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Review

The neurobiology of positive emotions

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Abstract

Compared to the study of negative emotions such as fear, the neurobiology of positive emotional processes and the associated positive affect (PA) states has only recently received scientific attention. Biological theories conceptualize PA as being related to (i) signals indicating that bodies are returning to equilibrium among those studying homeostasis, (ii) utility estimation among those favoring neuroeconomic views, and (iii) approach and other instinctual behaviors among those cultivating neuroethological perspectives. Indeed, there are probably several distinct forms of positive affect, but all are closely related to ancient sub-neocortical limbic brain regions we share with other mammals. There is now a convergence of evidence to suggest that various regions of the limbic system, including especially ventral striatal dopamine systems are implemented in an anticipatory (appetitive) positive affective state. Dopamine independent mechanisms utilizing opiate and GABA receptors in the ventral striatum, amygdala and orbital frontal cortex are important in elaborating consummatory PA (i.e. sensory pleasure) states, and various neuropeptides mediate homeostatic satisfactions.

Keywords: Affect; Emotions; Pleasure; Play; Seeking; Foraging; Vocalizations; Dopamine

Contents

1. Introduction

Recently, scientific study of positive emotions has been receiving increased experimental attention. Extroversion and gregariousness are among the best predictors of subjective well-being and positive affectivity; along with being happier, people who experience high subjective well-being typically have better health outcomes and

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longevity (Fredrickson, 2004; Seligman and Csikszentmihalyi, 2000). In this paper, we will review the recent scientific evidence on the neurobiology of positive emotions that has emerged from human and animal research.

An abundance of neuroscience evidence indicates that whereas the cognitive aspects of emotions, such as the recognition of happy and sad faces, require neocortical processing, the experiential states of happiness and sadness, as well as the other basic affective states are strongly dependent on sub-neocortical limbic circuitries that we share with the other mammals (Damasio et al., 2000; Liotti and Panksepp, 2004; Panksepp, 1998). Although there are no unambiguous objective indicators of subjectively experienced affective states that commonly accompany emotional and motivational arousals in humans, because of abundant corroborative evidence (Panksepp, 2005), it is becoming more acceptable to entertain that such affective states of consciousness may arise from sub-neocortical brain dynamics that we share with other animals as well.

Throughout the 20th century, there was resistance to entertaining brain/mind entities such as affective states in animals, but modern neuroscience, with its many well-demonstrated neuroanatomical and neurochemical homologies across all mammalian species, now provides ways to evaluate such possibilities in more scientifically rigorous ways than was possible during earlier eras (Panksepp, 1998, 2005). For instance, it is now clear that the neurochemistries of opiate and psychostimulant addictions are organized similarly in the brains of all mammals, and it has been argued that we cannot make sense of such behavioral changes unless we begin to take affective experiences more seriously in the lives of other animals (Knutson et al., 2002; Panksepp et al., 2002; Panksepp et al., 2005). Although there is still a strong and re-vitalized neo-behaviorist tendency to see all behavioral change in animals as arising from unexperienced, pre-conscious brain processes, our goal for this essay is to discuss why it may be wiser to provisionally conclude that ancient forms of consciousness such as affective experiences do exist in the neurodynamics of other animals, and why such brain functions may be all important for behavioral neuroscientists to consider more openly (Panksepp, 2003a, 2005). Animal behaviorists (e.g. Marc Bekoff, Marian Dawkins, and Don Griffin) are increasingly accepting the likelihood that animals experience their lives, and that such issues are essential for discussing animal welfare issues (see McMillan, 2005 for a recent summary of such work). In our estimation, such views are more consistent with the mass of available evidence, and they provide a straight-forward strategy for shedding empirical light on very important neuro-mental functions, critical for advancing understanding that can inform psychiatric practice (Panksepp, 2004). Such issues are almost impossible to study with any neuroscientific precision in human beings. In this paper, we will largely restrict our coverage to anticipatory eagerness and gustatory pleasure, since those are among the best studied and least controversial positive affective responses that are conserved across most mammalian species.

Although not covered in detail, we would also note that the primitive emotional concepts of positive and negative affect (PA and NA, respectively), which are increasingly central to modern psychological analyses of emotional experiences (Lambie and Marcel, 2002; Russell, 2003), are rather general and non-specific ways to conceptualize emotional feelings. It could be argued that PA and NA are merely semantic-conceptual ways to parse the many kinds of 'good' and 'bad' feelings that the nervous system can construct, and that a neuroscientific analysis must seek endophenotypes that are neurobiologically ingrained affective processes. For instance, a recent personality test designed to evaluate various basic emotional tendencies in humans provides evidence that NA states can be constituted of specific negative feelings such as fear, anger and sadness, while PA can be constituted of specific positive feelings such as those related to playfulness, nurturance and exploratory-seeking urges (Davis et al., 2003). Whether the more general categories of PA and NA simply reflect convenient ways to talk about such conceptual groupings of desirable and undesirable feelings, or whether they have neurobiological realities above and beyond their class identifier status, is an issue that remains to be resolved. Since so much effort in psychology has been devoted to development of general PA and NA concepts (Davidson et al., 2000, *Handbook of Affect Science)*, we will here utilize that scheme as a guide to talking about more specific affective feelings that require a more resolved taxonomy. Although all investigators of such neuro-mental processes surely recognize that they can only be indirectly monitored through the use of various psychological and behavioral measures, it remains to be widely recognized that affective states cannot be scientifically understood without neural analyses.

1.1. Measurement of positive affective states

Positive affective (PA) states can either be scientifically measured via self-report Likert-type rating scales or by examining unconditioned behavioral responses. Thus, the positive emotion of happiness is typically measured by asking subjects to rate their current level of happiness using either a verbally anchored scale or a pictorial one such as the self-assessment manikin in which subjects identify their emotional state by choosing cartoon characters that match their mood states along valence (bad to good mood), arousal, and power/surgency dimensions (Lang, 1995). For example, emotional states elicited by viewing pictures of human babies are rated high on positive valence and moderately on arousal (Lang, 1995). Alternatively, happiness could be measured behaviorally, for instance by the presence of Duchenne smiling, which has been found to be

positively correlated with human subjective self-report of positive emotion (Ekman et al., 1990).

In animals, the utilization of conceptual-psychological scales is not possible, and hence all measures have to rely on behavioral analyses. In general, investigators have the option of focusing on the study of unconditioned-instinctual behavioral tendencies or conditioned-learned behavioral changes. Both are useful, but the former may be more useful for a brain systems analysis of the critical neural components, if one makes the simplifying *dual-aspect monism* assumption that affective feelings may directly reflect the neurodynamics of brain systems that generate instinctual tendencies (Panksepp, 2005). However, the study of learned behaviors is also critical, for that level of analysis provides the opportunity to validate the likely presence of experiential components as measured by various approach and avoidance behaviors, especially conditioned place preferences and aversions to locations where organisms experienced experimental imposed variation of their internal states (studies that are very hard to conduct ethically and logistically in humans).

