CHAPTER

8

Brain Reward Systems for Food Incentives and Hedonics in Normal Appetite and Eating Disorders

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What brain reward systems mediate motivational "wanting" and hedonic "liking" for food rewards? And what roles might these systems play in eating disorders? This chapter identifies recent discoveries in hedonic "liking" mechanisms, such as the location of opioid hedonic hotspots in nucleus accumbens

and ventral pallidum that paint a pleasure gloss onto sweet sensation. It also considers other incentive motivation systems that mediate only a nonhedonic "wanting" component of reward, such as nearby limbic opioid "wanting" zones, mesolimbic dopamine contributions to incentive salience, and other components of brain limbic systems, and discusses potential roles in eating disorders.

I. INTRODUCTION

Obesity, bulimia, anorexia, and related eating disorders have risen in recent decades, leading to increasing concern. Can improved knowledge about brain reward systems guide us in thinking about eating disorders and normal eating?

First it is important to recognize that brain reward systems are active participants, not just passive conduits, in the act of eating. Sweetness and other food tastes are merely sensation, and their pleasure arises within the brain. Hedonic brain systems must actively paint the pleasure onto sensation to generate a "liking" reaction—as a sort of "pleasure gloss." What brain systems paint a pleasure gloss onto sensation? And what brain systems convert pleasure into a desire to eat? Answers to these questions requires combining information from neuroimaging experiments and studies of eating in humans and information from brain manipulation and pharmacological experiments that ethically can be done only in animals.

II. POSSIBLE ROLES OF BRAIN REWARD SYSTEMS IN EATING DISORDERS

To begin with, we can sketch several alternative possibilities for how brain reward systems might function in any particular eating disorder. Let us set out some alternatives to frame the issue.

A. Reward Dysfunction as Cause

First, it is possible that some aspects of brain reward function may go wrong and actually cause an eating disorder. Foods might become hedonically "liked" too much or too little via reward dysfunction. Or incentive salience "wanting" to eat might detach from normal close association with hedonic "liking," leading to changes in motivated food consumption that are no longer hedonically driven. Or yet again, suppression of positive hedonic reward systems or activation of dysphoric stress systems might prompt persistent attempts to self-medicate by eating palatable food. All of these possibilities have been suggested at one time or another. Each of them deserves consideration because different answers might apply to different disorders.

B. Passively Distorted Reward Function as Consequence

As a second category of possibilities, brain reward systems might remain intrinsically normal and have no essential pathology in eating disorders, but still become distorted in function as a passive secondary consequence of disordered intake. In that case, brain systems of "liking" and "wanting" might well attempt to function normally. The abnormal feedback from physiological signals that are altered by binges of eating or by periods of anorexia might induce reward dysfunction as a consequence of the behavioral disorder that arose from other causes. This would provide a potential red herring to neuroscientists searching for causes of eating disorders, because brain abnormalities might appear as neural markers for a particular disorder, but be mistaken as causes when they were actually consequences. However, it might still provide a window of opportunity for medication treatments that aim to correct eating behavior in part by modulating reward function back to a normal range.

C. Normal Resilience in Brain Reward

Third, it is possible that most aspects of brain reward systems will function even more normally than suggested by the passively distorted consequence model above. Many compensatory changes can take place in response to physiological alterations, to oppose them via homeostatic or negative feedback corrections. The final consequence of those compensations might restore normality to brain reward functions. In such cases, the causes of eating disorder might then be found to lie completely outside brain reward functions. Indeed, brain reward functions would persist largely normally, and may even serve as aids to eventually help spontaneously normalize eating behavior even without treatment.

The answer to which of these alternative possibilities is best may well vary from case to case. Different eating disorders may require different answers. Perhaps even different individuals with the "same" disorder will involve different answers, at least if there are distinct subtypes within the major types of eating disorder.

It is important to strive toward discovering which answers are most correct for particular disorders or subtypes, because those answers carry implications for what treatment strategy might be best. For example, should one try to restore normal eating by reversing brain reward dysfunction via medications to correct the underlying problem? That would be appropriate if reward dysfunction is the underlying cause.

Or should one use drugs instead only as compensating medications, not cures? Such a medication might aim to boost aspects of brain reward function and so correct eating, even though it may not address the original underlying cause? For example, just as aspirin often helps treat pain, even though the original cause of pain was never a deficit in endogenous aspirin, so a medication that altered reward systems might still help to oppose whatever original underlying factors are altering eating, even though it will not reverse those causal factors.

Or instead should treatment be focused entirely on separate brain or peripheral targets that are unrelated to food reward? That might be the best choice if brain reward systems simply remain normal in all cases of eating disorders, and thus perhaps essentially irrelevant to the expression of pathological eating behavior.

Placing these alternatives side by side helps illustrate that there are therapeutic implications that would follow from a better understanding of brain reward systems. Only if we know how food reward is processed normally in the brain will we be able to recognize pathology in brain reward function. And only if we can recognize reward pathology when it occurs will we be able to judge which of the possibilities above best applies to a particular eating disorder.

III. UNDERSTANDING BRAIN REWARD SYSTEMS FOR FOOD "LIKING" AND "WANTING"

This section turns to some issues involved in measuring and understanding components of brain reward function (Berridge and Robinson, 2003; Everitt and Robbins, 2005). At the heart of reward is hedonic impact or pleasure, and so it is fitting to begin with the practical problem of measuring pleasure "liking" for food rewards in affective neuroscience studies.

A. Measuring Pleasure

Fortunately for psychologists and neuroscientists, pleasure is not just a metaphysical will-o'-the-wisp. Pleasure is a psychological process with neural reality, and has objective markers in brain and behavior. These objective aspects give a tremendously useful handle to neuroscientists

and psychologists in their efforts to gain a scientific purchase on pleasure.

To identify the brain mechanisms that generate pleasure we must be able to identify when pleasure "liking" occurs or changes in magnitude. A useful "liking" reaction to measure taste pleasure is the affective facial expression elicited by the hedonic impact of sweet tastes in newborn human infants. Fortunately for pleasure causation studies, many animals display "liking–disliking" reactions elicited by sweet/bitter tastes that are similar and homologous to affective facial expressions to the same tastes displayed by human infants (Grill and Norgren, 1978b; Steiner, 1973; Steiner et al., 2001). These affective expressions seem to have developed from the same evolutionary source in humans, orangutans, chimpanzees, monkeys, and even rats and mice (Berridge, 2000; Steiner et al., 2001). Sweet tastes elicit positive facial "liking" expressions (tongue protrusions, etc.), whereas bitter tastes instead elicit facial "disliking" expressions (gapes, etc.).

A particular set of taste "liking–disliking" reactions are remarkably similar across species, and even their apparent differences often reflect a deeper shared identity, such as identical allometric timing laws for expression duration that are scaled to the size of the species. For example, human or gorilla tongue protrusions to sweetness or gapes to bitterness may appear languidly slow, whereas the same reactions by rats or mice seem blinkingly fast, yet, they are actually the "same" reactions durations in what is called an allometric sense; that is, each species is timed proportionally to their evolved sizes and that timing is programmed deep in their brains. Such shared universals further underline the common brain origins of these "liking" and "disliking" reactions in rats and humans. That sets the stage for animal affective neuroscience studies to use these affective expressions to identify brain mechanisms that generate hedonic impact.

