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Clinical Psychological Science 2014 2: 472
DOI: 10.1177/2167702614535913

The online version of this article can be found at:
http://cpx.sagepub.com/content/2/4/472
Affective Neuroscience Strategies for Understanding and Treating Depression: From Preclinical Models to Three Novel Therapeutics

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Abstract
Mammalian brains contain seven primary-process affective substrates for primal emotional feelings and behaviors. Scientific labels for these interactive systems are SEEKING, RAGE, FEAR, LUST, CARE, PANIC, and PLAY. Understanding these brain substrates could lead to new treatments of emotional disturbances that accompany mental illnesses. We summarize how understanding of such emotional affects—especially those of separation distress (PANIC, promoting excessive sadness and grief), SEEKING (promoting enthusiasm), and PLAY (promoting social joy)—may regulate depressive affect through a focus on the following: (a) reducing PANIC, namely, “psychic pain” with “safe opioids” such as buprenorphine; (b) facilitating enthusiasm with deep brain stimulation of the transdiencephalic medial forebrain bundle–based SEEKING urges; and (c) how studies of brain neurochemical pathways that facilitate social joy (PLAY) in animals have yielded novel neurochemical interventions (e.g., GLYX-13, a partial agonist of glycine receptors) currently in successful human testing. Affective neuroscience principles that have led to these advances are summarized.

Keywords
depression, preclinical models, PLAY system, PANIC system, SEEKING system, medial forebrain bundle, anterior cingulate area, deep brain stimulation, GLYX-13

Received 4/3/13; Revision accepted 3/21/14
Our major premises are (perhaps many clinical colleagues would agree) that (a) most emotional behavioral arousals are accompanied by various distinct affects, which are powerful forces in controlling human perceptions, thoughts, and actions; (b) such feelings, whether normal or excessive, reflect poorly understood functions of human brains and the brains of other mammals; and (c) researchers will not understand the fundamental (neurobiological) sources of psychopathologies until gaining an understanding of the nature of excessive human emotions and the cognitive activities they channel and energize. Our contention is that general principles concerning evolutionarily homologous emotional processes in the brains of other animals may provide insights for the human condition. Although relevant brain and bodily correlates of emotional feelings are more readily harvested in humans, we envision a fruitful blending of correlative relations from human studies with cross-species “causal” insights for improving both human and nonhuman animal welfare (see the Elaborations, Limitations, and Qualifications section).

Our goal here is to focus on new perspectives on the underlying brain affective dysfunctions that lead to depression. By understanding the neurobiological nature of relevant brain emotional systems, optimally studied in detail in animal models, novel ways to envision and treat human depression should emerge. We introduce new, affective neuroscience-informed preclinical (animal) model approaches to understanding affective shifts that characterize depression—work that has already led to three promising novel interventions that have exhibited potential in ameliorating depressive affect in humans.

Our coverage proceeds in a three-pronged way: First, we briefly summarize key conceptual issues about three genetically ingrained emotional-affective systems of mammalian brains of paramount importance for understanding depressive feelings. Second, we describe how new preclinical studies of these systems provide brain circuit-based understanding of the neuroaffective sources of depressive affects. Finally, we summarize three novel therapeutic approaches, currently being evaluated for efficacy in humans, that have arisen from these perspectives. We also include five supplementary sections (see the Supplemental Material) on related issues that help flesh out the arguments. There is insufficient space here to extend the discussion to psychotherapeutic implications of this knowledge, but see Panksepp (2009, 2013) and Panksepp and Biven (2012) for potential connections.

How Basic Emotional Feelings Arise From Homologous Brain Processes Across Mammalian Species

Although the view that emotional feelings are passive, neocortically mediated perceptions of aroused bodily autonomic responses has been prominent in psychology (e.g., the James-Lange theory), it is also clear that there are core subcortical brain mechanisms that engender both emotional actions and associated feelings. These feelings do not require neocortical participation; they arise from homologous subcortical brain circuits that humans share, in kind, with many other animals (for overviews, see Damasio, 2010; Denton, 2006; MacLean, 1990; Panksepp, 1998). Thus, William James was largely mistaken in situating the primary origins of emotional feelings in body arousals that are read out by neocortex. His peripheralist view of emotional feelings has led to the widespread misunderstanding that primal emotional feelings are largely passive end results of emergency bodily reactions, rather than manifestations of ancient brain systems that mediate instinctual emotional behaviors. In fairness, James also conjectured that every emotional instinct (which we now know are brain functions) was accompanied by certain feelings.

The passive James-Lange view of emotional arousals had various unfortunate consequences across the past century. Perhaps the most insidious was the still-common view that emotions simply arise secondary to cognitions in the control of behavior (e.g., see the bear, recognize the danger, run, and then feel the emotion). This may be the sequence of events in mature, emotionally well-regulated adults, but it fails to recognize the proper evolutionary and developmental ordering of the mental apparatus, which is better described as a set of nested hierarchies (see the schematic in Fig. 1) with primal raw emotions and their affective emissaries arising from the very foundations (Solms & Panksepp, 2012). Psychological development, from infancy on, surely starts as a bottom-up affair, which sets the stage for top-down regulations. In other words, despite important prevailing top-down views of psychological causation, modern affective neuroscience highlights that bottom-up brain-mind maturation must precede top-down adult controls; that is, various intrinsic brain emotional-affective systems (primary processes) prevail during early childhood and help create stable behavior patterns through learning and memory (secondary processes), which forever continue to influence our thinking patterns (tertiary processes) that, only through learning, come to instigate emotional states. After the developmental construction of the higher cognitive apparatus, top-down control of emotionality and other behavior patterns begin to prevail (see Fig. 1), thereby yielding complex patterns of “circular causation,” as discussed in greater detail elsewhere (Northoff, Wiebking, Feinberg, & Panksepp, 2011; Panksepp, 2011a, 2011b; Panksepp & Biven, 2012; Wright & Panksepp, 2012). Affective states obviously channel and promote a great deal of cognitive activity ranging from impulsive to deliberate actions (there is insufficient space here to detail such claims, but
Circular causation—namely, bidirectional bottom-up and top-down interactions viewed from neuroevolutionary perspectives—has important consequences: Early in development, (a) core emotional systems mature long before most cognitive skills, which provides an evolutionary foundation for mind (defined here as the capacity to have subjective experiences, namely, consciousness; see Supplement 1 in the Supplemental Material); (b) the higher mental apparatus emerges under the tutelage of lower mental processes that have arbitrarily been considered as unconscious, which may be incorrect from the phenomenal, albeit not reflective “awareness,” perspectives (Panksepp, 1998; Solms & Panksepp, 2012; also see Reflections on the Dilemma of Unconscious Affects in Humans in Supplement 1 in the Supplemental Material for a critique of “unconscious affects”); and, as already noted, (c) affective arousals remain remarkably influential throughout life, controlling what we do and how we think. Emotional feelings are neither simply passive epiphenomenal consequences of bodily arousals nor secondary derivatives of higher mental processes, as often assumed (see Rolls, 2014, for one influential dissenting view). Although the body always remains important in many affective arousals, because of reentrant autonomic and enteric nervous system inputs, it is the higher brain that parses raw affects, encoded by subcortical systems, into cognitive contexts (e.g., secondary and tertiary processes interacting in cortices to generate thoughts and awareness of one’s raw valenced experiences, namely, “affective qualia”).

Subcortical emotional systems clearly evolved in concert with central brain autonomic and somatic controls because their work needed to be coordinated (Panksepp, 1998). We submit that raw affects were foundational for the evolution of the rest of the mind; that is, all the intrinsic affective potentials of the brain promote survival by heuristically anticipating future survival probabilities/gradients, thereby serving as foundations for experientially refined (learned reflexive as well as deliberative) decision making. For instance, brain mechanisms of hunger anticipate the body’s future need for nutrients, as do those of thirst for water needs. Cognitive activities extend these intrinsic survival functions much further in space and time. Psychotherapy can facilitate top-down regulation of imbalanced affective dynamics; optimal psychiatric medicines should assist by directly regulating problematic affects in a bottom-up way.