A great deal of animal work has been conducted on various negative affective processes (Panksepp, 1998), especially fearful behaviors, even though many leading investigators still do not accept the concept of affect as being of any relevance (or even reality) within their neuro-behavioristic ontologies. They commonly ignore abundant work done on other negative emotions, such as separation-distress, which has relied heavily on vocal measures of emotions such as the analysis of separation calls (Panksepp, 2003b), not to mention the variety of positive emotions such as playfulness and other social emotions that exist in animal brains (Panksepp, 1998, 2005). However, it is becoming increasingly clear that the mapping of the separation distress system in animal brains has striking anatomical correspondences to human sadness systems highlighted by PET imaging (Damasio et al., 2000; Panksepp, 2003b), even to the extent that human sadness is accompanied by low opioid tone in the relevant limbic circuits (Zubieta et al., 2003), a principle first revealed through animal brain research (Panksepp, 1981, 2003b). However, to keep this contribution manageable, our coverage here will be restricted to several key exemplars of positive affect.

1.2. Biological approaches to understanding positive affect

Many psychometric models of positive emotions conceptualize positive affective states as originating from approach and various consummatory behaviors. From this perspective, all emotions can be categorized on a two or three-dimensional Cartesian planes, with an approach-avoidance valence dimension and an arousal dimension (Cabanac, 1979; Knutson et al., 2002; Lang, 1995; Russell, 2003; see Fig. 1), and often a third, and less well-conceptualized dimension of surgency or power of a feeling. For example, joy would be categorized as approach + high arousal whereas sensory postprandial pleasure would be approach + low arousal. Approach based psychometric models of positive emotion have also been used to conceptualize stable PA traits states such as subjective well-being (Davidson et al., 2000; Panksepp et al., 2002) as well as the personality trait of extroversion which is associated with high levels of PA (Diener, 1998). However, as already noted, both positive and negative affect could be broken down into a variety of specific emotions, affording a more refined view of the many distinct species of affect that may exist in the brain (Davis et al., 2003; Panksepp, 1998).

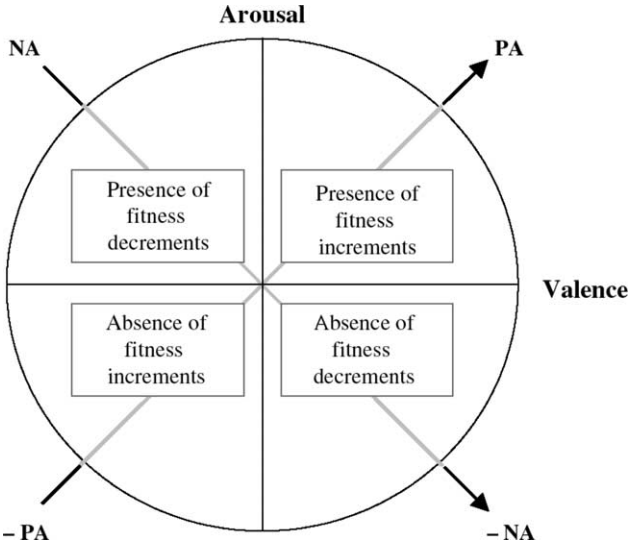

Fig. 1. Mapping of fitness concerns to an affective circumplex. Potential increases in fitness create a vector moving up and to the right, which generates positive feelings (i.e. PA: positive affect) involving high arousal, while removal of potential decrements in fitness creates a vector moving down and to the right, which generates positive feelings involving low arousal. Potential decreases in fitness create a vector moving up and to the left, which generates negative feelings (i.e. NA: negative affect) involving high arousal, while removal of potential increments in fitness creates a corresponding vector moving down and to the right, which may generate different negative feelings involving low arousal. Adapted from Panksepp et al., (2002).

From this perspective, what is needed in the study of affect is a more resolved taxonomy that hopefully will eventually map onto distinct brain systems. For instance, it could be argued that positive and negative affect are simply conceptual class identifiers rather than 'natural kinds' and it is easy to envision many distinct categories of positive affects—for instance, (i) those that emerge from homeostatic bodily need states which are alleviated by specific sensory–motor consummatory activities, (ii) those that reflect emotional action processes (e.g. play and investigation), and (iii) those that emerge as general background feelings related to various forms of satisfaction, distress, and relief (Ostow, 2004; Panksepp, 2004; Panksepp and Pincus, 2004). So far neuroscience has had relatively little to say about such issues, except for the recognition that many of

these feelings are substantially due to activities of the limbic system (MacLean, 1990) and specific sub-systems coursing through those sub-neocortical regions of the brain (Panksepp, 1998). Since most of that work comes from the study of laboratory animals, where discussion of internal subjective states continues to be shunned, it is an understatement to say that the nature of affective experience remains a conceptually and empirically underdeveloped territory. Future developments along these lines will require investigators to be willing to take objective behavioral measures, especially of spontaneous behaviors (e.g. emotional vocalizations) and parallel preference and aversion paradigms, as potential indicators of affective experiences.

An emerging human research tradition does, in fact, attempt to infer PA from unconditioned behaviors that are correlated to self-reported PA states. Perhaps, the classic example is the Duchenne smile, also known as the felt smile (Ekman et al., 1990). Such approaches suggest that from a felt smile one can infer PA due in part to the strong positive correlation between Duchenne smiling and subjective self-report of positive affect in humans (Ekman et al., 1990). However, it is increasingly recognized that such measures may lack validity in many adult human studies, because of various cognitive-instrumental ways humans regulate their affects, including cultural display rules that commonly make such indicators fuzzy signals of emotional feelings. However, such instinctual displays may be more veridical readouts of internal affective states in infants who are not yet skilled in cognitive control of their behavioral displays, since they have not fully assimilated cultural expectations.

In fact, human infants exhibit certain patterns of oral-facial behaviors exclusively to sweet solutions that adults find highly palatable (Ganchrow et al., 1983; Rosenstein and Oster, 1998). Adult primates as well as rodents also exhibit these hedonic taste reactivity reactions exclusively to highly palatable solutions (Berridge, 2000, 2004). Positive emotional vocalizations that are exhibited during anticipation of rewards, as well as during pro-social interactions such as conspecific reunion as well as rough and tumble play, have also been used as a behavioral index of positive affective states in primates (Jürgens, 1979, 1998) and rodents (Knutson et al., 2002; Panksepp et al., 2002). Many of the conclusions derived from the study of these unconditional behaviors have been validated by corresponding place preference and place aversion paradigms (Burgdorf et al., 2001b).

With regard to the sensory aspects of positive affects, various pleasures reflect the capacity of certain stimuli to return the body to homeostasis. Although there are many historical antecedents to this idea from Plato onward, the modern discussion goes back to the work of Michel Cabanac (1971). For example, a warm stimulus would be experienced as pleasurable by a cold individual, with the magnitude of the pleasure being proportional to the ability of the stimulus to return the body to homeostatic conditions. This has been referred to as sensory *alliesthesia* (Cabanac, 1992). Positive emotional responses are also thought to reflect the relative utility of eliciting stimulian old idea (e.g. Bindra, 1978; Young, 1966) that fits modern neuroeconomic principles (Shizgal, 1997; Panksepp et al., 2002).

