Pleasures of the brain

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Abstract

How does the brain cause positive affective reactions to sensory pleasure? An answer to causation requires knowing not only which brain regions are activated by pleasurable events, but also which regions actually generate the positive affective reactions to them. This paper focuses on brain causation of behavioral positive affective reactions to pleasant sensations, such as sweet tastes. Evidence suggests that activation of a subcortical network involving portions of the nucleus accumbens shell, ventral pallidum, and brainstem causes increased positive affective reactions to 'liked' stimuli. Lesions of ventral pallidum also impair normal sensory pleasure. This network causes core 'liking' reactions, and by connection to other brain systems involved in cognitive representations, may also result in the conscious experience of pleasure.

How does a pleasurable event elicit a positive affective reaction from the brain? In other words, how are positive affective reactions actually *caused*? The causation of positive affective reactions is the central question for this paper.

Affect is key. Emotional reactions typically involve extensive cognitive processing (Clore & Ortony, 2000; Ellsworth & Scherer, in press; Erickson & Schulkin, in press; Parrott & Schulkin, 1993), but affective neuroscience is distinguishable from cognitive neuroscience in that emotional processes must also always involve an aspect of *affect*, the psychological quality of being good or bad (Frijda, 1999; Panksepp, 1998; Zajonc, 1998).

Contemporary affective neuroscience has been somewhat preoccupied with the bad over the good. How the brain produces negative affective reactions such as pain or fear to stimuli that predict pain is relatively well understood, thanks to decades of excellent research (e.g., Fanselow & LeDoux, 1999; LeDoux, 2000; Liebeskind, Sherman, & Cannon, 1982). Yet the causation of positive affective reaction is equally important for affective neuroscience and psychology (Kahneman, Diener, & Schwarz, 1999; Panksepp, 1998).

Measuring positive affective reactions. Affective reactions reflect the affective quality of pleasant or unpleasant events that trigger them, and may be either subjective or objective. Finding the neural causes of positive affective reactions in particular presupposes being able to recognize and measure a reaction to sensory pleasure when it occurs. There are several different approaches to measurement, which tap into different senses of the meaning of positive affect. These measurement approaches are: 1) measurement of subjective ratings to assess conscious pleasure in human subjects, 2) measurement of instrumental performance in rewarded tasks to assess neurobehavioral systems of reward in animals and humans, or 3) measurement of elicited behavioral or physiological affective reactions to the immediate hedonic impact of sensory pleasure in animals and humans. Each measure is appropriate to certain questions about positive affect, but no measure can be applied to all questions. It is important to understand the special uses and limitations of each approach.

Subjective ratings of conscious pleasure. By the term positive affect, almost everyone means a *conscious feeling of pleasure*, a quintessentially subjective phenomenon. Conscious pleasure is

the only form pleasure of which many people can conceive. Take away consciousness and for them you take away also the meaning of pleasure, for they regard an unconscious pleasure as a contradiction in terms (even if they allow other implicit psychological processes such as unconscious memory, unconscious perception, etc.) This tendency to define *affective as necessarily meaning a conscious feeling* of pleasure/displeasure is exactly why many have sometimes asserted that "affect can be studied only in humans who can say what they feel." The insistence on conscious feeling as the defining feature of affect is understandable, but in my view mistaken.

Unspeakable "feelings": unconscious core processes of affective reaction. Implicit or unconscious affective psychological processes may occur in the mind and brain independent of conscious feelings (Berridge, 1999; Damasio, 1999; LeDoux, 1996; Zajonc, 2000), just as psychological processes of perception, learning, and cognition can occur independent of any conscious awareness of them (Kihlstrom, 1999). "Core processes" of implicit affective reaction are manifest in observable affective reactions. Core 'liking' ordinarily might help cause conscious pleasure, though it is itself not intrinsically accessible to subjective introspection (Berridge & Winkielman, 2000; Damasio, 1999; LeDoux, 1996; Zajonc, 2000).

To suggest the possibility of unconscious affective reactions as real psychological processes is not in any way to diminish the crucial importance of conscious feelings of pleasure. I fully concur with the reader who believes that conscious pleasure has a special status and interest for psychology and neuroscience, and deserves special consideration on its own. But there are several reasons why an affective neuroscience or hedonic psychology of pleasure would be wise not to restrict itself to the study of subjective reports.

A core process view posits that conscious introspection lacks direct access to basic hedonic processes, just as it lacks direct access to many cognitive processes, and must interpret affective reactions cognitively as it must interpret perception of other complex stimuli (Berridge & Winkielman, 2000; Wilson, Lindsey, & Schooler, 2000; Zajonc, 2000). The primary limitation of subjective reports of conscious pleasure is that they are limited to just that – the subset of pleasurable feelings that can be consciously accessed or even invented by cognitive processes of representation and self-monitoring. Yet some positive affective reactions may occur to an event without a person being aware of that causal event (Winkielman, Berridge, & Wilbarger, 2000; Winkielman, Zajonc, & Schwarz, 1997; Zajonc, 1980; Zajonc, 2000). Further, in a subset of those cases, the person might not even be aware of having an affective reaction at all (Berridge & Winkielman, 2000; Damasio, 1999; Fischman & Foltin, 1992; Winkielman et al., 2000). For example, a photograph of a happy facial expression that is presented subliminally and masked may fail to produce any conscious report of affect or emotion or shift in hedonic feelings at all, yet still increase a person's subsequent behavioral consumption of a fruit drink and subjective affective rating of it later (Winkielman et al., 2000). Conversely, a subliminally presented angry face can reduce those subsequent reactions to the affect-laden drink, again without producing any conscious emotion at the moment the face is presented (Winkielman et al., 2000).

Behavioral and physiological measures of positive affective reaction. Behavioral and physiological measures provide one means of studying affective reactions whether or not a conscious affective reaction is reported. Physiological autonomic and brain imaging techniques provide other potential measures. These measures can be applied to animals as well as humans, which considerably extends the range of opportunity available for probing the brain mechanisms involved. The question of what an animal feels is fascinating, though difficult, but the question of how an animal reacts through behavioral and physiological responses to a positive affective event is as approachable and objectively answerable as the question of how a person reacts.

Diverse measures and concepts of positive affect in animals. Even affective neuroscientists who primarily study positive affective reactions and reward in animals have taken a spectrum of different approaches to measure and understand positive affective reactions and their brain mechanisms. For example, Rolls takes an essentially behaviorist approach, identifying positive affective reaction or emotion with the occurrence of behavioral response reinforcement (e.g. Rolls, 1999). "The essence of the proposal is that *emotions are states elicited by rewards and punishments*, including changes in rewards and punishments. A *reward is anything for which an animal will work*. A punishment is anything that an animal will work to escape or avoid" (p. 60-61 Rolls, 1999). Thus for Rolls' positive emotion is the state produced by any worked for reinforcer.

This approach defines the *psychological process* of positive affect in terms of the *behavioral event* that caused it (e.g. presentation of a worked-for reward). It does not attempt to identify intrinsic psychological features of positive affective reaction that distinguish it from other psychological processes elicited by the reinforcer. This approach has the advantage of simplicity and behavioral objectivity, but gives little insight into the affective nature of emotion for those who wish to understand its psychology. Defining positive emotion as reinforcement also encounters empirical difficulties (as Rolls acknowledges) in certain cases where response reinforcement learning is dissociated from other aspects of positive emotion (i.e., positive affective reaction in absence of behavioral reinforcement, or conversely, behavioral reinforcement in absence of positive affective reaction).

A nearly opposite stance is taken by Panksepp, who has argued that positive affect is similar in animals and humans, and that a positive affective reaction is always a conscious feeling (Panksepp, 1998). For example, in defining a brain system of emotion, he stipulates it must be "capable of elaborating *subjective feeling states* that are affectively valenced" as one of the "neural criteria that provisionally define emotional systems" for both animal and human brains (p. 48, Panksepp, 1998; italics added). This approach has the advantage of positing a degree of psychological richness that might more closely approach reality, and attempts to specify particular psychological features of emotion, such as affectively valenced subjective feelings. However, a subjectivist definition has a cost. It does not easily distinguish between emotional reactions that are conscious and those that are not, and indeed may not conceive at all of unconscious emotional processes. That is because the assertion "emotional circuits must be able to generate affective feelings" (p. 49, Panksepp, 1998) appears to exclude circuits as not emotional if they don't directly generate affective feelings.

