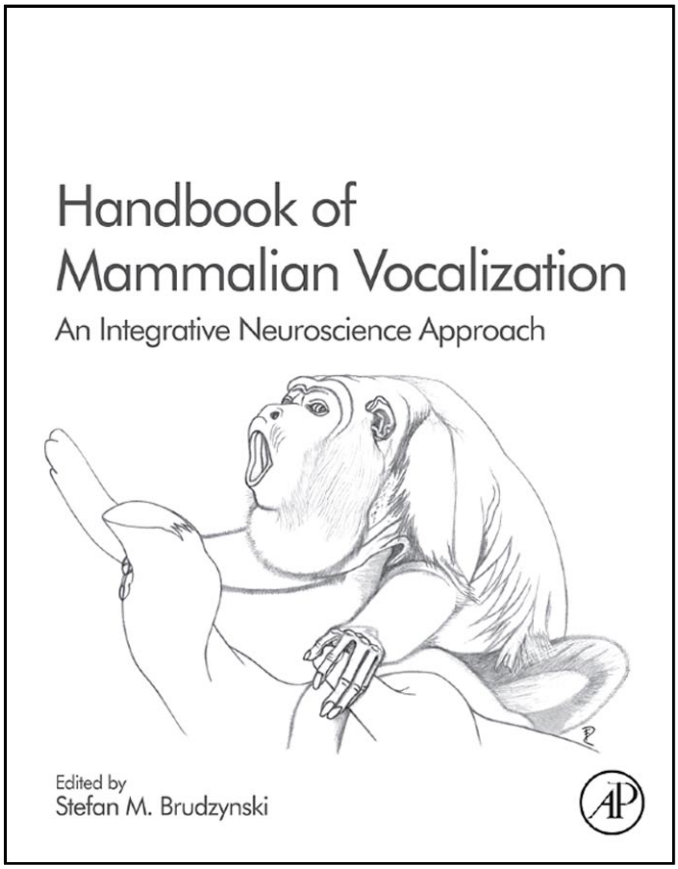

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CHAPTER 6.2

Frequency modulated 50 kHz ultrasonic vocalizations reflect a positive emotional state in the rat: neural substrates and therapeutic implications

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Abstract: The evidence that frequency modulated (FM) 50 kHz ultrasonic vocalizations (USVs) reflect a positive emotional state in rats is reviewed. Positive emotional states in humans are measured by facial/vocal displays (e.g., Duchenne smiling and laughter), approach behavior and subjective self-reporting of feeling states. In laboratory animals, only facial–vocal displays, along with approach behavior, can be measured. FM 50 kHz USVs are uniquely elevated by hedonic stimuli and suppressed by aversive stimuli. Rates of FM 50 kHz USVs are positively correlated to the rewarding value of the eliciting stimulus. Playbacks of these vocalizations are also rewarding. The neural and pharmacological substrates of 50 kHz USVs are consistent with those of human positive affective states. By experimentally eliciting FM 50 kHz USVs, the novel molecular underpinning of positive affect can be elucidated and may be similar to those in humans. In humans, positive emotional states confer resilience to depression and anxiety, as well as promote overall health. Therefore, novel antidepressants that promote positive affect-induced resilience to depression may emerge from this research.

Keywords: ultrasonic vocalizations; emotion; rat; human; frequency modulation; dopamine; depression; nucleus accumbens; 50 kHz calls

I. Positive affective states in humans

I.A. Measuring positive affective states in humans

Subjective well-being appears to be a unitary concept in humans, with self-reported well-being having a high correlation with independent third-party rating (spouse or friend) and the objective physiological measures of Duchenne smiling and EEG lateralization (Ekman et al., 1990; Rosenkranz et al., 2003; Lyubomirsky et al., 2005). The most consistent personality traits associated with subjective well-being are a positive correlation with extroversion and a negative correlation with neuroticism (Diener et al., 2003). In both adults and adolescents, the activity eliciting the most positive affective state is socializing with friends or romantic partners (Csikszentmihalyi and Hunter, 2003; Kahneman and Krueger, 2006; Stone et al., 2006). It is important to note that not all socializing is hedonic. The same studies showed that socializing with friends or one's romantic partner elicit positive affective states, while interacting with supervisors and other family members is not consistently hedonic. Therefore, positive affective states are primarily related to positive pro-social interactions.