1.3. Conditioned place preference studies of limbic chemistries

Many studies have found that the rewarding effects of addictive/euphoric drugs are mediated by sub-neocortical systems as indicated via self-injections studies as well as conditioned place preference studies (McBride et al., 1999). Opiate agonists that bind preferentially to μ-opiate receptors are euphorgenic, whereas kappa selective opiates generate negative affect in humans (Schlaepfer et al., 1998). When injected directly into the brain, μ-opiate agonists (morphine, endomorphin 1, DAMGO) produce conditioned place preference consistently when injected into the ventral tegmental area, nucleus accumbens, periaqueductal gray and lateral ventricle (Bals-Kubik et al., 1993; Olmstead and Franklin 1997; Terashvili et al., 2004), whereas kappa selective agonists (U50,488H) produce conditioned place *aversion* when injected into many of these same brain regions (Bals-Kubik et al., 1993). Cocaine produces conditioned place preferences and self-administration when injected directly into the accumbens, prefrontal cortex, and olfactory tubercle (Goeders and Smith, 1993; Gong et al., 1996; Ikemoto, 2003), whereas amphetamine place preference seems restricted to the accumbens and -ventral palladium (Carr and White, 1986; Gong et al., 1996). Alcohol and nicotine produce place preference and self-administration when injected into the ventral tegmental area (Laviolette and van der Kooy, 2003; Rodd et al., 2004). In sum, most of the drugs that are euphorigenic in humans are rewarding when injected directly into the ventral striatum or its cortical afferents in rats.

A number of peptide systems have been implicated in positive affective states since the peptides have been rewarding when given peripherally or microinjected directly into the rodent brains. Neurotensin and CART, peptides closely associated with brain dopamine, exhibit place preferences when injected into the ventral striatum (Glimcher et al., 1987; Kimmel et al., 2000). Neuropeptide Y, a peptide involved in food intake and alleviating anxiety, yields place preference when injected into accumbens and perifornical hypothalamic nuclei, with its rewarding effects being partially dissociable from its hyperphagic effects (Brown et al., 2000). Oxytocin, which is involved in creating social bonds and the pleasures of social contacts shows place preference when given peripherally (Liberzon et al., 1997), but it has been difficult to see this effect centrally, even though in unpublished work we find socially induced place preference to be facilitated by oxytocin

(Panksepp, 1998). These studies implicate a number of sub-neocortical circuits in the generation of affective states.

1.4. Affect is largely a sub-neocortical process

Before we proceed, let us briefly emphasize why investigators should entertain the likelihood that affect largely has a sub-neocortical locus of control. At present, many investigators and theoreticians remain skeptical about the fundamental role of sub-neocortical systems in the elaboration of affect, partly because they feel consciousness is only a characteristic of the higher heteromodal cortical functions in humans and perhaps several other highly cerebrated species. Modern brain imaging studies which demonstrate results contrary to the evidence long provided by animal brain research, tend to highlight the arousal of many higher cortical regions in the emotional-cognitive processes aroused by exteroceptive stimuli (for summaries, see Lane and Nadel, 2000).

Modern brain imaging, especially with fMRI may be yielding deceptive findings, at least for understanding *the nature of affect*: Investigators, by using perceptually driven methodologies, are typically visualizing the cognitive components of emotional processing rather than core affective states. fMRI does not appear to have the ideal characteristics to detect true affective changes (which have a time-course which is not well suited for fMRI parameters). PET is much better; indeed Damasio et al.'s (2000) study picked up patterns that are rarely evident in fMRI studies. The ever increasing imaging of unconscious emotional processes is pertinent for understanding the sensory–perceptual aspects of emotional stimuli, not affective states. Indeed, most investigators that use such methodologies fail to evaluate potential affective changes empirically, which may compromise the generality of conclusions concerning the affective dimensions of experience, which may be most relevant for clarifying psychiatrically relevant emotional issues. Thus, although fMRI may be a fine tool for identifying brain cognitive correlates of emotional experiences (generated very rapidly to specific sensory or cognitive contingencies), as currently used, it is a blunt tool for analyzing how affect is generated in the brain. Since emotional affects emerge relatively slowly (e.g. sadness), they may not be as readily linked temporally to precipitating stimulus events as are emotional perceptions.

Fortunately, PET imaging is better suited for visualizing affective responses of the brain, and an increasing number of experiments using PET during the past few years have been more concordant with the animal data then fMRI studies. Perhaps, the most compelling evidence comes from Damasio et al. (2000), who asked individuals to achieve deep, existentially experienced feeling states of anger, fear, sadness and happiness via personal reminiscences. When subjects truly experienced those feelings, radioactive water was infused and PET images were constructed. The results affirmed abundant arousals in sub-neocortical brain regions, accompanied by substantial reductions of blood flow in many higher brain areas, suggesting a narrowing of information processing in neocortical systems during intense emotional states (Liotti and Panksepp, 2004).

Various studies have also highlighted the importance of sub-neocortical regions in human affective experiences such as air hunger (Liotti et al., 2001), the taste of chocolate (Small et al., 2001), the appetite for various rewards including winning money (Knutson et al., 2001a,b), the sex-specific appeal of pretty faces (Aharon et al., 2001), the pleasure of musical peak experiences (Blood and Zatorre, 2001), male sexual arousal (Redoute et al., 2000) and orgasmic pleasure (Holstege et al., 2003). All of these studies report arousals of various subcortical brain areas implicated in the generation of affect by animal research, as well as those mesocortical zones, especially orbitofrontal, anterior cingulate and insular cortices that MacLean (1990) originally highlighted in his Limbic System concept (which has been increasingly attacked by a growing number of cognitive neuroscientists more accustomed to working on the higher informational functions of the brain). It is claimed that the Limbic System is not a coherent anatomical or functional entity (which can be said for any region of the brain), without realizing that the concept was originally used to designate visceral regions of the brain that are critical for elaborating emotionality, a general conclusion that continues to be supported by modern research.

The extended viscerally focused brain regions known as the limbic system, descending deep into the medial diencephalon and upper brainstem, do appear to comprise the fundamental neuro-geography of spontaneous emotional behavior and affective experience in both humans and other mammals (and probably birds and reptiles also). These systems are regulated and further parsed by higher cortical activities, but aside from the role of mesocortical areas like the insula in the pleasures and displeasures (e.g. disgust and pain) of certain sensations, there is little evidence that higher neocortical regions are essential for generating affective experiences that accompany emotional arousal, even though they are be essential for the cognitive memories associated with those states. Accordingly, we should be devoting more effort to studying the details of basic emotional systems in appropriate animal models (e.g. as summarized in Panksepp, 1998). These systems, which appear to be homologously organized in all mammals, are largely inaccessible for *causal* human research.

In this vein, we should also recall that emotional feelings have typically been much easier to activate in humans through stimulation of sub-neocortical circuits that mediate the instinctual emotional behaviors in our fellow animals, than through higher brain stimulation (for reviews see Heath, 1996; Panksepp, 1985). A most recent striking example was Bejjani et al.'s (1999) observation of sudden onset of depression by stimulating midline diencephalic structures near the subthalamic nuclei, and mirth by stimulating the nucleus accumbens (Okun et al., 2004). In

sum, the evidence is substantial for a sub-neocortical locus of control for the generation of experienced affects that accompany various emotional states and consummatory responses.