In their potential role as governors of intrinsic survival-relevant “anticipations” (i.e., all positive affects signal survival trajectories and negative affects signal potentially destructive ones), the fluctuations of core affects may mediate reinforcement-based learning (via yet-to-be-specified laws of affect), thereby becoming major forces in the development of cognitive patterns that promote adaptive and maladaptive thinking. With regard to emerging psychopathologies, it is commonly difficult to change persistent cognitive patterns that result from negative feelings, including persistent and affectively negative ruminations that accompany depression. Although top-down psychological therapies surely work, evidenced by abundant literature regarding benefits of cognitive-behavioral and psychodynamic therapies, maladaptive cognitive patterns are most easily remolded by first changing individuals’ core affects, as with dynamic emotive therapies (e.g.,

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**Fig. 1.** Schematic of nested hierarchies of psychobehavioral control within the brain: a summary of the hierarchical bottom-up and top-down (circular) causation that is proposed to operate in every primate emotional system of the brain. The schematic summarizes the hypothesis that for higher mind-brain functions to mature and function (via bottom-up control), they would have to be integrated with the lower brain-mind functions. Primary processes are depicted as rectangles (the SEEKING level), secondary-process learning is depicted as circles (the “wanting” level of analysis—as developed by Kent Berridge and colleagues; Berridge, 1996; Berridge & Robinson, 1998; Berridge, Robinson, & Aldridge, 2009), and tertiary processes are depicted as squares (the “reward-prediction-error” level of analysis, as proposed by Wolfram Schultz and colleagues; Schultz, 2000, 2010; Schultz & Dickinson, 2006). For further relevant discussion, see Wright and Panksepp (2012) and Panksepp and Wright (2012, especially Fig. 1, p. 60). The schematic aims to convey the manner in which bottom-up evolution of nested hierarchies can integrate lower brain functions with higher brain functions to eventually exert top-down regulatory control, with distinctly labeled levels of control. Bottom-up controls prevail in early infancy and early childhood development; top-down control is optimized in adolescence and especially in adulthood. Each emotional system has abundant descending and ascending components that work together in a coordinated fashion to generate various instinctual emotional behaviors as well as the raw feelings normally associated with those behaviors.
Abass, Hancock, Henderson, & Kisely, 2006; Fosha, Siegel, & Solomon, 2009; Shedler, 2010) or psychotropic/psychiatric medicines. Here, we concentrate on brain affective approaches in partnership with diverse psychotherapies. We first focus on primary-process, cross-species neuroscience best studied with direct/deep brain stimulation (DBS) in animals.

**Preclinical foundations: Cross-mammalian emotional systems and affective feelings**

Affective neuroscience research has indicated that core emotional feelings arise from diverse neurochemically driven electrodynamics of the brain. The defining line of argumentation is based on the empirically demonstrated rewarding and punishing properties of specific emotional circuits that engender distinct emotional displays during localized DBS of subcortical brain regions. An understanding of affective primary-process systems has so far been achieved largely with animal models (see Panksepp, 1998, 2005, 2011a, 2011b); secondary processes have been illuminated through studies of fear learning (e.g., LeDoux, 1996, 2012a) and cognitive, tertiary processes with explicit decision-making models (e.g., Rolls, 2014, who asserted that consciousness is derived from linguistic abilities).

In fact, primal neuroaffective states (e.g., pain) are not only fundamental aspects of human nature but also brain endowments in all mammals. Human understanding typically arises from the study of human phenomenological experience—through the analysis of what people verbally report. But how can we ever know that nonhuman animals have emotional feelings? To reiterate, in creatures that do not speak, the gold standard for emotional feelings is what they behaviorally report, through simple operant and instrumental learning tasks. The most compelling “feeling reports” from nonhuman animals come from evaluating affective shifts during electrical DBS of subcortical emotional circuits, which are monitored by their rewarding and punishing states (Panksepp, 1982, 1998). The evidence is simple: Wherever one can evoke coherent emotional behaviors with DBS—effects exclusively obtained from deep subcortical brain regions, especially diencephalon and midbrain (but not neocortex)—nonhuman animals uniformly treat those arousals as being rewarding or punishing using simple learning tasks. For instance, DBS rewards are commonly measured via self-stimulation and punishments by escape/avoidance behaviors. Humans routinely give corroborative verbal reports of corresponding affective shifts following DBS in the same brain regions (for reviews, see Heath, 1996; Panksepp, 1985). For instance, when DBS was applied to the periaqueductal grey (PAG), a brain region that mediates FEAR and PANIC in animals, a person stimulated in this brain region promptly reported, “I’m scared to death!” (Nashold, Wilson, & Slaughter, 1969, p. 19).

Abundant evidence has now affirmed that both humans and other animals exhibit great “value” during artificially (e.g., DBS) evoked emotional behavioral arousals, thereby indicating shifting affective states of mind. Although one cannot be certain of phenomenal details, valence shifts can be inferred from evoked rewarding and punishing states. Humans can readily provide distinctions among various negative and positive feelings through language-based reports. Nonhuman animals cannot, given that they cannot speak, but distinct affect-indicative vocalizations can be evoked; as we discuss later, those circuits mediate rewards and punishments. Furthermore, nonhuman animals can make discriminations among certain rewarding sites, for instance, those in septal and lateral hypothalamic regions (as originally described by Stutz, Rossi, Hastings, & Brunner, 1974), which humans also distinguish readily (Panksepp, 1985). Thus, we claim that DBS-induced emotional reactions in nonhuman animals are validly interpreted as affectively significant when accompanied by rewarding and punishing effects. Other researchers still claim that such rewards and punishments can be unconscious (e.g., LeDoux, 2012a, 2012b; Rolls, 2014), but without demonstrations that similar brain manipulations are unconscious in humans, it is premature (perhaps unreasonable) to assume they are not experienced in other animals (see the Supplemental Material, in which we critique claims of unconscious affects in humans in Supplement 1 and introduce all seven primary emotional systems in Supplement 2: A Synopsis of Seven Primal Emotional Systems, hereafter, Supplement 2).

It is commonly believed that affects help guide and energize cognitive activities. For instance, affective arousals govern the words and intonations humans employ in communicating concerns. Emotional vocalizations of humans often convey feelings clearly, for instance, the laughter of childhood PLAY, the sounds of sexual pleasure and orgasm (LUST), the growls and yells of RAGE, the screams of pain that can arouse FEAR, and the soothing murmurs and sweet whispers of CARE. The social-separation cries of young animals (PANIC) arouse various concerned behaviors in parents, perhaps reflecting how their corresponding distress systems are aroused by distress of their infants (Panksepp, 1981a). On the basis of current knowledge, artificial (DBS) arousal of brain emotional vocalization circuits communicate feelings of emotionally aroused animals veridically: Rats choose to turn on DBS to brain circuits that mediate positive-affective “chirps” (approximately 50-kHz ultrasonic vocalizations, USVs) that occur abundantly during play and sex.
they turn off DBS-evoked 22-kHz USVs from the PAG (Wright & Panksepp, 2011), which is well known to provoke horrible feelings in humans and other primates (Jürgens, 2002). Such emotional systems have a strong imprint of evolution emblazoned on their neural infrastructure not only neuroanatomically but also neurochemically—they are brain systems shared homologously by all mammals.

We have claimed that abundant existing data are consistent with the possibility that raw affects lie at the very foundation of human and nonhuman animal consciousness (Panksepp, 1998; Solms & Panksepp, 2012), thereby suggesting that the higher mental apparatus may be deeply entwined with various affective values, which come, as noted, in emotional flavors (ones most relevant for psychiatry) but also in homeostatic (e.g., hunger, thirst) and sensory (e.g., taste, smell) varieties. It remains empirically defensible that various affective experiences are evolutionary birthrights of humans and other animals (Panksepp, 2011a, 2011b).

**Toward an understanding of the constitution of emotional feelings and three primal emotional systems most relevant for depression**

During the past 33 years, seven basic emotional systems—SEEKING, RAGE, FEAR, LUST, CARE, PANIC, and PLAY—have been extensively described (Panksepp, 1981a, 1981b, 1982, 1998, 2005; Panksepp & Biven, 2012). As clarified in Supplement 2 in the Supplemental Material, the capitalization is used as a scientific terminological convention for primary-process emotional systems (see Fig. 1), thereby allowing clear communication while skirting problems with vernacular emotional usages (e.g., mereological fallacies). The studies cited at the beginning of this paragraph provide extensive descriptions of these emotional networks, but it is not critical to reiterate details here, given that our focus will be on SEEKING, PANIC, and PLAY as being most relevant for understanding and treating depression. In the vernacular, we believe the putative respective feelings of these emotional systems are enthuism/exuberance (SEEKING), separation distress/grief/sadness (PANIC), and social joy/happiness (PLAY). We contend that these systems will help illuminate depression better than the study of more general state-control brain systems, such as biogenic amine theories of depression, in which brainstem norepinephrine and serotonin systems have riveted attention for the past half century. We suggest that a focus on more specific affective systems, especially the three highlighted in the following discussion (all modulated by serotonin and norepinephrine), should better promote development of new treatments for depression (Panksepp, 2004, 2006; Watt & Panksepp, 2009).