Experimental studies that elicit positive affective states generally use social positive affective stimuli (i.e., positive feedback, giving a small gift, or watching a video tape eliciting positive affective state). Positive affective states that are elicited in an experimental

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setting by these social stimuli have been shown to increase gregariousness, optimism and openness to new experiences (Lyubomirsky et al., 2005). These effects of positive affective state inductions have been referred to as "broaden and build" (Fredrickson et al., 2004).

A functional distinction can be made between positive pro-social affective states primarily associated with subjective well-being and consummatory pleasures. Experimental study of nonsocial hedonic stimuli (i.e., food or thermal regulation) showed that these pleasures function primarily to maintain homeostasis. 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 (Cabanac, 1971). This emotionally-driven change in sensation associated with a return to homeostasis is referred to as sensory alliesthesia (Cabanac, 1971, 1992).

Positive affective states, as studied longitudinally in humans, confer resilience to depression and anxiety, and lead to an increase in overall health and a decrease in mortality from all causes (Lyubomirsky et al., 2005). The psychological and physical health benefits of positive affective states appear to be mediated through increased resilience, defined as continued global functioning despite the presence of stressors. For example, following a major life stressor individuals exhibiting greater resilience are less likely to develop psychological disorders, such as anxiety or depression (Fredrickson et al., 2003). Longitudinal studies also showed that positive affective states precede the health benefit effect of positive affect (Lyubomirsky et al., 2005). Therefore, positive affect is not simply a secondary consequence of overall good health. Positive affective states are stable across the lifespan, with major positive and negative life events having little long-term effect on these states (Lykken and Tellegen, 1996). Conversely, individuals who have low levels of positive affective states are at greater risk of developing anxiety disorders, depression and global health problems (Lyubomirsky et al., 2005). Interventions that increase positive affective states have been shown to reduce levels of depression and anxiety (Duckworth et al., 2005).

I.B. Neurobiology of positive affective states in the human brain

The primary neuroanatomical underpinnings of positive emotional states are associated with the ascending mesolimbic dopamine system, and have relied primarily on correlational brain imaging studies (i.e., functional magnetic resonance imaging or positron emission tomography), as well as on the direct elicitation of positive affective states through drug administration or electrical brain stimulation. Brain imaging studies using recall of positive affective memories (Damasio et al., 2000), listening to positive music (Blood and Zatorre, 2001), male orgasm (Holstege et al., 2003) and positive anticipation of monetary reward (Knutson et al., 2001) have all been shown to activate aspects of the ascending mesolimbic dopamine system that includes the ventral tegmental area, nucleus accumbens, medial prefrontal and orbital frontal cortices (Burgdorf and Panksepp, 2006). The euphoric effects of intravenous amphetamine have been shown to be directly related to dopamine activity in the nucleus accumbens (Drevets et al., 2001; Oswald et al., 2005). Direct electrical brain stimulation of the accumbens has been shown to elicit Duchenne laughter and self-report of positive affect (Okun et al., 2004). Patients given the opportunity to self-administer electrical stimulation to the nucleus accumbens (then called the nucleus accumbens septi as a ventral extension of the lateral septum) or to an area at or near the ventral tegmental area, repeatedly self-administered this stimulation and reported that the stimulation elicited a positive affective state (Heath, 1960, 1972).