2. Neurobiological findings in positive affect

Causal analysis of the brain substrates of affective change have been typically achieved by direct electrical and chemical stimulation of human and animal brains, findings which have often been corroborated with PET imaging of brain activity changes in humans. The weight of evidence suggests that brain systems which support affective change are concentrated in similar subcortical regions of the brain.

2.1. Electrical stimulation of the brain (ESB) studies

In the late 1940s Robert Heath discovered that human psychiatric patients would press a button to self-administer electrical brain stimulation to a variety of brain areas. During these self-stimulation sessions some subjects would occasionally report that the stimulation produced a PA state, with one subject describing the switch that electrically stimulated his mesencephalic tegmentum as his 'happy button' (Heath, 1960); another of Robert Heath's patients described electrical stimulation of the septum as the most pleasurable experience of his life (Heath, 1972). It is important to note that Heath's definition of the septum included the nucleus accumbens (Heath, 1954, 1972). Electrical stimulation of the accumbens has been shown to elicit smiling laughter and euphoria, with laughter changes being highly correlated with euphoric response (Okun et al., 2004). Patients treated for Parkinson's disease with deep brain stimulation electrodes in the subthalamic nucleus show hedonically experienced laughter in response to ESB (Krack et al., 2001). Hedonic felt laughter has also been elicited from electrical brain stimulation of the supplementary motor cortex in one epileptic patient (Fried et al., 1998), but the affect may have been coincident to the recruitment of sub-neocortical systems.

In non-human primates, deep brain electrical stimulation of the striatum as well as the midbrain regions can elicit vocalizations that are normally exhibited when the animals unexpectedly find palatable food or are reunited with conspecifics, and in most cases ESB that elicits these vocalizations can serve as a positive reinforcer for that animal (Jürgens, 1976). Similarly, ESB of many of these same regions also produces PA vocalizations in other mammals (Kyuhou and Gemba, 1998; Burgdorf and Panksepp, unpublished observation).

2.2. Ventral striatum systems

Psychostimulants such as cocaine or amphetamine elicit positive affective states in humans, which have been found to depend in part by the action of these drugs on dopamine (Volkow and Swanson, 2003). Additionally, global dopamine function in humans as measured by a metabolite of dpoamine has been found to be implemented in subjective well-being as well as extroversion (Depue and Collins, 1999). Psychostimulant induced PA has been found to be positively correlated with increases in DA levels (inferred from a decrease in raclopride binding) in the ventral but not the dorsal striatum in humans (Drevets et al., 2001; Volkow and Swanson, 2003; Martinez et al., 2003). Similarly, microinjections of psychostimulants into the ventral but not the dorsal striatum elicit PA vocalizations in rats (Burgdorf et al., 2001a; Brudzynski, personal communication). A - synopsis of the evidence for dopamine arousal in PA is summarized in Table 1.

Table 1
Evidence that dopamine modulates an appetitive type of positive affective states

1. Psychostimulant induced PA is associated with dopamine activity in the ventral striatum (Drevets et al., 2001; Martinez et al., 2003; Volkow and Swanson, 2003)
2. Psychostimulant induced PA is attenuated by dopamine receptor antagonists (Jönsson et al., 1971; Newton et al., 2001; Romach et al., 1999)
3. People with 9/9 dopamine transporter polymorphisms show diminished subjective and physiological effects of amphetamine including the euphoric effects (Lott et al., 2005)
4. Personality trait of extroversion (which is highly correlated with positive affect) is associated with dopamine functioning (Depue and Collins, 1999)
5. The dysphoric effects of dopamine receptor antagonists is associated with striatal dopamine binding (Voruganti et al., 2001)
6. Drugs of abuse (but not aversive stimuli) increase dopamine levels in the accumbens shell region of rat brain (Di Chiara, 2002)
7. 50-kHz ultrasonic vocalizations, which is a rat model of PA, is modulated by dopamine (Knutson et al., 2002)

Dopamine does not seem to be involved in consummatory positive affective states (Berridge and Robinson, 2003). Although the positive case for the role of dopamine in PA is given, in whole we agree that brain dopamine is only 'loosely correlated with subjective pleasure' (Wise, 2004).

The ventral striatum has been found to be recruited in multiple forms of positive affective states. Increases in brain metabolic activity as measured by brain imaging in humans have been found in response to PA induced by anticipation of reward (Knutson et al., 2001a,b), as well as to PA induced by music (Blood and Zatorre, 2001a,b). In addition, whereas increases in metabolic activity are seen in anticipation of reward in the ventral striatum, the actual receipt of a monetary reward is related to a decrease in ventral striatal activity (Knutson et al., 2001b). Human male orgasm/ejaculation is associated with increases in ventral tegmental area (VTA) activity (Holstege et al., 2003). In non-human animals the ventral striatum has also been implicated in various PA states, perhaps ones that can be psychologically distinguished. Whereas injections of dopamine agonists into the ventral striatum elicit PA vocalizations in rats (Burgdorf et al., 2001a), injections of morphine into the ventral

striatum facilitates hedonic taste reactivity responses (Peciña and Berridge, 2000).

2.3. Frontal cortex

The orbital frontal cortex has been found to be activated in fMRI brain imaging of positive emotional states related to taste induced PA (Kringelbach et al., 2003) olfactory induced PA (Rolls et al., 2003a) as well as somatosensory induced PA (Rolls et al., 2003b). PA states induced by music (Blood and Zatorre, 2001) as well as mothers viewing pictures of their newborn babies (Nitschke et al., 2004) have also been shown to increase orbital frontal activity. In non-human primates, a subset of orbital frontal cortex neurons are activated specifically by taste stimuli that are palatable to the monkey (Thorpe et al., 1983).

Lesion studies of the frontal cortex show definitively that the right frontal cortex is important in the neurobiology of positive affect, strongly suggesting laterality of positive affect in humans. Patients with right frontal lesions are more likely to present with symptoms of mania, whereas left frontal lesions patient are more likely to present with depression (Robinson et al., 1984, 1988; Sackeim et al., 1982). Additional evidence for the laterality of PA comes from EEG studies, with generalized PA states associated with increased left cortical power in the alpha frequency compared to the right hemisphere, and generalized negative affective states associated with decreased left cortical activation (Davidson, 2004; Tomarken et al., 1992).