My colleagues and I have taken a different "core process" approach to thinking about the brain and positive affective reactions, and to measuring them (Berridge, 1996, 1999; Robinson & Berridge, 2000; Winkielman et al., 2000). Our view of positive affective reaction is that psychological reality lies somewhat intermediate between the behaviorist reinforcement definition and the subjective feeling definition (Berridge, 1996, 1999). A 'core process' approach aims to identify psychological features of affective reactions, both conscious and unconscious. This approach recognizes the special status of conscious pleasure or liking as a subjective positive affective, but it also recognizes the possibility that unconscious affective core processes exist, such as 'liking'. Core 'liking' processes are not manifest directly in conscious awareness, yet truly cause positive behavioral affective reactions. Unconscious 'liking' is a legitimate psychological process in the same sense that unconscious or implicit perception, implicit memory, and implicit cognition are psychological processes --- with the additional feature that emotional core processes also have positively or negatively *affective* features. Unconscious core processes of 'liking' may ordinarily be a cause of conscious liking or subjective pleasure, when they activate further psychological processes of conscious awareness involving additional brain systems. But by itself core 'liking' can sometimes remain unconscious (Berridge & Winkielman, 2000).

In addition, our core process view distinguishes 'liking' incentives from 'wanting' incentives and from other psychological core processes contained within reward (Berridge & Robinson, 1998; Robinson & Berridge, 2000). The crucial feature of the core process of 'liking' is that it is reflected in positive patterns of behavioral affective reactions to the immediate hedonic impact of pleasurable events, regardless of whether those positive affective processes are directly represented in conscious awareness, and whether or not the 'liked' event is worked for or 'wanted'.

A prototype positive affective reaction: hedonic reactions to sweet taste. The facial expression of a human infant to a sweet taste is one example of a behavioral positive affective reaction to sensory pleasure (Steiner, 1973; Steiner, Glaser, Hawilo, & Berridge, 2001). Normal human infants have essentially just two patterns of facial expressions to tastes: positive affective versus negative affective (Figure 1). The sweet taste of sugar normally elicits positive affective patterns of lip smacking and rhythmic series of tongue protrusion movements. These are accompanied by relaxation of the muscles of the middle face, and on rare occasions, even a smile that can extend to the full classic Duchenne type involving simultaneous crinkling of the corners of the eye (Steiner et al., 2001). By contrast the bitter taste of quinine elicits negative or aversive gapes, and complex grimaces involving retraction of the lips, 'scrinching' of the brows and nose, flailing of the hands, and shaking

of the head. Salt, sour, water, and other tastes evoke various degrees of intermediate reactions between these positive and negative extremes (Ganchrow, Steiner, & Daher, 1983; Rosenstein & Oster, 1988; Steiner et al., 2001).

Insert Figure 1 about here

Although elicited by taste sensations, the pattern is an *affective reaction* to their hedonic impact and not a *sensory reflex* to their distinct taste sensation. No observer can tell what a taste's sensory quality is by watching a human infant's reaction. A mild salt taste can elicit a similar positive reaction to a mild sweet taste. A sour taste, very salty taste, and bitter taste also elicit similar negative reactions. But an observer can be quite confident in inferring whether the infant '*likes'* a taste based on her or his facial expression, depending on whether it is positive or negative (for reviews of evidence on facial reactions to taste 'liking', see Berridge, 2000; Steiner et al., 2001).

Many nonhuman species from primates to rodents also display facial affective reactions to taste, with a degree of similarity to human expression that corresponds closely to their taxonomic or evolutionary distance from humans (Berridge, 2000; Steiner et al., 2001). Chimpanzees, orangutans, and gorillas, which are all great apes, have positive and negative affective reactions that are remarkably similar to those of humans (Steiner et al., 2001). Humans and great apes belong to the same taxonomic superfamily of hominoids, making us closely related, and distinct from other primates such as monkeys. Orangutans and chimpanzees, when sampling sweet tastes, even show occasional symmetrical raisings of their mouth corners into a smile (although the smiling movements of the lips and mouth by great apes are never accompanied by the eye crinkle used for human Duchenne-style happy smiles). Conversely, great apes show some middle-face expressions of negative affective reaction to bitter tastes similar to those of humans (Steiner et al., 2001).

Primates that are not apes, such as Old World monkeys from Africa and Asia or New World monkeys from central or South America, are more distantly related to humans. They lack the middle-face affective reactions of hominoids, due in part to differences in their facial musculature (Steiner et al., 2001). But Old World and New World monkeys show virtually all of the other positive and negative affective reactions to tastes of human infants and great apes. For example, sweet tastes elicit positive affective patterns of repeated, rhythmic tongue protrusions. By contrast, bitter tastes tend to elicit negative affective reactions of gapes, headshakes, and other aversive components from both Asian/African and American monkeys. In addition, monkeys that evolved in Asia and Africa have certain shared reactions that are distinct to them alone, whereas monkeys that evolved in the Americas have their own unique affective reaction components (Steiner et al., 2001).

Evolution seems to have given all primates a common set of basic affective reactions, and to have made minor modifications of expression for each evolutionary subgroup, imposing slight variations on a common pattern of affective reaction. And primates are not alone in their capacity for behavioral affective reactions. Even from rats, sweet tastes elicit positive affective reactions, such as a series of rhythmic tongue protrusions, whereas bitter tastes elicit negative affective reactions, such as gapes, head shakes, and arm shakes (Berridge, 2000; Grill & Norgren, 1978). The rats' affective reactions have underlying parameters (e.g., allometric timing) identical to humans and primates, indicating that they may be homologous or derived from the same evolutionary source and produced by similar neural systems (Steiner et al., 2001). For humans and animals alike, these homologous affective reactions reveal positive versus negative valence in the immediate hedonic impact of any taste.

In affective neuroscience studies that use rats as subjects, the eliciting taste stimulus can be controlled typically by delivering the taste-containing solution directly into the mouth via implanted oral cannulae (Grill & Norgren, 1978). The onset, quality, quantity and duration of an eliciting gustatory stimulus can thus all be controlled. Positive affective reactions are videotaped for objective quantitative analysis later. My own laboratory has focused on these affective reactions to taste because they are highly sensitive to neural manipulations, as well as being quantifiable measures of 'liking'. That makes them suitable for use in identifying the underlying brain substrates that generate a positive affective reaction to sensory pleasure (Berridge, 2000).

Other behavioral measures of positive affective reaction in animals. Are there other objective affective reactions that reliably reflect the positive affective impact of an event? If so, then those affective reactions too could be used to verify brain mechanisms of positive affective reaction.

A few new behavioral and physiological candidates may be on the horizon. For example, building on early suggestions by Jurgens and colleagues that vocalizations of monkeys reflect positive emotion when elicited by rewarding brain stimulation (Jurgens, 1976), Panksepp and colleagues suggest that 50 kHz ultrasonic vocalizations is a form of "tickle-induced 'laughter'" in rats that may reflect "fundamental brain processes for joyful affect" (p. 183, Panksepp, 2000). Such vocalizations have been reported especially during play, or during anticipation just before predicted rewards, or during physical tickling (Knutson, Burgdorf, & Panksepp, 1998, 1999; Panksepp, 1998, 2000). Panksepp argues that "such laughter responses may arise from the neuronal infrastructure of joy within the mammalian brain" (p. 184, Panksepp, 2000). The suggestion that ultrasonic 50kHz vocalizations by rats might reflect a specific form of positive affect such as "joyful affect" is intriguing. On the other hand, 50 kHz vocalizations also are emitted by rats in aggressive situations when one rat invades the home territory of another (Haney & Miczek, 1993; Thomas, Takahashi, & Barfield, 1983). An aggressive situation seems potentially complex, and might involve both negative and positive processes, or even mostly negative ones. If so, one might hesitate to infer that an intruding rat is in a state of unalloyed "joyful affect". In any case, the story of 50 kHz vocalization continues to unfold, and more information will be useful to evaluate its affective significance.

Physiological measures of positive affective reaction

Physiological reactions (e.g., EEG, galvanic skin response), brain imaging techniques (e.g., PET, fMRI), and neuronal monitoring techniques (e.g., electrophysiological recording) provide another potentially exciting means to objectively measure positive affective reactions (Bechara, Damasio, Tranel, & Damasio, 1997; Davidson & Sutton, 1995; Fox & Davidson, 1986; Larsen & Fredrickson, 1999). Central measures of brain activation have special potential to reveal positive affective reactions, and have been used to detect individual differences in human affective reactions representing individual affective styles (Davidson & Sutton, 1995). Of course, the difficult challenge is to identify which physiological or neural reactions are reliable markers for positive affect in particular (versus markers of other processes evoked by the stimulus), but several promising ones have been suggested (see Davidson, this volume and Damasio, this volume, Damasio et al., 2000; Davidson & Sutton, 1995).

Conceptual issues for affective & cognitive neuroscience: What does it mean to mediate pleasure? A major conceptual issue for the science of mind-brain relations concerns the idea that brain systems mediate psychological functions such as positive affect. On the surface "to mediate" seems clear enough, and is commonly used without further definition. But the concept actually has several possible meanings, which can be mixed, leading to confusion. A better understanding of mind brain relations can be gained by keeping clear the different meanings (Berridge, in press-a; Sarter, Berntson, & Cacioppo, 1996).

