebrain, including ventral pallidum, nucleus accumbens, amygdala, hippocampus and neostriatum (all these structures together with neocortex belong to the brain level called the telencephalon). A thalamic rat or cat shows only aversive quinine-like rejection reactions even to a sweet taste, and lacks any positive hedonic response to normally pleasant stimuli (Bard, 1934; Grill and Norgren, 1978b). The thalamic animal's unbalanced affective negativity suggests that the diencephalon contains circuitry which pushes brainstem reactions into 'disliking', unless opposed by signals from forebrain structures further above.

What structure above the thalamus adds enough positive affect to flip affective reactions back to 'liking' balance again? That could be answered by adding back forebrain structures 'one-by-one', or more practically, taking one or several structures above the thalamus away from normal animals, to find out which one is needed for normal 'liking'. One might have thought that the answer would be the neocortex. However, it turns out that affective balance can be restored by merely adding the sub-neocortical parts of the upper forebrain or telencephalon. Adding the cortex itself beyond that may add little more to basic 'liking' reactions. This is shown by observations that 'decorticate rats', which have had the neocortex completely removed but still have all their sub-neocortical forebrain structures, upper as well as lower, show completely normal positive 'liking' reactions to sweet tastes and 'disliking' to bitter tastes (and can even learn complex tasks to get rewards) (Bard, 1934; Grill and Norgren, 1978b; Wirsig and Grill, 1982).

Of the subcortical upper forebrain structures needed for normal pleasure, we suggest that the ventral pallidum might be particularly important; perhaps especially its positive hedonic hotspot, due to its necessary and sufficient causal roles in generating 'liking' reactions to pleasure (Cromwell and Berridge, 1993; Smith and Berridge, 2005). This would mean that the addition of all of the forebrain to the brainstem, *except* the ventral pallidum, would actually unbalance affect in a negative direction as much as a total 'thalamic ablation' of everything above the thalamus.

Essentially, that anatomical configuration is what a brain with only ventral pallidum lesions has. Mapping the exact forebrain sites responsible for anhedonia, or loss of normal 'liking', is an interesting goal for future exploration. It is interesting to note that normal levels of 'liking' are relatively robust in the face of damage to widespread brain areas. Hedonic robustness may reflect the evolutionary importance of pleasure reactions, as well as the neural re-re-representation of 'liking' function at several levels. Robustness of normal pleasure reactions also contrasts to the relative fragility of 'liking' *enhancement* above normal, which requires unanimous 'opioid consent' by multiple forebrain hotspots simultaneously as described earlier (Smith and Berridge, 2007).

In summary, the brainstem has not lost hedonic functions when higher brain areas are present, but rather has been incorporated into a larger neural hierarchy of pleasure controlled by forebrain circuits. Hierarchy means that brainstem has lost its autonomy, so that the forebrain adds new hedonic functions and overrides the preexisting ones (Gallistel, 1980). The hotspots we described in nucleus accumbens and ventral

pallidum are examples of forebrain 'liking' mechanisms that can override brainstem functions to enhance sensory pleasure.

*A benzodiazepine/GABA hedonic substrate in the parabrachial nucleus*

A concrete residue of basic hedonic function in the brainstem is the existence of a hedonic hotspot in the pons of rats. The brainstem hedonic hotspot appears to be located near the parabrachial nucleus of the pons and uses a benzodiazepine/GABA signal to augment hedonics (Peciña and Berridge, 1996; Soderpalm and Berridge, 2000b) (Figure 4). Benzodiazepine drugs are probably most famous for their anti-anxiety and tranquilizing effects. However, benzodiazepines also stimulate appetite via separate brain mechanisms, and were originally suggested by Cooper in the 1980s to augment the hedonic impact of food rewards (Cooper, 1980; Cooper and Estall, 1985).