2.4. Amygdala

The classic description of the Klüver–Bucy syndrome is that after bilateral temporal lobe lesions (including the amygdala) monkeys exhibit flat affect (Bucy and Klüver, 1955). Recently, it has been shown that monkeys with specific lesions of the cell bodies in the amygdala show deficits in the expression of fear (Kalin et al., 2001). Similar to animal studies, patients with amygdala damage have more deficits in processing static negative emotional than positive emotional stimuli (Adolphs et al., 1999), even though they are more responsive to dynamic-moving stimuli (Adolphs et al., 2003). Also, there is considerable evidence that selective bilateral amygdala damage, as in Urbach–Wiethe disease, does not seriously compromise the ability of patients to have many affective experiences (Damasio, 1999). Brain imaging studies reveal that PA inducing stimuli such as music (Blood and Zatorre, 2001) odor (reviewed in Zald, 2003), self-generated PA (Damasio et al., 2000) and male orgasm (Holstege et al., 2003) *decrease* amygdala activation. In general, negative emotional stimuli are more effective in increasing amygdala activity than positive ones in fMRI studies (Zald, 2003). Taken together, these studies suggest that positive emotions tend to reduce amygdala activation, and that the principal role of the amygdala in emotion is in the information processing related to negative valenced emotions.

3. A recent analysis of social-joy in the rat brain

Our work on the play systems of the brain was initiated over a quarter of a century ago (first summarized in Panksepp et al., 1984). Eventually, this work led to the discovery of play vocalizations (Knutson et al., 1998) and soon thereafter, the remarkable finding that tickling could also evoke these 50-kHz chirpy laughter-like vocalizations (Panksepp and Burgdorf, 1999, 2000). After extensive behavioral analysis, it seemed evident that it is justified to provisionally consider this substrate as one that may mediate ancient forms of social joy and laughter (Panksepp and Burgdorf, 2003). The aim of this short section is to highlight recent experiments that bring us closer to understanding the underlying circuitry.

3.1. Rat 50-kHz ultrasonic vocalizations as a measure of positive affect

Just as in humans, we believe emotion-related vocalizations are one of the best ways to map out positive affect circuits of the mammalian brain. Abundant ultrasonic chirps of the 50-kHz variety are evident during the anticipatory phase of rat sexual behavior (Barfield and Thomas, 1986), anticipation of rewarding brain stimulation (Burgdorf et al., 2000) or drugs of abuse (Burgdorf et al., 2001a,b) during rough-and-tumble play behaviors (Knutson et al., 1998), as well playful, experimenter administered manual somatosensory stimulation (i.e. tickling) (Panksepp and Burgdorf,

Table 2
Alternative non-affective interpretations of 50-kHz ultrasonic vocalizations in rats, with rebuttal

Hypothesis 1: 50-kHz cannot reflect a positive affective state because they occur during aggression
Response: 50-kHz calls occur primarily *before* the onset of aggression, after which aversive 20-kHz calls predominate (Miczek and de Boer, 2005; Burgdorf and Panksepp, unpublished observation). Male resident intruder interactions that result in aggressive behavior exhibit 50% less 50-kHz vocalizations than non-aggressive encounters (Burgdorf and Parksepp, unpublished observation). Resident winner animals exhibited only 50-kHz positive emotional calls and no 20-kHz negative emotional calls and find aggressive interactions rewarding, whereas intruder looser animals exhibit both 50 and 20-kHz calls, and find aggressive interactions ambivalent (Takahashi et al., 1983; Thomas et al., 1983; Taylor, 1979)
Hypothesis 2: 50-kHz calls are an artifact of locomotion
Response: In a recent study (Panksepp and Burgdorf, 2003), we found that only 9% of 50-kHz calls occur within 0.5 s of locomotor activity. Also, we have found increases in 50-kHz calls with manipulations that increased, did not change, or decreased locomotion (Knutson et al., 2002)
Hypothesis 3: 50-kHz calls reflect states of high arousal without necessarily positive affect
Response: High arousing negative affective stimuli such as foot shock, predatory odor, bright light, flustrative non-reward, and lithium chloride *decrease* levels of 50-kHz calls (Knutson et al., 2002)

2000, 2003) that can reinforce arbitrary operant responses (Burgdorf and Panksepp, 2001). In humans, the anticipation of an eminent and highly predictable reward elicits PA (Knutson et al., 2002). Similarly, anticipation of imminent reward in rats has been shown to elicit 50-kHz vocalizations. However, when the reward is omitted during an extinction trial (e.g. empty food cup place into the animals cage for their daily 1 h feeding session, instead of the full food cup they have received each day for a week), 50-kHz calls decrease and negative affective 20-kHz calls increase although the motivation for the reward presumably remains high. Therefore, 50-kHz calls seem to reflect a positively valenced incentive motivational state. Modest amounts of 50-kHz calls are also evident during aggressive behavior (Thomas et al., 1983; Takahashi et al., 1983). However, 50-kHz calls during aggressive encounters occur primarily during the brief social investigation that occurs before biting occurs, after which negative affective 20-kHz ultrasonic calls dominate (Panksepp and Burgdorf, 2003; see Table 2) 20-kHz ultrasonic calls have been associated with negative affective states including morphine and cocaine withdrawal (Covington and Miczek, 2003), footshock, aversive drugs, and social defeat (Knutson et al., 2002).

Of all manipulations that elicit 50-kHz ultrasonic calls in rats, experimenter administered tickling in individually housed adolescent rats elicits the highest rates of calling, which are strongly and positively correlated with the rewarding effects of the stimulation (Burgdorf and Panksepp, 2000; Panksepp and Burgdorf, 2001). This relationship also holds true for 50-kHz vocalizations that occur during rough-and-tumble play among adolescent rats (Burgdorf and Panksepp, in preparation), electrical brain stimulation (Burgdorf and Panksepp, in preparation), and administration of drugs of abuse (Knutson et al. 2002;

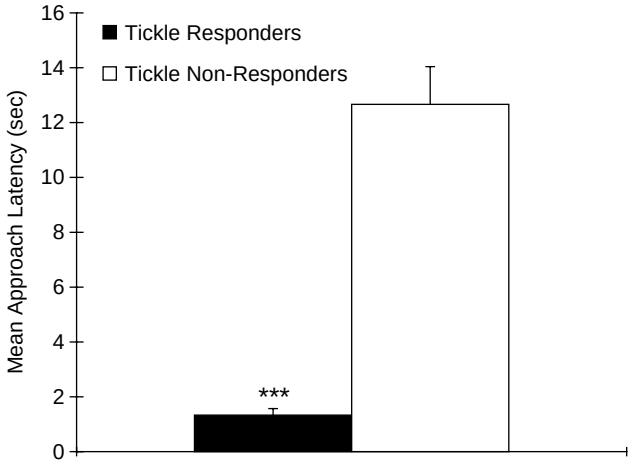

Fig. 2. Mean (±SEM) latency to approach the experimenters hand to self-administer tickling stimulation in adult female long evens rats which have previously been found to exhibit either low or high levels of 50-kHz ultrasonic vocalizations in response to tickling. Testing protocol was similar to Panksepp and Burgdorf (2000). ***$P<0.001$, between subjects *t*-test, two-tailed.