Meanings of mediate: Neural consequence, sufficient cause, and/or necessary cause When cognitive, affective, or behavioral neuroscientists assert that a brain structure mediates a psychological process they generally mean one or more of three things, which I will call *neural marker, sufficient cause*, and *necessary cause* definitions. Often all three meanings are meant simultaneously. But these meanings need not and sometimes do not go together. So it is helpful to consider the differences among these meanings before we attempt to answer the question of which brain systems mediate positive affective reactions.

1) To mediate as a *neural marker* means to be a brain correlate or consequence of a psychological process. It requires merely that the brain structure be activated as a marker whenever the psychological process occurs (e.g., a positive affective reaction). Correlated activation might sometimes also reflect causation of the psychological process, but alternatively might instead reflect only a consequence of the psychological process (or a second consequence of the eliciting stimulus). If only a consequence, then the neural activation would not be necessary for or sufficient to cause the process, even though activation typically co-occurs with the affective reaction. Correlation is thus an open-ended or ambiguous category of mediation, which contains several quite different possibilities regarding causation.

The question of neuropsychological *causation* requires additional evidence (beyond correlation) that a manipulation of the brain activation actually has causal effects on a positive affective reaction.

2) We can define a *sufficient cause* in this context to mean that the *neural event is sufficient to cause the generation of the psychological process* (in an otherwise normal brain – that is, in the absence of other simultaneous brain manipulations or lesions). A neural system that is a sufficient cause for positive affective reactions will result when activated in increased positive affective reaction.

3) To be a *necessary cause* for positive affective reactions means something slightly different regarding a brain system. It means that the *integrity of that brain system is necessary in order to have normal positive affective reactions*. In other words, damage to that neural system will eliminate or diminish positive affective reactions even to stimuli that are ordinarily quite pleasant.

Necessary causation is typically inferred from studies of brain damage in humans or animals that disrupt a normal psychological function. By contrast, sufficient causation is inferred from studies that produce an enhanced psychological effect after activation of a neural system (e.g., by drug microinjections or electrical stimulation). Neural marker/correlation is inferred from studies that measure brain activation correlated to a psychological process (such as PET or fMRI neuroimaging studies in humans, or electrophysiological or neurochemical activation studies in animals).

Brain causation of positive affective reaction

Now we are ready to examine more closely which brain systems actually *cause* positive affective reactions to sensory pleasure, either as sufficient causes for super-normal 'liking' or necessary causes for normal pleasure. We will consider specifically several brain systems that are thought to be involved in positive affect: prefrontal and cingulate cortex, the nucleus accumbens and its mesolimbic projections, lateral hypothalamus and other structures associated with brain stimulation reward, the ventral pallidum, and the brainstem (especially the parabrachial nucleus).

Insert Figure 2 about here

Orbitofrontal cortex (Prefrontal cortex). Activation of the prefrontal cortex, especially its orbitofrontal or bottom region positioned close above the eyes, has been implicated as a neural marker for diverse positive and negative aspects of emotional response (for reviews, see Bechara, Damasio, & Damasio, 2000; Damasio, 1999; Rolls, 1999). Regarding positive affective reactions to pleasant events in particular, human brain imaging PET and fMRI studies find responses in orbitofrontal cortex to cocaine and other rewarding drugs (Breiter et al., 1997; Firestone et al., 1996; Volkow et al., 1996), pleasant tastes and odors (Zald, Lee, Fluegel, & Pardo, 1998; Zald & Pardo, 1997), pleasant touch (Francis et al., 1999), pleasant music (Blood, Zatorre, Bermudez, & Evans, 1999), and even winning money (Thut et al., 1997).

Animal studies of brain activation support a role for orbitofrontal activity as encoding reward impact too. For example, Rolls and colleagues report that orbitofrontal neurons of a monkey fire vigorously when it tastes a favorite food, or sees the food (as do neurons in hypothalamus and amygdala) (Rolls, 2000). Orbitofrontal cortex also fires when the monkey sees a reward cue that predicts tasty reward. Most uniquely, Rolls suggests, the firing of neurons in monkey orbitofrontal cortex tracks *changes* in the reward significance of a cue if its predictive value is switched back and forth (predictor vs. nonpredictor) (Rolls, 2000). Orbitofrontal neurons also track other changes in reward value, such as alliesthesia, changes in sensory pleasure of a stimulus (Cabanac, 1971; Rolls, 2000). For example, monkey orbitofrontal neurons reduce firing to food after food's positive affective value is reduced by a physiological shift from hunger to satiety. In rats prefrontal cortex neurons respond to the positive affective value of food, and to changes in its reward value (Bassareo & DiChiara, 1997). Neurons in rat prefrontal cortex also fire action potentials in response to cocaine or heroin (Chang, Janak, & Woodward, 1998) and in response to reward cues (Schoenbaum, Chiba, & Gallagher, 1999).

Consequence versus cause and generation versus use in action. It seems clear that orbitofrontal cortex activation is a good neural *marker* for positive affective reactions (as well as for negative affective reactions). However, orbitofrontal status is less clear as a *cause* for generating positive affective reactions. While there are a few reports that rats will work to administer a microinjection of cocaine or related drugs directly into their medial prefrontal cortex (Carlezon & Wise, 1996; Goeders & Smith, 1983), there is little other evidence regarding sufficient causation. And self-administration itself is open to the question of whether the rats actually 'like' as well as 'want' prefrontal microinjections, though it is at least suggestive for a sufficient cause of positive affective reaction. If so, such causation might be indirect rather than direct. The prefrontal cortex projects massively to the subcortical

nucleus accumbens (Zahm, 2000), and there is strong evidence that neurotransmission in accumbens can be a sufficient cause for positive affective reactions (discussed below, e.g., Peciña & Berridge, 2000). Orbitofrontal cortex might possibly *regulate* activation of positive affective reaction (Davidson, Jackson, & Kalin, 2000) via descending projections to causal systems in accumbens, whether or not orbitofrontal cortex directly generates positive affect itself.

There is less evidence that orbitofrontal cortex is a *necessary cause* for a normal positive affective reaction. Although a degree of apathy and lack of affect is sometimes reported for human patients after damage to the dorsomedial prefrontal cortex, the nearly opposite symptoms of euphoria, impulsiveness, and general emotional disinhibition are more often reported after damage to the ventromedial prefrontal and orbitofrontal cortex (Tucker, Luu, & Pribram, 1995). And even these changes may involve not so much a change in core processes of positive affective reaction themselves, so much as a more subtle change in how patients *act upon their emotions* (see Damasio, this volume, Davidson this volume, and Bechara et al., 2000).

Animals also show subtle evaluative deficits rather than loss of positive affective reactions after prefrontal damage. For example, rats have deficits in cognitively-guided responses that require tracking the changing affective value of an expected reward (such as the reward value of a food after it has been changed by a satiety manipulation or pairing), and in responses based on cognitive representation of the causal contingency between an instrumental act and its outcome (Balleine & Dickinson, 1998; Baxter, Parker, Lindner, Izquierdo, & Murray, 2000). Orbitofrontal cortex thus may play a causal role in generating emotional expectations under some circumstances, in voluntary regulation of emotion, and in generating appropriate strategies relative to an affect-laden goal. But at the present time, there is little reason to believe that prefrontal cortex is necessary to cause any positive affective reaction per se.

Cingulate cortex. Cingulate cortex is a strip of neocortex running front to back along the inner middle surface at the top of the brain. Cingulate cortex, especially its anterior portion, is activated by positive and negative affective stimuli in a manner similar to orbitofrontal or prefrontal cortex (Breiter et al., 1997; Firestone et al., 1996; Mathew, Wilson, Coleman, Turkington, & DeGrado, 1997; Rauch et al., 1999). Cingulate activation is often therefore a neural marker for positive affective reaction.

Little evidence is available to suggest a role for cingulate cortex as a sufficient cause for positive affective reaction. However, it is possible to gain some sense of whether the cingulate cortex is a necessary cause for normal affective reaction from studies of individuals who have undergone deliberate neurosurgical ablation of it, usually as a last attempt to treat intractable pain (or, more rarely, to treat psychiatric conditions such as obsessive-compulsive disorder) (Hay et al., 1993). Cingulate ablation sometimes produces limited relief from these painful conditions, though cingulotomy patients may also have subtle deficits afterwards in attention-related cognitive processes (Cohen, Kaplan, Moser, Jenkins, & Wilkinson, 1999). However, aside from the partial blunting of pain distress, it does not appear that cingulate cortex is a necessary cause for negative affective reactions. More important, there seems to be no strong evidence that it is necessary to cause basic positive affective reactions. Extending our view to animal studies, cingulate cortex damage makes rats respond relatively indiscriminately to both rewarded and nonrewarded stimuli (Bussey, Everitt, & Robbins, 1997) (perhaps consistent with an attentional deficit), but they still approach rewards as readily as normal animals. It seems safe to conclude that cingulate cortex damage does not eliminate core processes of positive affective reaction to 'liked' rewards.