Subsequent studies identified the brainstem, particularly its parabrachial nucleus area in the pons, as the chief site where benzodiazepines appear to act to enhance taste palatability and appetite. Microinjections of a benzodiazepine drug into the rat brainstem as a whole or directly into the parabrachial nucleus causes a doubling of the number of 'liking' reactions to sugar (Peciña and Berridge, 1996; Soderpalm and Berridge, 2000b) (Figure 4). Similar parabrachial microinjections also make rats 'want' to eat more food (Higgs and Cooper, 1996).

The existence of the hedonic hotspot in the parabrachial nucleus of the pons in the brainstem may explain why a brainstem microinjection of a benzodiazepine causes higher increases in 'liking' reactions than forebrain microinjections of the same drug: the forebrain has no known hotspot for benzodiazepine amplification of hedonic impact (Berridge and Peciña, 1995; Peciña and Berridge, 1996; Soderpalm and Berridge, 2000a). It may also explain why even decerebrate rats, which have only a brainstem (hindbrain and midbrain), still show an elevation in positive reactions to sucrose taste if given a systemic injection of benzodiazepine drug to activate their remaining brainstem GABA signals (Berridge, 1988).

The parabrachial nucleus is a relay nucleus where ascending taste sensation signals are processed after leaving the hindbrain nucleus of the solitary tract in the rodent brain (Norgren, 1995; Spector, 2000). In human and other primates, a few studies have indicated that the ascending taste pathway may bypass the parabrachial nucleus on its way to forebrain targets (Beckstead et al., 1980; Pritchard et al., 2000). Until more is known, it is difficult to be sure about whether primate brains really lack a parabrachial taste relay. However, even if the parabrachial nucleus is not part of the direct taste pathway, it is still possible that the human parabrachial nucleus contributes indirectly to taste 'liking'. That is because the parabrachial nucleus also receives indirect descending projections from limbic forebrain sites, which are able to modulate taste sensation (Lundy and Norgren, 2004). Indeed, in humans, taste deficits can occur with pontine lesions near the parabrachial nucleus and taste intensity discrimination recruits parabrachial activity (Landis et al., 2006; Small et al., 2003).

A retained hedonic role would also be compatible with the suggestion that the parabrachial nucleus mediates emotional representations of body states in humans (Damasio, 1999). Thus although differences may exist between rats and people in as-

cending taste circuits, it is possible that the parabrachial nucleus might still contribute as a hedonic hotspot in humans too.

In addition, some evidence from rat experiments indicates that the parabrachial GABA signal may require opioid signals, perhaps in the forebrain, to amplify 'liking' reactions. Pretreatment with an injection of the opioid antagonist naloxone can block the typical 200% elevation of sucrose 'liking' reactions that is usually caused by an injection of a benzodiazepine drug (Richardson et al., 2005). A possible neural explanation for naloxone blocking is if the parabrachial nucleus activates endogenous opioid signals in hedonic hotspots, perhaps in the nucleus accumbens and ventral pallidum, as the next step in the neural circuit for enhancing 'liking'. This is consistent with the notion that a distributed brain circuit connects together hotspots in brainstem and forebrain, and functions as an integrated whole to amplify sensory pleasure (Figure 4).

*Hedonics at the top end of the brain: pleasure-causing substrates in the neocortex?*

We have described so far how taste pleasure can arise from a number of hedonic hotspots in brainstem and subcortical forebrain. What about at the very top of the brain? Does the neocortex contain hotspots of its own capable of elevating hedonic reward?