**SEEKING.** Depression is characterized by a general amotivational state accompanied by feelings of dysphoria, and there is abundant converging evidence that these are the kinds of affective changes that SEEKING depletion produces. For instance, if the medial forebrain bundle (MFB) is bilaterally lesioned, animals develop life-threatening diminution of all aspects of self-care (Teitelbaum & Epstein, 1962). Selective depletion of dopamine, a key transmitter along the MFB, produces similar, albeit weaker patterns, and psychostimulants that facilitate this system “energize” animal behaviors and human mental processes (yielding transitory antidepressant effects), often in addictively rewarding ways (for a summary, see Koob & Volkow, 2010). Self-stimulation of this circuitry dramatically highlights how “enlivened” animals become when this brain region is stimulated. This system mediates the strongest brain reward ever described. It is postulated that biomedical maneuvers that can nonaddictively elevate activity in subcomponents of this system may be robustly antidepressive. As we discuss later, DBS of this system in humans has now been very effectively used to treat depressed individuals, clearly promoting “enthusiasm” for life.

**PANIC.** Panksepp and colleagues (Herman & Panksepp, 1981; for summaries, see Panksepp 1982, 1998) were the first to map neurochemical controls and anatomical trajectories of the PANIC system with DBS (given that readers often become confused by the PANIC terminology, we have also referred to this system as GRIEF; see Panksepp & Biven, 2012). Ever since John Bowlby’s (1980) synthesis, it has generally been accepted that emotions of social loss may be critical in promoting depressive despair. The first neurochemistries shown to profoundly inhibit this system were the endogenous opioids and oxytocin, which are excited by a key chemistry of the brain stress axis, namely, corticotrophin releasing factor (for a summary, see Panksepp, Normansell, Herman, Bishop, & Crepeau, 1988). Accordingly, we have long hypothesized that brain opioids may be especially highly effective antidepressants, and possible antisuicide agents, if they could be used safely (i.e., nonaddictively). Consequently, we have evaluated and demonstrated the ability of low doses of the “safe” opioid buprenorphine to manage the psychological pain that often characterizes depression and suicidality (Yovell et al., 2013).

**PLAY.** Our group was the first to develop straightforward procedures to study the play of laboratory animals, which led to the initial understanding of the neurochemistries
Our goal for the remainder of this article is to summarize new therapies for human depression that have arisen from this type of cross-species affective neuroscience thinking. To reiterate, our guiding premise is that the neural understanding of primary-process emotional systems provides foundational knowledge for novel neuro-psychiatric medicinal as well as direct “brain affective-pacemaker” discoveries. Our preclinical work has set the stage for development of more specific and effective treatments for depression than currently exist. This move toward a focus on specific emotional networks allows preclinical modeling of affective disorders to aspire to beneficially regulate troublesome feelings more explicitly, via therapeutic modulation of specific emotional/affective systems, as opposed to simply focusing on global behavioral symptoms, pursuant to biogenic amine theories of emotion (Schildkraut, 1965) that currently remain the focus of most preclinical research (which space does not allow to be described here in detail; see Watt & Panksepp, 2009, as well as a selective critique of current behavior-only animal models in Supplement 3: Historical Perspectives of Preclinical Modeling in Biological Psychiatry: From the Era of Slow-Acting Antidepressants Discovered by Serendipity Toward New Affective Preclinical Models of Depression Yielding More Robust and Rapid Effects, hereafter Supplement 3, in the Supplemental Material).

Here, we simply note that many specific behavioral methodologies have sought to model depression (for diverse reviews, see Markou, 2005). It is regrettable that these models do not focus directly on brain affective circuits. Thus, across almost 40 years of intensive deployment of behavioral models, no new and effective medicinal concepts have emerged (see the editorial by Panksepp, 2012). We suspect that a shift of focus to specific brain emotional systems that control relevant affective feelings—enthusiasm, grief, and social joy, to use the vernacular—may bring better treatments for depressed brains and minds. Specifically, we propose that sustained overactivity of the PANIC and underactivity of the SEEKING and PLAY networks substantially contribute to depression. Our studies of PANIC have suggested ways to deploy safe opioids to control suicidal ideation (for which no medicines currently exist). Indeed, we have completed a successful double-blind study in Israel in which we evaluated the ability of ultralow doses of buprenorphine (less than 1 mg sublingually) to reduce suicidality (Yovell et al., 2013). Likewise, our conceptualization of SEEKING provides straightforward ideas for optimal DBS-facilitated treatment of depression (Coenen, Panksepp, Hurwitz, Urbach, & Mäddler, 2012; Coenen, Schlaepfer, Allert, & Mäddler, 2012). Our studies of brain gene-expression changes resulting from PLAY arousals (Burgdorf et al., 2011) have yielded a new antidepressant medicine currently in human testing.

Given how recent knowledge of affective processing in animal brains has emerged, we are not surprised how few new treatments for depression have come from preclinical research (Panksepp, 2012). Considering decades of relatively fruitless preclinical research (i.e., clinically insignificant), we think a turn toward explicit affective modeling of depression and other psychiatric disorders is warranted. That said, it is not without reason that most animal researchers ignore the affective states of the animals they study (e.g., LeDoux, 2012a, 2012b; Rolls, 2014). Attempts to scientifically study the experiential aspects of...
emotional arousals in animals has been fraught with conceptual dangers, such as overinterpretation (see Supplement 1 in the Supplemental Material), which is not the case with explicit rewarding and punishing states of the brain. But historical forces have allowed behaviorist biases to retard such developments. We have generated validated animal models of affective states, for instance, through neural circuit-based vocal measures of emotionality, in which the underlying subcortical systems are distinctly rewarding and punishing to animals.

**The use of emotional vocalization screening methods for rapid monitoring of depressive affect**

It is generally agreed that laboratory rats have a fairly simple repertoire of emotional vocalizations that reflect positive and negative emotions (Brudzynski, 2009). Rats emit a flurry of USVs in a number of social-emotional scenarios. As already noted, USVs that occur around 50-kHz are emitted at particularly high rates during social play (Knutson, Burgdorf, & Panksepp, 1998), preceding copulation (Barfield & Thomas, 1986), and in anticipation of or after the administration of cocaine or amphetamine (Burgdorf, Knutson, Panksepp, & Ikemoto, 2001; Wright, Gourdon, & Clarke, 2010). Evidence supports the use of approximately 50-kHz USVs as indicators of appetitive positive affect (Panksepp & Burgdorf, 2003), specifically of increased SEEKING-system activity (Burgdorf et al., 2007)—the fundamental substrate for appetitive enthusiasm, which appears to be underactive in most animal models of depression (Nestler & Carlezon, 2006; Watt & Panksepp, 2009; Wright & Panksepp, 2011).

To reiterate, the likelihood that 50-kHz chirps of play- ing rats accurately index positive social affect is supported by the finding that animals will self-stimulate all brain sites in which DBS reliably provokes 50-kHz USVs (Burgdorf et al., 2007). These calls are also robustly increased by cues predicting various environmental rewards (for an overview, see Burgdorf & Panksepp, 2006; Knutson, Burgdorf, & Panksepp, 2002; Panksepp, 2007). Evidence that 50-kHz calls represent a positive appetitive state includes experiments that have demonstrated that such calls are emitted in anticipation of all positive rewards, from social play to rewarding brain stimulation and drugs of abuse (Browning et al., 2011; Burgdorf et al., 2001; Burgdorf, Knutson, & Panksepp, 2000). In addition, appetitive approach occurs in response to playback of 50-kHz calls (Burgdorf et al., 2008; Wöhr & Schwarting, 2007, 2009). Conversely, these calls are routinely abolished by all aversive stimuli, including just a hint of cat smell (Panksepp, 1998).

The power of 50-kHz vocalizations as a positive-affect measure comes from knowledge about the underlying neural system necessary for their production. Lesions to either the dopamine-rich ventral tegmental area (VTA) or the MFB, through which all monoamine systems (namely, dopamine, norepinephrine, and serotonin) ascend, with neuronal cell bodies in lower brainstem, provide some critical evidence: As noted earlier, physical damage to the MFB provokes a profound amotivational syndrome resembling severe depression. Such lesions also dramatically reduce 50-kHz USVs, particularly the frequency-modulated-type chirps, which are optimal indicators of positive affect (Burgdorf et al., 2007).

All positive social situations reliably elevate such chirping. Likewise, so does manual human tickling of young rats (see Fig. 2a; Panksepp & Burgdorf, 2000), an effect that continues into adulthood with stable, albeit lower, response rates (Mällo et al., 2007; but only if animals received abundant tickling during adolescence). Our tickling procedure, systematically used, has provided the first psychoassay—with superb retest and intertickler reliability. Thus, we can phenotype animals for temperament-al positive social affect with brief 2-min psycho-assays, during which 15-s no-tickling periods are systematically interspersed with 15-s tickling periods (see Fig. 2b; also see Free Science Lectures, 2007, for a video example of this effect).