I.C. Molecular underpinnings of positive affective states

The molecular mechanisms that are involved in the regulation of positive affective states are largely unknown. In order to establish a causal link between a molecular mechanism associated with positive affect, the following conditions must be fulfilled: (1) concentrations of key molecules associated with the mechanism under investigation should be significantly altered in critical brain regions following positive affective stimuli; (2) these molecular changes should change in the opposite direction or not change significantly at all, following presentation of negative affective stimuli; (3) direct injection of the target molecules or agonists should produce a positive affective state; and (4) pharmacological agonism/antagonism of the key molecules should increase/decrease positive affective states. Thus far, no molecular mechanism reported to be associated with positive affective states that has been characterized could meet all four of these criteria.

Endogenous opiates acting on μ-receptors (endomorphins, met-enkephalin, and β-endorphin) and dopamine have been the most extensively examined (reviewed in Burgdorf and Panksepp, 2006). Mu(μ)-opiate and dopamine levels in the mesolimbic positive affect circuit have been found to be positively correlated with the euphoric effect of exercise and amphetamine respectively (Drevets et al., 2001; Boecker et al., 2008). Intravenous administration of μ-opiate and dopamine agonists produced positive affective states in humans (Zacny et al., 1994; Drevets et al., 2001). Mu(μ)-opiate antagonists have been shown to blunt the positive affective state elicited by exercise and alcohol (Janal et al., 1984; Davidson et al., 1999), and dopamine antagonists decreased positive affective states associated with psychostimulants (Jönsson et al., 1971; Romach et al., 1999; Newton et al., 2001) and could produce a state of dysphoria (Voruganti et al., 2001). However, aversive stimuli also increase μ-opiate and dopamine levels in the nucleus accumbens (Tidey and Miczek, 1996; Marinelli et al., 2004). Therefore, the μ-opiate and dopamine systems are not completely specific to positive emotions.

II. Measuring positive affective states in laboratory animals

In order to establish that an animal behavior reflects a positive affective state, several criteria must be met. In humans, positive affective states are measured primarily via subjective self-report and behaviorally by facial/vocal displays such as felt- or Duchenne-smiling (Ekman et al., 1990). Therefore, in laboratory animal experiments, where we can rely only on observations, a positive affective state should be expressed as facial or vocal displays with the predicted changes in approach/avoidance behavior. In humans, positive affective states are elicited primarily by rewarding social interaction, food and exercise, and are decreased by negative affective stimuli (Csikszentmihalyi and Hunter, 2003; Kahneman and Krueger, 2006; Stone et al., 2006). Therefore, in laboratory animals, the same categories of positive affective (appetitive) stimuli should increase the facial/vocal displays and aversive stimuli should decrease them. Finally, what is known about the neurobiological mechanisms of the facial/vocal displays in animals should be consistent with the neurobiological mechanisms of human positive affective states. To date, only two such animal behaviors meet all of these criteria; emission of ultrasonic vocalizations (USVs) that are discussed below, and hedonic taste reactivity (reviewed in Berridge et al., 2008).

II.A. 50 kHz social vocalizations in rats

Fifty kHz ultrasonic vocalizations (50 kHz USVs) have been shown to reflect a positive affective state in rats. Rewarding social interactions (i.e., mating and rough-and-tumble play in juveniles), anticipation of food and action of euphorigenic drugs of abuse increased the number of emitted 50 kHz USVs (Burgdorf et al., 2000, 2001a, 2007, 2008; Panksepp and Burgdorf, 2000) (see example in Fig. 1), whereas aversive stimuli such as social defeat, frustrative non-rewarding situations, sickness-inducing doses of lithium chloride and foot-shock all decreased the number of 50 kHz USVs (Burgdorf et al., 2000, 2001b, 2008). The rewarding value of the stimuli eliciting positive affective states was positively correlated with the rates of 50 kHz USVs elicited by positive social, drug and electrical brain stimulation rewards (Burgdorf et al., 2007, 2008). Mu(μ)-opiate and dopamine agonists, as well as electrical brain stimulation of the mesolimbic dopamine system, also increased rates of 50 kHz USVs in rats (Burgdorf et al., 2000, 2007).