In favor of the possibility, impressive neuroimaging studies have demonstrated that sites in prefrontal and related limbic regions of neocortex *code* positive affect and the hedonic impact of many pleasures (Bechara et al., 2000; Burke and Schoenbaum, this volume; Davidson and Irwin, 1999; Kringelbach, this volume; O'Doherty, 2004; Small and Veldhuizen, this volume). Most prominent among cortical sites activated by pleasure may be the orbitofrontal region of prefrontal cortex (Knutson et al., 2001; Kringelbach, 2005; Rolls, 2000; Small, 2006). In humans the orbitofrontal cortex, particularly its medial region, is activated by pleasant tastes and odors, pleasant touch sensations, and other pleasant stimuli (de Araujo et al., 2003; Francis et al., 1999; O'Doherty, 2004; Rolls et al., 2003b; Small et al., 2003). Orbitofrontal cortex activity in rats, monkeys and humans also tracks changes in pleasure of a constant food stimulus, or the alliesthetic reductions in hedonic impact caused by eating foods to satiety (Burke and Schoenbaum, this volume; Faurion et al., 1998; Hollerman et al., 2000; Kringelbach, this volume; Kringelbach et al., 2003; O'Doherty, 2004; Rolls et al., 1989; Simon et al., 2006; Small et al., 2001). For example, the taste of chocolate activates the orbitofrontal cortex in hungry people who like chocolate, but activation declines after subjects eat chocolate to satiety (Small and Veldhuizen, this volume; Small et al., 2001). More complex human pleasures, such as pleasurable music or winning money, have also been reported to activate orbitofrontal cortex and other sites (Blood and Zatorre, 2001).

Other cortical regions that might possibly play a role in causing pleasure include anterior cingulate cortex and insular cortex. Cingulate cortex has been observed to be activated by a number of hedonic stimuli, including sexual arousal, taste and olfactory rewards, pleasant music, and rewarding drug stimulation (Breiter et al., 1997; Brown et al., 2004; de Araujo et al., 2003; Firestone et al., 1996; Gottfried, this volume; Komisaruk, this volume; McCoy et al., 2003; Platt, this volume; Rauch et al., 1999; Small and Veldhuizen, this volume). The insular cortex has been suggested to contain an anterior gustatory site and a posterior hedonic

site (Kringelbach et al., 2003; Yaxley et al., 1988). Insular cortex is activated by pleasant tastes or odors in hungry humans and rats, and satiety causes a decline in activation to the same stimuli (de Araujo et al., 2006; Kringelbach et al., 2003; O'Doherty et al., 2000; Small et al., 2003; Small et al., 2001). Insular cortex has been suggested to perhaps be especially important for mediating learned likes for initially aversive stimuli, such as the taste of cigarette smoke (Naqvi et al., 2007), and also for learned dislikes such as nausea-induced taste aversions or pictures of rotten foods (Gutierrez et al., 1999).

However, it remains an open question to what extent any of these cortical areas actually *cause* basic hedonic 'liking' reactions to pleasant events, beyond coding pleasure for cognitive or other functions (including hedonic consciousness, discussed below). As yet, little direct evidence exists to know if activity in a cortical area is ever sufficient to generate increases in hedonic impact, or necessary for normal hedonic impact, in the same sense as in hedonic hotspots of subcortical brain structures. Alternatively, cortical hedonic coding may not actually cause basic pleasure, but rather re-represent subcortical pleasure reactions for other functions, such as cognitive representations or even conscious awareness. Cognition and consciousness are crucial causal functions too, of course, but distinct from the generation of a basic 'liking' reaction. Thus the issue of whether specific cortical areas actually cause pleasure 'liking' reactions awaits future evidence (Kringelbach, this volume).

*Subcortical hedonic systems: conscious or unconscious?*

A related fascinating question concerns how in the brain the consciousness of pleasure arises. Do subcortical hedonic hotspots or generating circuits ever directly cause a conscious pleasure feeling, in addition to causing core 'liking' reactions? Or is the subjective awareness of pleasure something that must be added by cortex re-representations? Terminologically, it is easy to distinguish between objective and subjective senses of pleasure. We have always used the term 'liking' (in quotes) to mean objective hedonic reactions, whether or not accompanied by subjective feelings (which might not even exist in decerebrates, anencephalics and similar cases). A 'liking' reaction is held to be a core component of normal hedonic feelings, but can sometimes occur by itself without those conscious feelings. By contrast, we use the word liking (without quotes), to mean its normal sense of a conscious experience of pleasure. This use helps to distinguish between conscious and unconscious forms of pleasure, and to highlight the possibility of unconscious pleasure in basic 'liking' reactions.