In addition, natural play has been effectively used to screen for brain neurochemistries that promote appetitive positive affect, thereby guiding discovery of brain systems that may yield antidepressant effects. Panels of brain-chemical candidates were derived using genetic microarray technologies by screening which molecular pathways significantly enhanced chirping and social play (i.e., oligonucleotide microarray indices of gene-expression profiles were harvested from the neocortices of animals that had experienced strictly positive play and with no emission of 22-kHz USV complaints arising from brain circuits that are punishing). Expression profiles for 1,200 genes were monitored 1 and 6 hr after the end of such play sessions; approximately one third of the genes exhibited significantly changed expression patterns in frontal executive-motor and posterior sensory-perceptual projection regions of the neocortex (Burgdorf et al., 2011; Moskal et al., 2011). Subsequently, researchers demonstrated that infusions of IGF-1 (one of the most intensely expressed genes) into the ventricular system of rats elevated 50-kHz chirping, whereas chemical blockade of this receptor system reduced indices of positive affect (Burgdorf, Kroes, Beinfeld, Panksepp, & Moskal, 2010).

A second candidate targeted (on the basis of strong gene-expression profiles) was the NR2B subunit of the glutamate-glycine receptor complex. As described elsewhere (see Burgdorf et al., 2011; Moskal et al., 2011), potential “partial agonist” medicinal agents were designed to interact in therapeutic ways—facilitating (agonist)
ways at low doses and inhibitory (antagonist) ways at higher doses—with glycine receptors. Through three decades of work, a potentially useful medicinal vector was identified, code-named GLYX-13 (a tetrapeptide with the sequence threonine-proline-proline-threonine), which is a partial agonist for the glycine site on NMDA receptors, thereby promoting glutamate transmission at low doses and blockade at high doses. It is fortunate that this positive-social-affect-facilitating medicinal agent sailed smoothly through nonhuman animal and human toxicology and is currently in Food and Drug Administration (FDA) approved Phase 2B of clinical testing, passing Phase 2A with effect sizes considerably larger than selective serotonin reuptake inhibitors (see http://www.news-medical.net/news/20140304/Naurexs-GLYX-13-receives-FDA-Fast-Track-designation.aspx). GLYX-13 represents a totally novel antidepressant concept. If it proceeds through the whole gamut of FDA testing, namely, the remaining Phase 3 double-blind placebo-controlled evaluation, it will be the first antidepressant arising from human understanding of specific affective brain processes in animal models, that is, tickling of rats, rather than through mere serendipity (Panksepp, 2012). If this does not open up a reasoned conversation about the true neurobiological nature of affective states across mammalian species, something yet to happen in academic psychology and neuroscience, nothing will.

In any event, our novel tickling technique (easily learned) is the first rigorous preclinical behavioral psychophysical assay for positive social feelings (see Fig. 2b) ever developed. It has been effectively used to monitor depressogenic states in rats, and the feelings associated with PLAY provide a systematic way to search for other new antidepressants. We have long used the assay routinely to analyze individual phenotypic variability in outbred rats for their resistance to depression. Indeed, the level of responsivity to tickling is a stable affective phenotype (Mällo et al., 2007); animals that exhibit high levels of chirps are resistant to depressogenic stressors, and animals that exhibit low levels of chirping are depression prone. These phenotypic differences can be easily bred (Burgdorf, Panksepp, Brudzynski, & Moskal, 2005; Panksepp & Burgdorf, 1999), which indicates strong genetic underpinnings.

On the negative side of the affective spectrum, investigators can now use 22-kHz USVs in rats to index negative affect, which is equally relevant for understanding depression: Unlike 50-kHz calls, these vocalizations are integrated in affectively negative brain regions, such as the dorsal PAG (dPAG), in which DBS produces strong averse states accompanied by 22-kHz USVs (Wright & Panksepp, 2011). And negative emotions are infectious (Panksepp & Panksepp, 2013): Animals that are simply allowed to listen to playbacks of 22-kHz USVs show neural activity in the PAG (Sadananda, Wöhr, & Schwarting, 2008). Another simple assay that may be implemented to evaluate sensitivity to this kind of negative affect is the use of repeated air puffs to the nape of the neck (Knapp & Pohorecky, 1995). We recently encouraged close colleagues to use this method to effectively analyze affective changes resulting from heroin or alcohol withdrawal; they found that withdrawal from both opioids and alcohol precipitated higher rates of 22-kHz USVs than those evoked in controls (Williams et al., 2012).

Although rats’ 22-kHz USV complaints may be excellent indicators of FEAR-type feelings, we think the feelings associated with PANIC arousal are different. The evidence indicates that nonhuman animals, just like humans, have several primal negative-affect states. The study of separation-distress vocalizations of young nonhuman animals separated from caretakers has allowed us to conceptualize a PANIC system that mediate the psychological pain of social loss that also promotes depressive despair. This may be an especially important factor in suicidal ideation.

**A synoptic fleshing out: Affective system–based induction of depressive-like states**

With the goal of creating affective animal models with the potential of helping to unravel how depression develops, we sought to fix both the independent (input) and dependent (output) variables within the brain, thinking this would facilitate our ability to understand how the two interact. Our premise was that repeated negative experience (depressogenic input) would suppress appetitive 50-kHz USVs (depression-indicative output) in rats, which relate directly to diminished arousal of the SEEKING system. We selected the dPAG as our input target for proof-of-concept experiments. The dPAG was chosen because it has been well characterized to generate FEAR-type aversion in both humans and rats (for an overview, see Graeff, 2004), thereby facilitating transential interpretations. This midbrain region also mediates DBS-invoked separation-distress PANIC-type vocalizations in guinea pigs (Herman, 1979; Herman & Panksepp, 1981). As already noted, humans report feelings of intense fear, agitation, and impending doom when the dPAG is electrically stimulated (Nashold et al., 1969; Young & Rinaldi, 1997). There are many other examples in the early neurosurgery literature (Panksepp, 1985), with good physiological correlates described in animals: For instance, the autonomic and physiological alterations accompanying human panic attacks are similar to those observed in humans and rats when the dPAG of the midbrain is electrically stimulated (Graeff, 2004; Jenck,
Moreau, & Martin, 1995; Lovick, 2000; Schenberg, Bittencourt, Sudre, & Vargas, 2001).

The PAG runs from the dorsal tegmental nucleus caudally up to the posterior commissure rostrally. It is easily recognized by the densely packed neurons that surround the cerebral aqueduct and has been broken into four functionally distinct longitudinal columns—the dorsal, dorsolateral, lateral, and ventrolateral (Beitz, 1985; DePaulis & Bandler, 1991)—which may mediate different affective-emotional processes, including RAGE, FEAR, and PANIC dorsally as well as positive emotions such as CARE, LUST, and SEEKING more ventrally and laterally. Overall, stimulation of the dorsal half causes bodily tension often accompanied by flight along with tachycardia and increased blood pressure, whereas the ventral half tends to be more parasympathetically inclined, as reflected by reduced activity, bradycardia, and decreased blood pressure (Green et al., 2005).

Our recent study (Wright & Panksepp, 2011) revealed that acute electrical stimulation of the dPAG elicited robust 22-kHz USVs and almost entirely suppressed 50-kHz USVs (see Fig. 3a for Experiment 1 results). In another experiment, we investigated the long-term consequences of chronic dPAG stimulation: Test animals received 30 s of stimulation administered in 1-s bursts over a 10-min period every day for 15 days, whereas sham-operated control animals, also with dPAG electrode implants, were placed in the chamber for the same period of time but received no stimulation. Using simple behavioral tests, we found that 50-kHz USVs were diminished not only on treatment days but also for 30 days after the final stimulation treatment (see Fig. 3b for Experiment 2 results). The long-term effect of the treatment offers a workable window to test potential treatments able to reverse the induced phenotype. These sustained depression-like effects may be the first example of findings from a preclinical test that sought to overactivate relevant negative-affective brain systems, as opposed to just imposing environmental stressors, to provoke a depressive phenotype, thereby providing a novel model to evaluate various antidepressant treatments to restore affective homeostasis.

Of course, at this stage, there are interpretive limitations to the Wright and Panksepp (2011) experiments that will need to be clarified by further research. Electrical brain stimulation has various limitations besides being time intensive. For example, passing fibers can be influenced and the electric field produced from the stimulation can arouse surrounding tissue. In the experiments discussed, it is impossible to rule out electrical influence of the deep layers of the colliculi or even the lateral columns of the PAG. With the advent of modern brain-stimulation techniques, such as optogenetics and DREADD (designed receptors exclusively activated by designer...
drugs), ever-more precision will be had using directed brain-stimulation procedures in the future (for an explanation of these procedures, see Supplement 4: Looking Into the Future: Novel Modern Brain Stimulation Procedures, hereafter Supplement 4, in the Supplemental Material).