Also, alternative non-hedonic interpretations of the emission of 50 kHz USVs (e.g., non-positively valenced arousal, non-positively valenced seeking behavior, or

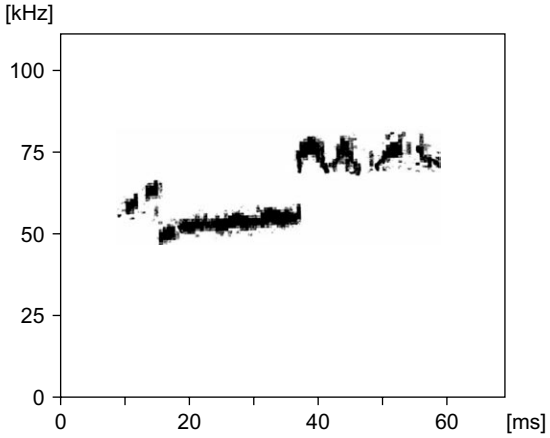

Fig. 1. An exemplary sonogram of a developed frequency modulated (FM) 50 kHz call of an adult rat induced by amphetamine. It contains two forms of frequency modulation: a step (seen at 18 ms); and a trill (seen from 40 to 60 ms). Total duration of the call is 50 ms. Courtesy of Melanie Komadoski.

Table 1. Non-affective hypotheses of 50 kHz USVs emission with their rebuttal

I. 50 kHz USVs are an artifact of locomotor activity-induced thoratic compressions (Blumberg, 1992). Only 10% of 50 kHz were coincident with thoratic compressions, and could be dissociated from locomotion (Panksepp and Burgdorf, 2003).
II. 50 kHz USVs are a non-affective contact call (Schwarting et al., 2007). Flat 50 kHz calls appear to be a contact call, occurring at the highest rates during non-positive affective social interactions. However, FM 50 kHz calls appeared to be selective for positive affective social interactions (Burgdorf et al., 2008).
III. 50 kHz calls are evident during aggression (Berridge, 2003). 50 kHz calls occur primarily before the onset of aggression, and the vast majority of the 50 kHz calls were of the non-affective flat variety (Panksepp and Burgdorf, 2003; Burgdorf et al., 2008).
IV. 50 kHz calls reflect a non-positive affective "wanting" state (Schwarting et al., 2007). 50 kHz USVs were increased in the anticipation of delivered reward, which in humans has been shown to elicit a positive affective state (Knutson et al., 2001). However, during extinction bursts or "frustrative non-reward" such appetitive behavior decreased rates of 50 kHz calls and increased rates of aversive 22 kHz calls (Burgdorf et al., 2000).
V. Adult and infant rat ultrasonic calls reflect a state of high arousal that is not specific to positive affective states (Bell, 1974). Highly arousing aversive stimuli such as predatory odor, foot-shock and bright light, decrease rates of 50 kHz calls, whereas rewarding stimuli increase rates of 50 kHz calls (Knutson et al., 2002).

non-affective social contacts) are not supported by the available experimental data (for details, see Table 1).

II.B. 22 kHz aversive vocalizations in adult rats and isolation calls (35–40 kHz) in infants

Adult 22 kHz USVs and infant isolation calls (35–40 kHz) may represent a negative emotional state associated with human anxiety and/or depressive states (e.g., aversive facial expressions such as crying, and behavioral inhibition) (Knutson et al., 2002). Despite significant sonographic differences between these adult and infant vocalizations (see Panksepp, Chapter 6.1 in this volume), both of them share similar characteristics to the aversive and dangerous situations which elicit them. In humans, these affective states are often elicited by social loss and anticipation of perceived threats (Knutson et al., 2002). In rats, infant isolation 35–40 kHz USVs are best elicited by separating the pup from the mother. Twenty-two kHz USVs are best elected by social defeat and the presence of a predator (Blanchard and Blanchard, 1989; Brunelli and Hofer, 2007; Panksepp et al., 2007). Emission of 22 kHz USVs calls is strongly related to avoidance behavior and freezing during social defeat testing (Panksepp et al., 2007). Environments paired with drugs causing aversive states also elicit 22 kHz USVs, and rates of emitted calls are positively correlated with drug-induced conditioned place avoidance (Burgdorf et al., 2001b). Anxiolytic benzodiazepines and antidepressants reduce rates of 22 kHz calls and 35–40 kHz USVs (Carden and Hofer, 1990; Covington and Miczek, 2003).