Beyond mere words, there is also reason to consider conscious pleasure and unconscious pleasure both as real psychological processes with distinct brain mechanisms (Frijda, this volume; Schooler, this volume). Although the idea of an unconscious pleasure is counterintuitive to many people, evidence is accumulating that unconscious pleasure processes may exist, often tucked within normal conscious experiences of pleasure and sometimes even on its own.

For example, Winkielman et al. (Winkielman et al., 2005) recently demonstrated that normal human adults can have unconscious 'liking' and 'disliking' reactions that

fail to reach conscious awareness. Participants were subliminally shown happy facial expressions (or neutral or angry expressions), followed by a masking stimulus and a task designed to wipe out any subjective feelings produced by the subliminal expressions, using a modification of subliminal emotional priming procedures (Monahan et al., 2000; Winkielman et al., 1997). Participants then rated their own hedonic and arousal feelings, and also sampled and rated a novel fruit beverage. No changes in ratings of conscious hedonic/arousal feelings were produced by subliminal exposure to emotional expressions (and participants reported afterwards that they had not seen any emotional expression, and were unable to pick the one they saw out of a lineup). Yet thirsty participants who had subliminally seen a happy subliminal expression poured and drank twice as much of the beverage as those who had seen angry expressions, and gave up to four times higher ratings of value to the beverage (Winkielman et al., 2005). Those results indicated that under appropriately masked subliminal conditions, ordinary people could have core 'liking' and 'disliking' reactions to emotional expressions that were completely unfelt at the moment they were caused, yet were strong enough to go on to markedly shift consumption behavior and reactions to a valence-laden stimulus.

Several human clinical cases also seem consistent with the notion of unconscious pleasure under certain conditions. For example, human drug addicts have been reported to self-administer drugs like cocaine even at doses too low to produce subjective effects or autonomic responses (Fischman and Foltin, 1992; Hart et al., 2001). Similarly, after gustatory cortex damage, a patient has been described to display a clear preference for a sweet beverage over a salty one, yet was unable to tell the two tastes apart in a subjective sensory test and subjectively rated them as equally pleasant (Adolphs et al., 2005).

Some evidence suggests that subliminal stimuli might trigger core 'liking' reactions in the brains of normal people by activating subcortical hedonic hotspots in the absence of conscious awareness. Such studies use neuroimaging measures to show that subliminal presentation of positive hedonic stimuli, too brief to be consciously seen, can still activate limbic brain structures such as ventral pallidum or amygdala? For example, the ventral pallidum is reported to be activated by subliminal presentation of pictures of happy faces (Whalen et al., 1998) and by subliminal presentation of money cues that signal that a large reward is about to be earned (Pessiglione et al., 2007). Such examples suggest that subjective awareness may not always have access to underlying core affective reactions in subcortical brain structures, which might conceivably mediate behavioral manifestations of unconscious 'liking' (Winkielman et al., 2005).

We presume that conscious feelings of liking always incorporate these core 'liking' reactions, but also involve an additional neural and psychological stage that elaborates the core affective reaction into conscious awareness. A traditional and relatively simple brain-based explanation might be that activation of subcortical hedonic hotspots could generate a core 'liking' signal that is not itself directly accessible to consciousness, and that higher brain systems such as cortex might use coded 'liking' signals as an input to generate conscious pleasure experience (liking, without quotes).