**Toward Future Depression-Focused Cross-Species Studies of PANIC, PLAY, and SEEKING**

Affective neuroscience modeling of depression is based on the premise that imbalances in certain primary-process emotional systems are most influential in promoting depressive cascades in the brain. For simplicity, in the current discussion, we have focused on the possible interactions of the separation-distress PANIC system and the general-purpose, enthusiasm-generating SEEKING and PLAY systems. In this vision, therapeutic manipulations that inhibit the PANIC system may provide new ways to reduce depression and, conversely, as we have already discussed, those that promote SEEKING or PLAY arousal may be effective in increasing the type of appetitive positive affect (e.g., enthusiasm) that is diminished in depression.

Opioids, at tiny doses, are very effective in reducing PANIC, and it has long been known that opioids are effective antidepressants in the short term (Tenore, 2008). The challenge is to develop less addictive alternatives. Indeed, mildly safer opioids, such as buprenorphine, are effective antidepressants (e.g., Bodkin, Zornberg, Lukas, & Cole, 1995) but are not currently medically conditioned for psychiatric use. They deserve more attention than they have received.

Thus, parallel studies of PANIC responses in laboratory animals may provide better clues as to the initiation of neuropsychological shifts that result in depression. Although separation-distress vocalizations indicative of PANIC are readily studied only in young nonhuman animals, there are reasons to suspect that these systems continue to participate in social affect as animals mature. Exactly what occurs in the brain when separation-distress calls diminish as animals mature remains unknown. Although we do know that this is partly due to testosterone elevations as males go through puberty, we also know that the circuitry is still there because we can continue to produce separation calls in adult male guinea pigs with DBS long after they no longer show spontaneous social-separation calls (Herman & Panksepp, 1981; Panksepp et al., 1988), an effect we have seen in *Octodon degus* as well (Wright & Panksepp, unpublished observations; see also Supplement 3 in the Supplemental Material for more on this interesting species with a rich social repertoire).

So far, most of what is known about the neuroanatomy of the PANIC system has come from a series of experiments conducted 30 years ago in guinea pigs and chickens, in which it was discovered that animals under general anesthesia could be made to emit separation-distress vocalizations by electrically stimulating different parts of the brain (Herman & Panksepp, 1981). The findings have proven to be remarkably predictive of the general anatomy of the PANIC system in humans, more recently uncovered with modern functional brain imaging (Damasio et al., 2000; Panksepp, 2003; see also Supplement 5: Human Brain fMRI Imaging of Emotional Changes, hereafter Supplement 5, in the Supplemental Material).

What are the broader implications of such affectively focused studies? Many scientists, particularly molecular biologists and electrophysiologists, are interested in the puzzling features of the fine-grained nervous system and are constantly on the lookout for applications of their research. Here, we have offered a simple tickling method by which such investigators might contribute to affect-based depression research. As outlined, wild-type rats can be easily phenotyped into “high” and “low” 50-kHz responders using our evoked-USV method. Given that the complexity of the nervous system is truly incomprehensible, it is likely that whatever an investigator’s specific area of interest, looking for differences between such high and low tickle responders might yield useful knowledge. In this context, it is noteworthy that tickling has already been shown to promote neurogenesis in the hippocampus (Wöhr et al., 2009; Yamamura et al., 2010); this is an effect that many researchers believe is needed for the clinical benefits of currently used antidepressants. This maneuver also makes rats more optimistic when evaluated by how they respond to affectively ambiguous cues of forthcoming potential rewards or punishments (Rygula, Pluta, & Popik, 2012). Data such as these suggest that behavioral therapeutic approaches may be most effective if they arouse the SEEKING system (note that PLAY is intimately related to SEEKING; indeed, it looks like all of the other basic emotional systems employ SEEKING urges as part of their repertoire).

A fundamental property of the SEEKING system is its ability to spontaneously learn to anticipate the future, independent of an animal’s behavior. Using this quality, we designed a temporal conditioning study to isolate the SEEKING system for investigation. For example, rats emit increased rates of 50-kHz USVs immediately preceding electrical stimulation of the SEEKING system after repeated fixed-interval stimulation (i.e., one electrical pulse delivered to the system every 20 s; see Burgdorf et al., 2000). In keeping with our vision of brain-based affective studies, we are currently searching for a neural signal (electroencephalography) output measure in
response to fixed-interval stimulation of the SEEKING system to understand how primary-process SEEKING molds secondary-process learning. Such studies may eventually inform how diminishments in SEEKING could potentially influence more cognitive aspects of depression, such as pathological avoidance that might stem, in part, from an inability to learn to positively anticipate future events. Reshaping of the functionality of the SEEKING system through learning might also facilitate psychotherapeutic recovery from depressive cascades as the brain is reshaped through progressive psychotherapeutic goals, such as the reconsolidation concepts that have emerged from preclinical research on the plasticity of memories to human therapeutic applications (Ecker, Ticic, & Hulley, 2012).

**Historical Perspectives and How Affective Neuroscience Translational-Research Strategies Have Led to Three Novel Treatments of Human Depression**

As preclinical approaches become more focused on specific affective systems in the brain, findings in animal models of affective states may become increasingly applicable to the clinical treatment of human depression. Reciprocally, this may mean clinical research on humans may become better positioned to inform preclinical research. In this section, we elaborate how the two have become mutually informative as our affectively focused preclinical research leads the way toward new therapeutic options for the treatment of depression with DBS and two new medicines.

**DBS: How clinical research can inform nonhuman animal research and vice versa**

More often than not, experimental advances in animal models precede and inform clinical applications. However, in the case of DBS, animal and clinical research advanced in parallel worlds that rarely interacted (Kringelbach, Jenkinson, Owen, & Aziz, 2007). The discovery of self-stimulation in animals with electrodes implanted first into the septal area and then into the MFB (which, as already noted, generate feelings animals can discriminate from septal DBS-induced reward; Stutz et al., 1974) provides a poignant example. The seminal discovery by Olds and Milner (1954) was a great advance but had little impact on the clinical treatment of psychopathologies at the time, except for some work of Robert Heath (1954, 1996) in people with schizophrenia. Gradually, the discovery of the so-called brain reward system fostered a revolution in systems neuroscience but all too often without any ethologically disciplined understanding of what this system actually does for organisms (Panksepp, 1981a, 1981b). Thus, from the 1870s (Bartholow, 1874), when the first electrical brain stimulation of human and other animal cortices took place (climaxing with the 1949 Nobel Prize–winning DBS work of Walter Hess, 1957), clinical application and basic science in the area each progressed in relative isolation. It is only recently that rich arteries of translational-information flow have become apparent through a better understanding of what type of affect the brain reward system truly generates.

Experimental work investigating depression has a much longer history than does the clinical application of DBS for therapeutic purposes (Anderson et al., 2012; Taghva, Malone, & Rezai, 2013). At the same time, with exceptions noted earlier, comparatively little work on animal models of depression uses DBS to monitor and manipulate affective changes, except for a few self-stimulation studies (see Nestler & Carlezon, 2006; Wright & Panksepp, 2011); this needs to change to promote a robust flow of affectively informed translational evidence, as envisioned by Panksepp and Watt (2011).

Classically, focusing on animal models along with ongoing clinical research can promote and give insights into our understanding of the diseases in question (thereby providing rigorous clarification of behavioral, pathological, and anatomical features), but in the case of depression, consensus on etiologies has not yet emerged. Of course, as already noted, depression has been linked to various neurotransmitter systems (see Nestler & Carlezon, 2006; Wright & Panksepp, 2009), and many neural regions and pathways have been implicated, including cortico-limbic (Mayberg, 2003), dorsal raphe (Bach-Mizrachi et al., 2006; Haghhighi et al., 2008), hippocampal (Airan et al., 2007), amygdalar (Sheline et al., 2001), striatal (Zhu, Peng, Zhang, & Zhang, 2011), and mesolimbic pathways (Binfaré, Mantovani, Budni, Santos, & Rodrigues, 2010; Burgdorff et al., 2007; Dailly, Chen, Renard, & Bourin, 2004). The affective neuroscience theory of depression does not suggest any of these views are wrong; rather, it promotes the perspective that there are many possible "distal" causative factors sufficient to induce a major depressive episode but only a limited number or proximal affective changes, due to shifts in the underlying dynamics between specific emotional systems of the brain that are both necessary and sufficient for depression to occur—for instance, the reciprocal inhibition between PANIC and SEEKING systems we focus on here.