Hypothalamic electrical-stimulation reward. More promising candidates for causes of positive affective reaction come from subcortical brain structures. At first sight, the best sufficient cause for positive affect might seem to be stimulation of the "pleasure centers of the brain" discovered 50 years ago (Olds, 1956). The early discovery by Olds and Milner that rats would work to deliver electrical stimulation to the lateral hypothalamus and nearby septal area (Olds & Milner, 1954), was originally conceived in terms of positive affect and pleasure, as suggested by Olds' "pleasure centers" title. Self-stimulation sites include the ventral tegmentum in the midbrain up through the ventral pallidum, ventral thalamus and nucleus accumbens, and prefrontal cortex (McBride, Murphy, & Ikemoto, 1999; Phillips, 1984; Shizgal, 1999; Yeomans, 1989).

"Pleasure centers" (or pleasure circuits) unambiguously connotes a neural substrate for positive affect. Elicited pleasure was an inference based on observations that brain stimulation served as a potent reward. Rats would quickly

learn to go back to the place they had received the stimulation, or learn to perform a response to activate their own electrode. Because self-stimulation was obviously *wanted* by the rats in some sense, Olds and others inferred that it must therefore also be *liked*.

Liking and wanting go together often enough in everyone's life to give a certain face validity to the assumption that the observation of wanting implies existence of liking. On the assumption that people and animals always like rewards to the degree they want them, many affective neuroscience studies have inferred brain causes of pleasure based on whether rewards were wanted (e.g., Gardner, 1997; Koob & Le Moal, 1997; Shizgal, 1999; Wise, 1985). For example, Peter Shizgal, a leader in the affective neuroscience field of brain-stimulation reward, recently posited that an electrode in the lateral hypothalamus produces a brain state that he calls positive instant utility (Shizgal, 1999). Positive instant utility is conceived by Shizgal to potentiate ongoing action and, if it becomes represented in working memory and is the focus of conscious attention, to cause conscious pleasure. He writes, "instant utility is experienced along an opponent hedonic dimension ("good/bad") while biasing the individual to continue or terminate the current course of action. States and stimuli that produce *positive values of instant utility are experienced as pleasurable*…" (p. 502, Shizgal, 1999) (italics added). In other words, Shizgal posits that lateral hypothalamic stimulation generates a positive utility signal, which if consciously attended to, produces a subjective feeling of pleasure. His inference of pleasure is somewhat similar (though more complex) to that of Olds, who surmised that reward electrodes induced pleasure in rats because they sought out the stimulation.

Shizgal's clear statement is enormously helpful because it brings into light the hypothesis that lateral hypothalamic stimulation causes positive affect, in the strong sense of a pleasurable state. It should be pointed out that Shizgal was writing for a broad audience when he asserted that stimulated positive utility is "experienced as pleasurable", and might not have been so explicit about psychological process if he had been writing solely for behavioral neuroscientists. But explicit statement of hypotheses is a strength, not a weakness, because it clarifies what is really thought about the underlying reality. Many behavioral neuroscientists who study brain self-stimulation behavior (or drug self-administration behavior) in rats probably share at least an implicit form of his pleasure hypothesis. Similar logic applies to many behavioral neuroscientists who activate brain reward systems with pharmacological drug stimulation rather than with electrodes. Although all such behavioral neuroscientists typically restrict themselves to terms such as "reinforcement" or "reward", it is difficult to imagine what they would say differently from Shizgal if asked to explicitly describe exactly what psychological process they think is activated by a reward electrode or reinforcing drug (and behaviorists/reductionists who decline to posit this psychological explanation typically have little or noting to offer in its stead). Not many would posit a specific psychological process other than pleasurable utility as a psychological definition of reward or reinforcement. I say this to make clear that I do not mean to attack Shizgal's position in particular, by singling out his clear statement, but rather to use his commendable candor to highlight the issues involved.

Pleasurable utility can be rephrased as 'liking', if it means a neurally embodied core process of positive affect that under some conditions can rise to conscious pleasure (liking in the ordinary sense). By contrast, a very different psychological alternative is incentive salience, or 'wanting', which my colleagues and I have suggested is the psychological component of reward activated by electrical stimulation of the lateral hypothalamus, and by activation of the mesolimbic dopamine reward system (Berridge & Robinson, 1998; Berridge & Valenstein, 1991; Robinson & Berridge, 2000). Our suggestion extends several earlier views of mesolimbic function and incentive motivation (Fibiger & Phillips, 1986; Panksepp, 1986; Toates, 1986; Valenstein, 1976; Wise, 1985).

'Wanting' is not 'liking'. It is not a sensory pleasure, and is not a core process of positive affect in the sense of an intrinsically hedonic state. It does not potentiate positive affective reactions to pleasure. Instead incentive salience is essentially nonhedonic in nature, even though we believe it to serve as one component of the larger composite psychological mechanism of reward learning and incentive motivation (Berridge & Robinson, 1998).

Incentive salience is a core process of reward that serves to make stimuli and their central representations more attractive (Berridge, 2001). It is especially attributed to conditioned stimuli or reward cues. Encounters with reward cues cause cue-triggered 'wanting' of the associated reward (Wyvell & Berridge, 2000). It

makes cues and their associated rewards more compelling pursuit targets, and can lead even to irrationally intense pursuit if activated highly (Berridge, in press-b; Wyvell & Berridge, 2000). Irrationally intense 'wanting' may well be an important process of a variety of psychological phenomena, including human drug addiction (Robinson & Berridge, 1993, 2000). But incentive salience does not make its targets more pleasurable, nor activate a state of hedonic pleasure. It cannot produce by itself a genuine positive affective reaction no matter how strongly activated (Berridge, in press-b; Berridge & Robinson, 1998; Wyvell & Berridge, 2000).

Which view is correct regarding the reward effects of electrical brain stimulation? Does the electrode activate a neural substrate of 'liking' or merely one of 'wanting' alone? Elliot Valenstein and I addressed this issue in a study of the effect of lateral hypothalamic electrical stimulation on rats' positive affective reactions to pleasantly sweet tastes (Berridge & Valenstein, 1991). We drew upon a well-known property of rewarding hypothalamic stimulation, namely, that it also triggers motivated behavior – most often eating behavior – even if the stimulation is delivered freely (Hoebel & Teitelbaum, 1962; Margules & Olds, 1962; Valenstein, Cox, & Kakolewski, 1970). Based on 'pleasure electrode' interpretations, some affective neuroscientists had suggested that stimulation made rats eat food because it made them 'like' it more (e.g., Hoebel, 1988). But instead, in support of the 'wanting' hypothesis, Valenstein and I found that positive affective reactions of rats to the sensory pleasure of sweetness were not at all increased during lateral hypothalamic stimulation, even for rats who ate avidly during the electrode stimulation. If anything, the electrode increased negative or aversive affective reactions to tastes – despite making the rats eat. Paradoxically, the stimulation made the rats 'want' food that it did not make them 'like'. That paradox poses a distinct problem for the assumption that 'wanting' necessarily implies 'liking', as well as direct evidence against the hypothesis that the behavioral effects of lateral hypothalamic stimulation are due to activation of a positive affect state or "pleasurable utility".

Human brain stimulation: primarily liking or wanting? But rats are not human, and behavioral affective reactions are not subjective pleasure. It is possible that an electrode produces its own subjective pleasure, whether or not it enhances the pleasure of motivated behavior that it prompts individuals to perform (e.g., eating). Insight may be gained by asking people who have experienced rewarding brain stimulation to tell exactly what they felt.

Even though people may not have direct access to underlying core processes of 'liking' and 'wanting', they can at least tell of their own conscious liking and wanting that might be produced in turn by activation of a 'liking' core process. They can certainly say something about the subjective psychological experience of brain stimulation reward. People have been known to press a button that stimulated an electrode in their brain up to thousands of times in succession (Heath, 1972; Sem-Jacobsen, 1976; Valenstein, 1974). Such intense pursuit seems consistent with pleasure electrodes. Yet anyone who looks to the accounts of such people for a clear declaration of exquisite pleasure may be disappointed. Intense pleasure thrills are generally not what is reported.

Humans who have been implanted with rewarding brain stimulation electrodes typically received them either because they already had intractable pain or another neurological or psychiatric disorder (Heath, 1996; Portenoy et al., 1986; Sem-Jacobsen, 1976). Rewarding electrodes have been implanted usually in the ventral subcortical forebrain, in regions ranging from the ventral thalamus to the ventral pallidum or lateral septal area, which correspond closely to the stimulation reward sites of animal studies.

Perhaps the most enthusiastic proponent of the idea that such electrodes actually do produce pleasure thrills in humans was Robert Heath, a psychiatrist and neurologist who implanted dozens of men and women with stimulating reward electrodes. Heath's electrodes were usually directed toward the lateral septal area (Heath, 1972), but he later acknowledged that their sites were as often in the nucleus accumbens, ventromedial caudate, and nucleus basalis of Meynert, among other structures (Heath, 1996).