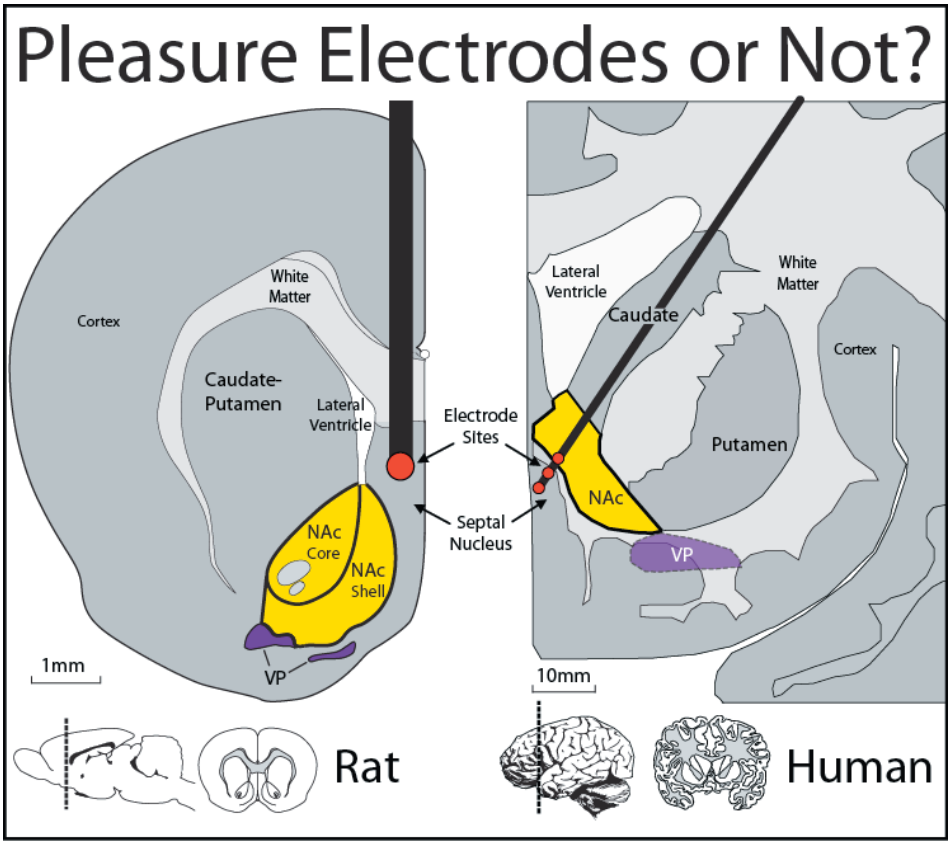


**Figure 5: Pleasure electrodes or not?**
*Examples of famous so-called 'pleasure electrode' placements in rat (from Olds, 1961) and in human (patient B-19, a young man, from Heath, 1972). Thick black lines show the electrodes (insulated except at tips; red dots indicate their stimulating tips) near the nucleus accumbens. The nearby ventral pallidum is also shown, though it is mostly posterior to the depicted coronal section. Both the rat and the human pressed for electrode stimulation up to thousands of times, but we suggest both electrodes might have produced merely a pure form of 'wanting' (incentive salience) rather than actual 'liking' (true hedonic pleasure).*

## Rethinking Old Pleasure Sources: Electrodes and Dopamine

*False Pleasure electrodes?*

By contrast to the pleasure substrates described above, some brain substrates once thought to cause pleasure may be turning out not to do so. Perhaps the most famous candidate for a brain substrate that generates pleasure were so-called "pleasure electrodes", which used brain electrical stimulation of the subcortical limbic forebrain to reinforce self-administration behavior such as pressing a lever or pushing a button (Aziz and Green, this volume; Delgado, 1969; Heath, 1972; Kringelbach, this volume; Kringelbach et al., 2007; Olds and Milner, 1954; Sem-Jacobsen, 1976; Shizgal, this volume). Pleasure electrodes were typically aimed at the septum or lateral hypothalamus, though a number of the sites fell within what neuroanatomists would now call the

nucleus accumbens, and most electrodes likely activated mesolimbic dopamine systems (Heath, 1972; Hernandez et al., 2006; Olds, 1961; Olds and Milner, 1954) (Figure 4). Some patients stimulated these 'pleasure electrodes' thousands of times in a single 3-hour session (Heath, 1972; Sem-Jacobsen, 1976; Valenstein, 1974). Many textbooks cite these cases as examples of intense brain-induced pleasure. But despite such dramatic self-administration, it is questionable whether many of those electrodes ever actually caused pleasure (Berridge, 2003b; Peciña et al., 2006). If one reads the transcripts of verbal responses closely, it is not clear that the patients experienced intense pleasure per se during stimulation.