B. Brain Systems for Food Pleasure

What brain systems paint a pleasure gloss onto mere sensation? Many brain sites are activated in humans by food pleasures: Cortical sites in the front of the brain implicated in the regulation of emotion, such as orbitofrontal cortex and anterior cingulate cortex, gustatory-visceral-emotion-related zones of cortex such as insular cortex; sub-cortical forebrain limbic structures such as amygdala, nucleus accumbens, and ventral pallidum; mesolimbic dopamine projections and even deep brainstem sites (Berns et al., 2001; Cardinal et al., 2002; Everitt and Robbins, 2005; Kringelbach, 2004; Kringelbach et al., 2004; Levine et al., 2003; O'Doherty et al., 2002; Pelchat et al., 2004; Rolls, 2005; Schultz, 2006; Small et al., 2001; Volkow et al., 2002; Wang et al., 2004a). All of these code pleasurable foods, in the sense of sometimes activating during the experience of seeing, smelling, tasting, or eating palatable foods.

But let us also ask: Which of these many brain structures actually cause the pleasure of foods? Do all generate pleasure "liking" or only some? Some activations might reflect causes of pleasure, whereas other activations might reflect consequences of pleasure that was caused elsewhere. How can causation be identified? Typically only by results of brain manipulation studies: a manipulation of a particular brain system will reveal pleasure causation if it produces an increase or decrease in "liking" reactions to food pleasure.

Recent years have seen progress in identifying brain systems responsible for generating the pleasure gloss that makes palatable foods "liked" (Berridge, 2003; Cardinal et al., 2002; Cooper, 2005; Higgs et al., 2003; Kelley et al., 2005a; Levine and Billington, 2004; Rolls, 2005; Wise, 2004; Yeomans and Gray, 2002). What has emerged most recently is a connected network of forebrain sites that use opioid neurotransmission to increase taste "liking"

and "wanting" together to enhance food reward.

Pleasure "liking" appears to be generated by a distributed network of brain islands scattered across sites like an archipelago that trails throughout the limbic forebrain and brainstem (Berridge, 2003; Kelley et al., 2005a; Levine and Billington, 2004; Peciña and Berridge, 2005; Smith and Berridge, 2005). These sites include nucleus accumbens, ventral pallidum, and possibly amygdala and even limbic cortical sites, and also deep brainstem sites including the parabrachial nucleus in the pons. These distributed "liking" sites are all connected together so that they interact as a single integrated "liking" system, which operates by largely hierarchical control rules.

C. Pleasure Brain Hierarchy

Certain elemental reaction circuits within brain affective systems are contained in the brainstem. By themselves, brainstem circuits have a basic autonomy in the sense of functioning as simple reflexes when they have no other signals to modulate them. For example, basic positive or negative facial expressions are still found in human anencephalic infants born with a midbrain and hindbrain, but no cortex, amygdala, or classic limbic system, due to a congenital defect that prevents prenatal development of their forebrain. Yet, sweet tastes still elicit normal positive affective facial expressions from anencephalic infants, and bitter or sour tastes elicit negative expressions (Steiner, 1973). Similarly, a decerebrate rat has an isolated brainstem because a surgical transaction that separates the brainstem's connections from the forebrain, but the decerebrate brainstem also remains able to generate normal taste reactivity expressions to sweet or bitter tastes placed in the decerebrate's mouth (Grill and Norgren, 1978a).

However, brainstem generation of basic reactions does not mean "liking" lives only in the brainstem. Normal "liking" reactions are not brainstem reflexes in a whole-brained individual. This becomes obvious when we consider a related example: anencephalic infants cry and vocalize and even a decerebrate rat squeaks and emits distress cries if its tail gets pinched. But no one would suggest the vocal ability of anencephalic infants to cry and decerebrate rats to squeak means that normal human speech is merely a brainstem reflex. Obviously neither speech nor normal affective expressions generated by an entire brain is merely a brainstem reflex when forebrain systems determine them via hierarchical control.

When brainstem is connected to the forebrain, the entire affective system operates in a hierarchical, flexible, and complex fashion. In a neural hierarchy, forebrain operations overrule brainstem elements, and dictate the output of the whole system. This means that brainstem reflex aspects of affective reactions are largely an artifact of brainstem isolation in decerebrates and anencephalics. In a fully connected brain, affective "liking" and "disliking" reactions are determined by an extensive forebrain network, and the final behavioral expression of affective taste reactivity reflects forebrain "liking" processes.

D. Forebrain Limbic Hedonic Hot Spot in Nucleus Accumbens

One forebrain hedonic island able to cause "liking" is an opioid hot spot in the nucleus accumbens. The nucleus accumbens contains major subdivisions called core and shell. While the core appears especially important for learning about rewards, the shell is more important for generating actual affective and motivational components of rewards themselves, including the pleasure gloss of "liking" for food rewards (Fig. 1).

The shell of nucleus accumbens is an L-shaped structure: its vertical back (called
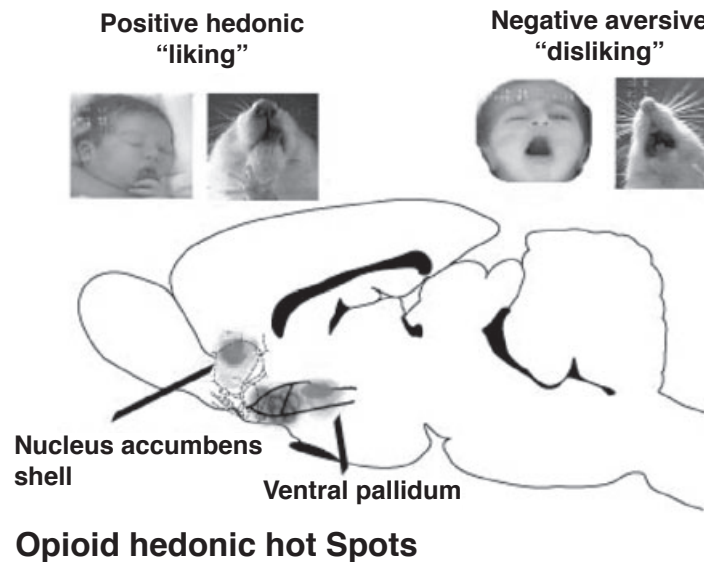
Positive hedonic "liking"

Negative aversive "disliking"

Nucleus accumbens shell

Ventral pallidum

Opioid hedonic hot Spots

FIGURE 1   "Liking" reactions and brain hedonic hot spots. Top: Positive hedonic "liking" reactions are elicited by sucrose taste from human infant and adult rat (e.g., rhythmic tongue protrusion). By contrast, negative aversive "disliking" reactions are elicited by bitter quinine taste. Lower: Forebrain hedonic hot spots in limbic structures where μ-opioid activation causes a brighter pleasure gloss to be painted on sweet sensation. Red/yellow shows hot spots in nucleus accumbens and ventral pallidum where opioid microinjections caused the biggest increases in the number of sweet-elicited "liking" reactions. Modified from Peciña and Berridge (2005) and Smith and Berridge (2005).

medial shell), stands against the middle of the brain in each hemisphere, and its bottom horizontal foot points outward toward the lateral sides of the brain (the core is held in the concave crook formed between vertical back and lateral foot). It is the medial shell, the vertical upright of the L, which has received most attention in the search for pleasure generators—with success.

The pleasure generator in the medial shell runs in part on opioid neurotransmitters. Opioids are natural brain neurotransmitters, such as enkephalin, endorphin, and dynorphin, that act on the same receptors as opiate drugs such as morphine or heroin. Opioid neurotransmitters that activate the μ type of opioid receptor appear particularly important to causing food reward "wanting" and "liking."