But what did stimulation of those electrodes actually achieve psychologically? Did these people feel intense pleasure, as has sometimes been asserted? I think not. The patients' reports were actually rather murky, even when vaguely positive. As Heath put it in a retrospective book: "Although descriptions by the patients of their response to the stimulation was usually limited to "I feel good… it must have been something you did," a striking change occurred in attitude. The subjects were much more positive toward the people around them and their general surroundings. Any conversation dealt with

pleasant subjects. Even when pressed to give details of how they felt, however, the simply repeated "I just feel good". (Most of us would probably be hard put to describe pleasurable feelings otherwise)" (p 88-89, Heath, 1996).

We can certainly acknowledge with Heath the difficulty of describing feelings of pleasure, beyond simple exclamations of delight (which seem missing here). But it is also true that it would be difficult to describe 'wanting', or any nonpleasurable yet vaguely positive psychological process, in any terms other than "feels good". How would one describe a sudden feeling that things, people, and places were suddenly more attractive, desirable, and compelling to pursue, and that generally the world was a better and brighter place? Those are the features I conjecture to characterize the subjective experience of an individual who suddenly activates their brain system of incentive salience or 'wanting'. A person who suddenly perceives the world as motivationally brighter and more attractive, and feels a compelling urge to press again the stimulation button, might well say "I feel good" even if no real 'liking' or true affective pleasure had been produced. What else can they say to account for their sudden perceptual brightening and compulsive impulse to press the stimulation button again? Subjective experience is slippery, subtle, and hard to describe – as Heath points out. So how should one interpret reports of "feeling good" during septal/accumbens/hypothalamic/thalamic brain stimulation? How pleasant really was the psychological state produced by activation of the electrode? Perhaps we should examine a few case studies.

One of the most dramatic cases described by Heath was "B-19", a young man treated for chronic depression, delusions, thoughts of suicide, epilepsy, and (circa 1960s) for being gay (Heath, 1972). He voraciously self-stimulated his septal/accumbens/pallidal electrode: "on one occasion he stimulated his septal region 1,200 times, on another occasion 1,500 times, and on a third occasion 900 times. He protested each time the unit was taken from him, pleading to self-stimulate just a few more times." (p. 6, Heath, 1972). In addition, wrote Heath, the stimulation caused "feelings of pleasure, alertness, and warmth (goodwill); he had feelings of sexual arousal and described a compulsion to masturbate" (p. 6). The stimulation evoked strong sexual arousal and interest. But it did not produce pleasurable sexual orgasm, not even after a thousand consecutive stimulations, unless B-19 was allowed to simultaneously masturbate (or to copulate with a prostitute who was persuaded to provide 'therapy' on one occasion, in what must be one of the most astounding accounts ever published in scientific literature) (Heath, 1972; for ethical commentary, see Baumeister, 2000).

Despite Heath's assertion of pleasure, it is not after all clear the patient ever said the stimulation caused a pleasant sensation. There were no exclamations of delight reported, not even a "Oh -- that feels nice!". Instead the stimulation seemed to fail to provide the particular sensory pleasure it made him most eager to pursue. The stimulation did not serve as a hedonic sexual pleasure, and did not substitute for sexual acts. What it did instead was to make him *want* to do sexual acts, and to make a wider array of stimuli sexually arousing (such as heterosexual pornographic films that ordinarily were unexciting to him). Pleasure may well have been deduced by Heath (and even perhaps to an extent by the patient himself), on the same grounds that Shizgal and others surmise that a rat that self-stimulates must activate a neural substrate for pleasurable utility. Namely, on the grounds that brain stimulation *must* be liked if it is wanted a thousand times in a row. Heath simply had no other way to explain it. Still, in this case the actual evidence for true pleasure is equivocal.

Another seemingly promising report comes from different investigators, who documented a case of compulsive electrical brain self-stimulation by a woman patient treated for intractable pain with a stimulating electrode in the ventral posteriolateral thalamus (Portenoy et al., 1986). The electrode did help her a bit with the pain, but it did much more than that. The woman was brought to the attention of Portenoy's team by her family, who complained that while she lived at home with them where she could control the electrode, she would self-stimulate by activating the electrode compulsively and to the exclusion of other normal activities. As described by Portenoy and colleagues: "At its most frequent, the patient self-stimulated throughout the day, neglecting personal hygiene and family commitments… At times, she implored her family to limit her access to the stimulator, each time demanding its return after a short hiatus. During the past 2 years, compulsive use has become associated with frequent attacks of anxiety, depersonalization, periods of psychogenic polydipsia (excessive desire to drink without physical cause), and virtually complete inactivity." (p. 279).

When the electrode was stimulated in the clinic, it produced a strong desire to drink liquids,

and some erotic feelings, as well as a continuing desire to stimulate again. However, "Though sexual arousal was prominent, no orgasm occurred" (p. 279). This is becoming a familiar story.

Here is some more detail: "During the stimulation session, the patient expressed an irresistible urge to momentarily maximize stimulation every 5-10 min. She described erotic sensations often intermixed with an undercurrent of anxiety. She also noted extreme thirst, drinking copiously during the session, and alternating generalized hot and cold sensations" (p. 282).

Clearly a mixture of subjective feelings was produced in the woman by the electrode. These included sexual feelings, a possible source of pleasure if they include actual hedonic feelings. But the description of "erotic sensations" does not seem so pleasant as to be able to account for the intensity of her compulsion to activate the electrode. No report is made of other pleasant sensations or feelings of positive affect. Featured at least as prominently in the description are feelings of anxiety, thirst, and hot and cold sensations – all feelings that might be classed as affectively negative rather than pleasant. We have the difficulty here of dealing only with an observer's account, and not her own words. Still, according to the observer, the woman's intense focus, aside from the electrode itself, was upon drinking and negatively-tinged sensations of "extreme thirst". There is nothing in the phrase extreme thirst to suggest that her copious drinking was motivated primarily by a potentiated pleasure of the drink. As far as one can tell, she didn't want to drink more because the electrode made her like it more. All in all, it is difficult to find in this account any evidence of pleasure thrills sufficiently intense to explain why she should stimulate to the exclusion of everything else. This is not what we deserve to expect from a pleasure electrode – at least, not if the description we have reflects the reality.

What can we conclude from such murky accounts? Not much, I think. There is a need for better psychological investigations of the actual subjective experience of people who have encountered "rewarding" ventral forebrain stimulation. In the meantime, what we are left with is a clouded picture.

These are only two case studies. But I think they are among the very strongest cases that can be presented in support of the "pleasure electrode" hypothesis, because of the compulsive nature or excessive degree to which these people stimulate their own brain, and the reports of some subjective "good feelings". If these cannot stand up to close inspection, there may be none that can.

Should we conclude that it is impossible for a stimulating electrode to elicit a strong, pure thrill of pleasure? Probably not. After all, pleasure is a psychological reality, and it must have a brain substrate. My point is not that pleasure cannot be caused by brain stimulation, nor even that it never has been so caused. Instead, it is simply that intense pleasure actually does not seem to be generally caused, so far as we can tell from the published record, even in cases where people most avidly sought the brain stimulation. And that raises a need for an alternative psychological explanation for why these people self-stimulated so excessively, an explanation not based solely on pleasure (such as activation of a nonhedonic process such as incentive salience or 'wanting'). Note: For readers interested in this issue, my colleague Terry Robinson and I have reviewed in detail more evidence that brain mesolimbic dopamine systems mediate 'wanting' rather than sensory pleasure (Berridge & Robinson, 1998), and implications for understanding the compulsive pursuit of rewards (such as addictive drugs) (Robinson & Berridge, 2000).

True brain substrates for core 'liking'

So how does the brain cause real pleasure? Here is where a core process approach becomes useful to identify true brain causes of positive affective reaction. Observable positive affective reactions to immediate hedonic impact of pleasant stimuli can be quite informative. Once we allow the possibility that people like rats might avidly self stimulate an electrode that does not give them pleasure, we are left in a quandary. When we further allow that people themselves might not always know or be able to say clearly whether the stimulation is pleasurable, we are unable to ascertain in usual ways whether real pleasure has ever been caused by electrical brain stimulation – or by other brain manipulations that are worked for as rewards.

To resolve how the brain *causes* core processes for pleasure it is useful to be able to assess the immediate positive affective impact of pleasant stimuli, the degree to which they are 'liked'. Equipped with a reliable 'liking' measure, we can discover whether a brain manipulation actually makes a '*wanted'* reward into a *'liked'* reward.

'Liking' for sweetness is reflected when a taste elicits positive affective reactions from a human infant, ape, monkey or rat, as discussed above. The immediate hedonic impact or palatability of sweetness can be increased or decreased by brain manipulations, which correspondingly changes the positive behavioral affective reaction. Thus taste reactivity measures of hedonic impact can help build an affective neuroscience understanding of how brains cause core 'liking' for pleasant stimuli such as sweet tastes.

It is an open question whether conscious feelings of pleasure are also produced by each brain manipulation that increases positive behavioral affective reactions to core 'liking'. Conscious liking may or may not accompany a given instance of core 'liking' (Berridge, 1999; Berridge & Winkielman, 2000). For present purposes, it will be enough to identify brain systems that at least cause 'liking' -- whether or not accompanied by conscious liking.