For example, "B-19", a young man with chronic electrodes implanted by Heath and colleagues in the 1960s, voraciously self-stimulated his electrode located in septum and nucleus accumbens (Figure 4), and protested when the stimulation button was taken away (Heath, 1996). Still, B-19 was never reported to utter exclamations of delight or to say that the electrodes caused pleasure thrills. Instead, B19 reported that stimulating his electrode evoked desire to stimulate again, as well as a strong desire to engage in sexual activities. Another Heath patient said his electrode "made him feel as if he were building up to sexual orgasm" but left him "unable to achieve the orgastic end point", an outcome which often "was frustrating and produced a "nervous feeling" that seems nearly opposite to pleasure (Heath, 1964). Although stimulation caused patients to become strongly sexually aroused, or to want to eat or drink or pursue other incentives, it never produced feelings like sexual orgasm, and it did not serve as a substitute for sexual acts or other reward consumption.

In more recent years, brain electrodes programmed to spontaneously stimulate reward structures have been implanted in a number of patients with Parkinson's disease, in attempts to alleviate problems with movement and low mood (Kringelbach et al., 2007). One interesting motivational effect of such brain stimulation has been to make people and objects in the environment sometimes be perceived as more attractive. For example, one patient developed "fondness" of other people in the clinic and "was in love with two neurologists, and tried to embrace and kiss people" (Herzog et al., 2003). Compulsive pursuits of objects, stimuli, or activities may also sometimes result. For example, the same patient above also "engaged in unrestrained buying of clothing". Urges to engage in activities, such as the desire to visit particular tourist sites or to take up again former hobbies that had lapsed, have been reported (Schlaepfer et al., 2007), as has the development of compulsive gambling, compulsive sex, or stealing (Houeto et al., 2002; Mandat et al., 2006).

Why would anyone press a self-stimulation button thousands of times for electrode stimulation if it is not intensely pleasant? Or why engage in compulsive and intense levels of motivated behavior during brain stimulation if the electrode doesn't make those acts more pleasurable? One possible alternative to pleasure is that the electrode causes incentive salience to be attributed to events associated with the stimulation – such as the button stimulus and the act of pressing it. That might cause people to 'want' to press again even if they didn't especially 'like' it. This incentive salience explanation was originally suggested by observations that stimulation of a rewarding electrode also makes rats 'want' to eat more

food – but does so without ever causing them to 'like' the food more (Berridge and Valenstein, 1991). For the rats, the presence of food had been repeatedly paired with the electrode stimulation. For humans in self-stimulation situations, the button and pressing it are the events most closely paired with stimulation, and therefore likely to be the target of greatest 'wanting'. For the patient who suddenly perceives the whole world as motivationally brighter, other people as more desirable, and certain pursuits as compulsively attractive, the act of button pressing should be even more attractive, especially after pressing it several times. In such cases the button itself could become the greatest motivational magnet. A person therefore could intensely come to 'want' to press the button again even if the electrode never caused a hedonic pleasure or 'liking'.

We hasten to say that our claim that most 'pleasure electrodes' failed to generate true 'liking' is not to say that none ever did. A few electrode cases sound more plausibly like true pleasure. For example, chronic electrode stimulation of the subthalamic nucleus in the forebrain basal ganglia was described as "morphine like" or similar to "sexual climax" (Morgan et al., 2006), which might be a candidate for true pleasure (though even here it is still open as to whether the stimulation was truly hedonic in a morphine-euphoric sense or rather a mere sensation of visceral relaxation, and whether it was the hedonic feeling of climax or merely sexual sensations, either of which could be caused by deep forebrain stimulation).