Using social defeat as a method to elicit negative emotional states associated with 22 kHz USVs, we conducted a transcriptomic analysis of gene expression in the periaqueductal gray, one of the regions found to be critical for the generation of negative affect and 22 kHz USVs in rats (Kroes et al., 2007). These studies revealed that mRNA expression of genes associated with acetylcholine metabolism and receptor function was altered in the PAG following social defeat. This finding is consistent with the previously reported role of the tegmental cholinergic system in the generation of 22 kHz USVs (Brudzynski, 2001). Carbachol has been shown to be the best elicitor of these vocalizations in both rats, cats and squirrel monkeys (Lu and Jürgens, 1993; Brudzynski, 2007; see also Brudzynski, Chapter 7.3 in this volume). Recent studies in humans demonstrated that depressed patients have alteration in cholinergic transmission (Wang et al., 2004), and scopolamine has been shown to be a potent rapid antidepressant (Furey and Drevets, 2006).

II.C. Selective breeding for differential rates of 50 kHz and 22 kHz ultrasonic vocalizations

In order to further elucidate the molecular mechanisms that are involved in the regulation of positive and negative emotional states, rats were selectively bred for differential rates of hedonic 50 kHz USVs (Burgdorf et al., 2005, 2008). Animals selectively bred for low rates of 50 kHz USVs (low line) had a concomitant increase in 22 kHz USVs and showed elevated levels of anxiety in the open field, in the social contact test and in infant distress vocalization tests, as compared to randomly bred animals (Burgdorf et al., 2008). Conversely, animals selectively bred for high rates of 50 kHz USVs (high line) had a concomitant decrease in the 22 kHz USVs, and showed lower levels of anxiety in the open field test, decreased rates of aggression and increased sensitivity to sucrose reward, compared to randomly breed animals (Burgdorf et al., 2008). These animals

have been selectively bred for 18 generations to date and have displayed stable differences in USVs from adolescence through adulthood (three months).

Studies on the molecular mechanisms associated with the USV patterns of the high line and low line animals to date are consistent with a depressant-resilient and a depressant-prone phenotype, as discussed above. For example, high line animals exhibited higher levels of the μ-opiate acting Metenkephalin-like immunoreactivity in the hypothalamus and other related limbic structures (Burgdorf et al., 2008). Injections of the μ-opiate agonist DAMGO into the ventral tegmental area (a region included in the hypothalamus dissection) increased rates of 50 kHz USVs and was rewarding to the animals (Burgdorf et al., 2007). Low line animals exhibited higher levels of cholecystokinin-like immunoreactivity in the posterior neocortex. Cholecystokinin (CCK) content in the posterior cortex was elevated by social defeat and was correlated with 22 kHz USVs rate of the defeated animal (Panksepp et al., 2004). It has also been shown that social defeat, which elevates levels of 22 kHz USVs, increased CCK-like immunoreactivity in cortical microdialysates (Becker et al., 2001) and CCK administration promoted social defeat-induced behaviors, including 22 kHz USVs (Becker et al., 2007).

III. Conclusions

Fifty kHz ultrasonic vocalizations (50 kHz USVs) have been shown to reflect a positive affective state in rats. By studying positive pro-social emotional states in rats, the neuroantomical basis and molecular mechanisms of this form of positive affect can now be elucidated. These studies should lead to a deeper understanding of the brain mechanisms of positive affect in humans, and should lead to the development of novel therapeutics for the treatment of depression and other affective disorders.

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