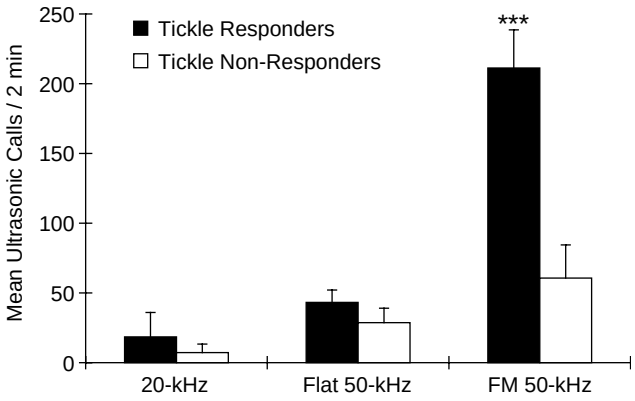

Fig. 3. Mean (±SEM) ultrasonic vocalizations in animals which have previously been shown to exhibit either high or low levels of 50-kHz ultrasonic vocalizations. Testing protocol was similar to Panksepp and Burgdorf (2000). Ultrasonic vocalizations were recorded from the high frequency (untransformed) output of a Pettersson D980 bat detector onto a fostex fr-2 field recorder with a 196-kHz, 24 bit sampling rate. ***$P<0.001$, between subjects *t*-test, two-tailed.

Burgdorf and Panksepp, submitted). From this evidence, we have hypothesized that 50-kHz calls reflect an appetitive positive affective state akin to primitive human joy and laughter (Panksepp and Burgdorf, 2003; Knutson et al., 2002).

Tickling responsivity generally declines in adulthood, especially in animals that have not been offered such experiences during adolescence (males generally become less responsive than females). Approximately half of such socially housed adult female rats, placed into isolation housing several days before tickle testing, do show reasonably high levels of tickle induced 50-kHz ultrasonic vocalizations but the remaining half remain very unresponsive. The adult female rats that show high levels of tickle induced 50-kHz calls find the tickling stimulation to be more rewarding than the low responder animals (Fig. 2), a similar relationship between the 50-kHz vocalizations and reward has been found using place preference, instrumental choice, and bar-pressing paradigms (Knutson et al., 2002). With the aide of digital sound acquisition equipment (Fostex, USA) and a computer based sonographic analysis program (Avasoft Bioaccustics, Germany), which do not modify the ultrasonic signal to be heard in the human audible range with a bat detector, we are able to detect a variety of different types of 50-kHz calls first described in White et al. (1990). Of these various 50-kHz subtypes, it is the frequency modulated variety (primarily with trill components) in which the high tickle adult females exhibit more then the low responders (Fig. 3), USVs.

3.2. Neurochemical control of 50-kHz ultrasonic vocalizations

Given that dopamine receptor antagonists have been found to reduce positive affective states in humans (e.g.

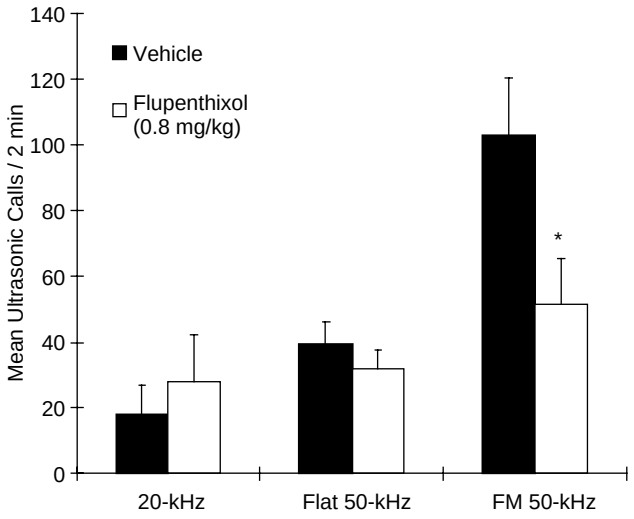

Fig. 4. Mean (±SEM) ultrasonic vocalization in adult female long evens rats during tickling following pretreatment with vehicle or alpha-flupenthixol (0.8 mg/kg, i.p). Testing protocol was similar to Panksepp and Burgdorf (2000). Ultrasonic vocalizations were recorded from the high frequency (untransformed) output of a Pettersson D980 bat detector onto a Fostex fr-2 field recorder with a 196-kHz, 24 bit sampling rate. *$P<0.05$, within subjects *t*-test, two-tailed.

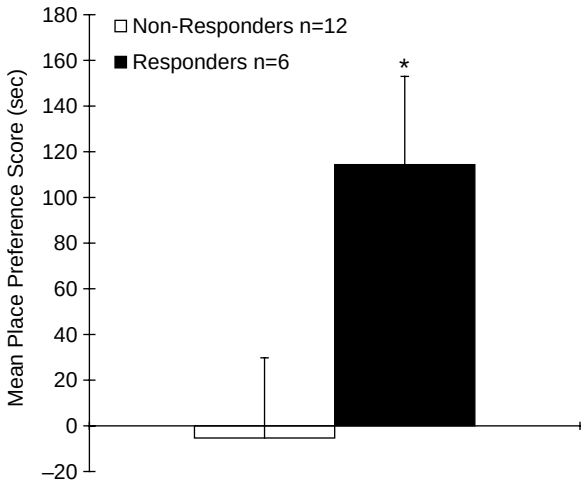

Fig. 5. Mean (±SEM) place preference score (time on drug side testing minus habituation) in rats conditioned with a single 30 min pairing of 100 ng DAMGO in 500 nl over 1 min microinjected unilaterally into the VTA on the drug paired side, and a single 30 min pairing of vehicle microinjection in the vehicle paired compartment using an unbiased place preference procedure. The responder group consisted of animals which exhibited at least twice as many 50-kHz calls during the first 5 min proceeding, or more calls during first and second 5 min in response to DAMGO injection as compared to vehicle injection. *$P<0.05$, within subjects *t*-test, two-tailed.

those induced by psychostimulants), we tested the D1/D2 receptor antagonist alpha-flupenthixol in our tickling paradigm at a dose shown to block the rewarding effects of psychostimulants, but that does not produce conditioned place aversion (Mackey and van der Kooy, 1985). We found that alpha-flupenthixol specifically reduced the frequency modulated 50-kHz calls, without affecting non-frequency modulated 50-kHz calls or aversive 20-kHz calls (Fig. 4).

Conversely, psychostimulant induced positive affect has been found to be positively correlated with increased dopamine levels in the nucleus accumbens (NAcc) as inferred by decreased raclopride binding (e.g. Drevets et al., 2001). In rats, injecting amphetamine directly into the NAcc robustly elevates local dopamine levels at doses that are rewarding to the animal. We found that amphetamine given peripherally or directly into the NAcc increases levels of 50-kHz ultrasonic vocalizations (Burgdorf et al., 2001a; Knutson et al., 1999). The greatest elevations in 50-kHz calls were seen in animals injected with amphetamine directly into the medial shell subregion of the NAcc. In this subregion, only rewarding stimuli have been found to elevate dopamine levels, with aversive stimuli decreasing dopamine levels (Di Chiara, 2002).