An important fact about opioid neurotransmitters in food reward is that they stimulate eating behavior in nearly the entire nucleus accumbens, and in quite a number of other forebrain limbic structures too (Cooper and Higgs, 1994; Kelley, 2004; Kelley et al., 2005a; Levine and Billington, 2004; Yeomans and Gray, 2002). So if opioid activation causes taste pleasure wherever it stimulates appetite for palatable food, then the widespread brain distribution of appetite-promoting sites means the brain has an extensive opioid pleasure network that stretches throughout much of the forebrain. That happy possibility would give every brain a really large hedonic causation system for generating pleasure.

But alternatively, if opioid circuits of food hedonic ("liking") versus motivational ("wanting") functions are organized somewhat differently from each other, then opioid activation might enhance taste pleasure at only some of the sites where it stimulates appetite. In that case, we must grapple with a complexity in opioid psychology and brain function. In other words,

brain opioid activation might contribute to "liking" food and "wanting" food in different ways in different brain places. Understanding precisely how each opioid brain region contributes psychologically is a demanding but also interesting task for affective neuroscientists.

This issue was more recently addressed in a hedonic mapping study by Susana Peciña at the University of Michigan (Peciña and Berridge, 2005). It turns out that only one relatively small site in the medial shell may generate food "liking" as an opioid pleasure island or hedonic hot spot. That hedonic hot spot is in the rostral and dorsal one-quarter of medial shell. Here, μ-opioid activation acts as a hedonic generator to paint a pleasure gloss on sweetness, generating more "liking" for the food it also makes more "wanted."

Peciña's study used a "Fos plume" mapping technique to find where microinjections of a drug that activates opioid circuits causes increased "liking" reactions to the hedonic impact of a pleasant taste. To map pleasure generation, Peciña first made painless microinjections into rats' brains of tiny droplets of a drug known as DAMGO, which stimulates μ opioid receptors (natural neurotransmitter receptors for heroin or morphine). The opioid drug caused nearby neurons with appropriate receptors to begin transcribing genes on chromosomes in their cellular nucleus. One is a rapid-onset or immediate early gene called c-*fos*, which is transcribed to produce a protein called Fos that plays important roles in subsequent neuronal function. Fos protein stains very dark in appearance when postmortem brain slices are appropriately processed later with chemicals and antibodies that bind to the protein, and as a result the neurons with drug-induced Fos could be seen later as forming a dark plume on a slice of brain tissue. The size of each microinjection plume showed how far in the brain its drug had acted.

Some opioid drug microinjections caused sweet taste to carry increased positive hedonic impact. That increase in apparent pleasure-activating quality was reflected by dramatic increases in sucrose-elicited facial "liking" expressions, which often doubled or even tripled in number above control levels. But the "liking" increase was anatomically restricted to a single hedonic hot spot in the brain's medial shell of nucleus accumbens (Peciña and Berridge, 2005). In rats, the hedonic hot spot was roughly just a cubic millimeter in size, contained entirely in the rostral and dorsal quadrant of medial shell. Inside the hedonic hot spot, opioid activation made sweet sucrose taste "liked" even more than normal, and made bitter quinine taste "disliked" less (not as aversive)—shifting both positive/negative dimensions toward a positive pole. Outside the hot spot, positive hedonic impact was no longer increased, even though the "disliking" suppression zone extended more caudally. In fact, in one posterior site outside the hedonic hot spot affective suppression applied to both sweet "liking" and bitter "disliking"—essentially an affective cold spot of general suppression. Thus Peciña's mapping of opioid mechanisms indicates that a localized hedonic island in the medial shell of nucleus accumbens helps generate the pleasure gloss that opioid circuits paint onto sweet sensation to make it positively "liked."

1. Larger Opioid Sea of "Wanting" in Nucleus Accumbens

In addition to causing increased "liking," almost all opioid microinjections in nucleus accumbens also caused the rats to eat more food soon afterward, increasing "wanting" for food reward too, even outside the hedonic hot spot (and even in the suppressive cold spot). The appetite-increasing zone was much larger than the pleasure hot spot: it was as though a large opioid sea of "wanting" in the shell of nucleus accumbens contains a smaller opioid island of "liking" for the same reward (Peciña and Berridge, 2005).

The large size of the opioid "wanting" zone fits with many earlier results from elegant appetite-mapping studies that have shown that many limbic brain structures support opioid-increased eating of palatable sweet or fatty foods (Gosnell and Levine, 1996; Kelley et al., 2005b; Levine and Billington, 2004; Will et al., 2003, 2004; Zhang and Kelley, 2000). But the opioid "liking" island identified by Peciña indicates that only in the rostral/dorsal hedonic hot spot does opioid activation in medial shell also increase "liking" reactions to food at the same time as increasing "wanting" to eat.

2. Implications for Normal Eating and Disorders

So it seems that the same μ-opioid neurotransmitter stimulation does different psychological things in different spots within the same brain structure. This leads us to outline several speculative possibilities by which eating disorders might relate endogenous opioid neurotransmission in nucleus accumbens shell.

First, one could speculate that pathological overactivation in regions of the opioid hedonic hot spot might cause enhanced "liking" reaction to taste pleasure in some individuals. An endogenously produced increase in opioid tone there could magnify the hedonic impact of foods, making an individual "like" food more than other people, and "want" to eat more.

A second and alternative speculative possibility is that activation in the opioid sea of "wanting" outside the hedonic island could cause people to "want" to overeat palatable, without making them "like" food more. If so, the preceding results would predict that this increased appetite would occur from excessive opioid function in a relatively large region of nucleus accumbens shell. The resulting "wanting" to eat would occur without any concomitant increase in the perceived palatability of food if the major locus of elevated activity lay outside the anterior and dorsal region of medial shell.

3. Beyond Opioid "Liking": Other Hedonic Neurotransmitters in Nucleus Accumbens?

Opioid activation is only one type of neurochemical signal received by neurons in the shell nucleus accumbens. Are any others able to modulate "liking" reactions to food hedonic impact? The answer appears to be yes.

4. Cannabinoid "Liking"

Neurons in the nucleus accumbens also manufacture an endogenous cannabinoid neurochemical called anandamide, the CB1 receptors for which are activated by active ingredient THC in the drug, marijuana. Anandamide has been suggested to be a reverse neurotransmitter, which would be released by a target neuron in the shell to float back to nearby presynaptic axon terminals.

Marijuana, in addition to its own central rewarding effects, is widely known to cause an appetite-stimulating effect sometimes called the "marijuana munchies," raising intake especially of palatable snack foods. Several investigators have suggested that endogenous cannabinoid receptor activation stimulates appetite in part by enhancing "liking" for the perceived palatability of food (Cooper, 2004; Dallman, 2003; Higgs et al., 2003; Kirkham and Williams, 2001; Kirkham, 2005; Sharkey and Pittman, 2005).

A more recent taste reactivity study by Jarrett and Parker found that THC causes increased "liking" reactions to sugar tastes in rats, just as opiate drugs do (Jarrett et al., 2005). Focusing on natural endogenous brain cannabinoids, a microinjection study by Stephen Mahler and Kyle Smith in our laboratory pinned the neural causation of cannabinoid "liking" on activation of natural anandamide receptors in the nucleus accumbens shell (Mahler et al., 2004). Microinjections of anandamide directly into the medial shell of nucleus

accumbens promoted positive "liking" reactions to the pleasure of sucrose taste.

The ability of natural anandamide to magnify the hedonic impact of natural food reward raises interesting questions about whether natural sensory reward functions will be disrupted in people by taking drugs that have been proposed to help dieters or addicts suppress their excessive consumption by blocking the natural CB1 receptors for anandamide and other endogenous cannabinoids (Cooper, 2004; Higgs et al., 2003; Kirkham and Williams, 2004). The answer is currently not known: the fact that a brain event can cause enhanced pleasure (i.e., sufficient cause for hedonic impact) does not necessarily mean that the brain mechanism is needed for normal pleasure (i.e., necessary cause for hedonic impact). The two questions must be separately answered by future research.