Thus, to make progress with direct brain interventions, such as DBS, it is necessary to better theoretically conceptualize and empirically visualize the relevant affective networks in the human brain (for some work...
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relevant to our thesis, see Supplement 5 in the Supplemental Material). Modern mathematical and technological breakthroughs now allow for computations of the orientation of water molecules in neuronal branches, such as axons, which allows researchers to see brain systems within living humans with a clarity that was unimaginable just a decade ago. Indeed, in our attempt to visualize two key emotion systems involved in depression, PANIC and SEEKING (which, as noted, is recruited in PLAY), we have used diffusion tensor imaging (DTI) to characterize their trajectories in human brains (see Fig. 4 for schematics; see also Coenen, Panksepp, Hurwitz, Urbach, & Mädler, 2012; Coenen, Schlaepfer, Allert, & Mädler, 2012). This anatomical work has served as a foundation for situating DBS electrodes in the human SEEKING system in 14 treatment-refractory-depressed individuals so far, and as we discuss later, results from 7 have been published (Schlaepfer, Bewernick, Kayser, Mädler, & Coenen, 2013), of which 6 patients exhibited substantial benefits (see Fig. 5 for a summary of clinical improvements). Parenthetically, the findings fit well with our SEEKING/enthusiasm concept already introduced, which we believe is more accurate, at least at the primary-process level, than Berridge and colleagues’ (Berridge, 1996; Berridge & Robinson, 1998; Berridge, Robinson, & Aldridge, 2009) useful secondary-process “wanting” concept, which does not explicitly acknowledge affective states in nonhuman animals. Our MFB-DBS human responders reported no rewarding-pleasurable feelings during brain stimulation; they just manifested an increased enthusiasm for life, with active planning for future activities that might be enjoyable.

In sum, clinical research does not currently put forward a single target for antidepressant effects of DBS (for a review, see Supplement 5 in the Supplemental Material) but, instead, emphasizes that depression is a widespread brain disorder with primary symptoms emerging principally from the subcortical “limbic system,” which influences many other brain areas and neurochemistries. That said, the assessment of a multitude of brain regions implicated in human clinical depression, permitted especially by modern functional brain imaging, is paralleled by nonhuman animal studies that have investigated the

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**Fig. 4.** Schematics illustrating target areas for deep brain stimulation and diffusion tensor imaging. The left schematic provides a sketch of the MFB that highlights areas for targeted MFB deep brain stimulation for human patients. LH = lateral hypothalamus; MFB = medial forebrain bundle (sl = superiolateral branch; im = inferiormedial branch); ALIC = anterior limb of the internal capsule and the nucleus accumbens; RN = red nucleus; STN = subthalamic nucleus; SNr = substantia nigra pars reticulata; VTA = ventral tegmental area; ATR = anterior thalamic radiations; fx = fornix; mtt = mammilo-thalamic tract; PAG = periaqueductal gray (v = ventral; d = dorsal); rc Hipp = retrocommisural hippocampus; PT = pyramidal tract; PFC = prefrontal cortex; VIII = third ventricle; ANT = anterior nucleus of the thalamus; DMT = dorsomedial nucleus of the thalamus. The right schematic shows diffusion tensor imaging of a 3-D probability map of putative human MFB SEEKING (green) and ATR PANIC (orange) as visualized in an axial scan of the human brain (for color renditions, see Coenen, Panksepp, Hurwitz, Urbach, & Mädler, 2012; Coenen, Schlaepfer, Allert, & Mädler, 2012). The schematic shows anatomical linkages near the VTA in which PANIC systems mediating psychic pain may interact with SEEKING urges. Adapted from Coenen, Panksepp, et al. (2012) and Coenen, Schlaepfer, et al. (2012), which can be consulted for other views of the human MFB.
translational utility of DBS and focused on many brain areas implicated by brain imaging (for a cross-species meta-analysis, see Alcaro, Panksepp, Witczak, Hayes, & Northoff, 2010). Nonhuman animal DBS targets already evaluated include the lateral habenula (Meng et al., 2011), the medial prefrontal cortex (Hamani, Diwan, Isabella, Lozano, & Nobrega, 2010; Hamani et al., 2012; Hamani & Nobrega, 2012), the nucleus accumbens (NAcc; Falowski et al., 2011), and the VTA (Friedman et al., 2009). DBS in each study produced positive behavioral effects and reversed the “depressed-like” behavior within the diverse behavioral paradigms used, although a detailed review of those findings is beyond the scope of this article. However, we emphasize how difficult the sifting of the wheat from the chaff in this area of research can be. The problem is that it is currently impossible to know how relevant the various behavior-only depression paradigms are to understanding basic affects in animals or clinical depression in humans. Although an enormous number of brain regions and neurochemistries have been implicated by preclinical depression research (for an overview of animal models, see Harro, Kanarik, Matrov, & Panksepp, 2011; Markou, 2005; see also Supplement 3 in the Supplemental Material), their roles in promoting the negative affect of depression and the positive affects that can ameliorate depression are rarely the focus of investigation among preclinical investigators. Likewise, genetic variables remain an active area of inquiry (for critiques of

Fig. 5. Summary of therapeutic effect of deep brain stimulation (DBS) of the human medial forebrain bundle (MDF). The top graph shows affective (antidepressant) changes, using the Montgomery-Asberg Depression Rating Scale (MADRS), in response to MFB-DBS for up to 33 weeks. Antidepressant effects (percentage reductions in MADRS score) from baseline are shown in 6 of 7 patients. The bottom graph shows individual response scores contrasted to group means (blue line), which highlights the robustness of the effect; the “nonresponder” (Patient 5) had surgical problems (hemorrhage at one of the electrode sites). Data from Schlaepfer, Bewernick, Kayser, Madler, and Coenen (2015).
traditional and promising genetic models, see Overstreet, 2012; Overstreet & Wegener, 2013), but little of this work has had direct therapeutic implications.

However, improved understanding of the anatomical correlates between experimental models (mainly rodent) and the neural pathways clinically associated with depression could improve the ability to test theories concerning DBS, which could then feed back into better clinical treatments. Our understanding of the human MFB has been much advanced by using DTI and fiber-tracking methods (Coenen, Panksepp, et al., 2012; Coenen, Schlaepfer, et al., 2012), thereby allowing us to better situate DBS pacemakers for human depression, as described later.

To ensure the future clinical progression of this particular approach, we have started developing a chronic bilateral MFB-stimulation model in rats as a platform to test emerging theories, with the aim of selectively modulating the ascending mesolimbic dopaminergic circuitry originating in the A10 VTA. By using a validated animal model of depression to identify the appropriate coordinates in the rat MFB (through classical pathway tracing and MRI studies with fiber-tracking ability), researchers can produce a useful tool to test the limits of experimental MFB-DBS treatments in human depression.

**Treatment-resistant depression and DBS in humans**

In contrast to some discrete neurological disorders, the pathological interplay of several brain regions contributes to the behavioral, emotional, and cognitive symptoms of psychiatric disorders. Functional neuroimaging studies have suggested that different depressive symptoms are mediated by different brain regions (Berton & Nestler, 2006; Krishnan & Nestler, 2008; Yurgelun-Todd, Sava, & Dahigren, 2007). According to such models, depression results from a dysregulation of limbic-cortical connections: Pathological changes in dorsal brain regions (including the dorsolateral prefrontal cortex, inferior parietal cortex, and striatum) are associated with cognitive symptoms (e.g., apathy, anhedonia, hopelessness, deficits in attention and executive function), and changes in ventral areas (hypothalamic-pituitary-adrenal axis, subgenual cingulate, and brainstem) contribute to the vegetative and somatic aspects of depression (e.g., sleep disturbance, appetite, endocrine dysregulation). This model underlines the role of the rostral cingulate cortex, a rostral node of the PANIC system in regulating sadness (Mayberg 1997), along with other human DBS studies in treatment of depression summarized in Supplement 5 in the Supplemental Material. The involvement of other regions in depression is evident: The hippocampus contributes to memory deficits, and the NAcc is clearly associated with anhedonia and lack of motivation (Berton & Nestler, 2006).

These conceptualizations of major depression were brought about mainly by advances in functional neuroimaging but also through electrophysiological and molecular studies, which, taken together, have paved the road to hypothesis-guided studies on targeted reversible neuromodulation with DBS in depression. The NAcc was chosen as a target for DBS because of its aforementioned prominent role in brain reward. This brain region has long been known to act as a motivational gateway between systems involved in motor control and limbic systems in charge of emotion processing, especially the ventral striatum, which is uniquely located to modulate other regions of the brain (Schlaepfer et al., 2008). Stimulation here was particularly effective at reversing anhedonia, without producing any explicit “pleasure” responses but, rather, psychological states characterized by enthusiasm, namely, planning for the future. Normalization of brain metabolism in fronto-striatal networks as a result of NAcc stimulation was also observed (Schlaepfer et al., 2008). Notably, no side effects due to DBS were observed. Overall, 9 patients in this study showed acute and long-term antidepressant effects of DBS at this target, with an overall response rate of 50% (Bewernick et al., 2010).