A major enterprise of my colleagues and I has been to identify brain systems that truly cause 'liking' in terms of their neuroanatomical location and neurochemical identity. Our affective neuroscience studies of positive taste reactivity have begun to outline a subcortical brain circuit of neural systems that serve as necessary and/or sufficient causes for positive affective reactions or 'liking' for sweetness. This brain circuit contains the nucleus accumbens shell, the ventral pallidum, and the brainstem parabrachial nucleus, which all are connected together to cause positive affective reactions to 'liked' tastes.

Nucleus accumbens shell: Sufficient cause for positive affective 'liking'. A principal sufficient cause for enhanced sweetness 'liking' appears to be the shell of the nucleus accumbens (Figure 2). Specifically positive affective reactions are increased by activation of opioid neurotransmitter receptors within the medial caudal portion of this brain structure (Peciña & Berridge, 2000).

The nucleus accumbens lies at the front of the brain beneath the neocortex. It is divided into two primary divisions, shell and core. The shell is positioned a bit like an elongated pastry pie shell with core as the pie filling. The shell wraps around the bottom and the sides of the core, as though it held the core within it. But unlike a pie shell, the accumbens shell has its own special psychological functions. The shell is the only accumbens region shown so far to directly cause increases in positive affective reactions to sweet tastes (Peciña & Berridge, 2000). Activation of brain opioid circuitry in the nucleus accumbens shell seems to be a true sufficient cause for 'liking'.

In animal affective neuroscience studies, microinjection of a drug directly into the brain can be made gently and painlessly through previously-implanted brain cannulae. The rat is totally anesthetized weeks before the experiment so microinjection cannula can be surgically placed into the accumbens. When the rat recovers, the microinjection cannula provides a channel directly to the brain structure. If a microinjection of a tiny droplet of a drug that mimics a neurotransmitter is made, it activates receptors for that neurotransmitter specifically on nearby neurons.

Susana Peciña provided the first demonstration that opioid neurons in the shell of the nucleus are a sufficient cause for enhancing positive affective reactions in a dissertation project in our laboratory (Peciña & Berridge, 2000). She showed that a microinjection of morphine into the posterior shell of the nucleus accumbens caused the sweet component of a bittersweet taste to elicit more positive facial affective reactions from rats than it normally would. The sugar taste became more than ordinarily 'liked' within minutes of morphine activation of the opioid receptors in the nucleus accumbens shell. Microinjections also caused the rats subsequently to 'want' to eat more of the food that they now 'liked' more.

In order to be sure that the opioid cause of positive affective reactions was specifically in the shell of the nucleus accumbens, Peciña mapped the precise borders of the positive affect site using a technique based on 'Fos plumes'. Fos plumes are visible markers that show where a drug microinjection activates receptors in the brain. Visualizing them is a bit like dripping food coloring into a glass of water, where drops form distinct plumes for several moments before dispersing (Figure 3). When molecules of a drug or neurotransmitter activate receptors on a neuron, a cascade of biochemical changes triggered in the internal metabolic processes of the neuron can cause activation of 'early intermediate genes', such as c-fos. Gene activation of c-fos causes the production of corresponding Fos protein inside the neuron. Neurons with dense Fos protein can be seen by treating slices of brain tissue with chemicals that causes Fos to stain dark, and then examining the brain slice under a microscope. A distinct 'Fos plume' of stained neurons can be identified on the brain slice (if processed within an hour or so of the microinjection), which shows where the drug microinjection triggered

neurotransmitter receptors sufficiently to cause changes in neuronal function.

Insert Figure 3 about here

When the opioid 'liking' and 'wanting' site was mapped, it appeared restricted to the medial and posterior portion of the shell of the nucleus accumbens (Peciña & Berridge, 2000). Thus the caudal region of the shell of the nucleus accumbens seems to contain special opioid neural circuits where morphine activation is a sufficient cause of enhanced 'liking' for food. This accumbens 'liking' subsystem is embedded in larger mesolimbic neural systems related to 'wanting' for food and other types of reward (Berridge & Robinson, 1998; Everitt et al., 1999; Kelley, 1999; Panksepp, 1998; Wyvell & Berridge, 2000).

An opioid neural circuit in accumbens shell for taste 'liking' is consistent with earlier studies that showed positive affective reactions to sweetness were enhanced by peripheral morphine injections (Doyle, Berridge, & Gosnell, 1993; Rideout & Parker, 1996) and by morphine microinjection into the brain ventricles (Peciña & Berridge, 1995). The same opiate drugs tend to suppress negative aversive reactions, such as gapes, that are normally elicited by bitter tastes (Parker, Maier, Rennie, & Crebolder, 1992), just as they suppress pain. Thus opiate drugs shift all affective reactions to taste towards a positive affective pole, making sweetness generally more 'liked' and bitterness less 'disliked'. Conversely, drugs that block opioid receptors make tastes less 'liked' in rat taste reactivity studies, (Hill & Kiefer, 1997; Parker et al., 1992), and make humans rate sweetness and foods as less pleasant than normal (Drewnowski, Krahn, Demitrack, Nairn, & Gosnell, 1995; Yeomans & Gray, 1997).

Opiate drugs that enhance food 'liking' also cause enhanced food 'wanting', reflected in higher eating (Glass, Billington, & Levine, 1999; Higgs & Cooper, 1997; Hill & Kiefer, 1997; Wise, 1998; Zhang & Kelley, 2000). And accumbens opioid activation is 'wanted' for itself, as animals will work to receive drug microinjections there or in related brain sites, and will approach and return to places where they received the activation before (Phillips & LePiane, 1980; van der Kooy, Mucha, O'Shaughnessy, & Bucenieks, 1982). Thus neurons with opioid receptors in the nucleus accumbens shell appear to be a necessary and sufficient cause for both 'liking' and 'wanting', mediating a general core process of positive affective reaction.

Circuits for feeling: cortical connections with accumbens core affect. A core process view of emotion faces the challenge of understanding how core 'liking' is ever converted to conscious pleasure. This would presumably require secondary modulation of other brain systems that causally mediate conscious feelings. There must be interaction between neural systems that generate consciousness and those that generate core processes of emotion. Similar interaction might also sometimes occur in the reverse direction, when core processes of emotion are subject to voluntary regulation by cognitive systems (Davidson et al., 2000). How could a core process for positive affective reaction, caused in the nucleus accumbens shell, interact with cortical brain systems for cognitive representation?

Pathways exist to relay a core process of positive affect in accumbens shell to affective cortical systems in just a few synapses, and so perhaps to create conscious pleasure feelings (Figure 3). By one path, neurons in nucleus accumbens shell project to a deep subcortical forebrain site directly behind the accumbens, namely, the ventral pallidum (especially its medial portion), which in turn projects to the mediodorsal nucleus in the thalamus (Heimer, Zahm, Churchill, Kalivas, & Wohltmann, 1991; Zahm, 2000). Mediodorsal thalamus finally projects directly to the prefrontal cortex regions that have been implicated in affective reactions. Thalamic mediodorsal relays also project to insular cortex, which processes taste sensations and related affect and cognition. This provides one potential way for an opioid-induced activation of hedonic 'liking' in the accumbens shell to influence feelings of pleasure that might be instantiated by limbic regions of neocortex.

In return, these emotional neocortical systems might hierarchically regulate core processes of positive affective reaction occurring in the nucleus accumbens, by sending downwards signals back to subcortical 'liking' structures. That would allow opportunity for the triggering of core emotional reactions by cognitive thoughts or for voluntary inhibition of emotional reactions to events (Berridge, in press-a; Davidson et al., 2000). For example, heavy projections from the prefrontal cortex and insular cortex extend to the nucleus accumbens shell (Wright & Groenewegen, 1996; Zahm, 2000). These may allow opportunity for those neocortical regions to modulate activation of 'liking' and 'wanting' core processes in nucleus accumbens circuits.

Alternative 'basic emotion' pathways also exist for pleasant stimuli to trigger affective reactions via accumbens 'liking' circuits directly without extensive cognitive modulation and without passing through the neocortex (LeDoux, 1996; Zajonc, 2000). For example, a sweet taste sensation could activate opioid circuits for a 'liking' core process in the nucleus accumbens shell without going through the neocortex at all, via direct sensory routes that ascend nonstop to accumbens from brainstem gustatory nuclei. Ascending projections to the accumbens shell are sent by the hindbrain's nucleus of the solitary tract (Brog, Salyapongse, Deutch, & Zahm, 1993), which processes taste sensations via cranial nerves from the tongue.