In either case, it appears that the cannabinoid pleasure zone overlaps with the opioid hedonic hot spot described previously in medial shell of nucleus accumbens. That suggests that both natural opioids and natural cannabinoids act in overlapping hedonic islands of the nucleus accumbens shell. In those overlapping zones, both neurochemicals act to enhance "liking" for the hedonic impact of natural sensory pleasures.

This raises possibilities for potential interactions between these two neurochemical forms of pleasure gloss, opioid and cannabinoid (Vigano et al., 2005). And there are additional "liking" interactions to consider too. Beyond neurotransmitters related to classic drugs of abuse, other neurotransmitters such as GABA are also used by the same neurons in the medial shell. These neurons both send and receive GABA signals. In addition, these neurons receive further neurochemical inputs, such as glutamate from the neocortex, hippocampus, and basolateral amygdala, and dopamine from mesolimbic neurons in the midbrain ventral tegmental area.

Of these various neurochemical signals, GABA at least can potently alter "liking" reactions to the hedonic impact of sugar tastes. But the positive/negative valence of GABA on "liking" versus "disliking" depends very much on precisely where in the shell the GABA is (Reynolds and Berridge, 2002). For example, GABA stimulation in the anterior subregion of the shell can increase "liking" reactions as well as food intake. GABA in most of the front half of the shell increases food intake without increasing "liking" reactions to hedonic impact, a bit like opioid activation in much of the shell described before. And GABA delivered to the posterior half of the shell dramatically suppresses intake, and makes sweet tastes "disliked," reversing their usual hedonic impact (Reynolds and Berridge, 2002).

It remains to be known whether similar changes in "liking" are evoked by nucleus accumbens glutamate blockade, by microinjections of a drug that blocks AMPA receptor signals, and so which may similarly hyperpolarize neurons in medial shell. However, glutamate AMPA blockade does alter eating behavior and food intake in ways similar to GABA (Reynolds and Berridge, 2003), which increases the plausibility that "liking" might be modulated by glutamate just as "wanting" is. The role of cortico-amygdala-hippocampal glutamate signals to nucleus accumbens in modulating "liking" reactions to hedonic impact of sweetness is a topic of substantial interest.

E. Ventral Pallidum: "Liking" and "Wanting" Pivot Point for Limbic Food Reward Circuits

Leaving the nucleus accumbens, output projections head to several destinations but the single heaviest projections are posteriorly to two nearby neighbors, the ventral pallidum and lateral hypothalamus. Of these two structures, the lateral hypothalamus has long been famous for roles in food intake and food reward. Lesions of

the lateral hypothalamus disrupt eating and drinking behaviors, sending food and water intakes to zero (Teitelbaum and Epstein, 1962; Winn, 1995). After electrolytic lesions to lateral hypothalamus, rats would starve to death unless they were given intensive nursing care and artificial intragastric feeding.

Decades ago, lateral hypothalamic lesions were thought not only to abolish food "wanting," but also to abolish food "liking" too. Even sweet tastes were reported to elicit bitter-type disliking reactions (Schallert and Whishaw, 1978; Stellar et al., 1979; Teitelbaum and Epstein, 1962). However, it appears that lateral hypothalamus may have been blamed through a case of mistaken identity for the effects of lesions that stretched beyond it in lateral and anterior directions. Early studies on this topic indicated that sucrose "liking" would be replaced by sucrose "disliking" only if the lesion were in the anterior zone of lateral hypothalamus—and not if the lesion were in the posterior part of lateral hypothalamus, where it would produce loss of eating and drinking, but leave "liking" reactions essentially normal (Schallert and Whishaw, 1978). Further lesion studies by Cromwell mapped more carefully the boundaries of sites where neuron death caused aversion, and found that the "disliking" lesions might actually have to be so far anterior and lateral that they actually were outside the lateral hypothalamus itself—and in another structure, now called the ventral pallidum (Cromwell and Berridge, 1993).

Until about 10 years ago the ventral pallidum was known often as the substantia innominata, or brain structure without a name, and earlier than 20 years ago it was often mistaken for part of the lateral hypothalamus, as we have seen. Today it has a name, actually several names that correspond to different divisions of this intriguing part of the ventral forebrain. The chief names today are "ventral pallidum" for the part known to cause "liking" for sensory pleasure, and "sublenticular extended

amygdala" for a bit behind that lies between ventral pallidum and lateral hypothalamus.

Ventral pallidum is the chief target of the heaviest projections emanating from the nucleus accumbens, and so it is the primary output channel through which mesocorticolimbic circuits must work (Zahm, 2000). The ventral pallidum is relatively new on the affective neuroscience scene, but there is reason to believe this chief target of nucleus accumbens is crucial for both normal reward "liking" and for enhanced "liking" caused under some neurochemical conditions.

An astounding fact is that the ventral pallidum is the only brain region known so far where the loss of neurons is capable of abolishing all "liking" for sweetness. It is the only brain site absolutely necessary for normal sucrose "liking" in the sense that damage to it makes "liking" go away (at least for several weeks). Sucrose no longer elicits "liking" reactions from a rat that has an excitotoxin lesion of its ventral pallidum, a type of lesion that selectively destroys the neurons that live in that structure while preserving fibers from neurons elsewhere that are simply passing through. Instead sucrose taste elicits only "disliking" reactions after the ventral pallidal lesion, as though the sweet taste had become bitter quinine (Cromwell and Berridge, 1993).

Ventral pallidum can also generate enhancement of natural pleasure, at least when it is intact. Ventral pallidum contains its own hedonic hot spot where μ opioid activation can increase the pleasure gloss that gets painted on sweetness. In a hedonic mapping study, Kyle Smith discovered that opioid DAMGO microinjections into a hedonic hot spot within the posterior VP caused sucrose to elicit over twice as many "liking" reactions than it normally did (Smith and Berridge, 2005). Opioid activation in the posterior ventral pallidum increased the hedonic impact of the natural taste reward, and also caused rats to eat over twice as much food. The hedonic hot

spot was localized quite tightly within only the posterior one-third of ventral pallidum. If the same opioid microinjections were moved anteriorly toward the front of the structure, it actually suppressed hedonic "liking" reactions to sucrose and suppressed food intake too (Smith and Berridge, 2005).

A final reason to suppose ventral pallidum mediates hedonic impact is that the activity of neurons in the posterior hedonic hot spot appears to code "liking" for sweet and other tastes (Tindell et al., 2004, 2005). Recording electrodes can be permanently implanted in the ventral pallidum, and neurons there fire faster when rats eat a sweet taste. The firing of sucrose-triggered neurons appears to reflect hedonic "liking" for the taste. For example, the same neurons will not fire to an intensely salty solution that is unpleasant (three times saltier than seawater). However, the neurons suddenly begin to fire to the triple-seawater taste if a physiological state of "salt appetite" is induced in the rats, by administering hormones that causes the body to need more salt, and which increase the perceived "liking" for intensely salty taste (Smith et al., 2004). Thus neurons in the ventral pallidum code taste pleasure in a way that is sensitive to the physiological need of the moment. When a taste becomes more pleasant during a particular physiological hunger, in a hedonic shift called "alliesthesia," the ventral pallidum neurons code the increase in salty pleasure. The observation that those hedonic neurons are in the same hedonic hot spot where opioid activation causes increased "liking" reactions to taste suggests that their firing rate might actually be part of the causal mechanism that paints the pleasure gloss onto taste sensation.