**DBS to the MFB.** As already noted, the original work of Olds and Milner (1954) on brain reward has been a historical benchmark for all subsequent work. Even though the original report showed that septal stimulation was rewarding, it soon became clear that the MFB had a much more widespread role in brain reward.

The MFB of humans has been described only recently, with the help of DTI (Coenen, Panksepp, et al., 2012; Coenen, Schlaepfer, et al., 2012). It appears to be somewhat different from the structure that has been described in rodents in that it has a superolateral branch that connects the VTA with forebrain structures, including the NAcc and the medial prefrontal cortex. As a result of this work and related imaging of other emotional systems in humans (see Fig. 4), we assessed the role of the main MFB-based trajectory of the SEEKING system as a therapeutic target—which has now led to the highest recovery rate in treatment-resistant depression ever documented (Schlaepfer et al., 2013). At a very low current application (less than 3 mA), 6 out of 7 patients reached the response criterion (Montgomery-Asberg Depression Rating Scale improvement of 50%) and stayed there up to a maximal observation time of 33 weeks (see Fig. 5). Patients clearly showed acute effects reminiscent of increased appetitive motivation (enthusiasm), which probably indicates elevated appetitive SEEKING urges. This could also be consistent with Berridge’s concept of wanting (Berridge,
1996; Berridge et al., 2009; Berridge & Robinson, 1998), which arose from the unpredicted (and, hence, paradoxical) findings originally described by Berridge and Valenstein (1991). In any event, no excessive euphoria or hypomania was observed in any of the patients, whereas antidepressive effects were clear and rapid.

**Nonhuman animal experiments and how they inform our future clinical work.** DBS consists of the temporal and spatial delivery of electrical signals of defined parameters to deep subcortical structures of the brain with the aim of modulating neural circuits. One of the major benefits of DBS is its reversibility and the fact that the strength of stimulation can be adjusted by reprogramming the implant to retain the therapeutic impact. However, what is scientifically frustrating—despite the clinical relevance—is that the mechanisms of action of DBS remain largely unknown: The electrical signal does not distinguish between cellular phenotypes, projection or interneurons, neuronal or nonneuronal cells, or white or grey matter, but all biological material within the stimulation range of the electrode tip are affected in a nonselective, nondiscriminatory fashion that produces an overall effect; potentially, preclinical work can help identify the most important components. As more is known about the neurocircuits implicated in depression, including possible interindividual differences, novel, customized, and selective treatment approaches might be possible. This, however, is currently beyond the capacity of both the clinical application and the current experimental models of DBS (but see the emergence of new techniques described in Supplement 3 in the Supplemental Material).

**Elaborations, Limitations, and Qualifications**

It may deserve reemphasis that our work is not based on any traditional “behavioral neuroscience” approach to preclinical modeling but one in which core affective processes are front and center in the analysis. The strict behavioral approach has yet to yield a new treatment of depression, and our assumption is that this is due to the failure to try to deal scientifically with the diverse nature of mammalian brain affective processes (e.g., Panksepp, 1998, 2012; Wright & Panksepp, 2011, 2012). Our ability to go to the affective level is premised completely on our appreciation that no “rewards” or “punishments” exist in humans without shifts in affective feelings, and there is no cogent reason to believe it is any different in other animals. However, there is profound resistance to such straightforward concepts: As one highly critical reviewer of this article said, “To equate animal behavior with emotional feelings, an anthropomorphic assumption which only those who do not employ scientific methods would support,” is unacceptable; the reviewer concluded with the observation that “those of us that actually study emotional processing in animals could and would never swallow that pill.”

We regret such adversarial attitudes toward accepting “affective-circuit modeling” in preclinical psychiatry. Although space limitations have allowed us to share only a cursory coverage of the vast preclinical behavioral modeling literature in the area of depression, we have provided a sampler in Supplement 2 in the Supplemental Material (and emphasize the detailed coverage of that literature in the special full issue of *Neuroscience & Biobehavioral Reviews* on that topic edited by Markou, 2005). Of course, we use behavioral techniques in animals just like other behavioral neuroscientists, but, atypically, we focus mainly on ethological measures and, thus, mostly on unconditional emotional behaviors controlled by affectively validated neural circuits. We suggest this is a substantive advance over the traditional behaviorist model (especially learning-based ones) of how investigators could proceed. We think replicable evidence exists that primary-process (namely, evolutionarily created) emotional affects are indeed elaborated by the brains of other animals, and we argue that they are capable of being modeled, with the potential for more rapid progress in psychiatric therapeutic discovery research. If this argument is on the right track, it is long past time for investigators to reopen the conversation about emotional feelings in animals, discussing the weight of evidence pro and con as opposed to indulging in reflexive skepticism passed down from a “never-mind” behaviorist era that at one time had no need for brain (i.e., “black-box”) research. In this vein, it is refreshing to see some discussion of “anhedonia” and “dysphoria” processes in preclinical modeling of depression (e.g., Treadway & Zald, 2011), but we suggest that the semantic implication of “hedonia” is sensory pleasure, which, as in the love of chocolate, has not been documented to be markedly deficient in human depression.

Furthermore, we think human evidence has indicated that the internal feeling generated by DBS of the MFB-based brain reward system engenders a mental state more akin to the human concept of “enthusiasm,” accompanied by consistent and concordant unconditional behavioral changes: energized forward locomotion, with diverse exploratory-foraging-investigatory activities, accompanied by vigorous sniffing (Panksepp, 1981a, 1982), which is absolutely critical for pursuit of all the rewarding objects needed for survival in olfaction-dependent animals (parenthetically, this helps explain why olfactory bulbectomy is one of the few highly effective brain-based models of depression in rats). In short, our goal is to explicitly pry open the long-closed Pandora’s box of various primary-process emotional feelings in
animals for the betterment of psychiatric and psychological clinical sciences.

In this context, we reemphasize that the potential role of diminished activity of dopamine in the brain reward system has been envisioned to have a major role in depression by various psychiatrically oriented investigators (e.g., Nestler & Carlezon, 2006). But we have also envisioned how other emotional systems, for instance, sustained PANIC overarousal, can be a gateway to depression (by dampening SEEKING feelings and urges), which has allowed, for the first time, evidence-based affective-network modeling of depression (Panksepp & Watt, 2011; Wright & Panksepp, 2011, 2012). This, of course, is not to deny the intrinsic limitations of all animal models of human depression, especially given that many cognitive factors, such as social marginalization, are surely not readily modeled in rodents. That said, it is clearly the case that social defeat, which is a common model of depression in animals (for review, see Panksepp, Moskal, Panksepp, & Kroes, 2002), does facilitate sustained dysregulation of the brain reward SEEKING system (Der-Avakian, Mazei-Robison, Kesby, Nestler, & Markou, 2014).

Because of space limitations, we have provided only a sketchy coverage of the vast area of preclinical behavioral modeling of psychiatric disorders in this article and have emphasized the topic of affective states in animals that are largely ignored or spoken of only in very undifferentiated ways, using general terms such as dysphoria and motivational changes (e.g., Treadway & Zald, 2011)—namely, amorphous, but traditional, psychological concepts that could be more emotionally precise by focusing on specific affective brain systems, especially changes in PANIC, SEEKING, and PLAY. In this vein, we note that work most closely related to ours, in the behavioral neuroscience tradition, is the wanting perspective of Berridge and colleagues (Berridge, 1996; Berridge et al., 2009; Berridge & Robinson, 1998), which, in part, historically is derivative of our SEEKING concept; Berridge and his colleagues have never explicitly acknowledged or considered experienced affective-emotional states of rats in their sophisticated studies of learning (indeed, that was the original reason for their use of scare quotes around wanting—thereby serving to acknowledge that a subjective perspective still remains taboo within most traditional nonhuman animal research). We believe such skepticism is contradicted by abundant evidence at the primary-process level.

So What About the Long-Standing Basic-Emotion Controversy in Psychology?

Without delving into fine detail, we provide a synopsis, informed largely by modern brain imaging data, of the “basic-emotion” controversy in Supplement 5 in the Supplemental Material. As noted there, we think abundant weight of evidence supports the existence of at least four basic experienced emotions in humans—anger, fear, joy, and sadness. In our estimation, because of problems with functional MRI data, positron emission tomography imaging is even more compelling for this conclusion, as documented by Damasio et al. (2000). We share the unpublished summary images from that fine study, kindly shared by Antonio Damasio (see Fig. 6), which depict brain changes during self-motivated feelings of sadness, happiness, anger, and fear. The overall concentrations of brain arousals across emotions were subcortically situated (reds and yellows), in distinct brain regions, with predominant inhibitory foci in cortical regions (purples and blues). As quantified in data summary histograms in Supplement 5 in the Supplemental Material, predominant increased arousals across four emotions were evident in subcortical brain regions, with sadness and anger showing the largest effects, and preponderant increased inhibitions (i.e., decreased arousals) were evident in neocortical brain regions, with sadness (i.e., PANIC-related brain regions, in our terminology) showing the largest effects and anger the second largest.