It is intriguing to speculate that subcortical 'liking' circuits might help cause unconscious affective reactions when they occur in humans. For example, as mentioned earlier, masked subliminal presentation of a happy facial expression can cause a person to later drink more of a fruit beverage, and give it higher subjective value ratings, without being aware of any intervening emotional reaction at all at the time of exposure to the facial expression (Winkielman et al., 2000). Conceivably this could involve activation of the nucleus accumbens shell or related circuits, without activating cognitive neural systems that generate conscious affective representations. The nucleus accumbens shell projects directly to dopamine sites in the tegmental area of the midbrain, as well as to other subcortical targets, which feed signals into basal ganglia loops involved in generating 'wanting' and appropriate behavior. Thus there are parallel routes for accumbens-based 'liking' signals to enter both cortical loops and subcortical loops, as well as extensive opportunities for connecting jumps across those loops.

Second sufficient cause for positive affective reactions: Hindbrain parabrachial nucleus. Sensory pleasure originates from activity across widespread brain systems. Core processes of positive affective reaction are not localized to a single brain site, but distributed in neural circuits that stretch across the brain. The nucleus accumbens shell is not the only brain site able to cause increased positive affective reactions to an event. Recent studies have identified another neurotransmitter circuit in another part of the rat brain equally able to cause enhanced positive affective reactions to a sweet taste: namely, a benzodiazepine/GABA circuit in the parabrachial nucleus of the hindbrain (Higgs & Cooper, 1996; Peciña & Berridge, 1996; Peciña & Berridge, 2000).

It was a bit of a surprise that benzodiazepine drugs can enhance 'liking' for a sensory pleasure, because those drugs are much better known for their strong sedative and anxiety reduction effects (Cooper, Higgs, & Clifton, 1995). But drugs can act in multiple parts of the brain, and do different things at each place. Anxiety reduction may be mediated in part by forebrain structures, whereas positive affective effects of benzodiazepines occur in the hindbrain. It is now well documented that benzodiazepine drugs, such as diazepam or midazolam, cause animals to eat large quantities of food (Cooper & Higgs, 1994), and can cause humans to overeat too (Haney, Comer, Fischman, & Foltin, 1997). Cooper proposed nearly 20 years ago that benzodiazepine enhancements of food 'wanting' might be mediated by enhancement of 'liking' or positive reaction to the hedonic impact of a taste (Cooper & Estall, 1985). There is now robust evidence to support his suggestion that this 'wanting' reflects 'liking' (Berridge & Peciña, 1995; Berridge & Treit, 1986; Gray & Cooper, 1995; Parker, 1995; Söderpalm & Hansen, 1998).

Benzodiazepine drugs act on neurons to promote the effect of the neurotransmitter GABA, or gamma-amino-butyric-acid (Macdonald & Olsen, 1994). Enhancement of core 'liking' for pleasant tastes results from benzodiazepine actions primarily in the brainstem. The first hint of the brainstem's importance was that benzodiazepines enhanced positive affective reactions to sweet tastes even in rats that had been surgically rendered "decerebrate", meaning that the brain had been transected so that only brainstem structures could participate in the reaction (Berridge, 1988). Thus, a residual core process for enhancing positive affective reactions could be detected remaining in the brainstem.

In a normal brain, the brainstem is still the most important structure for positive affective reactions caused by benzodiazepines. This was shown by Susana Peciña in our laboratory, who demonstrated that microinjections of low doses of benzodiazepine were more effective in the brainstem ventricle than microinjections into a forebrain ventricle at enhancing both appetite and positive affective reactions to tastes (Peciña & Berridge, 1996). For example, a very low benzodiazepine dose was able to increase both eating and positive reactions to sweetness if microinjection were made into the 4th ventricle in the hindbrain, but the same dose simply had no effect at all on either food-related behavior if the

microinjection were made into the lateral ventricles in the forebrain.

The exact location within the brainstem where benzodiazepine drugs cause positive affective reactions has been tentatively pinpointed as the parabrachial nucleus near the top of the pons (which lies above the medulla and beneath the midbrain; Figure 4). Anna Söderpalm found in our laboratory that the parabrachial nucleus was the only one of several brainstem sites where benzodiazepine microinjection increased positive affective reactions to a sweet taste (Söderpalm & Berridge, 2000). Her observation followed a related demonstration by Higgs and Cooper that the same site was best for causing rats to 'want' food and eat it (Higgs & Cooper, 1996).

Parabrachial connections to the rest of the brain. The parabrachial nucleus is interconnected with the shell of the nucleus accumbens (and with several of the other brain sites discussed above for positive affect). In addition to receiving direct taste sensation and other visceral inputs, the rat parabrachial nucleus receives descending forebrain inputs that might hierarchically modulate brainstem processing of sensory pleasure. The accumbens shell could send signals to modulate hedonic reactions via a single synapse in lateral hypothalamus, and gustatory and frontal regions of neocortex project directly to the parabrachial nucleus (Pritchard, Hamilton, & Norgren, 2000; Spector, 2000; Usuda, Tanaka, & Chiba, 1998; Zahm, 2000). In return, the parabrachial nucleus sends signals up to higher brain structures via two principal paths, one which reaches the gustatory neocortex via a relay nucleus in the thalamus, and the other that goes directly to limbic subcortical sites including the nucleus accumbens and the ventral pallidum (Pritchard et al., 2000).

In other words, there appears to be a neural loop among core process sites for positive affective reaction, and also extensive cross talk between that loop and neocortical systems that might mediate cognitive evaluations of affect and conscious pleasure (Figure 3). Thus the brainstem parabrachial nucleus is embedded in a larger brain circuit for the core sensory pleasure of taste, and for its hierarchical modulation by cortically mediated cognitive systems.

Ventral pallidum: Necessary cause for one form of positive affective reaction. The ventral pallidum is a final site that has been shown to cause changes in positive affective reactions to sensory pleasure. The ventral pallidum is so far unique in that it is a *necessary* cause for normal taste pleasure (rather than just a sufficient cause to elevate positive reactions above normal). The ventral pallidum lies immediately adjacent to the lateral hypothalamus, and has often been confused with it. Excitotoxin lesions that destroyed neurons in the ventral pallidum were found by Howard Cromwell in our laboratory to cause rats to respond to a sweet taste with aversion as though it were a bitter taste (Cromwell & Berridge, 1993). That is, after loss of ventral pallidum neurons all positive affective reactions were totally abolished for weeks. They were replaced by strong negative affective reactions, even to normally pleasant stimuli (Figure 4). Older lesion studies had suggested that lesions of lateral hypothalamus itself produced similar loss of positive reaction to sweetness, but those early lesions damaged the ventral pallidum too (e.g., Teitelbaum & Epstein, 1962). Analysis that is more selective suggests that only ventral pallidum lesions abolish positive affective reactions (Cromwell & Berridge, 1993; Berridge, 1996). So far, the ventral pallidum is the only distinct brain structure that has been shown to be *necessary* for generating a normal positive affective reaction to a sweet or otherwise pleasant taste.

Insert Figure 4 about here

Electrophysiological studies of animals have also implicated ventral pallidum activation as a correlate of food reward, cocaine reward, and brain stimulation reward (Gong, Neill, & Justice, 1997; Johnson & Stellar, 1994; McBride et al., 1999; Panagis et al., 1997; Rolls, 1999). In humans, electrical stimulation close to the ventral pallidum may induce bouts of affective mania that can last for days (Miyawaki, Perlmutter, Troster, Videen, & Koller, 2000), though the psychological characteristics of these bouts have not yet been examined in detail. Also intriguing is a report that sexual arousal and competitive arousal cause PET activation of this brain region in normal men (Rauch et al., 1999). Thus, ventral pallidal neurons play an important role in positive affective reaction, and are especially important as perhaps the only brain system known to be a necessary cause for a normal positive affective reaction to sensory pleasure. The ventral pallidum is a primary target of neurons from the shell of the nucleus accumbens, and relay to medial thalamus and cortex, providing a potential gateway of for limbic 'liking' signals to cortical systems of cognitive representation, and may share links also to the parabrachial nucleus (Sarter, Bruno, & Turchi, 1999; Zahm, 2000). The ventral pallidum is therefore a central fulcrum for the distributed brain circuit of core 'liking', as well as a potential

jumping point to cortical systems of conscious pleasure.

Pleasure: One brain circuit or many?

How many types of pleasure are there in the brain? Does one brain circuit mediate a core process of 'liking' shared by all types of pleasure? Or does each type of pleasure have its own core process and neural substrate? This is a question that has hardly begun to be asked in experimental studies, let alone to be answered. However there is at least evidence to suggest that several basic types of sensory pleasure, including food pleasure, drug pleasure, and sex pleasure, all share in common at least certain stages of their neural circuits.

Parts of the mesolimbic reward system, involving the nucleus accumbens shell (opioid system) and its projections to ventral pallidum, are especially good candidates to cause 'liking' for multiple types of basic sensory pleasure. Many studies have also indicated the mesolimbic dopamine projection to this system to be a shared substrate at least for 'wanting' (though probably not 'liking') for multiple types of reward, including food, sex, heroin, cocaine and related drugs, rewarding electrical brain stimulation, maternal interaction with infants and even social and culturally based rewards (e.g. money and videogames for humans) (Berridge & Robinson, 1998; Depue & Collins, 1999; Everitt, 1990; Fiorino, Coury, & Phillips, 1997; Mermelstein & Becker, 1995; Panksepp, 1998; Shizgal, 1999; Thut et al., 1997; Wise, 1998). Future studies may clarify the precise role of components within this system in 'liking' versus 'wanting', and in relating those core processes to each other, or in other roles regarding basic sensory pleasures.