1. Speculative Implications for Eating Disorders

Just as for the hedonic island in nucleus accumbens, it is easy to imagine that if a human pathology caused increased opioid activation effects in the posterior ventral pallidum, that change would cause a person to experience foods as more pleasant and would stimulate appetite accordingly. Conversely, if it were possible to target opioid activation to the opposite anterior end of ventral pallidum, both food pleasure and food intake would be expected to be suppressed. Whether either of these events actually occurs in any human eating disorder is unknown. At the moment, they are simply possibilities to be compared against future observations that may carry the answer.

In any case, it seems likely that the hedonic hot spot in ventral pallidum ordinarily interacts together with its counterpart in the nucleus accumbens shell. There are extensive intercommunications between these two brain structures. A consequence is that the two hedonic islands probably actually function together as part of a single hedonic system, in close synchrony with each other. The details of this interaction remain to be unraveled by experiments but when they are, an integrative network of hedonic "liking" likely will be revealed by which opioid limbic circuits modulate the final hedonic impact and appetite for foods.

IV. "WANTING" WITHOUT "LIKING"

A very different product of affective neuroscience studies of taste "liking" reactions is the revelation of a number of false hedonic brain mechanisms, which turn out to mediate motivational "wanting" to eat without mediating hedonic "liking" for the same food. False hedonic mechanisms do not mediate "liking" for sensory pleasures—even though some were once thought to do so by neuroscientists. Their production of "wanting" without "liking" opens up fascinating possibilities for understanding particular pathologies of appetite and desire, including cases of irrational desire.

Perhaps the most famous false hedonic mechanism is dopamine: the mesolimbic projection of fibers to the nucleus accumbens from dopamine neurons in the midbrain ventral tegmental area. Dopamine release is triggered by pleasant foods and many other pleasant rewards, and dopamine neurons themselves fire more to pleasant food (especially when it is suddenly and unexpectedly received) (Ahn and Phillips, 1999; Di Chiara, 2002; Hajnal and Norgren, 2005; Montague et al., 2004; Roitman et al., 2004; Schultz, 2006; Small et al., 2003). Everyone agrees that dopamine release has important consequences on some aspect of reward, but the question is which aspect (Berridge and Robinson, 2003; Everitt and Robbins, 2005). Beyond correlative activations by rewards, the causal importance of dopamine is seen in the well-known observation that drugs that are rewarding or addictive typically cause dopamine activation—either directly or by acting on other neurochemical systems that in turn cause dopamine activation (Everitt and Robbins, 2005; Koob and Le Moal, 2006). Conversely, dopamine suppression reduces the degree to which animals and people seem to want rewarding foods, or rewards of other types (Berridge and Robinson, 1998; Dickinson et al., 2000; Wise, 2004).

The suppression of reward "wanting" by dopamine blockade or loss gave rise decades ago to the idea that dopamine must also mediate reward "liking" (Wise, 1985). The view of most neuroscientists has shifted subsequently, although some correlative evidence collected in more recent years can still be viewed as consistent with this dopamine-pleasure hypothesis of reward. For example, PET neuroimaging studies have suggested that obese people may have lower levels of dopamine D_2 receptor binding in their brains' striatum than others (Wang et al., 2001, 2004b). At first take, if one supposes that dopamine causes pleasure, reduced dopamine receptors in obese individuals can be viewed as

reducing the pleasure they get from food. By that view, reduced pleasure has been suggested to cause those individuals to eat more food in a quest to regain normal amounts of pleasure. A difficulty may arise for this account in that it also seems to require that the less people like a food the more they will eat it. By contrast, much evidence from psychology and neuroscience indicates that reducing the value of a food reward causes reduced pursuit of it as an incentive, rather than increasing pursuit and consumption (Cooper and Higgs, 1994; Dickinson and Balleine, 2002; Grigson, 2002; Kelley et al., 2005b; Levine and Billington, 2004). One might perhaps rescue this anhedonia account of D_2 decrement by supposing that all other life pleasures are reduced even more by dopamine receptor suppression than food pleasure, so that food remains the only pleasure available for consumption. However, we can see that actually getting increased food consumption from reduced pleasure out of any known psychological-brain system of food reward may prove trickier than first appears. So alternatives are worth entertaining too. A reverse interpretation of reduced dopamine D_2 binding in obese people is that the reduction is a consequence of overeating and obesity, rather than its cause. As a parallel example, overconsumption of drug rewards that provide increased stimulation to dopamine receptors eventually causes the receptors to reduce in number, even if dopamine receptors were normal to begin with—this is a down regulation mechanism of drug tolerance and withdrawal (Koob and Le Moal, 2006). So it is conceivable that similar sustained overactivation of dopamine systems by overeating food rewards in obese individuals perhaps could cause a similar eventual down regulation of their dopamine receptors. In a related vein, other physiological aspects of preexisting obesity states might also send excessive signals to brain systems sensitive to body weight, which indirectly cause reduction of D_2 receptor as

a negative feedback consequence or a sort of long-term satiety signal that down regulates incentive systems. These speculative alternatives are enough to illustrate that possibilities exist by which reduced dopamine receptor binding could be a consequence, not the cause, of sustained obesity. Future research will be needed to resolve the fascinating question of whether correlated changes in levels of dopamine receptors is a cause or a consequence of human obesity.

If we turn to evidence from animal studies in which dopamine's causal roles can be manipulated, then dopamine does not appear to be important for "liking" the hedonic impact of food rewards after all. For example, mutant mice that lack any dopamine in their brains remain quite able to register the hedonic impact of sucrose or food rewards (Cannon and Palmiter, 2003; Robinson et al., 2005). Similarly, dopamine suppression or complete lesion in normal rats does not suppress taste "liking" facial expressions elicited by the taste of sucrose (Berridge and Robinson, 1998). Instead, the hedonic impact of sweetness remains robust even in a nearly dopamine-free forebrain (also, still robust is the ability to learn some new reward values for a sweet taste, which indicates that "liking" expressions remain faithful readouts of forebrain "liking" systems after dopamine loss (Berridge and Robinson, 1998).

And conversely, too much dopamine in the brain, either in mutant mice whose gene mutation causes extra dopamine to remain in synapses or in ordinary rats given amphetamine that causes dopamine release (or that have drug-sensitized dopamine systems), show elevated "wanting" for sweet food rewards, but no elevation in "liking" sweet rewards (Peciña et al., 2003; Tindell et al., 2005; Wyvell and Berridge, 2000). Supporting evidence that dopamine mediates "wanting" but not "liking" also comes from PET neuroimaging studies of humans, which report that dopamine release triggered when people encounter a food or drug reward may better correlate to their subjective ratings of wanting the reward than to their pleasure ratings of liking the same reward (Leyton et al., 2002; Volkow et al., 2002).

Thus, the idea that dopamine is a pleasure neurotransmitter may have faded in neuroscience, with only a few hedonia pockets remaining (though dopamine seems important to "wanting" rewards, even if not to "liking" rewards). Separating true "liking" substrates from false ones is a useful step in identifying the real affective neural circuits for hedonic processes in the brain.

A. What Is "Wanting"?

"Wanting" is a shorthand term for the psychological process of incentive salience attribution, which helps determine the motivational incentive value of a pleasant reward (Berridge and Robinson, 1998; Everitt and Robbins, 2005; Robinson and Berridge, 2003; Salamone and Correa, 2002). But incentive "wanting" is not a sensory pleasure. "Wanting" is purely the incentive motivational value of a stimulus, not its hedonic impact.