Conclusion

Preclinical behavioral modeling of depression is a flourishing field. However, it is regrettable that few researchers have attempted to clarify the precise affective foundations of dysphoria, especially lack of enthusiasm and diminished social joy, when separation distress (PANIC arousal) remains overactive for too long (Panksepp & Watt, 2011; Watt & Panksepp, 2009). In our estimation, this is finally possible within the recognition that various primary-process emotional pathways exist in mammalian brains with remarkable relevance for depression—namely, the affect-generating circuitries of SEEKING, PANIC, and PLAY—and that they can be studied with behavioral psychoassays, which should allow more rapid progress in identification of new neurochemical targets that can promote novel and more effective therapeutic interventions than currently exist, which, overall, are marginal at best (as revealed by STAR*D analyses; Sinsky, Schaffer, & Levitt, 2010).

To summarize, studies of the neural and neurochemical substrates of separation distress and positive social affect have already provided both a scientific justification for an old neurochemical maneuver to diminish depression and suicidal ideation (the use of a moderately safe opioid; indeed, across the past half dozen years, we have evaluated the efficacy of low dose buprenorphine to treat suicidality, with promising results; Yovell et al., 2013) and a direct way to counteract the lack of dysphoria and lack of...
enthusiasm by direct DBS facilitation of activity in the brain’s rewarding SEEKING system (Coenen, Schlaepfer, Maedler, & Panksepp, 2011; Schlaepfer et al., 2013). Finally, our genetic analysis of social joy on cortical gene-expression changes has yielded a novel antidepressant (GLYX-13), which is currently in FDA-approved human testing. Because this molecule also facilitates learning and memory, with no negative side effects so far (Burgdorf et al., 2011; Burgdorf et al., 2013), it could have substantial uses in strengthening the benefits of various affectively focused psychotherapies that increasingly integrate solid neuroscientific knowledge, such as the systematic use of positive affect in memory reconsolidation processes to facilitate therapeutic change (Ecker et al., 2012).

We are impressed by DBS therapeutics along the MFB-centered SEEKING system, which seem to facilitate enthusiasm for living once treatment-resistant depression has set in. However, there are many challenges to face. One crucial issue is not whether researchers are able to achieve such technical feats of medicine, or even whether medicine and society will learn to accept them—for example, the use of innocuous viruses as tools in human medicine (as are needed for DREADD and optogenetic approaches; for relevant details, see Supplement 4 in the Supplemental Material)—but whether researchers can concurrently understand the underlying affective and molecular mechanisms involved in the genesis of depression to intervene in scientifically rational ways. Given the many uncertainties, it is more important than ever to better integrate clinical and experimental research efforts with a fuller understanding of the brain that does not marginalize aspects of the brain as subtle as affective feelings (especially in the other animals), which could be a cross-species psychological benchmark for future

![Fig. 6. Positron emission tomography–monitored changes in brain arousals and inhibitions during self-evoked strong emotional feelings. An overview of brain arousals (reds and yellows) and inhibitions (purples) are depicted on lateral surfaces of the right and left hemispheres (top of each panel) and medial surfaces of the corresponding hemispheres (bottom of each panel) while human participants experience various basic emotions evoked by autobiographical reminiscing. The directionality of changes, as monitored by changes in blood flow, is highlighted by indicating inhibitory foci with downward arrows (predominating in neocortical regions) and arousals with upward arrows (predominantly in subcortical regions in which emotional behaviors can be evoked by brain stimulation in animals). Data from Damasio et al. (2000); these overall patterns of activation and inhibition were graciously provided by Antonio Damasio.](cpx.sagepub.com)
progress. Our preclinical work has, for the first time, been guided by the affective circuits of nonhuman animals, as validated by their rewarding and punishing properties. Our position is that the conceptualization of brain-mind imbalances in affective terms may be capable of engendering new therapeutic strategies that have not yet been achieved by models that restrict analyses simply to behavioral issues.

Although this approach is not yet well represented in preclinical modeling, we suggest that an affective view better addresses key issues for understanding various psychiatric problems than do behavior-only approaches. Understanding of emotional networks could provide new therapeutic targets and integrative perspectives to help flesh out endophenotypic thinking (e.g., Panksepp, 2006) and provide fresh perspectives for future research domain criteria (e.g., Dillon et al., 2014; Lenzenweger, 2013).

In conclusion, for readers to think clearly about key alternatives that are out there, it may be useful to highlight three key approaches to nonhuman animal studies of emotion, as seen through the ontological perspectives of three major investigators of animal emotions. First, Joseph LeDoux (2012a, 2012b), as noted earlier, has solidified the position that the scientific book on emotional feelings in other animals is epistemologically closed, thereby mandating a continued use of behavior-only models of emotions in animals, as represented by his ongoing fine empirical work on classical fear conditioning, which is emulated by many labs. Second, Edmund Rolls (2014) has advocated the perspective that diverse emotional feelings are constructed through reinforcement-learning processes from primal Wundtian dimensions of valence and arousal and that the conscious experiences of these feelings exist only in humans, because such psychological experiences can be ordained only through higher cognitive-linguistic reflective processes that are unique to humans. Finally, as discussed in the present article, we (Jaak Panksepp and colleagues) have taken the position that there are diverse primary (evolutionarily constructed) neural processes for emotional feelings that are best studied with DBS procedures, whether implemented electrically, optogenetically, or via DREADD procedures (see Supplement 4 in the Supplemental Material). We assert that a fuller consideration of the subcortical neural underpinnings of these primal affective processes, experienced phenomenally by other animals on the basis of empirically demonstrated rewarding and punishing properties of emotion-system dynamics, is an optimal strategy to make the most rapid and most accurate empirical progress on understanding the nature of the affective states that are imbalanced in so many psychiatric disorders. It may be noteworthy that the first two research programs have been remarkably well funded by government granting agencies. The third has not.

Where shall society invest future resources that can have optimal impact on human welfare?

**Author Contributions**

J. Panksepp and J. S. Wright conceptualized and wrote the manuscript and the supplemental material available online. V. A. Coenen, M. D. Döbrössy, and T. E. Schlaepfer provided critical conceptual input to the manuscript, including editing and substantively supplementing the arguments, and conducted critical research describing the anatomy and rewarding functions of the antidepressive affects (e.g., facilitated “enthusiasm”) mediated by the medial forebrain bundle; they empirically evaluated the predicted antidepressive effect of deep brain stimulation of the medial forebrain bundle–based SEEKING system (which has traditionally been called “The Brain Reward”), yielding results summarized in Figures 4b and 5. Although not discussed herein, the authors acknowledge some differences in perspectives on how the psychological functions of this emotional system should be affectively conceptualized (for a fuller analysis, see Wright & Panksepp, 2012, accompanied by a set of expert commentaries). The authors note that the different theoretical viewpoints in the field are summarized and analyzed in Panksepp and Moskal (2008).

**Declaration of Conflicting Interests**

V. A. Coenen has received honorariums and travel support from Medtronic Inc. (Europe, United States). T. E. Schlaepfer is a member of the project group Deep Brain Stimulation in Psychiatry: Guidance for Responsible Research and Application, which is funded by the Volkswagen Foundation (Hannover, Germany) and has received limited funding from Medtronic Inc. for an investigator-initiated study on the effects of DBS in major depression (from 2004–2007).

**Funding**

Research summarized in this article was supported by grants from the Hope for Depression Research Foundation (HDRF) to V. A. Coenen and J. Panksepp, and the Neuropsychoanalytic Research Foundation to J. Panksepp. V. A. Coenen has received limited funding for DBS trials from Medtronic.

**Supplemental Material**

Additional supporting information may be found at http://cpx.sagepub.com/content/by.supplemental-data

**Note**

1. As a matter of information, J. Panksepp started his graduate student career at the University of Massachusetts in the area of clinical psychology. Realizing that discussion about the nature of emotions in psychiatric disorders was impoverished (during the “behavioral modification” era) and that there was little understanding of the primal nature of emotions, and after having been awarded a Veteran's Administration Traineeship, he saw the opportunity and necessity to shift into what was called “physiological psychology” to study emotions using DBS.
procedures. After paying his dues in areas such as energy-balance research and sleep physiology, and having received tenure at his first position at Bowling Green State University, he promptly shifted his focus to understanding emotional systems in preclinical models. His work in this area has never been supported explicitly by any government agency, and this is not because of lack of asking.

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