In future research it would be useful to ask questions that more specifically assess the pleasure of electrode stimulation. Is the stimulation nice? How nice, and compared to what? If the electrode makes a person want to eat or drink or engage in sex, then does the stimulation make those targets any more liked when they are consumed? Affirmative answers to such questions should be found if electrode stimulation acts to activate a true hedonic hotspot (Kringelbach et al., 2007).

*Dopamine: not a pleasure transmitter?*

Another false pleasure-causing substrate may be brain dopamine, especially the mesolimbic system that projects from midbrain to nucleus accumbens (which was likely to have been stimulated, directly or indirectly, by many of the electrodes described above) (Figure 5). Dopamine has been famous as a so-called pleasure neurotransmitter for over 30 years (Hoebel et al., 1999; Shizgal, 1999; Wise and Bozarth, 1985). One reason dopamine was thought to mediate pleasure is that dopamine neurons are turned on by pleasurable stimuli ranging from foods, sex and drugs to social and cognitive rewards (Ahn and Phillips, 1999; Aragona et al., 2006; Becker et al., 2001; Fiorino et al., 1997; Robinson et al., 2005; Schultz, 1998; Wise, 1998). Further, if dopamine was blocked in animals, all rewards seemed to lose rewarding properties in certain instrumental paradigms, becoming no longer 'wanted' in a way that led many neuroscientists to conclude the rewards were no longer 'liked' (Hoebel et al., 1999; Shizgal, 1999; Wise and Bozarth, 1985).

But dopamine is probably not a pleasure neurotransmitter, even if it causes some other component of reward (which we have suggested is incentive salience 'wanting') (Berridge, 2007b; Robinson and Berridge, 2003). Dopamine is not needed to cause normal pleasure of food or drugs of abuse. For example, even massive destruction of

ascending dopamine projections does not impair affective 'liking' reactions elicited by a sweet taste (Berridge and Robinson, 1998; Berridge et al., 1989). Similarly, complete gene-based elimination of dopamine has been suggested to not impair 'liking' in dopamine-deficient mutant mice (Robinson et al., 2005). Nor does dopamine blockade by neuroleptic drugs reduce 'liking' facial reactions of rats to sweetness (Peciña et al., 1997). In humans, the perceived pleasantness of chocolate milk is not reduced by the loss of brain dopamine neurons in Parkinson's disease (Sienkiewicz-Jarosz et al., 2005). Similarly, human subjective ratings of the pleasantness of amphetamine, cocaine or cigarettes have been reported to persist unsuppressed by dopamine-blocking drugs or dietary-induced dopamine depletion, even when those treatments do suppress wanting for more of the same drug (Brauer et al., 2001; Brauer and de Wit, 1997; Leyton, this volume; Leyton et al., 2005).

Elevation of dopamine is not a sufficient cause for pleasure any more than a reduction of dopamine impairs pleasure as a necessary cause (Leyton, this volume). Elevation of dopamine neurotransmission in mutant mice by a gene that raises released dopamine levels to more than one-and-a-half times above normal does not enhance their hedonic 'liking' reactions to sweetness, even though the mutant mice appear to 'want' food rewards more (working harder, faster, and longer to obtain sweet rewards, and resisting distractions more) (Cagniard et al., 2006; Peciña et al., 2003). Similarly, raising dopamine levels by administering amphetamine, either systemically or directly into the nucleus accumbens, also completely fails to increase hedonic 'liking' reactions even when 'wanting' of the same reward is increased (Tindell et al., 2005; Wyvell and Berridge, 2000). Also, in humans, dopamine increases caused by amphetamine or L-Dopa are reported to correlate well with subjective ratings of 'wanting' to take more drug, but not with ratings of liking for the same drug (e.g. "Do you like the effects you are feeling right now?") (Evans et al., 2006; Leyton et al., 2002).