Why did brains evolve separate "wanting" and "liking" mechanisms for the same reward? Originally, "wanting" might have evolved separately as an elementary form of goal directedness to pursue particular innate incentives even in advance of experience of their hedonic effects. Later incentive salience became harnessed by evolution to serve learned "wanting" for predictors of "liking," following learned or conditioned incentive motivation rules, guided by Pavlovian associations (Berridge, 2001; Dickinson and Balleine, 2002; Schultz, 2006; Toates, 1986). "Wanting" may also have evolved as distinct from "liking" to provide a common neural currency of incentive salience shared by all rewards, which could compare and decide competing choices for food, sex, or other rewards that might each involve partly distinct

neural "liking" circuits (Shizgal, 1997). The important point is that "liking" and "wanting" normally go together, but they can be split apart under certain circumstances, especially by certain brain manipulations.

"Liking" without "wanting" can be produced, and so can "wanting" without "liking." "Liking" without "wanting" happens after brain manipulations that cause mesolimbic dopamine neurotransmission to be suppressed. For example, disruption of mesolimbic dopamine systems, via neurochemical lesions of the dopamine pathway that projects to nucleus accumbens or by receptor-blocking drugs, dramatically reduces incentive salience or "wanting" to eat a tasty reward, but does not reduce affective facial expressions of "liking" for the same reward (Berridge and Robinson, 1998; Peciña et al., 1997).

Dopamine suppression can leave individuals nearly without motivation for any pleasant incentive at all: food, sex, drugs, brain-stimulation reward, etc. (Cannon and Palmiter, 2003; Everitt and Robbins, 2005; Salamone and Correa, 2002; Wise, 2004). Yet, "liking," or the hedonic impact of the same incentives, remains intact after dopamine loss or suppression, at least in many studies where it can be specifically assessed by either facial affective expressions or subjective ratings. Intact "liking" in animal affective neuroscience studies has usually been manifest via normal positive affective facial expressions elicited by the hedonic impact of sweet tastes, or by normal learning about food reward, after dopamine lesion, blockade, or genetic lack (Berridge and Robinson, 1998; Cannon and Palmiter, 2003; Peciña et al., 1997; Robinson et al., 2005). Similarly, in humans, drugs that block dopamine receptors may completely fail to reduce the subjective pleasure ratings that people give to a reward stimulus such as amphetamine (Brauer and De Wit, 1997; Brauer et al., 1997; Wachtel et al., 2002).

Conversely, "wanting" without "liking" can be produced by several brain

manipulations in rats (and perhaps by real-life brain sensitization in human drug addicts, see later). For example, electrical stimulation of the lateral hypothalamus in rats, as mentioned before, triggers a number of motivated behaviors such as eating. In normal hunger, increased appetite is accompanied by increased hedonic appreciation of food, a phenomenon named alliesthesia (Cabanac, 1971). But during lateral hypothalamic stimulation that made them eat avidly, rats facial expressions to a sweet taste actually became more aversive, if anything, as though the taste became bitter (Berridge and Valenstein, 1991). In other words, the hypothalamic stimulation did not make them "want" to eat by making them "like" the taste of food more. Instead, it made them "want" to eat more despite making them "dislike" the taste.

Similarly, eating or pursuit of food caused by a variety of dopamine, GABA, or other neurochemical manipulations of nucleus accumbens or ventral pallidum is not accompanied by enhanced hedonic reactions to the taste of food. Mutant mice with brain receptors that receive more dopamine than normal, because of a genetic mutation that causes released dopamine to remain in synapses, also show excessive "wanting" of sweet reward, while nonetheless "liking" sweetness less than normal mice do (Peciña et al., 2003). Similarly increased food intake without increased "liking" occurs in rats that have received accumbens microinjections of amphetamine or a GABA agonist or opioid agonist in certain shell regions, or ventral pallidum microinjections of a GABA antagonist (Peciña et al., 2003; Peciña and Berridge, 2005; Reynolds and Berridge, 2002; Smith and Berridge, 2005; Tindell et al., 2005; Wyvell and Berridge, 2000). All of these brain manipulations make animals "want" to eat food more, though they fail to make the animals "like" food more (and sometimes even make them "like" it less).

What is "wanting" if it is not "liking?" According to the incentive salience concept,

"wanting" is a mesolimbic-generated process that can tag certain stimulus representations in the brain that have Pavlovian associations with reward. When incentive salience is attributed to a reward stimulus representation, it makes that stimulus attractive, attention grabbing, and that stimulus and its associated reward suddenly become enhanced motivational targets. Because incentive salience is often triggered by Pavlovian conditioned stimuli or reward cues, it often manifests as cue-triggered "wanting" for reward. When attributed to a specific stimulus, incentive salience may make an autoshaped cue light appear foodlike to the autoshaped pigeon or rat that perceives it, causing the animal to try to eat the cue. In autoshaping, animals sometimes direct behavioral pursuit and consummatory responses toward the Pavlovian cue, literally trying to eat the conditioned stimulus if it is a cue for food reward (Jenkins and Moore, 1973; Tomie, 1996). When attributed to the smell emanating from a bakery, incentive salience can rivet a person's attention and trigger sudden thoughts of lunch—and perhaps it can do so under some circumstances even if the person merely vividly imagines the delicious food.

But "wanting" is not "liking," and both together are necessary for normal reward. "Wanting" without "liking" is merely a sham or partial reward, without sensory pleasure in any sense. However, "wanting" is still an important component of normal reward, especially when combined with "liking." Reward in the full sense cannot happen without incentive salience, even if hedonic "liking" is present. Hedonic "liking" by itself is simply a triggered affective state—there is no object of desire or incentive target, and no motivation for reward. It is the process of incentive salience attribution that makes a specific associated stimulus or action the object of desire, and that tags a specific behavior as the rewarded response. "Liking" and "wanting" are needed together for full

reward. Fortunately, both usually happen together in human life.

B. Addiction and Incentive Sensitization

For some human addicts, however, drugs such as heroin or cocaine may cause real-life "wanting" without "liking" because of long-lasting sensitization changes in brain mesolimbic systems. Addicts sometimes take drugs compulsively even when they do not derive much pleasure from them (Everitt and Robbins, 2005). For example, drugs such as nicotine generally fail to produce great sensory pleasure in most people, but still are infamously addictive.

In the early 1990s, Terry Robinson and I proposed the incentive-sensitization theory of addiction, which combines neural sensitization and incentive salience concepts (Robinson and Berridge, 1993, 2003). The theory does not deny that drug pleasure, withdrawal, or habits are all reasons people sometimes take drugs, but suggests that something else, sensitized "wanting," may be needed in order to understand the compulsive and long-lasting nature of addiction, and especially for why relapse occurs even after weeks or months of abstinence from any drugs, and even when addicts do not expect to gain much pleasure from their relapse.

Many addictive drugs cause neural sensitization in the brain mesocorticolimbic systems (e.g., cocaine, heroin, amphetamine, alcohol, nicotine). Sensitization means that the brain system can be triggered into abnormally high levels of activation by drugs or related stimuli. Sensitization is nearly the opposite of drug tolerance. Different processes within the same brain systems can simultaneously instantiate both sensitization (e.g., via increase in dopamine release) and tolerance (e.g., via decrease in dopamine receptors) (Koob and Le Moal, 2006; Robinson and Berridge, 1993, 2003; Vezina, 2004). However, tolerance mechanisms usually

recover within days to weeks once drugs are given up, whereas neural sensitization can last for years. If the incentive-sensitization theory is true for drug addiction, it helps explain why addicts may sometimes even "want" to take drugs that they do not particularly "like." The long-lasting nature of neural sensitization may also help explain why recovered addicts, who have been drug-free and out of withdrawal for months or years, are still sometimes liable to relapse back into addiction.