In general, the drugs that are addictive to humans (e.g. opiates and psychostimulants) also elevate dopamine levels in the NAcc (Di Chiara and Imperato, 1988). In addition to their addictive and dopamine facilitating qualities, these drugs have also been shown increase positive affect when given to humans. While drug craving and withdrawal effects may better account for the long-term addictive effects of these drugs (Robinson and Berridge, 1993; Koob and Le Moal, 2001), they do not contravene the acute euphorigenic effects. In addition to amphetamine, we have tested a subset of these positive affect inducing drugs injected directly into the brain areas in which they are most rewarding. So far, we have found elevations in 50-kHz calls in response to nicotine, opiates, and barbiturates when injected directly into the VTA (Burgdorf and Panksepp, in preparation), which is the brain area most closely tied to their rewarding effects.

In the case of opiates, only the animals which show elevated 50-kHz ultrasonic vocalizations in response to opiates administered into the VTA find these same microinjections to be rewarding (Fig. 5). We have shown that re-exposure to an environment previously paired with a rewarding dose of morphine elevates levels of 50-kHz calls, whereas aversive drug paired environments decrease 50-kHz calls compared to vehicle (Burgdorf et al., 2001b). When injected into the VTA, both the GABA-A receptor agonist muscimol and antagonist bicuculline are rewarding, while only the rewarding effect of muscimol is blocked by dopamine receptor antagonists (Laviolette and van der Kooy, 2001). We have found that VTA injections of muscimol but not bicuculline elevate levels of 50-kHz calls (Fig. 6), again suggesting that the rewarding effects of dopamine are linked to 50-kHz calls.

The final link to the human neuroscience literature on positive emotion is intracranial self-stimulation. In their research programs both Robert Heath and Sem-Jacobsen and their colleagues reported some patients in which electrical brain stimulation produced positive affective

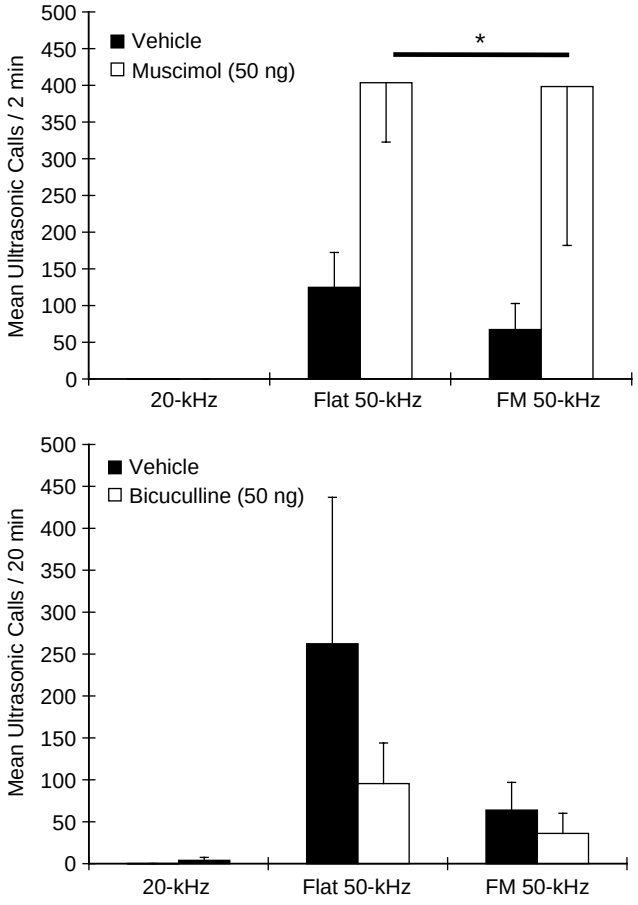

Fig. 6. Mean (±SEM) Ultrasonic vocalizations following unilateral microinjections of 50 ng muscimol (Top) or 50 ng bicuculline (Bottom) into the ventral tegmetal area in 500 nl over 1 min. *$P<0.05$ within subject *t*-test (two-tailed) comparing total 50-kHz calls (flat+frequency modulated) in muscimol vs. vehicle conditions.

states. When self-stimulation was evaluated, electrode placements yielding 50-kHz calls were repeatedly self-activated. While positive affect may have been sufficient for self-stimulation, it does not appear to be necessary, with some patients self-administering stimulation which lead to frustration and not to positive affect (Health, 1960). In rats, we have shown that stimulation of electrode sites that supported self-stimulation provoke more 50-kHz calls than sites which do not support self-stimulation (Fig. 7). In the subset of animals in which electrical stimulation triggered 50-kHz calls in a reproducible manner, all of these animals showed self-stimulation. Similar to tickle induced USVs, D1/D2 antagonist alpha-flupenthixol decreased frequency modulated 50-kHz calls in animals that showed reliable ESB induced 50-kHz calls (Fig. 8). However, some animals did show self-stimulation without showing ESB induced 50-kHz calls. Therefore, similar to the human studies, positive affect seems to be sufficient but not necessary for self-stimulation. In other words, self-stimulation may reflect several distinct affective processes—an issue in need of

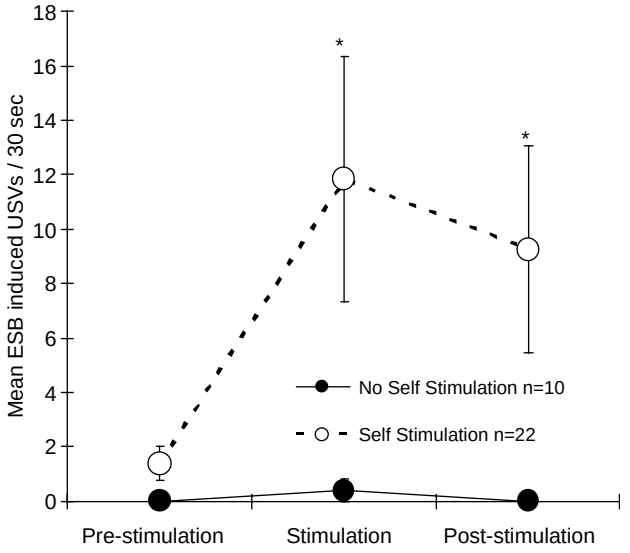

Fig. 7. Mean (±SEM) 50-kHz ultrasonic vocalizations in response to non-contingent electrical stimulation (120 μA, 60 Hz for 10 s) in adult female long evens rats implanted with bipolar electrodes in the ventral tegmental area, accumbens, Cingulate, bed nucleus stria terminalis, and tegmental pedunculopontine nucleus. The self-stimulator group consisted of animals which subsequently showed reliable self-stimulation behavior (3≥bar-presses min). *$P<0.05$ within subjects *t*-test, two-tailed.

further attention through sophisticated neuro-behavioral analyses.