Overall in both animals and humans, dopamine now appears neither necessary for generating normal pleasure nor sufficient for enhancing pleasure (Leknes and Tracey, this volume; Leyton, this volume).

*Questions for Future Research*

Many questions remain for future research on pleasure generation in the brain. We end simply by highlighting a few outstanding ones.

Are there additional hedonic hotspots in the brain? Beyond the hedonic hotspots described here, it seems likely that other brain sites may participate in causal generation of 'liking' reactions. Chief among them might be the orbitofrontal cortex in the prefrontal lobe, which is perhaps the most promising candidate for pleasure generation among all cortical structures. Activation of the orbitofrontal cortex appears to show the best cortical correlation with pleasure in humans (Kringelbach, 2005; Kringelbach, this volume; Small and Veldhuizen, this volume; Small et al., 2001) and other animals (Burke and Schoenbaum, this volume; Rolls, 2000; Rolls et al., 1989; Schoenbaum and Roesch, 2005). Most intriguingly, orbitofrontal cortex has been suggested to segregate positive and negative affective valence into separate areas, coding positive rewards by medial activation and negative aversion by more lateral activation (Kringelbach, 2005; Rolls et al., 2003a; Small et al., 2001).

If orbitofrontal cortex acts to cause basic affective reactions, then local stimulation of it might increase positive or negative affective reactions, respectively, or focused lesions might disrupt particular affective reactions. It would be of great interest to find a cortical region that exerts clear causal influence on a core 'liking' reaction. Other cortical candidates for causal hedonic hotspots might include the insular cortex or anterior cingulate cortex. Other subcortical candidates also remain to be examined more thoroughly: these include the lateral shell of nucleus accumbens (only the medial shell has been thoroughly mapped so far), and perhaps the core of the nucleus accumbens, amygdala nuclei and the related 'extended amygdala', and other limbic structures that are closely wired to hotspots in the nucleus accumbens and ventral pallidum. Discovery of new hedonic hotspots will be useful to extend neuroscientific understanding of the unique brain circuit that is able to generate amplification of pleasure.

A related wonderful opportunity to assess whether specific brain sites in humans can actually cause pleasure is offered by the new crop of deep brain stimulation procedures that have recently begun to be reapplied to pathological conditions such as Parkinson's disease and depression (Kringelbach et al., 2007). We have argued that some of the classic cases of brain stimulation-induced pleasure may be equivocal at best, but future studies may be more successful at demonstrating true pleasure electrodes (Aziz and Green, this volume; Kringelbach, this volume; Shizgal, this volume). Finding stimulation sites that do support pleasure in this way would be a significant step forward in mapping human hedonic hotspots. It would be useful to have clear evidence that electrode stimulation was truly 'liked' in a genuinely hedonic sense, more than merely 'wanted'.

Beyond finding more hotspots in the brain, it will also be important in the future to better understand how hotspots work normally to generate pleasure in the brain. This issue touches on an essential question: what does it mean to have a brain-based explanation of pleasure? Something more is needed than merely pointing to neurochemical activation in a crucial brain hotspot. We need a better explanation of why hotspot activation causes pleasure. Tracing that path of neural-psychological causation will require considerably more information on hedonic brain mechanisms, and perhaps major conceptual developments as well.

## Conclusions

The question of how pleasure is caused in the brain is fundamentally one of how hedonic value gets added to a mere sensation. Modern experimental tools, such as microinjection Fos plume mapping techniques combined with behavioral 'liking' reaction measures, have revealed an interactive network of hedonic hotspots in the nucleus accumbens, ventral pallidum, and other brain structures (Figure 4). These hedonic hotspots appear to be the crucial brain mechanisms that actively paint a gloss of pleasure onto sensations such as sweetness and cause them to be 'liked'.

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