Sensitization of incentive salience does not mean that addicts "want" all rewards more in a general fashion. "Wanting" increases instead are highly specific, in target object and in time. In target object, only specific conditioned stimuli or cues for reward get attributed with higher incentive salience after sensitization (Tindell et al., 2005; Wyvell and Berridge, 2001). Other unrelated stimuli get no increase at all (e.g., CS-). And when multiple reward targets are available, some targets get much more increase than others (Nocjar and Panksepp, 2002; Tindell et al., 2005). The key to which stimulus becomes "wanted" may lie in Pavlovian learning mechanisms that control the direction of incentive salience attribution, the relative intensities of reward unconditioned stimuli, and in other features that differentially distribute elevated attribution (Berridge and Robinson, 1998; Robinson and Berridge, 1993). This directional specificity may relate to why a drug addict particularly "wants" drug, whereas someone with an eating disorder might particularly "want" food.

In time, sensitized cue-triggered "wanting" is specific to sudden intense peaks that rapidly fall off when the cue is taken away, only to reappear later when it is reencountered again (Tindell et al., 2005; Wyvell and Berridge, 2001). High incentive salience comes and goes with cues for the particularly "wanted" reward (and in people possibly also with vivid reward imagery). This may relate to why addicts are particularly vulnerable to relapse on occasions when they reencounter drug-associated cues such as drug paraphernalia or places and social contexts where drugs were taken before.

C. Is There a Neural Sensitization Role in Food Addictions?

Could incentive-sensitization apply to food addictions too? A conclusive answer cannot yet be given. In favor of the possibility, once sensitized, brain mesolimbic systems do overrespond to cues for sugar rewards with excessive incentive salience (Tindell et al., 2005; Wyvell and Berridge, 2001), and repeated exposure to drugs can produce sensitization-type increases in food intake (Bakshi and Kelley, 1994; Nocjar and Panksepp, 2002).

But does sensitization occur to food incentives in the absence of drugs? More recently, several investigators have suggested that sensitization-like changes in brain systems are indeed produced by exposure to certain regimens of food and restriction that model oscillations between dieting and binging on palatable foods (Avena and Hoebel, 2003a,b; Bell et al., 1997; Bello et al., 2003; Carr, 2002; Colantuoni et al., 2001; de Vaca and Carr, 1998; Gosnell, 2005). These food-sensitization studies have generally shown that when rats are given a number of brief chances to consume sucrose (sucrose binges) a number of accumulating sensitization-like changes are seen, especially when binges are separated by periods of food restriction. These include an increasing propensity to overconsume when allowed, an enduring enhanced neural response to the presentation of food reward and cues, and an over-response to the psychostimulant effects of drugs such as amphetamine (a typical behavioral marker of drug-induced neural sensitization, which suggests a common underlying mechanism).

The possibility of food-induced sensitization suggests the speculative scenario that some diet–binge combinations

conceivably might be able to induce incentive-sensitization for food rewards. That is, individuals who develop neural sensitization profiles to food might come to "want" to eat, perhaps even with compulsive intensity that ordinary individuals do not usually encounter, that outstrips their "liking" for the foods they eat. This is an intriguing possible mechanism for a "food addiction" that certainly deserve further consideration.

However, several cautions are in order before concluding that sensitized food addictions do indeed exist. Repeated food presentation and repeated food restriction both introduce complications that could masquerade as neural sensitization, and these complications could interact. For example, repeated presentation of a palatable food is likely to induce strong Pavlovian conditioning, creating conditioned incentive stimuli that strongly activate mesolimbic systems for incentive salience. It is no surprise that a strong conditioned food incentive would activate dopamine systems more than in an individual that has not undergone the same conditioning experience. It would be an error to mistake conditioned incentive activation of mesolimbic systems via serial experiences for an underlying neural sensitization.

Hunger itself also may promote mesolimbic activation under some conditions (Ahn and Phillips, 1999; Nader et al., 1997; Wilson et al., 1995). The use of food restriction can be expected to enhance the psychological incentive properties of food directly, with consequences for underlying neurobiological activations too. During hunger, sucrose tastes more pleasant than when one is full (alliesthesia) (Cabanac, 1971). When foods become more potent unconditioned incentives, a variety of unconditioned and conditioned food-related stimuli might be expected to more strongly activate mesolimbic incentive systems too (Toates, 1986).

Further interactions between these potential confounds may ensue. If hunger facilitates the unconditioned activation of mesolimbic systems by food, then it may also promote stronger incentive conditioning, leading to later enhanced mesolimbic responses to food conditioned stimuli. Essentially hunger would make food into a better and stronger hedonic reward, which would function as a stronger unconditioned stimulus in a Pavlovian sense to promote greater learning. Animals that repeatedly consume while hungry, in alternating dieting-binge periods, could essentially develop a stronger learned or conditioned incentive motivation triggered by predictive cues than animals that are not food-restricted between periods of sucrose access. Those more strongly conditioned animals might well be expected to show enhanced mesolimbic activation later whenever related cues are presented later. If these things occurred, the resulting picture might look a bit like sensitization, without actually being it.

This is not to discount the possibility that real sensitization might occur induced by diet–binge cycles or similar exposure regimens, or to deny that the studies mentioned before might be examples of food incentive-sensitization. Sensitization-like states do indeed seem to be implicated by certain types of physiological deprivation states (Dietz et al., 2005; Roitman et al., 2002). However, the previous cautions point to the need to better disentangle direct effects of true food-induced sensitization from masquerading confounds of unconditioned deprivation states and ordinary incentive conditioning on mesolimbic activation. Otherwise these confounds could mimic sensitization patterns of enhanced activation, and mislead us into thinking sensitization has occurred when it has not.

Future studies may be able to better assess these potential confounds, and perhaps separate them from sensitization and set them to rest. If so, it will put food-induced sensitization of incentive salience on a stronger empirical basis, and raise

incentive-sensitization as a possible mechanism for food addiction.

D. Cognitive Goals and Ordinary Wanting

Before leaving this topic of incentive salience and "wanting," it is useful to note how the incentive salience meaning of the word "wanting" above differs from what most people mean by the ordinary sense of the word wanting. A subjective feeling of desire meant by the ordinary word wanting implies something both cognitive (involving an explicit goal) and conscious (involving a subjective feeling). When you say you want something, you usually have in mind a cognitive expectation or idea of the something-you-want: a declarative representation of your goal. Your representation is based usually on your experience with that thing in the past. Or, if you have never before experienced that thing, then, the representation is based on your imagination of what it would be like to experience. In other words, in these cases, you know or imagine cognitively what it is you want, you expect to like it, and you may even have some idea of how to get it. This is a very cognitive form of wanting, involving declarative memories of the valued goal, explicit predictions for the potential future based on those memories, and cognitive understanding of causal relationships that exist between your potential actions and future attainment of your goal.

By contrast, none of this cognition need be part of incentive salience "wants" discussed before (Berridge, 2001; Dickinson and Balleine, 2000). Incentive salience attributions do not need to be conscious and are mediated by relatively simple brain mechanisms (Berridge and Winkielman, 2003). Incentive salience "wants" are triggered by relatively basic stimuli and perceptions (not requiring more elaborate cognitive expectations). Cue-triggered "wanting" does not require understanding of causal relations about the hedonic outcome. Sometimes as a result of this difference, as described for addiction, excessive incentive salience may lead to irrational "wants" for outcomes that are not cognitively wanted, and that are neither liked nor even expected to be liked.