Also to be explored are the brain bases of more abstract forms of positive affect, including social joy, love, intellectual pleasures, aesthetic appreciation, and moral appreciation. Do such elevated positive emotions share neural underpinnings with sensory 'liking'? That remains to be seen. The search for understanding of how positive affective reactions are generated by the brain will long remain a source of cerebral pleasure for those who have a taste for that sort of thing.

Conclusion

Positive affective reactions provide a window into how the brain generates positive affect. Even when affective reactions are not directly read out into conscious awareness, core processes of affect and motivation may nonetheless be manifest as positive affective reactions. Behavioral affective reactions to taste have allowed progress in identifying how the brain causally mediates core processes of positive affect. Subsystems of the nucleus accumbens shell, the ventral pallidum, and brainstem nuclei play a special role in causing 'liking' in the brain. The relation of core processes to conscious pleasure, the role of particular subcomponents, and the relation among multiple types of positive affective reaction continue to be exciting topics for research on pleasures of the brain.

Figure Captions

Figure 1. Behavioral affective reactions to taste. Positive affective reactions are elicited by sweet tastes from human infants, great apes, monkeys, and rats (A). Human affective reactions switch from positive to negative across sweet to bitter tastes. (B) Affective reactions by rats show a similar gradual switch from positive to negative across tastes. (C) Affective reaction components of individual human infants also cluster into positive versus negative groups. (D) Pooled human affective reactions show the gradual change from sweet to water, sour, and finally bitter tastes. (E) Affective reactions of great apes (chimpanzee, orangutan) and monkeys (New World tamarin and marmoset) to sweet and bitter tastes also cluster into positive hedonic versus negative aversive groups (F). From (Steiner et al., 2001).

Figure 2. Brain structures for core 'liking' and affective neural circuits discussed here.

Figure 3. Sufficient cause for 'liking' in shell of nucleus accumbens of the rat brain. Fos plumes of microinjections that identified the opioid site of 'liking' in nucleus accumbens shell (A & B). Morphine microinjections in the site increased positive affective reactions elicited by a sweet taste (C). The positive site is finally mapped in the accumbens shell (D). From (Peciña & Berridge, 2000).

Figure 4. Site within ventral pallidum that is a necessary cause for normal positive affective reactions to sweet tastes (A). Excitotoxin lesions in the ventral pallidum (black zone) cause rats to respond with negative aversive reaction even to sweet tastes that are normally palatable -- as though it made them bitter. Larger grey zone represents the adjacent lateral hypothalamus. From (Cromwell & Berridge, 1993). (B) Brainstem parabrachial nucleus in the pons where microinjection of benzodiazepine causes increased positive reactions to a sweet taste. Modified from (Söderpalm & Berridge, 2000). Sideways views in A & B show anterior-posterior position of the section in the rat brain, and position of the equivalent structures in human brain.

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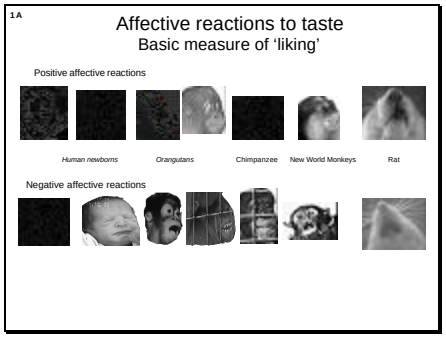

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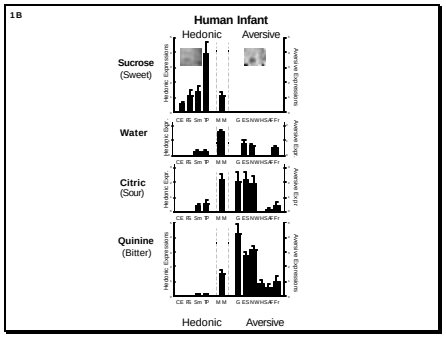

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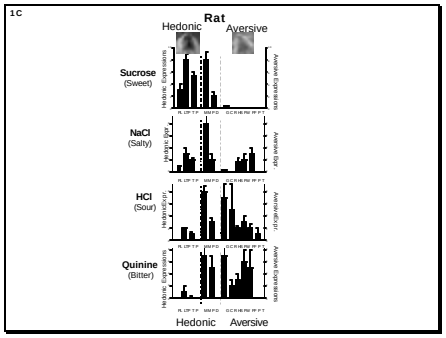

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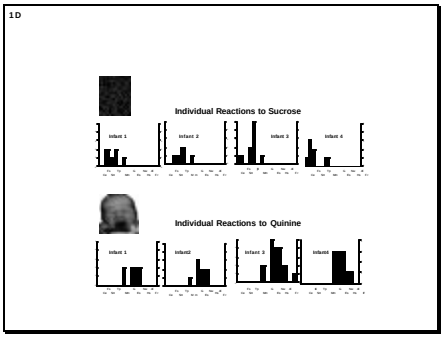

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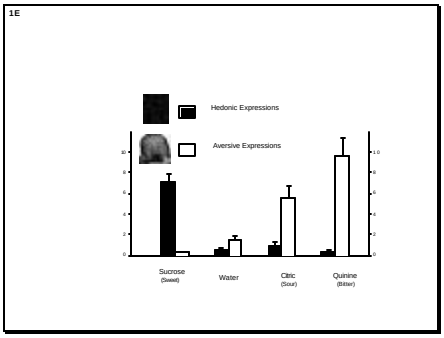

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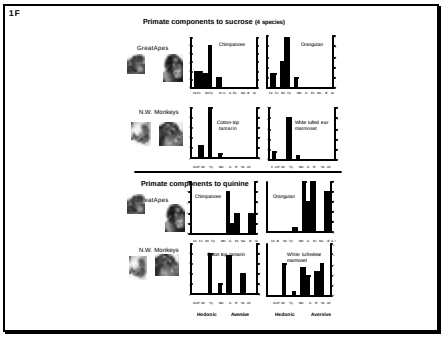

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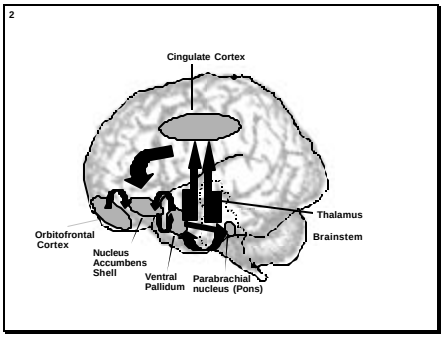

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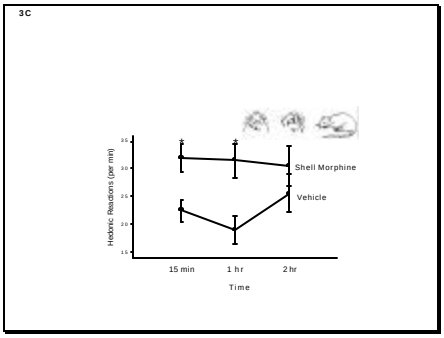

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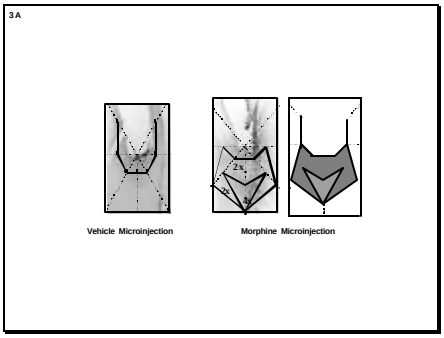

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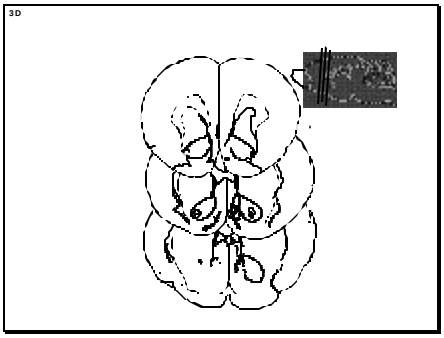

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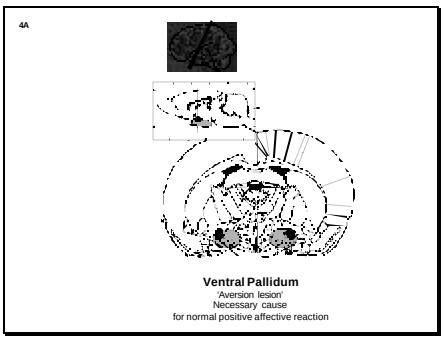

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