4. The locus of control for affective processes

Although experimental manipulations of sub-neocortical limbic areas of the brain tend to produce the strongest affective experiential changes in humans, and emotional behaviors in animals, there is still considerable controversy about whether other animals can have affective experiences. The traditional solution has been to suggest that all

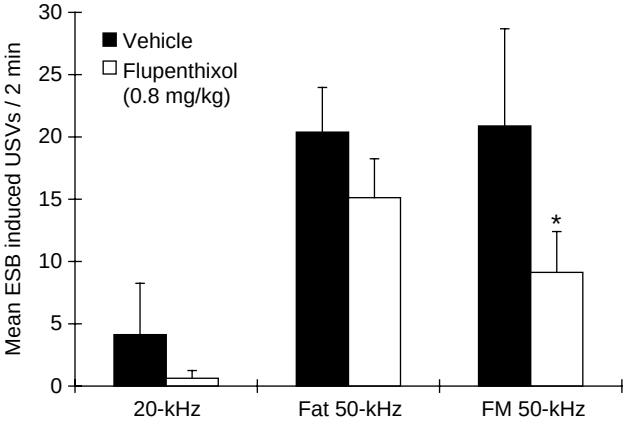

Fig. 8. Mean (±SEM) 50-kHz ultrasonic vocalizations in response to non-contingent electrical stimulation (120 μA, 60 Hz for 10 s) in the subset of animals that reliably showed ESB elicited 50-kHz vocalizations following pretreatment with vehicle or alpha-flupenthixol (0.8 mg/kg, i.p). *$P<0.05$ within subjects *t*-test, two-tailed.

conscious experiences require neo-cortical participation. However, we would argue that the more parsimonious, data-based view is that ancient pre-propositional forms of consciousness, such as raw affective experiences, can be elaborated completely within sub-neocortical limbic regions of the brain, and that a host of affective processes are elaborated there (Panksepp, 1998, 2003a,b, 2005). There are strategic benefits to be had if we accept, as a provisional working hypothesis, that all other mammals have basic forms of affective consciousness, not that dissimilar from our own. Such reasonable views offer many new and robust research strategy for working out important experiential aspects of the human mind from thirst and hunger to lust and loneliness (Panksepp, 1998, 2003a,b). This, of course, is not the same as to argue that the other animals have much propositional cognitive consciousness that would allow them to think about their affective states in ways we humans are prone to do, even though the analysis of cognitive–emotional interactions is a challenge that needs to be addressed (Paul et al., 2005).

If one considers all the available evidence, the following conclusion seems inescapable: a variety of affective networks were present in all our mammalian ancestors, and still exist in all living mammals. These internal value codes allow the nervous system to reference many other behaviors with respect to the survival value (utility) of environmental objects and behavioral actions. The importance of such brain mechanisms for survival may have 'discouraged' the weeding or dramatic genetic modifications of the infrastructures. Even though there are surely abundant species-specific elaborations upon these foundations (e.g. rats intrinsically fear the smell of cats; humans and most other mammals do not), the general neural principles may be conserved (e.g. executive neurochemistires). As higher brain functions emerged, some of the lower functions may have actually become less affectively conscious because those higher functions operated more effectively by inhibiting lower functions (Liotti and Panksepp, 2004). Thus, it remains possible that other animals are, in fact, more intensely affective than humans, at least with respect to the core affects which do not depend heavily on cognitions (e.g. sensory alliestesia, Cabanac, 1979, 2005). To find some support for such a view, we have to go no further than young children who are typically much more emotional than their parents. In other words, some of our lower affective functions may have been experienced more intensely prior to the emergence of the higher cognitive functions–higher mental functions that many cognitive scientists still deem essential for having any form of internally experienced states at all.

A cortical 'read-out' explanation of affective experience is unparsimonious, and proponents of such a perspective have yet to effectively deal with many apparent paradoxes with such a view, the main one being the strong evidence that we always get much stronger affective responses by manipulating the sub-neocortical limbic loci of control for emotions, than by manipulating higher neocortical functions of the brain.

What is 'gained' by a sub-neocortical limbic focus? We could capitalize on simple and straightforward empirical strategies for pursuing many of the important human issues, such as psychiatrically relevant feeling-disorders through animal research (Panksepp, 2004). Why do so many still find it more important to marginalize the affective consciousness of animals, when the acceptance of such processes opens up robust mechanistic strategies to tackle some of the greatest problems that neuroscience has yet to solve? It is all too easy to simply assert that these ancient limbic mechanisms only generate unconscious emotional outputs, but that is an opinion that currently flies against a rather large body of evidence (Panksepp, 1998, 2005). Although many of our cognitive capacities may be deeply unconscious, that may not be the case for affective states that help to conditionally and unconditionally *valuate* the world.

In making such arguments, it is important to re-emphasize that most modern fMRI brain-imaging studies of 'unconscious emotions' are dealing with unconsciousness at the cognitive (perceptual information-processing) level, and practically none of those studies has monitored affect (by taking measures of changes in valence, arousal and surgency levels). Until they do that, they should only claim that they are dealing with cognitively unconscious processes, while saying nothing about affective states. In other words, too many investigators have simply failed to even consider the possibility that affective consciousness has distinct neural principles (Panksepp, 2003a,b). Indeed, it has recently been demonstrated that emotional information presented tachistoscopically under the absolute detection threshold (1 ms) can yield reliable changes in emotional feelings, specifically on the measure of surgency, using Lang's Mannakins (For summary see Panksepp, 2004).

Our own work is based on the assumption that the animal work can tell us more about affective consciousness than any type of ethically conceivable human work. Conversely, the animal work may tell us much less about how the human cognitive apparatus (most people's meaning for the term 'consciousness') operates. Although it may be strategically wise for the time being to simply focus on positive and negative affect measures (as can be done by various preference and aversion studies), in the future we may need a more resolved taxonomy to make sense of how the mammalian brain is functionally organized (Panksepp, 1998).

5. Conclusions

There appear to be at least two distinct classes of PA states represented in the brain, with separate but overlapping

neuroanatomical substrates. An appetitive PA system, devoted to foraging and reward-seeking, associated in part with the effects of psychostimulants such as cocaine and amphetamine is dependent in part on the ventral striatal dopamine system. A nearby PA system involved in processing sensory pleasure such as pleasurable touch and hedonic tastes involves the opiate and GABA system in the ventral striatum and orbital frontal cortex. These classical distinctions between appetitive and consummatory processes have been encapsulated in motivational theories which distinguish the brain substrates of expectancy type processes, such as seeking and wanting, from consummatory reward processes (Berridge and Robinson, 2003; Ikemoto and Panksepp, 1999; Panksepp, 1981, 1982, 1986, 1998).

This distinction between appetitive and consummatory PA systems is well illustrated by the work of Jürgens (1976), in which electrical brain stimulation revealed two distinct rewarding brain circuits that elicited two separate call types. The more appetitive PA call is normally exhibited when monkeys unexpectedly find palatable food or are reunited with a conspecific after a long separation, whereas the second call is exhibited during nursing as well as conspecific grooming.

Although there is still a vigorous movement to relate activity in the appetitive part of this system under the concept of reward consummation pleasures (Wise, 2004), we believe that a disciplined distinction between the positive feelings from sensory pleasures and the appetitive energization (encapsulated well in human exclamations such as 'I was so excited, It was such fun!') needs to be made in order to understand how emotional behaviors and subjective affective experiences are generated by specific types of brain activities. Some are finally beginning to make such distinctions, while others continue find such 'spooky' neurodynamic concepts troublesome in our aspirations to have a mechanistic understanding of brain and mind.

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