Behavioral neuroscience experiments have indicated that these forms of wanting may depend on different brain structures. For example, incentive salience "wanting" depends highly on subcortical mesolimbic dopamine neurotransmission, whereas cognitive forms of wanting depend instead on cortical brain regions such as orbitofrontal cortex, prelimbic cortex, and insular cortex (Corbit and Balleine, 2003; Dickinson et al., 2000; Rolls, 2005). The implication is that there may be multiple kinds of wanting, with different neural substrates (Berridge, 2001).

If eating disorders involve a pathology in a particular "wanting" system such as incentive salience, it would be possible that such an individual would "want" to eat food at the same time that they cognitively do not want to eat, and when "liking" would not be enhanced. In other words, the sight, smell, or vivid imagination of food could trigger a compulsive urge to eat, even though the person would not expect to find the experience very pleasurable. Neural sensitization of incentive salience systems, if it truly happens in any eating disorder, might be one way by which excessive "wanting" to eat could generate excessive food intake.

V. A BRIEF HISTORY OF APPETITE: FOOD INCENTIVES, NOT HUNGER DRIVES

To place into a better perspective the role of "liking" and "wanting" mechanisms we have discussed, it might be helpful to consider here a brief overview of how psychologists and neuroscientists' view of appetite has evolved in recent decades. For many years it was thought that eating

behavior is driven directly by hunger drives, and that food was a reward because it reduces hunger drive. But actually, physiological hunger works primarily by modulating food incentive values, not driving behavior directly through deficit or drive signals.

And food is rewarding primarily because of its hedonic value in taste, texture, and the act of eating, not by its eventual drive reduction. A vivid early example against pure drive reduction is the anecdotal medical case of a man named Tom, from the timber and mining frontier of upper Michigan a century ago, whose esophagus was permanently damaged in childhood when he accidentally drank scalding soup without knowing it was too hot (Wolf and Wolff, 1943). The burn sealed his esophagus and, thereafter, blocked the passage of food to the stomach. To help him live, a surgical opening or gastrostomy fistula was implanted in his stomach, and he was sustained afterwards by placing food and drink directly through the fistula into his stomach. There was no longer any apparent purpose in putting food in his mouth first because food in the mouth could not descend though the closed esophagus.

Yet, Tom insisted on munching food at meals, when he would chew and then spit out the food before placing it in his stomach. Why? Because "introducing (food) directly into his stomach failed to satisfy his appetite" (p. 8, (Wolf and Wolff, 1943)).

A. Separating Reward and Drive Reduction

The most important evidence against drive reduction concepts came in the 1960s from studies of brain stimulation reward and related studies of motivated behavior elicited by "free" brain stimulation. A single electrode in the lateral hypothalamus could both elicit motivated behavior (if just turned on freely) and have reward or pun-

ishment effects (if given contingent on the animal's response). Many behavioral neuroscientists of the time believed in drive reduction theory. So, at first, they expected to find that the brain sites where stimulation would reduce eating (presumably by reducing drive) would also be the sites where stimulation was rewarding (again, presumably by reducing drive). Conversely, they believed the opposite would be true too. They expected to find that punishing electrodes would sometimes activate drives like hunger.

The best descriptions of these beliefs come from the experimenters' own words. As James Olds (the codiscoverer of brain stimulation reward; (p. 89, (Olds, 1973)) put it, he was originally guided by the drive reduction hypothesis that an "electrical simulation which caused the animal to respond as if it were very hungry might have been a drive-inducing stimulus and might therefore have been expected to have aversive properties." In other words, if the drive reduction theory were true, an "eating electrode" should also have been a "punishment electrode."

Conversely, a "satiety electrode" that stopped eating should have been a "reward electrode." As Miller (pp. 54–55, (Miller, 1973)), a major investigator of brain stimulation effects, recounted later in describing how drive reduction concepts guided his research.

If I could find an area of the brain where electrical stimulation had the other properties of normal hunger, would sudden termination of that stimulation function as a reward? If I could find such an area, perhaps recording from it would provide a way of measuring hunger which would allow me to see the effects of a small nibble of food that is large enough to serve as a reward but not large enough to produce complete satiation. Would such a nibble produce a prompt, appreciable reduction in hunger, as demanded by the drive-reduction hypothesis?

Thus, if the drive reduction theory were true, you might actually be able to watch

hunger drive shrink by recording the shrinking activity of the drive neuron each time a nibble of food reduced that drive and caused reward.

But the drive-reduction theory was not true, and nearly all of the predictions based on it turned out to be wrong. In many cases, the opposite results were found instead. The brain sites where the stimulation caused eating behavior were almost always the same sites where stimulation was rewarding (Valenstein et al., 1970; Valenstein, 1976). Eating electrodes were not punishing electrodes. Instead, the eating electrodes were reward electrodes. Stimulation-induced reward and stimulation-induced hunger drive appeared identical or, at least, had identical causes in the activation of the same electrode. This meant that the reward could not be due to drive reduction. The reward electrode increased the motivation to eat, it did not reduce that drive. Instead reward must be understood as a motivational phenomenon of its own, involving its own active brain mechanisms. This is a reason why many affective neuroscientists of recent decades have rejected drive-reduction explanations of appetite and food reward, and instead focused on understanding hedonic/incentive brain mechanisms of reward in their own right.

VI. CONNECTING BRAIN REWARD AND REGULATORY SYSTEMS

A fascinating final topic is the interaction between brain systems of mesolimbic reward on the one hand and of hypothalamic hunger and body weight regulation on the other (Baldo et al., 2003; Berthoud, 2002, 2004; Kelley et al., 2005b). How do these brain systems connect and influence each other?

Control signals go back and forth between mesolimbic reward systems and hypothalamic systems for hunger regulation. For example, hypothalamic orexin-hypocretin neurons send projections to modulate the nucleus accumbens in ways that might allow hunger states to enhance food reward (Scammell and Saper, 2005), and even interact with other rewards such as drugs (Harris et al., 2005). In return, nucleus accumbens influences hypothalamic circuits. For example, manipulations of nucleus accumbens that cause increased food intake and that modulate reward, such as GABA microinjections into the medial shell, send descending signals that activate orexin neurons in the hypothalamus (Baldo et al., 2004; Zheng et al., 2003).

Neuroscientists have only begun to understand the nature and role of interactions between mesolimbic reward systems and hypothalamic hunger systems, but more recent developments show that such interactions are there and of great importance. They undoubtedly play major roles in modulating the pleasure and incentive value of food rewards during normal hunger versus satiety states, possibly also connecting reward modulation to longer term body weight elevation and dieting states, and finally perhaps even in allowing food reward cues to influence the activation of hunger deficit systems. These interactions also provide avenues, at least in principle, by which eating disorders cause distortion in the function of reward systems, so that they become either exaggerated or suppressed in function. Such interactions will be important to try to understand better in the future.

VII. CONCLUSION

For most people, eating patterns and body weights remain within normally prescribed bounds. Perhaps it is the prevalence of normal body weights, rather than obesity, that should be most surprising in modern affluent societies where tasty foods abound. As is often pointed out, brain mechanisms for food reward and appetite evolved under pressures to protect us from

scarcity. As a result, overeating in the face of present abundance could be an understandable overshoot inherited from our evolutionary past.

When eating patterns and body weight do diverge from the norm, questions arise concerning the involvement of food reward systems in the brain. All eating patterns are controlled intimately by brain mechanisms of food reward, whether those mechanisms operate in normal mode or abnormal modes. A primary signpost to help guide future thinking is to know whether any pathological patterns of eating are caused by identifiable pathologies in brain reward function. Can distorted patterns of eating be corrected by medications that alter brain reward mechanisms? Or are the causes of eating disorders essentially independent of brain reward systems? These remain questions to guide future research on how brain substrates of food reward relate to eating disorders.

Acknowledgments

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